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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 10-Q

(Mark One)

☒ **QUARTERLY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

FOR THE QUARTERLY PERIOD ENDED SEPTEMBER 30, 2021

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

COMMISSION FILE NUMBER 001-36279

CARA THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**75-3175693**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
4 Stamford Plaza **107 Elm Street, 9th Floor** **Stamford, Connecticut**	
(Address of registrant's principal executive offices)	**06902** **(Zip Code)**

Registrant's telephone number, including area code: (203) 406-3700

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol	Name of each exchange on which registered
Common Stock, par value $0.001 per share	CARA	The Nasdaq Stock Market LLC

Indicate by check mark whether the registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. ☒ Yes ☐ No.

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). ☒ Yes ☐ No.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company or an emerging growth company. See the definitions of "large accelerated filer", "accelerated filer", "smaller reporting company", and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large Accelerated Filer	☒	Accelerated Filer	☐
Non-Accelerated Filer	☐	Smaller Reporting Company	☐
		Emerging Growth Company	☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). ☐ Yes ☒ No.

The number of outstanding shares of the registrant's common stock, par value $0.001 per share, as of November 4, 2021 was: 53,458,679.

CARA THERAPEUTICS, INC.

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FOR THE QUARTERLY PERIOD ENDED SEPTEMBER 30, 2021

PART I –FINANCIAL INFORMATION

PART I
FINANCIAL INFORMATION

Item 1. ***Financial Statements.***

CARA THERAPEUTICS, INC.

CONDENSED BALANCE SHEETS
(amounts in thousands, excluding share and per share data)
(unaudited)

	September 30, 2021	December 31, 2020
Assets		
Current assets:		
Cash and cash equivalents	$ 22,991	$ 31,683
Marketable securities	121,203	149,242
Income tax receivable	697	1,507
Other receivables	20,350	557
Prepaid expenses	6,258	12,076
Total current assets	171,499	195,065
Operating lease right-of-use assets	3,310	4,279
Marketable securities, non-current	49,221	70,565
Property and equipment, net	654	840
Restricted cash	408	408
Total assets	$ 225,092	$ 271,157
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable and accrued expenses	$ 13,812	$ 16,881
Operating lease liabilities, current	1,716	1,602
Total current liabilities	15,528	18,483
Operating lease liabilities, non-current	2,373	3,673
Commitments and contingencies (Note 15)	—	—
Stockholders' equity:		
Preferred stock; $0.001 par value; 5,000,000 shares authorized at September 30, 2021 and December 31, 2020, zero shares issued and outstanding at September 30, 2021 and December 31, 2020	—	—
Common stock; $0.001 par value; 100,000,000 shares authorized at September 30, 2021 and December 31, 2020, 50,175,988 shares and 49,872,213 shares issued and outstanding at September 30, 2021 and December 31, 2020, respectively	50	50
Common stock subscribed in Vifor stock purchase, or Private Offering; $0.001 par value; 3,282,391 shares at September 30, 2021	3	—
Additional paid-in capital	699,482	641,195
Stock subscription receivable	(44,969)	—
Accumulated deficit	(447,376)	(392,317)
Accumulated other comprehensive income	1	73
Total stockholders' equity	207,191	249,001
Total liabilities and stockholders' equity	$ 225,092	$ 271,157

See Notes to Condensed Financial Statements.

CARA THERAPEUTICS, INC.

CONDENSED STATEMENTS OF COMPREHENSIVE LOSS
(amounts in thousands, excluding share and per share data)
(unaudited)

	Three Months Ended		Nine Months Ended	
	September 30, 2021	September 30, 2020	September 30, 2021	September 30, 2020
Revenue:				
License and milestone fees	$ 20,031	$ 9,257	$ 21,223	$ 22,377
Collaborative revenue	—	—	706	—
Clinical compound revenue	241	9	278	616
Total revenue	20,272	9,266	22,207	22,993
Operating expenses:				
Research and development	15,514	21,067	59,870	80,711
General and administrative	5,882	5,219	17,898	15,187
Total operating expenses	21,396	26,286	77,768	95,898
Operating loss	(1,124)	(17,020)	(55,561)	(72,905)
Other income, net	111	379	502	1,970
Loss before benefit from income taxes	(1,013)	(16,641)	(55,059)	(70,935)
Benefit from income taxes	—	132	—	436
Net Loss	$ (1,013)	$ (16,509)	$ (55,059)	$ (70,499)
Net Loss per share:				
Basic and Diluted	$ (0.02)	$ (0.35)	$ (1.10)	$ (1.51)
Weighted average shares:				
Basic and Diluted	50,114,710	46,885,424	50,031,615	46,803,659
Other comprehensive income (loss), net of tax of $0:				
Change in unrealized gains (losses) on available-for-sale marketable securities	6	(272)	(72)	193
Total comprehensive loss	$ (1,007)	$ (16,781)	$ (55,131)	$ (70,306)

See Notes to Condensed Financial Statements.

CARA THERAPEUTICS, INC.

CONDENSED STATEMENTS OF STOCKHOLDERS' EQUITY
(amounts in thousands except share and per share data)
(unaudited)

	Common Stock		Common Stock Subscribed in Private Offering		Additional Paid-In	Stock Subscription		Accumulated Other Comprehensive	Total Stockholders'
	Shares	Amount	Shares	Amount	Capital	Receivable	Accumulated Deficit	Income (Loss)	Equity
Balance at December 31, 2020	49,872,213	$ 50	—	$ —	$ 641,195	$ —	$ (392,317)	$ 73	$ 249,001
Stock-based compensation expense	—	—	—	—	2,744	—	—	—	2,744
Shares issued upon exercise of stock options	45,035	—	—	—	688	—	—	—	688
Shares issued upon vesting of restricted stock units	109,419	—	—	—	1,388	—	—	—	1,388
Net loss	—	—	—	—	—	—	(23,301)	—	(23,301)
Other comprehensive loss	—	—	—	—	—	—	—	(61)	(61)
Balance at March 31, 2021	50,026,667	$ 50	—	$ —	$ 646,015	$ —	$ (415,618)	$ 12	$ 230,459
Stock-based compensation expense	—	—	—	—	3,376	—	—	—	3,376
Shares issued upon exercise of stock options	25,494	—	—	—	293	—	—	—	293
Shares issued upon vesting of restricted stock units	36,000	—	—	—	100	—	—	—	100
Net loss	—	—	—	—	—	—	(30,745)	—	(30,745)
Other comprehensive loss	—	—	—	—	—	—	—	(17)	(17)
Balance at June 30, 2021	50,088,161	$ 50	—	$ —	$ 649,784	$ —	$ (446,363)	$ (5)	$ 203,466
Subscription of common stock in Vifor stock purchase ($15.23 per share)	—	—	3,282,391	3	44,966	(44,969)	—	—	—
Stock-based compensation expense	—	—	—	—	3,487	—	—	—	3,487
Shares issued upon exercise of stock options	43,825	—	—	—	339	—	—	—	339
Shares issued upon vesting of restricted stock units	44,002	—	—	—	906	—	—	—	906
Net loss	—	—	—	—	—	—	(1,013)	—	(1,013)
Other comprehensive income	—	—	—	—	—	—	—	6	6
Balance at September 30, 2021	50,175,988	$ 50	3,282,391	$ 3	$ 699,482	$ (44,969)	$ (447,376)	$ 1	$ 207,191

CONDENSED STATEMENTS OF STOCKHOLDERS' EQUITY (continued)
(amounts in thousands except share and per share data)
(unaudited)

	Common Stock		Common Stock Subscribed in Private Offering		Additional Paid-In Capital	Stock Subscription Receivable	Accumulated Deficit	Accumulated Other Comprehensive Income (Loss)	Total Stockholders' Equity
	Shares	Amount	Shares	Amount					
Balance at December 31, 2019	46,720,225	$ 47	—	$ —	$ 587,223	$ —	$ (400,727)	$ 170	$ 186,713
Stock-based compensation expense	—	—	—	—	2,846	—	—	—	2,846
Shares issued upon exercise of stock options	7,500	—	—	—	75	—	—	—	75
Net loss	—	—	—	—	—	—	(28,922)	—	(28,922)
Other comprehensive loss	—	—	—	—	—	—	—	(238)	(238)
Balance at March 31, 2020	46,727,725	$ 47	—	$ —	$ 590,144	$ —	$ (429,649)	$ (68)	$ 160,474
Stock-based compensation expense	—	—	—	—	2,993	—	—	—	2,993
Shares issued upon exercise of stock options	16,846	—	—	—	201	—	—	—	201
Shares issued upon vesting of restricted stock units	119,834	—	—	—	1,625	—	—	—	1,625
Net loss	—	—	—	—	—	—	(25,068)	—	(25,068)
Other comprehensive income	—	—	—	—	—	—	—	703	703
Balance at June 30, 2020	46,864,405	$ 47	—	$ —	$ 594,963	$ —	$ (454,717)	$ 635	$ 140,928
Stock-based compensation expense	—	—	—	—	3,305	—	—	—	3,305
Shares issued upon exercise of stock options	28,147	—	—	—	395	—	—	—	395
Net loss	—	—	—	—	—	—	(16,509)	—	(16,509)
Other comprehensive loss	—	—	—	—	—	—	—	(272)	(272)
Balance at September 30, 2020	46,892,552	$ 47	—	$ —	$ 598,663	$ —	$ (471,226)	$ 363	$ 127,847

See Notes to Condensed Financial Statements.

CARA THERAPEUTICS, INC.

CONDENSED STATEMENTS OF CASH FLOWS
(amounts in thousands)
(unaudited)

	Nine Months Ended	
	September 30, 2021	**September 30, 2020**
Operating activities		
Net loss	$ (55,059)	$ (70,499)
Adjustments to reconcile net loss to net cash used in operating activities:		
Stock-based compensation expense	12,001	10,770
Depreciation and amortization	186	147
Amortization expense component of lease expense	969	496
Amortization of available-for-sale marketable securities, net	590	28
Realized gain on sale of available-for-sale marketable securities	(39)	(126)
Realized gain on sale of property and equipment	(70)	—
Deferred revenue	—	(21,751)
Changes in operating assets and liabilities:		
Income tax receivable	810	(436)
Other receivables	(19,793)	509
Prepaid expenses	5,818	(1,391)
Accounts payable and accrued expenses	(3,069)	(4,608)
Operating lease liabilities	(1,186)	(714)
Net cash used in operating activities	(58,842)	(87,575)
Investing activities		
Proceeds from maturities of available-for-sale marketable securities	134,220	119,895
Proceeds from redemptions of available-for-sale marketable securities, at par	13,500	22,035
Proceeds from sale of available-for-sale marketable securities	10,029	23,148
Purchases of available-for-sale marketable securities	(108,989)	(21,016)
Proceeds from sale of property and equipment	70	—
Purchases of property and equipment	—	(182)
Net cash provided by investing activities	48,830	143,880
Financing activities		
Proceeds from the exercise of stock options	1,320	671
Net cash provided by financing activities	1,320	671
Net (decrease) increase in cash, cash equivalents and restricted cash	(8,692)	56,976
Cash, cash equivalents and restricted cash at beginning of period	32,091	18,713
Cash, cash equivalents and restricted cash at end of period	$ 23,399	$ 75,689
Noncash investing and financing activities		
Stock subscription receivable from Vifor	$ 44,969	$ —

See Notes to Condensed Financial Statements.

CARA THERAPEUTICS, INC.

NOTES TO CONDENSED FINANCIAL STATEMENTS
(amounts in thousands, except share and per share data)
(unaudited)

1. Business

Cara Therapeutics, Inc., or the Company, is an early commercial-stage biopharmaceutical company formed on July 2, 2004. The Company is focused on developing and commercializing new chemical entities designed to alleviate pruritus by selectively targeting peripheral kappa opioid receptors. The Company's primary activities to date have been organizing and staffing the Company, developing its product candidates and raising capital.

On August 23, 2021, the Company received U.S. Food and Drug Administration, or FDA, approval for KORSUVA™ (CR845/difelikefalin) injection, or KORSUVA injection, for the treatment of moderate-to-severe pruritus associated with chronic kidney disease in adults undergoing hemodialysis.

As of September 30, 2021, the Company had raised aggregate net proceeds of approximately $519,600 from several rounds of equity financing, including its initial public offering, or IPO, which closed in February 2014 and four follow-on public offerings of common stock, which closed in July 2019, July 2018, April 2017 and August 2015, respectively, and the issuance of convertible preferred stock and debt prior to the IPO. The Company had also earned approximately $224,100 under its license agreements for CR845/difelikefalin, primarily with Vifor (International) Ltd., or Vifor, Vifor Fresenius Medical Care Renal Pharma Ltd., or VFMCRP, Maruishi Pharmaceutical Co. Ltd., or Maruishi, and Chong Kun Dang Pharmaceutical Corp., or CKDP, and an earlier product candidate for which development efforts ceased in 2007. In October 2021, the Company received net proceeds of $44,969 from the issuance and sale of 3,282,391 shares of the Company's common stock to Vifor in connection with U.S. regulatory approval for KORSUVA injection in August 2021 (see Notes 9, *Stockholders' Equity* and 16, *Subsequent Events*). Additionally, in October 2020, the Company received net proceeds of $38,449 from the issuance and sale of 2,939,552 shares of the Company's common stock to Vifor in connection with the Company's license agreement with Vifor. Furthermore, in May 2018, the Company received net proceeds of $14,556 from the issuance and sale of 1,174,827 shares of the Company's common stock to Vifor in connection with the Company's license agreement with VFMCRP (see Note 10, *Collaboration and Licensing Agreements*).

As of September 30, 2021, the Company had unrestricted cash and cash equivalents and marketable securities of $193,415 and an accumulated deficit of $447,376. The Company has incurred substantial net losses and negative cash flows from operating activities in nearly every fiscal period since inception and expects this trend to continue for the foreseeable future. The Company recognized net losses of $1,013 and $16,509 for the three months ended September 30, 2021 and 2020, respectively, and $55,059 and $70,499 for the nine months ended September 30, 2021 and 2020, respectively, and had net cash used in operating activities of $58,842 and $87,575 for the nine months ended September 30, 2021 and 2020, respectively.

The Company is subject to risks common to other life science companies including, but not limited to, uncertainty of product development and commercialization, lack of marketing and sales history, development by its competitors of new technological innovations, dependence on key personnel, market acceptance of products, product liability, protection of proprietary technology, ability to raise additional financing, and compliance with FDA and other government regulations. If the Company does not successfully commercialize KORSUVA injection or any of its product candidates, it will be unable to generate recurring product revenue or achieve profitability.

2. Basis of Presentation

The unaudited interim condensed financial statements included herein have been prepared pursuant to the rules and regulations of the Securities and Exchange Commission, or SEC. Accordingly, they do not include all information and disclosures necessary for a presentation of the Company's financial position, results of operations and cash flows in conformity with generally accepted accounting principles in the United States of America, or GAAP. In the opinion of

CARA THERAPEUTICS, INC.

NOTES TO CONDENSED FINANCIAL STATEMENTS
(amounts in thousands, except share and per share data)
(unaudited)

management, these unaudited interim financial statements reflect all adjustments, consisting primarily of normal recurring accruals, necessary for a fair presentation of results for the periods presented. The results of operations for interim periods are not necessarily indicative of the results for the full year. Certain information and footnote disclosures normally included in financial statements prepared in accordance with GAAP have been condensed or omitted from this report, as is permitted by SEC rules and regulations; however, the Company believes that the disclosures are adequate to make the information presented not misleading. The condensed balance sheet data as of December 31, 2020 were derived from audited financial statements, but do not include all disclosures required by GAAP. These unaudited interim condensed financial statements should be read in conjunction with the audited financial statements and accompanying notes thereto included in the Company's Annual Report on Form 10-K for the year ended December 31, 2020.

Use of Estimates

The preparation of financial statements in conformity with GAAP requires the Company to make estimates and assumptions that affect the reported amounts of assets and liabilities, and disclosure of contingent assets and liabilities, as of the date of the financial statements as well as the reported amounts of revenues and expenses during the reporting period. The more significant estimates include the fair value of marketable securities that are classified as level 2 of the fair value hierarchy, the periods over which certain revenues will be recognized, including licensing and collaborative revenue recognized from non-refundable up-front and milestone payments, the determination of prepaid research and development, or R&D, clinical costs and accrued research projects, the amount of non-cash compensation costs related to share-based payments to employees and non-employees and the periods over which those costs are expensed, the incremental borrowing rate used in lease calculations and the likelihood of realization of deferred tax assets.

The ongoing COVID-19 pandemic has interrupted business operations across the globe. Estimates and assumptions about future events and their effects cannot be determined with certainty and therefore require the exercise of judgment. As of the date of issuance of these condensed financial statements, the Company is not aware of any specific event or circumstance that would require the Company to update its estimates, assumptions and judgments or revise the reported amounts of assets and liabilities or the disclosure of contingent assets and liabilities. These estimates, however, may change as new events occur and additional information is obtained, and are recognized in the condensed financial statements as soon as they become known.

Actual results could differ materially from the Company's estimates and assumptions.

Significant Accounting Policies

There have been no material changes to the significant accounting policies previously disclosed in Note 2 to the Financial Statements in the Company's Annual Report on Form 10-K for the year ended December 31, 2020, except for the recent adoption of new accounting pronouncements as disclosed below.

Accounting Pronouncements Recently Adopted

In December 2019, the Financial Accounting Standards Board, or FASB, issued Accounting Standards Update, or ASU, No. 2019-12, *Income Taxes (Topic 740)*, or ASU 2019-12, which removes specific exceptions to the general principles in Topic 740. ASU 2019-12 eliminates the need for an organization to analyze whether the following apply in a given period: (1) exception to the incremental approach for intra-period tax allocation; (2) exceptions to accounting for basis differences when there are ownership changes in foreign investments; and (3) exception to the general methodology for calculating income taxes in an interim period when a year-to-date loss exceeds the anticipated loss. ASU 2019-12 also simplifies the accounting for income taxes for: (i) franchise taxes that are partially based on income; (ii) transactions with a government that result in a step up in the tax basis of goodwill; (iii) separate financial statements

CARA THERAPEUTICS, INC.

NOTES TO CONDENSED FINANCIAL STATEMENTS
(amounts in thousands, except share and per share data)
(unaudited)

of legal entities that are not subject to tax; and (iv) enacted changes in tax laws in interim periods. The amendments in ASU 2019-12 are effective for fiscal years, and interim periods within those fiscal years, beginning after December 15, 2020. The amendments in ASU 2019-12 related to separate financial statements of legal entities that are not subject to tax should be applied on a retrospective basis for all periods presented. The amendments related to changes in ownership of foreign equity method investments or foreign subsidiaries should be applied on a modified retrospective basis through a cumulative-effect adjustment to retained earnings as of the beginning of the fiscal year of adoption. The amendments related to franchise taxes that are partially based on income should be applied on either a retrospective basis for all periods presented or a modified retrospective basis through a cumulative-effect adjustment to retained earnings as of the beginning of the fiscal year of adoption. All other amendments should be applied on a prospective basis. The Company adopted ASU 2019-12 on January 1, 2021 and it did not have a material effect on its results of operations, financial position, and cash flows due to the full valuation allowance recorded.

3. Available-for-Sale Marketable Securities

As of September 30, 2021 and December 31, 2020, the Company's available-for-sale marketable securities consisted of debt securities issued by the U.S. Treasury, U.S. government-sponsored entities and investment grade institutions as well as municipal bonds.

The following tables summarize the Company's available-for-sale marketable securities by major type of security as of September 30, 2021 and December 31, 2020:

As of September 30, 2021

Type of Security	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
U.S. Treasury securities	$ 10,067	$ 3	$ —	$ 10,070
U.S. government agency obligations	17,046	3	(5)	17,044
Corporate bonds	46,920	17	(23)	46,914
Commercial paper	78,452	6	(4)	78,454
Municipal bonds	17,938	19	(15)	17,942
Total available-for-sale marketable securities	$ 170,423	$ 48	$ (47)	$ 170,424

As of December 31, 2020

Type of Security	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
U.S. Treasury securities	$ 20,710	$ 41	$ (1)	$ 20,750
U.S. government agency obligations	22,125	4	(1)	22,128
Corporate bonds	49,080	61	(23)	49,118
Commercial paper	116,139	5	(17)	116,127
Municipal bonds	11,680	12	(8)	11,684
Total available-for-sale marketable securities	$ 219,734	$ 123	$ (50)	$ 219,807

The following tables summarize the fair value and gross unrealized losses of the Company's available-for-sale marketable securities by investment category and disaggregated by the length of time that individual debt securities have been in a continuous unrealized loss position as of September 30, 2021 and December 31, 2020:

CARA THERAPEUTICS, INC.

NOTES TO CONDENSED FINANCIAL STATEMENTS
(amounts in thousands, except share and per share data)
(unaudited)

As of September 30, 2021

	Less than 12 Months		12 Months or Greater		Total	
	Fair Value	Gross Unrealized Losses	Fair Value	Gross Unrealized Losses	Fair Value	Gross Unrealized Losses
U.S. government agency obligations	$ 9,495	$ (5)	$ —	$ —	$ 9,495	$ (5)
Corporate bonds	24,488	(23)	—	—	24,488	(23)
Commercial paper	25,976	(4)	—	—	25,976	(4)
Municipal bonds	7,319	(15)	—	—	7,319	(15)
Total	$ 67,278	$ (47)	$ —	$ —	$ 67,278	$ (47)

As of December 31, 2020

	Less than 12 Months		12 Months or Greater		Total	
	Fair Value	Gross Unrealized Losses	Fair Value	Gross Unrealized Losses	Fair Value	Gross Unrealized Losses
U.S. Treasury securities	$ 12,682	$ (1)	$ —	$ —	$ 12,682	$ (1)
U.S. government agency obligations	2,500	(1)	—	—	2,500	(1)
Corporate bonds	23,553	(23)	—	—	23,553	(23)
Commercial paper	68,897	(17)	—	—	68,897	(17)
Municipal bonds	6,259	(8)	—	—	6,259	(8)
Total	$ 113,891	$ (50)	$ —	$ —	$ 113,891	$ (50)

As of September 30, 2021 and December 31, 2020, no allowance for credit losses were recognized on the Company's available-for-sale debt securities as no portion of the unrealized losses associated with those securities were due to credit losses. The information that the Company considered in reaching the conclusion that an allowance for credit losses was not necessary is as follows:

As of September 30, 2021 and December 31, 2020, the Company held a total of 26 out of 59 positions and 30 out of 59 positions, respectively, that were in an unrealized loss position, none of which had been in an unrealized loss position for 12 months or greater. Unrealized losses individually and in aggregate were not considered to be material for each respective period. Based on the Company's review of these securities, the Company believes that the cost basis of its available-for-sale marketable securities is recoverable.

U.S. government agency obligations. The unrealized losses on the Company's investments in direct obligations of U.S. government agencies were due to changes in interest rates and non-credit related factors. The contractual terms of these investments do not permit the issuer to repay principal at a price less than the amortized cost bases of the investments, which is equivalent to the par value on the maturity date. The Company expects to recover the entire amortized cost bases of these securities on the maturity date. The Company does not intend to sell these investments, and it is not more likely than not that the Company will be required to sell these investments before recovery of their amortized cost bases. The Company held 3 out of 5 positions for its U.S. government agency obligations that were in unrealized loss positions as of September 30, 2021.

Corporate bonds, commercial paper, and municipal bonds. The unrealized losses on the Company's investments in corporate bonds, commercial paper and municipal bonds were due to changes in interest rates and non-credit related factors. The credit ratings of these investments in the Company's portfolio have not been downgraded below investment

CARA THERAPEUTICS, INC.

NOTES TO CONDENSED FINANCIAL STATEMENTS
(amounts in thousands, except share and per share data)
(unaudited)

grade status. The contractual terms of these investments do not permit the issuer to repay principal at a price less than the amortized cost bases of the investments, which is equivalent to the par value on the maturity date. The Company expects to recover the entire amortized cost bases of these securities on the maturity date. The Company does not intend to sell these investments, and it is not more likely than not that the Company will be required to sell these investments, before recovery of their amortized cost bases. The Company held 10 out of 20 positions for its corporate bonds, 7 out of 19 positions for its commercial paper, and 6 out of 12 positions for its municipal bonds, that were in unrealized loss positions as of September 30, 2021.

The Company classifies its marketable debt securities based on their contractual maturity dates. As of September 30, 2021, the Company's marketable debt securities mature at various dates through September 2024. The amortized cost and fair values of marketable debt securities by contractual maturity were as follows.

	As of September 30, 2021		As of December 31, 2020	
Contractual maturity	Amortized Cost	Fair Value	Amortized Cost	Fair Value
Less than one year	$ 121,189	$ 121,203	$ 149,164	$ 149,242
One year to three years	49,234	49,221	70,570	70,565
Total	$ 170,423	$ 170,424	$ 219,734	$ 219,807

All available-for-sale marketable securities are classified as Marketable securities, current or Marketable securities, non-current depending on the contractual maturity date of the individual available-for-sale security. Other income, net includes interest and dividends, accretion/amortization of discounts/premiums, realized gains and losses on sales of securities and credit loss expense due to declines in the fair value of securities, if any. The cost of securities sold is based on the specific identification method.

During the three and nine months ended September 30, 2021, the Company sold certain shares of its available-for-sale debt securities with a total fair value of $1,000 and $10,029, respectively, which resulted in no realized gains or losses for the three months ended September 30, 2021, and $39 of realized gains for the nine months ended September 30, 2021, respectively. During the three and nine months ended September 30, 2020, the Company sold certain shares of its available-for-sale debt securities with a total fair value of $12,471 and $23,148, respectively, which resulted in realized gains of $66 and $126 for the three and nine months ended September 30, 2020, respectively.

As of September 30, 2021 and December 31, 2020, accrued interest receivables on our available-for-sale debt securities were $318 and $311, respectively.

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4. Accumulated Other Comprehensive Income (Loss)

The following table summarizes the changes in accumulated other comprehensive income (loss), net of tax, from unrealized gains (losses) on available-for-sale marketable securities, the Company's only component of accumulated other comprehensive income (loss), for the nine months ended September 30, 2021 and September 30, 2020.

	Total Accumulated Other Comprehensive Income (Loss)
Balance, December 31, 2020	$ 73
Other comprehensive loss before reclassifications	(33)
Amount reclassified from accumulated other comprehensive income	(39)
Net current period other comprehensive loss	(72)
Balance, September 30, 2021	$ 1
Balance, December 31, 2019	$ 170
Other comprehensive income before reclassifications	319
Amount reclassified from accumulated other comprehensive income	(126)
Net current period other comprehensive income	193
Balance, September 30, 2020	$ 363

Amounts reclassified out of accumulated other comprehensive income (loss) into net loss are determined by specific identification. The reclassifications out of accumulated other comprehensive income (loss) and into net loss were as follows:

Component of Accumulated Other Comprehensive Income (Loss)	Three Months Ended September 30,		Nine Months Ended September 30,		Affected Line Item in the Condensed Statements of Comprehensive Income (Loss)
	2021	2020	2021	2020	
Unrealized gains (losses) on available-for-sale marketable securities:					
Realized gains on sales of securities	$ —	$ 66	$ 39	$ 126	Other income, net
Income tax effect	—	—	—	—	Benefit from income taxes
Realized gains on sales of securities, net of tax	$ —	$ 66	$ 39	$ 126	

5. Fair Value Measurements

As of September 30, 2021 and December 31, 2020, the Company's financial instruments consisted of cash, cash equivalents, available-for-sale marketable securities, prepaid expenses, restricted cash, accounts payable and accrued liabilities. The fair values of cash, cash equivalents, prepaid expenses, restricted cash, accounts payable and accrued liabilities approximate their carrying values due to the short-term nature of these financial instruments. Available-for-sale marketable securities are reported at their fair values, based upon pricing of securities with the same or similar investment characteristics as provided by third-party pricing services, as described below.

The valuation techniques used by the Company are based on observable and unobservable inputs. Observable inputs reflect readily obtainable data from independent sources, while unobservable inputs reflect the Company's assumptions about the inputs that market participants would use in pricing the asset or liability and are developed based on the best information available in the circumstances.

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The Company classifies its investments in a fair value hierarchy that is intended to increase consistency and comparability in fair value measurements and related disclosures. The fair value hierarchy is divided into three levels based on the source of inputs as follows:

- Level 1 – Observable inputs – quoted prices in active markets for identical assets and liabilities.
- Level 2 – Observable inputs other than the quoted prices in active markets for identical assets and liabilities – such as quoted prices for similar instruments, quoted prices for identical or similar instruments in inactive markets, or other inputs that are observable or can be corroborated by observable market data.
- Level 3 – Unobservable inputs – includes amounts derived from valuation models where one or more significant inputs are unobservable and require the Company to develop relevant assumptions.

Valuation Techniques - Level 2 Inputs

The Company estimates the fair values of its financial instruments categorized as level 2 in the fair value hierarchy, including U.S. Treasury securities, U.S. government agency obligations, corporate bonds, commercial paper and municipal bonds, by taking into consideration valuations obtained from third-party pricing services. The pricing services use industry standard valuation models, including both income- and market-based approaches, for which all significant inputs are observable, either directly or indirectly, to estimate fair value. These inputs include reported trades of and broker/dealer quotes on the same or similar securities, benchmark yields, issuer credit spreads, benchmark securities, and other observable inputs. The Company obtains a single price for each financial instrument and does not adjust the prices obtained from the pricing service.

The Company validates the prices provided by its third-party pricing services by reviewing their pricing methods, obtaining market values from other pricing sources and comparing them to the share prices presented by the third-party pricing services. After completing its validation procedures, the Company did not adjust or override any fair value measurements provided by its third-party pricing services as of September 30, 2021 or December 31, 2020.

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The following tables summarize the Company's financial assets measured at fair value on a recurring basis as of September 30, 2021 and December 31, 2020.

Fair value measurement as of September 30, 2021:

Financial assets Type of Instrument	Total	Quoted prices in active markets for identical assets (Level 1)	Significant other observable inputs (Level 2)	Significant unobservable inputs (Level 3)
Cash and cash equivalents:				
Money market funds and checking accounts	$ 22,991	$ 22,991	$ —	$ —
Available-for-sale marketable securities:				
U.S. Treasury securities	10,070	—	10,070	—
U.S. government agency obligations	17,044	—	17,044	—
Corporate bonds	46,914	—	46,914	—
Commercial paper	78,454	—	78,454	—
Municipal bonds	17,942	—	17,942	—
Restricted cash:				
Commercial money market account	408	408	—	—
Total financial assets	$ 193,823	$ 23,399	$ 170,424	$ —

Fair value measurement as of December 31, 2020:

Financial assets Type of Instrument	Total	Quoted prices in active markets for identical assets (Level 1)	Significant other observable inputs (Level 2)	Significant unobservable inputs (Level 3)
Cash and cash equivalents:				
Money market funds and checking accounts	$ 31,683	$ 31,683	$ —	$ —
Available-for-sale marketable securities:				
U.S. Treasury securities	20,750	—	20,750	—
U.S. government agency obligations	22,128	—	22,128	—
Corporate bonds	49,118	—	49,118	—
Commercial paper	116,127	—	116,127	—
Municipal bonds	11,684	—	11,684	—
Restricted cash:				
Commercial money market account	408	408	—	—
Total financial assets	$ 251,898	$ 32,091	$ 219,807	$ —

There were no purchases, sales or maturities of Level 3 financial assets and no unrealized gains or losses related to Level 3 available-for-sale marketable securities during the three and nine months ended September 30, 2021 and 2020, respectively. There were no transfers of financial assets into or out of Level 3 classification during the three and nine months ended September 30, 2021 and 2020, respectively.

6. Restricted Cash

The Company is required to maintain a stand-by letter of credit as a security deposit under its leases for its office space in Stamford, Connecticut (refer to Note 15, *Commitments and Contingencies: Leases*). The fair value of the letter of credit approximates its contract value. The Company's bank requires the Company to maintain a restricted cash

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balance to serve as collateral for the letter of credit issued to the landlord by the bank. As of September 30, 2021, the restricted cash balance for the Stamford Lease was invested in a commercial money market account.

As of September 30, 2021 and December 31, 2020, the Company had $408 of restricted cash related to the Stamford Lease in long-term assets.

The following table provides a reconciliation of cash, cash equivalents, and restricted cash reported within the Condensed Balance Sheets that sum to the total of the same such amounts shown in the Condensed Statements of Cash Flows.

	September 30, 2021	December 31, 2020
Cash and cash equivalents	$ 22,991	$ 31,683
Restricted cash, long-term assets	408	408
Total cash, cash equivalents, and restricted cash shown in the Condensed Statements of Cash Flows	$ 23,399	$ 32,091

7. Prepaid expenses

As of September 30, 2021, prepaid expenses were $6,258, consisting of $4,098 of prepaid R&D clinical costs, $855 of prepaid insurance and $1,305 of other prepaid costs. As of December 31, 2020, prepaid expenses were $12,076, consisting of $11,286 of prepaid R&D clinical costs, $223 of prepaid insurance, and $567 of other prepaid costs.

8. Accounts Payable and Accrued Expenses

Accounts payable and accrued expenses consist of the following:

	September 30, 2021	December 31, 2020
Accounts payable	$ 5,369	$ 4,893
Accrued research projects	3,496	6,194
Accrued compensation and benefits	4,125	4,955
Accrued professional fees and other	822	839
Total	$ 13,812	$ 16,881

9. Stockholders' Equity

In August 2021, the Company earned a $50,000 regulatory milestone from Vifor for the purchase of the Company's common stock at a price of $15.23 per share. As of September 30, 2021, the Company recorded a stock subscription receivable of $44,969 in connection with the U.S. regulatory approval of KORSUVA injection, representing $15.23 per share, as well as license and milestone fees revenue of $5,031 representing the excess of the stock purchase price over the cost of the purchased shares at the closing price of the Company's common stock on the date of the achievement of the milestone. In October 2021, after the expiration of the requisite waiting period under the Hart-Scott-Rodino Antitrust Improvement Act of 1976, or the HSR Act, the Company received the $50,000 payment and issued 3,282,391 shares of its common stock in connection with U.S. regulatory approval of KORSUVA injection on August 23, 2021 (see Notes 10, *Collaboration and Licensing Agreements* and 16, *Subsequent Events*).

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In August 2021, as a result of the achievement of certain performance targets, an aggregate of 44,002 performance-based restricted stock units of various executive officers vested and were settled in shares of the Company's common stock (see Note 13, *Stock-Based Compensation*).

In June 2021, as a result of the completion of the one-year vesting period, an aggregate of 36,000 restricted stock units of members of the Board of Directors vested and were settled in shares of the Company's common stock (see Note 13, *Stock-Based Compensation*).

In February and March 2021, as a result of the achievement of certain performance targets, an aggregate of 76,750 performance-based restricted stock units of various executive officers vested and were settled in shares of the Company's common stock (see Note 13, *Stock-Based Compensation*).

In February 2021, as a result of the completion of the first year of the three-year vesting period, an aggregate of 32,669 time-based restricted stock units of various executive officers vested and were settled in shares of the Company's common stock (see Note 13, *Stock-Based Compensation*).

In October 2020, the Company issued 2,939,552 shares of its common stock to Vifor in connection with the license agreement entered into with Vifor (see Note 10, *Collaboration and Licensing Agreements*).

In June 2020, as a result of the completion of the one-year vesting period, an aggregate of 24,000 restricted stock units of members of the Board of Directors vested and were settled in shares of the Company's common stock (see Note 13, *Stock-Based Compensation*).

In April and June 2020, as a result of the achievement of certain performance targets, an aggregate of 95,834 restricted stock units of various executive officers vested and were settled in shares of the Company's common stock (see Note 13, *Stock-Based Compensation*).

10. Collaboration and Licensing Agreements

Vifor (International) Ltd.

In October 2020, the Company entered into a license agreement with Vifor, or the Vifor Agreement, under which the Company granted Vifor an exclusive license solely in the United States to use, distribute, offer for sale, promote, sell and otherwise commercialize CR845/difelikefalin injection for all therapeutic uses relating to the inhibition, prevention or treatment of itch associated with pruritus in hemodialysis and peritoneal dialysis patients in the United States. Under the Vifor Agreement, the Company retains all rights with respect to the clinical development of, and activities to gain regulatory approvals of, CR845/difelikefalin injection in the United States.

The Vifor Agreement provides full commercialization rights in dialysis clinics to Vifor in the United States under a profit-sharing arrangement. Pursuant to the profit-sharing arrangement, the Company will generally be entitled to 60% of the net profits (as defined in the Vifor Agreement) from sales of CR845/difelikefalin injection in the United States (excluding sales to Fresenius Medical Center dialysis clinics, compensation for which is governed by the VFMCRP Agreement) and Vifor is entitled to 40% of such net profits, subject to potential temporary adjustment in future years based on certain conditions. Under the Vifor Agreement, in consideration of Vifor's conduct of the marketing, promotion, selling and distribution of CR845/difelikefalin injection in the United States, the Company will pay a marketing and distribution fee to Vifor based on the level of annual net sales. This fee will be deducted from product sales in calculating the net profits that are subject to the profit-sharing arrangement under the Vifor Agreement.

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Under the terms of the Vifor Agreement, the Company received from Vifor an upfront payment of $100,000 and an additional payment of $50,000 for the purchase of an aggregate of 2,939,552 shares of the Company's common stock at a price of $17.0094 per share, which represents a premium over a pre-determined average closing price of the Company's common stock. The purchase of the Company's common stock was governed by a separate stock purchase agreement, or the Vifor Stock Purchase Agreement.

After U.S. regulatory approval of KORSUVA injection in August 2021, the Company received an additional $50,000 in October 2021 for the purchase of an aggregate of 3,282,391 shares of the Company's common stock at a price of $15.23 per share, which represents a 20% premium to the 30-day trailing average price of the Company's common stock as of the date of the achievement of the milestone. The purchase of the Company's common stock was governed by the Vifor Stock Purchase Agreement. The excess of the stock purchase price over the cost of the purchased shares at the closing price of the Company's common stock on the date of the achievement of the milestone of $5,031 was included as license and milestone fees revenue for accounting purposes for the three and nine months ended September 30, 2021.

In addition, pursuant to the Vifor Agreement, the Company is eligible to receive payments of up to $240,000 upon the achievement of certain sales-based milestones.

The Company retains the rights to make and have made CR845/difelikefalin injection, or the Licensed Product, on a non-exclusive basis, in the United States for commercial sale of the Licensed Product for use in all therapeutic uses to prevent, inhibit or treat itch associated with pruritus in hemodialysis and peritoneal-dialysis patients, or the Field, anywhere in the world and for supply of Licensed Product to Vifor under the terms of a supply agreement, or the Vifor Supply Agreement, which was executed in September 2021. The supply price is the Company's cost of goods sold, as calculated under GAAP, plus an agreed upon margin. The Vifor Supply Agreement will co-terminate with the Vifor Agreement.

The Vifor Supply Agreement will be accounted for as a customer option that is not a material right because the selling price of the Licensed Product under the Vifor Supply Agreement is the Company's cost of goods sold plus an agreed upon margin, which is commensurate with the "cost of goods sold plus" model that the Company would charge other parties under similar agreements (the standalone selling price) and not at a discount. Therefore, the sale of commercial supply to Vifor is not a performance obligation under the Vifor Agreement but rather the Vifor Supply Agreement is a separate agreement from the Vifor Agreement. The only performance obligation under the Vifor Supply Agreement is the delivery of the Licensed Product to Vifor for commercialization. Revenue from the sale of the Licensed Product to Vifor will be recognized in the Company's Condensed Statements of Comprehensive Loss as sales of the Licensed Product occur. There were no sales of Licensed Product to Vifor through September 30, 2021.

Vifor Fresenius Medical Care Renal Pharma Ltd.

In May 2018, the Company entered into a license agreement, or the VFMCRP Agreement, with VFMCRP under which the Company granted VFMCRP an exclusive, royalty-bearing license, or the VFMCRP License, to seek regulatory approval to commercialize, import, export, use, distribute, offer for sale, promote, sell and otherwise commercialize the Licensed Product for all therapeutic uses to prevent, inhibit or treat itch associated with pruritus in the Field worldwide (excluding the United States, Japan and South Korea), or the Territory.

Upon entry into the VFMCRP Agreement, VFMCRP made a non-refundable, non-creditable $50,000 upfront payment to the Company and Vifor purchased 1,174,827 shares of the Company's common stock, or the Vifor Shares, for $20,000 at a price of $17.024 per share, which represents a premium over a pre-determined average closing price of the Company's common stock. The purchase of the Company's common stock was governed by a separate stock

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purchase agreement. The excess of the stock purchase price over the cost of the Vifor Shares at the closing price of the Company's common stock on the purchase date of $5,444 was added to the upfront payment for accounting purposes.

After U.S. regulatory approval of KORSUVA injection in August 2021, the Company was entitled to receive a $15,000 regulatory milestone payment which was received in October 2021, and was recorded as license and milestone fees revenue for the three and nine months ended September 30, 2021, based on the identification of one combined performance obligation at contract inception.

The Company is eligible to receive from VFMCRP additional regulatory and commercial milestone payments in the aggregate of up to $455,000, consisting of up to $15,000 in regulatory milestones and up to $440,000 in tiered commercial milestones, all of which are sales-related. The Company is also eligible to receive tiered double-digit royalty payments based on annual net sales, as defined in the VFMCRP Agreement, of CR845/difelikefalin injection in the Licensed Territories. The Company retains full commercialization rights for CR845/difelikefalin injection for the treatment of CKD-aP in the United States except in the dialysis clinics of Fresenius Medical Care North America, or FMCNA, where VFMCRP and the Company will promote CR845/difelikefalin injection under a profit-sharing arrangement (subject to the terms and conditions of the VFMCRP Agreement) based on net FMCNA clinic sales recorded by the Company.

The Company retains the rights to make and have made the Licensed Product in the Territory for commercial sale by VFMCRP in the Field in or outside the Territory and for supply of Licensed Product to VFMCRP under the terms of a supply agreement, or the VFMCRP Supply Agreement, which was executed in May 2020. The supply price is the Company's cost of goods sold, as calculated under GAAP, plus an agreed upon margin. The VFMCRP Supply Agreement will co-terminate with the VFMCRP Agreement.

The VFMCRP Supply Agreement is accounted for as a customer option that is not a material right because the selling price of the Licensed Product under the VFMCRP Supply Agreement is the Company's cost of goods sold plus an agreed upon margin, which is commensurate with the "cost of goods sold plus" model that the Company would charge other parties under similar agreements (the standalone selling price) and not at a discount. Therefore, the sale of commercial supply to VFMCRP is not a performance obligation under the VFMCRP Agreement but rather the VFMCRP Supply Agreement is a separate agreement from the VFMCRP Agreement. The only performance obligation under the VFMCRP Supply Agreement is the delivery of the Licensed Product to VFMCRP for commercialization. Revenue from the sale of the Licensed Product to VFMCRP will be recognized in the Company's Condensed Statements of Comprehensive Loss as sales of the Licensed Product occur. During each of three and nine months ended September 30, 2021, the Company recognized clinical compound revenue of $241 from the sale of clinical compound to VFMCRP and as a result, the Company incurred R&D expense of $228 during these periods. During the nine months ended September 30, 2020, the Company recognized clinical compound revenue of $88 from the sale of clinical compound to VFMCRP and as a result, the Company incurred R&D expense of $79 during this period. There were no sales of clinical compound to VFMCRP during the three months ended September 30, 2020.

Maruishi Pharmaceutical Co., Ltd.

In April 2013, the Company entered into a license agreement with Maruishi, or the Maruishi Agreement, under which the Company granted Maruishi an exclusive license to develop, manufacture, and commercialize drug products containing CR845/difelikefalin for acute pain and/or uremic pruritus in Japan. Maruishi has the right to grant sub-licenses in Japan, which entitles the Company to receive sub-license fees, net of prior payments made by Maruishi to the Company. Under the Maruishi Agreement, the Company and Maruishi are required to use commercially reasonable efforts, at their own expense, to develop, obtain regulatory approval for and commercialize CR845/difelikefalin in the

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United States and Japan, respectively. In addition, the Company provided Maruishi specific clinical development services for CR845/difelikefalin used in Maruishi's field of use.

Under the terms of the Maruishi Agreement, the Company is eligible to receive milestone payments upon the achievement of defined clinical and regulatory events as well as tiered, low double-digit royalties with respect to any sales of the licensed product sold in Japan by Maruishi, if any, and share in any sub-license fees.

There were no sales of clinical compound to Maruishi during each of the three months ended September 30, 2021 and 2020. During the nine months ended September 30, 2021 and 2020, the Company recognized clinical compound revenue of $37 and $528, respectively, from the sale of clinical compound to Maruishi, and as a result, the Company incurred R&D expense of $33 and $476, respectively, during these periods.

Chong Kun Dang Pharmaceutical Corporation

In April 2012, the Company entered into a license agreement, or the CKDP Agreement, with CKDP in South Korea, under which the Company granted CKDP an exclusive license to develop, manufacture and commercialize drug products containing CR845/difelikefalin in South Korea. The Company and CKDP are each required to use commercially reasonable efforts, at their respective expense, to develop, obtain regulatory approval for and commercialize CR845/difelikefalin in the United States and South Korea, respectively. The Company identified the granting of the license as its only performance obligation under the CKDP Agreement.

Under the terms of the CKDP Agreement, the Company is eligible to receive milestone payments upon the achievement of defined clinical and regulatory events as well as tiered royalties, with percentages ranging from the high single digits to the high teens, based on net sales of products containing CR845/difelikefalin in South Korea, if any, and share in any sub-license fees.

11. Revenue Recognition

The Company currently recognizes revenue in accordance with FASB Accounting Standards Codification, or ASC, Topic 606, *Revenue from Contracts with Customers*, as amended, or ASC 606, for the Vifor, VFMCRP, Maruishi and CKDP agreements (see Note 10, *Collaboration and Licensing Agreements*). Under each of these agreements, the Company has recognized revenue from (1) upfront payments; (2) regulatory milestone payments under the Vifor and VFMCRP agreements; and (3) clinical development milestone payments under the Maruishi and CKDP agreements. The Company has also recognized revenue from a sub-license payment earned under the Maruishi Agreement. Under the Maruishi and CKDP agreements, the Company may earn additional future milestone payments upon the achievement of defined clinical events, and under the VFMCRP, Maruishi and CKDP agreements, upon the achievement of defined regulatory events, and under the Vifor, VFMCRP and Maruishi agreements, from sales milestones. The Company may also recognize revenue in the future from royalties on net sales under the VFMCRP, Maruishi and CKDP agreements. In addition, the Company has recognized revenue upon the delivery of clinical compound to VFMCRP and Maruishi in accordance with separate supply agreements.

Contract balances

As of September 30, 2021 and December 31, 2020, there were no material balances of receivables, and no other assets or deferred revenue related to the Maruishi and CKDP agreements. As of September 30, 2021, the Company recorded receivables from Vifor and VFMCRP for $20,031 in aggregate ($15,000 from VFMCRP and $5,031 premium related to the Vifor equity issuance) as a result of milestones being achieved during the period, which were included

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within Other receivables. In addition, the Company recorded a stock subscription receivable for $44,969 as of September 30, 2021 in connection with the U.S. regulatory milestone from Vifor. There were no other assets or deferred revenue related to the Vifor and VFMCRP agreements as of September 30, 2021 and December 31, 2020.

Performance obligations

Under the Vifor Agreement, the Company's only performance obligation is granting a license to allow Vifor to commercialize CR845/difelikefalin in the United States, which occurred at inception of the contract in October 2020 (see Note 10, *Collaboration and Licensing Agreements*).

Under the VFMCRP Agreement, the Company's performance obligations of granting a license to allow VFMCRP to commercialize CR845/difelikefalin injection worldwide, except in the United States, Japan and South Korea, which occurred at inception of the contract in May 2018, and performing R&D services by the Company to obtain sufficient clinical data which will be shared with VFMCRP to allow them to receive regulatory approval to sell CR845/difelikefalin in the licensed territory, were not distinct, and were accounted for as a single performance obligation during the period that the R&D services were rendered (see Note 10, *Collaboration and Licensing Agreements*).

The Company's distinct performance obligations under the Maruishi Agreement include transfer of the license to the Company's IP, which allowed Maruishi to develop and commercialize CR845/difelikefalin, for acute pain and uremic pruritus indications in Japan, which occurred at inception of the contract in 2013, and performance of R&D services, which occurred from 2013 to 2015, as those services were rendered. The Company agreed to conduct limited work on an oral tablet formulation of CR845/difelikefalin and to conduct Phase 1 and proof-of-concept Phase 2 clinical trials of an intravenous formulation of CR845/difelikefalin to be used to treat patients with uremic pruritus. The Company agreed to transfer the data and information from such development to Maruishi for its efforts to obtain regulatory approval in Japan. These activities are referred to as R&D services (see Note 10, *Collaboration and Licensing Agreements*).

The Company's only performance obligation under the supply agreement with Maruishi is to deliver clinical compound to Maruishi in accordance with the receipt of purchase orders. The Company's only performance obligation under the VFMCRP Supply Agreement is to deliver CR845/difelikefalin injection to VFMCRP in accordance with the receipt of purchase orders.

Under the CKDP Agreement, the Company's only performance obligation is to transfer the license to the Company's IP related to CR845/difelikefalin, which occurred at inception of the contract in 2012 (see Note 10, *Collaboration and Licensing Agreements*).

Upon execution of the Vifor, VFMCRP, Maruishi and CKDP agreements, the Company received a single fixed payment from each counterparty in exchange for granting the respective licenses and performing its other obligations. In addition, each of the counterparties made an equity investment in the Company's common stock.

Transaction price allocated to the remaining performance obligations

At inception of the Vifor Agreement, the entire transaction price of $111,551 was allocated to the one performance obligation, as described above, and was recognized as license and milestone fees revenue for the year ended December 31, 2020 as the license was granted to Vifor in October 2020. As of September 30, 2021, there were no remaining performance obligations under the Vifor Agreement. The Company is eligible to receive milestone payments in the future.

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At inception of the VFMCRP Agreement, the entire transaction price of $55,444 was allocated to the one combined performance obligation, as described above. As of September 30, 2021, there were no remaining performance obligations, and the entire transaction price has been recognized as license and milestone fees revenue through December 31, 2020 since R&D services have been completed during 2020. The Company is eligible to receive milestone payments and sales royalties in the future.

As of September 30, 2021, there were no remaining performance obligations under either the Maruishi or CKDP agreements, although the Company is eligible to receive milestone payments and sales royalties in the future.

Significant judgments

In applying ASC 606, as amended, to its four contracts, the Company made the following judgments that significantly affect the timing and amount of revenue recognition:

1. Determination of the number of distinct performance obligations in a contract

The VFMCRP Agreement contains one combined performance obligation, which includes the Company's two performance obligations to grant a license to VFMCRP and conduct R&D services. Both of those performance obligations are inputs to the promise, within the context of the contract, to transfer a combined output for which VFMCRP has contracted (the ability of VFMCRP to commercialize the Licensed Product) (see Note 10, *Collaboration and Licensing Agreements*, for further discussion).

The Maruishi Agreement contains two distinct performance obligations: the granting of the license and the promise to deliver defined R&D services. Under the Maruishi Agreement, the license and the R&D services represent distinct goods or services from each other because Maruishi is able to benefit from the license on its own or together with other resources that are readily available to it (i.e., capable of being distinct). Maruishi's ability to benefit from the license without the R&D services is indicated by its ability to conduct clinical trials of CR845/difelikefalin on its own and by the provision in the Maruishi Agreement whereby if the Company suspends or discontinues its development activity, the Company will provide information regarding its development efforts up to that point so that Maruishi may continue development and commercialization of the product in Japan. Therefore, the R&D services do not significantly affect Maruishi's ability to use and benefit from the license.

In addition, the Company's promise in the Maruishi contract to transfer the license is separately identifiable from the promise to provide defined R&D services (i.e., distinct within the context of the contract) because the Company is not using the goods or services as inputs to produce or deliver the combined output or outputs specified by the customer. The combined output specified by Maruishi is its right to conduct development activities related to CR845/difelikefalin in Japan, which could result in regulatory approval in Japan. That right is derived from the Company's grant of the license. Maruishi is conducting clinical trials on its own and does not require the R&D services provided by the Company. Furthermore, the R&D services do not significantly modify or customize the license and vice versa. Finally, the license and R&D services are not highly interdependent or highly interrelated because the Company is able to fulfill its promise to transfer the initial license independently from its promise to subsequently provide the R&D services, which Maruishi can obtain on its own.

The only performance obligation in the Vifor and CKDP agreements is the granting of the license.

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2. Determination of the transaction price, including whether any variable consideration is included at inception of the contract

The transaction price is the amount of consideration that the Company expects to be entitled to in exchange for transferring promised goods or services to the customer. The transaction price must be determined at inception of a contract and may include amounts of variable consideration. However, there is a constraint on inclusion of variable consideration, such as milestone payments or sales-based royalty payments, in the transaction price related to licenses of IP, if there is uncertainty at inception of the contract as to whether such consideration will be recognized in the future.

The decision as to whether or not it is probable that a significant reversal of revenue will occur in the future, depends on the likelihood and magnitude of the reversal and is highly susceptible to factors outside the entity's influence (for example, the Company cannot determine the outcome of clinical trials; the Company cannot determine if or when they or the counterparty will initiate or complete clinical trials; and the Company's ability to obtain regulatory approval is difficult). In addition, the uncertainty is not expected to be resolved for a long period of time (in the order of years) and finally, the Company has limited experience in the field.

Therefore, at inception of the Vifor, VFMCRP, Maruishi and CKDP agreements, milestones and sales-based royalty payments were not included in the transaction price based on the factors noted above.

Under the Vifor Agreement, the one performance obligation was satisfied when the license was granted to Vifor in October 2020, and as a result, $111,551 (including the upfront payment of $100,000 and the premium on the common stock purchased by Vifor of $11,551) was recognized as license and milestone fees revenue during the year ended December 31, 2020. The remaining potential consideration was considered to be variable consideration and was constrained at inception of the contract, which includes regulatory and sales milestones (see Note 10, *Collaboration and Licensing Agreements*).

Under the VFMCRP Agreement, the single combined performance obligation was satisfied as the R&D services were rendered and the transaction price, including the upfront payment of $50,000 and the premium on the common stock purchased by VFMCRP of $5,444, was recognized as revenue as the R&D services were performed based on the costs incurred as a percentage of the estimated total costs to be incurred to complete the performance obligation. The remaining potential consideration was considered to be variable consideration and was constrained at inception of the contract, including regulatory and sales milestones and sales royalties (see Note 10, *Collaboration and Licensing Agreements*).

All performance obligations under the Maruishi and CKDP agreements were satisfied by the end of 2015. In the future, any milestone event will be recognized as milestone and license fee revenue and collaboration revenue based upon the relative standalone selling prices of the two performance obligations at inception of the Maruishi Agreement, and as milestone and license fee revenue under the CKDP Agreement. The remaining potential consideration was considered to be variable consideration and was constrained at inception of the contract, including clinical, regulatory and sales milestones, and sales royalties (see Note 10, *Collaboration and Licensing Agreements*).

3. Determination of the estimate of the standalone selling price of performance obligations

In order to recognize revenue under ASC 606, as amended, for contracts for which more than one distinct performance obligation has been identified, the Company must allocate the transaction price to the performance obligations based upon their standalone selling prices. The best evidence of standalone selling price is an observable price of a good or service when sold separately by an entity in similar circumstances to similar customers. If such evidence is not available, standalone selling price should be estimated so that the amount that is allocated to each

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performance obligation equals the amount that the entity expects to receive for transferring goods or services. The Company has identified more than one performance obligation only in the Maruishi Agreement. Since evidence based on observable prices is not available for the performance obligations under the Maruishi Agreement, the Company considered market conditions and entity-specific factors, including those contemplated in negotiating the agreements, as well as certain internally developed estimates.

At inception of the Maruishi Agreement, the Company determined the estimate of standalone selling price for the license performance obligation by using the adjusted market assessment approach. Under this method, the Company forecasted and analyzed CR845/difelikefalin in the Japanese market, the phase of clinical development as well as considered recent similar license arrangements within the same phase of clinical development, therapeutic area, type of agreement, etc. To estimate the standalone selling price of the R&D services, the Company forecasted its expected costs of satisfying that performance obligation and added a margin for that service.

4. Determination of the method of allocation of the transaction price to the distinct performance obligations

At inception of the Maruishi Agreement, the Company allocated the transaction price of $15,337 between the two performance obligations based on their relative standalone selling prices, determined as described above. The Company determined that the license and the R&D services had estimated standalone selling prices of $10,200 and $6,200, respectively. The resulting percentage allocations were applied to the $15,337 of total transaction price, which resulted in $9,637 being allocated to the license performance obligation, which was recognized immediately as license revenue, while $5,700 was allocated to the R&D services performance obligation. The amount allocated to the R&D services performance obligation was initially recorded as deferred revenue and was recognized as collaborative revenue as the R&D services were provided through July 2015.

Since the Vifor, VFMCRP and CKDP agreements each contain only one distinct performance obligation, at the inception of each of those agreements, the entire transaction price was allocated to the respective performance obligation.

5. Determination of the timing of revenue recognition for contracts

Revenue should be recognized when, or as, an entity satisfies a performance obligation by transferring a promised good or service to a customer; i.e., when the customer obtains control of the good or service. The licenses granted to Vifor, Maruishi and CKDP were accounted for as distinct performance obligations. As discussed below, both licenses relate to functional IP for which revenue is recognized at a point in time – in the case of these three license agreements, the point in time is at inception of the contract because the customer obtained control of the license at that point.

The licenses grant Vifor, Maruishi and CKDP the right to use the Company's IP relating to CR845/difelikefalin as it existed at the point in time that the licenses were granted. That IP has significant standalone functionality as it provides the customer with the ability to perform a function or task, such as to manufacture CR845/difelikefalin and conduct clinical trials and is considered to be functional IP.

During the license periods, the Company is continuing to develop and advance CR845/difelikefalin by conducting clinical trials. Those development efforts are for its own benefit and do not substantively change the significant standalone functionality of the licensed IP granted to Vifor, Maruishi or CKDP. Therefore, the Company's ongoing development efforts do not significantly affect the IP's utility to which Vifor, Maruishi or CKDP have rights. Furthermore, if the Company abandons its development efforts, Vifor, Maruishi or CKDP may still continue to develop CR845/difelikefalin in their respective countries.

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The R&D services performance obligation under the Maruishi Agreement represents a separate performance obligation. The R&D services were provided to Maruishi by the Company from inception of the agreement in 2013 through the third quarter of 2015, at which time the Company had fulfilled its promise related to the R&D services. Revenue related to the R&D services performance obligation was recognized as services were performed based on the costs incurred as a percentage of the estimated total costs to be incurred to complete the performance obligation.

Similarly, under the VFMCRP Agreement, revenue related to the single distinct performance obligation, which includes both granting of the license and performance of the R&D services, was recognized as the R&D services were performed, based on the costs incurred as a percentage of the estimated total costs to be incurred to complete the performance obligation. As of September 30, 2021, there is no remaining amount of the transaction price to be recognized as license and milestone fees revenue as all R&D services were completed in 2020.

6. *Determination of consideration as variable consideration, including factors related to inclusion in the transaction price at inception of the contract and timing of recognition as revenue.*

The Vifor, VFMCRP, Maruishi and CKDP agreements contain potential payments related to achievement of defined milestone events and royalties (excluding Vifor) upon net sales of future products, which are considered to be variable consideration because of the uncertainty of occurrence of any of those events specified in those agreements at inception of the agreements. Therefore, those potential payments were not included in the transaction price at the inception of the agreements.

Revenue related to achievement of milestone events is recognized when the Company has determined that it is probable that a milestone event will be achieved and there will not be a significant reversal of revenue in future periods. Upon probability of achievement of a milestone event, the most likely amount of variable consideration is included in the transaction price. Subsequent changes to the transaction price, after contract initiation, are allocated to the performance obligations in the contract on the same basis as at contract inception. Revenue for variable consideration is recognized in the same manner (point in time or over time) as for the performance obligations to which the payment amounts were allocated.

The Maruishi Agreement and the CKDP Agreement specify that certain development milestones will be achieved at pre-specified defined phases of a clinical trial (such as initiation or completion or other pre-specified time during a clinical trial as specified in the agreements).

After U.S. regulatory approval of KORSUVA injection in August 2021, the Company received an additional $50,000 milestone payment in October 2021 from Vifor for the purchase of an aggregate of 3,282,391 shares of the Company's common stock at a price of $15.23 per share, which represents a 20% premium to the 30-day trailing average price of the Company's common stock as of the date of the achievement of the milestone. The excess of the stock purchase price over the cost of the purchased shares at the closing price of the Company's common stock on the date of the achievement of the milestone of $5,031 was included as license and milestone fees revenue for the three and nine months ended September 30, 2021, as the variable consideration was deemed probable upon the FDA approval in August 2021.

After U.S. regulatory approval of KORSUVA injection in August 2021, the Company received a $15,000 milestone payment in October 2021 from VFMCRP, which was recorded as license and milestone fees revenue for the three and nine months ended September 30, 2021, as the variable consideration was deemed probable upon the FDA approval in August 2021.

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In January 2021, the criteria for revenue recognition for a milestone event set forth in the Maruishi Agreement was achieved, and the Company recorded $1,192 as license and milestone fees revenue and $706 as collaboration revenue based on the relative standalone selling prices described above at contract inception for the nine months ended September 30, 2021. In May 2021, the Company received the $1,898 payment (after contractual foreign currency exchange adjustments) from Maruishi for the milestone event achieved.

There were no milestone events related to the Maruishi Agreement that were probable of occurrence or achieved during the three months ended September 30, 2021, or during the three and nine months ended September 30, 2020.

In May 2020, the criteria for revenue recognition for a milestone event set forth in the CKDP Agreement was achieved, and the Company recorded $626 (net of South Korean taxes) as license and milestone fees revenue in its Condensed Statements of Comprehensive Loss for the nine months ended September 30, 2020. No milestone events were probable of occurrence or achieved during the three and nine months ended September 30, 2021, or during the three months ended September 30, 2020.

Sublicense payments

Vifor's, VFMCRP's, Maruishi's and CKDP's right to grant sub-licenses is explicitly stated in their respective license agreements. The amount of any potential sub-license fees to be received by the Company, which is based on a formula, is considered to be variable consideration and is constrained from inclusion in the transaction price at inception of the contract since at that time it was probable that there would be a reversal of such revenue in the future because the Company did not know if a sublicense would be granted in the future.

Sales-based Royalty Payments

The VFMCRP, Maruishi and CKDP agreements each allow the Company to earn sales-based royalty payments in exchange for a license of intellectual property. In that case, the Company will recognize revenue for a sales-based royalty only when (or as) the later of the following events occurs:

a. The subsequent sale or usage occurs.

b. The performance obligation to which some or all of the sales-based royalty has been allocated has been satisfied (or partially satisfied).

Since the sale (item a, above) occurs after the license was delivered (item b, above), the sales-based royalty exception, to exclude such royalty payments from the transaction price, applies to the overall revenue stream. Therefore, sales-based royalty payments are recognized as revenue when the customer's sales occur. To date, no royalties have been earned or were otherwise due to the Company.

12. Net Loss Per Share

The Company computes basic net income (loss) per share by dividing net income (loss) by the weighted-average number of shares of common stock outstanding. Diluted net income per share includes the potential dilutive effect of common stock equivalents as if such securities were exercised during the period, when the effect is dilutive. Common stock equivalents may include outstanding stock options or restricted stock units, which are included using the treasury stock method when dilutive. For the three and nine months ended September 30, 2021 and 2020, the Company excluded the effects of potentially dilutive shares that were outstanding during those respective periods from the denominator as their inclusion would be anti-dilutive due to the Company's net losses during those periods.

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The denominators used in the net loss per share computations are as follows:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
Basic:				
Weighted average common shares outstanding	50,114,710	46,885,424	50,031,615	46,803,659
Diluted:				
Weighted average common shares outstanding - Basic	50,114,710	46,885,424	50,031,615	46,803,659
Common stock equivalents*	—	—	—	—
Denominator for diluted net loss per share	50,114,710	46,885,424	50,031,615	46,803,659

* No amounts were considered as their effects would be anti-dilutive.

Basic and diluted net loss per share are computed as follows:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
Net loss - basic and diluted	$ (1,013)	$ (16,509)	$ (55,059)	$ (70,499)
Weighted-average common shares outstanding:				
Basic and diluted	50,114,710	46,885,424	50,031,615	46,803,659
Net loss per share, Basic and Diluted:	$ (0.02)	$ (0.35)	$ (1.10)	$ (1.51)

As of September 30, 2021, 5,974,549 stock options and 365,029 restricted stock units were outstanding, which could potentially dilute basic earnings per share in the future, but were not included in the computation of diluted net loss per share because to do so would have been anti-dilutive as a result of the net loss for the period.

In addition, the Company entered into the Vifor Agreement in October 2020. The Company issued 3,282,391 shares of its common stock in October 2021 upon U.S. regulatory approval of KORSUVA injection in August 2021. These shares were not included in the computation of basic or diluted net loss per share.

As of September 30, 2020, 5,265,642 stock options and 272,000 restricted stock units were outstanding, which could potentially dilute basic earnings per share in the future, but were not included in the computation of diluted net loss per share because to do so would have been anti-dilutive as a result of the net loss for the period.

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13. Stock-Based Compensation

2019 Inducement Plan

In October 2019, the Company's Board of Directors adopted the 2019 Inducement Plan, or the 2019 Plan, which is a non-stockholder approved stock plan adopted pursuant to the "inducement exception" provided under Nasdaq Listing Rule 5635(c)(4), or Rule 5635, for the purpose of awarding (i) non-statutory stock options, (ii) restricted stock awards, (iii) restricted stock unit awards, (iv) other stock awards (collectively, the Inducement Awards) to new employees of the Company, as inducement material to such new employees entering into employment with the Company. On November 20, 2019, the Company filed a Registration Statement on Form S-8 with the SEC covering the offering of up to 300,000 shares of its common stock, par value $0.001, pursuant to the Company's 2019 Plan. Initial grants of Inducement Awards made to employees vest as to 25% on the first anniversary of the date of grant and the balance ratably over the next 36 months and subsequent grants vest monthly over a period of four years from the grant date.

2014 Equity Incentive Plan

The Company's 2014 Equity Incentive Plan, or the 2014 Plan, is administered by the Company's Board of Directors or a duly authorized committee thereof, referred to as the Plan administrator. The 2014 Plan provides for the grant of incentive stock options, non-statutory stock options, restricted stock awards, restricted stock unit awards, stock appreciation rights, performance stock awards and other forms of equity compensation, collectively referred to as Stock Awards. Additionally, the 2014 Plan provides for the grant of performance cash awards. Incentive stock options may be granted only to employees. All other awards may be granted to employees, including officers, non-employee directors, and consultants. No incentive stock options may be granted under the 2014 Plan after the tenth anniversary of the effective date of the 2014 Plan. Stock Awards granted under the 2014 Plan vest at the rate specified by the Plan administrator. Initial grants of Stock Awards made to employees and non-employee consultants generally vest as to 25% on the first anniversary of the date of grant and the balance ratably over the next 36 months and subsequent grants vest monthly over a period of four years from the grant date. Stock options initially granted to members of the Company's Board of Directors vest over a period of three years in equal quarterly installments from the date of the grant, subject to the option holder's continued service as a Director through such date. Subsequent grants to Directors that are made automatically at Annual Meetings of Stockholders vest fully on the earlier of the first anniversary of the date of grant and the next Annual Meeting of Stockholders. The Plan administrator determines the term of Stock Awards granted under the 2014 Plan up to a maximum of ten years.

The aggregate number of shares of the Company's common stock reserved for issuance under the 2014 Plan has automatically increased on January 1 of each year, beginning on January 1, 2015 and will continue to increase on January 1 of each year through and including January 1, 2024, by 3% of the total number of shares of the Company's capital stock outstanding on December 31 of the preceding calendar year, or a lesser number of shares determined by the Company's Board of Directors. On January 1, 2021, the aggregate number of shares of common stock that may be issued pursuant to Stock Awards under the 2014 Plan automatically increased from 7,488,513 to 8,984,679. The maximum number of shares that may be issued pursuant to the exercise of incentive stock options under the 2014 Plan is 30,000,000 shares.

Restricted Stock Units

Pursuant to the Company's non-employee director compensation policy, an aggregate of 43,200 restricted stock units were granted to non-employee directors on June 3, 2021, the date of the Company's 2021 Annual Meeting of Stockholders, under the 2014 Plan with a grant date fair value of $13.06 per share. The restricted stock units will vest on the earlier of (i) June 3, 2022 and (ii) immediately prior to the Company's next Annual Meeting of Stockholders

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following the grant date, subject to the recipient's continued service through such date. As a result, the Company recognizes compensation expense associated with these restricted stock units ratably over the one-year vesting period following the grant date. For the three and nine months ended September 30, 2021, stock compensation expense of $142 and $184, respectively, was recognized in general and administrative, or G&A, expense. As of September 30, 2021, none of the 43,200 restricted stock units were vested or settled in shares of the Company's common stock.

On March 30, 2021, the Compensation Committee of the Company's Board of Directors approved and granted a total of 176,000 restricted stock units to executive officers under the 2014 Plan with a grant date fair value of $20.59 per share. Vesting of the restricted stock units is contingent on the achievement of certain performance targets related to clinical and regulatory milestones, subject to the recipient's continuous service through each performance target. Recognition of compensation expense associated with these awards begins when, and to the extent, the performance criteria is probable of achievement and the employee has met the service conditions. In August 2021, performance targets relating to 44,002 restricted stock units had been achieved and thus restricted stock units vested and the awards were settled in shares of common stock. For each of the three and nine months ended September 30, 2021, the Company recognized $906 of stock compensation expense, with $329 recorded in R&D expense and $577 recorded in G&A expense. As of September 30, 2021, 44,002 of the 176,000 restricted stock units vested and were settled in shares of the Company's common stock.

Additionally on March 30, 2021, the Compensation Committee of the Company's Board of Directors also approved and granted a total of 100,000 time-based restricted stock units to certain executive officers under the 2014 Plan with a grant date fair value of $20.59 per share. The restricted stock units vest in three equal installments annually from the date of the grant. As a result, the Company recognizes compensation expense associated with these restricted stock units ratably over the three-year vesting period following the grant date. For the three months ended September 30, 2021, the Company recognized $173 of stock compensation expense, with $55 recorded in R&D expense and $118 in G&A expense. For the nine months ended September 30, 2021, the Company recognized $344 of stock compensation expense, with $110 recorded in R&D expense and $234 in G&A expense. As of September 30, 2021, none of the 100,000 restricted stock units were vested or settled in shares of the Company's common stock.

Pursuant to the Company's non-employee director compensation policy, an aggregate of 36,000 restricted stock units were granted to non-employee directors on June 4, 2020, the date of the Company's 2020 Annual Meeting of Stockholders, under the 2014 Plan with a grant date fair value of $15.62 per share. The restricted stock units fully vested on June 3, 2021. As a result, the Company has recognized compensation expense associated with these restricted stock units ratably over the one-year vesting period following the grant date. For the nine months ended September 30, 2021, stock compensation expense of $239 was recognized in G&A expense. No stock compensation expense relating to these restricted stock units were recognized during the three months ended September 30, 2021 as these restricted stock units fully vested and were settled in shares of the Company's common stock in June 2021. For the three and nine months ended September 30, 2020, $142 and $182, respectively, of stock compensation expense relating to these restricted stock units was recognized in the Condensed Statements of Comprehensive Loss, all of which related to G&A expense.

In February 2020, the Compensation Committee of the Company's Board of Directors approved and granted a total of 138,000 restricted stock units to executive officers under the 2014 Plan with a grant date fair value of $16.36 per share. Vesting of the restricted stock units is contingent on the achievement of certain performance targets related to clinical and regulatory milestones, subject to the recipient's continuous service through each performance target. Recognition of compensation expense associated with these awards begins when, and to the extent, the performance criteria is probable of achievement and the employee has met the service conditions. In February and March 2021, performance targets relating to 36,750 and 40,000 restricted stock units, respectively, had been achieved and thus restricted stock units vested and the awards were settled in shares of common stock. For the nine months ended September 30, 2021, the Company recognized $1,256 of stock compensation expense relating to the vesting of these

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restricted stock units, with $524 recorded in R&D expense and $732 in G&A expense. For the three months ended September 30, 2021, and the three and nine months ended September 30, 2020, no stock compensation expense relating to these restricted stock units were recognized. As of September 30, 2021, 113,500 of the 138,000 restricted stock units vested and were settled in shares of the Company's common stock.

Additionally in February 2020, the Compensation Committee of the Company's Board of Directors also approved and granted a total of 98,000 time-based restricted stock units to executive officers under the 2014 Plan with a grant date fair value of $16.36 per share. The restricted stock units vest in three equal installments annually from the date of the grant. As a result, the Company recognizes compensation expense associated with these restricted stock units ratably over the three-year vesting period following the grant date. In February 2021, 32,669 of these restricted stock units vested and were settled in shares of the Company's common stock in satisfaction of the first year of vesting. For the three months ended September 30, 2021, the Company recognized $135 of stock compensation expense, with $44 recorded in R&D expense and $91 in G&A expense. For the nine months ended September 30, 2021, the Company recognized $400 of stock compensation expense, with $130 recorded in R&D expense and $270 recorded in G&A expense. For the three months ended September 30, 2020, the Company recognized $134 of stock compensation expense, with $44 recorded in R&D expense and $90 in G&A expense. For the nine months ended September 30, 2020, the Company recognized $320 of stock compensation expense, with $105 recorded in R&D expense and $215 recorded in G&A expense. As of September 30, 2021, 32,669 of the 98,000 restricted stock units vested and were settled in shares of the Company's common stock.

Pursuant to the terms of the Company's non-employee director compensation policy, an aggregate of 24,000 restricted stock units were granted to non-employee directors on June 4, 2019, the date of the Company's 2019 Annual Meeting of Stockholders, under the 2014 Plan with a grant date fair value of $20.47 per share. The restricted stock units vested on the earlier of (i) June 4, 2020 and (ii) immediately prior to the Company's next Annual Meeting of Stockholders following the grant date, subject to the recipient's continued service through such date. As a result, the Company recognized compensation expense associated with these restricted stock units ratably over the one-year vesting period following the grant date. For the nine months ended September 30, 2020, the Company recognized $205 of stock compensation expense, all of which related to G&A expense. No stock compensation expense relating to these restricted stock units were recognized during the three months ended September 30, 2020 as these restricted stock units fully vested and were settled in shares of the Company's common stock in June 2020.

In March 2019, the Compensation Committee of the Company's Board of Directors approved and granted a total of 215,000 restricted stock units to executive officers under the 2014 Plan with a grant date fair value of $16.10 per share. Vesting of the restricted stock units was contingent on the achievement of certain performance targets related to clinical milestones, subject to the recipient's continuous service through the vesting events. Recognition of compensation expense associated with these awards begins when, and to the extent, the performance criteria is probable of achievement and the employee has met the service conditions. In April and June 2020, performance targets relating to 65,834 and 30,000 restricted stock units, respectively, had been achieved and thus such restricted stock units vested, and the awards were settled in shares of common stock. During the nine months ended September 30, 2020, the Company recognized $1,543 of stock compensation expense relating to the vesting of these restricted stock units, with $1,087 recorded in R&D expense and $456 recorded in G&A expense. No stock compensation expense relating to these restricted stock units were recognized during the three months ended September 30, 2020 as these restricted stock units either fully vested and were settled in shares of the Company's common stock or were forfeited as of June 30, 2020.

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A summary of restricted stock unit activity related to employees and non-employee members of the Company's Board of Directors as of and for the nine months ended September 30, 2021 is presented below:

	Number of Units	Weighted Average Grant Date Fair Value
Outstanding, December 31, 2020	235,250	$ 16.25
Awarded	319,200	19.57
Vested and released	(189,421)	17.20
Outstanding, September 30, 2021	365,029	$ 18.66
Restricted stock units exercisable (vested and deferred), September 30, 2021	—	

Stock Options

Under the 2014 Plan, the Company granted 30,000 and 345,000 stock options during the three months ended September 30, 2021 and 2020, respectively, and 819,250 and 1,165,350 stock options during the nine months ended September 30, 2021 and 2020, respectively. No stock options were granted under the 2019 Inducement Plan during the three and nine months ended September 30, 2021 and 2020. The fair values of stock options granted during the three and nine months ended September 30, 2021 and 2020 were estimated as of the dates of grant using the Black-Scholes option pricing model with the following assumptions:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
Risk-free interest rate	0.92% - 1.01%	0.35% - 0.43%	0.66% - 1.23%	0.35% - 1.57%
Expected volatility	83.0% - 83.4%	72.6% - 73.3%	71.6% - 83.5%	72.6% - 74.8%
Expected dividend yield	0%	0%	0%	0%
Expected life of employee and Board options (in years)	6.25	6.25	6.25	6.25

The weighted-average grant date fair value per share of options granted to employees and non-employee members of the Company's Board of Directors for their Board service during the three months ended September 30, 2021 and 2020 was $9.24 and $11.11, respectively, and during the nine months ended September 30, 2021 and 2020 was $12.14 and $10.70, respectively. No options were granted to non-employee consultants during the three and nine months ended September 30, 2021 and 2020.

During the three and nine months ended September 30, 2021 and 2020, the Company recognized compensation expense relating to stock options as follows:

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2021	2020	2021	2020
Research and development	$ 1,833	$ 1,724	$ 5,228	$ 5,003
General and administrative	1,205	1,305	3,444	3,517
Total stock option expense	$ 3,038	$ 3,029	$ 8,672	$ 8,520

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The following were excluded from the table above as they are not related to stock options: compensation expense for (i) the vesting of executives' restricted stock units for $429 in R&D expense and $785 in G&A expense for the three months ended September 30, 2021, and $1,094 in R&D expense and $1,812 in G&A expense for the nine months ended September 30, 2021; (ii) the vesting of executives' restricted stock units for $44 in R&D expense and $90 in G&A expense for the three months ended September 30, 2020, and $1,192 in R&D expense and $671 in G&A expense for the nine months ended September 30, 2020; (iii) compensation expense relating to the Board of Directors' restricted stock units for $142 and $423 in G&A expense for the three and nine months ended September 30, 2021, respectively; and (iv) compensation expense relating to the Board of Directors' restricted stock units for $142 and $387 in G&A expense for the three and nine months ended September 30, 2020, respectively.

A summary of stock option award activity related to employees, non-employee members of the Company's Board of Directors and non-employee consultants as of and for the nine months ended September 30, 2021 is presented below:

	Number of Shares	Weighted Average Exercise Price
Outstanding, December 31, 2020	5,469,393	$ 15.02
Granted	819,250	18.72
Exercised	(114,354)	11.55
Forfeited	(199,506)	17.20
Expired	(234)	18.93
Outstanding, September 30, 2021	5,974,549	$ 15.52
Options exercisable, September 30, 2021	3,860,433	

The Company does not expect to realize any tax benefits from its stock option activity or the recognition of stock-based compensation expense because the Company currently has net operating losses and has a full valuation allowance against its deferred tax assets. Accordingly, no amounts related to excess tax benefits have been reported in cash flows from operations for the three and nine months ended September 30, 2021 and 2020.

14. Income Taxes

For the three months ended September 30, 2021 and 2020, pre-tax losses were $1,013 and $16,641, respectively, and for the nine months ended September 30, 2021 and 2020, pre-tax losses were $55,059 and $70,935, respectively. The Company recognized a full tax valuation allowance against its deferred tax assets as of September 30, 2021 and December 31, 2020. The tax benefit related to the exercise of stock options is recognized as a deferred tax asset that is offset by a corresponding valuation allowance.

The benefit from income taxes of $132 and $436 for the three and nine months ended September 30, 2020, respectively, relates to state R&D tax credits exchanged for cash pursuant to the Connecticut R&D Tax Credit Exchange Program, which permits qualified small businesses engaged in R&D activities within Connecticut to exchange their unused R&D tax credits for a cash amount equal to 65% of the value of the exchanged credits. Because the Company's revenue in 2020 exceeded $70,000, it is not eligible to exchange its 2021 R&D tax credit for cash, therefore there was no benefit from income taxes for the three and nine months ended September 30, 2021.

As of September 30, 2021 and December 31, 2020, the Company did not have any foreign subsidiaries and the international aspects of the Tax Cuts and Jobs Act are not applicable for the respective periods.

CARA THERAPEUTICS, INC.

NOTES TO CONDENSED FINANCIAL STATEMENTS
(amounts in thousands, except share and per share data)
(unaudited)

On March 27, 2020, former President Trump signed into law the Coronavirus Aid, Relief, and Economic Security Act of 2020, or the CARES Act (H.R. 748), which was further expanded with the signing of the Consolidation Appropriations Act of 2021 (H.R. 133) on December 27, 2020. The CARES Act (and December expansion) includes a variety of economic and tax relief measures intended to stimulate the economy, including loans for small businesses, payroll tax credits/deferrals, and corporate income tax relief. Due to the Company's history of tax loss carryforwards and full valuation allowance, the CARES Act did not have a significant effect to the income tax provision, as the corporate income tax relief was directed towards cash taxpayers.

15. Commitments and Contingencies

License Agreement with Enteris Biopharma, Inc.

In August 2019, the Company entered into a non-exclusive license agreement, or the Enteris License Agreement, with Enteris Biopharma, Inc., or Enteris, pursuant to which Enteris granted to the Company a non-exclusive, royalty-bearing license, including the right to grant sublicenses, under certain proprietary technology and patent rights related to or covering formulations for oral delivery of peptide active pharmaceutical ingredients with functional excipients to enhance permeability and/or solubility, known as Enteris's Peptelligence® technology, to develop, manufacture and commercialize products using such technology worldwide, excluding Japan and South Korea.

As consideration for the licensed rights under the Enteris License Agreement, the Company paid an upfront fee equal to $8,000, consisting of $4,000 in cash and $4,000 in shares of the Company's common stock pursuant to the Purchase Agreement with Enteris.

The Company is also obligated, pursuant to the Enteris License Agreement, to pay Enteris (1) milestone payments upon the achievement of certain development, regulatory and commercial milestones and (2) low-single digit royalty percentages on net sales of licensed products, subject to reductions in specified circumstances. Until the second anniversary of the entry into the Enteris License Agreement, the Company has the right, but not the obligation, to terminate its obligation to pay any royalties under the Enteris License Agreement in exchange for a lump sum payment in cash, or the Royalty Buyout. The Company did not exercise its Royalty Buyout right and such right expired in August 2021. In June 2021, the Company paid a $10,000 milestone payment to Enteris based on a successful End of Phase 2 Meeting with the FDA in April 2021, which was recorded in R&D expense for the nine months ended September 30, 2021. In October 2020, the Company paid $2,500 to Enteris for a milestone earned, which was recorded in R&D expense for the three and nine months ended September 30, 2020.

Manufacturing Agreements

In July 2021, the Company entered into an API Commercial Supply Agreement with Polypeptide Laboratories S.A., or PPL, that defines each party's responsibilities with respect to PPL's manufacture and supply of the active pharmaceutical ingredient CR845/difelikefalin, or API, for the CR845/difelikefalin injection product candidate. Under the API Commercial Supply Agreement, PPL shall manufacture API at its facility for sale and supply to the Company, in the amounts as set forth in purchase orders to be provided by the Company. The Company will be required to purchase its requirements of API for each year of the term of the agreement, based on internal forecasts.

The API Commercial Supply Agreement will continue until the fifth anniversary of the approval by the FDA of the new drug application for KORSUVA injection, unless the API Commercial Supply Agreement is earlier terminated, and will automatically be extended for successive five-year periods unless either party gives notice to the other party of its intention to terminate.

CARA THERAPEUTICS, INC.

NOTES TO CONDENSED FINANCIAL STATEMENTS
(amounts in thousands, except share and per share data)
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In July 2019, the Company entered into a Master Manufacturing Services Agreement, or MSA, with Patheon UK Limited, or Patheon. The MSA governs the general terms under which Patheon, or one of its affiliates, will provide non-exclusive manufacturing services to the Company for the drug products specified by the Company from time to time. Pursuant to the MSA, the Company has agreed to order from Patheon at least a certain percentage of its commercial requirements for a product under a related Product Agreement. Each Product Agreement that the Company may enter into from time to time will be governed by the terms of the MSA, unless expressly modified in such Product Agreement.

In July 2019, the Company entered into two related Product Agreements under the MSA, one with each of Patheon and Patheon Manufacturing Services LLC, or Patheon Greenville, to govern the terms and conditions of the manufacture of commercial supplies of CR845/difelikefalin injection, the Company's lead product candidate. Pursuant to the Product Agreements, Patheon and Patheon Greenville will manufacture commercial supplies of CR845/difelikefalin injection at the Monza, Italy and Greenville, North Carolina manufacturing sites, respectively, from active pharmaceutical ingredient supplied by the Company. Patheon and Patheon Greenville will be responsible for supplying the other required raw materials and packaging components, and will also provide supportive manufacturing services such as quality control testing for raw materials, packaging components and finished product.

Leases

In December 2015, the Company entered into a lease agreement, or the Stamford Lease, for office space in Stamford, Connecticut, or the Premises, for the purposes of relocating its headquarters. The initial term of the Stamford Lease commenced in May 2016, or the Commencement Date, and ends in December 2023 and is renewable for one five-year term. The Stamford Lease requires monthly lease payments, including rent escalations and rent holidays, during the initial lease term. The Company began to make rental payments from the Commencement Date.

In connection with the signing of the Stamford Lease, the Company entered into a standby letter of credit agreement which serves as a security deposit for the Premises. The standby letter of credit is automatically renewed annually through November 2023. This standby letter of credit is secured with restricted cash in a money market account (refer to Note 6, *Restricted Cash*).

On January 1, 2019, the Company adopted FASB ASC 842: Leases, or ASC 842. Under ASC 842, since the Company adopted the practical expedients not to re-evaluate whether a contract is or contains a lease and to maintain the lease classification under ASC 840, the Stamford Lease continues to be accounted for as an operating lease.

Upon adoption of ASC 842, the Company was required to establish an operating lease right-of-use, or ROU, asset and operating lease liability for the Stamford Lease. In establishing the ROU asset, the operating lease liability of $5,198 was reduced by lease incentives relating to tenant improvements of $698 and deferred lease obligation of $864, which were outstanding upon adoption.

In June 2020, the Company entered into an amendment to the Stamford Lease to add additional office space, or the Lease Amendment. The term of the Lease Amendment began when renovation of the additional space was completed and the Company took possession of the additional space in October 2020, or the Amendment Commencement Date, and ends on December 31, 2023. The Lease Amendment is also renewable for one five-year term. The rent for the Lease Amendment is at market rate as of the signing of the Lease Amendment. The Lease Amendment requires monthly lease payments, including rent escalations, during the lease term. The Company began paying rent for the Lease Amendment on the Amendment Commencement Date.

CARA THERAPEUTICS, INC.

NOTES TO CONDENSED FINANCIAL STATEMENTS
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In October 2020, the Company recorded an operating lease liability of $1,934 for the Lease Amendment as the sum of the present value of the future minimum lease payments over the term for the new lease. The Company also recorded a corresponding ROU asset of $1,934, as no lease incentives were identified in the Lease Amendment.

Under ASC 842, lease expenses on the Stamford Lease and Lease Amendment are recognized on a straight-line basis over the lease term. As a result, $406 and $239 of operating lease cost, or lease expense, was recognized for the three months ended September 30, 2021 and 2020, respectively, consisting of $284 relating to R&D lease expense and $122 relating to G&A lease expense for the Stamford Lease and Lease Amendment in the 2021 period, and $167 relating to R&D lease expense and $72 relating to G&A lease expense for the Stamford Lease in the 2020 period. For the nine months ended September 30, 2021 and 2020, $1,218 and $709, respectively, of operating lease cost, or lease expense, was recognized, consisting of $853 relating to R&D lease expense and $365 relating to G&A lease expense for the Stamford Lease and Lease Amendment in the 2021 period, and $496 relating to R&D lease expense and $213 relating to G&A lease expense for the Stamford Lease in the 2020 period.

Other information related to the Stamford Lease and Lease Amendment was as follows:

	Three Months Ended		Nine Months Ended	
	September 30, 2021	September 30, 2020	September 30, 2021	September 30, 2020
Cash paid for amounts included in the measurement of lease liabilities:				
Operating cash outflows relating to operating leases	$ 482	$ 312	$ 1,436	$ 927
ROU assets obtained in exchange for new operating lease liabilities	$ —	$ —	$ —	$ —
Remaining lease term - operating leases (years)	2.3	3.3	2.3	3.3
Discount rate - operating leases	7.0 %	7.0 %	7.0 %	7.0 %

Future minimum lease payments under non-cancellable operating leases, as well as a reconciliation of these undiscounted cash flows to the operating lease liability as of September 30, 2021, were as follows:

Year Ending December 31,	
2021 (Excluding the nine months ended September 30, 2021)	$ 485
2022	1,957
2023	1,992
Total future minimum lease payments, undiscounted	4,434
Less imputed interest	(345)
Total	$ 4,089
Operating lease liabilities reported as of September 30, 2021:	
Operating lease liabilities - current	$ 1,716
Operating lease liabilities - non-current	2,373
Total	$ 4,089

CARA THERAPEUTICS, INC.

NOTES TO CONDENSED FINANCIAL STATEMENTS
(amounts in thousands, except share and per share data)
(unaudited)

16. Subsequent Events

In October 2021, the Company and its President and Chief Executive Officer, or CEO, agreed to the transition of the role from CEO to Senior Advisor beginning on November 9, 2021. In addition, the Company and the CEO entered into a Separation Agreement dated November 2, 2021, pursuant to which the CEO will provide transitional consulting services as a Senior Advisor to the Company from November 9, 2021 through June 30, 2022.

The Company appointed a current non-employee director of the Company's Board of Directors to the position of Senior Advisor, effective October 29, 2021 until November 8, 2021, and as President and CEO, effective as of November 9, 2021.

In October 2021, after the expiration of the requisite waiting period under the HSR Act, the Company received the $50,000 milestone payment from Vifor and issued 3,282,391 shares of its common stock to Vifor at a price of $15.23 per share, in connection with U.S. regulatory approval of KORSUVA injection on August 23, 2021.

In October 2021, the Company received the $15,000 milestone payment from VFMCRP.

Item 2. ***Management's Discussion and Analysis of Financial Condition and Results of Operations.***

Cautionary Note Regarding Forward-Looking Statements

This Quarterly Report on Form 10-Q contains forward-looking statements, within the meaning of the Private Securities Litigation Reform Act of 1995, that involve substantial risks and uncertainties. In some cases, you can identify forward-looking statements by the words "aim," "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "might," "objective," "ongoing," "plan," "predict," "project," "potential," "should," "will," or "would," and or the negative of these terms, or other comparable terminology intended to identify statements about the future. These statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. Although we believe that we have a reasonable basis for each forward-looking statement contained in this Quarterly Report on Form 10-Q, we caution you that these statements are based on a combination of facts and factors currently known by us and our expectations of the future, about which we cannot be certain.

The forward-looking statements in this Quarterly Report on Form 10-Q include, among other things, statements about:

- our ability to commercialize KORSUVA™ (CR845/difelikefalin) injection, or KORSUVA injection, including the timing of additional regulatory submissions and approvals, such as the Transition Drug Add-on Payment Adjustment, or TDAPA, and execute on our marketing plans for any other drugs or indications that may be approved in the future;
- our ability to obtain and maintain coverage and adequate reimbursement for KORSUVA injection;
- the performance of our current and future collaborators and licensees, including Vifor Fresenius Medical Care Renal Pharma Ltd., or VFMCRP, Vifor (International) Ltd., or Vifor, Maruishi Pharmaceuticals Co. Ltd., or Maruishi, and Chong Kun Dang Pharmaceutical Corp., or CKDP, as well as sub-licensees, including Kissei Pharmaceutical Co. Ltd., or Kissei, and our ability to maintain such collaborations;
- risks that KORSUVA injection revenue, expenses and costs may not be as expected;
- risks relating to KORSUVA injection's market acceptance, competition, reimbursement and regulatory actions;
- the size and growth of the potential markets for pruritus management, including chronic kidney disease associated pruritus, or CKD-aP, in hemodialysis and non-dialysis markets, chronic liver disease associated pruritus, or CLD-aP, pruritus associated with atopic dermatitis, or AD-aP, and pruritus associated with notalgia paresthetica, or NP, markets as well as post-operative care markets;
- the success and timing of our clinical trials and reporting of our results from these trials, including our clinical trial programs for Oral KORSUVA (CR845/difelikefalin) in CKD-aP, CLD-aP, AD-aP, and NP;
- our plans to develop and commercialize Oral KORSUVA (CR845/difelikefalin) and any future product candidates;
- the potential results of ongoing and planned preclinical studies and clinical trials and future regulatory and development milestones for our product candidates;
- the potential regulatory development pathway for CR845/difelikefalin injection in acute post-operative setting;
- the rate and degree of market acceptance of any other future approved products;

- our ability to obtain and maintain additional regulatory approval of our product candidates, and the labeling under any approval we may obtain;
- the anticipated use of Enteris Biopharma, Inc.'s, or Enteris's, Peptelligence® technology to develop, manufacture and commercialize Oral KORSUVA (CR845/difelikefalin);
- our ability to establish additional collaborations for our product candidates;
- the continued service of our key scientific or management personnel;
- our ability to establish commercialization and marketing capabilities for any other future approved products;
- regulatory developments in the United States and foreign countries;
- our ability to obtain and maintain coverage and adequate reimbursement from third-party payers for any other future approved products;
- our planned use of our cash and cash equivalents and marketable securities and the clinical milestones we expect to fund with such proceeds;
- the accuracy of our estimates regarding expenses, future revenues and capital requirements;
- our ability to obtain funding for our operations;
- our ability to obtain and maintain intellectual property protection for our product candidates and our ability to operate our business without infringing on the intellectual property rights of others;
- the success of competing drugs that are or may become available;
- the performance of third-party manufacturers and clinical research organizations, or CROs; and
- the potential effects of the ongoing COVID-19 pandemic on our business, operations and clinical development and regulatory timelines and plans as well as commercial and clinical drug supply chain continuity and the commercial launch of KORSUVA injection.

You should refer to the "Risk Factors" section of this Quarterly Report on Form 10-Q for a discussion of material factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements in this Quarterly Report on Form 10-Q will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame or at all. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

You should read this Quarterly Report on Form 10-Q and the documents that we reference in this Quarterly Report on Form 10-Q and have filed as exhibits to this Quarterly Report on Form 10-Q completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of our forward-looking statements by these cautionary statements.

The following *Management's Discussion and Analysis of Financial Condition and Results of Operations* should be read in conjunction with: (i) the Condensed Financial Statements and related notes thereto which are included in this Quarterly Report on Form 10-Q; and (ii) our Annual Report on Form 10-K for the year ended December 31, 2020.

Overview

We are an early commercial-stage biopharmaceutical company focused on developing and commercializing new chemical entities designed to alleviate pruritus by selectively targeting peripheral kappa opioid receptors, or KORs. We are developing a novel and proprietary class of product candidates, led by KORSUVA (CR845/difelikefalin), a first-in-class KOR agonist that targets KORs located in the peripheral nervous system and on immune cells.

In our KALM™-1 and KALM-2 Phase 3 trials and two Phase 2 trials, KORSUVA injection (intravenous formulation) has demonstrated statistically significant reductions in itch intensity and concomitant improvement in pruritus-related quality of life measures in hemodialysis patients with moderate-to-severe CKD-aP. We have partnered with VFMCRP, a joint venture between Vifor Pharma Group and Fresenius Medical Care, and Vifor to commercialize KORSUVA injection in dialysis patients with CKD-aP in the U.S. under profit share agreements. We have partnered with VFMCRP to commercialize KORSUVA worldwide, excluding Japan (Maruishi/sub-licensee Kissei), and South Korea (CKDP).

The U.S. Food and Drug Administration, or FDA, has accepted KORSUVA as the trade name for CR845/difelikefalin injection. On August 23, 2021, the FDA approved KORSUVA injection for the treatment of moderate-to-severe pruritus in hemodialysis patients. Our U.S. commercial partner, Vifor Pharma Group, submitted the payment reimbursement application for TDAPA, and the Healthcare Common Procedure Coding System, or HCPCS, to the U.S. Center for Medicare & Medicaid Services, or CMS, in September 2021. Once the TDAPA application is reviewed and approved by CMS, we expect that KORSUVA injection will be available to patients for commercial use in the U.S. Based on the timing of CMS review, we expect commercial launch of KORSUVA injection and associated revenues in the first half of 2022.

CR845/difelikefalin has also demonstrated statistically significant pain reduction in clinical trials in patients with moderate-to-severe acute pain in the post-operative setting, without inducing many of the undesirable side effects typically associated with currently available opioid pain therapeutics. We retain rights to all KORSUVA/CR845 formulations and indications worldwide, excluding KORSUVA injection in dialysis patients with CKD-aP under our agreements with VFMCRP and Vifor for U.S. and certain ex-U.S. territories in Japan (Maruishi/sub-licensee Kissei) and South Korea (CKDP).

We were incorporated and commenced operations in 2004, and our primary activities to date have been organizing and staffing our company, developing our product candidates, including conducting preclinical studies and clinical trials of CR845/difelikefalin-based product candidates and raising capital. To date, we have financed our operations primarily through sales of our equity and debt securities and payments from license agreements. We have no products currently available for sale, and substantially all of our revenue to date has been revenue from license agreements, although we have received nominal amounts of revenue under research grants and the sale of clinical compound.

Recent Developments

COVID-19 Update

The extent of the impact of the ongoing COVID-19 pandemic on our business, operations and clinical development and regulatory timelines and plans as well as commercial and clinical drug supply chain continuity and the commercial launch of KORSUVA injection remains uncertain, and will depend on certain developments, including the duration, subsequent waves and variants and its impact on our clinical trial enrollment, trial sites, partners, CROs, third-party manufacturers, and other third parties with whom we do business, as well as its impact on regulatory authorities and our key scientific and management personnel. The COVID-19 pandemic has affected the initiation of certain trial sites and patient enrollment for certain of our clinical trials, including our ongoing Phase 2 clinical trials of Oral KORSUVA (CR845/difelikefalin) for NP and for the treatment of pruritus in patients with hepatic impairment due to primary biliary cholangitis, or PBC, and the pandemic may continue to affect these and other planned future trials. While we currently do not expect any significant delays in our clinical development or commercial timelines, the ultimate impact of the evolving COVID-19 pandemic remains difficult to predict.

To the extent possible, we are conducting business as usual, with necessary or advisable modifications to employee travel and employee work locations. We are continuing to actively monitor the rapidly evolving situation related to COVID-19 and may take further actions that alter our operations, including those that may be required by federal, state or local authorities, or that we determine are in the best interests of our employees, partners and other third-parties with whom we do business. The extent to which the ongoing and evolving COVID-19 pandemic may affect our business, operations and clinical development and regulatory timelines and plans, including the resulting impact on our expenditures and capital needs, remains uncertain.

Chief Executive Officer Transition

In October 2021, we and Dr. Derek Chalmers, our President and Chief Executive Officer, or CEO, agreed to the transition of the role from CEO to Senior Advisor beginning on November 9, 2021. In addition, we and Mr. Chalmers entered into a Separation Agreement dated November 2, 2021, pursuant to which he will provide transitional consulting services as a Senior Advisor to us from November 9, 2021 through June 30, 2022.

We appointed Mr. Christopher Posner, a current non-employee director of our Board of Directors, to the position of Senior Advisor, effective October 29, 2021 to November 8, 2021, and as President and CEO, effective as of November 9, 2021. Mr. Posner joins us from LEO Pharma, Inc., or LEO, the U.S. affiliate of LEO Pharma A/S, a global leader in medical dermatology, where he was President and CEO. While at LEO, Mr. Posner was responsible for a portfolio of innovative medical dermatology products in atopic dermatitis, psoriasis, and rosacea. Mr. Posner has more than 23 years of global pharmaceutical management, sales and product launch experience involving products such as Xeljanz® and Enbrel®.

API Commercial Supply Agreement

In July 2021, we entered into an API Commercial Supply Agreement with Polypeptide Laboratories S.A., or PPL, that defines each party's responsibilities with respect to PPL's manufacture and supply of the active pharmaceutical agreement CR845/difelikefalin, or API, for the CR845/difelikefalin injection product candidate (see *Manufacturing and License Agreements* within Management's Discussion and Analysis of Financial Condition and Results of Operations).

FDA Acceptance

In August 2021, the FDA approved KORSUVA injection for the treatment of moderate-to-severe pruritus in hemodialysis patients. Our U.S. commercial partner, Vifor Pharma Group, submitted the payment reimbursement application for TDAPA and HCPCS to CMS in September 2021. Once the TDAPA application is reviewed and approved by CMS, we expect that KORSUVA injection will be available to patients for commercial use in the U.S. Based on the timing of CMS review, we expect commercial launch of KORSUVA injection and associated revenues in the first half of 2022.

Marketing Authorization Application Submission

Our partner, VFMCRP, submitted a Marketing Authorization Application, or MAA, to the European Medicines Agency, or EMA, in March 2021, which was accepted for review by the EMA. If approved, KORSUVA injection would receive marketing authorization in all member states of the European Union, or EU, as well as in Iceland, Liechtenstein, and Norway. The EMA's decision on the EU MAA is expected in the second quarter of 2022.

Overview of Our Product Candidates

Our product candidate, CR845/difelikefalin, is a new chemical entity, which is designed to selectively stimulate kappa, rather than mu, and delta opioid receptors. CR845/difelikefalin has been designed with specific chemical characteristics to restrict its entry into the CNS and further limit its mechanism of action to KORs in the peripheral nervous system and on immune cells. Activation of kappa receptors in the CNS is known to result in some undesirable effects, including dysphoria. Since CR845/difelikefalin modulates kappa receptor signals peripherally without any significant activation of opioid receptors in the CNS, it is generally not expected to produce the CNS-related side effects

of mu opioid agonists (such as addiction and respiratory depression) or centrally-active kappa opioid agonists (such as dysphoria and hallucinations). CR845/difelikefalin has been administered to more than 3,000 human subjects in Phase 1, Phase 2 and Phase 3 clinical trials as an I.V. infusion, bolus intravenous injection or oral capsule or tablet, and thus far has been observed to be generally well tolerated in multiple clinical trials.

Based on the non-clinical and clinical studies we have completed to date, we believe that KORSUVA injection and CR845/difelikefalin for our other product candidates, if approved, would be attractive to both patients and physicians as a treatment for moderate-to-severe pruritus associated with systematic conditions such as CKD and CLD, dermatological conditions such as AD, and neurological conditions such as NP, as well as moderate-to-severe pain due to the following attributes:

- novel, peripherally-acting, KOR agonist mechanism of action;
- evidence of efficacy in completed clinical trials of pruritus and pain;
- potential for reducing mu opioid use and opioid-related adverse events, or AEs, such as nausea and vomiting;
- potential for reduction of post-operative nausea and vomiting, or PONV;
- avoidance of mu opioid-related CNS side effects, such as respiratory depression and euphoria;
- lower potential for addiction or abuse liability;
- avoidance of interactions with other drugs because CR845/difelikefalin is not metabolized in the liver and does not interact with liver enzymes responsible for the metabolism of most commonly used classes of drugs; and
- availability in injectable form for the treatment of pruritus in CKD patients undergoing hemodialysis in the hospital and dialysis center settings as well as for pain and/or PONV treatment in the acute care setting and oral form for treatment of pruritus or chronic pain conditions in the outpatient setting.

Our current product and product candidate pipeline is summarized in the table below:

Program	Product Candidate	Primary Indication	Status	Commercialization Rights
Pruritus	KORSUVA (CR845/difelikefalin) Injection	Pruritus CKD - Hemodialysis	• FDA approved in August 2021 • TDAPA application submitted in September 2021 to CMS • EMA MAA accepted in March 2021	VFMCRP/Vifor (United States); Maruishi (Japan); CKDP (South Korea); VFMCRP (Worldwide, other than United States, Japan and South Korea)
	Oral KORSUVA (CR845/difelikefalin)	Pruritus Atopic Dermatitis (AD-aP)	• Phase 2 trial completed; top-line data reported	Cara (Worldwide, other than South Korea); CKDP (South Korea)
	Oral KORSUVA (CR845/difelikefalin)	Pruritus NDD-CKD	• Phase 2 trial completed; top-line data reported	Cara (Worldwide, other than Japan and South Korea); Maruishi (Japan); CKDP (South Korea)
	Oral KORSUVA (CR845/difelikefalin)	Pruritus CLD - Primary Biliary Cholangitis (PBC)	• Phase 2 efficacy trial ongoing	Cara (Worldwide, other than South Korea); CKDP (South Korea)
	Oral KORSUVA (CR845/difelikefalin)	Notalgia Paresthetica (NP)	• KOMFORT Phase 2 efficacy trial ongoing	Cara (Worldwide, other than South Korea); CKDP (South Korea)
Post-Op Setting	CR845/difelikefalin Injection	Acute Post-Operative Pain/PONV	• Adaptive Phase 2/3 trial completed; top-line data reported	Cara (Worldwide, other than Japan and South Korea); Maruishi (Japan); CKDP (South Korea)

KORSUVA Injection for Treatment of Chronic Kidney Disease-Associated Pruritus (CKD-aP)

CKD-aP is an intractable systemic itch condition with high prevalence for which there are no approved therapeutics in the United States or Europe. On August 23, 2021, based on the results from our efficacy and safety trials, the FDA approved KORSUVA injection for the treatment of moderate-to-severe pruritus in hemodialysis patients.

Our partner, VFMCRP, submitted a MAA to the EMA in March 2021, which was accepted for review by the EMA. If approved, KORSUVA injection would receive marketing authorization in all member states of the EU, as well as in Iceland, Liechtenstein, and Norway. The EMA's decision on the EU MAA is expected in the second quarter of 2022.

In April 2020, we announced positive top-line results from our KALM-2 pivotal Phase 3 trial of KORSUVA injection in hemodialysis patients with moderate-to-severe CKD-aP. The trial met the primary and key secondary endpoints after 12 weeks of treatment. The open label extension phase of this trial is also complete.

Our U.S. commercial partner, Vifor Pharma Group, submitted the payment reimbursement application for TDAPA and HCPCS to CMS in September 2021. Once the TDAPA application is reviewed and approved by CMS, we expect that KORSUVA injection will be available to patients for commercial use in the U.S. Based on the timing of CMS review, we expect commercial launch of KORSUVA injection and associated revenues in the first half of 2022.

Oral KORSUVA (CR845/difelikefalin) for Treatment of Moderate-to-Severe Pruritus Associated with Atopic Dermatitis (AD-aP)

In April 2021, we announced top-line data from our Phase 2 KARE clinical trial. The KARE Phase 2 trial was a randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of Oral KORSUVA (CR845/difelikefalin) for moderate-to-severe pruritus in 401 adult subjects with AD-aP. Patients were stratified across treatment groups by disease severity. KARE enrolled 64% of patients characterized as mild-to-moderate (BSA<10%)

and 36% falling into the moderate-to-severe category (BSA>10%). Subjects were randomized to three tablet strengths of Oral KORSUVA (CR845/difelikefalin): 0.25 mg, 0.5 mg and 1 mg taken twice daily (BID) versus placebo for 12 weeks followed by 4 weeks of an active extension phase. A prespecified interim conditional power assessment was conducted after approximately 50% of the originally targeted patient number completed the designated 12-week treatment period. Based on the Independent Data Monitoring Committee's recommendation, the sample size for each of the 0.5 mg dose and placebo groups were increased by approximately 60%.

KARE's primary efficacy endpoint was change from baseline in the weekly mean of the daily 24-hour Itch NRS score at week 12 of the treatment period for the intent to treat, or ITT, population. Although no dose group met this endpoint, a statistically significant improvement from baseline was evident as early as week 1 for the 1.0 mg dose group, which was sustained through 75% of the treatment period.

In a prespecified analysis, a statistically significant change in the primary efficacy endpoint was observed in the mild-to-moderate (BSA<10%) patient population (p=0.036, All doses vs placebo), which was evident at week 1 and sustained through the treatment period.

The key secondary endpoint for KARE was the assessment of the proportion of patients achieving an improvement from baseline of ≥4 points with respect to the weekly mean of the daily 24-hour Itch NRS score at week 12 (4-point Responder Analysis). No dose group met this endpoint for the ITT population.

Prespecified analysis by disease severity indicated a statistically significant improvement in the 4-point Responder Analysis in the mild-to-moderate (BSA<10%) patient population with 32% of KORSUVA-treated patients achieving a ≥4 point reduction in NRS at Week 12 versus 19% in the placebo group (p=0.033, All doses vs placebo). A statistically significant improvement was also achieved for the 0.5 mg dose (p=0.046, 0.5 mg vs placebo).

Oral KORSUVA (CR845/difelikefalin) was generally well-tolerated across all doses. Overall, the incidence of treatment-emergent AEs was generally similar across Oral KORSUVA (CR845/difelikefalin) and placebo groups.

We conducted an End of Phase 2 Meeting with the FDA in the third quarter of 2021 and aim to initiate a Phase 3 program for the treatment of pruritus in AD patients in the first quarter of 2022.

Oral KORSUVA (CR845/Difelikefalin) for Treatment of Non-Dialysis Dependent (NDD) Chronic Kidney Disease-Associated Pruritus (CKD-aP)

In December 2019, we announced top-line data from our Phase 2 trial of Oral KORSUVA (CR845/difelikefalin) for the treatment of pruritus in NDD–CKD patients. The Phase 2, multicenter, randomized, double-blind, placebo-controlled 12-week trial is designed to evaluate the safety and efficacy of three tablet strengths (0.25 mg, 0.5 mg and 1 mg, once daily administration) of Oral KORSUVA (CR845/difelikefalin) versus placebo in approximately 240 stage III - V (moderate to severe) CKD patients with moderate-to-severe pruritus. The primary efficacy endpoint was the change from baseline in the weekly mean of the daily 24-hour worst itching NRS score at week 12 of the treatment period. Secondary endpoints include change from baseline in itch-related quality of life scores at the end of week 12, as assessed by the total Skindex-10 and 5-D itch scores, as well as the proportion of patients achieving an improvement from baseline ≥3 points with respect to the weekly mean of the daily 24-hour worst itching NRS score at week 12.

Patients treated with the 1.0 mg tablet strength of Oral KORSUVA (CR845/difelikefalin) achieved the primary endpoint of statistically significant reduction in weekly mean of the daily worst itching NRS scores vs. placebo after the 12-week treatment period (-4.4 KORSUVA vs. -3.3 placebo, p=0.018). The treatment was statistically significant after two weeks of treatment and sustained through the 12-week treatment period. Regarding secondary endpoints, the proportion of patients on 1.0 mg tablet strength achieving a 3 point or greater improvement from baseline in the weekly mean of the daily worst itching NRS score at week 12 was 72% vs. 58% for placebo but did not achieve statistical significance. Furthermore, patients on 1.0 mg tablet strength showed positive improvements vs. placebo in itch quality of life endpoints as measured using self-assessment Skindex-10 and 5-D Itch scales but did not achieve statistical significance. Oral KORSUVA (CR845/difelikefalin) was generally well-tolerated with a safety profile consistent with that seen in earlier KORSUVA clinical trials. Overall, the incidence of treatment AEs were similar across KORSUVA

and placebo groups. The most common AEs reported in >5% of patients in the 1.0 mg KORSUVA group vs. placebo were dizziness (7.5% KORSUVA vs. 0% placebo), fall (6% KORSUVA vs. 0% placebo), diarrhea (6% KORSUVA vs. 1.5% placebo) and constipation (6% KORSUVA vs. 3% placebo).

In April 2021, we held an End of Phase 2 Meeting with the FDA to discuss the results of the Phase 2 trial of Oral KORSUVA (CR845/difelikefalin) in NDD CKD-aP and the potential Phase 3 program. The FDA indicated the acceptability of Stage 5 pre-dialysis CKD patients as a viable patient population for a program. In November 2021, the FDA provided written guidance indicating the patient population can be expanded to include the group of Stage 4 pre-dialysis patients with advanced CKD in a registration program consisting of two pivotal Phase 3 clinical trials. We expect to initiate the program in the first quarter of 2022.

Oral KORSUVA (CR845/Difelikefalin) for Treatment of Chronic Liver Disease-Associated Pruritus (CLD-PBC)

Pruritus is a common and serious symptom in patients with CLD, especially those with chronic cholestatic disease. Pruritus has a prevalence of up to 70% in patients with PBC. Severe pruritus can have debilitating effects and can lead to a significant reduction in a patient's quality of life. Although the pathogenesis of CLD-aP remains poorly understood, it is likely multifactorial including evidence for an imbalance in the endogenous opioid system driven by higher mu receptor activation (pruritic) versus kappa receptor activation (antipruritic). Consequently, the use of selective kappa-opioid receptor agonists has been suggested for the treatment of pruritus in patients with CLD.

In June 2019, we announced the initiation of a Phase 2 trial of Oral KORSUVA (CR845/difelikefalin) for the treatment of pruritus in patients with hepatic impairment due to PBC. The Phase 2 multicenter, randomized, double-blind, placebo-controlled 16-week trial is designed to evaluate the safety and efficacy of 1 mg tablet of Oral KORSUVA (CR845/difelikefalin) taken twice daily or BID versus placebo in approximately 60 patients with PBC and moderate-to-severe pruritus. The primary efficacy endpoint is the change from baseline in the weekly mean of the daily 24-hour worst itching NRS score at week 16 of the treatment period. Secondary endpoints include change from baseline in itch-related quality of life scores at the end of week 16 as assessed by the Skindex-10 and 5-D itch scales, as well as the assessment of proportion of patients achieving an improvement from baseline of ≥3 points with respect to the weekly mean of the daily 24-hour worst itching NRS score at week 16. We continue to screen patients in this ongoing Phase 2 trial of Oral KORSUVA (CR845/difelikefalin) and, primarily due to the ongoing effects of the COVID-19 pandemic on patient enrollment, we currently aim to have top-line data in the first half of 2022.

In the fourth quarter of 2017, we submitted an investigational new drug application, or IND, to the FDA for Oral KORSUVA (CR845/difelikefalin) for the symptomatic relief of CLD-aP and initiated a Phase 1 safety and PK clinical trial of Oral KORSUVA (CR845/difelikefalin) in patients with CLD in the first quarter of 2018. The open-label study was designed to evaluate the safety and PK profile of repeated doses of Oral KORSUVA (CR845/difelikefalin) taken twice daily in up to 60 patients with CLD and up to 12 matched healthy control subjects. Oral KORSUVA (CR845/difelikefalin) was evaluated over an eight-day treatment period in patients with CLD based on their Child-Pugh classification (i.e., Class A, B and C). The study is now complete. The PK parameters were dose-proportional in patients with mild-to-moderate CLD and Oral KORSUVA (CR845/difelikefalin) was generally well tolerated with no unexpected safety signals reported.

Oral KORSUVA (CR845/difelikefalin) for Treatment of Moderate-to-Severe Pruritus Associated with Notalgia Paresthetica (NP)

In January 2021, we initiated a Phase 2 randomized, double-blind, placebo-controlled trial that is designed to evaluate the efficacy and safety of Oral KORSUVA (CR845/difelikefalin) for moderate-to-severe pruritus in approximately 120 adult subjects with NP. Subjects will be randomized to receive Oral KORSUVA (CR845/difelikefalin) 2.0 mg twice daily versus placebo for eight weeks followed by a 4-week active extension period and follow up visit approximately 14 days after the last dose of the study. The primary efficacy endpoint is the change from baseline in the weekly mean of the daily 24-hour worst itching NRS score at week 8 of the treatment period. Secondary endpoints include improvement in itch-related quality of life assessed by the change from baseline to Week 8 and a change from baseline in itch-related sleep disturbance subscale measured by the itch medical outcomes study at week 8. We currently plan to complete enrollment in the trial by year-end 2021.

Intravenous CR845/Difelikefalin for Treatment of Acute Postoperative Pain (PONV)

We have also investigated CR845/difelikefalin for the treatment of pain in an acute care setting. CR845/difelikefalin is designed to provide pain relief without stimulating mu opioid receptors and therefore potentially without mu opioid-related side effects, such as nausea, vomiting, respiratory depression and euphoria.

In June 2018, we reported positive top-line date from the adaptive Phase 2/3 study of CR845/difelikefalin in patients undergoing abdominal surgery. CR845 injection achieved statistical significance for the primary endpoint of pain relief as measured by Area Under the Curve, or AUC, over 24 hours (AUC 0-24) post-surgery with the 1.0 mcg/kg dose versus placebo (p=0.032). The 0.5 mcg/kg dose did not achieve statistical significance over the 0-24 hour period (p=0.076). In addition, improvement in pain AUC was statistically significant for both the 0.5 and 1.0 mcg/kg doses over 0 to 6 hours (p=0.041, p=0.001) and 0 to 12 hours (p=0.035, p=0.004) periods and also statistically significant for the 1.0 mcg/kg dose over the 0 to 18-hour period (p=0.013) post-surgery. At 6 and 24 hours after baseline dose post-surgery, there were statistically significant improvements in PONV impact scores with both doses of CR845 injection compared to placebo: 0.5 mcg/kg (6 hrs.: p=0.0072, 24 hrs.: p<0.006) and 1.0 mcg/kg (6 hrs.: p<0.0001, 24 hrs.: p<0.0001). There were statistically significant differences between placebo and both doses of CR845 with respect to the total use of anti-emetic medication over the first 24 hours post-surgery (0.5 mcg/kg: p=0.0003; 1.0 mcg/kg: p< 0.0001). There was a 73% reduction in the incidence of patient-reported vomiting in the group receiving the 1.0 mcg/kg dose versus placebo (p=0.029). Although the 0.5 mcg/kg also showed reduction in vomiting, it did not reach statistical significance. Both doses of CR845 exhibited numerical trends toward reduced use of rescue analgesic medication compared to placebo, but did not achieve statistical significance. There was no significant effect, compared to placebo, on patient's global assessment of medication for either dose of CR845 over the 24-hour period. Common adverse effects reported in the placebo and both CR845 groups were generally low and similar in incidence, and included nausea, constipation, vomiting, flatulence, headache and dyspepsia.

We have completed an advisory meeting with the FDA regarding the potential regulatory path forward for PONV and we are currently evaluating potential next steps.

Collaboration and License Agreements

Vifor (International) Ltd.

In October 2020, we entered into a license agreement, or the Vifor Agreement, with Vifor under which we granted Vifor an exclusive license solely in the United States to use, distribute, offer for sale, promote, sell and otherwise commercialize KORSUVA (CR845/difelikefalin) injection for all therapeutic uses relating to the inhibition, prevention or treatment of itch associated with pruritus in hemodialysis and peritoneal dialysis patients in the United States. Under the Vifor Agreement, we retain all rights with respect to the clinical development of, and activities to gain regulatory approvals of, KORSUVA (CR845/difelikefalin) injection in the United States.

Under the terms of the Vifor Agreement, we received from Vifor an upfront payment of $100.0 million and an additional payment of $50.0 million for the purchase of an aggregate of 2,939,552 shares of our common stock at a price of $17.0094 per share, which represents a premium over a pre-determined average closing price of our common stock. The purchase of the Company's common stock was governed by a separate stock purchase agreement, or the Vifor Stock Purchase Agreement.

After U.S. regulatory approval of KORSUVA injection in August 2021, we received an additional $50.0 million in October 2021 for the purchase of an aggregate of 3,282,391 shares of our common stock at a price of $15.23 per share, which represents a 20% premium to the 30-day trailing average price of our common stock. The purchase of our common stock was governed by the Vifor Stock Purchase Agreement. The excess of the stock purchase price over the cost of the purchased shares at the closing price of our common stock on the date of the achievement of the milestone of $5,031 was included as license and milestone fees revenue for accounting purposes for the three and nine months ended September 30, 2021. In addition, pursuant to the Vifor Agreement, we are eligible to receive payments of up to $240.0 million upon the achievement of certain sales-based milestones.

We retain the right to make and have made KORSUVA injection, on a non-exclusive basis, in the United States for commercial sale of KORSUVA injection for use in all therapeutic uses to prevent, inhibit or treat itch associated with pruritus in hemodialysis and peritoneal-dialysis patients anywhere in the world and for supply of Licensed Product to Vifor under the terms of a supply agreement, or the Vifor Supply Agreement, which was executed in September 2021. The supply price is our cost of goods sold, as calculated under GAAP, plus an agreed upon margin. The Vifor Supply Agreement will co-terminate with the Vifor Agreement. There were no sales of KORSUVA injection to Vifor through September 30, 2021.

The Vifor Agreement provides full commercialization rights in dialysis clinics to Vifor in the United States under a profit-sharing arrangement. Pursuant to the profit-sharing arrangement, we will generally be entitled to 60% of the net profits (as defined in the Vifor Agreement) from sales of KORSUVA injection in the United States (excluding sales to Fresenius Medical Center dialysis clinics, compensation for which is governed by the VFMCRP Agreement) and Vifor is entitled to 40% of such net profits, subject to potential temporary adjustment in future years based on certain conditions. Under the Vifor Agreement, in consideration of Vifor's conduct of the marketing, promotion, selling and distribution of KORSUVA injection in the United States, we will pay a marketing and distribution fee to Vifor based on the level of annual net sales. This fee will be deducted from product sales in calculating the net profits that are subject to the profit-sharing arrangement under the Vifor Agreement.

Vifor Fresenius Medical Care Renal Pharma Ltd.

In May 2018, we entered into a license agreement, or the VFMCRP Agreement, with VFMCRP, a joint venture between Vifor Pharma Group and Fresenius Medical Care, under which we granted VFMCRP a license to seek regulatory approval to commercialize, import, export, use, distribute, offer for sale, promote, sell and otherwise commercialize KORSUVA (CR845/difelikefalin) injection for all therapeutic uses to prevent, inhibit or treat itch associated with pruritus in hemodialysis and peritoneal-dialysis patients worldwide (excluding the United States, Japan and South Korea). We retain full development and commercialization rights for KORSUVA injection for the treatment of CKD-aP in dialysis patients in the U.S. except in the dialysis clinics of Fresenius Medical Care North America, or FMCNA, where we and VFMCRP will promote KORSUVA injection under a profit-sharing arrangement.

Upon entry into the VFMCRP Agreement, VFMCRP made a non-refundable, non-creditable $50.0 million upfront payment to us and Vifor purchased 1,174,827 shares of our common stock for $20.0 million, at a premium for the price of $17.024 per share.

After U.S. regulatory approval of KORSUVA injection in August 2021, we were entitled to receive a $15.0 million regulatory milestone payment which was received in October 2021, and was recorded as license and milestone fees revenue for the three and nine months ended September 30, 2021, as the variable consideration was deemed probable upon the regulatory approval in August 2021 (see Notes 10 and 11 of Notes to Condensed Financial Statements, *Collaboration and Licensing Agreements* and *Revenue Recognition*, respectively, in this Quarterly Report on Form 10-Q).

We are eligible to receive from VFMCRP additional regulatory and commercial milestone payments in the aggregate of up to $455.0 million, consisting of up to $15.0 million in regulatory milestones and up to $440.0 million in tiered commercial milestones, all of which are sales-related. We are also eligible to receive tiered double-digit royalty payments based on annual net sales, as defined, of KORSUVA (CR845/difelikefalin) injection in the licensed territories. In the United States, we and VFMCRP will promote KORSUVA (CR845/difelikefalin) injection in the dialysis clinics of FMCNA under a profit-sharing arrangement (subject to the terms and conditions of the VFMCRP Agreement) based on net FMCNA clinic sales recorded by us.

We retain the right to make and have made KORSUVA (CR845/difelikefalin) injection worldwide (excluding the United States, Japan and South Korea), or the Territory, for commercial sale by VFMCRP in or outside the Territory, and for supply of KORSUVA (CR845/difelikefalin) injection to VFMCRP under the terms of a supply agreement, or the VFMCRP Supply Agreement, which was executed in May 2020. The supply price is the Company's cost of goods sold, as calculated under GAAP, plus an agreed upon margin. The VFMCRP Supply Agreement will co-terminate with the VFMCRP Agreement.

Maruishi Pharmaceutical Co., Ltd.

In April 2013, we entered into a license agreement with Maruishi, or the Maruishi Agreement, under which we granted Maruishi an exclusive license to develop, manufacture and commercialize drug products containing CR845/difelikefalin in Japan in the acute pain and uremic pruritus fields. Maruishi has a right of first negotiation for any other indications for which we develop CR845/difelikefalin and, under certain conditions, Maruishi may substitute another pruritus indication for the uremic pruritus indication originally included in its license from us. If we abandon development of CR845/difelikefalin and begin development of another kappa opioid receptor agonist that is covered by the claims of the patents we licensed to Maruishi, such other agonist will automatically be included in the license to Maruishi. Maruishi is required to use commercially reasonable efforts, at its expense, to develop, obtain regulatory approval for and commercialize CR845/difelikefalin in Japan. We are required to use commercially reasonable efforts, at our expense, to develop, obtain regulatory approval for and commercialize CR845/difelikefalin in the United States.

Under the terms of the Maruishi Agreement, we received a non-refundable and non-creditable upfront license fee of $15.0 million and are eligible to receive up to an aggregate of $10.5 million in clinical development and regulatory milestones (before contractual foreign currency exchange adjustments). In January 2021, we met the milestone criteria, as set forth in the Maruishi Agreement, for Maruishi's first initiation of a Phase 3 trial for uremic pruritus in Japan. As a result, we received the $2.0 million milestone payment ($1.9 million after contractual foreign currency exchange adjustments) in May 2021. As of September 30, 2021, we have received $4.5 million (before contractual foreign currency exchange adjustments) of clinical development and regulatory milestones from Maruishi. We are also eligible to receive a one-time sales milestone of one billion Yen when a certain sales level is attained. We also receive a mid-double-digit percentage of all non-royalty payments received by Maruishi from its sublicensees, if any. We are also eligible to receive tiered royalties based on net sales, if any, with minimum royalty rates in the low double digits and maximum royalty rates in the low twenties. Maruishi's obligation to pay us royalties continues, on a product-by-product basis, until the expiration of the last-to-expire licensed patent covering such product or the later expiration of any market exclusivity period. The Maruishi Agreement continues until terminated.

Chong Kun Dang Pharmaceutical Corporation

In April 2012, we entered into a license agreement with CKDP, or the CKDP Agreement, under which we granted CKDP an exclusive license to develop, manufacture and commercialize drug products containing CR845/difelikefalin in South Korea. CKDP is required to use commercially reasonable efforts, at its expense, to develop, obtain regulatory approval for and commercialize CR845/difelikefalin in South Korea. We are required to use commercially reasonable efforts, at our expense, to develop, obtain regulatory approval for and commercialize CR845/difelikefalin in the United States.

Under the terms of the CKDP Agreement, we received a non-refundable and non-creditable $0.6 million upfront payment and are eligible to receive up to an aggregate of $3.8 million in development and regulatory milestones (before South Korean withholding taxes). As of September 30, 2021, we have received $2.3 million (before South Korean withholding tax) of development and regulatory milestones. We are also eligible to receive a mid-double-digit percentage of all non-royalty payments received by CKDP from its sublicensees, if any, and tiered royalties ranging from the high single digits to the high teens based on net sales, if any. CKDP's obligation to pay us royalties continues, on a product-by-product basis, until the expiration of the last-to-expire licensed patent covering such product or the later expiration of any market exclusivity period. The CKDP Agreement continues until CKDP no longer has any obligation to pay us royalties on any product.

Manufacturing and License Agreements

Polypeptide Laboratories S.A. (PPL)

In July 2021, we entered into an API Commercial Supply Agreement with PPL that defines each party's responsibilities with respect to PPL's manufacture and supply of API for the CR845/difelikefalin injection product candidate. Under the API Commercial Supply Agreement, PPL shall manufacture API at its facility for sale and supply

to us, in the amounts as set forth in purchase orders to be provided by us. We will be required to purchase our requirements of API for each year of the term of the agreement, based on internal forecasts.

The API Commercial Supply Agreement will continue until the fifth anniversary of the approval by the FDA of the new drug application for KORSUVA injection, unless the API Commercial Supply Agreement is earlier terminated, and will automatically be extended for successive five-year periods unless either party gives notice to the other party of its intention to terminate.

Enteris Biopharma, Inc.

In August 2019, we entered into a license agreement with Enteris, or the Enteris License Agreement. Pursuant to the Enteris License Agreement, Enteris granted to us a non-exclusive, royalty-bearing license, including the right to grant sublicenses, under certain proprietary technology and patent rights related to or covering formulations for oral delivery of peptide active pharmaceutical ingredients with functional excipients to enhance permeability and/or solubility, known as Enteris's Peptelligence® technology, to develop, manufacture and commercialize products using such technology worldwide, excluding Japan and South Korea.

As consideration for the licensed rights under the Enteris License Agreement, we paid an upfront fee equal to $8.0 million, consisting of $4.0 million in cash and $4.0 million in shares of our common stock.

We are also obligated, pursuant to the Enteris License Agreement, to pay Enteris (1) milestone payments upon the achievement of certain development, regulatory and commercial milestones and (2) low-single digit royalty percentages on net sales of licensed products, subject to reductions in specified circumstances. Until the second anniversary of the entry into the Enteris License Agreement, we have the right, but not the obligation, to terminate our obligation to pay any royalties under the Enteris License Agreement in exchange for a lump sum payment in cash, or the Royalty Buyout. We did not exercise our Royalty Buyout right and such right expired in August 2021. In June 2021, we paid a $10.0 million milestone payment to Enteris based on a successful End of Phase 2 Meeting with the FDA in April 2021, which was recorded in R&D expense for the nine months ended September 30, 2021. In October 2020, we paid $2.5 million to Enteris for a milestone earned, which was recorded in R&D expense for the three and nine months ended September 30, 2020.

The Enteris License Agreement will expire on a country-by-country, licensed product-by-licensed product basis upon the later of (1) the expiration (or invalidation) of all valid claims in licensed patent rights that cover such product in such country, (2) the end of the calendar quarter in which generic competition (as defined in the Enteris License Agreement) occurs for such product in such country and (3) ten years from the first commercial sale of such product.

Patheon UK Limited

In July 2019, we entered into an MSA with Patheon. The MSA governs the general terms under which Patheon, or one of its affiliates, will provide non-exclusive manufacturing services to us for the drug products specified by us from time to time. Pursuant to the MSA, we have agreed to order from Patheon at least a certain percentage of our commercial requirements for a product under a related Product Agreement. Each Product Agreement that we may enter into from time to time will be governed by the terms of the MSA, unless expressly modified in such Product Agreement.

The MSA has an initial term ending December 31, 2023, and will automatically renew after the initial term for successive terms of two years each if there is a Product Agreement in effect, unless either party gives notice of its intention to terminate the MSA at least 18 months prior to the end of the then current term.

Also in July 2019, we entered into two related Product Agreements under the MSA, one with each of Patheon and Patheon Manufacturing Services LLC, or Patheon Greenville, to govern the terms and conditions of the manufacture of commercial supplies of CR845/difelikefalin injection, our lead product candidate. Pursuant to the Product Agreements, Patheon and Patheon Greenville will manufacture commercial supplies of CR845/difelikefalin injection at the Monza, Italy and Greenville, North Carolina manufacturing sites, respectively, from active pharmaceutical ingredient supplied by us. Patheon and Patheon Greenville will be responsible for supplying the other required raw materials and packaging

components, and will also provide supportive manufacturing services such as quality control testing for raw materials, packaging components and finished product.

Components of Operating Results

Revenue

To date, we have not generated any revenue from product sales. Substantially all of our revenue recognized to date has consisted of upfront and milestone payments under license agreements with Vifor, VFMCRP, Maruishi and CKDP, some or of all of which was deferred upon receipt, and sub-license payments under our license agreement with Maruishi for CR845/difelikefalin, as well as license agreements for CR665, our first-generation drug program for which development efforts have ceased and clinical compound sales from certain license agreements. Through September 30, 2021, we have earned a total of $73.8 million in clinical development or regulatory milestone payments (including the $50.0 million equity investment from Vifor and $15.0 million milestone payment from VFMCRP for the U.S. regulatory approval of KORSUVA injection in August 2021) and clinical compound sales from certain license agreements. Of the $50.0 million equity milestone, $5.0 million, representing the premium of the purchase price over the market price of our common stock, was recognized as revenue. We have not yet received any royalties under any of our collaborations.

Based on the timing of CMS review, we expect commercial launch of KORSUVA injection and associated revenues in the first half of 2022.

Research and Development (R&D)

Our R&D expenses relate primarily to the development of CR845/difelikefalin. R&D expenses consist of expenses incurred in performing R&D activities, including compensation and benefits for full-time R&D employees, clinical trial and related clinical manufacturing expenses, third-party formulation expenses or milestone payments, fees paid to CROs and other consultants, stock-based compensation for R&D employees and consultants and other outside expenses. Our R&D expenses also included expenses related to preclinical activities for our earlier stage programs in prior periods and may include such expenses in the future.

R&D costs are expensed as incurred. Non-refundable advance payments for goods or services to be received in the future for use in R&D activities are deferred and capitalized. The capitalized amounts are expensed as the related goods are delivered or the services are performed. Most of our R&D costs have been external costs, which we track on a program-by program basis. Our internal R&D costs are primarily compensation expenses for our full-time R&D employees. We do not track internal R&D costs on a program-by-program basis.

R&D activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. Based on our current development plans, we presently expect that our R&D expenses for 2021 will be lower than 2020. However, it is difficult to determine with certainty the duration and completion costs of our current or future nonclinical programs and clinical trials of our product candidates, or if, when or to what extent we will generate revenues from the commercialization and sale of any of our product candidates that obtain regulatory approval. We may never succeed in achieving regulatory approval for any of our product candidates.

The duration, costs and timing of clinical trials and development of our product candidates will depend on a variety of factors including, but not limited to:

- per patient trial costs;
- the number of patients that participate in the trials;
- the number of sites included in the trials;

- the countries in which the trial is conducted;
- the length of time required to enroll eligible patients;
- the number of doses that patients receive;
- the drop-out or discontinuation rates of patients;
- potential additional safety monitoring or other studies requested by regulatory agencies;
- the duration of patient follow-up; and
- the efficacy and safety profile of the product candidate.

In addition, the probability of success for each product candidate will depend on numerous factors, including competition, manufacturing capability and commercial viability. We will determine which programs to pursue and how much to fund each program in response to the scientific and clinical success of each product candidate, as well as an assessment of each product candidate's commercial potential.

General and Administrative

General and administrative expenses consist primarily of salaries and other related costs, including stock-based compensation, for personnel in executive, finance, accounting, legal, business development, information technology, or IT, and human resources functions. Other costs include facility costs not otherwise included in R&D expenses, legal fees, insurance costs, investor relations costs, patent costs and fees for accounting and consulting services.

We anticipate that our general and administrative expenses for 2021 will be consistent with 2020 to support our continued R&D activities and for our product candidates. These expenses will likely include costs related to the hiring of additional personnel, fees to outside consultants, lawyers, accountants and investor relations firms. In addition, if Oral CR845/difelikefalin or any future product candidate obtains regulatory approval for marketing, we expect to incur expenses associated with building a sales and marketing team.

Other Income, Net

Other income, net consists of interest and dividend income earned on our cash, cash equivalents, marketable securities and restricted cash, realized gains and losses on the sale of marketable securities and property and equipment, as well as accretion of discounts/amortization of premiums on purchases of marketable securities. In the event we record a credit loss expense on our available-for-sale debt securities, those expenses would be offset against other income.

Benefit from Income Taxes

The benefit from income taxes relates to state R&D tax credits exchanged for cash pursuant to the Connecticut R&D Tax Credit Exchange Program, which permits qualified small businesses engaged in R&D activities within Connecticut to exchange their unused R&D tax credits for a cash amount equal to 65% of the value of the exchanged credits. Because our revenue in 2020 exceeded $70.0 million, we are not eligible to exchange our 2021 R&D tax credit for cash, therefore there was no benefit from income taxes for the three and nine months ended September 30, 2021.

Results of Operations

Comparison of the Three and Nine Months Ended September 30, 2021 and 2020

Revenue

	Three Months Ended September 30,			Nine Months Ended September 30,		
	2021	2020	% change	2021	2020	% change
	Dollar amounts in thousands			Dollar amounts in thousands		
License and milestone fees	$ 20,031	$ 9,257	116%	$ 21,223	$ 22,377	-5%
Collaborative revenue	—	—	N/A	706	—	N/A
Clinical compound revenue	241	9	2523%	278	616	-55%
Total revenue	$ 20,272	$ 9,266	119%	$ 22,207	$ 22,993	-3%

License and milestone fees revenue

License and milestone fees revenue of $20.0 million for the three months ended September 30, 2021 was related to the milestone payments we earned from Vifor and VFMCRP that was allocated to the license fee performance obligation under the Vifor and VFMCRP agreements, as the variable consideration was deemed probable upon the regulatory approval in August 2021. This included $5.0 million of the $50.0 million equity milestone investment under the agreement with Vifor. License and milestone fees revenue of $9.3 million for the three months ended September 30, 2020 was related to license fees earned by us in connection with the VFMCRP Agreement (see Notes 10 and 11 of Notes to Condensed Financial Statements, *Collaboration and Licensing Agreements* and *Revenue Recognition*, respectively, in this Quarterly Report on Form 10-Q).

License and milestone fees revenue of $21.2 million for the nine months ended September 30, 2021 was related to milestone payments of $20.0 million we earned from Vifor and VFMCRP that was allocated to the license fee performance obligation under the Vifor and VFMCRP agreements, as the variable consideration was deemed probable upon the regulatory approval in August 2021, and a milestone payment of $1.2 million that we earned in January 2021 from Maruishi's first initiation of a Phase 3 trial for uremic pruritus in Japan that was allocated to the license fee performance obligation under the Maruishi Agreement. License and milestone fees revenue of $22.4 million for the nine months ended September 30, 2020 was related to license fees of $21.8 million earned by us in connection with the VFMCRP Agreement, as well as $0.6 million (net of South Korean withholding taxes) earned by us for achieving a development milestone under the CKDP Agreement (see Notes 10 and 11 of Notes to Condensed Financial Statements, *Collaboration and Licensing Agreements* and *Revenue Recognition*, respectively, in this Quarterly Report on Form 10-Q).

Collaborative Revenue

Collaborative revenue of $0.7 million for the nine months ended September 30, 2021 was related to the milestone payment we earned in January 2021 from Maruishi's first initiation of a Phase 3 trial for uremic pruritus in Japan that was allocated to the R&D services performance obligation under the Maruishi Agreement. There were no collaborative revenues for the three months ended September 30, 2021, and for the three and nine months ended September 30, 2020 (see Notes 10 and 11 of Notes to Condensed Financial Statements, *Collaboration and Licensing Agreements* and *Revenue Recognition*, respectively, in this Quarterly Report on Form 10-Q).

Clinical compound revenue

Clinical compound revenue of $241,000 for the three months ended September 30, 2021 was related to the sale of clinical compound to VFMCRP. Clinical compound revenue for the three months ended September 30, 2020 was not material.

Clinical compound revenue of $278,000 for the nine months ended September 30, 2021 was related to the sale of clinical compound to VFMCRP for $241,000 and to Maruishi for $37,000. Clinical compound revenue of $616,000 for the nine months ended September 30, 2020 was related to the sales of clinical compound to VFMCRP for $88,000 and to Maruishi for $528,000.

Research and Development Expense

	Three Months Ended September 30,			Nine Months Ended September 30,		
	2021	2020	% change	2021	2020	% change
	Dollar amounts in thousands			Dollar amounts in thousands		
Direct clinical trial costs	$ 6,264	$ 10,976	-43%	$ 22,983	$ 53,777	-57%
Consultant services in support of clinical trials	1,296	1,385	-6%	3,526	4,058	-13%
Stock-based compensation	2,262	1,768	28%	6,322	6,195	2%
Depreciation and amortization	31	27	12%	93	82	14%
Other R&D operating expenses	5,661	6,911	-18%	26,946	16,599	62%
Total R&D expense	$ 15,514	$ 21,067	-26%	$ 59,870	$ 80,711	-26%

For the three months ended September 30, 2021 compared to the three months ended September 30, 2020, the net decrease in direct clinical trial costs and related consultant costs primarily resulted from decreases totaling $4.3 million, mainly from activities related to the KALM-2 Phase 3 efficacy trial of KORSUVA injection in CKD patients undergoing hemodialysis, the KALM-1 Phase 3 efficacy trial and the 52-week open-label extension study of KORSUVA injection in CKD patients undergoing hemodialysis, the Phase 2 efficacy trial for pruritus associated with AD-aP, and costs associated with preparing for our NDA submission. There was also a decrease of $1.9 million in clinical and commercial drug manufacturing costs. These decreases were partially offset by an increase of 1.3 million, mainly from the Phase 2 efficacy and safety trial for pruritus associated with NP, and other general costs. The increase in stock-based compensation expense was primarily related to additional stock option and time-based restricted stock unit grants to new and existing employees, as well as the vesting of performance-based restricted stock units, for which performance conditions were achieved during the three months ended September 30, 2021, as compared to the three months ended September 30, 2020. The decrease in other R&D operating expenses primarily resulted from a $2.5 million milestone earned by Enteris during the three months ended September 30, 2020, partially offset by increases in payroll and related costs and cost of compound sales.

For the nine months ended September 30, 2021 compared to the nine months ended September 30, 2020, the net decrease in direct clinical trial costs and related consultant costs primarily resulted from decreases totaling $37.9 million, mainly from activities related to the KALM-2 Phase 3 efficacy trial of KORSUVA injection in CKD patients undergoing hemodialysis, the Phase 3 (up to 12 weeks) safety trial of KORSUVA injection in CKD patients undergoing hemodialysis, the KALM-1 Phase 3 efficacy trial and the 52-week open-label extension study of KORSUVA injection in CKD patients undergoing hemodialysis, the Phase 2 efficacy trial for pruritus associated with AD-aP, the Phase 2 efficacy trial of Oral CR845 in CKD-aP patients, costs associated with supportive Phase 1 studies, and costs associated with preparing for our NDA submission. These decreases were partially offset by an increase of $6.2 million, mainly from the Phase 2 efficacy and safety trial for pruritus associated with NP, start-up costs related to Oral CKD Phase 3 programs in non-hemodialysis patients, and other general costs. There was also an increase of $0.4 million in clinical and commercial drug manufacturing costs. The increase in stock-based compensation expense was primarily related to additional stock option and time-based restricted stock unit grants to new and existing employees, partially offset by lower stock-based compensation expense associated with the vesting of performance-based restricted stock units during the nine months ended September 30, 2021, as compared to the comparable period in 2020. The increase in other R&D operating expenses primarily resulted from a $10.0 million milestone earned by Enteris during the nine months ended September 30, 2021 as compared to $2.5 million during the nine months ended September 30, 2020, and increases in payroll and related costs, partially offset by a decrease in cost of compound sales.

The following table summarizes our R&D expenses by programs for the three and nine months ended September 30, 2021 and 2020:

	Three Months Ended September 30,			Nine Months Ended September 30,		
	2021	2020	% change	2021	2020	% change
	Dollar amounts in thousands			Dollar amounts in thousands		
External research and development expenses:						
I.V. CR845 - Pruritus	$ 1,296	$ 5,046	-74%	$ 6,672	$ 36,197	-82%
I.V. CR845 - Pain	1	22	-95%	13	78	-84%
Oral CR845 - Pruritus	6,217	7,127	-13%	19,671	21,322	-8%
Oral CR845 - Pain	—	1	-100%	5	16	-70%
Internal research and development expenses/milestone payments[1]	8,000	8,871	-10%	33,509	23,098	45%
Total research and development expenses	$ 15,514	$ 21,067	-26%	$ 59,870	$ 80,711	-26%

[1] Includes a $10.0 million milestone payment to Enteris for the nine months ended September 30, 2021, as well as $2.5 million related to an Enteris milestone incurred during the three and nine months ended September 30, 2020.

General and Administrative Expenses

	Three Months Ended September 30,			Nine Months Ended September 30,		
	2021	2020	% change	2021	2020	% change
	Dollar amounts in thousands			Dollar amounts in thousands		
Professional fees and public/investor relations	$ 1,042	$ 569	83%	$ 3,277	$ 3,006	9%
Stock-based compensation	2,131	1,536	39%	5,679	4,575	24%
Depreciation and amortization	31	24	28%	93	66	42%
Other G&A operating expenses	2,678	3,090	-13%	8,849	7,540	17%
Total G&A expense	$ 5,882	$ 5,219	13%	$ 17,898	$ 15,187	18%

For the three months ended September 30, 2021 compared to the three months ended September 30, 2020, the increase in professional fees and public/investor relations expenses was primarily the result of an increase in consultants' costs and legal fees. The increase in stock-based compensation expense was primarily related to the vesting of performance-based restricted stock units, for which performance conditions were achieved during the three months ended September 30, 2021, as compared to the three months ended September 30, 2020. The decrease in other G&A operating expenses was primarily the result of decreases in commercial costs, partially offset by increases in insurance costs.

For the nine months ended September 30, 2021 compared to the nine months ended September 30, 2020, the increase in professional fees and public/investor relations expenses was primarily the result of an increase in legal fees, partially offset by a decrease in consultants' costs. The increase in stock-based compensation expense was primarily related to higher stock-based compensation expense associated with the vesting of performance-based restricted stock units during the nine months ended September 30, 2021, as compared to the comparable period in 2020. The increase in other G&A operating expenses was primarily the result of increases in payroll and related costs, insurance costs, and IT related costs.

Other Income, Net

	Three Months Ended September 30,			Nine Months Ended September 30,		
	2021	2020	% change	2021	2020	% change
	Dollar amounts in thousands			Dollar amounts in thousands		
Other income, net	$ 111	$ 379	-71%	$ 502	$ 1,970	-75%

For the three months ended September 30, 2021 compared to the three months ended September 30, 2020, the decrease in other income, net was primarily due to a decrease in interest income and an increase in net amortization expense of available-for-sale marketable securities resulting from a lower yield on our portfolio of investments in the 2021 period.

For the nine months ended September 30, 2021 compared to the nine months ended September 30, 2020, the decrease in other income, net was primarily due to a decrease in interest income and an increase in net amortization expense of available-for-sale marketable securities resulting from a lower yield on our portfolio of investments in the 2021 period.

Benefit from Income Taxes

For the three months ended September 30, 2021 and 2020, pre-tax losses were $1.0 million and $16.6 million, respectively, and we recognized a benefit from income taxes of $132,000 for the three months ended September 30, 2020.

For the nine months ended September 30, 2021 and 2020, pre-tax losses were $55.1 million and $70.9 million, respectively, and we recognized a benefit from income taxes of $436,000 for the nine months ended September 30, 2020.

Because our revenue in 2020 exceeded $70.0 million, we are not eligible to exchange our 2021 R&D tax credit for cash, therefore there was no benefit from income taxes for the three and nine months ended September 30, 2021.

The benefit from income taxes relates to state R&D tax credits exchanged for cash pursuant to the Connecticut R&D Tax Credit Exchange Program, as discussed above. We recognized a full valuation allowance against deferred tax assets at September 30, 2021 and December 31, 2020.

Liquidity and Capital Resources

Sources of Liquidity

Since our inception to date, we have raised an aggregate of approximately $841.7 million to fund our operations, including (1) net proceeds of $446.3 million from the sale of shares of our common stock in five public offerings, including our initial public offering; (2) proceeds of $73.3 million from the sale of shares of our convertible preferred stock and from debt financings prior to our initial public offering; (3) payments of approximately $224.1 million under our license agreements, primarily with Vifor, VFMCRP, Maruishi, CKDP and an earlier product candidate for which development efforts ceased in 2007; and (4) net proceeds of $98.0 million from the purchase of our common stock in relation to the license agreements with Vifor and VFMCRP (see Note 10 of Notes to Condensed Financial Statements, *Collaboration and Licensing Agreements*, in this Quarterly Report on Form 10-Q).

In order to fund our future operations, including our planned clinical trials, we filed the Shelf Registration Statement (File No. 333-230333), which provides for aggregate offerings of up to $300.0 million of common stock, preferred stock, debt securities, warrants or any combination thereof and was declared effective on April 4, 2019. The securities registered under the Shelf Registration Statement include unsold securities that had been registered under our previous Registration Statement on Form S-3 (File No. 333-216657) that was declared effective on March 24, 2017. To date, we have offered and sold an aggregate of approximately $145.5 million of securities under this Shelf Registration Statement. We believe that our Shelf Registration Statement provides us with the flexibility to raise additional capital to finance our operations as needed.

We may offer additional securities under our Shelf Registration Statement from time to time in response to market conditions or other circumstances if we believe such a plan of financing is in the best interests of our stockholders.

As of September 30, 2021, we had $193.4 million in unrestricted cash and cash equivalents and available-for-sale marketable securities. We believe our current unrestricted cash and cash equivalents and available-for-sale marketable securities, including the milestone payments totaling $65.0 million received from Vifor and VFMCRP in October 2021, will be sufficient to fund our currently anticipated operating expenses and capital expenditures through 2023, without giving effect to any additional potential milestone payments or potential product revenue we may receive under our licensing and collaboration agreements with Vifor, VFMCRP, Maruishi and CKDP. Our anticipated operating expenses include contractually committed costs as well as non-contractually committed clinical trial costs for trials that may be delayed or not initiated and other non-committed controllable costs.

Under the Vifor Agreement, we are eligible to receive commercial milestone payments in the aggregate of up to $240.0 million upon the achievement of certain sales-based milestones. As of September 30, 2021, we had earned a milestone payment of $50.0 million upon U.S. regulatory approval of KORSUVA injection in August 2021 for the purchase of our common stock under the Vifor Agreement. In October 2021, we received the $50.0 million milestone payment from Vifor in exchange for the issuance to Vifor of 3,282,391 shares.

Under the VFMCRP Agreement, we are eligible to receive additional regulatory and commercial milestone payments in the aggregate of up to $455.0 million, consisting of up to $15.0 million in regulatory milestones and up to $440.0 million in tiered commercial milestones, all of which are sales-related. We are also eligible to receive tiered

double-digit royalty payments based on annual net sales, as defined in the VFMCRP Agreement, of CR845/difelikefalin injection in the Licensed Territories. As of September 30, 2021, we were entitled to a $15.0 million regulatory milestone payment which was received in October 2021 and was recorded as license and milestone fees revenue for the three and nine months ended September 30, 2021, as the variable consideration was deemed probable upon the regulatory approval in August 2021.

Under the Maruishi Agreement, we are also potentially eligible to earn up to an aggregate of $6.0 million in clinical development milestones and $4.5 million in regulatory milestones, before any foreign exchange adjustment, as well as tiered royalties, with percentages ranging from the low double digits to the low twenties, based on net sales of products containing CR845/difelikefalin in Japan, if any, and share in any sub-license fees. In January 2021, we met the milestone criteria, as set forth in the Maruishi Agreement, for Maruishi's first initiation of a Phase 3 trial for uremic pruritus in Japan. As a result, we received the $2.0 million milestone payment ($1.9 million after contractual foreign currency exchange adjustments) in May 2021. As of September 30, 2021, we have received $4.5 million (before contractual foreign currency exchange adjustments) of clinical development and regulatory milestones from Maruishi.

Under the CKDP Agreement, we are potentially eligible to earn up to an aggregate of $2.3 million in clinical development milestones and $1.5 million in regulatory milestones, before South Korean withholding tax, as well as tiered royalties with percentages ranging from the high single digits to the high teens, based on net sales of products containing CR845/difelikefalin in South Korea, if any, and share in any sub-license fees. As of September 30, 2021, we have received $2.3 million (before South Korean withholding tax) of development and regulatory milestones from CKDP.

Additionally, Vifor Pharma Group submitted the payment reimbursement application for TDAPA and HCPCS to CMS in September 2021. Once the TDAPA application is reviewed and approved by CMS, we expect that KORSUVA injection will be available to patients for commercial use in the U.S. Based on the timing of CMS review, we expect commercial launch of KORSUVA injection and associated revenues in the first half of 2022.

Our ability to earn these payments and their timing is dependent upon the outcome of I.V. and Oral CR845/difelikefalin development activities and successful commercialization of KORSUVA injection. However, our receipt of any further such amounts is uncertain at this time and we may never receive any more of these amounts.

Funding Requirements

Our primary uses of capital have been, and we expect will continue to be, compensation and related expenses, third-party clinical R&D services and clinical costs. In the past, we have also previously used capital for laboratory and related supplies.

Since inception, we have incurred significant operating and net losses. Our net losses were $1.0 million and $16.5 million for the three months ended September 30, 2021 and 2020, respectively, and $55.1 million and $70.5 million for the nine months ended September 30, 2021 and 2020, respectively. As of September 30, 2021, we had an accumulated deficit of $447.4 million. Although we generated net income for the year ended December 31, 2020 as a result of a commercial license transaction, we expect to continue to incur significant expenses and operating and net losses in the foreseeable future, as we continue to prepare for the commercialization of KORSUVA (CR845/difelikefalin) and to develop and seek marketing approval for Oral CR845/difelikefalin. Our financial results may fluctuate significantly from quarter to quarter and year to year, depending on the success of our commercialization efforts, timing of our clinical trials, the receipt of additional milestone payments, if any, under our licensing and collaborations with Vifor, VFMCRP, Maruishi and CKDP, the receipt of payments under any future collaborations and/or licensing agreements we may enter into, and our expenditures on other R&D activities.

We anticipate that our expenses will increase as we:

- continue the development of Oral KORSUVA (CR845/difelikefalin) for AD-aP, NDD-CKD, CLD-PBC and NP;

- explore further development of CR845/difelikefalin injection in the post-operative setting;
- seek regulatory approvals for any product candidates that successfully complete clinical trials;
- establish a sales, marketing and distribution infrastructure and scale up external manufacturing capabilities to commercialize any other products for which we may obtain regulatory approval;
- maintain, expand and protect our global intellectual property portfolio;
- hire additional clinical, quality control and scientific personnel; and
- add operational, financial and management information systems and personnel, including personnel to support our drug development and potential future commercialization efforts.

The successful commercialization of KORSUVA injection and the successful development of any of our other product candidates is highly uncertain. As such, at this time, we cannot reasonably estimate or know the nature, timing and costs of the efforts that will be necessary to successfully commercialize KORSUVA injection, complete the development of I.V. CR845/difelikefalin, Oral CR845/difelikefalin or our other current and future programs. We are also unable to predict when, if ever, we will generate any further material net cash inflows from CR845/difelikefalin. This is due to the numerous risks and uncertainties associated with developing medicines, including the uncertainty of:

- successful enrollment in, and completion of clinical trials;
- receipt of marketing approvals from applicable regulatory authorities;
- establishing commercial manufacturing capabilities or making arrangements with third-party manufacturers;
- obtaining and maintaining patent and trade secret protection and regulatory exclusivity for our product candidates;
- launching commercial sales of the products, if and when approved, whether alone or in collaboration with others;
- achieving meaningful penetration in the markets which we seek to serve; and
- obtaining adequate coverage or reimbursement by third parties, such as commercial payers and government healthcare programs, including Medicare and Medicaid.

A change in the outcome of any of these variables with respect to the development of I.V. CR845/difelikefalin, Oral CR845/difelikefalin or any of our future product candidates would significantly change the costs and timing associated with the development of that product candidate. Further, the timing of any of the above may be impacted by the ongoing COVID-19 pandemic, introducing additional uncertainty.

Because we have not begun to commercialize KORSUVA injection to date, and our other product candidates are still in clinical development and the outcome of these efforts is uncertain, we cannot estimate the actual amounts necessary to successfully complete the commercialization of KORSUVA injection and the development and commercialization of our other product candidates or whether, or when, we may achieve profitability. Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity or debt financings and collaboration arrangements, including our existing licensing and collaboration agreements with Vifor, VFMCRP, Maruishi and CKDP.

We will require additional capital beyond our current balances of cash and cash equivalents and available-for-sale marketable securities and anticipated amounts as described above, and this additional capital may not be available when

needed, on reasonable terms, or at all, and our ability to raise additional capital may be adversely impacted by potential worsening global economic conditions and the disruptions to and volatility in the credit and financial markets in the United States and worldwide resulting from the ongoing COVID-19 pandemic and its variants. If we are not able to do so, we could be required to postpone, scale back or eliminate some, or all, of these objectives. To the extent that we raise additional capital through the future sale of equity or convertible debt, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our existing common stockholders. If we raise additional funds through the issuance of debt securities, these securities could contain covenants that would restrict our operations. If we raise additional funds through collaboration arrangements in the future, we may have to relinquish valuable rights to our technologies, future revenue streams or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our drug development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Outlook

Based on timing expectations and projected costs for our current clinical development plans, which include conducting supportive Phase 1 trials, Phase 2 trials, and Phase 3 trials of Oral KORSUVA (CR845/difelikefalin) in patients with pruritus associated with CKD, CLD, AD, and NP, we expect that our existing cash and cash equivalents and available-for-sale marketable securities as of September 30, 2021, including the milestone payments of $65.0 million received from Vifor and VFMCRP in October 2021, will be sufficient for us to fund our currently anticipated operating expenses and capital expenditures through 2023, without giving effect to any additional potential milestone payments or potential product revenue we may receive under our collaboration agreements with Vifor, VFMCRP, Maruishi and CKDP. Our anticipated operating expenses include contractually committed costs as well as non-contractually committed clinical trial costs for trials that may be delayed or not initiated and other non-committed controllable costs. Because the process of testing product candidates in clinical trials is costly and the timing of progress in these trials is uncertain, it is possible that the assumptions upon which we have based this estimate may prove to be wrong, and we could use our capital resources sooner than we presently expect.

Cash Flows

The following is a summary of the net cash flows provided by (used in) our operating, investing and financing activities for the nine months ended September 30, 2021 and 2020:

	Nine Months Ended	
	September 30, 2021	September 30, 2020
	Dollar amounts in thousands	
Net cash used in operating activities	$ (58,842)	$ (87,575)
Net cash provided by investing activities	48,830	143,880
Net cash provided by financing activities	1,320	671
Net (decrease) increase in cash, cash equivalents and restricted cash	$ (8,692)	$ 56,976

Net cash used in operating activities

Net cash used in operating activities for the nine months ended September 30, 2021 consisted primarily of a net loss of $55.1 million and a $17.4 million cash outflow from net changes in operating assets and liabilities, partially offset by a $13.6 million cash inflow from net non-cash charges. The change in operating assets and liabilities primarily consisted of a $19.8 million increase in Other receivables related to the milestone payments due from Vifor and VFMCRP, a cash outflow of $3.1 million from a decrease in accounts payable and accrued expenses, and a cash outflow of $1.2 million relating to operating lease liabilities associated with our lease agreements for our operating facility in Stamford, Connecticut, partially offset by a decrease in prepaid expenses of $5.8 million, primarily related to an decrease in prepaid clinical costs, and a cash inflow of $0.8 million due to a decrease in income tax receivable. Net non-cash charges primarily consisted of stock-based compensation expense of $12.0 million, the amortization expense component of lease

expense of $1.0 million relating to our Stamford operating leases, and the amortization of available-for-sale marketable securities, net of $0.6 million.

Net cash used in operating activities for the nine months ended September 30, 2020 consisted primarily of a net loss of $70.5 million, a $10.4 million cash outflow from net non-cash charges and a $6.7 million cash outflow from net changes in operating assets and liabilities. Net non-cash charges primarily consisted of a decrease of $21.8 million in deferred revenue associated with our VFMCRP Agreement, partially offset by stock-based compensation expense of $10.8 million. The change in operating assets and liabilities primarily consisted of a cash outflow of $4.6 million from a decrease in accounts payable and accrued expenses and a cash outflow of $1.4 million from an increase in prepaid expenses, primarily related to an increase in prepaid clinical costs.

Net cash provided by investing activities

Net cash provided by investing activities was $48.8 million for the nine months ended September 30, 2021, which primarily included cash inflows of $147.7 million from maturities and redemptions of available-for-sale marketable securities and proceeds of $10.0 million from the sales of available-for-sale marketable securities, partially offset by cash outflows of $109.0 million for the purchases of available-for-sale marketable securities.

Net cash provided by investing activities was $143.9 million for the nine months ended September 30, 2020, which primarily included cash inflows of $141.9 million from maturities and redemptions of available-for-sale marketable securities and proceeds of $23.1 million from sales of available-for-sale marketable securities, partially offset by cash outflows of $21.0 million for the purchases of available-for-sale marketable securities.

Net cash provided by financing activities

Net cash provided by financing activities for the nine months ended September 30, 2021 and 2020 consisted of proceeds of $1.3 million and $0.7 million, respectively, received from the exercise of stock options.

Contractual Obligations and Commitments

Contractual obligations and commitments as of September 30, 2021 consisted of operating lease obligations in connection with the Stamford operating leases we entered into in December 2015 and amended in June 2020, the Enteris License Agreement we entered into in August 2019, and the MSA we entered into with Patheon in July 2019. Based on our manufacturing service agreement with Patheon, we have a non-cancelable purchase capacity reservation of approximately $6.5 million through 2022. We expect the majority of this capacity reservation will be reimbursed upon the execution of the supply agreement with Vifor. We have no other material non-cancelable purchase commitments with any other contract manufacturers or service providers, as we have generally contracted on a cancelable purchase order basis. Furthermore, milestone payments potentially owed by us in connection with the Enteris License Agreement relate to milestone events that may or may not be achieved.

See Note 15, *Commitments and Contingencies* of our Condensed Financial Statements in this Quarterly Report on Form 10-Q for details about our contractual obligations and commitments, and Note 6, *Restricted Cash* of our Condensed Financial Statements in this Quarterly Report on Form 10-Q for details about our letter of credit associated with our Stamford operating leases.

Recent Accounting Pronouncements

Please refer to Note 2 of Notes to Condensed Financial Statements, *Basis of Presentation*, in this Quarterly Report on Form 10-Q.

Off-Balance Sheet Arrangements

We did not have, during the periods presented in our condensed financial statements included in this report, and we do not currently have, any off-balance sheet arrangements, as defined under SEC rules.

Discussion of Critical Accounting Policies

Our management's discussion and analysis of financial condition and results of operations is based upon our condensed financial statements, which have been prepared in accordance with GAAP. The preparation of these condensed financial statements requires us to make estimates, judgments and assumptions that affect the reported amounts of assets and liabilities and disclosures of contingent assets and liabilities as of the date of the condensed balance sheets and the reported amounts of revenues and expenses during the reporting periods. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances at the time such estimates are made. Actual results and outcomes may differ materially from our estimates, judgments, and assumptions. We periodically review our estimates in light of changes in circumstances, facts, and experience. The effects of material revisions in estimates are reflected in the condensed financial statements prospectively from the date of the change in estimate.

We define our critical accounting policies as those accounting principles generally accepted in the United States that require us to make subjective estimates and judgments about matters that are uncertain and are likely to have a material impact on our financial condition and results of operations as well as the specific manner in which we apply those principles.

During the three and nine months ended September 30, 2021, there were no significant changes to our critical accounting policies from those described in our Annual Report on Form 10-K for the year ended December 31, 2020.

Item 3. ***Quantitative and Qualitative Disclosures About Market Risk.***

Interest Rate Risk

As of September 30, 2021, we invested a majority of our cash reserves in a variety of available-for-sale marketable securities, including investment-grade debt instruments, principally corporate bonds, commercial paper, municipal bonds and direct obligations of the U.S. government and U.S. government-sponsored entities, and in cash equivalents. See Note 3 of Notes to Condensed Financial Statements, *Available-for-Sale Marketable Securities*, in this Quarterly Report on Form 10-Q for details about our available-for-sale marketable securities.

As of September 30, 2021, we had invested $170.4 million of our cash reserves in such marketable securities. Those marketable securities included $170.4 million of investment grade debt instruments with a yield of approximately 0.27% and maturities through September 2024. As of December 31, 2020, we had invested $219.8 million of our cash reserves in such marketable securities. Those marketable securities included $219.8 million of investment grade debt instruments with a yield of approximately 0.32% and maturities through December 2023.

We maintain an investment portfolio in accordance with our investment policy, which includes guidelines on acceptable investment securities, minimum credit quality, maturity parameters, and concentration and diversification. The primary objectives of our investment policy are to preserve principal, maintain proper liquidity and to meet operating needs. Our investments are subject to interest rate risk and will decrease in value if market interest rates increase. However, due to the conservative nature of our investments and relatively short duration, we do not believe we are materially exposed to changes in interest rates related to our investments. As a result, we do not currently use interest rate derivative instruments to manage exposure to interest rate changes.

Duration is a sensitivity measure that can be used to approximate the change in the fair value of a security that will result from a change in interest rates. Applying the duration model, a hypothetical 100 basis point, or 1%, increase in interest rates as of September 30, 2021 and December 31, 2020, would have resulted in immaterial decreases in the fair values of our portfolio of marketable securities at those dates.

Credit Quality Risk

Although our investments are subject to credit risk, our investment policy specifies credit quality standards for our investments and limits the amount of credit exposure from any single issue, issuer or type of investment. Nonetheless,

deterioration of the credit quality of an investment security subsequent to purchase may subject us to the risk of not being able to recover the full principal value of the security. For the three and nine months ended September 30, 2021 and 2020, we did not record any charges to credit loss expense for our available-for-sale securities. (Refer to Note 3 of Notes to Condensed Financial Statements, *Available-for-Sale Marketable Securities*, in this Quarterly Report on Form 10-Q.

As of September 30, 2021, we had $20.0 million included in Other receivables and $45.0 million included in Stock subscription receivable within equity in our Condensed Balance Sheet relating to milestone payments we earned from Vifor and VFMCRP during the three months ended September 30, 2021. In October 2021, we received full payment of $65.0 million for both milestone payments from Vifor and VFMCRP. As of December 31, 2020, we did not have material balances of receivables on our Condensed Balance Sheet.

Item 4. ***Controls and Procedures*****.**

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer, has evaluated the effectiveness of our disclosure controls and procedures (as such term is defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act) as of September 30, 2021. Based on such evaluation, our Chief Executive Officer and Chief Financial Officer have concluded that, as of September 30, 2021, our disclosure controls and procedures were effective to provide reasonable assurance that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is (1) recorded, processed, summarized, and reported within the time periods specified in the rules and forms of the SEC, and (2) accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate to allow timely decisions regarding required disclosures.

Changes in Internal Control Over Financial Reporting

There were no changes in our internal control over financial reporting that occurred during the quarter ended September 30, 2021 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Limitations on Controls and Procedures

Management, including our Chief Executive Officer and Chief Financial Officer, recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost benefit relationship of possible controls and procedures. Because of the inherent limitations in all control systems, no evaluation of controls and procedures can provide absolute assurance that all control issues and instances of fraud, if any, within Cara Therapeutics, Inc. have been detected.

PART II

OTHER INFORMATION

Item 1. ***Legal Proceedings***

From time to time, we may become subject to arbitration, litigation or claims arising in the ordinary course of business. We are not currently a party to any arbitration or legal proceeding that, if determined adversely to us, would have a material adverse effect on our business, operating results or financial condition. The results of any future claims or proceedings cannot be predicted with certainty, and regardless of the outcome, litigation can have an adverse impact on us because of defense and litigation costs, diversion of management resources, and other factors.

Item 1A. ***Risk Factors.***

In addition to other information contained in this Quarterly Report on Form 10-Q, the following risks should be considered in evaluating our business and future prospects and an investment in our common stock. The risks and uncertainties described below are not the only ones we face. If any of the following risks and uncertainties develops into actual events, our business, financial condition, results of operations and cash flows could be materially adversely affected. In that case, the price of our common stock could decline and you may lose all or part of your investment.

Risk Factors Summary

Investing in our common stock involves a high degree of risk because our business is subject to numerous risks and uncertainties, as fully described below. The principal factors and uncertainties that make investing in our common stock risky include, among others:

- We are substantially dependent on the success of our product and product candidates. If we are unable to successfully complete clinical development, obtain additional regulatory approvals and commercialize our product and product candidates, or experience significant delays in doing so, our business will be materially harmed.

- We rely, and expect to continue to rely, on third parties to conduct our preclinical studies and clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials.

- If the manufacturers upon whom we rely fail to produce our products or product candidates in the volumes that we require on a timely basis, or to comply with stringent regulations applicable to pharmaceutical drug manufacturers, we may face delays in the development and commercialization of, or be unable to meet demand for, our products and may lose potential revenues.

- Even if we obtain additional regulatory approvals for our product candidates, they may never be successfully launched or become profitable, in which case our business, prospects, operating results and financial condition may be materially harmed.

- If we or our collaborators are unable to establish effective marketing and sales capabilities, or if we are unable to enter into or maintain agreements with third parties to market and sell our products and product candidates, if they are approved, we may be unable to generate product revenues.

- We face significant competition from other pharmaceutical and biotechnology companies, academic institutions, government agencies and other research organizations. Our operating results will suffer if we fail to compete effectively.

- To the extent that KORSUVA™ (CR845/difelikefalin) injection, or KORSUVA injection, or our product candidates, if approved, do not achieve broad market acceptance, the revenues that we generate from sales will be limited.

- Our business, operations and clinical development and regulatory timelines and plans have been, and could continue to be, adversely affected by the effects of health epidemics, including the ongoing COVID-19 pandemic.

- The regulatory approval processes of the U.S. Food and Drug Administration, or FDA, and comparable foreign authorities are lengthy, time consuming and inherently unpredictable. If we are not able to obtain, or if there are delays in obtaining, required additional regulatory approvals, we will not be able to commercialize our product candidates as expected, and our ability to generate revenue will be materially impaired.

- For our approved product, KORSUVA injection, we will be subject to ongoing obligations and continued regulatory review, which may result in significant additional expense. Additionally, our product candidates, if approved, could be subject to labeling and other restrictions and market withdrawal and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our products.

- Our products, including KORSUVA injection, may have undesirable side effects that may require them to be taken off the market, require them to include safety warnings or otherwise limit their sales. Further, our product candidates may have serious adverse events or undesirable side effects that may limit dosing in development, delay or prevent regulatory or marketing approval.

- If we experience continuous delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.

- We have incurred significant losses from our inception, and although we generated net income in 2020, we anticipate that we may incur losses in the foreseeable future. Our first commercial product was only recently approved, and we may never maintain profitability.

- We are dependent on third parties to decide to utilize KORSUVA injection and to make it readily available at the point of care throughout their dialysis centers or hospitals.

- We rely on third parties to perform many essential services for KORSUVA injection and may do so in the future for any products that we commercialize, including services related to warehousing and inventory control, distribution, customer service, accounts receivable management, cash collection and adverse event reporting. If these third parties fail to perform as expected or to comply with legal and regulatory requirements, our ability to commercialize KORSUVA injection or any other product candidate, will be significantly impacted and we may be subject to regulatory sanctions.

- We are dependent on our collaboration agreements for certain revenues, and if our commercial partners do not perform their obligations under such agreements, we could lose revenues.

- Any collaboration arrangements that we are a party to or may enter into in the future may not be successful, which could adversely affect our ability to develop and commercialize our product candidates.

- If the government or other third-party payers fail to provide coverage and adequate reimbursement and payment rates for KORSUVA injection or any of our other current or future product candidates, if any, or if providers choose to use therapies that are less expensive, our revenue and prospects for profitability will be limited.

- We may need to license certain intellectual property from third parties, and such licenses may not be available or may not be available on commercially reasonable terms.

Risks Related to Our Business and the Development and Commercialization of Our Product and Product Candidates

We are substantially dependent on the success of our product and product candidates. If we are unable to successfully complete clinical development, obtain additional regulatory approvals and commercialize our product and product candidates, or experience significant delays in doing so, our business will be materially harmed.

Our business depends on the successful development, regulatory approval and commercialization of our product, KORSUVA injection, and product candidates. In August 2021, the FDA approved KORSUVA injection for the treatment of moderate-to-severe CKD-aP in adults undergoing hemodialysis. Our partner, VFMCRP, submitted an MAA to the EMA in March 2021, which was accepted for review by the EMA. If approved, KORSUVA injection would receive marketing authorization in all member states of the EU, as well as in Iceland, Liechtenstein, and Norway. The EMA's decision on the EU MAA is expected in the second quarter of 2022; however, we cannot assure you that the results of our trials will successfully support the additional regulatory applications for approval. Our ability to generate product revenues in the near term is dependent on our and our commercial partners' ability to successfully commercialize KORSUVA injection. We currently generate no revenues from sales of any products, and we may never be able to develop or successfully commercialize a marketable product.

KORSUVA injection in the U.S. will require marketing efforts by our commercial partners before we generate any revenues from product sales. For example, we are in the process of submitting required documents to the U.S. Centers for Medicare & Medicaid Services, or CMS, to ensure timely reimbursement and patient access to KORSUVA injection. Vifor Pharma Group submitted the application for a Healthcare Common Procedure Coding System, or HCPCS, reimbursement code and the payment reimbursement application for a Transitional Drug Add-on Payment Adjustment, or TDAPA, to CMS in September 2021. If we and our commercial partners do not successfully commercialize KORSUVA injection, we will not be able to generate revenue in the United States in the foreseeable future, or at all. Any significant delays in commercializing KORSUVA injection will have a substantial adverse impact on our business and financial condition.

Further, we cannot be certain that Oral KORSUVA (CR845/difelikefalin) or any future product candidates will be successful in clinical trials or receive regulatory approval. Regulatory authorities may interpret our data differently than we have. We are not permitted to market or promote any of our product candidates before we receive regulatory approval from the FDA or comparable foreign regulatory authorities, and we may never receive such regulatory approval for any of our product candidates.

The success of our products and product candidates depends on many factors, including but not limited to:

- successful enrollment in, and completion of, clinical trials, as well as completion of preclinical studies;
- safety and favorable efficacy and acceptable safety data from our clinical trials and other studies;
- receipt of additional regulatory approvals;
- managing our reliance on sole-source third parties such as our third-party suppliers and manufacturers;
- the performance by CROs or other third parties we may retain of their duties to us in a manner that complies with our protocols and applicable laws and that protects the integrity of the resulting data;
- obtaining and maintaining patent, trade secret and other intellectual property protection and regulatory exclusivity;
- ensuring we do not infringe, misappropriate or otherwise violate the valid patent, trade secret or other intellectual property rights of third parties;
- successfully launching our product, such as KORSUVA injection, with our commercial partners, including market acceptance, and our other product candidates, if and when approved;
- obtaining and maintaining favorable reimbursement from third-party payers for products and product candidates;
- competition with other products;
- post-marketing commitments, if any, to regulatory agencies following regulatory approval of our product candidates;
- continued acceptable safety profile following regulatory approval; and
- manufacturing or obtaining sufficient supplies of our products and product candidates that may be necessary for use in clinical trials for evaluation of our product candidates and commercialization of our products.

If we do not achieve and maintain one or more of these factors in a timely manner or at all, we could experience significant delays in our ability to, or be unable to obtain additional regulatory approvals for, and/or to successfully commercialize our products and product candidates, which would materially harm our business and we may not be able to generate sufficient revenues and cash flows to continue our operations.

We rely, and expect to continue to rely, on third parties to conduct our preclinical studies and clinical trials, and those third parties may not perform satisfactorily, including failing to meet deadlines for the completion of such trials.

We rely on third-party CROs to conduct our preclinical and clinical trials for all of our product candidates, and do not plan to independently conduct clinical trials of any other potential product candidates. We expect to continue to rely on third parties, such as CROs, clinical data management organizations, medical institutions and clinical investigators, to conduct our preclinical studies and clinical trials. These agreements might terminate for a variety of reasons, including a failure to perform by the third parties. If we need to enter into alternative arrangements, that would delay our product development activities and adversely affect our business.

Our reliance on these third parties for development activities will reduce our control over these activities. Nevertheless, we are responsible for ensuring that each of our studies is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards and our reliance on the CROs does not relieve us of our regulatory

responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial and for ensuring that our preclinical trials are conducted in accordance with FDA's good laboratory practice, or GLP, as appropriate. Moreover, the FDA and comparable foreign regulatory authorities require us to comply with standards, commonly referred to as good clinical practices, or GCPs, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Regulatory authorities enforce these requirements through periodic inspections of trial sponsors, clinical investigators and trial sites. If we or any of our CROs fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials complies with GCP regulations. In addition, our clinical trials must be conducted with product produced, under current good manufacturing practices, or cGMP, regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. We also are required to register certain clinical trials and post the results of certain completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within specified timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

Our CROs may also have relationships with other entities, some of which may be our competitors. In addition, our CROs are not our employees, and except for remedies available to us under our agreements with such CROs, we cannot control whether or not they devote sufficient time and resources to our on-going clinical, non-clinical and preclinical programs. In addition, the operations of our CROs may be constrained or disrupted by the ongoing COVID-19 pandemic. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our preclinical studies or clinical trials in accordance with regulatory requirements or our stated protocols, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our products and product candidates. As a result, our results of operations and the commercial prospects for our products and product candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed.

If any of our relationships with these third-party CROs terminate, we may not be able to enter into arrangements with alternative CROs or to do so on commercially reasonable terms. Switching or adding additional CROs involves additional cost and requires management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays could occur, which could compromise our ability to meet our desired development timelines. Though we carefully manage our relationships with our CROs, there can be no assurance that we will not encounter similar challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition and prospects.

If the manufacturers upon whom we rely fail to produce our products or product candidates in the volumes that we require on a timely basis, or to comply with stringent regulations applicable to pharmaceutical drug manufacturers, we may face delays in the development and commercialization of, or be unable to meet demand for, our products and may lose potential revenues.

We do not manufacture KORSUVA injection or any of our product candidates, and we do not currently plan to develop any capacity to do so. We currently rely, and expect to continue to rely, on third parties for the manufacture of our products for commercialization and product candidates for preclinical and clinical testing. It is our intention that by the time of additional regulatory approvals for commercialization, we will have negotiated long-term commitments with at least one primary supplier for each manufacturing and distribution function. In July 2019, we entered into a non-exclusive commercial manufacturing agreement with Patheon for KORSUVA (CR845/difelikefalin) injection and in July 2021, we entered into a commercial supply agreement with Polypeptide Laboratories S.A., or PPL, for the KORSUVA (CR845/difelikefalin) injection. Any problems or delays we experience in preparing for commercial-scale manufacturing of a product or product candidate may result in a delay in FDA approval of the product candidate or may impair our ability to manufacture commercial quantities, which would adversely affect our business. For example, our manufacturers will need to produce specific batches of our products and product candidates to demonstrate acceptable

stability under various conditions and for commercially viable lengths of time. We and our contract manufacturers will need to demonstrate to the FDA and other regulatory authorities this acceptable stability data for our products and product candidates, as well as validate methods and manufacturing processes, in order to receive and maintain regulatory approval to commercialize KORSUVA injection or any other product candidates. Furthermore, if our commercial manufacturers fail to deliver the required commercial quantities of bulk drug substance or finished product on a timely basis and at commercially reasonable prices, we would likely be unable to meet demand for our products and we would lose potential revenues.

The manufacture of pharmaceutical products requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of pharmaceutical products often encounter difficulties in production, particularly in scaling up initial production. These problems include difficulties with production costs and yields, quality control, including stability of the products and product candidate and quality assurance testing, shortages of qualified personnel, as well as compliance with strictly enforced federal, state and foreign regulations. Our manufacturers may not perform as agreed. If our manufacturers were to encounter any of these difficulties, our ability to provide products for commercialization and product candidates to patients in our clinical trials would be jeopardized. This could, among other things, lead to increased costs, lost revenue, damage to customer relationships, time and expense spent investigating the cause and, depending on the cause, similar losses with respect to other batches or products. If problems are not discovered before the product is released to the market, recall and product liability costs may also be incurred.

Further, we may rely on proprietary technology developed by our contract manufacturers for purposes of manufacturing certain of our products and product candidates and our failure to negotiate or maintain the long-term use of any such proprietary technology or the inability for our contract manufacturers to produce our products and product candidates or components of our products and product candidates in the volumes that we require on a timely basis, may lead to delays or interruptions in the regulatory approval or commercialization process, as well as increased costs. For example, in August 2019, we entered into the Enteris License Agreement and intend to use Enteris's Peptelligence® technology to develop, manufacture and commercialize Oral KORSUVA (CR845/difelikefalin). If we experience any interruptions in the manufacture, delivery or scale-up of the Enteris formulation technology, we may experience delays in the development and commercialization of Oral KORSUVA (CR845/difelikefalin). Further, if we are unable to maintain our relationship with Enteris, we may be forced to reformulate Oral KORSUVA (CR845/difelikefalin) which could result in significantly delaying commercializing Oral KORSUVA (CR845/difelikefalin) and require us to incur additional costs in connection with such reformulation and potentially needed to seek additional approvals from the FDA. The operations of our third-party manufacturers have been and may in the future be constrained or disrupted and their operating capacity may be reduced by the ongoing COVID-19 pandemic, which could negatively impact our clinical development and commercialization timelines.

In addition, all manufacturers of our products and product candidates must comply with cGMP requirements enforced by the FDA through its facilities inspection program. These requirements include quality control, quality assurance and the maintenance of records and documentation. Manufacturers of our products and product candidates may be unable to comply with these cGMP requirements and with other FDA, state and foreign regulatory requirements. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or other regulatory authorities, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities. In addition, regulatory agencies subject an approved product, its manufacturer and the manufacturer's facilities to continual review and inspections, including periodic unannounced inspections. The subsequent discovery of previously unknown problems with our current or any future approved products, including adverse events of unanticipated severity or frequency, or problems with the facilities where our current or any future approved products are manufactured, may result in restrictions on the marketing of our current or any such future approved products, up to and including withdrawal of the affected product from the market. We have little control over our manufacturers' compliance with these regulations and standards. If the FDA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our products and product candidates or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our products and product candidates, if approved. A failure to comply with these requirements may result in fines and civil penalties, suspension of production, suspension, delay or denial of product approval, product seizure or recall, or withdrawal of product approval.

If the safety of any quantities supplied is compromised due to our manufacturers' failure to adhere to applicable laws or for other reasons, we may not be able to obtain regulatory approval for or successfully commercialize our products and product candidates.

Even if we obtain additional regulatory approvals for our product candidates, they may never be successfully launched or become profitable, in which case our business, prospects, operating results and financial condition may be materially harmed.

In order to successfully launch our products and product candidates and have them become profitable, we anticipate that we will have to dedicate substantial time and resources. Our ability to generate revenues from our commercialized products will depend on a number of factors, including, but not limited to:

- achievement of broad market acceptance and coverage by third-party payers for our products;
- our partners' effectiveness in marketing and selling our products;
- our ability to have manufactured commercial quantities of our products at acceptable cost levels and in compliance with regulatory requirements;
- our ability to maintain a cost-efficient organization and, to the extent we seek to do so, to collaborate successfully with additional third parties;
- our ability to expand and maintain intellectual property protection for our products successfully;
- the efficacy and safety of our products; and/or
- our ability to comply with regulatory requirements, which are subject to change.

Because of the numerous risks and uncertainties associated with our commercialization efforts, we may not be able to achieve profitability. Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. A failure to become and remain profitable would depress the value of our company and could impair our ability to raise capital, expand our business, diversify our product offerings or continue our operations. A decline in the value of our company could also cause you to lose all or part of your investment.

If we or our collaborators are unable to establish effective marketing and sales capabilities, or if we are unable to enter into or maintain agreements with third parties to market and sell our products and product candidates, if they are approved, we may be unable to generate product revenues.

We currently do not have an internal commercial infrastructure for the marketing, sale and distribution of pharmaceutical products. In order to commercialize our product and product candidates (if approved), we must build our marketing, sales and distribution capabilities or make and maintain arrangements with third parties to perform these services. We have no prior experience in the marketing, sale and distribution of pharmaceutical products, and there are significant risks involved in the building and managing of a commercial infrastructure to the extent we choose to do so in the future. The establishment and development of our own sales force and related plans to market any products we may develop will be expensive and time consuming and could delay any product launch, and we may not be able to successfully develop this capability.

In August 2021, the FDA approved KORSUVA injection for the treatment of moderate-to-severe CKD-AP in adults undergoing hemodialysis in the U.S. We have entered into agreements with Vifor and VFMCRP to commercialize KORSUVA injection in the U.S. We are dependent on Vifor and VFMCRP to successfully commercialize KORSUVA injection with their own, or their collaborators', sales force. We have partnered with VFMCRP to commercialize KORSUVA worldwide (if and when approved), excluding Japan (Maruishi/sub-licensee Kissei), and South Korea

(CKDP). Based on the timing of CMS review, we expect commercial launch of KORSUVA injection and associated revenues in the first half of 2022.

We, or our partners or collaborators, will have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train, manage and retain marketing and sales personnel. In the event that we or our partners or our collaborators are unable to develop a marketing and sales infrastructure, we may not be able to commercialize KORSUVA injection or any of our other current or future product candidates, which would limit our ability to generate product revenues. Factors that may inhibit our or our partners' or collaborators' efforts to commercialize KORSUVA injection or our other current or future product candidates include:

- inability to recruit, train, manage and retain adequate numbers of effective sales and marketing personnel;
- inability of sales personnel to obtain access to physicians or educate adequate numbers of physicians on the benefits of prescribing KORSUVA injection or our other current or future product candidates;
- inability to effectively oversee a geographically dispersed sales and marketing team;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

Our or our partners' or our collaborators' sales force and marketing teams may not be successful in commercializing KORSUVA injection or any of our other current or future product candidates.

In the event that we are unable to successfully collaborate with a third-party marketing and sales organization to commercialize any approved product candidates outside the United States, our ability to generate product revenues may be limited. To the extent that we rely on third parties to commercialize products for which we obtain regulatory approval, we may receive less revenues than if we commercialized these products ourselves. In addition, we would have less control over the sales efforts of any other third parties involved in our commercialization efforts.

We face significant competition from other pharmaceutical and biotechnology companies, academic institutions, government agencies and other research organizations. Our operating results will suffer if we fail to compete effectively.

The development and commercialization of new drug products is highly competitive. We face competition with respect to our current products and product candidates and will face competition with respect to any product candidates that we may seek to develop or commercialize in the future, from major pharmaceutical companies, specialty pharmaceutical companies and biotechnology companies worldwide. There are a number of large pharmaceutical and biotechnology companies that currently market and sell products or are pursuing the development of products for the treatment of pain and pruritus. Potential competitors also include academic institutions, government agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for research, development, manufacturing and commercialization.

Among the companies that currently market or are developing therapies that, if approved, our products and product candidates may potentially compete with include: Pfizer, AbbVie, Eli Lilly, Amgen, Regeneron, Leo Pharma, Chugai and others. Additionally, the market for the prevention and treatment of PONV is highly fragmented. There are a number of different agents alone or in combination (particularly in patients with a high risk for PONV) with different mechanism of actions to try to manage PONV. If approved, I.V. CR845/difelikefalin would likely be competing within the overall PONV market, although we expect that it would primarily be utilized as an add-on therapy in patients with a higher risk of PONV. Although most of the PONV products are generically available, there is still a significant segment of high-risk patients where their PONV is not adequately managed, which can increase the hospital length of stay and add significant cost to managing a post-operative patient.

Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than our products or our current or future product candidates. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. In addition, our ability to compete may be affected in many cases by insurers or other third-party payers seeking to encourage the use of generic products. Generic products are currently on the market for our product KORSUVA injection and some of the indications that we are pursuing, and additional products are expected to become available on a generic basis over the coming years. We expect that KORSUVA injection, and our product candidates (if approved), will be priced at a significant premium over competitive generic products.

Many of the companies against which we are competing or against which we may compete in the future have significantly greater financial resources and expertise in R&D, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third parties compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

To the extent that KORSUVA injection or our product candidates, if approved, do not achieve broad market acceptance, the revenues that we generate from sales will be limited.

We have never successfully commercialized a product or product candidate for any indication. KORSUVA injection and our other current or future product candidates, if approved by the appropriate regulatory authorities for marketing and sale, may not gain acceptance among physicians, hospitals, dialysis providers, patients and third-party payers. If KORSUVA injection and any product candidates for which we obtain regulatory approval do not gain an adequate level of market acceptance, we may not generate significant product revenues or become profitable. Market acceptance of KORSUVA injection, Oral KORSUVA (CR845/difelikefalin) and any future product candidate by physicians, hospitals, dialysis providers, patients and third-party payers will depend on a number of factors, some of which are beyond our control. The degree of market acceptance of KORSUVA injection and any of our product candidates will depend on a number of factors, including:

- the prevalence and severity of adverse events associated with such product or product candidate;
- limitations or warnings contained in the product's FDA-approved labeling, including potential limitations or warnings for such product candidate, that may be more restrictive than other pain management or pruritus products;
- changes in the standard of care for the targeted indications for such product candidate, which could reduce the marketing impact of any claims that we could make following additional FDA approval, if obtained;
- the relative convenience and ease of administration of such product or product candidate;
- cost of treatment versus economic and clinical benefit in relation to alternative treatments or therapies;
- the availability of coverage and adequate reimbursement by third-party payers, such as insurance companies and other healthcare payers, and by government healthcare programs, including Medicare and Medicaid;
- the extent and strength of our marketing and distribution of such product or product candidate;
- the safety, efficacy and other potential advantages over, and availability of, alternative treatments already used to treat acute pain, chronic pain and/or pruritus;

- distribution and use restrictions, if any, imposed by the FDA with respect to such product candidate or to which we agree as part of a mandatory risk evaluation and mitigation strategy or voluntary risk management plan;
- the timing of market introduction of such product or product candidate, as well as competitive products;
- our ability to offer such product or product candidate for sale at competitive prices;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies; and
- the clinical indications for such product or product candidate if approved.

Our and our commercial partners' ability to effectively promote and sell KORSUVA injection and our current and future product candidates, if approved, will also depend on pricing and cost effectiveness, including our ability to produce a product at a competitive price and achieve acceptance of the product onto dialysis organization or hospital formularies, and our ability to obtain sufficient third-party coverage or reimbursement. Generally, before we or our commercial partners can attempt to sell a product in a hospital or dialysis provider, it must be approved for addition to that institution's list of drugs approved for use in that institution, or formulary list. In evaluating drugs for inclusion on the formulary list, hospitals and dialysis providers evaluate a variety of factors, including cost. The frequency with which hospitals and dialysis providers add and remove drugs from their formulary lists varies from organization to organization, and institutions often require additional information prior to adding new drugs to their formulary, which may result in substantial delays in our receiving formulary approval for KORSUVA injection. Since most hospitals are members of group purchasing organizations, which leverage the purchasing power of a group of entities to obtain discounts based on the collective buying power of the group, our and our commercial partners' ability to access customers in the hospital marketplace will also depend on our ability to effectively promote KORSUVA injection and our product candidates to group purchasing organizations. We will also need to demonstrate acceptable evidence of safety and efficacy, as well as relative convenience and ease of administration. Market acceptance could be limited depending on the prevalence and severity of any expected or unexpected adverse side effects associated with KORSUVA injection and our product candidates.

In addition, the potential market opportunity for KORSUVA injection and for our product candidates is difficult to precisely estimate. Our internal estimates of the potential market opportunity for our products and product candidates include several key assumptions based on our industry knowledge, industry publications, third-party research reports, assessment of competition, and other surveys. While we believe that our internal assumptions are reasonable, no independent source has verified such assumptions. If any of these assumptions proves to be inaccurate, then the actual market for our products and product candidates could be smaller than our estimates of our potential market opportunity. If the actual market for our products and product candidates is small, and/or smaller than we expect, our product revenue may be limited and it may be more difficult for us to achieve or maintain profitability.

Our and our commercial partners' efforts to educate the medical community and third-party payers on the benefits of KORSUVA injection and our product candidates may require significant resources and may never be successful. Even if the medical community accepts that KORSUVA injection or one of our product candidates is safe and effective for its approved indications, physicians and patients may not immediately be receptive to such product or product candidate and may be slow to adopt it as an accepted treatment of pain or pruritus. It is unlikely that any future labeling approved by the FDA will contain claims that one of our products or product candidates is safer or more effective than competitive products or will permit us to promote such products or product candidate as being superior to competing products. Further, the availability of inexpensive generic forms of products for acute and chronic pain as well as pruritus may also limit acceptance of KORSUVA injection and our product candidates among physicians, patients and third-party payers. If KORSUVA injection and our current and any future product candidate, if approved, does not achieve an adequate level of acceptance among physicians, patients and third-party payers, we may not generate meaningful revenues from KORSUVA injection or our current and future product candidates, and we may not become profitable.

We face potential product liability exposure, and if successful claims are brought against us, we may incur substantial liability for KORSUVA injection or our other current and future product candidates that we may develop and may have to limit their commercialization.

We face an inherent risk of product liability lawsuits related to the sale of our products to, use of our products by, and testing of our product candidates in, seriously ill patients. For example, product liability claims might be brought against us by consumers, healthcare providers or others using, administering or selling our products. We may be sued if any product we develop allegedly causes injury or is found to be otherwise unsuitable during clinical testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, negligence, strict liability or a breach of warranties. If we cannot successfully defend ourselves against these claims, we will incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- loss of revenue from decreased demand for our products and/or product candidates;
- impairment of our business reputation or financial stability;
- costs of related litigation;
- substantial monetary awards to patients or other claimants;
- diversion of management attention and scientific resources from our business operations;
- withdrawal of clinical trial participants and potential termination of clinical trial sites or entire clinical programs;
- the inability to successfully commercialize our products and/or product candidates;
- significant negative media attention;
- initiation of investigations by regulators or increased regulatory scrutiny;
- product recalls, withdrawals or labeling, marketing or promotional restrictions; and
- the inability to commercialize our product candidates.

With respect to KORSUVA injection and any of our other product candidates that are approved for commercial sale, we are, and will be, highly dependent upon physician and patient perceptions of us and the safety and quality of our products. We could be adversely affected if we are subject to negative publicity. We could also be adversely affected if any of our products or any similar products distributed by other companies prove to be, or are asserted to be, harmful to patients. Because of our dependence upon consumer perceptions, any adverse publicity associated with illness or other adverse effects resulting from patients' use or misuse of our products or any similar products distributed by other companies could have a material adverse impact on our financial condition or results of operations.

We have obtained limited product liability insurance coverage for our products and our clinical trials with a $10.0 million annual aggregate coverage limit in the United States and various other coverage limits outside of the United States. However, our insurance coverage may not reimburse us or may not be sufficient to reimburse us for any expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive, and, in the future, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. We intend to expand our insurance coverage to include the sale of commercial products for our product candidates in development, but we may be unable to obtain commercially reasonable product liability insurance for any products approved for marketing, or at all. On occasion, large judgments have been awarded in class action lawsuits based on drugs that had unanticipated side effects. A successful product liability claim or series of claims brought

against us could cause our stock price to fall and, if judgments exceed our insurance coverage, could decrease our cash and adversely affect our business.

Our business, operations and clinical development and regulatory timelines and plans have been, and could continue to be, adversely affected by the effects of health epidemics, including the ongoing COVID-19 pandemic.

Our business, operations and clinical development timelines and plans have been, and could continue to be, adversely affected by health epidemics in regions where we have concentrations of third-party manufacturers, clinical trial sites or other business operations, and could cause significant disruption in the operations of third-party manufacturers or CROs upon whom we rely. In response to the ongoing COVID-19 pandemic, many state, local and foreign governments have put in place, and continue to enforce in full or in part, quarantines, executive orders, shelter-in-place orders and similar government orders and restrictions in order to control the spread of the disease and its variants. Such orders or restrictions, and the perception that such orders or restrictions could occur, have resulted in business closures, work stoppages, slowdowns and delays, work-from-home policies, travel restrictions and cancellation of events, among other effects that have negatively impacted the global economy and could disrupt our business and operations. We have implemented a work-from-home policy for all employees, and we may take further actions that alter our operations as may be required by federal, state or local authorities, or which we determine are in the best interests of our employees. Moreover, our clinical development and regulatory timelines and plans could be affected by the ongoing COVID-19 pandemic. Site initiation and patient enrollment has been, and could in the future be, affected and some patients may not be able to comply with clinical trial protocols and the ability to conduct follow up visits with treated patients may be limited if quarantines impede patient movement or interrupt healthcare services. For example, the COVID-19 pandemic has affected the initiation of certain trial sites and patient enrollment for certain of our clinical trials, including our ongoing Phase 2 clinical trials of Oral KORSUVA (CR845/difelikefalin) for NP and for the treatment of pruritus in patients with hepatic impairment due to PBC. Similarly, our ability to recruit and retain patients and principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID-19 could be adversely impacted. Furthermore, our third-party manufacturers may be shut-down or have difficulty meeting their contractual obligations, which may disrupt commercial and clinical drug supply chain continuity and the commercial launch of KORSUVA injection. In addition, COVID-19 may cause our third-party manufacturers of KORSUVA injection to operate at reduced capacity. While we currently do not expect any significant delays in our clinical development or commercial timelines, the ultimate impact of the evolving COVID-19 pandemic remains difficult to predict.

Further, the spread of COVID-19, which has caused a broad impact globally, may materially affect us economically. While the potential economic impact brought by and the duration of COVID-19 may be difficult to assess or predict, a widespread pandemic could result in significant disruption of global financial markets, reducing our ability to access capital, which could in the future negatively affect our liquidity. In addition, a recession or market correction resulting from the spread of COVID-19 could materially affect our business and the value of our common stock.

The global COVID-19 pandemic continues to rapidly evolve, and we will continue to monitor the COVID-19 situation closely. The ultimate impact of the COVID-19 pandemic or a similar health epidemic is highly uncertain and subject to change. We do not yet know the full extent of the potential impacts on our business, our clinical trials, healthcare systems or the global economy as a whole.

We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Because we have limited financial and managerial resources, we focus on developing product candidates for specific indications that we identify as most likely to succeed, in terms of both its regulatory approval and commercialization. As such, we are currently primarily focused on the development of Oral KORSUVA (CR845/difelikefalin) for AD-aP, NDD-CKD, CLD-PBC and NP and of CR845/difelikefalin injection in the post-operative setting. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that may prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future R&D programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial

potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

Our future growth may depend on our ability to identify and develop products and if we do not successfully identify and develop product candidates or integrate them into our operations, we may have limited growth opportunities.

A component of our business strategy is to continue to develop a pipeline of product candidates by developing products that we believe are a strategic fit with our focus on pain and pruritus therapeutics. However, these business activities may entail numerous operational and financial risks, including:

- difficulty or inability to secure financing to fund development activities for such development;
- disruption of our business and diversion of our management's time and attention;
- higher than expected development costs;
- exposure to unknown liabilities;
- difficulty in managing multiple product development programs; and
- inability to successfully develop new products or clinical failure.

We have limited resources to identify and execute the development of products. Moreover, we may devote resources to potential development that are never completed, or we may fail to realize the anticipated benefits of such efforts. If we do not successfully develop and commercialize product candidates, we may not be able to obtain product revenues in future periods.

The regulatory approval processes of the FDA and comparable foreign authorities are lengthy, time consuming and inherently unpredictable. If we are not able to obtain, or if there are delays in obtaining, required additional regulatory approvals, we will not be able to commercialize our product candidates as expected, and our ability to generate revenue will be materially impaired.

The time required to obtain approval by the FDA and comparable foreign authorities is unpredictable but typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions. In August 2021, the FDA approved KORSUVA injection for the treatment of moderate-to-severe CKD-aP in adults undergoing hemodialysis in the U.S. Our partner, VFMCRP, submitted an MAA to the EMA in March 2021. We have not obtained regulatory approval for our other product candidates and it is possible that none of our existing product candidates, including KORSUVA (CR845/difelikefalin) injection in the EMA and Oral KORSUVA (CR845/difelikefalin), or any product candidates we may seek to develop in the future, will ever obtain regulatory approval.

Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by the EMA, and similar regulatory authorities outside the United States. Failure to obtain marketing approval for a product candidate will prevent us from commercializing that product candidate. We expect to continue to rely on third-party CROs and consultants to assist us in filing and supporting the applications necessary to gain marketing approvals. Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to regulatory authorities for each therapeutic indication to establish the product candidate's safety and

efficacy for that indication. Securing marketing approval also requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the regulatory authorities.

Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. The results of preclinical studies and early clinical trials of our product candidates may not be predictive of the results of later-stage clinical trials. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through preclinical studies and initial clinical trials. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials. Our future clinical trial results may not be successful. We may also experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent our ability to receive marketing approval or commercialize our product candidates, including:

- regulators or institutional review boards may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- we may experience delays in reaching, or fail to reach, agreement on acceptable clinical trial contracts or clinical trial protocols with prospective trial sites;
- clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- we may have to suspend clinical trials, as in the case of the IND clinical hold placed on our adaptive Phase 3 trial of I.V. CR845/difelikefalin for postoperative pain in February 2016, which was subsequently removed in April 2016, or terminate clinical trials of our product candidates for various reasons, including a finding that the participants are being exposed to unacceptable health risks;
- regulators or institutional review boards may require that we or our investigators suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements or a finding that the participants are being exposed to unacceptable health risks;
- changes in marketing approval policies during the development period;
- changes in or the enactment of additional statutes or regulations;
- changes in regulatory review for each submitted product application;
- the cost of clinical trials of our product candidates may be greater than we anticipate;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate; and
- our product candidates may have undesirable side effects or other unexpected characteristics, causing us or our investigators, regulators or institutional review boards to suspend or terminate the trials.

In addition, unfavorable changes in our industry or the global economy, including as a result of the ongoing COVID-19 pandemic, could contribute to some of the events listed above and further impact our ability to progress our clinical trials, submit for marketing approval or commercialize our product candidates, if approved, as planned. Further, if and to the extent, global health concerns prevent the FDA or other regulatory authorities from conducting their regular inspections, reviews, or other regulatory activities, it could significantly impact the ability of the FDA or other regulatory authorities to timely review and process our additional regulatory submissions, which could affect our ability to obtain marketing approval for any of our product candidates, including our MAA to the EMA submitted in March 2021.

Moreover, if we are required to conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, if we are unable to successfully complete clinical trials of our product candidates or other testing, if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we may:

- be delayed in obtaining marketing approval for our product candidates;
- not obtain marketing approval at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings;
- be subject to additional post-marketing testing requirements; or
- have the product removed from the market after obtaining marketing approval.

Furthermore, regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data is insufficient for approval and require additional preclinical, clinical or other studies, including with respect to third-party technology used in any of our product candidates such as the excipient we intend to use for Oral KORSUVA (CR845/difelikefalin). In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a product candidate. Any marketing approval we ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

Finally, even if we were to obtain approval, regulatory authorities may approve any of our product candidates for fewer or more limited indications than we request, may grant approval contingent on the performance of costly post-marketing clinical trials, or may approve a product candidate with a label that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. Any of these scenarios could compromise the commercial prospects for our product candidates to assure safe use of the product candidates, either as a condition of product candidate approval or on the basis of new safety information.

If we experience delays in obtaining approval, if we fail to obtain approval of a product candidate or if the label for a product candidate does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate, the commercial prospects for such product candidate may be harmed and our ability to generate revenues will be materially impaired.

For our approved product, KORSUVA injection, we will be subject to ongoing obligations and continued regulatory review, which may result in significant additional expense. Additionally, our product candidates, if approved, could be subject to labeling and other restrictions and market withdrawal and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our products.

KORSUVA injection and any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data (if any), labeling, packaging, distribution, adverse event reporting,

storage, recordkeeping, export, import, advertising and promotional activities for such product, will be subject to extensive and ongoing requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, registration and listing requirements, continued compliance with cGMP requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping and cGCPs for any clinical trials that we conduct post-approval. Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or to the conditions of approval, including any requirement to implement a Risk Evaluation and Mitigation Strategies, or REMS. If any of our product candidates receives marketing approval, the accompanying label may limit the approved use of our drug, which could limit sales of the product.

The FDA may also impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product. The FDA closely regulates the post-approval marketing and promotion of drugs to ensure drugs are marketed only for the approved indications and in accordance with the provisions of the approved labeling. The FDA imposes stringent restrictions on manufacturers' communications regarding off-label use and if we do not market our products for their approved indications, we may be subject to enforcement action for off-label marketing. Violations of the Federal Food, Drug, and Cosmetic Act relating to the promotion of prescription drugs may lead to investigations alleging violations of federal and state health care fraud and abuse laws, as well as state consumer protection laws.

In addition, later discovery of previously unknown adverse events or other problems with our products, manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may yield various results, including:

- restrictions on the products, manufacturers, manufacturing facilities or manufacturing process;
- imposition of restrictions on operations, including costly new manufacturing requirements;
- restrictions on the labeling or marketing of a product;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products and publicity requirements;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing or regulatory approvals;
- refusal to permit the import or export of our products;
- product seizure, detentions or import bans; or
- injunctions or the imposition of civil or criminal penalties.

The FDA's policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained.

Regulatory approval is limited by the FDA to those specific indications and conditions for which clinical safety and efficacy have been demonstrated, and we may be subject to fines, penalties or injunctions if we are determined to be promoting the use of our products for unapproved or "off-label" uses, resulting in damage to our reputation and business.

When the FDA or comparable foreign regulatory authorities issue regulatory approval for a product candidate, the regulatory approval is limited to those specific indications for which a product is approved. For example, the FDA approved KORSUVA injection for the treatment of moderate-to-severe CKD-AP in adults undergoing hemodialysis indication. If we are not able to obtain FDA approval for any desired future indications for our products and product candidates, our ability to effectively market and sell our products may be reduced and our business may be adversely affected.

While physicians may choose to prescribe drugs for uses that are not described in the product's labeling and for uses that differ from those tested in clinical studies and approved by the regulatory authorities, we are prohibited from marketing and promoting the products for indications that are not specifically approved by the FDA. These "off-label" uses are common across medical specialties and may constitute an appropriate treatment for some patients in varied circumstances. Regulatory authorities in the United States generally do not restrict or regulate the behavior of physicians in their choice of treatment within the practice of medicine. Regulatory authorities do, however, restrict communications by pharmaceutical companies on off-label use. If the FDA determines that our or our commercial partners' promotional activities constitute promotion of an off-label use, it could request that we modify our promotional materials. Further, off-label promotion could subject us to regulatory or enforcement actions by the FDA and other agencies, including issuance of warning letters or untitled letters, suspension or withdraw an approved product from the market, mandatory or voluntary recalls, civil fines, disgorgement of money, operating restrictions, additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement, injunctions or criminal prosecution, any of which could significantly harm our business.

Failure to obtain marketing approval in international jurisdictions would prevent our product candidates from being marketed abroad.

In order to market and sell our products in the EU and many other jurisdictions, we or our collaborators or partners must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. For example, our partner, VFMCRP, submitted an MAA to the EMA in March 2021, which was accepted for review by the EMA. Although we obtained FDA approval of KORSUVA injection in the U.S., the approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We or these third parties may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. However, the failure to obtain approval in one jurisdiction may compromise our or our collaborators' or partners' ability to obtain approval elsewhere. We or our collaborators or partners may not be able to file for marketing approvals and may not receive necessary approvals to commercialize our products in any market.

Our products, including KORSUVA injection, may have undesirable side effects that may require them to be taken off the market, require them to include safety warnings or otherwise limit their sales. Further, our product candidates may have serious adverse events or undesirable side effects that may limit dosing in development, delay or prevent regulatory or marketing approval.

Undesirable side effects caused by our product candidates could cause us or regulatory authorities to limit dosage in development or interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other comparable foreign authorities. For example, in February 2016, the FDA placed our adaptive trial of I.V. CR845/difelikefalin for postoperative pain on IND clinical hold pending a safety review. The clinical hold was based on a stopping rule related to elevated serum sodium levels of greater than 150 mmol/L. After the safety review was completed, the FDA removed this clinical hold in April 2016 and the clinical trial was resumed in June 2016. If other concerns are raised regarding the safety of a new drug as a result of undesirable side effects identified during clinical testing, the FDA may order us to cease further development, decline to approve the drug or issue a letter requesting additional data or information prior to making a final decision regarding whether or not to approve the drug. The number of such requests for additional data or information issued by the FDA in recent years has increased and resulted in substantial delays in the approval of several new drugs. Undesirable side effects caused by I.V. CR845/difelikefalin or any of our other current or future product candidates could also result in denial of regulatory approval by the FDA or other regulatory authorities for any or all targeted indications or the inclusion of unfavorable information in our product labeling, and in turn prevent us from commercializing and generating revenues from the sale of I.V. CR845/difelikefalin for acute post-operative pain or any other product candidate. Approval of our current or future product candidates may include aspects of product labeling that limit its commercial use, including a Boxed Warning, REMS or other limitations of use.

To date, the side effects observed in the completed I.V. CR845/difelikefalin clinical trials include dizziness, transient facial tingling, a state of near-sleep, or somnolence, and hypernatremia, an electrolyte disturbance that is defined by an elevated sodium level in the blood, which we believe is secondary, at least in part, to another side effect, aquaresis, that is defined as electrolyte-free urination. As described above, the observation of mild to moderate hypernatremia in our adaptive trial for postoperative pain triggered a stopping rule in the trial protocol and led the FDA to institute an IND clinical hold related to the trial, pending a safety review. Prolonged aquaresis can result in a negative fluid balance if the excreted water is not replaced by oral or intravenous fluids, and although we recommend steps to control fluid balance, we cannot be certain that such instructions will be followed by healthcare providers and/or patients, and failure to follow such instructions may be accompanied by adverse events associated with negative fluid balance, including disability and death. We believe that one such adverse event, which has been observed, postural tachycardia, an elevation of heart rate upon standing up, is a physiological reflex that can be triggered as a result of decreased intravascular volume caused by a negative fluid balance. We have observed transient prolactin elevations, which are brief increases in the concentration of the hormone prolactin in the bloodstream, in response to I.V. CR845/difelikefalin, which we have measured as a nonselective opioid biomarker since both kappa and mu opioids elicit this effect. We cannot be certain that such elevations in prolactin will be transient, safe, and well tolerated in all patients. In addition, previously developed kappa opioid agonists, the pharmacological class of drugs that CR845/difelikefalin belongs to, have been associated with poorly tolerated psychiatric side effects, such as a feeling of emotional and mental discomfort, or dysphoria, and hallucinations, at high doses, particularly for prior generations of kappa opioid agonists with substantially unrestricted or only partially restricted entry to the CNS. Although we have not observed psychiatric side effects in any CR845/difelikefalin clinical trials to date, we cannot be certain that these side effects or others will not be observed in the future, or that the FDA will not require additional trials or impose more severe labeling restrictions due to these side effects or other concerns. The drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. Any of these occurrences may harm our business, financial condition and prospects significantly.

Additionally, our products, including KORSUVA injection, are subject to continuing regulatory oversight. Drugs are more widely used by patients once approval has been obtained and therefore side effects and other problems may be observed after approval that were not seen or anticipated, or were not as prevalent or severe, during pre-approval clinical trials or nonclinical studies. The subsequent delivery of previously unknown problems with a product, or public speculation about adverse safety events, could face a number of potentially significant negative consequences could result, including:

- regulatory authorities may suspend or withdraw approvals of such product;
- regulatory authorities may require additional warnings on the label;
- we may be required to create a medication guide outlining the risks of such side effects for distribution to patients;
- issue warning letters;
- mandate modifications to promotional materials or require us to provide corrective information to healthcare practitioners;
- require us or our collaborators to enter into a consent decree, which can include imposition of various fines, reimbursements for inspection costs, required due dates for specific actions and penalties for noncompliance;
- impose other civil or criminal penalties;
- impose restrictions on operations, including costly new manufacturing requirements;
- seize or detain products or require a product recall;
- we could be sued and held liable for harm caused to patients;
- the sales of the product may decrease significantly; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of KORSUVA injection and the particular product candidate, if approved, and could significantly harm our business, results of operations and prospects.

If we experience continuous delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.

We may not be able to initiate or continue conducting clinical trials for our product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or similar regulatory authorities outside the United States. Some of our competitors have ongoing clinical trials for product candidates that treat the same indications as our product candidates, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' product candidates. Patient enrollment is affected by other factors including:

- the size and nature of the patient population;
- the severity of the disease under investigation;
- the eligibility criteria for, and design of, the trial in question;
- the perceived risks and benefits of the product candidate under study;
- competition in recruiting and enrolling patients in clinical trials;
- the efforts to facilitate timely enrollment in clinical trials;

- the patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment;
- the proximity and availability of clinical trial sites for prospective patients; and
- delays or difficulties due to the ongoing COVID-19 pandemic.

For example, we experienced a delay in patient enrollment for our Phase 2 clinical trial of Oral KORSUVA (CR845/difelikefalin) for the treatment of pruritus in patients with hepatic impairment due to PBC, and could in the future experience delays in either of our ongoing Phase 2 clinical trials as patient enrollment in both of these trials is not yet complete.

Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays and could require us to abandon one or more clinical trials altogether. We may encounter difficulties and/or delays in completing our planned enrollments. Enrollment delays in our clinical trials may result in increased development costs for our product candidates, or the inability to complete development of our product candidates, which would cause the value of our company to decline, limit our ability to obtain additional financing, and materially impair our ability to generate revenues.

Risks Related to Our Financial Condition and Capital Requirements

We have incurred significant losses from our inception, and although we generated net income in 2020, we anticipate that we may incur losses in the foreseeable future. Our first commercial product was only recently approved, and we may never maintain profitability.

We are an early commercial-stage biopharmaceutical company. For the last several years, we have focused our efforts primarily on developing KORSUVA injection and Oral CR845/difelikefalin with the goal of achieving regulatory approval and in August 2021, the FDA approved KORSUVA injection for the treatment of moderate-to-severe CKD-aP in adults undergoing hemodialysis. Since inception, we have incurred significant operating and net losses. We incurred net losses of $55.1 million and $106.4 million for the nine months ended September 30, 2021 and year ended December 31, 2019, respectively. As of September 30, 2021, we had an accumulated deficit of $447.4 million. Although we generated net income for the year ended December 31, 2020 as a result of a commercial license transaction, we expect to continue to incur significant expenses and operating and net losses in the foreseeable future, as we continue to prepare for the commercialization of KORSUVA (CR845/difelikefalin) and develop and seek marketing approval for our product candidates. Our financial results may fluctuate significantly from year to year, depending on the timing of our clinical trials, the receipt of additional milestone payments, if any, under our agreements with Vifor, VFMCRP, Maruishi and CKDP, the receipt of payments under any future agreements we may enter into, and our expenditures on other R&D activities as well as any payments owed under the License Agreement with Enteris and any future similar agreements.

In addition, we expect to incur significant sales, marketing and manufacturing expenses related to our product candidates, if they are approved by the FDA, and expenses related to the commercialization of KORSUVA (CR845/difelikefalin). As a result, we expect to continue to incur significant losses for the foreseeable future as we:

- continue the development of Oral KORSUVA (CR845/difelikefalin) for AD-aP, NDD-CKD, CLD-PBC and NP;
- explore further development of CR845/difelikefalin injection in the post-operative setting;
- seek regulatory approvals for any other product candidate that successfully completes clinical trials;
- establish a sales, marketing and distribution infrastructure and scale up external manufacturing capabilities to commercialize any other products for which we may obtain regulatory approval;

- maintain, expand and protect our global intellectual property portfolio;
- hire additional clinical, quality control and scientific personnel; and
- add operational, financial and management information systems and personnel, including personnel to support our drug development and potential future commercialization efforts.

To become and remain profitable from product sales, we must succeed in developing and eventually commercializing one or more products that generate significant revenue. For example, revenues from KORSUVA injection may not be sufficient to enable us to reach profitability. In order to commercialize any additional product candidates, we will need to be successful in a range of challenging activities, including successful registration of Oral KORSUVA (CR845/difelikefalin), discovering additional product candidates and completing preclinical testing and clinical trials for those product candidates, potentially entering into collaboration and license agreements, obtaining regulatory approval for product candidates and manufacturing, marketing and selling approved products and product candidates for which we may obtain regulatory approval. We may never succeed in these activities and, even if we do, may never achieve profitability.

Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve profitability. If we are required by the FDA or foreign regulatory authorities, to perform studies in addition to those currently expected, or if there are any delays in completing our clinical trials or the development of any of our product candidates, our expenses could increase.

Even if we do achieve profitability from product sales, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would depress the value of our company and could impair our ability to raise capital, expand our business, maintain our R&D efforts, diversify our product offerings or even continue our operations. A decline in the value of our company could also cause you to lose all or part of your investment.

Our operating history makes it difficult to evaluate our business and prospects.

We commenced operations in 2004, and our operations to date have been limited to organizing and staffing our company, business planning, raising capital and advancing our products and product candidates, including KORSUVA injection and Oral KORSUVA (CR845/difelikefalin), through clinical development. We have not yet demonstrated an ability to successfully commercialize a product. With the approval of KORSUVA injection, we will need to expand our capabilities to support commercial activities of our commercial partners. We may not be successful in adding such capabilities. Consequently, any predictions about our future performance may not be as accurate as they could be if we had a history of successfully developing and commercializing pharmaceutical products.

We may need additional funding and may be unable to raise capital when needed, which would force us to delay, reduce or eliminate our product development programs or commercialization efforts.

Conducting clinical trials, pursuing regulatory approvals, establishing outsourced manufacturing relationships and successfully manufacturing and commercializing our products and product candidates is expensive. We may need to raise additional capital to:

- fund our operations and continue our efforts to hire additional personnel for the commercialization of KORSUVA injection;
- qualify and outsource the commercial-scale manufacturing of our products, including KORSUVA injection, under cGMP;

- continue the further development of Oral KORSUVA (CR845/difelikefalin) for AD-aP, NDD-CKD, CLD-PBC and NP;
- explore further development of CR845/difelikefalin injection in the post-operative setting; and
- in-license other product candidates.

As of September 30, 2021, we believe that with our current unrestricted cash and cash equivalents and available-for-sale marketable securities, including the milestone payments totaling $65.0 million received from Vifor and VFMCRP in October 2021, will be sufficient to fund our currently anticipated operating expenses and capital expenditures through 2023, without giving effect to any additional potential milestone payments or potential product revenue we may receive under our licensing and collaboration agreements with Vifor, VFMPCRP, Maruisihi and CKDP. We have based this estimate on assumptions that may prove to be wrong and we could spend our available financial resources faster than we currently expect. Further, because we do not have sufficient financial resources to meet all of our development objectives, in particular the completion of our development of Oral KORSUVA (CR845/difelikefalin) for the treatment of AD-aP, NDD-CKD, CLD-PBC and NP, we will need to raise additional capital. If we are not able to do so, we could be required to postpone, scale back or eliminate some, or all, of these objectives. Our future funding requirements will depend on many factors, including, but not limited to:

- the success of the commercialization of KORSUVA injection and any current and future product candidates;
- the cost and timing of manufacturing sufficient supplies of KORSUVA injection for commercialization;
- the rate of progress and costs related to Phase 2 and Phase 3 development of Oral KORSUVA (CR845/difelikefalin) for our product candidates and other indications;
- the rate of progress and costs for the submission and review of an NDA for any product candidates that we may in-license or acquire in the future, and the potential that we may need to conduct additional clinical trials to support applications for regulatory approval;
- the costs of filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights associated with our product candidates, including any such costs we may be required to expend if our licensors are unwilling or unable to do so;
- the effect of competing technological and market developments; and
- the terms and timing of any collaborative, licensing, co-promotion or other arrangements that we may establish.

Future capital requirements will also depend on the extent to which we acquire or invest in additional complementary businesses, products and technologies. Until we can generate a sufficient amount of product revenue, if ever, we expect to finance future cash needs through public or private equity offerings, debt financings, milestone and royalty payments from corporate collaboration and licensing arrangements, as well as through interest income earned on cash and investment balances. We cannot be certain that additional funding will be available on acceptable terms, or at all, and our ability to raise additional capital may be adversely impacted by potential worsening global economic conditions and the recent disruptions to and volatility in the credit and financial markets in the United States and worldwide resulting from the ongoing COVID-19 pandemic. If adequate funds are not available, we may be required to delay, reduce the scope of, or eliminate, one or more of our development programs or our commercialization efforts.

Risks Related to Our Dependence on Third Parties

We are dependent on third parties to decide to utilize KORSUVA injection and to make it readily available at the point of care throughout their dialysis centers or hospitals.

In addition to extensive internal efforts, the successful commercialization of KORSUVA injection will require many third parties, over whom we have no control, to decide to utilize KORSUVA injection and to make it readily available at the point of care throughout their hospitals. These third parties include physicians, dialysis providers, pharmacists and hospital pharmacy and therapeutics committees, which are commonly referred to as P&T committees. Generally, before we can attempt to sell KORSUVA injection in a hospital or dialysis center, it must be approved for addition to that hospital or dialysis center's list of approved drugs, or formulary list, by the institution's P&T committee. An institutional P&T committee typically governs all matters pertaining to the use of medications within the institution, including review of medication formulary data and recommendations for the appropriate use of drugs within the institution to the medical staff. The frequency of P&T committee meetings at various institutions varies considerably, and P&T committees often require additional information to aid in their decision-making process, so we may experience substantial delays in obtaining formulary approvals. Additionally, institutions may be concerned that the cost of acquiring KORSUVA injection for use in their institutions will adversely impact their overall pharmacy budgets, which could cause institution staff to resist efforts to add KORSUVA injection to the formulary, or to implement restrictions on the usage of the drug in order to control costs, either initially or later, when the increasing use of KORSUVA injection within their institution begins to significantly impact their budgets. We cannot guarantee that we will be successful in getting the approvals we need from enough P&T committees and overcoming any financial objections raised by institution staff quickly enough to maintain and grow institutional sales of CR845/difelikefalin injection.

We rely on third parties to perform many essential services for KORSUVA injection and may do so in the future for any products that we commercialize, including services related to warehousing and inventory control, distribution, customer service, accounts receivable management, cash collection and adverse event reporting. If these third parties fail to perform as expected or to comply with legal and regulatory requirements, our ability to commercialize KORSUVA injection or any other product candidate, will be significantly impacted and we may be subject to regulatory sanctions.

We retain third-party service providers to perform a variety of functions related to the sale and distribution of KORSUVA injection and may do so in the future for our other current or future product candidates, key aspects of which will be out of our direct control. These service providers provide key services related to warehousing and inventory control, distribution, customer service, accounts receivable management and cash collection, and, as a result, most of our inventory are stored at a single warehouse maintained by one such service provider. Thus, we substantially rely on it as well as other third-party providers that perform services for us, including entrusting our inventories of products to their care and handling. If these third-party service providers fail to comply with applicable laws and regulations, fail to meet expected deadlines, or otherwise do not carry out their contractual duties to us, or encounter physical or natural damage at their facilities, our ability to deliver product to meet commercial demand would be significantly impaired. In addition, we have engaged third parties to perform various other services for us relating to adverse event reporting, safety database management, fulfillment of requests for medical information regarding our product candidates and related services. If the quality or accuracy of the data maintained by these service providers is insufficient, or these third parties otherwise fail to comply with regulatory requirements related to adverse event reporting, we could be subject to regulatory sanctions.

We are dependent on our collaboration agreements for certain revenues, and if our commercial partners do not perform their obligations under such agreements, we could lose revenues.

In October 2020, we entered into a license agreement with Vifor under which we granted Vifor an exclusive license solely in the United States to use, distribute, offer for sale, promote, sell and otherwise commercialize our product candidate KORSUVA (CR845/difelikefalin) injection for all therapeutic uses relating to the inhibition, prevention or treatment of itch associated with pruritus in hemodialysis and peritoneal dialysis patients in the United States. In May 2018, we entered into an agreement with VFMCRP under which we granted VFMCRP a license to seek regulatory approval to commercialize, import, export, use, distribute, offer for sale, promote, sell and otherwise commercialize KORSUVA (CR845/difelikefalin) injection for all therapeutic uses to prevent, inhibit or treat itch associated with

pruritus in hemodialysis and peritoneal-dialysis patients worldwide (excluding the United States, Japan and South Korea). In April 2013, we entered into an agreement with Maruishi under which we granted Maruishi an exclusive license to develop, manufacture and commercialize products containing CR845/difelikefalin in Japan. Also, in April 2012, we entered into an agreement with CKDP under which we granted CKDP an exclusive license to develop, manufacture and commercialize products containing CR845/difelikefalin in South Korea. Under the VFMCRP Agreement, we are responsible, at our own cost, to undertake clinical and non-clinical development. We are also responsible to provide all content and subject matter expertise required for registration with the EMA in the EU that will be needed by VFMCRP for such registration, including participation in regulatory meetings, as needed. If third-party costs incurred by us with respect to our clinical development for the EMA registration exceed $20,000, such excess costs will be shared equally by us and VFMCRP. VFMCRP will contribute, at its own cost, its clinical development expertise as reasonably useful for such development activities, such as preparing the clinical results that we present to it in a format acceptable to the EMA to obtain marketing approval in the EU. Maruishi and CKDP are required to use commercially reasonable efforts, at their expense, to develop, obtain regulatory approval for and commercialize CR845/difelikefalin in Japan and South Korea, respectively. Our receipt of milestone payments and royalties under these agreements is dependent on the continued efforts by VFMCRP, Maruishi and CKDP, respectively, and their failure to adequately develop or commercialize the licensed products, or any default or inability to meet their payment obligations under their respective agreements, could harm our revenues and business.

Any collaboration arrangements that we are a party to or may enter into in the future may not be successful, which could adversely affect our ability to develop and commercialize our product candidates.

Our business model is to commercialize our product and product candidates in the United States and generally to seek collaboration arrangements with pharmaceutical or biotechnology companies for the development or commercialization of our product candidates in the rest of the world. We currently have license agreements with Vifor and VFMCRP (KORSUVA injection for CKD-aP in dialysis patients) as well as Maruishi and CKDP (CR845/difelikefalin - both I.V. and Oral). In addition to our existing agreements, we may enter into additional collaboration arrangements in the future on a selective basis. Our existing collaborations and future collaboration arrangements may not be successful. The success of our existing and future collaboration arrangements will depend heavily on the efforts and activities of our collaborators.

Collaborators generally have significant discretion in determining the efforts and resources that they will apply to these collaboration arrangements. Disagreements between parties to a collaboration arrangement regarding clinical development and commercialization matters can lead to delays in the development process or commercializing the applicable product candidate and, in some cases, termination of the collaboration arrangement. These disagreements can be difficult to resolve if neither of the parties has final decision-making authority.

Collaborations with pharmaceutical companies and other third parties often are terminated or allowed to expire by the other party. For example, the Vifor, VFMCRP, Maruishi and CKDP Agreements may be terminated by our collaborator for our breach or insolvency, each of Vifor and VFMCRP may terminate its respective agreement (in its entirety or with respect to any countries within the Territory upon written notice to us) upon the earlier of (1) acceptance for filing of an NDA covering Licensed Product filed with the FDA (after completion of the Phase 3 program) or (2) the third anniversary of the Effective Date. Maruishi may terminate its agreement with us at will, and CKDP may terminate its agreement with us in certain circumstances relating to patent invalidity or unenforceability or generic entry by a third party, as further described in the section titled “Management’s Discussion and Analysis of Financial Condition and Results of Operations - Collaboration and License Agreements” above. Any such termination or expiration would adversely affect us financially and could harm our business reputation. Our current collaborations and any future collaborations we might enter into may pose a number of risks, including the following:

- collaborators may not perform their obligations as expected;
- collaborators may not pursue development and commercialization of our products or any product candidates that achieve regulatory approval or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators’ strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;

- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;

- collaborators could fail to make timely regulatory submissions for a product or product candidate;

- collaborators may not comply with all applicable regulatory requirements or may fail to report safety data in accordance with all applicable regulatory requirements;

- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;

- product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;

- a collaborator with marketing and distribution rights to one or more of our products or product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such product or products;

- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development, might cause delays or termination of the research, development or commercialization of products and product candidates, might lead to additional responsibilities for us with respect to products and product candidates, or might result in litigation or arbitration, any of which would be time-consuming and expensive;

- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;

- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; and

- collaborations, including our collaboration with Maruishi, may be terminated for the convenience of the collaborator and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates.

If our current collaborations or any other collaborations we might enter into in the future do not result in the successful development and commercialization of products or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, our development of our product candidates could be delayed and we may need additional resources to develop our product candidates and our product platform. All of the risks relating to our product development, regulatory approval and commercialization described in this Quarterly Report on Form 10-Q and our Annual Report on Form 10-K for the year ended December 31, 2020 also apply to the activities of our collaborators in their respective jurisdictions.

Additionally, if any current or future collaborator of ours is involved in a business combination, the collaborator might deemphasize or terminate development or commercialization of any product candidate licensed to it by us. If one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and our reputation in the business and financial communities could be adversely affected.

For KORSUVA injection and any other current or future product candidates, we may in the future determine to collaborate with additional pharmaceutical and biotechnology companies for their development and potential commercialization. We face significant competition in seeking appropriate collaborators. Our ability to reach a definitive agreement for collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. If we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms, or at all, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund and undertake development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates or bring them to market or continue to develop our product platform or successfully commercialize our products and our business may be materially and adversely affected.

Risks Related to Legal and Compliance Matters

If we fail to comply with federal and state healthcare laws, including fraud and abuse, and transparency laws, we could face substantial penalties and our business, results of operations, financial condition and prospects could be adversely affected.

As a pharmaceutical company, even though we do not and will not control referrals of healthcare services or bill directly to Medicare, Medicaid or other third-party payers, certain federal and state healthcare laws and regulations pertaining to fraud and abuse, transparency and patients' rights may be applicable to our business. The healthcare laws and regulations that may affect our ability, and our partners' and collaborators' ability, to operate include, but are not limited to:

- the federal Anti-Kickback Statute, which regulates, among other things, our marketing practices, educational programs, pricing policies, and relationships with healthcare providers or other entities, by prohibiting, among other things, any person or entity from knowingly and willfully soliciting, receiving, offering or paying any remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, the purchase, recommendation, lease, order or furnishing of an item or service reimbursable, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs;

- federal civil and criminal false claims laws, including without limitation the federal civil False Claims Act, and civil monetary penalties law, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, false or fraudulent claims for payment or approval from a federal health care program (including Medicare and Medicaid);

- Federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal statutes that prohibit, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or to obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any health care benefit program, regardless of the payer (e.g., public or private) and knowingly and willfully falsifying, concealing, or covering up by any trick, scheme or device a material fact or making any materially false statements in connection with the delivery of, or payment for, health care benefits, items or services relating to healthcare matters;

- federal transparency laws, including the federal Physician Payments Sunshine Act, that requires certain manufacturers of drugs, devices, biologics, and medical supplies for which payment is available under Medicare, Medicaid, or the Children's Health Insurance Program to report annually to CMS, or Centers for Medicare & Medicaid Services, information related to payments and other transfers of value provided to physicians (defined to include doctors of medicine, dentists, optometrists, podiatrists and chiropractors) and

teaching hospitals, and applicable manufacturers and group purchasing organizations to report annually to CMS ownership and investment interests held by physicians and their immediate family members; Beginning in 2022, applicable manufacturers also will be required to report such information regarding payments and transfers of value provided during the previous year to physician assistants, nurse practitioners, clinical nurse specialists, anesthesiologist assistants, certified nurse anesthetists and certified nurse-midwives;

- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payer, including commercial insurers; and

- state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws that require drug manufacturers to report information related to the pricing of certain drugs, as well as payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; and state and local laws that require the registration of pharmaceutical sales representatives, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Because of the breadth of these laws and the narrowness of the statutory exceptions and regulatory safe harbors available under these laws, it is possible that some of our business activities could be subject to challenge under one or more of such laws. Pharmaceutical and other healthcare companies continue to be prosecuted under the federal false claims laws for numerous activities, including those related to research, sales, marketing and promotional programs. In addition, recent health care reform legislation has strengthened these laws. For example, the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, or the Health Care Reform Law, among other things, amends the intent requirement of the federal Anti-Kickback Statute and certain other criminal healthcare fraud statutes. As a result, a person or entity no longer needs to have actual knowledge of these statutes or specific intent to violate them in order to commit a violation. Moreover, the Health Care Reform Law provides that the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act. To the extent that any product we make is sold in a foreign country, we may be subject to similar foreign laws and regulations. If we or our operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to significant penalties, including administrative, civil and criminal penalties, damages, fines, disgorgement, exclusion from participation in U.S. federal or state health care programs, contractual damages, reputational harm, imprisonment, diminished profits and future earnings, additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, and the curtailment or restructuring of our operations, any of which could materially adversely affect our ability to operate our business and our financial results. Although an effective compliance program can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. Moreover, achieving and sustaining compliance with applicable federal and state transparency and fraud and abuse laws may prove costly. If any of the physicians or other healthcare providers or entities with whom we do business, including our partners or collaborators, is found not to be in compliance with applicable laws, it may be subject to significant criminal, civil or administrative sanctions, including but not limited to, exclusions from participation in government healthcare programs, which could also materially affect our business.

Changes in and failures to comply with applicable U.S. and foreign privacy and data protection laws, regulations and standards may subject us to liabilities and adversely affect our business, operations and financial performance.

We are subject to or affected by numerous federal, state and foreign laws and regulations, as well as regulatory guidance, governing the collection, use, disclosure, retention, and security of personal data, such as information that we collect about participants and healthcare providers in connection with clinical trials in the U.S. and abroad. The global data protection landscape is rapidly evolving, and implementation standards and enforcement practices are likely to remain uncertain for the foreseeable future. This evolution may create uncertainty in our business, affect our or our

service providers' ability to operate in certain jurisdictions or to collect, store, transfer use and share personal data, result in liability or impose additional costs on us. The cost of compliance with these laws, regulations and standards is high and is likely to increase in the future. Any failure or perceived failure by us to comply with federal, state, or foreign laws or self-regulatory standards could result in negative publicity, diversion of management time and effort and proceedings against us by governmental entities or others. In many jurisdictions, enforcement actions and consequences for noncompliance are rising.

In the U.S., HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information without appropriate authorization by entities subject to the rule, including health plans, healthcare clearinghouses, certain healthcare providers, and their business associates and covered subcontractors that perform services for them that involve the creation, use, maintenance or disclosure of, individually identifiable health information. In the event we are subject to HIPAA and we or our covered subcontractors fail to properly maintain the privacy and security of certain individually identifiable health information, or we or our covered subcontractors are responsible for an inadvertent disclosure or security breach of such individually identifiable health information, we could be subject to enforcement measures, including civil and criminal penalties and fines for violations of state and federal privacy or security standards, such as HIPAA and HITECH, and their respective implementing regulations. Additionally, certain states have adopted comparable privacy and security laws and regulations, some of which may be more stringent than HIPAA. For example, on June 28, 2018, California enacted the California Consumer Privacy Act, or CCPA, which takes effect on January 1, 2020. The CCPA gives California residents expanded rights to access and delete their personal information, opt out of certain personal information sharing, and receive detailed information about how their personal information is used. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that is expected to increase data breach litigation. The CCPA may increase our compliance costs and potential liability. Some observers have noted that the CCPA could mark the beginning of a trend toward more stringent privacy legislation in the U.S., such as similar privacy legislation in Virginia and in Colorado, which could increase our potential liability and adversely affect our business.

Our operations abroad may also be subject to increased scrutiny or attention from data protection authorities. Many countries in these regions have established or are in the process of establishing privacy and data security legal frameworks with which we or our partners, collaborators, customers, or service providers must comply. For example, the EU has adopted the General Data Protection Regulation, or GDPR, which went into effect in May 2018 and introduced strict requirements for processing personal data. The GDPR is likely to increase compliance burden on us, including by mandating potentially burdensome documentation requirements and granting certain rights to individuals to control how we collect, use, disclose, retain and leverage information about them or how we obtain consent from them. The processing of sensitive personal data, such as physical health condition, may impose heightened compliance burdens under the GDPR and is a topic of active interest among foreign regulators and supervisory bodies involved in the review and approval of clinical trials. In addition, the GDPR provides for breach reporting requirements, more robust regulatory enforcement and fines of up to 20 million euros or up to 4% of the annual global revenue. As we continue to expand into other foreign countries and jurisdictions, we may be subject to additional laws and regulations that may affect how we conduct business.

U.S. and foreign data protection laws, regulations and standards are subject to interpretation by various courts and other governmental authorities, thus creating potentially complex compliance issues for us and our future customers and strategic partners. Any liability from failure to comply with the requirements of these laws, to the extent such requirements are deemed to apply to our operations, could adversely affect our financial condition. The costs of complying with privacy and security related legal and regulatory requirements are burdensome and could have a material adverse effect on our results of operations.

If the government or other third-party payers fail to provide coverage and adequate reimbursement and payment rates for KORSUVA injection or any of our other current or future product candidates, if any, or if providers choose to use therapies that are less expensive, our revenue and prospects for profitability will be limited.

In both domestic and foreign markets, sales of KORSUVA injection and our future products (if approved) will depend in part upon the availability of coverage and reimbursement from third-party payers. Such third-party payers

include government health programs such as Medicare and Medicaid, managed care providers, private health insurers and other organizations. Coverage decisions may depend upon clinical and economic standards that disfavor new drug products when more established or lower cost therapeutic alternatives are already available or subsequently become available. Assuming coverage is approved, the resulting reimbursement payment rates might not be adequate. KORSUVA injection for the treatment of pruritus in hemodialysis patients is expected to be designated as a component of the government's bundled reimbursement for end stage renal disease treatment.

On October 31, 2019, CMS issued a final rule that revises payment policies and rates under the End-Stage Renal Disease Prospective Payment System, or ESRD PPS, for renal dialysis services furnished to beneficiaries on or after January 1, 2020. The final rule also updates the TDAPA. In the final rule, CMS revised ESRD PPS eligibility to focus on innovative drugs and excluded certain drugs from being eligible for the TDAPA. CMS will pay the revised TDAPA adjustment, which is called the Transitional Add-on Payment Adjustment for New and Innovative Equipment and Supplies , or TPNIES, for equipment and supplies that: (1) have been designated by CMS as a renal dialysis service, (2) are new, meaning granted marketing authorization by FDA on or after January 1, 2020, (3) are commercially available by January 1 of the particular calendar year, meaning the year in which the payment adjustment would take effect, (4) have a HCPCS application submitted in accordance with the official Level II HCPCS coding procedures by September 1 of the particular calendar year, (5) are innovative, meaning they meet the substantial clinical improvement criteria specified in the Inpatient Prospective Payment System regulations and related guidance, and (6) are not capital-related assets. On November 2, 2020, CMS issued a final rule outlining its payment policies and rates under the ESRD PPS for the 2021 calendar year. In addition to the annual technical updates to the ESRD PPS, the final rule, among other things, expands eligibility under the TPNIES. In particular, the final rule provided for biannual coding cycles for new HCPCS Level II code applications, revised the definition of "new" to be three (3) years beginning on the date of FDA marketing authorization, and expanded eligibility under the TPNIES to include certain home dialysis capital-related assets. We expect KORSUVA injection will qualify for TDAPA payments for at least two years post approval. However, there is no assurance that KORSUVA injection will qualify for TDAPA payments or, even if it does, that it will be able to maintain its price established in the TDAPA period in the post-TDAPA timeframe.

Additionally, many U.S. hospitals receive a fixed reimbursement amount per procedure for certain surgeries and other treatment therapies they perform, or a pre-determined rate for all hospital inpatient care provided as payment in full. Because, in these instances, the amount of reimbursement that such providers receive may not be based on the actual expenses the provider incurs, providers may choose to use therapies which are less expensive when compared to our product candidates. Accordingly, KORSUVA injection or any of our other current or future product candidates, if approved, will face competition from other therapies and drugs for these limited provider financial resources. We may need to conduct post-marketing studies in order to demonstrate the cost-effectiveness of any future products to the satisfaction of hospitals, other target customers and their third-party payers. Such studies might require us to commit a significant amount of management time and financial and other resources. Our future products might not ultimately be considered cost-effective. Third-party coverage and adequate reimbursement might not be available to enable us to maintain price levels sufficient to realize an appropriate return on investment in product development.

Third-party payers, whether foreign or domestic, or governmental or commercial, are developing increasingly sophisticated methods of controlling healthcare costs. In addition, in the United States, no uniform policy of coverage and reimbursement for drug products exists among third-party payers. Therefore, coverage and reimbursement for drug products can differ significantly from payer to payer. Further, we believe that future coverage and reimbursement will likely be subject to increased restrictions both in the United States and in international markets. Third-party coverage and reimbursement for our products or product candidates for which we receive regulatory approval may not be available or adequate in either the United States or international markets, which could have a negative effect on our business, results of operations, financial condition and prospects.

We are subject to recent legislation, regulatory proposals and healthcare payer initiatives that may increase our costs of compliance and adversely affect our ability to market our products, obtain collaborators and raise capital.

In March 2010, President Obama signed the Health Care Reform Law, which includes provisions that have changed, and likely will continue to change, health care financing and the delivery of health care in the United States. Among the provisions of the Health Care Reform Law of importance to the pharmaceutical industry are the following:

- an annual, nondeductible fee on any entity that manufactures or imports certain branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs;

- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13% of the average manufacturer price for most branded and generic drugs, respectively;

- a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;

- a new Medicare Part D coverage gap discount program, in which manufacturers must now agree to offer 70% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D;

- extension of manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;

- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals with income at or below 133% of the Federal Poverty Level, thereby potentially increasing both the volume of sales and manufacturers' Medicaid rebate liability;

- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;

- new transparency requirements under the federal Physician Payments Sunshine Act;

- a new requirement to annually report certain drug samples that manufacturers and distributors provide to licensed practitioners, or to pharmacies of hospitals or other healthcare entities;

- a licensure framework for follow-on biologic products;

- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;

- establishment of a Center for Medicare & Medicaid Innovation at the CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending; and

- expansion of healthcare fraud and abuse laws, including the federal civil False Claims Act and the federal Anti-Kickback Statute, new government investigative powers and enhanced penalties for non-compliance.

There have been executive, judicial and Congressional challenges to certain aspects of the Health Care Reform Law. For example, on June 17, 2021 the U.S. Supreme Court dismissed a challenge on procedural grounds that argued the Health Care Reform Law is unconstitutional in its entirety because the "individual mandate" was repealed by Congress. Thus, the Health Care Reform Law will remain in effect in its current form. Further, prior to the Supreme Court ruling, on January 28, 2021, President Biden issued an executive order to initiate a special enrollment period for purposes of obtaining health insurance coverage through the Health Care Reform Law marketplace, which began on February 15, 2021 and remained open through August 15, 2021. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the Health Care Reform Law. It is also unclear how any such challenges and the healthcare reform measures of the Biden administration will impact the Health Care Reform Law and our business.

In addition, other legislative changes have been proposed and adopted since the Health Care Reform Law was enacted. These changes include, among other things, aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went effective on April 1, 2013 and, following passage of the Bipartisan Budget Act of 2015, and subsequent legislative amendments, including the BBA, will remain in effect until 2030, except for a temporary suspension from May 1, 2020 through December 31, 2021 due to the COVID-19 pandemic, unless additional Congressional action is taken. In January 2013, President Obama signed into law the American Taxpayer Relief Act of 2012, which, among other things, further reduced Medicare payments to several providers and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These new laws may result in additional reductions in Medicare and other healthcare funding, which could have a material adverse effect on customers for our drugs, if approved, and, accordingly, our financial operations.

We expect that the Health Care Reform Law, as well as other federal and state healthcare reform measures that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved drug. Any reduction in reimbursement from Medicare or other government healthcare programs may result in a similar reduction in payments from private payers. In addition, there have been several recent U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the cost of drugs under Medicare, and reform government program reimbursement methodologies for drugs. At the federal level, the Trump administration used several means to propose or implement drug pricing reform, including through federal budget proposals, executive orders and policy initiatives. For example, on July 24, 2020 and September 13, 2020, the Trump administration announced several executive orders related to prescription drug pricing that seek to implement several of the administration's proposals. As a result, the FDA released a final rule on September 24, 2020, effective November 30, 2020, providing guidance for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020, the U.S. Department of Health and Human Services, or HHS, finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of the rule has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which have also been delayed until January 1, 2023. On November 20, 2020, CMS issued an interim final rule implementing President Trump's Most Favored Nation executive order, which would tie Medicare Part B payments for certain physician-administered drugs to the lowest price paid in other economically advanced countries. As a result of litigation challenging the Most Favored Nation model, on August 10, 2021, CMS published a proposed rule that seeks to rescind the Most Favored Nation model interim final rule. Additionally, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug's average manufacturer price, for single source and innovator multiple source drugs, beginning January 1, 2024. Further, in July 2021, the Biden administration released an executive order that included multiple provisions aimed at prescription drugs. In response to Biden's executive order, on September 9, 2021, HHS released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform. The plan sets out a variety of potential legislative policies that Congress could pursue as well as potential administrative actions HHS can take to advance these principles. No legislation or administrative actions have been finalized to implement these principles. In addition, Congress is considering drug pricing as part of the budget reconciliation process. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, to encourage importation from other countries and bulk purchasing. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our drugs.

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for drugs. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product

labeling and post-marketing testing and other requirements. Moreover, the Drug Supply Chain Security Act imposes obligations on manufacturers of pharmaceutical products, among others, related to product tracking and tracing.

Legislation and regulations that, among other things, reduce drug prices or require the implementation of costly compliance measures could result in decreased net revenues from our pharmaceutical products and decrease potential returns from our development efforts, and we cannot predict what legislation will be enacted in the future. Further, it is possible that additional governmental action is taken in response to the COVID-19 pandemic.

Governments outside the United States tend to impose strict price controls, which may adversely affect our revenues, if any.

In international markets, reimbursement and health care payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies. In some countries, particularly the countries of the EU, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain coverage and reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. There can be no assurance that our products will be considered cost-effective by third-party payers, that an adequate level of reimbursement will be available or that the third-party payers' reimbursement policies will not adversely affect our ability to sell our products profitably. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed, possibly materially.

Our employees, independent contractors, consultants, and commercial partners may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could have a material adverse effect on our business.

We are exposed to the risk of fraud or other misconduct by our employees, independent contractors, consultants and commercial partners. Misconduct by such individuals could include intentional failures to:

- comply with FDA regulations and other similar foreign regulations;
- provide true, complete and accurate information to the FDA;
- comply with manufacturing standards;
- comply with federal and state data privacy, security, fraud and abuse and other healthcare laws and regulations in the United States and similar foreign laws;
- report financial information or data accurately; or
- disclose unauthorized activities to us.

In particular, the promotion, sales and marketing of healthcare items and services, as well as certain business arrangements in the healthcare industry, are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, including off label uses of our products, structuring and commission(s), certain customer incentive programs, patient assistance programs, and other business arrangements generally. Third party misconduct could also involve the improper use or misrepresentation of information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter such misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could

have a significant impact on our business and financial results, including the imposition of civil, criminal and administrative penalties, damages, disgorgement, monetary fines, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, individual imprisonment, contractual damages, reputational harm, diminished profits and future earnings, additional reporting requirements and/or oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, and curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

Our business involves the use of hazardous materials and we must comply with environmental laws and regulations, which can be expensive and restrict how we do business.

Our manufacturing activities involve the controlled storage, use and disposal of hazardous materials, including the components of our products, product candidates and other hazardous compounds. We are subject to federal, state and local laws and regulations governing the use, manufacture, storage, handling, release and disposal of, and exposure to, these hazardous materials. Violation of these laws and regulations could lead to substantial fines and penalties. Although we believe that our safety procedures for handling and disposing of these materials comply with the standards prescribed by these laws and regulations, we cannot eliminate the risk of accidental contamination or injury from these materials. In the event of an accident, state or federal authorities may curtail our use of these materials and interrupt our business operations. In addition, we could become subject to potentially material liabilities relating to the investigation and cleanup of any contamination, whether currently unknown or caused by future releases.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Risks Related to Intellectual Property

It is difficult and costly to protect our proprietary rights and as a result we may not be able to ensure their protection and all patents will eventually expire.

Our commercial success will depend in part on obtaining and maintaining patent protection and trade secret protection for CR845/difelikefalin for our KORSUVA injection or other product candidates and for any other product candidates that we may develop, license or acquire and the methods we use to manufacture them, as well as successfully defending these patents and trade secrets against third-party challenges. We will only be able to protect our technologies from unauthorized use by third parties to the extent that valid and enforceable patents or trade secrets cover them.

The patent prosecution process is expensive and time-consuming, and we may not be able to file and prosecute to issuance all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our R&D output before it is too late to obtain patent protection. Moreover, should we enter into additional collaborations we may be required to consult with or cede control to collaborators regarding the prosecution, maintenance and enforcement of our patents. Therefore, these patents and applications may not be successfully prosecuted to issuance and enforced in a manner consistent with the best interests of our business. The patent positions of pharmaceutical and biotechnology companies can be highly uncertain and involve complex legal and factual questions for which important legal principles remain unresolved. No consistent policy regarding the breadth of claims allowed in pharmaceutical or biotechnology patents has emerged to date in the United States. The patent situation outside the United States is even more uncertain. Changes in either the patent laws or in interpretations of patent laws in the United States and other countries may diminish the value of our intellectual property. Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in our patents or in third-party patents. The degree

of future protection for our proprietary rights is uncertain, because legal means afford only limited protection and may not adequately protect our rights or permit us to gain or keep our competitive advantage. Moreover, the patent application process is also subject to numerous risks and uncertainties, and there can be no assurance that we or any of our future development partners will be successful in protecting CR845/difelikefalin and any other product candidates that we may develop, license or acquire by obtaining and defending patents. For example:

- we may not have been the first to make the inventions covered by each of our pending patent applications and issued patents;
- we may not have been the first to file patent applications for these inventions;
- others may independently develop similar or alternative technologies or duplicate any of our product candidates or technologies;
- it is possible that none of the pending patent applications will result in issued patents;
- the issued patents covering our product candidates may not provide a basis for commercially viable active products, may not provide us with any competitive advantages, or may be challenged by third parties;
- we may not develop additional proprietary technologies that are patentable;
- patents of others may have an adverse effect on our business;
- competitors may file trademark infringement claims or challenges to the validity of our trademark(s);
- noncompliance with governmental patent agencies requirements can result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction, potentially allowing competitors to enter the market earlier than would otherwise have been the case;
- our competitors, many of whom have substantially greater resources than we do and many of whom have made significant investments in competing technologies, may seek or may have already obtained patents that will limit, interfere with, or eliminate our ability to make, use, and sell our potential product candidates; or
- there may be significant pressure on the U.S. government and international governmental bodies to limit the scope of available patent protection both inside and outside the United States for disease treatments that prove successful, as a matter of public policy regarding worldwide health concerns.

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to United States patent law. These include provisions that affect the way patent applications are prosecuted and may also affect patent litigation. The United States Patent Office has developed new regulations and procedures to govern administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, including and in particular, the first to file provisions, became effective on March 16, 2013. The Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our currently pending and future patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business and financial condition.

Patent applications in the United States are generally maintained in confidence for at least 18 months after their earliest effective filing date and in certain circumstances not until granted when no foreign counterpart patent applications are filed. Furthermore, published patent applications may issue at a later date with new and/or amended claims substantially different from those published earlier. Consequently, we cannot be certain we were the first to

invent or the first to file patent applications on CR845/difelikefalin or any other product candidates that we may develop, license or acquire.

Until recent changes to the U.S. Patent Laws, patents and patent applications relating to substantially similar claimed inventions were potentially subject to interference proceedings to determine the first applicant to invent the claimed subject matter. For an interference to be declared against our patents and patent applications, any such interference would be under the 1952 law which was eliminated by the America Invents Act, or AIA, enacted in 2011 and fully effective in 2013. Such an interference would therefore have to relate to a patent or application with an effective filing date before March 16, 2013. No interference with such a patent or application has been declared to date. Therefore, it seems extremely unlikely that we may have to participate in interference proceedings declared by the USPTO to determine priority of invention in the United States against one or more parties claiming the same or similar invention. However, in the unlikely event that such interference was to be declared, the costs of these proceedings could be substantial and it is possible that our efforts would be unsuccessful, resulting in a material adverse effect on our U.S. patent position. The results of these types of proceedings could reduce the scope of, or invalidate, our patent rights, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates. Such results could have a material adverse effect on our results of operations.

In addition, the patentability of claims in pending patent applications covering KORSUVA injection or other CR845/difelikefalin-based product can be challenged by third parties during prosecution in the USPTO under the new AIA law of 2013, for example by third party observations and derivation proceedings, and the validity of claims in issued patents can be challenged by third parties in various post-grant proceedings such as Post-Grant Review, Inter-partes Reexamination, and Inter-partes Review proceedings.

Furthermore, we may not have identified all United States and foreign patents or published applications that affect our business either by blocking our ability to commercialize our drugs or by covering similar technologies that affect our drug market. In addition, some countries, including many in Europe, do not grant patent claims directed to methods of treating humans, and in these countries patent protection may not be available at all to protect our product candidates. Even if patents issue, we cannot guarantee that the claims of those patents will be valid and enforceable or provide us with any significant protection against competitive products, or otherwise be commercially valuable to us.

We also rely on trade secrets to protect our technology, particularly where we do not believe patent protection is appropriate or obtainable. However, trade secrets are difficult to protect. While we use reasonable efforts to protect our trade secrets, our licensors, employees, consultants, contractors, outside scientific collaborators and other advisors may unintentionally or willfully disclose our information to competitors. Enforcing a claim that a third party illegally obtained and is using our trade secrets is expensive and time consuming, and the outcome is unpredictable. In addition, courts outside the United States are sometimes less willing to protect trade secrets. Moreover, our competitors may independently develop equivalent knowledge, methods and know-how.

If we fail to obtain or maintain patent protection or trade secret protection for CR845/difelikefalin or any other product candidate that we may develop, license or acquire, third parties could use our proprietary information, which could impair our ability to compete in the market and adversely affect our ability to generate revenues and achieve profitability.

Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our owned or licensed patents by developing similar or alternative technologies or products in a non-infringing manner.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable,

in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such product candidates might expire before or shortly after such product candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

If we or any current or future collaboration partner are sued for infringing intellectual property rights of third parties, it will be costly and time consuming, and an unfavorable outcome in any litigation would harm our business.

Our ability to develop, manufacture, market and sell KORSUVA injection or any of our other current of future product candidates depends upon our ability to avoid infringing the proprietary rights of third parties, and our commercial success depends upon our ability, and the ability of our collaborators, to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. There is considerable intellectual property litigation in the biotechnology and pharmaceutical industries. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the general field of pain management and cover the use of numerous compounds and formulations in our targeted markets. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future. Because of the uncertainty inherent in any patent or other litigation involving proprietary rights, we and our licensors may not be successful in defending intellectual property claims by third parties, which could have a material adverse effect on our results of operations. Regardless of the outcome of any litigation, defending the litigation may be expensive, time-consuming and distracting to management. In addition, because patent applications can take many years to issue, there may be currently pending applications, unknown to us, which may later result in issued patents that KORSUVA injection or our other current or future product candidates may infringe. There could also be existing patents of which we are not aware that KORSUVA injection or our other current or future product candidates may inadvertently infringe.

There is a substantial amount of litigation involving patent and other intellectual property rights in the biotechnology and biopharmaceutical industries generally. If a third-party claims that we infringe on their products or technology, we could face a number of issues, including:

- infringement and other intellectual property claims which, with or without merit, can be expensive and time consuming to litigate and can divert management’s attention from our core business;
- substantial damages for past infringement which we may have to pay if a court decides that our product infringes on a competitor’s patent;
- a court prohibiting us from selling or licensing our product unless the patent holder licenses the patent to us, which it would not be required to do;
- if a license is available from a patent holder, we may have to pay substantial royalties or grant cross licenses to our patents; and
- redesigning our processes so they do not infringe, which may not be possible or could require substantial funds and time.

If we are found to infringe a third party’s intellectual property rights, we could be required to obtain a license from such third party to continue developing and marketing our products and technology. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. We could be forced, including by court order, to cease commercializing the infringing technology or product. In addition, we could be found liable for monetary damages, including treble damages and attorneys’ fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could materially harm our business. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

We may be involved in lawsuits to protect or enforce our patents or the patents of our licensors, which could be expensive, time consuming and may ultimately be unsuccessful.

Competitors may infringe our issued patents or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents. In addition, in a patent infringement proceeding, a court may decide that a patent of ours is invalid or unenforceable, in whole or in part, construe the patent's claims narrowly or refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated or interpreted narrowly. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation.

Most of our competitors are larger than we are and have substantially greater resources. They are, therefore, likely to be able to sustain the costs of complex patent litigation longer than we could. In addition, the uncertainties associated with litigation could have a material adverse effect on our ability to raise the funds necessary to continue our clinical trials, continue our internal research programs, in-license needed technology, or enter into development partnerships that would help us bring our product candidates to market.

We may need to license certain intellectual property from third parties, and such licenses may not be available or may not be available on commercially reasonable terms.

A third party may hold intellectual property, including patent rights that are important or necessary to the development or commercialization of our products. It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our products, in which case we would be required to obtain a license from these third parties. Such a license may not be available on commercially reasonable terms or at all, which could materially harm our business.

We may be subject to claims that our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

As is common in the biotechnology and pharmaceutical industry, we employ individuals who were previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although no claims against us are currently pending, we may be subject to claims that these employees or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of their former employers. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management.

We may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement rights are not as strong as those in the United States. These products may compete with our product candidates and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries do not favor the enforcement of patents and other intellectual

property protection, which could make it difficult for us to stop the infringement of our patents generally. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

The validity and enforceability of the patents and applications that cover KORSUVA injection and our CR845/difelikefalin product candidates can be challenged by competitors.

For KORSUVA injection and if Oral KORSUVA (CR845/difelikefalin) or any future product candidate is approved by the FDA, one or more third parties may challenge the patents covering these products and product candidates, which could result in the invalidation of, or render unenforceable, some or all of the relevant patent claims. For example, if a third party files an Abbreviated New Drug Application, or ANDA, for a generic drug product containing CR845/difelikefalin, and relies in whole or in part on studies conducted by or for us, the third party will be required to certify to the FDA that either: (1) the patents listed in the Orange Book have expired; (2) the listed patents have not expired, but will expire on a particular date and approval is sought after patent expiration; or (3) the listed patents are invalid or will not be infringed by the manufacture, use or sale of the third-party's generic drug product. A certification that the new product will not infringe the Orange Book-listed patents for CR845/difelikefalin, or that such patents are invalid, is called a paragraph IV certification. If the third party submits a paragraph IV certification to the FDA, a notice of the paragraph IV certification must also be sent to us once the third-party's ANDA is accepted for filing by the FDA. We may then initiate a lawsuit to defend the patents identified in the notice. The filing of a patent infringement lawsuit within 45 days of receipt of the notice automatically prevents the FDA from approving the third-party's ANDA until the earliest of 30 months or the date on which the patent expires, the lawsuit is settled, or the court reaches a decision in the infringement lawsuit in favor of the third party. If we do not file a patent infringement lawsuit within the required 45-day period, the third-party's ANDA will not be subject to the 30-month stay. Litigation or other proceedings to enforce or defend intellectual property rights are often very complex in nature, may be very expensive and time-consuming, may divert our management's attention from our core business, and may result in unfavorable results that could adversely impact our ability to prevent third parties from competing with our products.

Risks Related to Employee Matters and Managing Growth

Our internal information technology systems, or those of our CROs, contract manufacturers or other contractors or consultants, may fail or suffer cybersecurity breaches, loss or leakage of data and other disruptions, which could result in a material disruption of our development programs, commercialization efforts, compromise sensitive information related to our business or prevent us from accessing critical information, potentially exposing us to liability, which could adversely affect our business.

We are increasingly dependent upon information technology systems, infrastructure and data to operate our business. In the ordinary course of business, we collect, store and transmit confidential information (including but not limited to intellectual property, proprietary business information and personal information). It is critical that we do so in a secure manner to maintain the confidentiality and integrity of such confidential information. We also have outsourced elements of our operations to third parties, and as a result we manage a number of third-party contractors who have access to our confidential information.

Despite the implementation of cybersecurity measures, given their size and complexity and the increasing amounts of confidential information that they maintain, our internal information technology systems and those of our third-party CROs, contract manufacturers and other contractors and consultants are potentially vulnerable to breakdown or other damage or interruption from service interruptions, system malfunction, natural disasters, terrorism, war and telecommunication and electrical failures, as well as cybersecurity breaches from inadvertent or intentional actions by our employees, contractors, consultants, business partners and/or other third parties, or from cyber-attacks by malicious third parties (including the deployment of harmful malware, ransomware, denial-of-service attacks, social engineering and other means to affect service reliability and threaten the confidentiality, integrity and availability of information),

which may compromise our system infrastructure or lead to data leakage. Cybersecurity risks have significantly increased in recent years in part because of the proliferation of new technologies, the use of the internet and telecommunication technologies to conduct financial transactions, especially as more employees are working remotely, and the increased sophistication and activities of organized crime, hackers, terrorists, nation-states and other external parties. To the extent that any disruption or cybersecurity breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and reputational damage and the further development and commercialization of our product candidates could be delayed.

While we have not experienced any such system failure, accident or cybersecurity breach to date, we cannot assure you that our data protection efforts and our investment in information technology will prevent significant breakdowns, data leakages, breaches in our systems or other cyber incidents that could adversely affect our business. For example, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our programs and the development and commercialization of KORSUVA injection, if approved, could be delayed. In addition, the loss of clinical trial data could result in delays in our marketing approval efforts and significantly increase our costs to recover or reproduce the data. Furthermore, significant disruptions of our internal information technology systems or cybersecurity breaches could result in the loss, misappropriation and/or unauthorized access, use, or disclosure of, or the prevention of access to, confidential information (including trade secrets or other intellectual property, proprietary business information and personal information), which could result in financial, legal, business and reputational harm to us. For example, any such event that leads to unauthorized access, use, or disclosure of personal information, including personal information regarding our clinical trial subjects or employees, could harm our reputation directly, compel us to comply with federal and/or state breach notification laws and foreign law equivalents, subject us to mandatory corrective action, and otherwise subject us to liability under laws and regulations that protect the privacy and security of personal information, which could result in significant legal and financial exposure and reputational damages that could adversely affect our business.

We may need to significantly increase the size of our organization, and we may experience difficulties in managing growth.

As of November 4, 2021, we had 84 employees. Our management and personnel systems and facilities currently in place may not be adequate to support future growth. In addition, we may not be able to recruit and retain qualified personnel in the future, particularly for sales and marketing positions, due to competition for personnel among pharmaceutical businesses, and the failure to do so could have a significant negative impact on our future product revenues and business results. Our need to effectively manage our operations, growth and various projects requires that we:

- ensure that our consultants and other service providers successfully carry out their contractual obligations, provide high quality results, and meet expected deadlines;
- continue to carry out our own contractual obligations to our licensors and other third parties; and
- continue to improve our operational, financial and management controls, reporting systems and procedures.

We may be unable to successfully implement these tasks on a larger scale and, accordingly, may not achieve our development and commercialization goals.

We may not be able to manage our business effectively if we are unable to attract and retain key personnel.

We may not be able to attract or retain qualified management and commercial, scientific and clinical personnel due to the intense competition for qualified personnel among biotechnology, pharmaceutical and other businesses. If we are not able to attract and retain necessary personnel to accomplish our business objectives, we may experience constraints that will significantly impede the achievement of our development objectives, our ability to raise additional capital and our ability to implement our business strategy.

Our industry has experienced a high rate of turnover of management personnel in recent years. We are highly dependent on the skills and leadership of our management team, including Derek Chalmers, our President and Chief Executive Officer. Our senior management may terminate their employment with us at any time. If we lose one or more members of our senior management team, our ability to successfully implement our business strategy could be seriously harmed. Replacing these employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to develop, gain regulatory approval of and commercialize products successfully. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate additional key personnel. We do not maintain "key person" insurance for any of our executives or other employees.

If we fail to maintain proper and effective internal controls, our ability to produce accurate financial statements on a timely basis could be impaired.

We are subject to the reporting requirements of the Securities Exchange Act of 1934, as amended, the Sarbanes-Oxley Act of 2002 and the rules and regulations of The Nasdaq Global Market. Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, we are now required to perform system and process evaluation and testing of our internal control over financial reporting to allow our management to report on the effectiveness of our internal control over financial reporting and we are also required to have our independent registered public accounting firm issue an opinion on the effectiveness of our internal control over financial reporting on an annual basis.

During the evaluation and testing process, if we identify one or more material weaknesses in our internal control over financial reporting, we will be unable to assert that our internal control over financial reporting is effective. Further, we may in the future discover weaknesses in our system of internal financial and accounting controls and procedures that could result in a material misstatement of our financial statements. Moreover, our internal controls over financial reporting will not prevent or detect all errors and all fraud. A control system, no matter how well designed and operated, can provide only reasonable, not absolute, assurance that the control system's objectives will be met. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that misstatements due to error or fraud will not occur or that all control issues and instances of fraud will be detected. Moreover, we are aware that the remote working arrangements implemented in connection with the COVID-19 pandemic potentially present new areas of risk, including cyber, privacy and productivity risks, and we are carefully monitoring any impact to our internal controls and procedures.

If we are unable to assert that our internal control over financial reporting is effective, or if our independent registered public accounting firm is unable to express an opinion on the effectiveness of our internal control over financial reporting, investors could lose confidence in the reliability of our financial statements, the market price of our stock could decline and we could be subject to sanctions or investigations by The Nasdaq Global Market, the SEC or other regulatory authorities.

Risks Related to Ownership of Our Common Stock

The market price of our common stock has been, and is likely to continue to be, highly volatile, and you may not be able to resell your shares at or above the price you paid for them.

Since our initial public offering in January 2014, our stock price has been volatile and it is likely that the trading price of our common stock will continue to be volatile. As a result of this volatility, investors may not be able to sell their common stock at or above the price paid for the shares. The market price for our common stock may be influenced by many factors, including:

- delays in the commencement, enrollment and ultimate completion of our clinical trials, including our planned trials for KORSUVA (CR845/difelikefalin) injection in the post-operative setting and Oral KORSUVA;
- any delay or refusal on the part of the FDA in approving an NDA for our other current or future product candidates;

- the commercial success of KORSUVA injection and, if approved by the FDA, Oral KORSUVA (CR845/difelikefalin) or any future product candidates;
- results of clinical trials of Oral KORSUVA (CR845/difelikefalin), such as our announcement of topline results from the Phase 2 clinical trial of Oral KORSUVA (difelikefalin tablets) for the treatment of moderate-to-severe pruritus in mild-to-severe AD in April 2021, or any future product candidate or those of our competitors;
- actual or anticipated variations in quarterly or annual operating results;
- failure to meet or exceed financial projections we provide to the public;
- failure to meet or exceed the estimates and projections of the investment community, including securities analysts;
- introduction of competitive products or technologies;
- changes or developments in laws or regulations applicable to our product candidates;
- the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;
- general trends in our industry or economic and market conditions and overall fluctuations in U.S. equity markets, including as a result of the ongoing COVID-19 pandemic;
- developments concerning our sources of manufacturing supply, warehousing and inventory control;
- disputes or other developments relating to patents or other proprietary rights;
- additions or departures of key scientific or management personnel;
- announcements of investigations or regulatory scrutiny of our operations or lawsuits filed against us;
- capital commitments;
- investors' general perception of our company and our business;
- announcements and expectations of additional financing efforts, including the issuance of debt, equity or convertible securities;
- sales of our common stock, including sales by our directors and officers or significant stockholders;
- changes in the market valuations of companies similar to us;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, or divestitures;
- changes in the structure of healthcare payment systems; and
- the other factors described in this "Risk Factors" section.

In addition, the stock market in general, and the market for small pharmaceutical and biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors, such as those related to the ongoing

COVID-19 pandemic, may negatively affect the market price of our common stock, regardless of our actual operating performance.

Further, in the past, stockholders have initiated class action lawsuits against pharmaceutical and biotechnology companies following periods of volatility in the market prices of these companies' stock. Such litigation, if instituted against us, could cause us to incur substantial costs and divert management's attention and resources from our business.

If equity research analysts cease to publish research or reports about us or if they publish unfavorable research or reports about us, our business or our market, our stock price and trading volume could decline.

The trading market for our common stock is likely to be influenced by the research and reports that equity research analysts publish about us and our business. We do not have any control over the analysts or the content and opinions included in their reports. The price of our stock could decline if one or more equity research analysts downgrade our stock or issue other unfavorable commentary or research. If one or more equity research analysts ceases coverage of our company or fails to publish reports on us regularly, demand for our stock could decrease, which in turn could cause our stock price or trading volume to decline.

Our quarterly operating results may fluctuate significantly.

We expect our operating results to be subject to quarterly fluctuations. Our operating results will be affected by numerous factors, including:

- our or our partners' or our collaborators' ability to establish the necessary commercial infrastructure to successfully launch KORSUVA injection without substantial delays, including hiring sales and marketing personnel and contracting with third parties for warehousing, distribution, cash collection and related commercial activities;
- the successful progress of our clinical trials for KORSUVA (CR845/difelikefalin) injection in the post-operative setting, Oral KORSUVA (CR845/difelikefalin) and other potential future product candidates;
- whether the FDA requires us to complete additional, unanticipated studies, tests or other activities prior to approving our other current or future product candidates, which would likely further delay any such approval;
- our ability to identify, enter into and maintain third party manufacturing arrangements capable of manufacturing KORSUVA injection or our other current or future product candidates in commercial quantities;
- our execution of other collaborative, licensing or similar arrangements and the timing of payments we may make or receive under these arrangements;
- variations in the level of expenses related to our future development programs;
- any product liability or intellectual property infringement lawsuit in which we may become involved;
- regulatory developments affecting KORSUVA injection, Oral KORSUVA (CR845/difelikefalin), any of our future product candidates, or the product candidates of our competitors; and
- for KORSUVA injection, and if Oral KORSUVA (CR845/difelikefalin) or any of our future product candidates receives regulatory approval, the level of underlying demand for such product and product candidate and wholesaler buying patterns.

If our quarterly or annual operating results fall below the expectations of investors or securities analysts, the price of our common stock could decline substantially. Furthermore, any quarterly or annual fluctuations in our operating results

may, in turn, cause the price of our stock to fluctuate substantially. We believe that quarterly comparisons of our financial results are not necessarily meaningful and should not be relied upon as an indication of our future performance.

Raising additional funds by issuing securities may cause dilution to existing stockholders and raising funds through lending and licensing arrangements may restrict our operations or require us to relinquish proprietary rights.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, debt financings, grants and license and development agreements in connection with any collaborations. We do not yet have any committed external source of funds. To the extent that we raise additional capital by issuing equity securities, our existing stockholders' ownership will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a common stockholder. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or KORSUVA injection or product candidates or grant licenses on terms that may not be favorable to us. Any debt financing that we enter into may involve covenants that restrict our operations. These restrictive covenants may include limitations on additional borrowing and specific restrictions on the use of our assets as well as prohibitions on our ability to create liens, pay dividends, redeem our stock or make investments. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

The use of our net operating loss carryforwards and research tax credits may be limited.

A portion of our net operating loss, or NOL, carryforwards and R&D tax credits may expire and not be used. As of December 31, 2020, we had federal and state NOL carryforwards of approximately $368.2 million and $273.0 million, respectively, and we also had federal and state R&D tax credit carryforwards of approximately $18.4 million and $1.8 million, respectively. Our NOL carryforwards will begin expiring in 2026 for federal purposes (to the extent such federal NOLs are generated in taxable years beginning on or before December 31, 2017) and 2027 for state purposes if we have not used them prior to that time, and our federal R&D tax credits will begin expiring in 2025 unless previously used. Under the TCJA, as modified by the Coronavirus Aid, Relief, and Economic Security Act, or the CARES Act, NOLs generated in taxable years beginning after December 31, 2017 can be carried forward indefinitely subject, in the case of tax years beginning after 2020, to a limitation of 80% of taxable income, but, except for NOLs arising in taxable years beginning after 2017 and before 2021, for which a 5-year carryback period applies, may not be carried back. It is uncertain if and to what extent various states will conform to the TCJA, as modified by the CARES Act. To the extent that we have not exchanged our Connecticut R&D tax credits for a tax refund, those tax credits carry forward indefinitely. Additionally, our ability to use any NOL and R&D tax credit carryforwards to offset taxable income or tax, respectively, in the future will be limited under Internal Revenue Code Sections 382 and 383, respectively, if we have a cumulative change in ownership of our stock of more than 50% within a three-year period. The completion of our initial public offering in 2014 and our follow-on public offerings in 2015, 2017, 2018 and 2019, together with private placements and other transactions that have occurred, may have triggered such ownership changes. We conducted a 382 analysis in the first quarter of 2021. This analysis showed a limited change of ownership had occurred, and the amount of NOL carryforwards and R&D tax credits that could be utilized annually in the future to offset taxable income or tax, respectively. In addition, since we will need to raise substantial additional funding to finance our operations, we may undergo ownership changes in the future. Any such annual limitation may significantly reduce the utilization of the NOL carryforwards and R&D tax credits before they expire. In addition, certain states have in the past suspended use of NOL carryforwards for certain taxable years (including without limitation legislation enacted by California in June 2020 that suspends the use of California NOLs and limits the use of California R&D tax credits for certain years), and other states are considering similar measures. As a result, we may incur higher state income tax expense in the future. Depending on our future tax position, limitations on our ability to use NOL carryforwards in states in which we are subject to income tax could have an adverse impact on our results of operations and financial condition.

New or future changes to tax laws could materially adversely affect our company.

On December 22, 2017, President Trump signed into law the TCJA, which significantly amends the Internal Revenue Code of 1986, which was modified by the CARES Act. The TCJA, as modified by the CARES Act, among other things, reduces the corporate tax rate from a top marginal rate of 35% to a flat rate of 21%, limits the tax deduction for interest expense to 30% of taxable income, eliminates certain NOL carrybacks, imposes a one-time tax on offshore earnings at reduced rates regardless of whether they are repatriated, allows immediate deductions for certain new investments instead of deductions for depreciation expense over time, and modifies or repeals many business deductions and credits. We continue to examine the impact these changes may have on our business. Notwithstanding the reduction in the corporate income tax rate, the overall impact of the TCJA and CARES Act, or any other future changes in tax laws, is uncertain and our business and financial condition could be adversely affected. For example, proposals have recently been made in Congress (which have not yet been enacted) to increase the federal income tax rate applicable to corporate income and make other tax law changes that could have a material adverse impact on us. The impact of the TCJA and CARES Act and any future changes in tax laws on holders of our common stock is also uncertain and could be adverse.

Because we do not intend to pay dividends on our common stock, your returns will be limited to any increase in the value of our stock.

We have never declared or paid any cash dividends on our capital stock. We currently intend to retain all available funds and any future earnings to support our operations and finance the growth and development of our business and do not anticipate declaring or paying any cash dividends on our common stock for the foreseeable future. Any return to stockholders will therefore be limited to the appreciation of their stock, if any. Investors seeking cash dividends should not purchase our common stock.

Provisions in our corporate charter documents and under Delaware law may prevent or frustrate attempts by our stockholders to change our management and hinder efforts to acquire a controlling interest in us, and the market price of our common stock may be lower as a result.

There are provisions in our certificate of incorporation and bylaws, as amended, that may make it difficult for a third party to acquire, or attempt to acquire, control of our company, even if a change in control was considered favorable by you and other stockholders. For example, our Board of Directors has the authority to issue up to 5,000,000 shares of preferred stock and to fix the price, rights, preferences, privileges, and restrictions of the preferred stock without any further vote or action by our stockholders. The issuance of shares of preferred stock may delay or prevent a change in control transaction. As a result, the market price of our common stock and the voting and other rights of our stockholders may be adversely affected. An issuance of shares of preferred stock may result in the loss of voting control to other stockholders.

Our charter documents also contain other provisions that could have an anti-takeover effect, including:

- our Board of Directors are divided into three classes, with only one class of directors elected each year;
- our stockholders are entitled to remove directors only for cause upon a 66 2/3% vote;
- our stockholders are not permitted to take actions by written consent;
- our stockholders are not permitted to call a special meeting of stockholders; and
- our stockholders must give us advance notice of their intent to nominate directors or submit proposals for consideration at stockholder meetings.

In addition, we are subject to the anti-takeover provisions of Section 203 of the Delaware General Corporation Law, which regulates corporate acquisitions by prohibiting Delaware corporations from engaging in specified business

combinations with particular stockholders of those companies. These provisions could discourage potential acquisition proposals and could delay or prevent a change in control transaction. They could also have the effect of discouraging others from making tender offers for our common stock, including transactions that may be in your best interests. These provisions may also prevent changes in our management or limit the price that investors are willing to pay for our stock.

Item 2. ***Unregistered Sales of Equity Securities and Use of Proceeds.***

None.

Item 3. ***Defaults upon Senior Securities.***

None.

Item 4. ***Mine Safety Disclosures.***

Not applicable.

Item 5. ***Other Information.***

None.

Item 6. ***Exhibits.***

Exhibit No.	Description of Exhibit	Incorporated by Reference			
		Form	File No.	Exhibit No.	Date Filed
3.1	Amended and Restated Certificate of Incorporation.	8-K	001-36279	3.1	February 7, 2014
3.2	Amended and Restated Bylaws.	8-K	001-36279	3.2	February 7, 2014
10.1†#	API Commercial Supply Agreement between Cara Therapeutics, Inc. and Polypeptide Laboratories S.A.				
10.2	Employment Agreement with Christopher Posner	8-K	001-36279	10.1	November 3, 2021
10.3	Separation Agreement with Derek Chalmers	8-K	001-36279	10.2	November 3, 2021
31.1†	Certification of Chief Executive Officer of Cara Therapeutics, Inc. pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934.				
31.2†	Certification of Chief Financial Officer of Cara Therapeutics, Inc. pursuant to Rule 13a-14(a)/15d-14(a) of the Securities Exchange Act of 1934.				
32.1†*	Certifications of Chief Executive Officer and Chief Financial Officer of Cara Therapeutics, Inc. pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.				
101.CAL†	Inline XBRL Taxonomy Extension Calculation Linkbase.				
101.INS†	Inline XBRL Instance Document.				
101.LAB†	Inline XBRL Taxonomy Extension Label Linkbase.				
101.PRE†	Inline XBRL Taxonomy Extension Presentation Linkbase.				
101.SCH†	Inline XBRL Taxonomy Extension Schema Linkbase.				
101.DEF†	Inline XBRL Taxonomy Extension Definition Linkbase Document.				
104†	Cover page interactive data file (formatted as Inline XBRL and contained in Exhibit 101).				

† Filed herewith.

Certain portions of this exhibit (indicated by asterisks) have been omitted because they are not material and are the type that the Registrant treats as private or confidential.

* This certification is furnished and will not be deemed filed for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to the liability of that section, nor shall it be deemed incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, irrespective of any general incorporation language contained in such filing.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

CARA THERAPEUTICS, INC.

Date: November 8, 2021

By /s/ DEREK CHALMERS
Derek Chalmers, Ph.D., D.Sc.
President, Chief Executive Officer and Director
(Principal Executive Officer)

Date: November 8, 2021

By /s/ THOMAS REILLY
Thomas Reilly
Chief Financial Officer
(Principal Financial and Accounting Officer)

CERTAIN PORTIONS OF THIS EXHIBIT (INDICATED BY ***) HAVE BEEN EXCLUDED PURSUANT TO ITEM 601(B)(10) OF REGULATION S-K BECAUSE THEY ARE BOTH NOT MATERIAL AND ARE THE TYPE THAT THE COMPANY TREATS AS PRIVATE AND CONFIDENTIAL.

API COMMERCIAL SUPPLY AGREEMENT

THIS **API COMMERCIAL SUPPLY AGREEMENT** (this "Agreement") is entered into and effective as of July, 5th, 2021 (the "Effective Date") by and between POLYPEPTIDE LABORATORIES S.A., a limited liability corporation organized under the laws of France and having its principal office at 7, rue de Boulogne, 67100 Strasbourg, France ("PolyPeptide"), and CARA THERAPEUTICS, a limited liability company having its principal offices at 4 Stamford Plaza, 107 Elm Street, 9th Floor, Stamford, CT, 06902 USA ("CARA").

PolyPeptide and CARA are sometimes referred to herein individually as a "Party" and collectively as the "Parties."

RECITALS

WHEREAS, CARA is engaged in the research, development and commercialization of proprietary pharmaceutical products.

WHEREAS, PolyPeptide is a company that has developed substantial expertise in manufacturing peptides, including the API (as defined herein), for use in pharmaceutical products; and

WHEREAS, the Parties desire to enter into a supply agreement pursuant to which PolyPeptide will manufacture and supply the API to CARA.

NOW, THEREFORE, in consideration of the foregoing recitals, mutual covenants, agreements, representations and warranties contained herein, the Parties hereby agree as follows:

Article I. Definitions

Section 1.01 "Affiliate" means, with respect to a particular Party, a corporation or other business entity that, directly or indirectly, controls, is controlled by, or is under common control with such Party, for so long as such control continues. As used in this Section, the term "controls" means (with correlative meanings for the terms "controlled by" and "under common control with") that the applicable entity: (a) owns, directly or indirectly, at least 50% of the voting securities or capital stock of the applicable Party, or owns (directly or indirectly) other comparable ownership interest with respect to the applicable Party if it is a business entity other than a corporation; or (b) otherwise possesses, directly or indirectly, the actual power to direct or cause the direction of the management and policies of the applicable Party, whether through the ownership or control of voting securities, by contract or otherwise.

Section 1.02 "Agreement" means this API Commercial Supply Agreement, including all Schedules and Appendixes hereto, as the same shall be amended or supplemented by a mutual written agreement of the Parties pursuant to Section 15.07.

Section 1.03 "API" means the active pharmaceutical ingredient containing the chemical substance known as CR845/DIFELIKEFALIN, having the structure set forth in Appendix 1 of this Agreement.

Section 1.04 "API Price" has the meaning provided in Section 3.01 of this Agreement.

Section 1.05 "API Product Developments" has the meaning provided in Section 7.02(a) of this Agreement.

Section 1.06 "API Specifications" means all specifications that are applicable to the API delivered under this Agreement; such specification are set forth in Appendix 2 of this Agreement.

Section 1.07 "Approved Representative" means an employee or consultant of a Party who is

designated by such Party and has a bona fide need to participate in the administration or management of this Agreement and who is bound by a confidentiality undertaking at least as protective as the provisions set forth in Article XII.

Section 1.08 "Batch" means the quantity of API produced by PolyPeptide in a single manufacturing run as indicated in Appendix 4.

Section 1.09 "Batch Records" means , with respect to a particular production run conducted by PolyPeptide for manufacturing one batch of API, the completed batch records, in the form of the Master Batch Records, containing all the relevant manufacturing details and information for such production run, including any deviations which, for clarity, shall be included in the completed batch records.

Section 1.10 "Calendar Quarter" means each three-month period beginning each January 1, April 1, July 1 and October 1 during the Term. The initial Calendar Quarter shall begin on the Effective Date and shall end on the expiration or earlier termination date of the Term.

Section 1.11 "Calendar Year" means each twelve-month period beginning each January 1 during the Term. The initial Calendar Year shall begin on the Effective Date and end on the first December 31 of the Term, and the last Calendar Year shall begin on January 1 of the last year of the Term and end on the expiration or earlier termination date of the Term.

Section 1.12 "CARA" has the meaning in the preamble of this Agreement.

Section 1.13 "CARA Confidential Information" has the meaning provided in Section 12.01 of this Agreement.

Section 1.14 "CARA Intellectual Property" means all Intellectual Property relating to [***] that (a) was owned, licensed or controlled by CARA or a CARA Affiliate as of the Effective Date, or (b) is developed or acquired by CARA or a CARA Affiliate after the Effective Date, including the API Product Developments.

Section 1.15 "CARA License" has the meaning provided in Section 7.03(a) of this Agreement.

Section 1.16 "Certificate of Analysis" means a document identified as such, to be provided by PolyPeptide to CARA in connection with its delivery of API ordered hereunder, that (a) sets forth the analytical test results for a specified lot of API shipped to CARA or its designee hereunder and includes a certified quality control protocol, (b) states that such API is in conformance with the API Specifications, and (c) states that such API is manufactured in accordance with the API Specifications, Legal Requirements and (c)GMPs.

Section 1.17 "Change of Control" means, with respect to a particular Party, any proposed transaction or series of transactions which shall result in (a) any Person other than a Party having direct or indirect ownership of more than 50% of the voting stock or assets of such Party or an Affiliate that controls such Party by Persons who are not shareholders of such Party or the Affiliate that controls such Party as of the Effective Date, or (b) the merger of a Party with or into a Third Party in a transaction in which such Party is not the surviving or acquiring Person.

Section 1.18 "CMC" means the chemistry, manufacturing and controls section(s) and data in a Drug Application.

Section 1.19 "Confidential Information" has the meaning provided in Section 12.01 of this Agreement.

Section 1.20 "Consent" means any consent, authorization, permit, certificate, license or approval of, exemption by, or filing or registration with, any Governmental Body or other Person.

Section 1.21 "Current Good Manufacturing Practices" or "(c)GMPs" means all applicable standards, laws and regulations relating to manufacturing practices for active pharmaceutical ingredients, including (a) the principles detailed in the Q7A Good Manufacturing Practice Guidance For Active Pharmaceutical Ingredients (ICH Q7A), and (b) the principles promulgated

by any applicable Governmental Body having jurisdiction over the manufacture of the API, in the form of laws, rules or regulations, in each case as in effect in France and the United States (to the extent the laws of the United States are directly applicable to the manufacture of API by PolyPeptide) at the Effective Date and as amended, promulgated or accepted by any applicable Governmental Body having jurisdiction over the manufacture of the API from time to time during the Term.

Section 1.22 "Days" (whether or not the word is capitalized) means, except where specified otherwise, calendar days.

Section 1.23 "Defect" or "Defective" means a failure to comply with or meet the API Specifications and/or the Quality Requirements at the time of delivery and as such term is further described or defined in the Quality Agreement in Appendix 5.

Section 1.24 "Readiness for Shipment" means the date specified by CARA in a Purchase Order that PolyPeptide shall ensure the API ordered in such Purchase Order is ready for shipment in accordance with this Agreement by such date.

Section 1.25 "Drug Application" means a 'new drug application' (as such term is used under the United States Federal Food, Drug and Cosmetic Act) filed with the FDA for the Product, including any amendments and/or supplements thereto, and any product license or any equivalent drug application or similar pharmaceutical product approval for the Product administered by any foreign Governmental Body, and any supplement, extension or renewal of any of the foregoing.

Section 1.26 "Effective Date" has the meaning in the preamble of this Agreement.

Section 1.27 "Facility" means Polypeptide's manufacturing facility located at 7, rue de Boulogne, 67100 Strasbourg, France, or such other FDA approved facility controlled by Polypeptide (or its Affiliate) as agreed in writing by the Parties.

Section 1.28 "FDA" means the United States Food and Drug Administration, or any successor agency thereof.

Section 1.29 "Force Majeure Event" has the meaning provided in Section 13.01 of this Agreement.

Section 1.30 "Forecast" has the meaning provided in Section 2.04 of this Agreement.

Section 1.31 "Governmental Body" means any government, any state, province or other political subdivision thereof, any entity with legal authority to exercise executive, legislative, judicial, regulatory or administrative functions, or any division of the FDA (as applicable) and any other applicable counterpart agency or foreign equivalent that administers the Legal Requirements.

Section 1.32 "Indemnified Party" has the meaning provided in Section 10.03 of this Agreement.

Section 1.33 "Indemnifying Party" has the meaning provided in Section 10.03 of this Agreement.

Section 1.34 "Initial Term" has the meaning provided in Section 14.01 of this Agreement.

Section 1.35 "Intellectual Property" means (a) patents, patent rights, provisional patent applications, patent applications, designs, registered designs, registered design applications, industrial designs, industrial design applications and industrial design registrations, including any and all divisions, continuations, continuations-in-part, extensions, restorations, substitutions, renewals, registrations, revalidations, reexaminations, reissues or additions, including supplementary certificates of protection, of or to any of the foregoing items; (b) copyrights, copyright registrations, copyright applications, original works of authorship fixed in any tangible medium of expression, including literary works (including all forms and types of computer software, including all source code, object code, firmware, development tools, files, records and data, and all documentation related to any of the foregoing), musical, dramatic, pictorial, graphic

and sculptured works; (c) trade secrets, technology, developments, discoveries and improvements, know-how, proprietary rights, formulae, confidential and proprietary information, technical information, techniques, inventions, designs, drawings, procedures, processes, models, formulations, manuals and systems, whether or not patentable or copyrightable, including all biological, chemical, biochemical, toxicological, pharmacological and metabolic material and information and data relating thereto and formulation, clinical, analytical and stability information and data which have actual or potential commercial value and are not available in the public domain; (d) trademarks, trademark registrations, trademark applications, service marks, service mark registrations, service mark applications, business marks, brand names, trade names, trade dress, names, logos and slogans, Internet domain names, and all goodwill associated therewith; and (e) all other intellectual property or proprietary rights worldwide, in each case whether or not subject to statutory registration or protection.

Section 1.36 "Lead-time" means the specified number of months set forth in Appendix 4 of this Agreement, which is the minimum amount of time required between the date Polypeptide receives a Purchase Order hereunder until the API covered by such order must be ready for shipment to CARA (or its designee). .

Section 1.37 "Legal Requirements" means, concerning PolyPeptide and its activities and obligations hereunder, any and all French national, local, municipal, state or provincial laws, statutes, ordinances, rules or regulations now or hereafter enacted or promulgated by any French Governmental Body, and, to the extent directly applicable to the manufacture of API by PolyPeptide pursuant to this Agreement, any and all laws and regulations now or hereafter enacted or promulgated by a relevant Governmental Body, in each case as applicable to the development, manufacture, supply and/or sale of the API by Polypeptide or to any aspect thereof. "Legal Requirements" means, concerning CARA and its activities and obligations hereunder, any and all national, local, municipal, state or provincial laws, statutes, ordinances, rules or regulations now or hereafter enacted or promulgated by any United States or other applicable relevant Governmental Body applicable to ordering, purchase, use, marketing and/or sale of the API supplied hereunder to CARA.

Section 1.38 "Losses" means, collectively, any and all liabilities, damages, losses, costs, expenses, including obligations, liens, judgments, fines and penalties imposed upon or incurred by an Indemnified Party.

Section 1.39 "Manufacturing SOPs" means the specific methods, techniques, processes and standard operating procedures that are to be used by PolyPeptide to manufacture API, including the applicable Quality Control Procedures applicable to the API.

Section 1.40 "Master Batch Records" means the master batch records for the API as established by the Parties under Section 2.08, including the applicable Manufacturing SOPs, the in-process testing and QA/QC testing for such API, which are to be used in the manufacture by PolyPeptide of the API hereunder.

Section 1.41 "Nonconforming API" means API delivered by PolyPeptide that breaches or otherwise does not meet or conform to the warranty in Section 9.01(b), other than due to defects that are shown to have been caused by damage or mishandling occurring after delivery by PolyPeptide of such API to the carrier under Section 3.05(a).

Section 1.42 "Party" and "Parties" have the meanings given such terms, respectively, in the preamble of this Agreement.

Section 1.43 "Person" means any individual, corporation, company, partnership, trust, incorporated or unincorporated association, joint venture or other entity of any kind.

Section 1.44 "PolyPeptide" has the meaning in the preamble of this Agreement.

Section 1.45 "PolyPeptide Approval(s)" means the approval(s) of the Facility as a (c)GMP facility for the manufacture of the API by the FDA and, as applicable, by any other applicable Governmental Body having jurisdiction to approve the Facility.

Section 1.46 "PolyPeptide Confidential Information" has the meaning provided in Section 12.02 of this Agreement.

Section 1.47 "PolyPeptide Intellectual Property" means (a) all Intellectual Property owned, licensed or controlled by PolyPeptide as of the Effective Date, and (b) all Intellectual Property developed or acquired by PolyPeptide after the Effective Date that does not directly relate to the API, the Product or the development or manufacture of the API or the Product.

Section 1.48 "PolyPeptide License" has the meaning provided in Section 7.03(b) of this Agreement.

Section 1.49 "PolyPeptide's Minimum Capacity" has the meaning provided in Section 2.03 of this Agreement.

Section 1.50 "Pre-Approval Inspection" means an inspection of manufacturing operations, records and facilities conducted prior to approval of a new product by the FDA or by any other applicable Governmental Body having jurisdiction to approve the Facility as a (c)GMP facility for the manufacture of the API.

Section 1.51 "Product" means any finished pharmaceutical product of CARA that incorporates the API supplied by PolyPeptide pursuant to this Agreement.

Section 1.52 "Purchase Order" has the meaning provided in Section 2.05 of this Agreement.

Section 1.53 "Quality Agreement" means the agreement identified in Section 4.05 of this Agreement, as amended or supplemented by the Parties as provided in Section 15.07. The latest version of PolyPeptide's form of the Quality Agreement is attached in Appendix 5 of this Agreement.

Section 1.54 "Quality Requirements" means any and all requirements, specifications, procedures etc. for the manufacture of API, as agreed from time to time by the Parties in writing, including the relevant standards for the industry and sector at any current time, the applicable legal requirements as specified by the relevant authorities, including as such matters are set forth in the Quality Agreement.

Section 1.55 "Readiness for Shipment" means the date specified by CARA in a Purchase Order that PolyPeptide shall ensure the API-readiness for shipment in accordance with this Agreement. ***]***

Section 1.56 "Secondary Supplier" has the meaning set forth in Section 2.05 of this Agreement.

Section 1.57 "Shipment Date" means the date specified by CARA in a Purchase Order that PolyPeptide shall ship the API covered by such Purchase Order in accordance with this Agreement.

Section 1.58 "Subcontractor" means any Third Party that performs on PolyPeptide's behalf any of the activities with respect to the manufacture and supply of API under this Agreement.

Section 1.59 "Term" has the meaning provided in Section 14.01 of this Agreement.

Section 1.60 "Third Party" means any Person other than the Parties or their respective Affiliates.

Section 1.61 "Third Party Materials" means (a) all main raw materials, components, work-in-process and other ingredients required to manufacture the API, and (b) all packaging materials used in the manufacture, storage and shipment of the API.

Section 1.62 "Validation" means a procedure for establishing documentation evidence that a specific system or facility is constructed and operates according to a predetermined set of specifications, protocols and guidelines.

Article II. Sale and Purchase of API

Section 2.01 Manufacture of API. Subject to and in accordance with the terms and conditions of this Agreement, PolyPeptide shall manufacture API at the Facility for sale and supply to CARA, in the amounts as set forth in Purchase Orders provided by CARA. PolyPeptide may not manufacture API at locations other than the Facility without the prior written Consent of CARA, such Consent not to be unreasonably withheld or delayed and as provided in the Quality Agreement. For the avoidance of doubt, the Parties agree that this Agreement obligate CARA to purchase all its requirements of the API from PolyPeptide, except as otherwise set forth in this Agreement.

Section 2.02 Minimum Purchase Requirement. CARA agrees to purchase from PolyPeptide, and PolyPeptide agrees to supply to CARA, during each Calendar Year during the Term, the amounts of API set forth in the Forecast for such Calendar Year (or such prorated amount in the case of a partial year) during the Term.

Section 2.03 Forecasts. The Forecast for 2021 as agreed between the Parties is set forth in Appendix 3 of this Agreement. Such Forecast for 2021 will be binding upon CARA and PolyPeptide. Not later than June, 30. 2021, CARA shall provide PolyPeptide with a rolling estimated forecast of its requirements for the API for each Calendar Quarter in the next eight Calendar Quarters (each such forecast, a "Forecast"), and CARA shall update such Forecast quarterly by the date 15 days prior to the commencement of the next Calendar Quarter to provide the rolling forecast for the following eight Calendar Quarters during the Term. Each such Forecast shall be a good faith rolling forecast of its expected orders of API quarterly during the subsequent eight Calendar Quarters (i.e. this rolling Forecast will always include estimated orders of API during each of the 8 Calendar Quarters following the date of the Forecast). In each case, the rolling Forecast for the next 2 upcoming Calendar Quarters shall be binding on CARA and PolyPeptide (i.e., CARA shall order during such 2 quarters, under Section 2.05, at least the amounts of API set forth in the applicable Forecast for such 2 subsequent quarters, and PolyPeptide shall supply such API so ordered), and for the next 2 Calendar Quarters in the Forecast, the estimates for orders cannot vary (in the final binding Forecast) by more than 25% from the amounts forecasted in such Forecast for such quarters, and the 4 last quarters of the applicable Forecast shall be non-binding. CARA shall give PolyPeptide notice as soon as possible if, at any time, CARA determines in good faith that the actual requirements for the API for any given quarter will be significantly different that the rolling Forecast most recently provided to PolyPeptide, and the Parties shall in such case discuss in good faith and seek to agree on modifying the applicable binding part of the Forecast, provided that in any case the binding part of such Forecast shall remain unchanged and shall remain binding upon CARA and PolyPeptide, as set forth in the applicable Forecast for the first 2 quarters covered by such Forecast unless the Parties otherwise agree in writing. Notwithstanding the above, each such Forecast is provided for the purpose of production planning and is not to be construed as a Purchase Order.

Section 2.04 Purchase Orders. From time to time during the Term, CARA shall deliver to PolyPeptide one or more purchase orders ("Purchase Orders") which shall order API volumes, in the amounts specified in such Purchase Order(s), for manufacture and supply to CARA by PolyPeptide hereunder. For each Calendar Quarter during the Term, CARA shall deliver to PolyPeptide Purchase Order(s) ordering in aggregate the amount of API at least equal to the binding portion of the most recent Forecast for such Calendar Quarter. Each Purchase Order shall specify the quantity of API ordered, the Shipment Date and the destination for delivery of the API. The Purchase Orders may be delivered electronically or by other means to such location as PolyPeptide shall designate. PolyPeptide shall deliver such ordered API to CARA's specified carrier on the Shipment Date as specified by CARA in the applicable Purchase Order. During any Calendar Quarter, CARA shall be entitled to submit Purchase Order(s) ordering amounts of API that in the aggregate exceed the amounts of API specified to be ordered during such Calendar Quarter in the most recent submitted Forecast for such Calendar Quarter, and such Purchase Orders shall be binding on PolyPeptide up to amounts of API in excess of 25% over the binding amounts in such

Forecast, and *provided that* for any amounts of API ordered in excess of such 25% amount, PolyPeptide shall use reasonable efforts to supply such excess amounts ordered (beyond the amount equal to 125% of the binding amount for the quarter) but PolyPeptide shall not otherwise be bound by such excess orders. If PolyPeptide shall not be able to deliver API to CARA's carrier by the Shipment Date specified in a Purchase Order, PolyPeptide shall notify CARA promptly in writing upon discovery of its inability to comply with the terms of this Section 2.05; provided, however, that such notification shall not relieve PolyPeptide of any liability for failure to deliver API to CARA's carrier on such Shipment Date. In case of any such delays in delivery of ordered API, and as a non-exclusive remedy for such delays, CARA shall be entitled to deduct a discount of 1% (one per cent) total API Price of the applicable order but limited to a penalty of maximum 10% (ten per cent), from the API Price per such purchase order, per week that the delivery is delayed beyond the specified Shipment Date, if the delivery is more than 5 (five) working days after such specified date, and provided that the shipment delay is not caused directly by CARA. In case of any such shipment delay, PolyPeptide is committed to discuss and agree corrective actions and in any event to use good faith diligent efforts to resolve the issue and to deliver the ordered API as soon as possible. In case of any delays in delivery of API, and including any further delays following agreement of such corrective actions, CARA shall be entitled to the aggregate suffered loss and to obtain all remedies for breach of contract.

If PolyPeptide fails to meet the Purchase Order or any portion thereof on or before the applicable Shipment Date, in addition to other remedies that may be available to CARA under the Legal Requirements for breach of contract or otherwise, CARA may purchase the shortage of such API from Third Parties (a "Secondary Supplier").

If, for any particular Calendar Quarter during the Term, CARA does not submit Purchase Order(s) during such Calendar Quarter ordering an aggregate amount of API from PolyPeptide in the amount specified in the binding portion of the Forecast for such Calendar Quarter, then as PolyPeptide's sole and exclusive remedy for CARA not submitting such Purchase Order amounts, CARA shall pay to Polypeptide, within 30 days of receipt of Polypeptide's corresponding invoice, an amount equal to then current [***] for such Calendar Quarter *less* the actual amount of API ordered by CARA under Purchase Orders submitted during such Calendar Quarter.

Section 2.05 Accommodations for Significant Excess Requirements. Should CARA require, during any Calendar Quarter, additional quantities of API significantly beyond those referred in the binding Forecast for such Calendar Quarter, the Parties shall negotiate in good faith to amend the Forecast to accommodate such requirement in whole or in part. PolyPeptide will do its best endeavours to deliver any such additional quantities amounts of API, in addition to its obligations under Section 2.05.

Section 2.06 Meetings Regarding Ordering and Forecasting. Unless otherwise mutually agreed, the Parties shall meet or otherwise communicate no less than once each Calendar Quarter to discuss the Forecasts delivered by CARA pursuant to this Agreement and other matters relevant to the ordering, manufacture and supply of API hereunder. Such meetings shall typically involve the Approved Representatives (and may involve other appropriate employees or agents designated by the applicable Party). The Parties shall use commercially reasonable efforts to accommodate technical meetings requested by both Parties.

Section 2.07 **Master Batch Records and Manufacturing SOPs.** During the Term, the Parties shall establish and maintain specific Master Batch Records, including Manufacturing SOPs, to be used by PolyPeptide to manufacture the API. The specific Manufacturing SOPs shall be based upon the applicable PolyPeptide Intellectual Property and applicable Cara technology, The Master Batch Records shall contain such items and requirements as typical in the industry for manufacturing processes applicable to similar bulk pharmaceutical manufacturing, and shall be set forth in a written document signed by both Parties. If appropriate during the Term (such as, to include new manufacturing Inventions that are useful to manufacturing the API), the Parties will meet and agree on appropriate amendments or

modifications to the applicable API Specifications, Manufacturing SOPs and/or the Master Batch Records; the details of the procedure for amending the API Specifications, Manufacturing SOPs and/or the Master Batch Records shall be as specified in the Quality Agreement. The Parties acknowledge and agree that current Master Batch Records have been agreed as of the Effective Date.

Article III. Financial Matters

Section 3.01 API Price: Appendix 4 of this Agreement sets forth the price per gram for the API (the "API Price") supplied to CARA hereunder under Purchase Orders.

Section 3.02 Commercial Invoices/ Invoicing specification. PolyPeptide will invoice an upfront payment to CARA for 30% of the API Price for the amount of API ordered under a given Purchase Order of API submitted by CARA, such invoice to be provided on or after the date that PolyPeptide receives the corresponding Purchase Order. The remaining 70% of the API Price for such order shall be invoiced upon the delivery of the total amount of API ordered under the corresponding Purchase Order.

Section 3.03 Payment. Payments for API invoiced consistent with Section 3.02 above shall be due 30 days from the date of invoice, subject in each case to CARA's right to dispute invoiced amounts and/or delay the payment of invoiced amounts disputed by CARA in good faith, including the rights set forth in Article V.

Section 3.04 Payment Denominations. The API Price, all invoiced amounts and all payments to be made under this Agreement shall be in paid in Euros.

Section 3.05 Shipment; Title; Transport.

(a) General. All API shall be sold [***] (as defined in INCOTERMS® 2020 of the I.C.C.) following shipment instructions provided by CARA. Freight charges will be supported by CARA and will be communicated in written form by PolyPeptide to CARA once the shipment instructions are confirmed by CARA. PolyPeptide shall package the API for shipment (including in containers, packaging, container closure systems and labeling) in accordance with the API Specifications and its customary practices as reasonably acceptable to CARA. Any additional costs or expenses for PolyPeptide resulting from CARA's required changes in the packaging and/or labeling of the API shall be paid by CARA to PolyPeptide. Delivery of a Batch of API ordered under a Purchase Order shall take place by PolyPeptide at the point in time when PolyPeptide has notified CARA that the Batch is ready for collection by CARA, which shall be on the Shipment Date specified in such Purchase Order (subject to the applicable terms of Section 2.05). At the time PolyPeptide delivers particular API under a Purchase Order pursuant to this Section 3.05(a), PolyPeptide shall deliver to CARA a Certificate of Analysis with respect to such API, attested to and signed by a corporate officer of PolyPeptide. CARA shall notify PolyPeptide if it is unable to collect the delivered Batch within that timeframe. [***] of a delivered Batch that is not collected with ten business Days of delivery.

(b) Title/Risk of Loss. Risk of loss for any API shall pass from PolyPeptide to CARA when such API is delivered to CARA's designated carrier as provided in Section 3.05(a); provided, however, that nothing in this Article III shall in any manner limit CARA's rights under Article VI. Title to any API shall pass from PolyPeptide to CARA when such API is fully paid by CARA to Polypeptide as provided in Section 3.02. If API is rejected by CARA after delivery under this Agreement, and such API is to be returned to PolyPeptide, then title to and risk of loss for such rejected API shall pass from CARA to PolyPeptide when such API is made available to the carrier selected by CARA. All returned API shall be shipped [***] (as defined in INCOTERMS® 2010) from the place where the API is stored when CARA makes the decision to return it.

Section 3.06 Single Order. To the extent reasonably possible, API that is purchased in a single Purchase Order shall be delivered by PolyPeptide in a single shipment, unless CARA directs that such API should be delivered to more than one location, in which case the order shall be delivered to the applicable carrier(s) for shipment to the differing locations in the amounts specified in the Purchase Order for delivery to each such location.

Section 3.07 Retest date. The API delivered by PolyPeptide under a particular Purchase Order shall have, as of the date of such delivery, a minimum retest date of 48 months as of the applicable date of manufacture. The minimum retest date set forth in the immediately preceding sentence is based on existing stability data. If future stability data justifies a longer retest date, the Parties agree to discuss in good faith an extended minimum retest date as of the applicable date of delivery.

Section 3.08 Taxes. CARA shall pay and otherwise be responsible for all applicable sales, VAT, goods, services, transfer and similar taxes, custom duties or charges in connection with the supply of API pursuant to this Agreement, excluding any income tax or taxes levied with respect to gross receipts or amounts of taxes assessable on PolyPeptide's operations as a whole (such as property taxes or utilities assessments), payable by PolyPeptide under the Legal Requirements with respect to amounts of API Price payable under this Agreement. Any tax that one Party is required to withhold and pay on behalf of the other Party with respect to amounts payable under this Agreement shall be deducted from said amounts prior to payment to the other Party; provided, however, that, in regard to any tax so deducted, the Party making the withholding shall give or cause to be given to the other Party such assistance as may reasonably be necessary to enable that other Party to claim exemption therefrom or credit therefore and in each case shall furnish the Party on whose behalf amounts were withheld proper evidence of the taxes paid on its behalf. Each Party shall comply with reasonable requests of the other Party to take any proper actions that may minimize any withholding obligation.

Article IV. Manufacture of API

Section 4.01 General. PolyPeptide shall manufacture, test, package, store, handle, label, release and ship all API in accordance with the API Specifications, applicable (c)GMPs, applicable Legal Requirements, and the terms of this Agreement and of the Quality Agreement.

Section 4.02 API Specification Changes.

(a) CARA Requested Changes. During the Term, except as set forth in Section 4.02(c), [***] in a manner that would materially negatively impact PolyPeptide's performance of its API manufacturing obligations hereunder unless it receives the written consent of PolyPeptide to the particular change, which consent shall not be unreasonably withheld or delayed. If CARA requests, and PolyPeptide consents, a discretionary change to the API Specifications, PolyPeptide shall make all revisions to the API Specifications requested by CARA and approved by PolyPeptide. CARA retains at all times the right and responsibility for final approval of the API Specifications. CARA shall pay PolyPeptide all documented reasonable amounts incurred in implementing a change to the API Specifications requested by CARA under this Section 4.02(a). For all changes to the API Specifications requested by CARA pursuant to this Section 4.02, CARA shall, in its discretion, following consultation with PolyPeptide, if reasonably practicable, either (i) perform, or arrange for the performance of, all development work in connection therewith or have PolyPeptide perform such development work at the Facility at CARA's expense. For the avoidance of doubt, Section 4.02(a) (i) does not give CARA any right to use or disclose (A) any PolyPeptide Intellectual Property (except as may be permitted by the PolyPeptide License), or (B) any PolyPeptide Confidential Information (except as may be permitted under Article XII hereof). PolyPeptide agrees to use commercially reasonable efforts to minimize its costs associated with any API Specification change. At the request of CARA, PolyPeptide shall evaluate and disclose to CARA the

estimated costs and timing of any such development work that would be needed by any potential revisions to the API Specifications.

(b) PolyPeptide Changes. PolyPeptide shall not make any revisions or changes to the API Specifications, the manufacturing process or Material Third Party Suppliers, without prior written Consent of CARA, which Consent shall not be unreasonably withheld or delayed (such changes as initiated by either PPL or Cara are subject to review and approval of regulatory authorities. The parties acknowledge that timing of such regulatory approval is unpredictable). If the Parties implement a change in the API Specifications or the manufacturing process under this Section 4.02, they shall negotiate any changes in any affected Purchase Order to provide reasonable accommodation for changed circumstances. The costs of revisions requested by PolyPeptide under this Section 4.02(b) and approved by CARA shall be borne by PolyPeptide without any increase in the API Price.

(c) Changes Mandated by Legal Requirements. Notwithstanding anything in subsections (a) and (b) of this Section 4.02 to the contrary, (i) PolyPeptide shall implement all changes to the API Specifications intended to maintain compliance with Legal Requirements, to bring the API Specifications into compliance with Legal Requirements or to accommodate the demands or requests of any Governmental Body; (ii) unless such changes are generally applicable to the Facility or PolyPeptide's manufacture of other products, CARA shall bear the expense of any of such changes implemented under this Section 4.03(c); and (iii) if the changes are generally applicable to the Facility or PolyPeptide's manufacture of other products, PolyPeptide shall bear the expense of any of such changes. Notwithstanding the foregoing, if changes to Legal Requirements generally affecting manufacturers of drugs containing the API significantly increase the cost for PolyPeptide to supply API hereunder, then the Parties agree to negotiate in good faith any appropriate adjustments to the API Price under this Agreement.

Section 4.03 Storage and Handling Obligations. When storing and handling API, Non-conforming API or API-derived wastes, PolyPeptide shall comply with, and shall maintain all storage facilities in compliance with, the API Specifications, (c)GMPs, Legal Requirements and the Quality Agreement.

Section 4.04 Validations and Stability Studies.

(a) Process Validation for Improved Manufacturing Processes. The Parties acknowledge that CARA or PolyPeptide may from time to time desire to pursue strategies and efficiencies for improving the manufacturing processes for the API. Each Party agrees to reasonably evaluate and discuss any such suggestions for improvements that the other Party reasonably believes in good faith may result in significant cost or time savings in the API manufacturing process.

(b) General. Without limiting the foregoing, at CARA's request, PolyPeptide shall perform for CARA on an on-going basis all Validations and stability studies required by the API Specifications, (c)GMPs or Legal Requirements in connection with the regular course of manufacturing the API for commercial supply to CARA hereunder. Such activities will be subject to price proposal(s) and purchase order(s) from CARA.

(c) Duties. In performing its duties under this Section 4.04, PolyPeptide shall implement and operate an ICH complaint stability program for commercial Batches supply.

(d) Manufacturing Process Review. At either Party's reasonable request, the Parties shall promptly meet, in person or telephonically, to review such matters related to manufacturing of the API as may be specified by a Party, including discussing strategies for improving the API manufacturing processes.

Section 4.05 LAST-TIME BUY

In the event of expiration or termination of this Agreement for any reason:

CARA has the right, within 60 (sixty) days from the date of expiration or termination , to place a last time buy order with PolyPeptide for API in quantities not exceeding the Binding Forecast ("Last Time Buy Order") with the same terms and conditions of this Agreement; however subject to the Parties' mutual agreement on the supply price applicable to such Last Time Buy Order, such price to be commercially reasonable. The applicable terms and conditions of this Agreement shall be deemed to survive any such termination or expiration solely with respect to such supply of the ordered API, and shall expire automatically upon completion of delivery of conforming API and payment therefor. For clarity, the supply exclusivity provision shall not survive any such expiration or termination. If this Agreement is terminated by either Party in accordance with Article XIV, a price increase (revising the reference prices by yearly French inflation rate as soon as published by Institut National de la Statistique at des Etudes Economiques (INSEE)) shall apply to such Last Time Buy Order.

The Parties agree that all deliveries of API ordered pursuant to this Section 4.05 are to be as follows and subject to delivery within a 18 (eighteen) months period following PolyPeptide receiving the last Forecast.

Should CARA' actual requirements be higher than the Last Time Buy Order, PolyPeptide will use all best efforts to meet CARA's excess requirements and provided further that demands.

Section 4.06 Inspection of API and Rejection if Nonconforming. CARA shall have the right to inspect and analyze API delivered hereunder and may reject any API determined to be Nonconforming API, all as provided in and in accordance with the terms of the Quality Agreement.

Article V. Testing and Quality Assurance

Testing and Quality Assurance are covered by the Quality Agreement in force between CARA and PolyPeptide. Reference to the Quality Agreement in force is given is Appendix 5. In the event of a conflict between any of the provisions of this Agreement and the Quality Agreement, the provisions of the Quality Agreement shall govern.

Article VI. Regulatory Matters

Section 6.01 Consents. PolyPeptide shall obtain and hold all Consents required to be obtained by PolyPeptide under the Legal Requirements for the performance of its obligations under this Agreement, and CARA shall reasonably cooperate with PolyPeptide with respect thereto. At all times during the Term, PolyPeptide shall maintain and comply with all Consents that may from time to time be required by any Governmental Body having jurisdiction with respect to PolyPeptide's manufacturing operations and facilities and otherwise to be obtained by PolyPeptide to permit the performance of its then-current obligations under this Agreement. PolyPeptide shall bear all expenses incurred in connection with its obligations under this Section 6.01. If any Consent held by PolyPeptide relating to the Facility or its ability to manufacture the API in accordance with this Agreement is hereafter suspended or revoked, or PolyPeptide has material restrictions imposed upon it by any Governmental Body affecting the API, any activities relating to manufacturing, storage or supply of API, or the Facility, PolyPeptide shall immediately provide written notification to CARA identifying such material restrictions, a schedule of compliance and such other information related thereto as is reasonably requested by CARA. Without limiting the foregoing, PolyPeptide will cooperate with CARA in a reasonable and timely manner in preparation for inspection of the Facility (as applicable to API manufacturing) or to API manufactured at the Facility by any Governmental Body.

Section 6.02 Maintenance of (c)GMP Facility. PolyPeptide shall use commercially reasonable best efforts to maintain the portion of the Facility relating to the supply of the API as

a (c)GMP facility during the Term, and CARA shall reasonably cooperate with PolyPeptide with respect thereto. CARA shall have the right, pursuant to the audit procedures in Section 9.02, to have its Approved Representatives undertake quality assurance audits of PolyPeptide's procedures and facilities for API production. If CARA undertakes such an audit, CARA shall provide PolyPeptide with a written audit report and, if applicable, shall highlight therein areas where CARA judges that PolyPeptide needs to make changes to procedures or facilities or to maintain the Facility as a (c)GMP facility. Both Parties shall cooperate in good faith to agree and implement the necessary changes. If CARA's written audit report identifies any areas for improvement, within 30 days following delivery of CARA's audit report, PolyPeptide shall prepare an action plan (and promptly deliver a copy of such plan to CARA for review and comment), which plan shall address the findings of the audit report and include accomplishment dates for corrective actions. CARA agrees to cooperate with PolyPeptide by making its Approved Representatives available for consultation and advice to PolyPeptide, as may be reasonably requested by PolyPeptide, regarding implementation of (c)GMP and related procedural systems and any other matters as may be mutually agreed.

Section 6.03 Compliance. In carrying out their respective obligations under this Agreement, the Parties shall comply in all respects with (c)GMPs and the Legal Requirements, as applicable to such Party, in effect from time to time.

Section 6.04 Drug Application Documentation. PolyPeptide agrees that CARA may reference PolyPeptide as the manufacturer of the API in CARA's Drug Application and any other documentation required under any regulatory filings for the Product, and PolyPeptide will provide the relevant Government Body with all required documentation, including development and analytical reports to support such filings. CARA shall own all regulatory files with respect to the API including regulatory data and documentation prepared by PolyPeptide under this Section 6.04 respecting the manufacture of the API, including without limitation the CMC section of any Drug Application related to the API. Upon reasonable request from PolyPeptide, CARA shall provide PolyPeptide with information regarding Drug Applications, or discrete sections thereof, to the extent available and necessary for PolyPeptide to perform its obligations under this Agreement; provided, however, that information provided hereunder shall be CARA's Confidential Information covered by Article XII of this Agreement. If any Governmental Body makes an inquiry of or provides any information to PolyPeptide that is or may be related to a Drug Application, PolyPeptide shall promptly forward such inquiry or information to CARA.

Section 6.05 Regulatory Changes. The Parties will promptly notify each other of any material revisions, amendments of or additions to the (c)GMPs and will confer with each other with respect to the best means to comply with such requirements.

Section 6.06 Regulatory Inspections. Regulatory Inspections are covered by the Quality Assurance in force between CARA and PolyPeptide. Reference to the Quality Agreement in force is given is Appendix 5.

Section 6.07 Other Regulatory Matters. Other Regulatory Matters are covered by the Quality Assurance in force between CARA and PolyPeptide. Reference to the Quality Agreement in force is given is Appendix 5.

Section 6.08 Confidential Information. Notwithstanding anything to the contrary contained herein, PolyPeptide may redact or limit from any deliveries of or access to data, reports or any other information, any Third-Party confidential information.

Article VII. Intellectual Property

Section 7.01 Ownership.

(a) PolyPeptide Ownership. As between the Parties, PolyPeptide owns all rights in and to the PolyPeptide Intellectual Property. Except as expressly provided in Section 7.03(b) below, nothing in this Agreement shall be deemed to transfer or convey to CARA, expressly or by

implication, any license or any other right, title or interest in or to the PolyPeptide Intellectual Property.

(b) CARA Ownership. As between the Parties, CARA owns all rights in and to the CARA Intellectual Property, including all Intellectual Property rights in and to the API, the documentation, specifications and processes associated with the API, the Product, the Drug Applications, and the documentation, specifications and processes associated with the API and the Product, but excluding any of the foregoing to the extent it is PolyPeptide Intellectual Property. Except as expressly provided in Section 7.03(a) below, PolyPeptide does not have, and nothing in this Agreement shall be deemed to transfer or convey to PolyPeptide, by virtue of this Agreement or otherwise, a license or any other right, title or interest in or to the CARA Intellectual Property.

Section 7.02 New Developments.

(a) API Product Developments. All Intellectual Property relating to the API or the development or manufacture or use of the API, that is conceived, reduced to practice, authored or otherwise invented, discovered, generated or developed in whole or in part by PolyPeptide in the course of its activities under this Agreement, whether patentable or not, and any authorship of works relating to the API that are created by PolyPeptide, including any trademarks, trade dress, trade secrets or copyrights, shall be "API Product Developments."

(b) Ownership of API Product Developments. Subject to the rights and licenses granted in Section 7.03 below, CARA shall own all right, title and interest in and to all API Product Developments and all rights to Intellectual Property appurtenant thereto or arising therefrom, such API Product Developments being works made for hire pursuant to this Agreement.

(c) Patents. Notwithstanding any obligation of confidentiality between PolyPeptide and CARA under this Agreement or any other agreement, but subject however to Section 12.03 of this Agreement, CARA, at its own expense and discretion, shall have the sole and exclusive rights to file and prosecute appropriate patent applications and maintain patents issuing therefrom covering inventions in such API Product Developments. Upon CARA's reasonable request and at CARA' expense, PolyPeptide shall take such reasonable actions as CARA deems necessary or appropriate to assist CARA in obtaining patent or other proprietary protection in CARA's name with respect to any such API Product Developments.

Section 7.03 Licenses.

(a) Grant of License to CARA Intellectual Property. Subject to the terms and conditions of this Agreement, CARA hereby grants PolyPeptide a worldwide, non-exclusive, royalty-free, non-transferable (except in connection with a permitted assignment under Section 15.04), limited license to use the applicable CARA Intellectual Property for the sole purpose of manufacturing the API for CARA pursuant to this Agreement. This license shall terminate upon the expiration or termination of this Agreement (except for limited survival solely as needed for the limited purpose of fulfilling any Last Time Buy Order). The license granted in this Section 7.03(a) shall be referred to as the "CARA License."

(b) Grant of License to PolyPeptide Intellectual Property. Subject to the terms and conditions of this Agreement, PolyPeptide hereby grants CARA a worldwide, non-exclusive, royalty-free, non-transferable (except in connection with a permitted assignment under Section 15.04), license to use the applicable PolyPeptide Intellectual Property for the manufacture and sale of Product using API supplied by PolyPeptide pursuant to this Agreement. CARA may grant sublicense(s) under the foregoing PolyPeptide License to its designated Product manufacturing contractors. This license shall terminate upon the later of (i) expiration or termination of this Agreement and (ii) such time as CARA is no longer in possession of API supplied by PolyPeptide, including API that has been incorporated into Product that has not reached expiry. The license granted in this Section 7.03(b) shall be referred to as the "PolyPeptide License." For the avoidance of doubt, regardless of the termination or expiration of this Agreement, CARA shall retain the PolyPeptide License to use the PolyPeptide

Intellectual Property for the manufacture and sale of the Product for so long as necessary to sell all inventory that incorporates API provided by PolyPeptide under this Agreement.

Section 7.04 Infringement.

Each Party shall promptly notify the other Party of any suspected or threatened infringement, misappropriation or other unauthorized use of the other Party's Intellectual Property that comes to such Party's attention. The notice shall set forth the facts of such suspected or threatened infringement in reasonable detail (but subject to any confidentiality obligations and to preservation of applicable legal privileges). The Party [***], but not the obligation, to institute, prosecute and control, at its expense, any action or proceeding against the Third-Party infringer of its Intellectual Property and to retain any and all amounts recovered or awarded in any such action (or settlement thereof). If a Party institutes an action against such infringer, the other Party shall give such Party, at its request, reasonable assistance regarding its filing and prosecution of the action as reasonably needed, such assistance at the expense of the Party who institutes the action.

Section 7.05 Data. As between PolyPeptide and CARA, CARA shall be and remain the sole and exclusive owner of all data and information, in any form, relating to: (a) the business of CARA; (b) licensees, customers and suppliers of CARA; (c) any and all API Product Developments, the API or the Product and the development, manufacture, use or commercialization thereof; (d) the API Specifications, and (e) all regulatory applications and documentation relating to API or Product or the manufacture thereof. All information provided to by one Party to the other by under this Article VII shall be handled by the receiving Party as the Confidential Information of the other Party, subject to Article XII.

Article VIII. Information; Access; Audit Rights

Section 8.01 Provision of Information.

(a) Data. PolyPeptide shall provide to CARA copies (in electronic or hard-copy form, as requested by CARA) of or access to data generated under this Agreement as may be reasonably requested from time to time by CARA on a bona fide need-to-know basis, except as may be restricted for the preservation trade secrets owned by PolyPeptide. PolyPeptide shall provide final reports for Batch failures, including recommendation for API disposition for all investigations involving (i) foreign matter or particulate contamination; or (ii) any test results indicating non-compliance with the applicable (c)GMPs or the API Specifications.

Annual Report. PolyPeptide shall prepare and provide to CARA a written annual report documenting (i) the prior Calendar Year's Batch records; (ii) packaging changes; (iii) process changes; (iv) changes in API testing methods performed pursuant to Article VI hereof; (v) Batches of API rejected or aborted; (vi) any other discrepancies that require reporting pursuant to (c)GMP or Legal Requirements; (vii) "trends" in the manufacture of API during the prior Calendar Year; and (viii) ICH stability data summary.

Section 8.02 Audit and Inspection Rights. In addition to specific audit rights set forth elsewhere in this Agreement, certain audit and inspection rights and responsibilities of the Parties are defined in the Quality Agreement.

Section 8.03 Record Retention. Each Party shall maintain, in accordance with and for the period required under the applicable Drug Application, (c)GMPs and Legal Requirements, complete and adequate records pertaining to all activities in connection with, and facilities used for, the manufacture, generation, storage, testing, treatment, holding, transportation, distribution or other handling or receiving of the API, Third Party Materials and Product.

Article IX. Representations and Warranties

Section 9.01 Representations and Warranties of PolyPeptide. PolyPeptide represents and warrants that:

(a) Compliance. The manufacture, generation, processing, transport, treatment, storage, disposal and other handling API by PolyPeptide hereunder (including handling and use of applicable Third Party Materials in connection therewith) shall be in accordance with and conform to the API Specifications, (c)GMPs, ICH guidelines, all Legal Requirements, this Agreement and the Quality Agreement.

(b) API Warranty. Upon receipt by CARA (or its designee) of a lot of API delivered hereunder, the API shall comply with the applicable (c)GMPs, the API Specifications, the applicable ICH guidelines and all Legal Requirements; shall be free from defects in materials and workmanship; and shall not be adulterated or misbranded within the meaning of applicable Legal Requirements.

(c) Status; Enforceability. PolyPeptide is a validly existing corporation in good standing under the laws of the jurisdiction of its incorporation; the execution, delivery and performance of this Agreement by PolyPeptide has been duly authorized by all requisite corporate action; this Agreement constitutes a legal, valid and binding obligation of PolyPeptide, enforceable against PolyPeptide in accordance with the terms hereof; and the execution, delivery and performance of this Agreement by PolyPeptide will not violate or conflict with any other agreement or instrument to which PolyPeptide is a party.

(d) Certain Persons. PolyPeptide has not used, and will not use, in any capacity associated with or related to the manufacture of the API, the services of any Persons who have been, or are in the process of being, (i) debarred under 21 U.S.C. § 335a(a) or (b) or any comparable Legal Requirements or (ii) excluded from participation in the Medicare program, any state Medicaid program or any other health care program. Furthermore, neither PolyPeptide nor any of its officers, employees or consultants has been convicted of an offense under either a federal or state law that is cited in 21 U.S.C. § 335(a) as a ground for debarment, denial of approval or suspension, any other law cited in any comparable Legal Requirements as a ground for debarment, denial of approval or suspension. PolyPeptide shall notify CARA immediately upon learning of any circumstance that would cause this representation to become false or inaccurate.

(e) Regulatory Consents. PolyPeptide has or will have all Consents necessary to timely perform its obligations hereunder and to manufacture the API used in Product for commercial sale.

(f) Maintenance of Facility. During the Term of this Agreement, PolyPeptide shall maintain the Facility, required local licenses, the equipment used to manufacture the API, PolyPeptide Intellectual Property and any applicable contracts necessary to manufacture the API in accordance with the API Specifications, Legal Requirements, (c)GMPs, the Quality Agreement and PolyPeptide's standard operating procedures.

(g) Negative Pledge. The transfer of the API by PolyPeptide to CARA is and shall be rightful and free and clear of any liens or encumbrances.

(h) Security Measures. PolyPeptide shall maintain reasonable security policies at the Facility and shall use commercially reasonable efforts to have security measures in place to protect the integrity of the API, Third Party Materials, data and works-in- process at the Facility.

(i) Non-Infringement. [***] PolyPeptide's performance of its obligations under this Agreement will not [***] of any Third Party.

Section 9.02 Representations and Warranties of CARA. CARA represents and warrants that:

(a) Status; Enforceability. CARA is a validly existing limited liability company in good standing under the laws of the jurisdiction of its incorporation; the execution, delivery and performance of this Agreement by CARA has been duly authorized by all requisite corporate action; this

Agreement constitutes the legal, valid and binding obligation of CARA, enforceable against CARA in accordance with the terms hereof (except as such enforcement may be limited by principles of equity or by debtor protection laws); and the execution, delivery and performance of this Agreement by CARA will not violate or conflict with any other agreement or instrument to which CARA is a party.

(b) Certain Persons. CARA has not used, and will not use, in any capacity associated with or related to the Product, the services of any Persons who have been, or are in the process of being, (i) debarred under 21 U.S.C. § 335a(a) or (b) or any comparable Legal Requirements, or (ii) excluded from participation in the Medicare program, any state Medicaid program or any other health care program. Furthermore, neither CARA nor any of its officers, employees or consultants has been convicted of an offense under either a federal or state law that is cited in 21 U.S.C. § 335(a) as a ground for debarment, denial of approval or suspension or any other law cited in any comparable Legal Requirements as a ground for debarment, denial of approval or suspension. CARA shall notify PolyPeptide immediately upon learning of any circumstance that would cause this certification under this Section 9.02(b) to become false or inaccurate.

(c) Regulatory Consents. [***] hereunder and will, prior to commercial sale of Product, have all [***] of the Product once the Product is approved by health authorities.

(d) Non-infringement. [***], (i) the manufacture and delivery of the API under this Agreement, (ii) the use by PolyPeptide of CARA' Intellectual Property to manufacture the API, and (iii) CARA's commercial sale of Product, will not [***] of any Third Party, *provided that* excluded from the foregoing warranty is any use of any PolyPeptide Intellectual Property. [***] by a Third Party that [***] by PolyPeptide's production of API under this Agreement using the manufacturing processes intended to be utilized hereunder, or (ii) [***] Polypeptide's performance of API manufacturing hereunder.

Section 9.03 Disclaimer. OTHER THAN THE WARRANTIES EXPRESSLY PROVIDED FOR IN THE FOREGOING PROVISIONS OF THIS AGREEMENT, NEITHER PARTY MAKES ANY WARRANTIES OR REPRESENTATIONS, EITHER EXPRESS OR IMPLIED, AND THE PARTIES EXPRESSLY DISCLAIM ALL OTHER WARRANTIES AND REPRESENTATIONS, INCLUDING THE IMPLIED WARRANTIES OF MERCHANTABILITY, FITNESS FOR A PARTICULAR PURPOSE, TITLE AND NONINFRINGEMENT.

Article X. Liability and Indemnification

Section 10.01 Indemnity by PolyPeptide. PolyPeptide shall defend, indemnify and hold harmless CARA and its Affiliates and their respective officers, directors, employees and agents (collectively, the "CARA Indemnitees") from and against all Losses resulting from any allegations, claims, suits, proceedings or actions (collectively, "Claims") by a Third Party against a CARA Indemnitee to the extent arising out of or resulting from (a) any breach, non-performance or failure to comply with any of PolyPeptide's covenants, agreements, obligations, representations or warranties under this Agreement or the terms of this Agreement; or (b) [***] of, PolyPeptide, its respective directors, officers, employees, agents or Subcontractors.

Section 10.02 Indemnity by CARA. CARA shall defend, indemnify and hold harmless PolyPeptide from and against all Losses resulting from any Claims by a Third Party against PolyPeptide to the extent arising out of or resulting from (a) any breach, nonperformance or failure to comply with any of CARA's covenants, agreements, obligations, representations or warranties under this Agreement or the terms of this Agreement; or (b) [***], CARA or CARA Affiliates, their respective directors, officers, employees, agents or contractors.

Section 10.03 Procedures. Any Person that may be entitled to indemnification under this

Agreement (an "Indemnified Party") shall give written notice to the Party obligated pursuant to the above Sections to indemnify it (an "Indemnifying Party") with reasonable promptness upon becoming aware of any Claim against such Indemnified Party that gives rise to such indemnification right and all the facts in such Person's possession relating to such Claim and/or upon which such claim for indemnification is based. The notice shall set forth such information with respect thereto as is then reasonably available to the Indemnified Party (excluding information subject to legal privilege). The Indemnifying Party shall have the right to undertake the defense of any such claim [***] to the Indemnified Party, and the Indemnified Party shall cooperate in such defense and make available all records, materials and witnesses reasonably requested by the Indemnifying Party at the Indemnifying Party's expense. If the Indemnifying Party shall have assumed the defense of the claim with counsel reasonably satisfactory to the Indemnified Party, the Indemnifying Party shall not be liable to the Indemnified Party for [***] the Indemnified Party in connection with the defense thereof. The Indemnifying Party shall not be [***] its Consent, which Consent shall not be unreasonably withheld. The Indemnifying Party shall obtain the written Consent of the Indemnified Party, which shall not be unreasonably withheld, prior to ceasing to defend, settling or otherwise disposing of any claim if, as a result thereof, the Indemnified Party would become subject to injunctive or other equitable relief or if the Indemnified Party may reasonably [***] on the Indemnified Party.

Section 10.04 No Special Damages. Notwithstanding anything to the contrary contained herein, except for breaches of confidentiality obligations, the Parties shall not be liable to each other for any special, indirect, incidental, punitive or consequential damages (including for lost profits).

Section 10.05 Liability Limitation. Further, notwithstanding anything to the contrary herein, except for breaches of confidentiality obligations, the liability of PolyPeptide in connection with any Purchase Order arising out of any terms or conditions in this Agreement or with respect to the performance thereto shall be in any case [***] under such Purchase Order.

Article XI. Insurance

Section 11.01 Coverage Requirements. Each Party shall maintain in full force and effect during the Term of this Agreement and for a period of two Calendar Years after expiration or termination of this Agreement, worker's compensation, property, general liability and product liability insurance coverage in such amounts and with such scope of coverages as are adequate to cover such Party's obligations under this Agreement and as are customary in the industry for companies of like size and activities and taking into account the nature of the API to be manufactured under this Agreement (for Polypeptide) and the Product (for CARA).

Article XII. Confidentiality

Section 12.01 Definition of Confidential Information. "Confidential Information" means, with respect to a Party, any and all data, results and other Know-How, which may include scientific, pre-clinical, clinical, regulatory, manufacturing, marketing, financial and commercial results, data and other information, that is or was provided or disclosed by such Party (or its Affiliate) to the other Party (or its Affiliate), whether communicated in writing or orally or by any other method, in connection with this Agreement including all such information that was disclosed under the Prior Agreement. Notwithstanding the foregoing, the term "Confidential Information" excludes particular information that, in each case as demonstrated by competent written documentation: (a) is publicly disclosed and made generally available to the public, either before or after it becomes known to the receiving Party, and other than through any act or omission of the receiving Party or its Affiliates in breach of this Agreement; (b) was known to the receiving Party or its Affiliate, without obligation to a Third Party to keep it confidential, prior to the date of first disclosure by the disclosing Party to the receiving Party; (c) is subsequently disclosed to the receiving Party or its Affiliate by a Third Party lawfully in

possession thereof without obligation to keep it confidential and without a breach of such Third Party's obligations of confidentiality; or (d) has been independently developed by the receiving Party or its Affiliate without the aid, application or use of the disclosing Party's Confidential Information (the competent written proof of which must be contemporaneous with such independent development).

Section 12.02 Nondisclosure and Limited Use Obligations. Each of the Parties agree that during the Term, and for a period of ten (10) years thereafter, each Party and its Affiliates shall (a) maintain in confidence the Confidential Information of the other Party, using efforts to protect such information that are at least as strong as those that such Party uses to maintains its own confidential information (but in no event less than reasonable efforts), (b) not disclose such Confidential Information to any Third Party without the prior written consent of the other Party, or as otherwise expressly permitted in this Agreement, and (c) not use such Confidential Information for any purpose except those permitted by this Agreement.

Section 12.03 Authorized Disclosure. Notwithstanding anything to the contrary in this Article 8, a Party may disclose particular Confidential Information of the other Party to the extent such disclosure is reasonably necessary in the following instances:

(a) Prosecuting, enforcing or defending applicable Patent Rights that are the subject of this Agreement in accordance with Article VII of this Agreement.

(b) making filings covering a Product with Governmental Bodies;

(c) complying with Legal Requirements (including securities laws and the requirements of the securities exchange on which a Party's stock is traded) or submitting information to tax or other Governmental Bodies; provided that if a Party is required by Law to make any public disclosure of Confidential Information of the other Party, to the extent it may legally do so, it will give reasonable advance notice to the other Party of such disclosure and will use its reasonable efforts to secure confidential treatment of such Confidential Information prior to its disclosure (whether through protective orders or otherwise);

(d) to its Affiliates, and to employees, accountants, and lawyers, on a need to know basis, each of whom prior to disclosure must be subject to appropriate obligations of confidentiality and non-use equivalent in scope to those set forth in this ARTICLE VIII and that are of reasonable duration in view of the circumstances of the disclosure; or

(e) to the extent mutually agreed to in writing by the Parties.

Article XIII. Force Majeure

Section 13.01 General. Except for any obligation to pay money, a Party shall not be held liable or responsible to the other Party and shall not be deemed to be in breach or default of its obligation under, or in breach of any provision of, this Agreement for a failure or delay in fulfilling or performing any specific obligation of such Party under this Agreement to the extent that such failure or delay is due to a Force Majeure Event that prevents or impairs such Party from performing such obligation, and without the fault or negligence of the Party so failing or delaying. For purposes of this Agreement, a "Force Majeure Event" is defined as: acts of God; war; civil commotion; destruction of production facilities or materials by fire, flood, earthquake, pandemics, explosion or storm; labor disturbances; epidemic; failure of manufacturing equipment; failure of public utilities and similar events that are beyond the reasonable control of the Party affected. In the event of a Force Majeure Event that causes a delay or failure of a Party performing its obligation hereunder, such Party shall notify the other Party as soon as practicable of such inability to perform, the nature of the Force Majeure Event, and the period for which such inability is expected to continue. The Party giving such notice shall thereupon be excused from such of its obligations under this Agreement as it is thereby disabled from performing for so long as it is so disabled, provided that it uses commercially reasonable efforts to avoid the effects of

the Force Majeure Event and to recommence performing the affected obligation as soon as practicable. To the extent possible, each Party shall use reasonable efforts to minimize the duration of any Force Majeure Event that affects such Party's performance hereunder.

Section 13.02 Termination Due to Event of Force Majeure; Transition. If, as a result of a Force Majeure Event referred to in Section 13.01, PolyPeptide is unable to perform any of its material obligations for a period of more than [***] days, the other Party shall have the right to terminate this Agreement upon [***] days' prior notice to the non-performing Party.

Article XIV. Term; Termination; Remedies

Section 14.01 Term. This Agreement shall commence on the Effective Date and will continue until the earlier of the fifth anniversary of the approval of the Drug Application by the FDA, or the earlier termination of the Agreement by either Party as provided below in this Article XIV (such period, the "Initial Term"), and (unless the Agreement is earlier terminated) the Agreement term shall renew and continue automatically for successive five year renewal terms (at the end of the then-current Term) unless either Party notifies the other Party of its intent to not renew by providing written notice to the other Party no less than two years prior to the expiration of the then current Term, and provided that either Party may earlier terminate the Agreement as provided below in this Article . The Initial Term together with any renewal term(s) (as such term(s) may be subject to early termination) is the "Term" of this Agreement.

Section 14.02 Termination for Breach. A Party may terminate this Agreement in the event of the material breach by the other Party of the terms and conditions of this Agreement, subject to the following condition: such Party shall first give to the breaching Party written notice of the proposed termination of this Agreement, specifying the grounds therefor including the detailed basis for the Party's assertion that the other Party has materially breached the Agreement. Upon receipt of such notice, the breaching Party shall have [***] to respond by curing such material breach. If the breaching Party does not cure such breach within such cure period, then (a) if PolyPeptide is the breaching Party, CARA (i) shall have the right thereafter to terminate this Agreement on written notice to PolyPeptide and (ii) shall have the rights and remedies set forth in Section 14.06; or (b) if CARA is the breaching Party, PolyPeptide (i) shall have the right thereafter to terminate this Agreement on written notice to CARA and (ii) shall have the remedies set forth in Section 14.08.

Section 14.03 Bankruptcy. To the extent permitted by Legal Requirements, each Party will have the right to terminate this Agreement immediately upon notice to the other Party, if any of the following occurs: (a) such other Party is declared bankrupt, (b) [***], (c) there is an assignment for the benefit of such other Party's creditors, (d) a receiver is appointed or there is a voluntary or involuntary petition filed or an action or proceeding commenced for bankruptcy, reorganization, dissolution or winding up of such other Party that is not dismissed within [***] days, or (e) there is a foreclosure or sale of all or substantially all of such other Party's assets by or for the benefit of any creditor or governmental agency.

Section 14.04 Discontinuance or Suspension of Product Program. CARA may terminate this Agreement upon [***] days' written notice to PolyPeptide if CARA, in its sole and absolute discretion, discontinues or indefinitely suspends the development and/or commercialization of the Product, whatever the reasons justifying such discontinuation. Upon the termination of this Agreement pursuant to this Section 14.04, CARA's sole obligations shall be for it to reimburse PolyPeptide for [***] by PolyPeptide pursuant to this Agreement up to the effective date of such termination in connection with CARA's then-outstanding obligation to purchase quantities of API forecasted with respect to the binding portion of an applicable Forecast; provided, however, that PolyPeptide shall use commercially reasonable [***] any cancelable orders for Third Party Materials, returning returnable Third Party Materials, and/or using non-returnable Third Party Materials for its own or its other customers' behalf. For avoidance of doubt, if CARA terminates this Agreement pursuant to this Section 14.04, CARA [***] the quantities of API set forth in any

Purchase Orders and the quantities of API set forth in the binding portion of the most recent Forecast for the next Calendar Quarter.

Section 14.05 Termination by CARA. Without limiting any other Section of this Article XIV, CARA may terminate this Agreement upon [***] days' written notice to PolyPeptide upon the occurrence of any of the following:

(a) Failure to Achieve Acceptance of Pre-Approval Inspection. PolyPeptide receives at any time correspondence from FDA indicating that the Facility is not approved for the manufacture of API.

(b) Failure to Supply Unrelated to Force Majeure. In the event of a Supply Failure by PolyPeptide (relating to failure to deliver conforming API ordered by CARA), CARA shall have the right to terminate this Agreement upon [***] to PolyPeptide. "Supply Failure" for purposes of this Section is deemed to have occurred in the event that PolyPeptide does not deliver [***] conforming API ordered by CARA under a Purchase Order by the Shipment Date specified in such Purchase Order, and PolyPeptide does not deliver to CARA all the missing quantity of conforming API by the date [***] days after such Shipment Date.

(c) Supply of Nonconforming API. PolyPeptide delivers Nonconforming API pursuant to [***] Purchase Orders in any [***] period.

(d) Late Shipment. PolyPeptide delivers API pursuant to two or more Purchase Orders more than [***] after the applicable Shipment Date during any [***] period.

(e) Failure to Obtain or Maintain Consents. PolyPeptide fails to obtain, maintain and comply with all Consents required for the performance of its obligations under this Agreement.

Section 14.06 Effect of Termination by CARA. If CARA terminates this Agreement pursuant to Sections 14.02 or 14.05, (a) CARA shall have the right to terminate, in whole or in part, any Purchase Order issued under this Agreement and (b) CARA shall be relieved of its requirement to purchase quantities of API associated with any binding portion of a Forecast.

Section 14.07 Termination by PolyPeptide. Without limiting any other Section of this Article XIV, PolyPeptide may terminate this Agreement upon [***] CARA upon the occurrence of any of the following:

(a) Failure to Obtain Approval of the Drug Application. CARA's failure to obtain approval of the Drug Application for the Product from the FDA [***] the Effective Date.

(b) Failure to Accept API Unrelated to a Force Majeure Event. CARA's [***] API delivered by PolyPeptide unrelated to a Force Majeure Event [***] for purposes of determining [***] API shall be [***] Batch of the API delivered over a [***] period.

(c) Failure to Pay. CARA's failure to pay PolyPeptide invoiced amounts for conforming API (that is, supplied API that is not subject to an active investigation of issues relating to whether it is Nonconforming API, or the API or invoiced amount is otherwise disputed in good faith by CARA) within [***] from the applicable due dates [***] Purchase Orders.

Section 14.08 Effect of Termination by PolyPeptide. If PolyPeptide terminates this Agreement pursuant to Sections 13.02, 14.02, 14.03 or 14.07, CARA shall purchase from PolyPeptide and pays all quantities of API set forth in any Purchase Orders and all quantities of API set forth in any binding portion of a Forecast.

Section 14.09 Survival. Articles I (to the extent required to enforce other surviving rights or obligations), VI, VII, VIII, IX, X, XI, XII, XIV and Sections 5.01, 5.03, 5.04, 5.05, 5.07, 5.08, 5.09, and 6.06, and any other provision which by its terms specifically shall so state, together with any obligations accrued hereunder at the time of termination or expiration, shall survive the termination or expiration of this Agreement.

Article XV. Miscellaneous

Section 15.01 Notices. In addition to the other specific procedures for notification provided herein, all notices, demands, requests and other communications made hereunder shall be in writing and shall be given either by personal delivery, by facsimile or by internationally recognized overnight courier (with charges prepaid) and shall be deemed to have been given or made: (a) if personally delivered, on the day of such delivery; (b) if sent by facsimile, on the day it is sent or, if not sent on a business day, the next business day; or (c) if sent by overnight courier, on the business day following the date deposited with such overnight courier service, in each case pending the designation of another address, addressed as follows:

If to CARA:
CARA THERAPEUTICS, Inc.
4 Stamford Plaza
107 Elm Street, 9th Floor
Stamford, CT 06902
Attn: Frederique Menzaghi, Chief Scientific Officer

With a mandatory copy to:

Office of the General Counsel
Cara Therapeutics, Inc.
4 Stamford Plaza
107 Elm Street, 9th Floor
Stamford, CT 06902

If to PolyPeptide:
PolyPeptide SA
7, rue de Boulogne
F-67100 Strasbourg, France
Attention: Mr. Vincent Mancuso, General Manager
E-mail address: vincent.mancuso@polypeptide.com

Section 15.02 Independent Contractors. Each Party shall be, and shall be treated as, an independent contractor of the other. Neither Party shall be, or shall be deemed to be, a co-venturer, partner, employee or a legal representative of the other Party for any purpose. Neither Party shall have the authority to bind, or to enter into any contracts in the name of or on behalf of, the other Party or incur any charges or expenses for or in the name of the other Party.

Section 15.03 Entire Understanding. The Parties agree, on their own and their respective Affiliates' behalf, that this Agreement, including Schedules and Appendixes hereto, constitutes the entire agreement between the Parties and their Affiliates relating to the subject matter hereof, and all prior agreements or arrangements, written or oral, between the Parties and their Affiliates relating to the subject matter hereof.

Section 15.04 Assignment. This Agreement will be binding upon and inure to the benefit of the Parties, their successors and permitted assigns. CARA shall be entitled to delegate, transfer, convey, assign or pledge this Agreement (the "**Assignment**" or to "**Assign**") to any Person, in whole or in part, or any of its rights or obligations under this Agreement, and PolyPeptide hereby grants its Consent to any such Assignment by CARA (though no such Consent is required for any such delegation, transfer, conveyance or assignment by CARA). Polypeptide may not Assign this Agreement without the prior written Consent of CARA in each instance, and any Assignment by PolyPeptide without Consent of CARA shall be void and have no effect. However, notwithstanding the foregoing, a Change of Control of either Party shall not be deemed to be an Assignment of this Agreement and shall not be subject to the other Party's Consent.

Section 15.05 Dispute Resolution. If the Parties are unable to resolve any issue, claim, dispute or controversy of whatever nature arising between the Parties out of or relating to this Agreement (a "Dispute") (other than one relating to [***], which shall not be subject to this Section 15.05), either of the Parties may refer the Dispute to their respective officers designated below, or to such other officers as the Parties may designate in writing from time to time, for attempted resolution, and after any such referral by a Party, such officers shall meet as soon as possible (by videoconference, telephone, or otherwise) and shall seek to resolve such Dispute by good faith negotiations within [***] days after so submitting the Dispute. The designated officers are as follows:

For CARA: Derek Chalmers, President & CEO

For PolyPeptide: Mr. Vincent Mancuso, General Manager

If such Dispute is not resolved by the end of the [***] period, then either Party shall be entitled to refer the matter to be finally settled by arbitration to be held in accordance with the then-current Rules of Arbitration and Conciliation of the International Chamber of Commerce by three arbitrators to be appointed in accordance with the said Rules, with each such arbitrator being completely independent of each Party and its Affiliates and experienced in the drafting and interpretation of pharmaceutical supply agreements. The Parties agree that any such unresolved Dispute, and any claim or dispute related to the validity of this arbitration clause, may be resolved solely by binding arbitration under this Section 15.05. The arbitration shall take place in [***]. The proceedings shall be conducted, and all documentation shall be presented in the English language. The award of the arbitrators shall be final, binding and without appeal. Any competent court shall be able to order enforcement of the award. Each Party will bear its own attorneys' fees and other costs and expenses incurred pursuant to this Section 15.05. For avoidance of doubt, the foregoing shall not prohibit or delay a Party from seeking appropriate injunctive or other equitable relief.

Section 15.06 Subcontractors. PolyPeptide may utilize Subcontractors with appropriate expertise and experience in the performance of its obligations under this Agreement; provided, however, that CARA must give its written Consent in each instance prior to the use of Subcontractors by PolyPeptide in connection with the manufacture or storage of the API (such Consent not to be unreasonably withheld or delayed). Nothing in this Section 15.06 shall relieve PolyPeptide from any obligation under this Agreement.

Section 15.07 Amendment. This Agreement, including any Schedule or Appendix hereto, may not be amended or modified in any manner except by an instrument in writing signed by a duly authorized officer of each Party.

Section 15.08 Severability. If and to the extent that any court of competent jurisdiction holds any provision (or any part thereof) of this Agreement to be invalid or unenforceable, such holding shall in no way affect the validity or enforceability of the remainder of this Agreement, and the invalid or unenforceable provision shall be fully severed from this Agreement, and there [***] as similar in terms and intent to such severed provision as may be legal, valid and enforceable.

Section 15.09 Waiver. Any failure of a Party to comply with any obligation, covenant, agreement or condition herein contained may be expressly waived, in writing only, by the other Party hereto, and such waiver shall be effective only in the specific instance and for the specific purpose for which made or given.

Section 15.10 Drafting Ambiguities. Each Party to this Agreement and its counsel have reviewed and revised this Agreement. The rule of construction to the effect that any ambiguities are to be resolved against the drafting Party shall not be employed in the interpretation of this Agreement or any amendment or Schedules hereto.

Section 15.11 Headings; Appendices; Counterparts.

(a) Headings. The headings of the Sections of this Agreement are for reference purposes only, are not part of this Agreement and shall not in any way affect the meaning or interpretation of this Agreement.

(b) Appendices. All Appendices delivered pursuant to this Agreement shall be deemed part of this Agreement and incorporated herein by reference as if fully set forth herein. If any Appendices conflicts with any of the terms or provisions of this Agreement, the terms and provisions of this Agreement shall prevail. The Appendices attached to this Agreement are:

- Appendix 1: Chemical structure of the API
- Appendix 2: Specification of the API
- Appendix 3: API Forecasts
- Appendix 4: API prices; Lead-times for the different scales
- Appendix 5: Quality Agreement

(c) Counterparts. This Agreement may be executed in one or more counterparts, each of which shall be deemed to be an original but all of which together shall constitute one and the same instrument. Facsimile signatures shall be treated as original signatures.

Section 15.12 Governing Law. This Agreement and all matters arising out of or relating to this Agreement shall be governed, construed and enforced in accordance with [***], without regard to principles of conflicts of law. The Parties agree that the provisions of the United Nations Convention on Contracts for the International Sale of Goods shall not apply to this Agreement or to any matters arising out of or relating to this Agreement.

Section 15.13 Remedies. Unless otherwise expressly provided in this Agreement, none of the remedies set forth in this Agreement are intended to be exclusive, and each Party shall have available to it all remedies available under law or in equity or in any other agreement between the Parties.

Section 15.14 Injunctive Relief. If either PolyPeptide or CARA breaches or threatens to breach any provision of Article VII or Article XII of this Agreement, the Parties agree that irreparable harm to the other Party may result, and the damages to such Party would probably be very difficult to ascertain and may be inadequate. Accordingly, in the event of such circumstances, each of PolyPeptide and CARA agree that, in addition to any other right and remedies available at law or in equity, the other Party shall have the right to seek injunctive relief from any court of competent jurisdiction.

Section 15.15 Standard Forms. In all communications, CARA and PolyPeptide may employ their standard forms, but nothing in those forms shall be construed to be in addition to or modify or amend the terms and conditions of this Agreement, and, in the case of any conflict herewith, the terms and conditions of this Agreement shall control.

Section 15.16 Further Assurances. Each Party agrees to execute, acknowledge and deliver such further instruments and to do all such other acts as may be necessary or appropriate to carry out the purposes and intent of this Agreement.

Section 15.17 Counterparts. This Agreement may be executed in two counterparts and by facsimile or PDF signature, each of which shall be deemed an original and which together shall constitute one instrument.

Section 15.18 English Language. The English language version of this Agreement will be controlling on the Parties. All information, documents, reports, notices, writings and communications to be provided by one Party to the other Party hereunder will be provided in the English language, except for manufacturing documentation and day to day quality documentation of PolyPeptide, which will be written in French by PolyPeptide’s employees.

Section 15.19 API Commercial Supply Agreement for CARA' Licensees. On CARA' written request, PolyPeptide will enter into an API Commercial Supply Agreement covering supply of API with any licensee of CARA for Product on terms no less favorable than those of this Agreement (including as to the API Price).

Section 15.20 Defects. PolyPeptide acknowledges that the Quality Agreement in place between the Parties (see Appendix 5) provides all terms covering CARA's right to analyze API supplied hereunder and to reject such supplied API if it is defective or as set forth in the Quality Agreement.

Signature Page Follows

IN WITNESS WHEREOF, each of the Parties hereto has caused this Agreement to be duly executed as of the date first written above.

CARA THERAPEUTICS	POLYPEPTIDE LABORATORIES S.A
By: /s/ Derek Chalmers	By: /s/ Jean Ruppert
Name: Derek Chalmers	Name: Mr. Jean Ruppert
Title: Chief Executive Officer	Title: Sales Director
Date: July 16th, 2021	Date: July 5th, 2021

EXHIBIT 10.1

Appendix 1:

API structure

H-DPhe-DPhe-DLeu-DLys-γ-(4-N-piperidinyl)amino carboxylic acid

EXHIBIT 10.1

Appendix 2:
API Specification

Reference is made to the Specification in force referenced Spec-SP070543-14
Between PolyPeptide Laboratories France SAS and Cara Therapeutics
signed by PolyPeptide Laboratories France SAS representatives on May 22nd, 23rd, 27th, 2019
and signed by Cara Therapeutics representatives on May 31st, 2019

Appendix 3:

API-Forecast - Shipment readiness

Exemplary the template for the forecast is shown below.
The forecasts as indicated below are CARA forecasts as of July 05th 2021 and are subject to an update by CARA on December 15, March 15, June 15, and September 15 of each year during the term of the contract.

Forecast for 2021 - API ready for Shipment (Shipment date to be mentioned on purchase order)
Order confirmation
07/2021:
08/2021:
09/2021:
10/2021:
11/2021:
12/2021: 1 batch of 2 kg

Forecast for 2022 - API ready for Shipment (Shipment date to be mentioned on purchase order)

01/2022:
02/2022:
03/2022:
04/2022:
05/2022:
06/2022:
07/2022:
08/2022:
09/2022:
10/2022:
11/2022:
12/2022:

Forecast for 2023 - API ready for Shipment (Shipment date to be mentioned on purchase order)

01/2023:
02/2023:
03/2023:
04/2023:
05/2023:
06/2023:

Appendix 4:

API prices; Lead-times for the different scales; Invoicing Specification

- For a commercial batch [***] scale (gross weight):
  [***] **Euros per gram**
- For a commercial batch [***] scale (gross weight):
  [***] **Euros per gram**
- For a commercial batch at [***] scale (gross weight):
  [***] **Euros per gram**

Lead-time per API-batch in the different scales:

Product Number (PolyPeptide)	**Product (CARA Name)**	**Scale**	**Lead-time/ batch**
512584	CR845/DIFELIKEFALIN	[***] gross weight	[***] months from purchase order reception at PolyPeptide
512584	CR845/DIFELIKEFALIN	[***] – gross weight	[***] months from purchase order reception at PolyPeptide
512584	CR845/DIFELIKEFALIN	[***] – gross weight	[***] months from purchase order reception at PolyPeptide

Lead-time means the time elapsed from Polypeptide accepts a purchase order until such order is ready for shipment to the Drug product manufacturer.

Prices for other batch sizes upon request and subject to confirmation with an amendment to the present Agreement and in any case after a risk assessment performed by PolyPeptide.

The unit price for production of API will remain valid until 31.12.2021 and will then be revised-on a yearly basis with retroactive effect on January, 1st of each year by revising the above-specified reference prices by yearly French inflation rate as soon as published by Institut National de la Statistique et des Etudes Economiques (INSEE).

Invoicing

POLYPEPTIDE shall submit invoices for payment of the Product only after the Product has been delivered.

All invoices shall be sent by email using apayable@caratherapeutics.com .
Invoices sent by email must attach the invoice in pdf file format. CARA may update email addresses from time to time and shall inform POLYPEPTIDE of any changes.

EXHIBIT 10.1

Appendix 5:
Quality Agreement

Reference is made to the Quality Agreement in force between
Cara Therapeutics and PolyPeptide Laboratories France SAS and PolyPeptide S.A
with effective date on June 29th, 2020

EXHIBIT 31.1

Certification of Chief Executive Officer Pursuant to Rule 13a-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002

I, Derek Chalmers, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Cara Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: November 8, 2021

By: /s/ Derek Chalmers
DEREK CHALMERS, Ph.D., D.Sc.
CHIEF EXECUTIVE OFFICER

EXHIBIT 31.2

Certification of Chief Financial Officer Pursuant to Rule 13a-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002

I, Thomas Reilly, certify that:

1. I have reviewed this Quarterly Report on Form 10-Q of Cara Therapeutics, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

(a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

(b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

(c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

(d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

(a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

(b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: November 8, 2021

By: /s/ Thomas Reilly
THOMAS REILLY
CHIEF FINANCIAL OFFICER

EXHIBIT 32.1

CERTIFICATIONS OF
CHIEF EXECUTIVE OFFICER AND CHIEF FINANCIAL OFFICER
OF CARA THERAPEUTICS, INC.
PURSUANT TO 18 U.S.C. SECTION 1350,
AS ADOPTED PURSUANT TO SECTION 906 OF THE
SARBANES-OXLEY ACT OF 2002

In connection with the Quarterly Report on Form 10-Q of Cara Therapeutics, Inc. (the "Company") for the quarter ended September 30, 2021, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), Derek Chalmers, Ph.D., D.Sc., as Chief Executive Officer of the Company, and Thomas Reilly, as Chief Financial Officer of the Company, each hereby certifies, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that, to the best of his knowledge, based upon a review of the Report:

(1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

/s/ DEREK CHALMERS
Name: Derek Chalmers, Ph.D., D.Sc.
Title: Chief Executive Officer
Date: November 8, 2021

/s/ THOMAS REILLY
Name: Thomas Reilly
Title: Chief Financial Officer
Date: November 8, 2021