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 March 31, 2015

OR

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

For the transition period from _____ to _____

Commission file number 000-30171

SANGAMO BIOSCIENCES, INC.

(exact name of registrant as specified in its charter)

Delaware	**68-0359556**
(State or other jurisdiction of incorporation or organization)	**(IRS Employer Identification No.)**

501 Canal Blvd
Richmond, California 94804
(Address of principal executive offices)

(510) 970-6000
(Registrant's telephone number, including area code)

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 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 and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted 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 and post such files). Yes ☒ No ☐

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

Large accelerated filer	☒	Accelerated filer	☐
Non-accelerated filer	☐ (Do not check if a smaller reporting company)	Smaller reporting company	☐

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

As of April 24, 2014, 69,582,797 shares of the issuer's common stock, par value $0.01 per share, were outstanding.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

Some statements contained in this report are forward-looking with respect to our operations, research, development and commercialization activities, clinical trials, operating results and financial condition. These statements involve known and unknown risks, uncertainties and other factors which may cause our actual results, performance or achievements to be materially different from any future results, performances or achievements expressed or implied by the forward-looking statements. Forward-looking statements include, but are not limited to, statements about:

- our strategy;
- product development and commercialization of our products;
- clinical trials;
- partnering;
- revenues from existing and new collaborations;
- our research and development and other expenses;
- sufficiency of our cash resources;
- our operational and legal risks; and
- our plans, objectives, expectations and intentions and any other statements that are not historical facts.

In some cases, you can identify forward-looking statements by terms such as: "anticipates," "believes," "continues," "could," "estimates," "expects," "intends," "may," "plans," "seeks," "should" and "will." These statements reflect our current views with respect to future events and are based on assumptions and subject to risks and uncertainties. Many of these risks are discussed in greater detail under the headings "Risk Factors" and "Management's Discussion and Analysis of Financial Conditions and Results of Operations" in this Form 10-Q. Sangamo undertakes no obligation to publicly release any revisions to forward-looking statements to reflect events or circumstances arising after the date of this report. Readers are cautioned not to place undue reliance on the forward-looking statements, which speak only as of the date of this Quarterly Report on Form 10-Q.

ZFP Therapeutic® is a registered trademark of Sangamo BioSciences, Inc.

PART I. FINANCIAL INFORMATION

ITEM 1. FINANCIAL STATEMENTS

SANGAMO BIOSCIENCES, INC.

CONDENSED CONSOLIDATED BALANCE SHEETS
(Unaudited; in thousands, except share and per share amounts)

	March 31, 2015	December 31, 2014
ASSETS		
Current assets:		
Cash and cash equivalents	$ 25,256	$ 6,030
Marketable securities	170,647	172,932
Interest receivable	398	423
Accounts receivable	6,638	10,368
Prepaid expenses	587	623
Restricted cash	320	320
Other current assets	100	183
Total current assets	203,946	190,879
Marketable securities, non-current	29,822	47,260
Property and equipment, net	2,995	1,479
Intangible assets, in-process research and development	—	1,870
Goodwill	1,585	1,585
Other assets	157	139
Total assets	$ 238,505	$ 243,212
LIABILITIES AND STOCKHOLERS' EQUITY		
Current liabilities:		
Accounts payable and accrued liabilities	$ 6,806	$ 8,704
Accrued compensation and employee benefits	1,703	2,853
Escrow liability	275	275
Deferred revenues	11,184	9,050
Total current liabilities	19,968	20,882
Deferred revenues, non-current	11,049	13,149
Contingent consideration liability	—	1,800
Deferred tax liability	—	748
Total liabilities	31,017	36,579
Commitments and contingencies		
Stockholders' equity:		
Common stock, $0.01 par value; 160,000,000 shares authorized, 69,497,256 and 69,062,394 shares issued and outstanding at March 31, 2015, and December 31, 2014, respectively	695	690
Additional paid-in capital	540,637	534,518
Accumulated deficit	(333,869)	(328,550)
Accumulated other comprehensive income (loss)	25	(25)
Total stockholders' equity	207,488	206,633
Total liabilities and stockholders' equity	$ 238,505	$ 243,212

See accompanying notes.

SANGAMO BIOSCIENCES, INC.

CONDENSED CONSOLIDATED STATEMENTS OF OPERATIONS
(Unaudited; in thousands, except per share amounts)

	Three months ended March 31,	
	2015	**2014**
Revenues:		
Collaboration agreements	$ 12,671	$ 7,568
Research grants	820	548
Total revenues	13,491	8,116
Operating expenses:		
Research and development	14,980	12,083
General and administrative	4,732	3,644
Total operating expenses	19,712	15,727
Loss from operations	(6,221)	(7,611)
Interest and other income, net	154	39
Loss before income taxes	(6,067)	(7,572)
Benefit from income taxes	748	—
Net loss	$ (5,319)	$ (7,572)
Basic and diluted net loss per share	$ (0.08)	$ (0.12)
Shares used in computing basic and diluted net loss per share	69,283	63,199

See accompanying notes.

SANGAMO BIOSCIENCES, INC.

CONDENSED CONSOLIDATED STATEMENTS OF COMPREHENSIVE LOSS
(Unaudited; in thousands)

	Three months ended March 31,	
	2015	**2014**
Net loss	$ (5,319)	$ (7,572)
Change in unrealized gain on available-for-sale securities	50	9
Comprehensive loss	$ (5,269)	$ (7,563)

See accompanying notes.

SANGAMO BIOSCIENCES, INC.

CONDENSED CONSOLIDATED STATEMENTS OF CASH FLOWS
(Unaudited: in thousands)

	Three months ended March 31,	
	2015	**2014**
Operating Activities:		
Net loss	$ (5,319)	$ (7,572)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	147	123
Amortization of premium on marketable securities	241	295
Stock-based compensation	2,953	1,907
Change in fair value of contingent consideration liability	(1,800)	50
Intangible impairment	1,870	—
Benefit from income taxes	(748)	—
Net changes in operating assets and liabilities:		
Interest receivable	25	(45)
Accounts receivable	3,730	(2,205)
Prepaid expenses and other assets	101	(71)
Accounts payable and accrued liabilities	(2,477)	1,732
Accrued compensation and employee benefits	(1,150)	(1,723)
Deferred revenues	34	18,888
Net cash provided by / (used in) operating activities	(2,393)	11,379
Investing Activities:		
Purchases of marketable securities	(39,423)	(16,773)
Maturities of marketable securities	58,955	20,786
Purchases of property and equipment	(1,084)	(126)
Net cash provided by investing activities	18,448	3,887
Financing Activities:		
Proceeds from public offering of common stock, net of issuance costs	—	93,786
Taxes paid related to net share settlement of equity awards	(7)	—
Proceeds from issuance of common stock	3,178	7,585
Net cash provided by financing activities	3,171	101,371
Net increase in cash and cash equivalents	19,226	116,637
Cash and cash equivalents, beginning of period	6,030	10,186
Cash and cash equivalents, end of period	$ 25,256	$ 126,823
Supplemental disclosure of noncash investing activities:		
Property, plant and equipment included in accrued liabilities	$ 579	$ —

See accompanying notes.

NOTE 1—BASIS OF PRESENTATION AND SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

Basis of Presentation

The accompanying unaudited condensed consolidated financial statements of Sangamo BioSciences, Inc. ("Sangamo" or the "Company") have been prepared in accordance with U.S. generally accepted accounting principles for interim financial information and pursuant to the rules and regulations of the Securities and Exchange Commission (SEC). Accordingly, they do not include all of the information and footnotes required by generally accepted accounting principles for complete financial statements. In the opinion of management, all adjustments (consisting of normal recurring adjustments) considered necessary for a fair presentation have been included. Operating results for the three months ended March 31, 2015 are not necessarily indicative of the results that may be expected for the year ending December 31, 2015. The condensed consolidated balance sheet data at December 31, 2014 were derived from the audited consolidated financial statements included in Sangamo's Form 10-K for the year ended December 31, 2014, as filed with the SEC. These financial statements should be read in conjunction with the financial statements and footnotes thereto for the year ended December 31, 2014, included in Sangamo's Form 10-K, as filed with the SEC.

Use of Estimates

The preparation of financial statements in conformity with generally accepted accounting principles requires management to make estimates and assumptions that affect the amounts reported in the financial statements and the accompanying notes. On an ongoing basis, management evaluates its estimates, including critical accounting policies or estimates related to revenue recognition, clinical trial accruals, fair value measurements, business combinations including the fair value of the contingent consideration liability for payments to former Ceregene, Inc. (Ceregene) stockholders and intangible assets related to the acquisition of Ceregene, and stock-based compensation. Estimates are based on historical experience and on various other market specific and other relevant assumptions that the Company believes to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results could differ from those estimates.

Revenue Recognition

Revenues from research activities made under strategic partnering agreements and collaborations are recognized as the services are provided when there is persuasive evidence that an arrangement exists, delivery has occurred, the price is fixed or determinable, and collectability is reasonably assured. Revenue generated from research and licensing agreements typically includes upfront signing or license fees, cost reimbursements, research services, minimum sublicense fees, milestone payments and royalties on future licensee's product sales.

Multiple Element Arrangements prior to the adoption of ASU No. 2009-13, Revenue Recognition—Multiple Deliverable Revenue Arrangements (ASU 2009-13). For revenue arrangements entered into before January 1, 2011, that include multiple deliverables, the elements of such agreements were divided into separate units of accounting if the deliverables met certain criteria, including whether the fair value of the delivered items could be determined and whether there was evidence of fair value of the undelivered items. In addition, the consideration was allocated among the separate units of accounting based on their fair values, and the applicable revenue recognition criteria are considered separately for each of the separate units of accounting. Prior to the adoption of ASU 2009-13, the Company recognized nonrefundable signing, license or non-exclusive option fees as revenue when rights to use the intellectual property related to the license were delivered and over the period of performance obligations if the Company had continuing performance obligations. The Company estimated the performance period at the inception of the arrangement and reevaluated it each reporting period. Changes to these estimates were recorded on a prospective basis.

Multiple Element Arrangements after the adoption of ASU 2009-13. ASU 2009-13 amended the accounting standards for certain multiple element revenue arrangements to:

- provide updated guidance on whether multiple elements exist, how the elements in an arrangement should be separated, and how the arrangement consideration should be allocated to the separate elements;
- require an entity to allocate arrangement consideration to each element based on a selling price hierarchy where the selling price for an element is based on vendor-specific objective evidence (VSOE), if available; third-party evidence (TPE), if available and VSOE is not available; or the best estimate of selling price (ESP), if neither VSOE nor TPE is available; and
- eliminate the use of the residual method and require an entity to allocate arrangement consideration using the relative selling price method.

For revenue agreements with multiple element arrangements, such as license and development agreements, entered into on or after January 1, 2011, the Company allocates revenue to each non-contingent element based on the relative selling price of each element. When applying the relative selling price method, the Company determines the selling price for each deliverable using VSOE of selling price or TPE of selling price. If neither exists, the Company uses ESP for that deliverable. Revenue allocated is then recognized when the basic four revenue recognition criteria are met for each element. The collaboration and license agreements entered into with Shire International GmbH, formerly Shire AG (Shire), in January 2012 and Biogen Inc., formerly Biogen Idec Inc. (Biogen) in January 2014 were evaluated under these amended accounting standards.

Additionally, the Company may be entitled to receive certain milestone payments which are contingent upon reaching specified objectives. These milestone payments are recognized as revenue in full upon achievement of the milestone if there is substantive uncertainty at the date the arrangement is entered into that the objectives will be achieved and if the achievement is based on the Company's performance.

Minimum annual sublicense fees are also recognized as revenue in the period in which such fees are due. Royalty revenues are generally recognized when earned and collectability of the related royalty payment is reasonably assured. The Company recognizes cost reimbursement revenue under collaborative agreements as the related research and development costs for services are rendered. Deferred revenue represents the portion of research or license payments received which have not been earned.

Sangamo's research grants are typically multi-year agreements and provide for the reimbursement of qualified expenses for research and development as defined under the terms of the grant agreement. Revenue under grant agreements is recognized when the related qualified research expenses are incurred to the extent such amounts have been agreed to with the respective collaboration partner.

Recent Accounting Standards

In August 2014 the Financial Accounting Standards Board issued Accounting Standards Update (ASU) No. 2014-15, *Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern* (ASU 2014-15). ASU 2014-15 requires management to evaluate whether there is substantial doubt about an entity's ability to continue as a going concern and to provide related footnote disclosures. In doing so, companies will have reduced diversity in the timing and content of footnote disclosures than under the current guidance. ASU 2014-15 is effective for the Company in the first quarter of 2016 with early adoption permitted. The Company does not believe the impact of adopting ASU 2014-15 on its consolidated financial statements will be material.

In May 2014 the Financial Accounting Standards Board issued ASU 2014-09, *Revenue from Contracts with Customers* (ASU 2014-09). This standard outlines a single comprehensive model for entities to use in accounting for revenue arising from contracts with customers and supersedes most current revenue recognition guidance, including industry-specific guidance. The main principle of ASU 2014-09 is to recognize revenues when promised goods or services are transferred to customers in an amount that reflects the consideration that is expected to be received for those goods or services. ASU 2014-09 provides companies with two implementation methods: (i) apply the standard retrospectively to each prior reporting period presented (full retrospective application); or (ii) apply the standard retrospectively with the cumulative effect of initially applying the standard as an adjustment to the opening balance of retained earnings of the annual reporting period that includes the date of initial application (modified retrospective application). This guidance is effective for annual reporting periods beginning after December 15, 2016, including interim periods within that reporting period, and early application is not permitted. The Company is currently in the process of evaluating the impact of the pending adoption of ASU 2014-09 on its consolidated financial statements.

NOTE 2—FAIR VALUE MEASUREMENT

The Company measures certain financial assets and liabilities at fair value on a recurring basis, including cash equivalents, available-for sale-securities and the contingent consideration liability. The fair value of these assets and contingent liability was determined based on a three-tier hierarchy under the authoritative guidance for fair value measurements and disclosures that prioritizes the inputs used in measuring fair value as follows:

Level 1: Unadjusted quoted prices in active markets that are accessible at the measurement date for identical, unrestricted assets or liabilities;

Level 2: Quoted prices in markets that are not active or inputs which are observable, either directly or indirectly, for substantially the full term of the asset or liability; and

Level 3: Prices or valuation techniques that require inputs that are both significant to the fair value measurement and unobservable (i.e., supported by little or no market activity).

The fair value measurements of our cash equivalents, available-for-sale marketable securities and contingent consideration liability are identified at the following levels within the fair value hierarchy (in thousands):

	March 31, 2015 Fair Value Measurements			
	Total	Level 1	Level 2	Level 3
Assets:				
Cash equivalents:				
Money market funds	$ 17,089	$ 17,089	$ —	$ —
Total	17,089	17,089	—	—
Marketable securities:				
Commercial paper securities	31,148	—	31,148	—
Corporate debt securities	23,266	—	23,266	—
U.S. government sponsored entity debt securities	146,055	—	146,055	—
Total	200,469	—	200,469	—
Total cash equivalents and marketable securities	$ 217,558	$ 17,089	$ 200,469	$ —

	December 31, 2014 Fair Value Measurements			
	Total	Level 1	Level 2	Level 3
Assets:				
Cash equivalents:				
Money market funds	$ 3,182	$ 3,182	$ —	$ —
Total	3,182	3,182	—	—
Marketable securities:				
Commercial paper securities	33,748	—	33,748	—
Corporate debt securities	22,813	—	22,813	—
U.S. government sponsored entity debt securities	163,631	—	163,631	—
Total	220,192	—	220,192	—
Total cash equivalents and marketable securities	$ 223,374	$ 3,182	$ 220,192	$ —
Liabilities:				
Contingent consideration liability	$ 1,800	$ —	$ —	$ 1,800
Total	$ 1,800	$ —	$ —	$ 1,800

Investments

The Company generally classifies its debt instruments as Level 2. Instruments can be classified as Level 2 when observable market prices for identical securities that are traded in less active markets are used. When observable market prices for identical securities are not available, such instruments are priced using benchmark curves, benchmarking of like securities, sector groupings, matrix pricing and valuation models. These valuation models are proprietary to the pricing providers or brokers and incorporate a number of inputs, including, listed in approximate order of priority: benchmark yields, reported trades, broker/dealer quotes, issuer spreads, two-sided markets, benchmark securities, bids, offers and reference data including market research publications. For certain security types, additional inputs may be used, or some of the standard inputs may not be applicable. Evaluators may prioritize inputs differently on any given day for any security based on market conditions, and not all inputs listed are available for use in the evaluation process for each security evaluation on any given day.

Contingent Consideration Liability

In October 2013, the Company acquired Ceregene and recorded a liability for the estimated fair value of contingent consideration payments to former Ceregene stockholders, as outlined under the terms of the merger agreement with Ceregene. These contingent payments are owed if the Company grants a third-party license to develop and commercialize certain product candidates acquired from Ceregene, or if the Company commercializes any of such product candidates itself. The fair value of this liability is estimated using a probability-weighted discounted cash flow analysis. Such valuations require significant estimates and assumptions including but not limited to: determining the timing and estimated costs to complete the in-process projects, projecting regulatory approvals, estimating future cash flows and developing appropriate discount rates. The Company has classified this liability as Level 3.

Subsequent changes in the fair value of this contingent consideration liability are recorded to the research and development (R&D) expense line item in the Condensed Consolidated Statements of Operations as operating expenses. During the three months ended March 31, 2015, the recognized amount of the liability for contingent consideration decreased by $1.8 million due to the decrease in the probability of incurring potential future royalty payments associated with the impairment of the in-process research and development (IPR&D) assets acquired from Ceregene (see Note 6).

Fair value as of December 31, 2014	$ 1,800
Change in fair value	(1,800)
Fair value as of March 31, 2015	$ -

NOTE 3—MARKETABLE SECURITIES

Sangamo generally classifies its marketable securities as available-for-sale and records its investments at fair value. Available-for-sale securities are carried at estimated fair value, with the unrealized holding gains and losses included in accumulated other comprehensive income. Investments that have maturities beyond one year as of the end of the reporting period are classified as non-current. The Company's investments are subject to a periodic impairment review, and the Company recognizes an impairment charge when a decline in the fair value of its investments below the cost basis is judged to be other-than-temporary. The Company considers various factors in determining whether to recognize an impairment charge, including the length of time and extent to which the fair value has been less than the Company's cost basis, the financial condition and near-term prospects of the investee, and the Company's intent and ability to hold the investment for a period of time sufficient to allow for any anticipated recovery in the market value.

The table below summarizes the Company's investments (in thousands):

	Amortized Cost	Gross Unrealized Gains	Gross Unrealized (Losses)	Estimated Fair Value
March 31, 2015				
Cash equivalents:				
Money market funds	$ 17,089	$ —	$ —	$ 17,089
Total	17,089	—	—	17,089
Available-for-sale securities:				
Commercial paper securities	$ 31,121	$ 27	$ —	$ 31,148
Corporate debt securities	23,261	5	—	23,266
U.S. government sponsored entity debt securities	146,062	—	(7)	146,055
Total	200,444	32	(7)	200,469
Total cash equivalents and available-for-sale securities	$ 217,533	$ 32	$ (7)	$ 217,558
December 31, 2014				
Cash equivalents:				
Money market funds	$ 3,182	$ —	$ —	$ 3,182
Total	3,182	—	—	3,182
Available-for-sale securities:				
Commercial paper securities	$ 33,715	$ 33	$ —	$ 33,748
Corporate debt securities	22,831	—	(18)	22,813
U.S. government sponsored entity debt securities	163,671	—	(40)	163,631
Total	220,217	33	(58)	220,192
Total cash equivalents and available-for-sale securities	$ 223,399	$ 33	$ (58)	$ 223,374

The Company had no other-than-temporary impairments of its investments for the three months ended March 31, 2015 or the twelve months ended December 31, 2014.

NOTE 4—BASIC AND DILUTED NET LOSS PER SHARE

Basic net loss per share has been computed by dividing the net loss by the weighted-average number of shares of common stock outstanding during the period. Diluted net loss per share is calculated by dividing net loss by the weighted average number of shares of common stock and potential dilutive securities outstanding during the period.

Because Sangamo is in a net loss position, diluted net loss per share excludes the effects of common stock equivalents consisting of stock options, which are anti-dilutive. The total number of shares subject to stock options outstanding excluded from

consideration in the calculation of diluted net loss per share for the three months ended March 31, 2015 and 2014 were 7,624,600 and 7,302,366, respectively.

NOTE 5—MAJOR CUSTOMERS, PARTNERSHIPS AND STRATEGIC ALLIANCES

Collaboration Agreements

Collaboration and License Agreement with Biogen Inc. in Human Therapeutics

In January 2014 Sangamo entered into a Global Research, Development and Commercialization Collaboration and License Agreement (the "Biogen Agreement") with Biogen, pursuant to which Sangamo and Biogen collaborate to discover, develop, seek regulatory approval for and commercialize therapeutics based on Sangamo's zinc finger DNA-binding protein (ZFP) technology for hemoglobinopathies, including beta-thalassemia and sickle cell disease (SCD).

Under the Biogen Agreement, Sangamo and Biogen jointly conduct two research programs: the beta-thalassemia program and the SCD program. For the beta-thalassemia program, Sangamo is responsible for all discovery, research and development activities through the first human clinical trial for the first ZFP Therapeutic developed under the Biogen Agreement for the treatment of beta-thalassemia. For the SCD program, both parties are responsible for research and development activities through the submission of an Investigational New Drug (IND) application for ZFP Therapeutics intended to treat SCD. For both programs, Biogen is responsible for subsequent world-wide clinical development, manufacturing and commercialization of licensed products developed under the Biogen Agreement. At the end of specified research terms for each program or under certain specified circumstances, Biogen retains the right to step in and take over any remaining activities of Sangamo. Furthermore, Sangamo has an option to co-promote in the United States any licensed product to treat beta-thalassemia and SCD developed under the Biogen Agreement, and Biogen agrees to compensate Sangamo for such co-promotion activities.

Sangamo received an upfront license fee of $20.0 million upon entering into the Biogen Agreement. In addition, the Company will also be eligible to receive $126.3 million in payments upon the achievement of specified research, regulatory, clinical development milestones, as well as $167.5 million in payments upon the achievement of specified commercialization and sales milestones. Biogen reimburses Sangamo for agreed upon costs incurred in connection with research and development activities conducted by Sangamo. In addition, Sangamo is eligible to receive contingent payments upon the achievement of specified regulatory, clinical development, commercialization and sales milestones. The total amount of potential regulatory, clinical development, commercialization and sales contingent payments, assuming the achievement of all specified milestone events in the Biogen Agreement, is $293.8 million, including Phase 1 contingent payments of $7.5 million for each of the beta-thalassemia and SCD programs. In addition, if products are commercialized under the Biogen Agreement, Biogen will pay Sangamo incremental royalties for each licensed product that are a tiered double-digit percentage of annual net sales of such product. To date, no milestone payments have been received and no products have been approved and therefore no royalty fees have been earned under the Biogen Agreement.

All contingent payments under the Biogen Agreement, when earned, will be non-refundable and non-creditable. The Company has evaluated the contingent payments under the Biogen Agreement based on the authoritative guidance for research and development milestones and determined that certain of these payments meet the definition of a milestone and that all such milestones are evaluated to determine if they are considered substantive milestones. Milestones are considered substantive if they are related to events (i) that can be achieved based in whole or in part on either the Company's performance or on the occurrence of a specific outcome resulting from the Company's performance, (ii) for which there was substantive uncertainty at the date the agreement was entered into that the event would be achieved and (iii) that would result in additional payments being due to the Company. Accordingly, consideration received for the achievement of milestones that are determined to be substantive will be recognized as revenue in their entirety in the period when the milestones are achieved and collectability is reasonably assured. Revenue for the achievement of milestones that are not substantive will be recognized over the remaining period of the Biogen Agreement, assuming all other applicable revenue recognition criteria have been met.

Subject to the terms of the Biogen Agreement, Sangamo grants Biogen an exclusive, royalty-bearing license, with the right to grant sublicenses, to use certain ZFP and other technology controlled by Sangamo for the purpose of researching, developing, manufacturing and commercializing licensed products developed under the Biogen Agreement. Sangamo also grants Biogen a non-exclusive, world-wide, royalty free, fully paid license, with the right to grant sublicenses, of Sangamo's interest in certain other intellectual property developed pursuant to the Biogen Agreement.

The Company has identified the deliverables within the arrangement as a license to the technology and on-going research services activities. The Company has concluded that the license is not a separate unit of accounting as it does not have stand-alone value to Biogen apart from the research services to be performed pursuant to the Biogen Agreement. As a result, the Company will recognize revenue from the upfront payment on a straight-line basis over a forty-month estimated initial research term during which the Company will perform research services. As of March 31, 2015, the Company has deferred revenue of $14.1 million related to the Biogen Agreement.

Revenues recognized under the agreement with Biogen for the three months ended March 31, 2015 and 2014 are as follows (in thousands):

	Three months ended March 31,	
	2015	2014
Revenue related to Biogen Collaboration:		
Recognition of upfront fee	$ 1,523	$ 660
Research services	1,533	423
Total	$ 3,056	$ 1,083

Related costs and expenses incurred under the Biogen agreement related to the beta-thalassemia project, which is co-funded with California Institute for Regenerative Medicine (CIRM), were $1.4 million and $1.3 million during the three months ended March 31, 2015 and 2014, respectively. Related costs and expenses for other projects including sickle cell disease under the Biogen agreement were $1.1 million and $0.0 million during the three months ended March 31, 2015 and 2014, respectively.

Collaboration and License Agreement with Shire International GmbH in Human Therapeutics and Diagnostics

In January 2012 the Company entered into a collaboration and license agreement (the "Shire Agreement") with Shire, pursuant to which the Company and Shire collaborate to research, develop and commercialize human therapeutics and diagnostics for monogenic diseases based on Sangamo's novel ZFP technology. Under the Shire Agreement, the Company and Shire may develop potential human therapeutic or diagnostic products for seven gene targets. The initial four gene targets selected were blood clotting Factors VII, VIII, IX and X, and products developed for such initial gene targets will be used for treating or diagnosing hemophilia. In June 2012, Shire selected a fifth gene target for the development of a ZFP Therapeutic for Huntington's disease. Shire has the right, subject to certain limitations, to designate two additional gene targets. Pursuant to the Shire Agreement, the Company granted Shire an exclusive, world-wide, royalty-bearing license, with the right to grant sublicenses, to use Sangamo's ZFP technology for the purpose of developing and commercializing human therapeutic and diagnostic products for the gene targets. The initial research term of the Shire Agreement is six years and is subject to extensions upon mutual agreement and under other specified circumstances.

Under the terms of the Shire Agreement, the Company is responsible for all research activities through the submission of an IND or European Clinical Trial Application (CTA), while Shire is responsible for clinical development and commercialization of products generated from the research program from and after the acceptance of an IND or CTA for the product. Shire reimburses Sangamo for agreed upon internal and external program-related research costs.

The Company received an upfront license fee of $13.0 million upon entering into the Shire Agreement. In addition, the Company will also be eligible to receive $33.5 million in payments upon the achievement of specified research, regulatory, clinical development milestones, including payments for each gene target through the acceptance of an IND or CTA submission totaling $8.5 million, as well as $180 million in payments upon the achievement of specified commercialization and sales milestones. The Company will also be eligible to receive royalty payments that are a tiered double-digit percentage of net sales of licensed product sold by Shire or its sublicensees developed under the collaboration, if any. To date, no products have been approved and therefore no royalty fees have been earned under the Shire Agreement.

All contingent payments under the Shire Agreement, when earned, will be non-refundable and non-creditable. The Company has evaluated the contingent payments under the Shire Agreement based on the authoritative guidance for research and development milestones and determined that certain of these payments meet the definition of a milestone and that all such milestones are evaluated to determine if they are considered substantive milestones. Milestones are considered substantive if they are related to events (i) that can be achieved based in whole or in part on either the Company's performance or on the occurrence of a specific outcome resulting from the Company's performance, (ii) for which there was substantive uncertainty at the date the agreement was entered into that the event would be achieved and (iii) that would result in additional payments being due to the Company. Accordingly, revenue for the achievement of milestones that are determined to be substantive will be recognized in their entirety in the period the milestones are achieved and collectability is reasonably assured. Revenue for the achievement of milestones that are not substantive will be recognized over the remaining period of the Shire Agreement, assuming all other applicable revenue recognition criteria have been met. In 2014 Sangamo recognized a $1.0 million milestone payment related to our hemophilia program.

The Company has identified the deliverables within the arrangement as a license to the technology and on-going research services activities. The Company has concluded that the license is not a separate unit of accounting as it does not have stand-alone value to Shire apart from the research services to be performed pursuant to the Shire Agreement. As a result, the Company will recognize revenue from the upfront payment on a straight-line basis over a six-year initial research term during which the Company

will perform research services. As of March 31, 2015, the Company has deferred revenue of $6.8 million related to the Shire Agreement.

Revenues recognized under the agreement with Shire for the three months ended March 31, 2015 and 2014, were as follows (in thousands):

	Three months ended March 31,	
	2015	2014
Revenue related to Shire Collaboration:		
Recognition of upfront fee	$ 542	$ 542
Research services	4,522	4,979
Total	$ 5,064	$ 5,521

Related costs and expenses incurred under the Shire agreement were $4.5 million and $4.8 million during the three months ended March 31, 2015 and 2014, respectively.

Agreement with Sigma-Aldrich Corporation in Laboratory Research Reagents, Transgenic Animal and Commercial Protein Production Cell-line Engineering

In July 2007 Sangamo entered into a license agreement (the "Sigma Agreement") with Sigma-Aldrich Corporation (Sigma). Under the Sigma Agreement, Sangamo agreed to provide Sigma with access to our proprietary ZFP technology and the exclusive right to use the technology to develop and commercialize research reagent products and services in the research field, excluding certain agricultural research uses that Sangamo previously licensed to Dow AgroSciences LLC (DAS). Under the Sigma Agreement, Sangamo and Sigma agreed to conduct a three-year research program to develop laboratory research reagents using Sangamo's ZFP technology during which time Sangamo agreed to assist Sigma in connection with its efforts to market and sell services employing the Company's ZFP technology in the research field. Sangamo has transferred its ZFP manufacturing technology to Sigma.

In October 2009 Sangamo expanded the Sigma Agreement. In addition to the original terms of the Sigma Agreement, Sigma received exclusive rights to develop and distribute ZFP-modified cell lines for commercial production of protein pharmaceuticals and certain ZFP-engineered transgenic animals for commercial applications. Under the terms of the Sigma Agreement as expanded in 2009, Sigma made an upfront cash payment of $20.0 million consisting of a $4.9 million purchase of 636,133 shares of Sangamo common stock and a $15.1 million upfront license fee. The upfront license fee was recognized on a straight-line basis from the effective date of the expanded license through July 2010, which represents the period over which Sangamo was obligated to perform research services for Sigma. Sangamo is also eligible to receive commercial license fees of $5.0 million based upon a percentage of net sales. As of March 31, 2015 Sangamo has received the entire $5.0 million of commercial license fees and is eligible to receive royalty payments of 10.5% of net sales and sublicensing revenue. In addition, upon the achievement of certain cumulative commercial milestones Sigma will make milestone payments to Sangamo up to an aggregate of $25.0 million.

Revenues recognized under the agreement with Sigma for the three months ended March 31, 2015 and 2014, were as follows (in thousands):

	Three months ended March 31,	
	2015	2014
Revenue related to Sigma Collaboration:		
Royalty revenues	$ 264	$ 106
License fee revenues	4,256	179
Total	$ 4,520	$ 285

Related costs and expenses incurred under the Sigma agreement were $0.2 million and $0.0 million during the three months ended March 31, 2015 and 2014, respectively.

Agreement with Dow AgroSciences in Plant Agriculture

In October 2005 Sangamo entered into an exclusive commercial license agreement with DAS (the "DAS Agreement"). Under the DAS Agreement, Sangamo provides DAS with access to our proprietary ZFP technology and the exclusive right to use the technology to modify the genomes or alter the nucleic acid or protein expression of plant cells, plants, or plant cell cultures. Sangamo has retained rights to use plants or plant-derived products to deliver ZFP transcription factors (ZFP TFs) or ZFP nucleases (ZFNs) into humans or animals for diagnostic, therapeutic or prophylactic purposes. The DAS Agreement provided for an initial three-year research term. In June 2008, DAS exercised its option under the agreement to obtain a commercial license to sell products incorporating or derived from plant cells generated using the Company's ZFP technology, including agricultural crops, industrial products and plant-derived biopharmaceuticals. The exercise of the option triggered a one-time commercial license fee of $6.0 million, payment of the remaining $2.3 million of the previously agreed $4.0 million in research milestones, development and commercialization milestone payments for each product, and royalties on sales of products. Furthermore, DAS has the right to sublicense Sangamo's ZFP technology to third parties for use in plant cells, plants or plant cell cultures. Sangamo will be entitled to 25% of any cash consideration received by DAS under such sublicenses. In December 2010, the Company amended the DAS Agreement to extend the period of reagent manufacturing services and research services through December 31, 2012.

The DAS Agreement also provides for minimum license fees each year due to Sangamo every October, provided the Agreement is not terminated by DAS. Annual fees range from $250,000 to $3.0 million and total $25.3 million over 11 years. The Company does not have any ongoing performance obligations under the agreement with DAS. DAS has the right to terminate the agreement at any time; accordingly, the Company's actual license fees over the term of the DAS Agreement could be lower than $25.3 million. In addition, each party may terminate the DAS Agreement upon an uncured material breach by the other party. In the event of any termination of the DAS Agreement, all rights to use the Company's ZFP technology will revert to Sangamo, and DAS will no longer be permitted access to Sangamo's ZFP technology or to develop or, except in limited circumstances, commercialize any products derived from the Company's ZFP technology.

There were no revenues or related costs and expenses recognized under the DAS Agreement during the three months ended March 31, 2015 and 2014, respectively.

Funding from Research Foundations

California Institute for Regenerative Medicine - HIV

In October 2009 CIRM, a State of California entity, granted a $14.5 million Disease Team Research Award to develop an HIV/AIDS therapy based on the application of ZFN gene editing technology in hematopoietic stem cells (HSCs). The four-year grant supports an innovative research project conducted by a multidisciplinary team of investigators, including investigators from the University of Southern California, City of Hope National Medical Center and Sangamo BioSciences. Sangamo received funds totaling $5.2 million from the total amount awarded based on expenses incurred for research and development efforts by Sangamo as prescribed in the agreement, and subject to its terms and conditions. The award is intended to substantially fund Sangamo's research and development efforts related to the agreement. The State of California has the right to receive, subject to the terms and conditions of the agreement between Sangamo and CIRM, payments from Sangamo resulting from sales of a commercial product resulting from research and development efforts supported by the grant. As of December 31, 2013, all revenues under the award had been recognized and all funds had been received.

There were no revenues attributable to research and development performed under the CIRM 2009 grant agreement during the three months ended March 31, 2015 and 2014, respectively. Related costs and expenses incurred under the CIRM grant agreement were $0.2 million and $0.3 million during the three months ended March 31, 2015 and 2014, respectively.

In May 2014 CIRM agreed to fund a $5.6 million Strategic Partnership Award to fund clinical studies of a potentially curative ZFP Therapeutic for HIV/AIDS based on the application of its ZFN genome editing technology in hematopoietic stem progenitor cells (HSPCs). The four year grant provides matching funds to support evaluation of the Company's stem cell-based ZFP Therapeutic in a clinical trial in HIV-infected individuals conducted at City of Hope. The Company expects funding for this grant to commence in 2015.

There were no revenues attributable to research and development performed under the Strategic Partnership Award during the three months ended March 31, 2015 and 2014, respectively. Related costs and expenses incurred under the CIRM Strategic Partnership Award were $0.3 million and $0.0 million during the three months ended March 31, 2015 and 2014, respectively.

California Institute for Regenerative Medicine - Beta-Thalassemia

In May 2013 CIRM granted Sangamo a $6.4 million Strategic Partnership Award to develop a potentially curative ZFP Therapeutic for beta-thalassemia based on the application of its ZFN gene editing technology in HSCs. The four-year grant provides

matching funds for preclinical work that will support an IND application and a Phase 1 clinical trial in transfusion-dependent beta-thalassemia patients. The State of California has the right to receive, subject to the terms and conditions of the agreement between Sangamo and CIRM, payments from Sangamo, or its collaborators, from sales of a commercial product resulting from research and development efforts supported by the grant, in accordance with Title 17, California Code of Regulations, Section 100600.

Revenue attributable to research and development performed under the CIRM grant agreement for beta-thalassemia was $0.7 million and $0.4 million during the three months ended March 31, 2015 and 2014, respectively. Related costs and expenses incurred under the CIRM grant agreement were $0.7 million and $0.4 million during the three months ended March 31, 2015 and 2014, respectively.

NOTE 6—INTANGIBLE ASSETS

Intangible assets for IPR&D consist of two clinical product candidates from our 2013 acquisition of Ceregene. IPR&D is an intangible asset classified as indefinite-lived until the completion or abandonment of the associated research and development effort, and will be amortized over an estimated useful life to be determined at the date the project is completed.

The carrying values of these intangibles assets are as follows (in thousands):

	As of March 31, 2015	As of December 31, 2014
CERE-110 for the treatment of Alzheimer's disease	$ —	$ 1,640
CERE-120 for the treatment of Parkinson's disease	—	230
Total identifiable intangible assets	$ —	$ 1,870

During the three months ended March 31, 2015, the Company received clinical data demonstrating no statistically significant difference between the control group and the group treated with CERE-110 for Alzheimer’s disease. Subsequently, the Company decided to discontinue the CERE-110 and CERE-120 clinical trial programs. As such, the probability of achieving projected revenues and cash flows associated with these programs were adversely affected. Given these results, the Company does not believe the programs have an alternative future use for itself or other market participants. Accordingly, during the three months ended March 31, 2015, the Company recognized a $1.9 million impairment charge related to these assets. The impairment is recorded in R&D expense in the accompanying condensed consolidated statements of operations.

NOTE 7—INCOME TAXES

The Company maintains deferred tax assets that reflect the net tax effects of temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. These deferred tax assets include net operating loss carryforwards, research credits and capitalized research and development costs. Realization of deferred tax assets is dependent upon future earnings, if any, the timing and amount of which are uncertain based on Sangamo’s history of losses. Accordingly, the Company’s net deferred tax assets have been fully offset by a valuation allowance. Utilization of operating losses and credits may be subject to substantial annual limitation due to ownership change provisions of the Internal Revenue Code of 1986, as amended and similar state provisions. The annual limitation may result in the expiration of net operating losses and credits before utilization.

During the three months ended March 31, 2015 the deferred tax liability of $0.7 million that was recorded upon acquiring the IPR&D assets in 2013 was adjusted due to the impairment of these assets. This resulted in the recognition of a $0.7 million income tax benefit.

NOTE 8—STOCK-BASED COMPENSATION

The following table shows total stock-based compensation expense included in the condensed consolidated statements of operations for the three months ended March 31, 2015 and 2014 (in thousands):

	Three months ended March 31,	
	2015	2014
Costs and expenses:		
Research and development	$ 1,691	$ 1,073
General and administrative	1,262	834
Total stock-based compensation expense	$ 2,953	$ 1,907

ITEM 2. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

The discussion in "Management's Discussion and Analysis of Financial Condition and Results of Operations" contains trend analysis, estimates and other forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended. These forward-looking statements include, without limitation, statements containing the words "believes," "anticipates," "expects," "continue," and other words of similar import or the negative of those terms or expressions. Such forward-looking statements are subject to known and unknown risks, uncertainties, estimates and other factors that may cause the actual results, performance or achievements of the Company, or industry results, to be materially different from any future results, performance or achievements expressed or implied by such forward-looking statements. You should read the following discussion and analysis along with the financial statements and notes attached to those statements included elsewhere in this report and in our annual report on Form 10-K for the year ended December 31, 2014 as filed with the SEC.

Overview

We are a clinical stage biopharmaceutical company focused on the research, development and commercialization of engineered DNA-binding proteins for the development of novel therapeutic strategies for unmet medical needs. Our current mission is to develop ZFP Therapeutics®, or human therapeutics based on our proprietary zinc finger DNA-binding protein (ZFP) technology, through early stage clinical testing, strategically partner with biopharmaceutical companies at points of value inflection and have the partner execute late-stage clinical trials and commercial development. In the long-term, our goal is to integrate marketing and development operations and to capture the value of late-stage and commercial ZFP Therapeutic products for ourselves.

We and our licensed partners are the leaders in the research, development and commercialization of ZFPs, a naturally occurring class of proteins. We have used our knowledge and expertise to develop a proprietary technology platform. ZFPs can be engineered to make ZFP nucleases (ZFNs), proteins that can be used to modify DNA sequences in a variety of ways and ZFP transcription factors (ZFP TFs), proteins that can be used to turn genes on or off. As ZFPs act at the DNA level, they have broad potential applications in several areas, including human therapeutics, plant agriculture and research reagents, as well as production of transgenic animals and cell-line engineering.

The main focus for our company is the development of novel human therapeutics and we are building a pipeline of ZFP Therapeutics. Our lead ZFP Therapeutic, SB-728-T, a ZFN-modified autologous T-cell product for the treatment of HIV/AIDS, is the first therapeutic application of our ZFN technology and is being evaluated in a Phase 2 clinical trial in HIV-infected subjects.

In January 2014 we entered into a collaborative partnership with Biogen Inc., formerly Biogen Idec Inc. (Biogen) to research, develop and commercialize our preclinical ZFP Therapeutic development program in hemoglobinopathies, targeting sickle cell disease (SCD) and beta-thalassemia. We also have a collaborative partnership with Shire International GmbH, formerly Shire AG (Shire), to research, develop and commercialize certain of our preclinical ZFP Therapeutic development programs, including programs in hemophilia, Huntington's disease (HD) and other monogenic diseases. We have proprietary preclinical programs in several lysosomal storage disorders (LSDs). In addition, we have research stage programs in other monogenic diseases, including certain immunodeficiencies, as well as central nervous system (CNS) disorders and cancer immunotherapy.

We believe the potential commercial applications of ZFPs are broad-based and we have entered into strategic partnerships in fields outside human therapeutics to facilitate the sale or licensing of our ZFP platform as follows:

- We have a license agreement with the research reagent company Sigma-Aldrich Corporation (Sigma). Sigma has the exclusive rights to develop and market high value laboratory research reagents based upon our ZFP technology as well as ZFP-modified cell lines for commercial production of protein pharmaceuticals and ZFP-engineered transgenic animals. Sigma is marketing ZFN-derived gene editing tools under the trademark CompoZr®.
- We have a license agreement with Dow AgroSciences, LLC (DAS), a wholly owned subsidiary of Dow Chemical Corporation. Under the agreement, we have provided DAS with access to our ZFP technology and the exclusive rights to use it to modify the genomes or alter protein expression of plant cells, plants or plant cell cultures. DAS markets our ZFN technology under the trademark EXZACT™ Precision Technology. We have retained rights to use plants or plant-derived products to deliver ZFP TFs or ZFNs into human or animals for diagnostic, therapeutic or prophylactic purposes.

We have incurred net losses since inception and expect to incur losses in the future as we continue our research and development activities. To date, we have funded our operations primarily through the issuance of equity securities, payments from corporate collaborations and research grants.

For the three months ended March 31, 2015, we incurred a consolidated net loss of $5.3 million, or $0.08 per share, compared to a net loss of $7.6 million, or $0.12 per share, for the same period in 2014. As of March 31, 2015, we had cash, cash equivalents, marketable securities and interest receivable totaling $226.1 million compared to $226.6 million as of December 31, 2014. As of March 31, 2015, we had an accumulated deficit of $333.9 million.

Our revenues have consisted primarily of revenues from partnerships of our ZFP technology platform in both therapeutic and non-therapeutic applications, including license fees, research reimbursement and milestones, royalties, as well as revenues from research grant funding. We expect revenues will continue to fluctuate from period to period, and there can be no assurance that new collaborations or partner funding will continue beyond their current terms.

In the development of our ZFP technology platform, we are focusing our resources on higher-value ZFP Therapeutic product development and less on our non-therapeutic applications. Development of novel therapeutic products is costly and is subject to a lengthy and uncertain regulatory process by the FDA. Our future products will be gene-based therapeutics. Adverse events in both our own clinical program and other programs may have a negative impact on regulatory approval, the willingness of potential commercial partners to enter into agreements and public perception.

Critical Accounting Estimates

The accompanying discussion and analysis of our financial condition and results of operations are based upon our condensed consolidated financial statements and the related disclosures, which have been prepared in accordance with generally accepted accounting principles in the United States. The preparation of these financial statements requires us to make estimates, assumptions and judgments that affect the reported amounts in our consolidated financial statements and accompanying notes. We base our estimates on historical experience and on various other assumptions that we believe to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions. We believe that there have been no significant changes in our critical accounting policies and estimates disclosed in our Annual Report on Form 10-K for the year ended December 31, 2014, as filed with the SEC.

Results of Operations

Three months ended March 31, 2015 and 2014

Revenues

	Three months ended March 31, (in thousands, except percentage values)			
	2015	2014	Change	%
Revenues:				
Collaboration agreements	$ 12,671	$ 7,568	$ 5,103	67%
Research grants	820	548	272	50%
Total revenues	$ 13,491	$ 8,116	$ 5,375	66%

Total revenues consist of revenues from collaboration agreements and research grants. We anticipate revenues over the next several years will be derived primarily from our collaboration agreements with Biogen, Shire, DAS and Sigma.

Revenues from our corporate collaboration agreements were $12.7 million for the three months ended March 31, 2015, compared to $7.6 million in the corresponding period in 2014. The $5.1 million increase in collaboration agreements revenues was primarily due to an increase of $6.2 million in revenues related to our collaboration and license agreements with Sigma and Biogen, which was offset by a decrease of $1.1 million in revenues related to our collaboration and license agreements with Shire and Open Monoclonal Technology, Inc. The revenues from Sigma included recognition of revenues under our license and royalty agreement of $4.5 million. The revenues from Biogen included partial recognition of an upfront payment of $20.0 million and $1.5 million in revenues from research services. Research grant revenues were approximately $0.8 million for the three months ended March 31, 2015, compared to $0.5 million in the corresponding period in 2014, primarily due to an increase in revenue from CIRM related to the beta thalassemia program under the collaboration agreement with Biogen.

Operating Expenses

	Three months ended March 31, (in thousands, except percentage values)			
	2015	2014	Change	%
Operating expenses:				
Research and development	$ 14,980	$ 12,083	$ 2,897	24%
General and administrative	4,732	3,644	1,088	30%
Total expenses	$ 19,712	$ 15,727	$ 3,985	25%

Research and development

Research and development expenses consist primarily of salaries and personnel related expenses, including stock-based compensation, laboratory supplies, preclinical and clinical studies, manufacturing expenses, allocated facilities expenses, subcontracted research expenses and expenses for technology licenses. We expect to continue to devote substantial resources to research and development in the future and expect research and development expenses to increase in the next several years if we are successful in advancing our HIV/AIDS program in the clinic and if we are able to move our earlier stage ZFP Therapeutic product candidates into clinical trials. We also expect that expenses related to research performed under our collaboration and license agreements with Biogen and Shire will increase our research and development expenses during the terms of the agreements. Pursuant to the terms of the agreements with Biogen and Shire, future expenses for research activities under the collaboration will be reimbursed, including internal employee and external research costs related to the programs. The reimbursement for these services will be recognized as revenue as the expenses are incurred and collection is reasonably assured.

Research and development expenses were $15.0 million for the three months ended March 31, 2015, compared to $12.1 million in the corresponding period in 2014. The increase of $2.9 million in research and development expenses was primarily due to an increase of $0.9 million in salaries and benefits, $0.7 million in external expenses, lab supplies and other expenses related to our hemophilia, beta-thalassemia, SCD and HD programs, $0.6 million in stock-based compensation expense and $0.5 million in clinical trial and manufacturing expenses.

General and administrative

General and administrative expenses consist primarily of salaries and personnel related expenses, including stock-based compensation, other expenses for executive, finance and administrative personnel, professional fees, allocated facilities expenses, patent prosecution expenses and other general corporate expenses. As we pursue clinical and commercial development of our therapeutic programs, we expect the business aspects of the Company to become more complex. In the future we may be required to add personnel and incur additional expenses related to the maturity of our business.

General and administrative expenses were $4.7 million for the three months ended March 31, 2015 compared to $3.6 million for the corresponding period in 2014. The increase was primarily related to an increase of $0.4 million in stock-based compensation expense and $0.2 million in salaries and benefits.

Liquidity and Capital Resources

Liquidity

Since inception, we have incurred significant net losses and we have funded our operations primarily through the issuance of equity securities, payments from corporate collaborators and strategic partners and research grants.

As of March 31, 2015, we had cash, cash equivalents, marketable securities and interest receivable totaling $226.1 million compared to $226.6 million as of December 31, 2014.

Our most significant use of capital pertains to salaries and benefits for our employees and external development expenses, such as manufacturing and clinical trial activities, related to our ZFP Therapeutic programs. Our cash and investment balances are held in a variety of interest bearing instruments, which can include obligations of U.S. government agencies, U.S. treasury debt securities, corporate debt securities, commercial paper securities and money market funds. Cash in excess of immediate requirements is invested in accordance with our investment policy with a view toward capital preservation and liquidity.

Under our agreement with Shire, we received an upfront license fee of $13.0 million. Shire will reimburse us for agreed upon costs incurred in connection with research and development activities conducted by us. We are also eligible to receive milestone payments based on our achievement of specified research, regulatory, clinical development, commercialization and sales milestones,

which depends upon ours and Shire's ability to continue to progress our programs under collaboration. In 2014 we recognized $1.0 million milestone related to our hemophilia program. We will also be eligible to receive royalty payments that are a tiered double-digit percentage of net sales of products developed under the collaboration, if any.

Under the agreement with Biogen, we received an upfront license fee of $20.0 million. Biogen will reimburse us for agreed upon costs incurred in connection with research and development activities conducted by us. In addition, we are eligible to receive development milestone payments upon the achievement of specified regulatory, clinical development and commercialization milestones. We will also be eligible to receive incremental royalties for each licensed product that are a tiered double-digit percentage of annual net sales of such product, if any.

Cash Flow

Operating activities. Net cash used in operating activities for the three months ended March 31, 2015 was $2.4 million. Net cash provided by operating activities for the three months ended March 31, 2014 was $11.4 million. Net cash used in operating activities for the three months ended March 31, 2015 primarily reflected the increases in net loss for the period as well as a decrease in accounts receivable, accounts payable and accrued compensation, partially offset by the increases in stock-based compensation. Net cash used in operating activities for the three months ended March 31, 2014 primarily reflected the increases in deferred revenues related to our collaboration agreement with Biogen, accounts payable and stock-based compensation, partially offset by an increase in accounts receivable and decrease in accrued compensation.

Investing activities. Net cash provided in investing activities for the three months ended March 31, 2015 was $18.4 million, while cash provided by investing activities was $3.9 million for the three months ended March 31, 2014. Cash flows from investing activities for both periods primarily related to purchases and maturities of investments.

Financing activities. Net cash provided by financing activities for the three months ended March 31, 2015 and 2014 was $3.2 million and $101.4 million, respectively. Net cash provided by financing activities for the three month period ended March 31, 2015 was primarily related to the issuance of common stock upon exercise of stock options. Net cash provided by financing activities for the three month period ended March 31, 2014 was primarily attributable to $93.8 million in net proceeds from the public offering of the Company's common stock completed in March 2014 as well as proceeds from the issuance of common stock upon exercise of stock options.

Operating Capital and Capital Expenditure Requirements

We anticipate continuing to incur operating losses for at least the next several years. While our rate of cash usage may increase in the future, in particular to support our product development endeavors, we believe that the available cash resources as well as funds received from corporate collaborators, strategic partners and research grants will enable us to maintain our currently planned operations through 2016. Future capital requirements will be substantial, and if our capital resources are insufficient to meet future capital requirements, we will need to raise additional capital to fund our operations, including ZFP Therapeutic development activities, through equity or debt financing. We regularly consider fund raising opportunities and may decide, from time to time, to raise capital based on various factors, including market conditions and our plans of operation. Additional capital may not be available on terms acceptable to us, or at all. If adequate funds are not available, or if the terms of potential funding sources are unfavorable, our business and our ability to develop our technology and our ZFP Therapeutic products would be harmed. Furthermore, any sales of additional equity securities may result in dilution to our stockholders, and any debt financing may include covenants that restrict our business.

Our future capital requirements will depend on many factors and are not limited to the following:

- the initiation, progress, timing and completion of clinical trials for our product candidates;
- the outcome, timing and cost of regulatory approvals;
- the success of our collaboration with Shire, Biogen and other partners;
- delays that may be caused by changing regulatory requirements;
- the number of product candidates that we pursue;
- the costs involved in filing and prosecuting patent applications and enforcing and defending patent claims;
- the timing and terms of future in-licensing and out-licensing transactions;
- the cost of procuring clinical and commercial supplies of our product candidates;
- the extent to which we acquire or invest in businesses, products or technologies; and
- the costs of litigation.

ITEM 3. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK

Our primary exposure to market risk is interest income sensitivity relating to our cash, cash equivalents and investments, which is affected by changes in the general level of U.S. interest rates. We do not have any foreign currency or other derivative financial instruments.

Our market risks at March 31, 2015 have not changed materially from those discussed in Item 7A of our Form 10-K for the year ended December 31, 2014 on file with the SEC.

ITEM 4. CONTROLS AND PROCEDURES

Disclosure Controls and Procedures

We maintain disclosure controls and procedures that are designed to provide reasonable assurance that information required to be disclosed in our Exchange Act reports is recorded, processed, summarized and reported within the time periods specified in the Securities and Exchange Commission's rules and forms and that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate, to allow timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable, and not absolute, assurance of achieving the desired control objectives. In reaching a reasonable level of assurance, management necessarily was required to apply its judgment in evaluating the cost benefit relationship of possible controls and procedures.

As required by the Securities and Exchange Commission Rule 13a-15(b), we carried out an evaluation, under the supervision of and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of the effectiveness of the design and operation of our disclosure controls and procedures as of the end of the period covered by this report. Based on the foregoing, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective at the reasonable assurance level.

Change in Internal Control over Financial Reporting

There has been no change in our internal controls over financial reporting during our most recent fiscal quarter that has materially affected, or is reasonably likely to materially affect, our internal controls over financial reporting.

PART II. OTHER INFORMATION

ITEM 1. LEGAL PROCEEDINGS

We are not party to any material pending legal proceedings.

ITEM 1A. RISK FACTORS

An investment in our common stock involves significant risk. You should carefully consider the information described in the following risk factors, together with the other information appearing elsewhere in this report, before making an investment decision regarding our common stock. While the risk factors set forth below update and supplement the risk factors set forth in our Annual Report on Form 10-K for the year ended December 31, 2014 (2014 Annual Report), you should review our 2014 Annual Report, including the section under the caption "Item 1A. Risk Factors," together with the other information appearing elsewhere in this report, before making an investment decision regarding our common stock. If any of the risks described below or in our 2014 Annual Report actually occur, our business, financial conditions, results of operation and future growth prospects would likely be materially and adversely affected. In these circumstances, the market price of our common stock could decline, and you may lose all or a part of your investment in our common stock. Moreover, the risks described below and in our 2014 Annual Report are not the only ones that we face. Additional risks not presently known to us or that we currently deem immaterial may also affect our business, operating results, prospects or financial condition. You should carefully consider these risk factors, together with all of the other information included in this Form 10-Q as well as our other publicly available filings with the Securities and Exchange Commission.

Risks Relating to Development, Commercialization and Regulatory Approval of our Products and Technology

ZFP Therapeutics have undergone limited testing in humans and our ZFP Therapeutics may fail safety studies in clinical trials.

We are conducting an on-going Phase 2 clinical trial (SB-728-mR-1401) of our ZFP Therapeutics for the treatment of HIV/AIDS. Preliminary data from these studies demonstrates that treatment of aviremic HIV-infected subjects with SB-728-T has been well-tolerated. In addition, data from Phase 1 and several Phase 2 clinical trials of our ZFP Therapeutic, SB-509, for diabetic neuropathy and ALS demonstrated that the drug was well tolerated in these studies. However, if one of our ZFP Therapeutic fails one of its safety studies, it could reduce our ability to attract new investors and corporate partners.

All of these studies are designed primarily to evaluate the safety and tolerability of this ZFP Therapeutic approach. Our clinical studies are a highly visible test of our ZFP Therapeutics and our investors assess the value of our technology primarily based on the continued progress of ZFP Therapeutic products into and through clinical trials. If clinical trials of our ZFP Therapeutic products were halted due to safety concerns, this would negatively affect our operations and the value of our stock.

Our progress in early Phase 1 and Phase 2 trials may not be indicative of long-term efficacy in late stage clinical trials.

The results in early phases of clinical testing are based upon limited numbers of patients and a limited follow-up period. Typically, our Phase 1 clinical trials for indications of safety enroll less than 25 patients. Our Phase 2 and late-stage clinical trials generally enroll a larger number of patients. Accordingly, any positive data obtained in early Phase 1 and Phase 2 trials may not be indicative of long-term efficacy in late-stage clinical trials.

In September 2011, we announced preliminary data from our Phase 1 clinical program to develop SB-728-T for the treatment of HIV/AIDS. The data demonstrated a statistically significant relationship between SB-728-T and the reduction of HIV viral load. In January 2012, we initiated a Phase 2 clinical study (SB-728-902, Cohort 5) and a Phase 1/2 clinical study (SB-728-1101) for the treatment of HIV/AIDS. In December 2013, we presented data from all cohorts of these two clinical trials. Three of seven evaluable subjects in Cohort 5 showed a decrease of greater than one log in their viral load during a sixteen week treatment interruption (TI) with one subject achieving a transiently undetectable viral load during the TI period and one subject achieving control of their viral load during TI for a prolonged period (>70 weeks as of January 2015). In subjects in which viral load decreased, a measurable anti-HIV immune response was also observed. Additional data were presented from the Company's Phase 1 study (SB-728-902, Cohorts 1-3) that demonstrated a long-term decrease in the peripheral blood mononuclear cell (PBMC) HIV reservoir using a sensitive test for integrated HIV DNA in nine of nine subjects over a 36 month period (median decrease 0.9 logs). Additional subjects were enrolled into the SB-728-1101 study to define the optimum dose of Cytoxan required to safely enhance engraftment and an additional 12 subjects have been enrolled to further test this dose including nine subjects in an ongoing Phase 2 clinical trial (SB-728mR-T-1401) that is also testing repeat dosing of modified T-cells. However, there is no guarantee that these and other future studies of SB-728-T in later stage trials involving larger patient groups may produce positive or similar results as those obtained in earlier trials.

A number of companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late stage clinical trials even after achieving promising results in earlier stage clinical trials. If a larger population of patients does not experience positive results, or if these results are not reproducible, our products may not receive approval from the FDA. Failure to confirm favorable results from earlier trials by demonstrating the safety and effectiveness of our ZFP Therapeutic products in late stage clinical trials with larger patient populations could have a material adverse effect on our business that would cause our stock price to decline significantly.

Our potential therapeutic products are subject to a lengthy and uncertain regulatory process, and we may encounter unanticipated toxicity or adverse events or fail to demonstrate efficacy, causing us to delay, suspend or terminate the development of a ZFP Therapeutic. If these potential products are not approved, we will not be able to commercialize those products.

The FDA must approve any human therapeutic product before it can be marketed in the United States. The process for receiving regulatory approval is long and uncertain, and a potential product may not withstand the rigors of testing under the regulatory approval processes.

Before commencing clinical trials in humans, we must submit an IND application to the FDA. The FDA has 30 days to comment on the application, and if the agency has no comments, we or our commercial partner may begin clinical trials. While we have stated our intention to file additional IND applications in the future, this is only a statement of intent, and we may not be able to do so because the associated product candidates may not meet the necessary preclinical requirements. In addition, there can be no assurance that, once filed, an IND application will result in the actual initiation of clinical trials. Clinical trials are subject to oversight by institutional review boards and the FDA. In addition, our proposed clinical studies require review from the Recombinant DNA Advisory Committee (RAC), which is the advisory board to the National Institutes of Health (NIH), focusing on clinical trials involving gene transfer. We will typically submit a proposed clinical protocol and other product-related information to the RAC three to six months prior to the expected IND application filing date.

Clinical trials:

- must be conducted in conformance with the FDA's good clinical practices, within the guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and other applicable regulations;
- must meet requirements for Institutional Review Board (IRB) oversight;
- must follow Institutional Biosafety Committee (IBC) and NIH RAC guidelines where applicable;
- must meet requirements for informed consent;
- are subject to continuing FDA oversight;
- may require oversight by a Data Safety Monitoring Board (DSMB);
- may require large numbers of test subjects; and
- may be suspended by a commercial partner, the FDA, or us at any time if it is believed that the subjects participating in these trials are being exposed to unacceptable health risks or if the FDA finds deficiencies in the IND application or the conduct of these trials.

While we have stated our goal is to file IND applications for several ZFP Therapeutic programs in the future, we may encounter difficulties that may delay, suspend or scale back our efforts.

We have previously announced a strategy for our ZFP Therapeutic programs that enables the potential filing of two to four new IND applications per year in the foreseeable future. The preparation and submission of IND applications requires us to conduct rigorous and time-consuming preclinical testing, studies, and documentation relating to, among other things, the toxicity, safety, manufacturing, chemistry and clinical protocol of new ZFP Therapeutic products. We may experience unforeseen difficulties that could delay or otherwise prevent us from executing this strategy successfully. For example, we may encounter problems in the manufacturing of our ZFP Therapeutic products and fail to demonstrate consistency in the formulation of the drug. Our preclinical tests may produce negative or inconclusive results, which may lead us to decide, or regulators may require us, to conduct additional preclinical testing. If we cannot obtain positive results in preclinical testing, we may decide to abandon the projects altogether. In addition, our ability to complete and file certain IND applications depends on the support of our partners and the timely performance of their obligations under relevant collaboration agreements. If our partners are not able to perform such obligations or if they choose to slow down or delay the progress, we may not be able to prepare and file the intended IND applications on a timely basis or at all. Furthermore, the filing of several IND applications involves significant cost and labor, and we may not have sufficient resources and personnel to complete the filing of all intended IND applications, which may force us to scale back the number of IND applications or forego potential IND applications that we believe are promising. Any delay, suspension or reduction of our efforts to pursue our preclinical and IND strategy could have a material adverse effect on our business and cause our stock price to decline.

We may not be able to find acceptable patients or may experience delays in enrolling patients for our clinical trials.

We may experience difficulties or delays in recruiting and enrolling a sufficient number of patients to participate in our clinical trials due to a variety of reasons, including competition from other clinical trial programs for the same indication, failure of patients to meet our enrollment criteria and premature withdraws of patients prior to the completion of clinical trials. The FDA and institutional review boards may also require large numbers of patients, and the FDA may require that we repeat a clinical trial. Any delay resulting from our failure to enroll a sufficient number of patients on a timely basis may have a material adverse effect on our business.

As we cannot predict whether or when we will obtain regulatory approval to commercialize our product candidates, we cannot predict the timing of any future revenue from these product candidates.

We cannot commercialize any of our ZFP Therapeutics to generate revenue until the appropriate regulatory authorities have reviewed and approved the applications for the product candidates. We cannot ensure that the regulatory agencies will complete their review processes in a timely manner or that we will obtain regulatory approval for any product candidate that we or our collaborators develop. Satisfaction of regulatory requirements typically takes many years, is dependent upon the type, complexity and novelty of the product and requires the expenditure of substantial resources. Regulatory approval processes outside the United States include all of the risks associated with the FDA approval process. In addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action or changes in FDA policy during the period of product development, clinical trials and FDA regulatory review.

We have limited experience in conducting clinical trials.

Our most advanced clinical program is our Phase 2 trials to evaluate the safety and efficacy of a ZFP Therapeutic for HIV/AIDS. However, the FDA will require additional clinical testing which involves significantly greater resources, commitments and expertise and so it is likely that we would need to enter into a collaborative relationship with a pharmaceutical company that could assume responsibility for late-stage development and commercialization.

We have limited experience in conducting advanced clinical trials and may not possess the necessary resources and expertise to complete such trials. We have entered into collaborative agreements with Shire and Biogen to provide funding and assistance in the development of our ZFP Therapeutics through the clinical trial process. Under the agreement with Shire, we are responsible for all activities through submission of IND applications and European CTAs and Shire is responsible for clinical development and commercialization of products arising from the alliance. Under the agreement with Biogen, we are responsible for all research and development through the first human clinical trial for the treatment of beta-thalassemia and both parties are responsible for research and development through the submission of IND for ZFP Therapeutics to treat sickle cell disease (SCD). However, there is no guarantee that we will be able to enter into future collaborative relationships with third parties that can provide us with the funding and expertise for later stage trials.

Regulatory approval, if granted, will be limited to specific uses or geographic areas, which could limit our ability to generate revenues.

Regulatory approval will be limited to the indicated use for which we can market a product. Further, once regulatory approval for a product is obtained, the product and its manufacturer are subject to continual review. Discovery of previously unknown problems with a product or manufacturer may result in restrictions on the product, manufacturer, and manufacturing facility, including withdrawal of the product from the market. In Japan and Europe, regulatory agencies also set or approve prices.

Even if regulatory clearance of a product is granted, this clearance is limited to those specific states and conditions for which the product is useful, as demonstrated through clinical trials. We cannot ensure that any ZFP Therapeutic product developed by us, alone or with others, will prove to be safe and effective in clinical trials and will meet all of the applicable regulatory requirements needed to receive marketing clearance in a given country.

Outside the United States, our ability to market a product is contingent upon receiving a marketing authorization from appropriate regulatory authorities; therefore we cannot predict whether or when we would be permitted to commercialize our product. These foreign regulatory approval processes include all of the risks associated with FDA clearance described above.

Commercialization of our technologies will depend, in part, on strategic partnering with other companies. If we are not able to find partners in the future or if our partners do not diligently pursue product development efforts, we may not be able to develop our technologies or products, which could slow our growth and decrease the value of our stock.

We expect to rely, to some extent, on our strategic partners to provide funding in support of our research and to perform independent research and preclinical and clinical testing. Our technology is broad-based, and we do not currently possess the resources necessary to fully develop and commercialize potential products that may result from our technologies or the resources or capabilities to complete the lengthy marketing approval processes that may be required for the products. Therefore, we plan to rely on strategic partnerships to help us develop and commercialize ZFP Therapeutic products. If we are unable to find partners or if the partners we find, such as Shire and Biogen, are unable or unwilling to advance our programs, or if they do not diligently pursue product approval, this may slow our progress and adversely affect our ability to generate revenues. In addition, our partners may sublicense or abandon development programs or we may have disagreements or disputes with our partners, which would cause associated product development to slow or cease. In addition, the business or operations of our partners may change significantly through restructuring, acquisition or other strategic transactions or decisions that may negatively impact their ability to advance our programs. There can be no assurance that we will be able to establish further strategic collaborations for ZFP Therapeutic product development. We may require significant time to secure collaborations or partners because we need to effectively market the benefits of our technology to these future collaborators and partners, which may direct the attention and resources of our research and development personnel and management away from our primary business operations. Further, each collaboration or partnering arrangement will involve the negotiation of terms that may be unique to each collaborator or partner. These business development efforts may not result in a collaboration or partnership.

The loss of partnering agreements would not only delay or terminate the potential development or commercialization of products we may derive from our technologies, but it may also delay or terminate our ability to test ZFP Therapeutic candidates for specific genes. If any partner fails to conduct the collaborative activities successfully or in a timely manner, the preclinical or clinical development or commercialization of the affected product candidates or research programs could be delayed or terminated.

Under typical partnering agreements, we would expect to receive revenue for the research and development of a ZFP Therapeutic product based on achievement of specific milestones, as well as royalties based on a percentage of sales of the commercialized products. Achieving these milestones will depend, in part, on the efforts of our partner as well as our own. If we, or any partner, fail to meet specific milestones, then the partnership may be terminated, which could reduce our revenues. For more information on risks relating to our third party collaborative agreements, see “Risks Relating to our Collaborative Relationships.”

We may be unable to license gene transfer technologies that we may need to commercialize our ZFP technology.

In order to regulate or modify a gene in a cell, the ZFP must be efficiently delivered to the cell. We have licensed certain gene transfer technologies for our ZFP in research including AAV and mRNA technology. We are evaluating these systems and other technologies that may need to be used in the delivery of ZFP into cells for *in vitro* and *in vivo* applications, including ZFP Therapeutics. However, we may not be able to license the gene transfer technologies required to develop and commercialize our ZFP Therapeutics. We have not developed our own gene transfer technologies, and we rely on our ability to enter into license agreements to provide us with rights to the necessary gene transfer technology. Our approach has been to license appropriate technology as required. The inability to obtain a license to use gene transfer technologies with entities which own such technology on reasonable commercial terms, if at all, could delay or prevent the preclinical evaluation, drug development collaborations, clinical testing, and/or commercialization of our therapeutic product candidates.

Our gene regulation and genome editing technology is relatively new, and if we are unable to use this technology in all our intended applications, it would limit our revenue opportunities.

Our technology involves a relatively new approach to gene regulation and genome editing. Although we have generated ZFPs for thousands of gene sequences, we have not created ZFPs for all gene sequences and may not be able do so, which could limit the usefulness of our technology. In addition, while we have demonstrated the function of engineered ZFNs and ZFP TFs in mammalian cells, yeast, insects, plants and animals, we have not yet demonstrated clinical efficacy of this technology in a controlled clinical trial in humans, and the failure to do so could restrict our ability to develop commercially viable products. If we, and our collaborators or strategic partners, are unable to extend our results to new commercially important genes, experimental animal models, and human clinical studies, we may be unable to use our technology in all its intended applications.

The expected value and utility of our ZFNs and ZFP TFs is in part based on our belief that the targeted editing of genes or specific regulation of gene expression may enable us to develop a new therapeutic approach as well as to help scientists better understand the role of genes in disease, and to aid their efforts in drug discovery and development. We also believe that ZFP-mediated targeted genome editing and gene regulation will have utility in agricultural applications. There is only a limited understanding of the role of specific genes in all these fields. Life sciences companies have developed or commercialized only a few products in any of these fields based on results

from genomic research or the ability to regulate gene expression. We, our collaborators or our strategic partners, may not be able to use our technology to identify and validate drug targets or to develop commercial products in the intended markets.

Effective delivery of ZFNs and ZFP TFs into the appropriate target cells and tissues is critical to the success of the therapeutic applications of our ZFP technology. In order to have a meaningful therapeutic effect, the ZFP Therapeutic must be delivered to sufficient numbers of cells in the targeted tissue. The ZFN or ZFP TF must be present in that tissue for sufficient time to effect either modification of a therapeutically relevant gene or regulation of its expression. In our current clinical and preclinical programs, we administer our ZFP Therapeutics as a nucleic acid that encodes the ZFN or ZFP TF. We use different formulations to deliver the ZFP Therapeutic depending on the required duration of expression, the targeted tissue and the indication that we intend to treat. However, there can be no assurances that we will be able to effectively deliver our ZFNs and ZFP TFs to produce a beneficial therapeutic effect.

We are conducting proprietary research to discover ZFP Therapeutic product candidates. These programs increase our financial risk of product failure, may significantly increase our research expenditures, and may involve conflicts with future collaborators and strategic partners.

Our proprietary research programs consist of research that is funded solely by us or by grant funding and in which we retain exclusive rights to therapeutic products generated by such research. This is in contrast to certain of our research programs that may be funded by corporate partners in which we may share rights to any resulting products. Conducting proprietary research programs may not generate corresponding revenue and may create conflicts with our collaborators or strategic partners over rights to our intellectual property with respect to our proprietary research activities. Any conflict with our collaborators or strategic partners could reduce our ability to enter into future collaborations or partnering agreements and negatively impact our relationship with existing collaborators and partners that could reduce our revenue and delay or terminate our product development. As we continue to focus our strategy on proprietary research and therapeutic development, we expect to experience greater business risks, expend significantly greater funds and require substantial commitments of time from our management and staff.

Even if our technology proves to be effective, it still may not lead to commercially viable products.

Even if our collaborators or strategic partners are successful in using our ZFP technology in drug discovery, protein production, therapeutic development or plant agriculture, they may not be able to commercialize the resulting products or may decide to use other methods competitive with our technology. To date, no company has received marketing approval or has developed or commercialized any therapeutic or agricultural products based on our technology. Should our technology fail to provide safe, effective, useful or commercially viable approaches to the discovery and development of these products, this would significantly limit our business and future growth and would adversely affect our value.

Even if our product development efforts are successful and even if the requisite regulatory approvals are obtained, our ZFP Therapeutics may not gain market acceptance among physicians, patients, healthcare payers and the medical community.

A number of additional factors may limit the market acceptance of our ZFP Therapeutic products including the following:

- rate of adoption by healthcare practitioners;
- rate of a product's acceptance by the target population;
- timing of market entry relative to competitive products;
- availability of alternative therapies;
- price of our product relative to alternative therapies;
- availability of third-party reimbursement;
- extent of marketing efforts by us and third-party distributors or agents retained by us; and
- side effects or unfavorable publicity concerning our products or similar products.

Therefore, even after we have obtained the required regulatory approval for our ZFP Therapeutic products, we may not be able to commercialize these products successfully if we cannot achieve an adequate level of market acceptance.

We currently rely on third parties to conduct some or all aspects of manufacturing of our ZFP Therapeutic product candidates for preclinical and clinical development. If one of our third-party manufacturers fails to perform adequately or fulfill our needs, we may be required to incur significant costs and devote significant efforts, to find new suppliers or manufacturers.

We currently have limited experience in, and we do not own facilities for, clinical-scale manufacturing of our product candidates and we rely upon third-party contract manufacturing organizations to manufacture and supply drug product for our preclinical and clinical studies. The manufacture of pharmaceutical products in compliance with the FDA's current good manufacturing practices (cGMP), 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, including difficulties with production costs and yields, quality control, including stability of the product candidate and quality assurance testing, shortages of qualified personnel, as well as compliance with strictly enforced cGMP requirements, other federal and state regulatory requirements and foreign regulations. If our manufacturers were to encounter any of these difficulties or otherwise fail to comply with their obligations to us or under applicable regulations, our ability to provide study drugs in our clinical studies would be jeopardized. Any delay or interruption in the supply of clinical study materials could delay the completion of our clinical studies, increase the costs associated with maintaining our clinical study programs and, depending upon the period of delay, require us to commence new studies at significant additional expense or terminate the studies completely.

All manufacturers of our product candidates must comply with cGMP requirements enforced by the FDA through its facilities inspection program. These requirements include, among other things, quality control, quality assurance and the maintenance of records and documentation. Manufacturers of our product candidates may be unable to comply with these cGMP requirements and with other FDA, state and foreign regulatory requirements. The FDA or similar foreign regulatory agencies may also implement new standards at any time, or change their interpretation and enforcement of existing standards for manufacture, packaging or testing of products. We have little control over our manufacturers' compliance with these regulations and standards. A failure to comply with these requirements may result in fines and civil penalties, suspension of production, suspension or delay in product approval, product seizure or recall or withdrawal of product approval. If the safety of any product 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 we may be held liable for any injuries sustained as a result. Any of these factors could cause a delay of clinical studies, regulatory submissions, approvals or commercialization of our product candidates, entail higher costs or impair our reputation.

Our current agreements with our suppliers do not provide for the entire supply of the drug product necessary for all anticipated clinical studies or for full scale commercialization. If we and our suppliers cannot agree to the terms and conditions for them to provide the drug product necessary for our clinical and commercial supply needs, we may not be able to manufacture the product candidate until a qualified alternative supplier is identified, which could also delay the development of, and impair our ability to commercialize, our product candidates.

The number of third-party suppliers with the necessary manufacturing and regulatory expertise and facilities is limited, and it could be expensive and take a significant amount of time to arrange for alternative suppliers, which could have a material adverse effect on our business. New suppliers of any product candidate would be required to qualify under applicable regulatory requirements and would need to have sufficient rights under applicable intellectual property laws to the method of manufacturing the product candidate. Obtaining the necessary FDA approvals or other qualifications under applicable regulatory requirements and ensuring non-infringement of third-party intellectual property rights could result in a significant interruption of supply and could require the new manufacturer to bear significant additional costs which may be passed on to us.

We do not currently have the infrastructure or capability to manufacture, market and sell therapeutic products on a commercial scale.

In order for us to commercialize our therapeutic products directly, we would need to develop, or obtain through outsourcing arrangements, the capability to manufacture, market and sell our products on a commercial scale. Currently, we do not have the ability nor the financial resources to establish the infrastructure and organizations needed to execute these functions, including such infrastructure needed for the commercialization of any product from our HIV/AIDS or AD programs, which can be complex and costly. If we are unable to establish adequate manufacturing, sales, marketing and distribution capabilities, we will not be able to directly commercialize our therapeutics products, which would limit our future growth.

Risks Relating to our Industry

If our competitors develop, acquire, or market technologies or products that are more effective than ours, this would reduce or eliminate our commercial opportunity.

Any products that we or our collaborators or strategic partners develop by using our ZFP technology platform will enter into highly competitive markets. Even if we are able to generate ZFP Therapeutics that are safe and effective for their intended use, competing technologies may prove to be more effective or less expensive, which, to the extent these competing technologies achieve market acceptance, will limit our revenue opportunities. In some cases, competing technologies have proven to be effective and less expensive. Competing technologies may include other methods of regulating gene expression or modifying genes. ZFNs and ZFP TFs have broad application in the life sciences industry and compete with a broad array of new technologies and approaches being applied

to genetic research by many companies. Competing proprietary technologies with our product development focus include but are not limited to:

- For ZFP Therapeutics:
  - small molecule drugs;
  - monoclonal antibodies;
  - recombinant proteins;
  - gene therapy/cDNAs;
  - antisense;
  - siRNA and microRNA approaches, exon skipping;
  - CRISPR/Cas9 technology;
  - TALE proteins and MegaTALs; and
  - meganucleases.
- For our Non-Therapeutic Applications:
  - *For protein production:* gene amplification, meganucleases, TALE technology, insulator technology, mini-chromosomes and CRISPR/Cas9 technology;
  - *For target validation:* antisense, siRNA, TALE technology and CRISPR/Cas9 technology;
  - *For plant agriculture:* recombination approaches, mutagenesis approaches, meganucleases, TALE technology, CRISPR/Cas9 technology, mini-chromosomes; and
  - *For transgenic animals:* somatic nuclear transfer, embryonic stem cell, TALE, CRISPR/Cas9 technology and transposase technologies.

In addition to possessing competing technologies, our competitors include pharmaceutical and biotechnology companies with:

- substantially greater capital resources than ours;
- larger research and development staffs and facilities than ours; and
- greater experience in product development and in obtaining regulatory approvals and patent protection.

These organizations also compete with us to:

- attract qualified personnel;
- attract parties for acquisitions, joint ventures or other collaborations; and
- license the proprietary technologies of academic and research institutions that are competitive with our technology, which may preclude us from pursuing similar opportunities.

Accordingly, our competitors may succeed in obtaining patent protection or commercializing products before us. In addition, any products that we develop may compete with existing products or services that are well established in the marketplace.

Adverse public perception in the field of gene therapy may negatively impact regulatory approval of, or demand for, our potential products.

Our potential therapeutic products are delivered to patients as gene-based drugs, or gene therapy. The clinical and commercial success of our potential products will depend in part on public acceptance of the use of gene therapy for the prevention or treatment of human diseases. Public attitudes may be influenced by claims that gene therapy is unsafe, and, consequently, our products may not gain the acceptance of the public or the medical community. Negative public reaction to gene therapy in general could result in greater government regulation and stricter labeling requirements of gene therapy products, including any of our products, and could cause a decrease in the demand for any products we may develop.

Laws or public sentiment may limit the production of genetically modified agricultural products, and these laws could reduce our partner's ability to sell such products.

Genetically modified products are currently subject to public debate and heightened regulatory scrutiny, either of which could prevent or delay production of agricultural products. We have a research license and commercial option agreement with DAS through which we provide DAS with access to our proprietary ZFP technology and the exclusive right to use our ZFP technology to modify the genomes or alter the nucleic acid or protein expression of plant cells, plants or plant cell cultures. The field-testing, production and marketing of genetically modified plants and plant products are subject to federal, state, local and foreign governmental regulation. Regulatory agencies administering existing or future regulations or legislation may not allow production and marketing of our genetically modified products in a timely manner or under technically or commercially feasible conditions. In addition, regulatory action or private litigation could result in expenses, delays or other impediments to our product development programs or the commercialization of resulting products.

The FDA currently applies the same regulatory standards to foods developed through genetic engineering as those applied to foods developed through traditional plant breeding. Genetically engineered food products, however, will be subject to pre-market review if these products raise safety questions or are deemed to be food additives. Governmental authorities could also, for social or other purposes, limit the use of genetically modified products created with our gene regulation technology.

Even if the regulatory approval for genetically modified products developed under our agreement with DAS was obtained, our success will also depend on public acceptance of the use of genetically modified products including drugs, plants, and plant products. Claims that genetically modified products are unsafe for consumption or pose a danger to the environment may influence public attitudes. Our genetically modified products may not gain public acceptance. The subject of genetically modified organisms has received negative publicity in the United States and particularly in Europe, and such publicity has aroused public debate. The adverse publicity in Europe could lead to greater regulation and trade restrictions on imports of genetically altered products. Similar adverse public reaction or sentiment in the United States to genetic research and its resulting products could result in greater domestic regulation and could decrease the demand for our technology and products.

Risks Relating to our Finances

We have incurred significant operating losses since inception and anticipate that we will incur continued losses for the foreseeable future.

We have generated operating losses since we began operations in 1995. Our net losses for the years ended December 31, 2014, 2013 and 2012 were $26.4 million, $26.6 million and $22.3 million, respectively. The extent of our future losses and the timing of profitability are uncertain, and we expect to incur losses for the foreseeable future. We have been engaged in developing our ZFP technology since inception, which has and will continue to require significant research and development expenditures. To date, we have generated our funding from issuance of equity securities, revenues derived from collaboration agreements, other strategic partnerships in non-therapeutic applications of our technology, federal government research grants and grants awarded by research foundations. As of March 31, 2015, we had an accumulated deficit of $333.9 million. Since our IPO in 2000, we have generated an aggregate of approximately $331.4 million in gross proceeds from the sale of our equity securities. We expect to continue to incur additional operating losses for the next several years as we continue to advance our ZFP Therapeutic product candidates. If the time required to generate significant product revenues and achieve profitability is longer than we currently anticipate or if we are unable to generate liquidity through equity financing or other sources of funding, we may be forced to curtail or suspend our operations.

We may be unable to raise additional capital, which would harm our ability to develop our technology and products.

We have incurred significant operating losses and negative operating cash flows since inception and have not achieved profitability. We expect capital outlays and operating expenditures to increase over the next several years as we expand our infrastructure and research and ZFP Therapeutic product development activities. While we believe our financial resources will be adequate to sustain our current operations at least through 2016, we may need to seek additional sources of capital through equity or debt financing. In addition, as we focus our efforts on proprietary human therapeutics, we will need to seek FDA approval of potential products, a process that could cost in excess of hundreds of millions of dollars per product. Furthermore, we may experience difficulties in accessing the capital market due to external factors beyond our control such as volatility in the equity markets for emerging biotechnology companies and general economic and market conditions both in the United States and abroad. We cannot be certain that we will be able to obtain financing on terms acceptable to us, or at all. Our failure to obtain adequate and timely funding will materially adversely affect our business and our ability to develop our technology and ZFP Therapeutic products. Furthermore, any sales of additional equity securities may result in dilutions to our stockholders and any debt financing may include business and financial covenants that restricts our operations.

We are at the development phase of operations and may not succeed or become profitable.

We began operations in 1995 and are in the early phases of ZFP Therapeutic product development, and we have incurred significant losses since inception. To date, our revenues have been generated from collaboration agreements, other collaborations in non-therapeutic applications of our technology, federal government research grants and grants awarded by research foundations. Our focus on higher-value therapeutic product development and related collaboration requires us to incur substantial expenses associated with product development. In addition, the preclinical or clinical failure of any single product may have a significant effect on the actual or perceived value of our stock. Our business is subject to all of the risks inherent in the development of a new technology, which includes the need to:

- attract and retain qualified scientific and technical staff and management, particularly scientific staff with expertise to develop our early-stage technology into therapeutic products;
- obtain sufficient capital to support the expense of developing our technology platform and developing, testing and commercializing products;
- develop a market for our products; and
- successfully transition from a company with a research focus to a company capable of supporting commercial activities.

Risks Relating to our Relationships with Collaborators and Strategic Partners

If conflicts arise between us and our collaborators or strategic partners, these parties may act in their self-interest, which may limit our ability to implement our strategies.

If conflicts arise between our corporate or academic collaborators or strategic partners and us, the other party may act in its self-interest, which may limit our ability to implement our strategies. Some of our academic collaborators and strategic partners are conducting multiple product development efforts within each area that is the subject of the collaboration with us. Our collaborators or strategic partners, however, may develop, either alone or with others, products in related fields that are competitive with the products or potential products that are the subject of these collaborations. Competing products, either developed by the collaborators or strategic partners or to which the collaborators or strategic partners have rights, may result in the withdrawal of partner support for our product candidates.

Some of our collaborators or strategic partners could also become our competitors in the future. Our collaborators or strategic partners could develop competing products, preclude us from entering into collaborations with their competitors, fail to obtain timely regulatory approvals, terminate their agreements with us prematurely, or fail to devote sufficient resources to the development and commercialization of products. Any of these developments could harm our product development efforts.

Our collaborators and strategic partners may control aspects of our clinical trials, which could result in delays and other obstacles in the commercialization of our proposed products.

For some programs, we depend on third party collaborators and strategic partners to design and conduct our clinical trials. As a result, we may not be able to conduct these programs in the manner or on the time schedule we currently contemplate, which may negatively impact our business operations. In addition, if any of these collaborators or strategic partners withdraws support for our programs or proposed products or otherwise impair their development; our business could be negatively affected.

In January 2012, we entered into a collaborative agreement with Shire, pursuant to which we are engaging in a joint program with Shire to research, develop and commercialize human therapeutics and diagnostics for hemophilia, Huntington's disease and other monogenic diseases based on our ZFP technology. Under this agreement, we are responsible for all research activities through the submission of an IND or CTA, while Shire is responsible for clinical development and commercialization of products generated from the research program from and after the acceptance of an IND or CTA for the product.

In addition, in January 2014 we entered into a collaborative agreement with Biogen for the clinical development and commercialization of therapeutics based on our ZFP technology for hemoglobinopathies, including beta-thalassemia and SCD. Under the agreement, we are responsible for all discovery, research and development activities through the first human clinical trial for the first ZFP Therapeutic developed for the treatment of beta-thalassemia. In the SCD program, both parties are responsible for research and development activities through the submission of an IND.

Under these agreements with Biogen and Shire, they will have control and broad discretion over all or certain aspects of the clinical development and commercialization of any product developed under the agreements, and we will have little, if any, influence on how these programs will be conducted. Our lack of control over the clinical development in our agreement with Biogen and Shire could cause delays or other difficulties in the development and commercialization of our product candidates, which may prevent us from completing the intended IND filings in a timely fashion and receiving any milestone, royalty payments and other benefits under

the agreement. In addition, under their respective agreement(s), Biogen and Shire have certain rights to terminate the agreements by providing us with advance notices, therefore, the actual milestone payments that we may receive under these agreements may be lower than the full amounts stated above.

Our collaborators or strategic partners may decide to adopt alternative technologies or may be unable to develop commercially viable products with our technology, which would negatively impact our revenues and our strategy to develop these products.

Our collaborators or strategic partners may adopt alternative technologies, which could decrease the marketability of ZFP technology. Additionally, because many of our collaborators or strategic partners are likely to be working on more than one development project, they could choose to shift their resources to projects other than those they are working on with us. If they do so, this would delay our ability to test our technology and would delay or terminate the development of potential products based on our ZFP technology. Further, our collaborators and strategic partners may elect not to develop products arising out of our collaborative and strategic partnering arrangements or to devote sufficient resources to the development, manufacturing, marketing or sale of these products. If any of these events occur, we may not be able to develop our technologies or commercialize our products.

If we do not successfully commercialize ZFP-based research reagents, ZFP-modified cell lines for commercial protein production, or ZFP-engineered transgenic animals under our license agreement with Sigma-Aldrich Corporation or ZFP-based agricultural products with Dow AgroSciences, or if Sigma-Aldrich Corporation or Dow AgroSciences terminates our agreements, our ability to generate revenue under these license agreements may be limited.

In July 2007, we entered into a license agreement with Sigma to collaborate in the application and development of ZFP-based products for use in the laboratory research reagents markets. The agreement provides Sigma with access to our ZFP technology and the exclusive right to use our ZFP technology to develop and commercialize products for use as research reagents and to offer services in related research fields. Under the agreement, Sigma has exclusive rights to develop and distribute ZFP-modified cell lines for commercial production of protein pharmaceuticals and, certain ZFP-engineered transgenic animals for commercial applications. In addition, under our license agreement with DAS relating to plant agriculture, DAS has the exclusive right to develop agricultural products using our ZFP technology in plant cells, plants or plant cell cultures. Both Sigma and DAS have the right to sublicense our technology in their respective areas. In addition to upfront payments, we may also receive additional license fees, shared sublicensing revenues, royalty payments and milestone payments depending on the success of the development and commercialization of the licensed products and services covered under both agreements. The commercial milestones and royalties are typically based upon net sales of licensed products.

We cannot be certain that we or our collaboration partners will succeed in the development of commercially viable products in these fields of use, and there is no guarantee that we or our collaboration partners will achieve the milestones set forth in the respective license agreements. To the extent we or our collaboration partners do not succeed in developing and commercializing products or if we or our collaboration partners fail to achieve such milestones, our revenues and benefits under the license agreements will be limited. In addition, the respective license agreements may be terminated by Sigma and DAS at any time by providing us with a 90-day notice. In the event Sigma or DAS decides to terminate the license agreements, our ability to generate revenue under such license agreements will cease.

Our collaborations with outside scientists may be subject to change, which could limit our access to their expertise.

We work with scientific advisors and collaborators at academic research institutions. These scientists are not our employees and may have other commitments that would limit their availability to us. Although our scientific advisors generally agree not to do competing work, if a conflict of interest between their work for us and their work for another entity arises, we may lose their services. Although our scientific advisors and academic collaborators sign agreements not to disclose our confidential information, it is possible that some of our valuable proprietary knowledge may become publicly known through them, which may cause competitive harm to our business.

Risks Relating to our Intellectual Property and Business Operation

Because it is difficult and costly to protect our proprietary rights, and third parties have filed patent applications that are similar to ours, we cannot ensure the proprietary protection of our technologies and products.

Our commercial success will depend in part on obtaining patent protection of our technology and successfully defending any of our patents that may be challenged. The patent positions of pharmaceutical and biotechnology companies can be highly uncertain and can involve complex legal and factual questions. No consistent policy regarding the breadth of claims allowed in biotechnology patents has emerged to date. Accordingly, we cannot predict the breadth of claims allowed in patents we own or license.

We are a party to various license agreements that give us rights under specified patents and patent applications. Our current licenses, as our future licenses frequently will, contain performance obligations. If we fail to meet those obligations, the licenses could be terminated. If we are unable to continue to license these technologies on commercially reasonable terms, or at all, we may be forced to delay or terminate our product development and research activities.

With respect to our present and any future sublicenses, since our rights derive from those granted to our sublicensor, we are subject to the risk that our sublicensor may fail to perform its obligations under the master license or fail to inform us of useful improvements in, or additions to, the underlying intellectual property owned by the original licensor.

We are unable to exercise the same degree of control over intellectual property that we license from third parties as we exercise over our internally developed intellectual property. We do not control the prosecution of certain of the patent applications that we license from third parties; therefore, the patent applications may not be prosecuted as we desire or in a timely manner.

The degree of future protection for our proprietary rights is uncertain, and we cannot ensure that:

- we or our licensors were the first to make the inventions covered by each of our pending patent applications;
- we or our licensors were the first to file patent applications for these inventions;
- the patents of others will not have an adverse effect on our ability to do business;
- others will not independently develop similar or alternative technologies or reverse engineer any of our products, processes or technologies;
- any of our pending patent applications will result in issued patents;
- any patents issued or licensed to us or our collaborators or strategic partners will provide a basis for commercially viable products or will provide us with any competitive advantages;
- any patents issued or licensed to us will not be challenged and invalidated by third parties; or
- we will develop additional products, processes or technologies that are patentable.

Others have filed and in the future are likely to file patent applications that are similar to ours. We are aware that there are academic groups and other companies that are attempting to develop technology that is based on the use of zinc finger, TALE, CRISPR/Cas9 and other DNA-binding proteins, and that these groups and companies have filed patent applications. Several patents have been issued, although we have no current plans to use the associated inventions. If these or other patents issue, it is possible that the holder of any patent or patents granted on these applications may bring an infringement action against our collaborators, strategic partners, or us claiming damages and seeking to enjoin commercial activities relating to the affected products and processes. The costs of litigating the claim could be substantial. Moreover, we cannot predict whether we, our collaborators, or strategic partners would prevail in any actions. In addition, if the relevant patent claims were upheld as valid and enforceable and our products or processes were found to infringe the patent or patents, we could be prevented from making, using, or selling the relevant product or process unless we could obtain a license or were able to design around the patent claims. We can give no assurance that such a license would be available on commercially reasonable terms, or at all, or that we would be able to successfully design around the relevant patent claims. There may be significant litigation in the genomics industry regarding patent and other intellectual property rights, which could subject us to litigation. If we become involved in litigation, it could consume a substantial portion of our managerial and financial resources.

We rely on trade secrets to protect technology where we believe patent protection is not appropriate or obtainable. Trade secrets, however, are difficult to protect. While we require employees, academic collaborators and consultants to enter into confidentiality agreements, we may not be able to adequately protect our trade secrets or other proprietary information or enforce these confidentiality agreements.

Our collaborators, strategic partners, and scientific advisors have rights to publish data and information in which we may have rights. If we cannot maintain the confidentiality of our technology and other confidential information in connection with our collaborations and strategic partnerships, then we may not be able to receive patent protection or protect our proprietary information.

If we use biological and hazardous materials in a manner that causes injury or violates laws, we may be liable for damages.

Our research and development activities involve the controlled use of potentially harmful biological materials as well as hazardous materials, chemicals, and various radioactive compounds typically employed in molecular and cellular biology. We routinely use cells in culture and gene delivery vectors, and we employ small amounts of radioisotopes in trace experiments. Although we maintain up-to-date licensing and training programs, we cannot completely eliminate the risk of accidental contamination or injury

from the use, storage, handling, or disposal of these materials. In the event of contamination or injury, we could be held liable for damages that result, and any liability could exceed our resources. We currently carry insurance covering certain claims arising from our use of these materials. However, if we are unable to maintain our insurance coverage at a reasonable cost and with adequate coverage, our insurance may not cover any liability that may arise. We are subject to federal, state, and local laws and regulations governing the use, storage, handling, and disposal of these materials and specified waste products. To date, we have not experienced significant costs in complying with regulations regarding the use of these materials.

Failure to attract, retain, and motivate skilled personnel and cultivate key academic collaborations will delay our product development programs and our research and development efforts.

Our success depends on our continued ability to attract, retain, and motivate highly qualified management and scientific personnel and our ability to develop and maintain important relationships with leading research and academic institutions and scientists. Competition for skilled and qualified personnel and academic and other research collaborations is intense. We have experienced a rate of employee turnover that we believe is typical of emerging biotechnology companies. If we lose the services of personnel with the necessary skills, including the members of our senior management team, it could significantly impede the achievement of our research and development objectives. If we fail to negotiate additional acceptable collaborations with academic and other research institutions and scientists, or if our existing collaborations are unsuccessful, our ZFP Therapeutic development programs may be delayed or may not succeed.

Risks Relating to our Common Stock and Corporate Organization

Our stock price has been volatile and may continue to be volatile, which could result in substantial losses for investors.

During the three months ended March 31, 2015, the closing price of our common stock, as reported by the NASDAQ Global Select Market, ranged from a low of $12.64 to high of $18.54. During the fiscal year ended December 31, 2014, our common stock price fluctuated, ranging from a low of $9.85 to a high of $23.86. Volatility in our common stock could cause stockholders to incur substantial losses. An active public market for our common stock may not be sustained, and the market price of our common stock may continue to be highly volatile. The market price of our common stock has fluctuated significantly in response to various factors, some of which are beyond our control, including but not limited to the following:

- announcements by us or collaborators providing updates on the progress or development status of ZFP Therapeutics;
- data from clinical trials;
- initiation or termination of clinical trials;
- changes in market valuations of similar companies;
- overall market and economic conditions, including the equity markets for emerging biotechnology companies;
- deviations in our results of operations from the guidance given by us;
- announcements by us or our competitors of new or enhanced products, technologies or services or significant contracts, acquisitions, strategic relationships, joint ventures or capital commitments;
- announcement of changes in business and operations by our collaborators and partners;
- regulatory developments;
- additions or departures of key personnel;
- future sales of our common stock or other securities by us, management or directors, liquidation of institutional funds that comprised large holdings of our stock;
- decreases in our cash balances; and
- changes, by one or more of Sangamo’s security analysts, in recommendations, ratings or coverage of our stock.

Our stock price is also influenced by public perception of gene therapy and government regulation of potential products.

Reports of serious adverse events in a retroviral gene transfer trial for infants with X-linked severe combined immunodeficiency (X-linked SCID) in France and subsequent FDA actions putting related trials on hold in the United States had a significant negative impact on the public perception and stock price of certain companies involved in gene therapy. Stock prices of these companies declined whether or not the specific company was involved with retroviral gene transfer for the treatment of infants with X-linked SCID, or whether the specific company’s clinical trials were placed on hold in connection with these events. Other potential adverse events in the field of gene therapy may occur in the future that could result in greater governmental regulation of our potential

products and potential regulatory delays relating to the testing or approval of our potential products. These external events may have a negative impact on public perception of our business, which could cause our stock price to decline.

Anti-takeover provisions in our certificate of incorporation and Delaware law could make an acquisition of the Company more difficult and could prevent attempts by our stockholders to remove or replace current management.

Anti-takeover provisions of Delaware law and in our certificate of incorporation and our bylaws may discourage, delay or prevent a change in control of our company, even if a change in control would be beneficial to our stockholders. In addition, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. In particular, under our certificate of incorporation our board of directors may issue up to 5,000,000 shares of preferred stock with rights and privileges that might be senior to our common stock, without the consent of the holders of the common stock. Moreover, without any further vote or action on the part of the stockholders, the board of directors would have the authority to determine the price, rights, preferences, privileges, and restrictions of the preferred stock. This preferred stock, if it is ever issued, may have preference over, and harm the rights of, the holders of common stock. Although the issuance of this preferred stock would provide us with flexibility in connection with possible acquisitions and other corporate purposes, this issuance may make it more difficult for a third party to acquire a majority of our outstanding voting stock.

Similarly, our authorized but unissued common stock is available for future issuance without stockholder approval.

In addition, our bylaws:

- state that stockholders may not act by written consent but only at a stockholders' meeting;
- establish advance notice requirements for nominations for election to the board of directors or proposing matters that can be acted upon at stockholders' meetings; and
- prohibit stockholders from calling a special meeting of stockholders.

We are also subject to Section 203 of the Delaware General Corporation Law, which provides, subject to certain exceptions, that if a person acquires 15% of our voting stock, the person is an "interested stockholder" and may not engage in "business combinations" with us for a period of three years from the time the person acquired 15% or more or our voting stock. The application of Section 203 may, in some circumstances, deter or prevent a change in control of our company even when such change may be beneficial to our stockholders.

ITEM 6. EXHIBITS

(a) Exhibits:

10.1†	Research, Development and Commercialization Agreement dated October 24, 2006 between Sangamo and Juvenile Diabetes Research Foundation International.
10.2†	First Amendment to the Research, Development and Commercialization Agreement between Sangamo and Juvenile Diabetes Research Foundation International, dated January 8, 2010.
31.1	Rule 13a — 14(a) Certification by President and Chief Executive Officer
31.2	Rule 13a — 14(a) Certification by Principal Financial and Accounting Officer
32.1	Certification Pursuant to 18 U.S.C. Section 1350
101.INS	XBRL Instance Document
101.SCH	XBRL Taxonomy Extension Schema Document
101.CAL	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	XBRL Taxonomy Extension Label Linkbase Document
101.PRE	XBRL Taxonomy Extension Presentation Linkbase Document

† *The Company is filing a full and unredacted version of the agreement following the expiration of the confidential treatment order previously granted by the Securities and Exchange Commission.*

SIGNATURES

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

Dated: April 28, 2015

SANGAMO BIOSCIENCES, INC.

/s/ H. WARD WOLFF

H. Ward Wolff
Executive Vice President and Chief Financial Officer
(Principal Financial and Accounting Officer)

Exhibit 10.1

EXECUTION COPY

RESEARCH, DEVELOPMENT AND COMMERCIALIZATION AGREEMENT

by and between

Sangamo BioSciences, Inc.

and

Juvenile Diabetes Research Foundation International

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EXECUTION COPY

RESEARCH, DEVELOPMENT AND COMMERCIALIZATION AGREEMENT

This Agreement (this "Agreement") is made on this 24th day of October, 2006, by and between Sangamo BioSciences, Inc., a Delaware corporation, with its principal office at 501 Canal Boulevard, Suite A100, Richmond, CA 94804 ("Sangamo") and Juvenile Diabetes Research Foundation International, a Pennsylvania nonprofit corporation with its principal offices at 120 Wall Street, New York, NY 10005 ("JDRF"). This Agreement shall become effective on the Effective Date (as defined below). Sangamo and JDRF are each a "Party," and, collectively, the "Parties."

WHEREAS, JDRF's principal charitable mission is the discovery and development of a cure for diabetes and its complications, to which JDRF brings significant scientific and human resources and financial support;

WHEREAS, Sangamo desires, among other things, to collect additional clinical endpoints during the Phase II Repeat Dosing Clinical Trial of SB-509 for the purpose of understanding the mechanistic basis of efficacy and reversal of neuropathy (as more fully described in the Research Plan); and

WHEREAS, JDRF wishes to support the Research Program.

NOW, THEREFORE, in consideration of the mutual covenants set forth in this Agreement, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Parties agree as follows:

ARTICLE I DEFINITIONS

For purposes of this Agreement, the terms defined in this Article 1 shall have the following meanings whether used in their singular or plural forms. Use of the singular shall include the plural and vice versa, unless the context requires otherwise:

1.1 "Affiliate" shall mean, with respect to any Person, any other Person who directly or indirectly, by itself or through one or more intermediaries, controls, or is controlled by, or is under direct or indirect common control with, such Person. The term "control" means the possession, direct or indirect, of the power to direct or cause the direction of the management and policies of a Person, whether through the ownership of voting securities, by contract or otherwise. Control will be presumed if one Person owns, either of record or beneficially, more than fifty percent (50%) of the voting stock of any other Person.

1.2 "Agreement" means this agreement, together with all appendices, exhibits and schedules hereto, and as the same may be amended or supplemented from time to time hereafter by a written agreement duly executed by authorized representatives of each Party hereto.

1.3 "Applicable Law" shall have the meaning set forth in Section 10.1(b).

1.4 "Application" shall mean Sangamo's submitted Industry Discovery & Development Partnerships Application, dated May 12, 2006 and approved by JDRF on June 29, 2006.

1.5 "Award" shall mean an amount up to, but not to exceed, Three Million Dollars ($3,000,000), which is to be paid by JDRF to Sangamo for the Research Program in accordance with the terms, and subject to the conditions, set forth in this Agreement.

1.6 "Award Received" shall mean the amount of the Award actually received by Sangamo from JDRF pursuant to this Agreement, not including any amounts refunded to JDRF pursuant to Section 3.2.3(b).

1.7 "Commercially Reasonable Efforts" shall mean a level of effort and application of expertise and resources that are consistent with a continuing intention to research, develop and commercialize the Product, including without limitation the reasonable time during which Sangamo is engaged in active efforts to identify a potential Third Party licensee or collaborator and negotiate a license or collaboration arrangement with such Third Party to research, develop and/or commercialize the Product, it being acknowledged by the Parties that there may be delays for regulatory or other reasons that are not within Sangamo's or its licensee's, sublicensee's or transferee's control and such delays shall not constitute a cessation of Commercially Reasonable Efforts.

1.8 "Confidential Information" shall have the meaning set forth in Section 5.1.1.

1.9 "Controlled" (except in the context of Section 1.1) shall mean the legal authority or right of a Party to grant a license or sublicense of intellectual property rights to the other Party hereto, or to otherwise disclose proprietary or trade secret information to such other Party, without breaching the terms of any agreement with a Third Party.

1.10 "Default" shall have the meaning set forth in Section 9.2.

1.11 "Diabetes" shall mean any one and/or all of the human diseases commonly known as diabetes and the complications of such diseases.

1.12 "Dispute" shall have the meaning set forth in Section 11.2(a).

1.13 "Dollars" shall have the meaning set forth in Section 3.1.4.

1.14 "Effective Date" shall mean the date the last Party signs this Agreement.

1.15 "FDA" shall mean the United States Food and Drug Administration, or any successor agency having regulatory jurisdiction over the manufacture, distribution and sale of drugs in the United States, and its territories and possessions.

1.16 "Field" shall mean the diagnosis, treatment and/or prevention of Diabetes in humans.

1.17 "First Commercial Sale" shall mean the first sale of the Product by Sangamo or an Affiliate, licensee, sublicensee, transferee or successor of Sangamo to an independent Third Party in a Major Market country following Regulatory Approval of the Product in that country.

1.18 "Five Percent Payment" shall have the meaning set forth in Section 4.2(b).

1.19 "Funding Date" shall mean each date set forth on **Exhibit B**.

1.20 "GAAP" shall mean United States generally accepted accounting principles, consistently applied.

1.21 "Indemnitee" shall mean either Sangamo Indemnitee or JDRF Indemnitee, as applicable.

1.22 "Interruption" shall occur if, at any time before the First Commercial Sale of the Product, Sangamo, its Affiliates, licensees, sublicensees, transferees and/or successors, all cease to conduct, or have ceased Commercially Reasonable Efforts with respect to, the research, development and/or commercialization of all Products for a period of one hundred eighty (180) consecutive days, except that no Interruption shall be deemed to have occurred, if Sangamo, its Affiliates, licensees, sublicensees, transferees, and/or successors suspend, postpone or discontinue the development or commercialization of a Product on account of (a) a serious adverse event; (b) a clinical hold; or (c) communications with a regulatory authority.

1.23 "Interruption License" shall have the meaning set forth in Section 9.5(e).

1.24 "Interruption Notice" shall have the meaning set forth in Section 9.5(a).

1.25 "Interruption Response" shall have the meaning set forth in Section 9.5(a).

1.26 "JDRF" shall have the meaning set forth in the preamble of this Agreement.

1.27 "JDRF Designees" shall have the meaning set forth in Section 2.5.1.

1.28 "JDRF Indemnitee" shall have the meaning set forth in Section 7.1.

1.29 "JDRF Interruption License Technology" shall mean all intellectual property, data, technical information, know-how, inventions (whether or not patented), trade secrets, processes and methods that are (a) discovered or developed by or on behalf of JDRF or its Affiliates, in the performance of the Research Program or exploitation of the Interruption License under this Agreement, (b) Controlled by JDRF, and (c) necessary or useful for the research, development and commercialization of the Product.

1.30 "JDRF Patents" shall mean any Patents Controlled by JDRF or its Affiliates that claim an invention that relates to the Research Program but is not a Joint Invention.

1.31 "JDRF Studies" shall mean the mechanistic add-on studies for the collection of Surrogate Endpoint Data that are described in the Application.

1.32 "Joint Invention" shall have the meaning set forth in Section 8.1.

1.33 "Joint Research Advisory Committee" or "JRAC" shall have the meaning set forth in Section 2.5.1.

1.34 "Major Markets" shall mean the United States, United Kingdom, Germany, France, Italy and Spain.

1.35 "Matched Funds" shall have the meaning set forth in Section 3.1.3.

1.36 "Milestones" shall mean the performance milestones for the Research Program set forth in **Exhibit B.**

1.37 "Net Sales" means, for any period, the gross price received for the Product sold or otherwise disposed of (other than for use as clinical supplies or free samples) for consideration by Sangamo or its Affiliates to Third Parties other than sublicensees, reduced by the following amounts (calculated in accordance with GAAP consistently applied by Sangamo and its Affiliates across its product lines), if not previously deducted from the amount invoiced: (a) amounts actually allowed as trade, volume or quantity discounts, including early pay cash discounts; (b) amounts repaid or credited by reason of defects, recalls, accrued or actual returns, rebates and allowances of goods or because of retroactive price reductions specifically identifiable to the Product; (c) rebates and administrative fees paid to medical health care organizations in line with approved contract terms; (d) rebates resulting from government (or agency thereof) mandated rebate programs or chargeback programs; (e) rebates paid to wholesalers for inventory management programs or distribution management agreements, in accordance with Sangamo's practice reasonably consistently applied; (f) discounts pursuant to indigent patient programs and patient discount programs to include coupons and vouchers to the extent included in Net Sales; (g)

retroactive and temporary price reductions that are actually allowed or granted; (h) sales commissions paid to Third Party distributors or selling agents (which shall not include sales organizations, whether contract or internal to Sangamo); (i) sales or excise taxes, custom duties, and other governmental charges (including payments made to United Kingdom government departments under the UK Pharmaceutical Pricing Regulatory Scheme or similar programs, and government taxes, charges or penalties, such as French Social Security rebates, which payments need not be calculated in accordance with GAAP) imposed directly on and actually paid by Sangamo or its Affiliates; and (j) transportation costs, including insurance and shipping, freight, and handling charges, to the extent billed separately to customers.

1.38 "Owner" shall have the meaning set forth in Section 5.1.2.

1.39 "Party(ies)" shall have the meaning set forth in the preamble of this Agreement.

1.40 "Patents" means all existing patents and patent applications and all patent applications hereafter filed, including any continuation, continuation-in-part, division, provisional or any substitute applications, any patent issued with respect to any such patent applications, any reissue, reexamination, renewal or extension (including any supplementary protection certificate) of any such patent, any confirmation patent or registration patent or patent of addition based on any such patent, and all foreign counterparts of any of the foregoing.

1.41 "Person' means any individual, corporation, partnership, association, joint-stock company, trust, unincorporated organization or government or political subdivision thereof.

1.42 "Policies" shall have the meaning set forth in Section 1 0.1(b).

1.43 "Primary Statistical Analysis" shall mean the analysis performed of the six (6) month follow up of all clinical endpoints of all evaluable patients participating in Sangamo 's Phase II Repeat Dosing Clinical Trial of SB-509.

1.44 "Prime Rate" shall mean the average prime rate published in the *Wall Street* Journal during the relevant period (calculated by dividing (a) the sum of the prime rates for each of the days during the relevant period, by (b) the number of days in the relevant period).

1.45 "Principal Investigator" shall mean the Chief Medical Officer of Sangamo, who will personally conduct or supervise the Research Program.

1.46 "Product" shall mean (a) the pharmaceutical product containing the Therapeutic Candidate or (b) any derivatives or related products that (i) encode a zinc finger DNA-binding protein designed to activate the expression of vascular endothelial growth factor (VEGF-A) and (ii) result from Sangamo's research for treatment of diabetic neuropathy.

1.47 "Program Material" shall have the meaning set forth in Section 2.3.2(d).

1.48 "Qualified Subject" is a human subject who, on enrollment into the Research Plan, has met all of the eligibility criteria and none of the exclusion criteria in the Research Plan and has given his or her written informed consent to participate in the Research Plan.

1.49 "Quarterly Report" shall have the meaning set forth in Section 3.2.3(a).

1.50 "Recipient" shall have the meaning set forth in Section 5.1.2.

1.51 "Recipient Notice Requirement" shall have the meaning set forth in Section 5.1.3.

1.52 "Registration" shall mean, with respect to each country in the Territory, Regulatory Approval for the Product filed in such country.

1.53 "Regulatory Approval" shall mean, with respect to any country, all authorizations by the appropriate governmental entity or entities necessary for commercial sale of the Product in that country including, without limitation and where applicable, approval of labeling, price, reimbursement and manufacturing, in the United States final approval of a new drug application or biologic license application, as the case may be, pursuant to the then-applicable provisions of the Code of Federal Regulations permitting marketing of the Product in interstate commerce in the United States, and in the European Union final approval of a Marketing Authorization Application, or equivalent.

1.54 "Research Plan" means the written protocol for Sangamo's Phase II Repeat Dosing Clinical Trial of SB-509, that shall be attached to this Agreement as **Exhibit A** upon approval by the FDA, which protocol was based on the Application, includes the JDRF Studies, and has been approved by the FDA, as modified from time to time by Sangamo in consultation with the FDA and in accordance with Section 2.4.

1.55 "Research Program" shall mean the work conducted by or on behalf of Sangamo in furtherance of the Research Plan.

1.56 "Research Termination Date" shall mean the date of completion of all activities specified in the Research Plan, including all follow-ups of Qualified Subjects and all analysis included in the JDRF Studies.

1.57 "Sangamo" shall have the meaning set forth in the preamble of this Agreement.

1.58 "Sangamo Designees" shall have the meaning set forth in Section 2.5.1.

1.59 "Sangamo Indemnitee" shall have the meaning set forth in Section 7.2.

1.60 "Sangamo Party" shall have the meaning set forth in Section 7.l(a).

1.61 "Sangamo Patents" shall mean any Patents Controlled by Sangamo or its Affiliates claiming Sangamo Research Program Technology.

1.62 "Sangamo Research Program Technology" shall mean all intellectual property, data, technical information, know-how, inventions (whether or not patented), trade secrets, processes and methods that are (a) discovered or developed by or on behalf of Sangamo or its Affiliates, in the performance of the Research Program under this Agreement, (b) Controlled by Sangamo, and (c) necessary or useful for the research, development and commercialization of the Product.

1.63 "Surrogate Endpoint Data" shall have the meaning set forth in Article VI.

1.64 "Territory" shall mean worldwide.

1.65 "Therapeutic Candidate" shall mean the plasmid, known as SB-509, that encodes a zinc finger DNA-binding protein designed to upregulate the expression of vascular endothelial growth factor (VEGF-A).

1.66 "Third Party" shall mean any Person which is not a Party or an Affiliate of any Party to this Agreement.

ARTICLE II RESEARCH PROGRAM

2.1 Overview. Sangamo shall be responsible for the conduct of the Research Program as set forth herein. JDRF shall provide the financial support hereinafter specified, and consultation and advice as provided herein through its participation on the JRAC as provided below.

2.2 Commencement of the Research Program. If not commenced prior to the Effective Date, the Research Program shall commence as soon after the Effective Date as practicable in light of the date of the FDA's approval of the Research Plan. If the Research Plan is approved by the FDA after the Effective Date and substantial changes are made to the JDRF Studies as described in the Application, then JDRF shall have the right to terminate this Agreement within ten (10) days following such approval of the Research Plan.

2.3 Research Diligence.

2.3.1 Generally. Sangamo shall use Commercially Reasonable Efforts to: (a) conduct the Research Program in accordance with the Research Plan; and (b) satisfy and achieve the Milestones. In furtherance of the foregoing, and in accordance with the terms and conditions of this Agreement (including, without limitation, Section 2.3.2 below), Sangamo shall commit to the Research Program directly or through Third Party contractors (i) the level of staffing required by the Research Plan, with staff that possesses appropriate experience, training and scientific expertise for the tasks to which they are assigned, and (ii) the infrastructure (e.g., laboratories, offices, equipment and facilities) required by the Research Plan.

2.3.2 Obligations of Sangamo. Subject to the terms and conditions of this Agreement, and without limiting the generality of Section 2.3.1 above, Sangamo directly or through its Third Party contractors shall be responsible for conducting the sponsorship, conduct and oversight of the Research Program, such responsibilities to include, without limitation:

(a) identifying appropriate clinical sites to conduct the Research Plan, and entering into clinical trial agreements with such clinical sites;

(b) providing the approved clinical sites with a copy of the Research Plan;

(c) identifying, selecting, and enrolling Qualified Subjects;

(d) providing the investigators at approved clinical sites with the required quantity of the Product or placebo (the "Program Material"), appropriately formulated in accordance with the Research Plan;

(e) monitoring compliance of the approved clinical sites with the Research Plan;

(f) monitoring adverse events arising in the course of the Research Program;

(g) providing the investigators at approved clinical sites and JDRF (the latter for informational purposes) with a copy of the current investigator brochure;

(h) performing laboratory analyses on biopsies collected from Qualified Subjects as outlined in the Research Plan;

(i) complying with all Applicable Law and guidelines regarding administration, transportation, manufacture and production of the Program Material and any other drugs or fluids which are to be supplied by Sangamo for use in connection with the Research Plan;

(j) abiding by and complying with the Policies; and

(k) promptly and thoroughly responding to all reasonable requests and inquiries of JDRF for information regarding the Research Program.

2.4 Modifications to JDRF Studies. Sangamo shall not propose to the FDA any changes to the Research Plan that would have a material impact on the JDRF Studies without first presenting such changes to the JRAC and obtaining the JRAC's recommendation of such changes.

2.5 Joint Research Advisory Committee.

2.5.1 Composition and Purposes. During the term of the Research Program, the Parties shall establish a Joint Research Advisory Committee ("JRAC") consisting of four (4) members, two (2) of whom shall be designated by Sangamo (the "Sangamo Designees"), and two (2) of whom shall be designated by JDRF (the "JDRF Designees"). Each Party (a) shall select a program coordinator from among its designees to the JRAC (who may be changed at any time or from time to time by such Party), and (b) may change any of its designees to the JRAC at any time or from time to time. The program coordinator of Sangamo shall serve as the Chairperson of the JRAC. The Sangamo Designees initially shall be Heidi Kim and Dale Ando, who also initially shall serve as Sangamo's program coordinator and the Chairperson of the JRAC, and the JDRF Designees initially shall be Richard Insel and Paul Burn, who also initially shall serve as JDRF's program coordinator.

The JRAC shall have the authority to:

(i) facilitate communication between the Parties with respect to the Research Program;

(ii) receive Quarterly Reports from Sangamo with respect to the progress of the Research Program and consider and discuss such reports;

(iii) determine whether the Milestones have been satisfied and achieved; and

(iv) decide whether to recommend any changes presented by Sangamo in accordance with Section 2.4.

2.5.2 Meetings. The JRAC shall meet once in each six (6) month period between the Effective Date and the Research Program Termination Date; provided, however, the JRAC shall meet within forty-five (45) days following JDRF's receipt from Sangamo of a written certification setting forth Sangamo's achievement of a Milestone. Meetings of the JRAC shall be held at such times and locations as may be mutually agreed upon by the program coordinators, which times and locations shall be communicated in writing (including, without limitation, by email) to the other members of the JRAC with reasonable advance notice of the meeting. At least one (1) Sangamo Designee and one (1) JDRF Designee shall be required to participate in a meeting for such meeting to be deemed to have a quorum of the JRAC members. So long as a quorum is present at a meeting, the JRAC may make, or decide to make, recommendations to Sangamo, or take, or decide to take, such actions as are within the scope of the JRAC's authority hereunder. Members of the JRAC may attend each meeting either in person or by means of telephone or other telecommunications device that allows all participants to hear and speak at such meeting simultaneously. At least ten (10) business days prior to each meeting, Sangamo shall deliver (including by email) to JDRF a written report detailing the progress made on the Research Program since the last meeting of the JRAC. In satisfaction of such written report, Sangamo may provide the most recent Quarterly Report supplemented by any new significant developments since the most recent Quarterly Report. Within thirty (30) days after the date of each meeting, the Sangamo Designees shall prepare and deliver (including by email) to the JDRF Designees written minutes of such meeting setting forth in detail all discussions and/or recommendations of the JRAC made at such meeting, which minutes shall be subject to revision to take account of the comments of JDRF's program coordinator.

2.5.3 Discussions/Recommendations.

(a) As a general matter, and except as otherwise provided for herein, recommendations of the JRAC shall be unanimous and non-binding.

(b) Notwithstanding the foregoing, the determination as to whether or not a Milestone has been achieved and satisfied shall be subject to the unanimous vote of the JRAC. In each such instance, the Sangamo Designees shall, collectively, have one (1) vote, and the JDRF Designees shall, collectively, have one (1) vote, which, in each instance, shall be cast by each Party's program coordinator (unless such Party's program coordinator expressly authorizes such Party's other JRAC designee to cast such Party's vote). In the event of a deadlock, the Sangamo Designees and the JDRF Designees shall attempt to resolve such deadlock for a period of twenty (20) days by engaging in good faith discussions. If such deadlock is not resolved after such twenty (20) day period, then, such deadlock shall be resolved in accordance with the dispute resolution process set forth in Section 11.2.

2.5.4 Expenses. Each Party shall pay its own expenses (including travel and lodging expenses) incurred in connection with its participation on the JRAC.

2.6 Delivery of Adverse Event Data to the JRAC. In the event of a serious adverse event (as defined by the ICH Harmonized Tripartite Guideline on Clinical Safety Data Management), directly or indirectly attributable to the use or application of the Product, Sangamo shall deliver to each JRAC member any information and other data related to such adverse event within a reasonable time after Sangamo has had an opportunity to discuss such adverse event with the FDA. Any disclosure of patient-identifiable information of any Qualified Subject in connection with the Quarterly Reports due under Section 3.2.3(a) or any other reporting requirements hereunder shall comply with the Health Insurance and Portability and Accountability Act of 1996 and regulations, laws and guidelines related thereto.

ARTICLE III RESEARCH FUNDING; RECORDS

3.1 Research Funding.

3.1.1 Payments. Subject to Section 3.1.2, JDRF shall make payments to Sangamo of the Award in accordance with **Exhibit B**.

3.1.2 Limitations. Notwithstanding Section 3.1.1 above, JDRF shall not be required to make any payment or additional payment in respect of the Award:

(a) in excess of Three Million Dollars ($3,000,000);

(b) unless at the time such payment is due, the Research Program is in compliance with all Applicable Law;

(c) if Sangamo is, at the time such payment is due, in material breach of any of its covenants or obligations under this Agreement (including, without limitation, Sangamo's obligations under Section 3.1.3 below) and JDRF provides Sangamo with written notification of such breach at least thirty (30) days before such payment due date;

(d) if, at the time such payment is due, a case or proceeding (i) under the bankruptcy laws of the United States now or hereafter in effect is filed against Sangamo or all or substantially all of its assets and such petition or application is not dismissed within sixty (60) days after the date of its filing or Sangamo shall file any answer admitting and not contesting such petition, or (ii) under the bankruptcy laws of the United States now or hereafter in effect or under any insolvency, reorganization, receivership, dissolution or liquidation law or statute of any jurisdiction now or hereafter in effect (whether at law or equity) is filed by Sangamo for all or substantially all of its assets; and/or

(e) if this Agreement previously is terminated by any Party in accordance with Article IX, provided, however, that any payments accrued prior to such termination shall immediately become due and payable to Sangamo upon such termination; provided, however, that JDRF shall pay Sangamo any amount not paid on account of subsection (b), (c) or (d) above as soon as the condition that caused such non-payment has been remedied or no longer exists.

3.1.3 Matched Funds. The Parties agree, acknowledge and recognize that the Award represents only partial financial support for the Research Program, and Sangamo agrees to provide the balance of the funds necessary to conduct and complete the Research Program. In furtherance of, but without limiting the generality of the foregoing, Sangamo shall contribute to the Research Program, in the aggregate, an amount that is at least equal to the Award Received (the "Matched Funds"). Sangamo hereby covenants and agrees to solely use the Award Received and the Matched Funds to fund the Research Program.

3.1.4 Payments. All payments to be made hereunder (including, without limitation, pursuant to Article IV) shall be made in United States dollars ("Dollars") and, at the option and direction of the receiving party, shall be made by cashier's or certified check or by wire transfer of immediately available funds.

3.1.5 Competition. Sangamo hereby agrees and acknowledges that nothing contained herein shall restrict or prevent JDRF's ability to provide funding to, or take any other action with respect to, any Person that competes with the business, operations and/or research of Sangamo, provided, however, that in no event shall JDRF disclose to such Persons any nonpublic information concerning the Research Program, including the results thereof.

3.2 Records; Reporting Obligations; Audits.

3.2.1 Records. Sangamo shall prepare and maintain complete and accurate books and records in accordance with GAAP documenting its expenditure of funds in connection with the Research Program (including financial records of expenditures of the Award Received and the Matched Funds), and shall keep all such books and records for no less than a period of three (3) years following the Research Termination Date.

3.2.2 Audit. At the request of JDRF not more often than once in each twelve (12) month period, Sangamo shall permit JDRF internal accounting personnel or representatives and agents of an independent, certified public accounting firm appointed by JDRF and reasonably acceptable to Sangamo, to audit and examine, during normal business hours, the financial records of Sangamo covering the previous twelve (12) month period as may be necessary to verify Sangamo's expenditures of funds in connection with performance of the Research Program in general and the JDRF Studies in particular. Any and all records audited and examined by JDRF personnel or such representatives and agents of such accounting firm shall be deemed Sangamo's Confidential Information. JDRF shall pay the costs of such audit and examination of such financial records, provided, however, that, if such audit and examination reveals an over-reporting by Sangamo to JDRF of Matched Funds or expenditures attributed to the JDRF Studies of more than five percent (5%), then the reasonable costs of such audit and examination shall be borne by Sangamo and Sangamo shall reimburse JDRF for all of the reasonable costs and expenses incurred by JDRF in connection with such audit and examination.

3.2.3 Reports; Notices. Sangamo shall (y) maintain a system of accounting in accordance with GAAP; and (z) furnish to JDRF the following reports and notices under the confidentiality provisions of Article V:

(a) As soon as practicable, and in any event within ninety (90) days after the end of each calendar quarter (including the calendar quarter ending December 31) prior to the Research Termination Date, a report describing (i) the actual costs of the Research Program during such quarter and how the Award Received and Matched Funds have been allocated and in fact used in respect of the Research Program, (ii) the Research Program work performed during such quarter, including, without limitation, Milestones achieved, (iii) a summary of all Research Program clinical data collected and analyzed during such quarter, (iv) a summary of all regulatory filings made during such calendar that materially alter the Research Plan, and (v) any other information that JDRF reasonably requests (each a "Quarterly Report").

(b) As soon as practicable, and in any event within ninety (90) days after the end of the calendar quarter in which the Research Termination Date occurs or the termination of the Agreement becomes effective, whichever is earlier, a closing report which (i) sets forth Sangamo's final analysis, summary tables, data listings, results and conclusions from the Research Program and

such other information and materials as JDRF may reasonably request and (ii) provides an accounting of the out-of-pocket expenses incurred by Sangamo since the Effective Date with respect to performance of the JDRF Studies. If the total amount of such expenses is less than the total Award Received, then, Sangamo shall, within thirty (30) days after delivery of the closing report, refund the difference between such total expenses and the total Award Received in such manner as JDRF shall reasonably instruct Sangamo. Such closing report shall be in lieu of a Quarterly Report covering the last calendar quarter of the Research Program.

(c) Within sixty (60) days after the end of each fiscal year, audited financial statements as of the end of such year (including, without limitation, a copy of the consolidated balance sheet of Sangamo as of the end of such year, together with consolidated statements of income, operations, cash flow and retained earnings of Sangamo for such year), prepared in accordance with GAAP, along with a comparison of such financial statements with the corresponding periods of the prior year. Notwithstanding the foregoing, the scope of the information to be included in the report due under this Section 3.2.3(c) shall be no more extensive or detailed than the scope of financial disclosures that Sangamo is required to make by the Securities and Exchange Act of 1934, as amended.

(d) As soon as practicable, and in any event within thirty (30) days after the end of each calendar year following the Research Termination Date, a report summarizing the Product development and commercialization activities performed by or on behalf of Sangamo or its Affiliates, collaborators, licensees or sublicensees during such year.

(e) As soon as practicable, and in any event promptly after the consummation thereof, any proposed license, sublicense, transfer, or subcontract by Sangamo of rights related to the research, development, and/or commercialization of the Product, any permitted assignment by Sangamo of this Agreement or its rights and/or obligations hereunder, or of any merger, acquisition, consolidation or similar transaction involving Sangamo and materially affecting JDRF's rights and/or obligations hereunder.

ARTICLE IV DILIGENCE; COMPENSATION TO JDRF

4.1 Development and Commercialization of Product. Following the Research Termination Date, Sangamo shall use Commercially Reasonable Efforts to develop, commercialize and bring one Product in the Field to market in the Major Markets. The activities of Sangamo's Affiliates, licensees, sublicensees, subcontractors, collaborators, transferees and successors shall be attributed to Sangamo for the purposes of determining Sangamo's satisfaction of the foregoing diligence obligation.

4.2 Compensation to JDRF.

(a) In consideration of JDRF's payments to Sangamo and JDRF's licenses to Sangamo hereunder, Sangamo shall pay JDRF an amount equal to three (3) times the Award Received less all payments made pursuant to Section 4.2(b) (such amount, the "JDRF ROI") as follows: within ninety (90) days of the first, second, third and fourth anniversaries of the First Commercial Sale, Sangamo shall pay JDRF an amount equal to: (i) one-fourth of the JDRF ROI, (ii) twenty-five percent (25%) of Net Sales during the 12-month period between such anniversary and the previous anniversary of the First Commercial Sale, as applicable (such period, the "Relevant Period"), or (iii) fifty percent (50%) of the royalties received by Sangamo during the Relevant Period from its licensees and sublicensees on account of the sale of the Product, whichever is less, provided that such amounts shall be reduced as necessary to ensure that the total amount paid, when this Section 4.2(a) is combined with all payments made pursuant to Section 4.2(b), shall not exceed three (3) times the Award Received. If the amount paid to JDRF in any year is less than one-fourth of the JDRF ROI plus any deficit from a preceding year of JDRF ROI (in each case after crediting all payments made in such year pursuant to Section 4.2(b)), any such deficit shall be carried forward and added to the amount applicable under Section 4.2(a)(i) for the following year. If the total amount paid by Sangamo to JDRF pursuant to this Section 4.2 by the date that is ninety (90) days after the fourth anniversary of the First Commercial Sale is less than the JDRF ROI, then Sangamo shall continue to make payments in accordance with this Section 4.2 in the following years equal to the lesser of the remaining JDRF ROI, or the lesser of the amounts in Sections 4.2(a)(ii) and (iii) to JDRF within ninety (90) days of each subsequent such anniversary until such time as the total amount paid by Sangamo equals the JDRF ROI.

(b) If Sangamo is commercializing the Product in connection with any license, transfer, or sale of the Sangamo Research Program Technology, any Sangamo Patents, or any Product, to a Third Party, then Sangamo shall pay to JDRF in cash five percent (5%) of the gross proceeds that are received by Sangamo on or after December 31, 2008 and prior to the time of Regulatory Approval of the Product in connection with any such license, transfer, or sale, whether such payments are upfront license fees, milestone payments, or other fees, but excluding FTE payments or purchases of equity at or below fair market value (the "Five Percent Payment"), up to an aggregate amount equal to two (2) times the amount of the Award Received. Such payments to JDRF will be made within ninety (90) days of receipt of such gross proceeds from any licensee, transferee or purchaser of Sangamo Research Program Technology. Thereafter, Sangamo shall pay any remaining JDRF ROI to JDRF in accordance with Section 4.2(a). For clarity,

Sangamo shall not be obligated to pay JDRF, in the aggregate, an amount more than three (3) times the Award Received when the amounts paid under this Section 4.2(b) and Section 4.2(a) are combined.

(c) If aggregate Net Sales of the Product exceed $1 billion Dollars on or before the fifth (5th) anniversary of the First Commercial Sale, Sangamo shall pay to JDRF within ninety (90) days after such Net Sales are achieved, an additional royalty equal to the amount of the Award Received.

(d) If aggregate Net Sales of the Product exceed $2 billion Dollars on or before the fifth (5th) anniversary of the First Commercial Sale, Sangamo shall pay to JDRF within ninety (90) days after such Net Sales are achieved, an additional royalty equal to the amount of the Award Received.

4.3 Sales Reports.

4.3.1 In connection with each payment made to JDRF pursuant to Section 4.2 above with respect to which the amount of Net Sales is relevant, Sangamo shall furnish or cause to be furnished to JDRF a written sales report setting forth in reasonable detail amounts received with respect to which Net Sales during such period were calculated. With respect to sales of the Product invoiced in Dollars, the Net Sales amounts and the amounts due to JDRF hereunder shall be expressed in Dollars. With respect to sales of the Product invoiced in a currency other than Dollars, the Net Sales and amounts due to JDRF hereunder shall be expressed in the domestic currency of the country in which the sale was made, together with the Dollar equivalent of the amount payable to JDRF, calculated by translating foreign currency sales into Dollars in a manner that is consistent with the then-current foreign currency calculations that Sangamo employs for purposes of its reporting obligations under the Securities and Exchange Act of 1934, as amended. If any licensee or sublicensee makes any sales invoiced in a currency other than its domestic currency, the Net Sales shall be converted to its domestic currency in accordance with the licensee's or sublicensee's normal accounting principles. Sangamo shall keep accurate records in sufficient detail to enable the amounts due hereunder to be determined and to be verified by JDRF.

4.3.2 Upon the written request of JDRF, at JDRF's expense and not more often than once a year, Sangamo shall permit an independent accountant selected by JDRF and reasonably acceptable to Sangamo to have access during normal business hours to the records of Sangamo from the previous twenty-four month period ("Audit Period") as may be reasonably necessary to verify the accuracy of the report furnished by Sangamo pursuant to Section 4.3.1. Such independent accountant may examine and audit the records from each Audit Period only once. Such independent accountants may be required by Sangamo to enter into a reasonably acceptable confidentiality agreement, and in no event shall such accountants disclose to JDRF any information, other than the accuracy of reports and payments made or due hereunder.

4.3.3 In case of any delay in payment by Sangamo to JDRF or by JDRF to Sangamo not occasioned by force majeure in accordance with Section 11.5, interest shall be calculated at the lesser of (i) the Prime Rate plus five (5) percentage points or (ii) the maximum rate allowed by law, calculated from the tenth (10th) day after the date upon which the applicable payment first becomes due from Sangamo.

4.4 Royalties to Sangamo. In the event that, pursuant to Section 9.5, the Interruption License becomes effective and thereafter is maintained by JDRF, in lieu of any other royalties pursuant to this Agreement (other than royalties or payments under Section 4.2 previously paid by Sangamo to JDRF in accordance with this Agreement), the Parties shall share equally, subject to this Section 4.4, any amount JDRF receives with respect to the Product (including amounts received in connection with sublicenses of the Interruption License). JDRF's share shall increase and Sangamo's share shall decrease by two percent (2%) for each one million Dollars ($1,000,000) JDRF spends in addition to the Award Received with respect to the research, development and/or commercialization of the Product after the Interruption License Effective Date (as defined in Section 9.5(d)), except that, in no event shall Sangamo's share decrease below twenty percent (20%). Thus, for example, if JDRF's expenditures after the Interruption License Effective Date are ten million Dollars ($10,000,000), JDRF's share will increase to seventy percent (70%) and Sangamo's share will decrease to thirty percent (30%).

ARTICLE V CONFIDENTIALITY

5.1 Confidentiality.

5.1.1 Definition of Confidential Information. For purposes of this Agreement, "Confidential Information" shall mean any trade secrets, know-how, confidential or proprietary information, data and test results relating to the Research Program and any other knowledge, information, documents or materials, owned, developed or possessed by Owner (as defined below), whether in tangible or intangible form, the confidentiality of which Owner takes or has taken reasonable measures to protect; provided, however, that "Confidential lnformation" shall not include any information of Owner that: (a) is already independently known to Recipient (as

defined below) at the time of its disclosure without any obligations of confidentiality; (b) becomes publicly known through no wrongful act of Recipient; (c) is received from a Third Party free to disclose it to Recipient without any obligations of confidentiality with respect thereto; or (d) is independently developed by Recipient without use of any Confidential Information of the Owner; provided, that, in each such instance, Recipient shall bear the burden of proving that any such information of Owner is not Confidential Information. Confidential Information of Sangamo shall include without limitation, investigator brochures, any reports, notices, data, results, case report forms and regulatory filings generated pursuant to the Research Program. The terms and conditions of this Agreement shall be the Confidential Information of both Parties.

5.1.2 Non-Disclosure. During the term of this Agreement and for a period of five (5) years thereafter, each Party ("Recipient") shall hold all Confidential Information it receives or received from the other Party ("Owner") in strict confidence, and, other than as expressly provided herein or without first obtaining the prior written consent of Owner, shall not disclose any Confidential Information to any Person, except to officers, directors, employees, consultants, committee members, volunteers, contractors, subcontractors, licensees, sublicensees, accountants or counsel of Recipient who have a need to know and who are bound to confidentiality obligations at least as restrictive as Recipient's obligations under this Agreement. Recipient shall use not less than the same degree of care it uses to avoid disclosure of its own Confidential Information.

5.1.3 Required Disclosure. Notwithstanding Section 5.1.2 above, Recipient's disclosure of Confidential Information shall not be prohibited if such disclosure is required by a valid and existing order of a court of competent jurisdiction or other governmental body or agency; provided, however, that, Recipient shall have first given prompt notice to Owner of any possible or prospective order and Owner shall have been afforded a reasonable opportunity to prevent or limit such disclosure (the "Recipient Notice Requirement"); provided, further, that the Recipient Notice Requirement shall not apply to proceedings which, by applicable law, are of a nature that the existence of such proceedings may not be disclosed or made public. In the event that Recipient discloses any Confidential Information pursuant to the immediately preceding sentence, Recipient shall cooperate with Owner, at Owner's sole cost and expense, in the prosecution of any appeal that Owner decides to pursue.

5.1.4 No Use of Confidential Information. Recipient hereby agrees and acknowledges that, other than as provided herein or without first obtaining Owner's prior written consent, Recipient shall not use any of Owner's Confidential Information.

5.2 Publicity; Use of Name.

5.2.1 As soon as practicable after the Effective Date and not later than the deadline for any required disclosure of the execution of this Agreement, the Parties shall issue a joint press release announcing the execution of this Agreement in substantially the same form as the press release attached as **Exhibit D**.

5.2.2 Except to the extent already disclosed in the initial press release referenced in Section 5.2.1 above, and except as may be otherwise provided herein, neither Party shall issue any press release or make any public announcement concerning the terms of this Agreement or the transactions described herein without the prior written consent of the other Party, which consent shall not be unreasonably withheld, conditioned or delayed; provided, however, that it shall not be unreasonable for any Party to withhold consent with respect to any press release or public announcement containing any of such Party's Confidential Information. This Section 5.2.2 shall not preclude any Party from issuing press releases or making public announcements if such Party reasonably believes that any such release or announcement is (a) legally required by Applicable Laws or (b) required by the rules of any stock exchange on which such Party's securities are listed. Sangamo shall accord JDRF the opportunity to review and comment on any submission of this Agreement and redaction thereof required to be submitted to the Securities and Exchange Commission by Sangamo. For clarity, Sangamo shall have the right to issue press releases without obtaining the consent of JDRF so long as such press releases contain substantially the same information as contained in Sangamo's Form 8-K filings made pursuant to the Securities and Exchange Act of 1934, as amended.

5.2.3 In each instance, the Party desiring to issue any press release or to make any public announcement shall provide the other Party with a written copy of the proposed release or announcement in sufficient time where practicable prior to public release to allow such other Party to comment upon such release or announcement prior to its public release. In addition, each press release and/or public announcement issued or made pursuant to this Section 5.2, where practicable, shall include JDRF-approved language acknowledging JDRF's funding of a portion of the Research Program.

5.2.4 Except as may be otherwise provided herein, no Party shall have any right, express or implied, to use in any manner the name or other designation of the other Party or any other trade name, trademark or logos of the other Party for any purpose.

5.2.5 Notwithstanding the foregoing or any contrary provision contained herein, in connection with: (a) any description by JDRF of its research portfolio and of its industry discovery and development program, and/or (b) JDRF's fundraising activities, marketing materials and/or reporting requirements, JDRF shall be entitled to use and/or disclose, and Sangamo hereby pre-approves

JDRF's use and/or disclosure of: (i) the names “Sangamo,” “Sangamo BioSciences, Inc.”, Sangamo’s logo and a general description of Sangamo, (ii) the existence and a general description of the nature of this Agreement in a form previously agreed upon by the Parties, and (iii) a general description of the nature of the Research Program in a form previously agreed upon by the Parties. In connection with: (w) any description of Sangamo’s intellectual property rights and drug pipeline; (x) Sangamo’s reporting requirements under the Securities and Exchange Act of l 934, as amended, and the Securities Act of l 933, as amended; (y) Sangamo’s fundraising activities or marketing materials; and (z) any description or acknowledgment of JDRF or JDRF funding as required hereunder, Sangamo shall be entitled to use and/or disclose, and JDRF hereby pre-approves Sangamo’s use and/or disclosure of: (i) the names “JDRF,” “Juvenile Diabetes Research Foundation International”, JDRF’s logo and a general description of JDRF in the context of describing the funding provided by JDRF, (ii) the existence and a general description of the nature of this Agreement in a form previously agreed upon by the Parties, and (iii) a general description of the nature of the Research Program in a form previously agreed upon by the Parties.

ARTICLE VI PUBLICATION

Sangamo shall have the first right to publish, publicly present, or otherwise make available the results of the Research Plan, including any data necessary for Third Parties to utilize any new discoveries and information regarding the surrogate clinical endpoints related to the JDRF Studies and identified by Sangamo during the Research Program (the “Surrogate Endpoint Data”). In the event that Sangamo does not exercise its publication rights by submitting within twelve (12) months after the Research Termination Date a manuscript for publication, JDRF shall have the right to publish, publicly present, or otherwise make available the Surrogate Endpoint Data, but only to the extent that such publication, presentation or availability of the data would not have an adverse impact on any ongoing or planned development and/or commercialization of the Product. If JDRF is the publishing party, JDRF will submit a draft of any proposed manuscript or speech to Sangamo for comments at least sixty (60) days prior to submission for publication or oral presentation. Sangamo shall notify JDRF in writing within thirty (30) days of receipt of such draft whether such draft contains (a) information which Sangamo considers to be Confidential Information under the provisions of Article V hereof, (b) information that if published would have an adverse effect on a patent application which Sangamo intends to file, or (c) information which Sangamo reasonably believes would be likely to have an adverse impact on the development or commercialization of the Product. In any such notification, Sangamo shall indicate with specificity its suggestions regarding the manner and degree to which JDRF may disclose such information. In the case of item (a) above, JDRF shall not publish the Confidential Information of Sangamo in violation of Article V of this Agreement. In the case of item (b) above, Sangamo may request a delay and JDRF shall delay such publication, for a period not exceeding an additional ninety (90) days, to permit the timely preparation and filing of a patent application or an application for a certificate of invention on the information involved. In the case of item (c) above, if JDRF disagrees with Sangamo’s assessment of the impact of the publication, then the program coordinator of each Party shall attempt in good faith to reach a fair and equitable resolution of such disagreement. If the disagreement is not resolved in this manner within fourteen (14) days of referral to the respective program coordinators, then the decision of Sangamo as to publication of any information generated by it, subject always to the confidentiality provisions of Article V hereof shall be final, provided that such decision shall be exercised with reasonable regard for the interests and rights of JDRF. The Parties agree that authorship of any publication will be determined based on the customary standards then being applied in the relevant scientific journal. JDRF shall comply with the foregoing publication requirements in the event that pursuant to Section 9.5, the Interruption License becomes effective.

Notwithstanding the foregoing, (a) Sangamo intends to advance the body of general scientific knowledge of Diabetes and its potential therapies and cures, all in a manner consistent with its general scientific and commercial objectives in entering into this Agreement with JDRF, and (b) the Parties acknowledge that Sangamo intends to publish the results of the placebo data from the Research Program in a major scientific peer reviewed publication as soon as practicable, following the completion of the Research Program; provided that Sangamo shall not be obligated to publish any information which Sangamo reasonably believes would be likely to have an adverse impact on the development or commercialization of the Product. Sangamo shall acknowledge the financial support of JDRF in all Research Program publications. In addition, Sangamo agrees to make available to requesting Third Parties the Surrogate Endpoint Data without charge but only after twelve (12) months have passed since the Research Termination Date.

ARTICLE VII INDEMNIFICATION

7.1 Indemnification by Sangamo. Sangamo shall indemnify, defend and hold harmless JDRF, its Affiliates, and each of their respective directors, officers, committee members, volunteers, employees, consultants, agents and representatives and their respective successors, heirs and assigns (including, without limitation, the JDRF Designees) (each, a "JDRF Indemnitee"), from and against any and all claims, suits and demands of Third Parties and losses, liabilities, damages for personal injury, property damage or otherwise, costs, penalties, fines and expenses (including court costs and the reasonable fees of attorneys and other professionals) arising therefrom (collectively "Losses"), to the extent that such Losses arise from:

(a) the conduct of the Research Program by Sangamo or its Affiliates or their respective directors, officers, employees, consultants, agents, representatives, licensees, sublicensees, subcontractors and/or investigators (each, a "Sangamo Party") under this Agreement and/or pursuant to one or more agreements between Sangamo and any Sangamo Party, or any actual or alleged violation of law resulting therefrom;

(b) the Product (not including any Product developed, manufactured or sold pursuant to the Interruption License) and/or any claim of infringement or misappropriation of intellectual property with respect thereto;

(c) Sangamo's breach of any of its representations, warranties, covenants and/or obligations under this Agreement, or the negligence or willful misconduct of any Sangamo Party in connection with Sangamo's performance of its obligations under this Agreement; or

(d) Any tort claims of personal injury (including death) arising out of, or in connection with, Sangamo's performance of the Research Program.

The above indemnification shall not apply to the extent that any Losses are due to the gross negligence or willful misconduct of JDRF or the practice of the Interruption License.

7.2 Indemnification by JDRF. In the event that, pursuant to Section 9.5, the Interruption License becomes effective, JDRF shall indemnify, defend and hold harmless Sangamo, its Affiliates, and their respective directors, officers, employees, consultants, agents and representatives and their respective successors, heirs and assigns (including, without limitation, the Sangamo Designees), (each a "Sangamo Indemnitee"), from and against any and all Losses that arise as a result of (a) practice of the Interruption License or (b) JDRF's activities after the Interruption License Effective Date and before the Reversion License Effective Date to the extent that such Losses arise from JDRF's breach of any of its obligations under this Agreement, or the negligence or willful misconduct of JDRF in connection with JDRF's performance of its obligations under this Agreement.

The above indemnification shall not apply to the extent that any Losses are due to the gross negligence or willful misconduct of Sangamo or a Sangamo Party.

7.3 Claims Procedures. The Party claiming indemnity under this Article VII (the "Indemnified Party") shall give written notice to the Party from whom indemnity is being sought (the "Indemnifying Party") promptly after learning of the commencement of the relevant Third Party action, suit or proceeding (the "Claim"). Subject to this Section 7.3, the Indemnifying Party shall have the right to assume and manage the defense thereof (with counsel selected by the Indemnifying Party and reasonably satisfactory to the Indemnified Party), including the right to settle, compromise and/or litigate with respect to any such Claim (but only after obtaining the Indemnified Party's prior written consent with respect to any proposed settlement, compromise or litigation; provided, however, that the Indemnifying Party shall not be required to obtain the Indemnified Party's prior written consent in connection with any proposed settlement, compromise or litigation if, in connection with and following any such settlement, compromise or litigation, the Indemnified Party (a) has no liability (monetary or otherwise), (b) has not waived any of its rights and has not admitted to any wrongdoing or guilt, (c) is not subject to any injunction or other equitable or non-monetary relief, and (d) receives a full and unconditional release of all applicable claims and liability).

7.4 Participation; Assuming Control of the Defense. Notwithstanding Section 7.3 above, the Indemnified Party may participate in the defense of any Claim at the Indemnified Party's sole expense, provided that, (a) the employment of counsel by the Indemnified Party has been authorized by the Indemnified Party; or (b) there is a conflict of interest that would prevent an Indemnitee from being represented by a single law firm in the defense of such action; in each such instance, the Indemnifying Party shall pay the reasonable fees and expenses of one law firm serving as counsel for the Indemnified Party, which law firm shall be subject to the prior consent of the Indemnifying Party, which such consent shall not be unreasonably withheld, conditioned or delayed.

7.5 Advance Payment of Expenses. The expenses of an Indemnified Party incurred in defending a Claim shall be paid by the Indemnifying Party as they are incurred and in advance of the final disposition of the action, suit or proceeding, upon receipt of an

undertaking by or on behalf of the Indemnified Party to repay the amount if it is ultimately determined by a court of competent jurisdiction that such Indemnified Party is not entitled to be indemnified by the Indemnifying Party. All costs and expenses incurred by an Indemnified Party in connection with enforcement of this Article VII also shall be reimbursed by the Indemnifying Party.

7.6 Limitation of Liability. NEITHER PARTY SHALL BE LIABLE TO THE OTHER PARTY FOR ANY SPECIAL, INDIRECT, INCIDENTAL, CONSEQUENTIAL, PUNITIVE OR EXEMPLARY DAMAGES, INCLUDING, BUT NOT LIMITED TO, LOST PROFITS, IN CONNECTION WITH SUCH PARTY'S PERFORMANCE OR BREACH OF THIS AGREEMENT. NOTWITHSTANDING THE FOREGOING, NOTHING IN THIS SECTION 7.6 IS INTENDED TO OR SHALL LIMIT OR RESTRICT THE INDEMNIFICATION RIGHTS OR DAMAGES AVAILABLE FOR A PARTY'S BREACH OF CONFIDENTIALITY OBLIGATIONS IN ARTICLE V.

7.7 Insurance. Sangamo shall maintain at its own expense, with a reputable insurance carrier reasonably acceptable to JDRF, full coverage for Sangamo, its Affiliates, and their respective employees that is commensurate with a reasonable estimate of the liability exposure associated with the Research Program, written on a per occurrence basis, which will name JDRF as an additional insured, including, without limitation, errors and omissions insurance encompassing claims relating to the performance and lack of performance of Sangamo's obligations under this Agreement and comprehensive general liability insurance for claims relating to the performance and lack of performance of Sangamo's obligations under this Agreement and comprehensive general liability insurance for claims for damages arising from bodily injury (including death) and property damages arising out of acts or omissions of a Sangamo Party which will be specifically endorsed to cover Sangamo's indemnification obligations under this Article VII. Maintenance of such insurance coverage will not relieve Sangamo of any responsibility under this Agreement for damage in excess of insurance limits or otherwise. On or prior to the Effective Date, Sangamo shall provide JDRF with an insurance certificate from insurer(s) evidencing each insurance coverage and the insurer's agreement to notify JDRF at least sixty (60) days in advance of any cancellation or modification of such insurance coverage.

In the event that the Interruption License becomes effective pursuant to Section 9.5, JDRF shall comply with the foregoing insurance requirements and shall maintain such insurance for as long as necessary to cover any claims that may arise from JDRF's activities during the effectiveness of the Interruption License.

ARTICLE VIII PATENTABLE INVENTIONS

8.1 Ownership. All inventions made and all data and know-how generated solely by either Party or its Affiliates (directly or through others acting on its behalf), as determined in accordance with United States laws of inventorship, prior to and during the term of this Agreement that relates to the Research Program shall be solely owned by the Party making the invention or generating the data or know-how, and all Patents claiming such inventions shall be solely owned by such Party. All inventions made and all data and know-how generated by both Parties jointly, as determined in accordance with United States laws of inventorship, prior to and during the term of this Agreement that relate to the Research Program (a "Joint Invention"), shall be owned jointly, with each Party having an undivided one-half interest in each Joint Invention and each Patent claiming a Joint Invention.

8.2 Preparation. Sangamo shall take initial responsibility for the preparation, filing, prosecution and maintenance of all Sangamo Patents, JDRF Patents, and any patents and patent applications claiming Joint Inventions. JDRF shall have the right to review, and Sangamo shall deliver to JDRF, all patent applications for JDRF Patents or claiming Joint Inventions prior to their filing. With respect to such patent applications, Sangamo shall include in the Quarterly Reports delivered to JDRF pursuant to Section 3.2.3(a) the name of each patent application filed by Sangamo in the United States and other jurisdictions for such Joint Inventions and/or JDRF Patents, along with a general summary of the claims made and the jurisdictions of filing.

8.3 Costs. Subject to Section 8.4, Sangamo shall be responsible for all costs incurred in the preparation, prosecution and maintenance of Sangamo Patents, JDRF Patents, and Joint Inventions.

8.4 Abandonment.

(a) Notwithstanding any contrary provision contained herein, prior to the Interruption License Effective Date, before Sangamo (or any Affiliate, licensee, sublicensee, transferee or successor of Sangamo) abandons any patent or patent application for any JDRF Patents or claiming any Joint Inventions (including abandonment for failure to pay any required fees), Sangamo shall promptly notify JDRF, or cause JDRF to be notified, of such pending abandonment, whereupon JDRF shall have the right and opportunity to take title to such patent and/or patent application by agreeing to maintain the issued patent or continue prosecution of the patent application at JDRF's own expense.

(b) Following the Interruption License Effective Date, before Sangamo (or any Affiliate, licensee, sublicensee, transferee or successor of Sangamo) abandons any patent or patent application for any JDRF Patents, claiming any Joint Inventions, or for any Sangamo Patents (including abandonment for failure to pay any required fees), Sangamo shall promptly notify JDRF, or cause JDRF to be notified, of such pending abandonment, whereupon JDRF shall have the right and opportunity to take title to such patent and/or patent application by agreeing to maintain the issued patent or continue prosecution of the patent application at JDRF's own expense. Sangamo shall reasonably cooperate with JDRF to obtain such consents, on JDRF's behalf, as may be necessary, advisable and/or appropriate for JDRF to exercise its rights under this Section 8.4.

ARTICLE IX TERM AND TERMINATION

9.1 Term. This Agreement shall become effective as of the Effective Date and, unless earlier terminated pursuant to the other provisions of this Article IX, shall terminate at such time as when there are no longer any payment obligations owing from either Party to the other Party under Article IV hereto.

9.2 Termination by JDRF With Cause. Notwithstanding any provision contained herein, JDRF may, without prejudice to any other remedies available to it at law or in equity, terminate this Agreement if, after the occurrence of a Default (as defined herein) and Sangamo's receipt of a written notice from JDRF identifying such Default, Sangamo fails to cure such Default within sixty (60) days after Sangamo's receipt of such notice. The following events shall constitute a "Default" hereunder:

(a) Any material breach by Sangamo of any applicable foreign, federal, state or local laws, statutes, rules or regulations in the course of its performance of the Research Program;

(b) Any material breach or default by Sangamo in the performance of any of its material covenants or obligations hereunder;

(c) Any representation or warranty made by Sangamo in this Agreement is not true in any material respects as of the Effective Date; and/or

(d) A case or proceeding (i) under the bankruptcy laws of the United States now or hereafter in effect is filed against Sangamo or all or substantially all of its assets and such petition or application is not dismissed within sixty (60) days after the date of its filing or Sangamo shall file any answer admitting and not contesting such petition, or (ii) under the bankruptcy laws of the United States now or hereafter in effect is filed by Sangamo for all or substantially all of its assets.

For clarity, an Interruption shall not, for the purposes of this Section 9.2, be considered a material breach or default by Sangamo in the performance of any of its material covenants or obligations hereunder. JDRF's remedies in the event of an Interruption are set forth in Section 9.5 rather than in this Section 9.2.

9.3 Termination for JDRF Breach. Sangamo may, without prejudice to any other remedies available to it at law or in equity, terminate this Agreement upon written notice to JDRF in the event JDRF shall have materially breached or defaulted in the performance of any of its material covenants or obligations hereunder, and JDRF fails to cure such breach or default within sixty (60) days after written notice thereof was provided to JDRF by Sangamo.

9.4 General Effect of Termination; Survival.

(a) Termination, relinquishment or expiration of this Agreement for any reason shall be without prejudice to any rights that shall have accrued to the benefit of any Party prior to such termination, relinquishment or expiration. Such termination, relinquishment or expiration shall not relieve any Party from obligations which are expressly indicated to survive termination of this Agreement.

(b) If this Agreement is terminated for any reason, all of the Parties' rights and obligations under, and/or the provisions contained in, Sections 3.2.1, 3.2.2, 3.2.3(b), and 9.4, Articles V, VI, VII, VIII, and XI shall survive expiration, termination or relinquishment of this Agreement. If this Agreement is terminated pursuant to Section 9.2 and no Interruption License is in effect at the time of such termination, in addition to the provisions specified in the preceding sentence, the Parties' rights and obligations under, and/or provisions contained in Sections 4.2, 4.3, 4.4 and 9.5 shall also survive such termination. In the event that, pursuant to Section 9.5, the Interruption License becomes effective prior to termination of this Agreement pursuant to Sections 9.1 or 9.2, in addition to the provisions specified in the first sentence of this Section 9.4(b), the Parties' rights and obligations under, and/or provisions contained in Sections 4.4, 9.5(e), 9.5(g) and 9.5(h) shall survive such termination.

(c) Sangamo will retain sole ownership of the Sangamo Research Program Technology.

9.5 Interruption License.

(a) In the event JDRF determines that an Interruption has occurred, it shall notify Sangamo in writing of such belief, stating in reasonable detail the basis for its belief that an Interruption has occurred (the "Interruption Notice"). If at the time of receipt of the Interruption Notice, Sangamo (i) has not licensed or otherwise transferred rights to a Third Party to the Sangamo Research Program Technology in the Field; or (ii) has successfully terminated the rights it licensed or otherwise transferred to a Third Party to the Sangamo Research Program Technology in the Field, then Sangamo shall have sixty (60) days after the receipt of the Interruption Notice to avoid the Interruption License Effective Date by (x) responding to the Interruption Notice by explaining why it believes an Interruption has not occurred (the "Interruption Response"); or (y) resuming Commercially Reasonable Efforts (either itself or through an Affiliate, collaborator, licensee, sublicensee, transferee, or successor); provided that, Sangamo may avoid the Interruption License Effective Date by any such resumption only once.

(b) If at the time of receipt of the Interruption Notice, Sangamo has licensed or otherwise transferred rights to a Third Party to the Sangamo Research Program Technology in the Field pursuant to an agreement that includes a provision that gives Sangamo the right to terminate such Third Party's rights under the Sangamo Research Program Technology in the Field upon a final determination that an Interruption has occurred and not been cured within the applicable time after the relevant notice, then Sangamo shall have sixty (60) days after the receipt of the Interruption Notice to avoid the Interruption License Effective Date by (i) providing an Interruption Response to JDRF; or (ii) commencing and continuing thereafter commercially reasonable efforts to effect such a termination. If Sangamo successfully effects such a termination then it shall have sixty (60) days after the termination effective date to avoid the Interruption License Effective Date by resuming Commercially Reasonable Efforts (either itself or through an Affiliate, collaborator, licensee, sublicensee, transferee, or successor); provided that, Sangamo may avoid the Interruption License Effective Date by any such resumption only once.

(c) If Sangamo provides an Interruption Response within the sixty (60) day period set forth in Section 9.5(a) or 9.5(b) and JDRF disagrees with the Interruption Response, JDRF may resolve such Dispute in accordance with Section 11.2. Sangamo shall have sixty (60) days after a final determination pursuant to Section 11.2 that an Interruption has occurred (or if earlier a subsequent written admission by Sangamo that an Interruption has occurred) to avoid the Interruption License Effective Date by (i) resuming Commercially Reasonable Efforts (either itself or through an Affiliate, collaborator, licensee, sublicensee, transferee, or successor); provided that, Sangamo may avoid the Interruption License Effective Date by any such resumption only once; or (ii) if Sangamo provided the Interruption Response pursuant Section 9.5(b), commencing and continuing thereafter commercially reasonable efforts to terminate such Third Party's rights under the Sangamo Research Program Technology in the Field upon a final determination that an Interruption has occurred and not been cured within the applicable time after the relevant notice. If Sangamo successfully effects such a termination then it shall have sixty (60) days after the termination effective date to avoid the Interruption License Effective Date by resuming Commercially Reasonable Efforts (either itself or through an Affiliate, collaborator, licensee, sublicensee, transferee, or successor); provided that, Sangamo may avoid the Interruption License Effective Date by any such resumption only once.

(d) The "Interruption License Effective Date" shall be the first of the following events to occur: (i) the expiration of the sixty (60) day period set forth in Section 9.5(a) without Sangamo having taken any of the actions specified in Section 9.5(a), (ii) Sangamo's agreement in writing, following receipt of the Interruption Notice, that an Interruption has occurred (provided, however, that none of Sangamo's written communications pursuant to Section 9.5(b)(ii) or 9.5(c)(ii) shall be considered such an agreement), (iii) the expiration of the applicable sixty (60) day period set forth in Section 9.5(b) without Sangamo having taken any of the actions specified in Section 9.5(b), or (iv) the expiration of the applicable sixty (60) day period set forth in Section 9.5(c) without Sangamo having taken any of the actions specified in Section 9.5(c).

(e) Upon the Interruption License Effective Date, Sangamo shall be deemed to have automatically granted to JDRF with respect to the Research Program an exclusive (even as to Sangamo) worldwide license, with the right to sublicense, under the Sangamo Research Program Technology, to manufacture, have manufactured, sell, offer to sell and import the Product in the Field (the "Interruption License"). Sangamo's obligations pursuant to Sections 3.2.3(d), 4.1 and 4.2 shall expire upon the Interruption License Effective Date.

(f) For clarity, prior to the Interruption License Effective Date, Sangamo shall be free to license to a Third Party the Sangamo Research Program Technology (including the grant of exclusive worldwide sublicensable rights under Sangamo Research Program Technology for such Third Party to research, develop, or commercialize the Product). In the event that Sangamo commences negotiations with a Third Party to transfer all of or certain of Sangamo's rights under the Sangamo Research Program Technology to such Third Party to develop and commercialize a Product in the Field, Sangamo shall use best commercial efforts to include in the agreement a provision that gives Sangamo the right to terminate such Third Party's rights under the Sangamo Research Program Technology in the Field upon a final determination that an Interruption has occurred and not been cured within the applicable time after the relevant notice; and solely for purposes of this Section 9.5, the term "Interruption" with respect to a Sangamo Third Party licensee or transferee shall be defined in a manner that is as close to the definition contained in Section 1.22 as Sangamo, by the

exercise of best commercial efforts, is able to include in the executed agreement with such Third Party. In the event that Sangamo does not successfully negotiate such a provision, then Sangamo shall so notify JDRF prior to Sangamo's execution of the agreement with such Third Party and, upon receipt of such notice, JDRF shall no longer have any right to obtain the Interruption License with respect to the Sangamo Research Program Technology licensed or transferred to such Third Party.

(g) In connection with this Section 9.5, Sangamo shall deliver to JDRF, within sixty (60) days of the Interruption License Effective Date, all materials and data generated in the performance of the Research Program and the Sangamo Research Program Technology and all other materials and data that Sangamo may Control that are reasonably required by JDRF to manufacture, have manufactured, sell, offer to sell and import the Product in the Field, provided that the foregoing obligations shall apply only to the extent such materials or data are reasonably accessible and available to Sangamo.

(h) Notwithstanding the foregoing or any contrary provision contained in this Section 9.5, if, following the Interruption License Effective Date, JDRF ceases to conduct Commercially Reasonable Efforts with respect to the research, development and commercialization of the Product in the Field for a period of one hundred eighty (180) consecutive days then upon the expiration of such 180-day period (the "Reversion License Effective Date") the Interruption License shall terminate and, in accordance with the terms and conditions of this Agreement, JDRF shall be deemed to have automatically granted to Sangamo a non-exclusive, royalty-free, fully paid, irrevocable, perpetual, worldwide license (with the right to grant sublicenses), under the JDRF Interruption License Technology to research, develop, make, have made, use, import, offer for sale and sell the Product in the Field. In addition, JDRF shall deliver to Sangamo within sixty (60) days of the Reversion License Effective Date all materials and data generated by JDRF and all other materials and data that JDRF may Control that are reasonably required by Sangamo to manufacture, have manufactured, sell, offer to sell and import the Product in the Field, provided that the foregoing obligations shall apply only to the extent such materials or data are reasonably accessible and available to JDRF.

ARTICLE X REPRESENTATIONS AND WARRANTIES

10.1 Representations, Warranties and Covenants of Sangamo.

(a) As of the Effective Date, Sangamo represents and warrants to JDRF that: (i) this Agreement has been duly executed and delivered by Sangamo and constitutes tbe valid and binding obligation of Sangamo, enforceable against Sangamo in accordance with its terms, except as enforceability may be limited by bankruptcy, fraudulent conveyance, insolvency, reorganization, moratorium and other laws relating to or affecting creditors' rights generally and by general equitable principles; (ii) the execution, delivery and performance of this Agreement have been duly authorized by all necessary action on the part of Sangamo and its directors and stockholders; (iii) the individual executing this Agreement on behalf of Sangamo is duly authorized to do so; and (iv) no provision contained in this Agreement violates any other agreement to which Sangamo is bound or otherwise subject.

(b) In addition to the foregoing, as of the Effective Date, Sangamo represents, warrants and covenants to JDRF that (i) while guaranteeing no specific results, it has the knowledge, skills, expertise and experience to perform the Research Program or the resources to engage Persons to perform the Research Program who have such knowledge, skills, expertise and experience; (ii) it has and shall maintain all licenses, permits and other approvals and authorizations required for Sangamo to conduct work under the Research Program consistent with its obligations pursuant to this Agreement and shall do so in conformity with all applicable laws, statutes, rules and regulations, and the applicable policies of any and all medical research institutions at which Sangamo is conducting work under the Research Program (collectively, "Applicable Law"); (iii) it shall abide by and comply with all of the applicable provisions and conditions set forth in the "JDRF Policies and Conditions Regarding Funding of Research Involving Human Clinical Trials," attached hereto as **Exhibit C** (the "Policies"), and Sangamo hereby acknowledges that it is a "Sponsor" within the meaning of such Policies; (iv) it shall not enter into any arrangement, understanding or agreement that conflicts in any marmer with this Agreement and Sangamo's obligations and responsibilities hereunder; provided that the foregoing shall not be interpreted as prohibiting Sangamo from entering into an agreement with a Third Party whereby such Third Party would research, develop, make, have made, use, import, offer for sale and sell the Product or participate in the Research Program; and (v) with respect to any Third Party to whom Sangamo subcontracts the performance of any aspect of the Research Program, Sangamo shall: (A) subcontract only with reputable entities that possess the knowledge, skills, expertise, and experience necessary to perform such services; (B) use Commercially Reasonable Efforts to ensure that each such subcontractor possesses and shall maintain all necessary licenses, permits, approvals or authorizations necessary for such subcontractor to conduct its work under the Research Program; and (C) use Commercially Reasonable Efforts to ensure that each such subcontractor conducts all work under the Research Program in conformity with Applicable Law.

10.2 Representations and Warranties of JDRF. As of the Effective Date, JDRF represents and warrants to Sangamo that: (a) this Agreement has been duly executed and delivered by JDRF and constitutes the valid and binding obligation of JDRF, enforceable against JDRF in accordance with its terms, except as enforceability may be limited by bankruptcy, fraudulent conveyance, insolvency,

reorganization, moratorium and other laws relating to or affecting creditors' rights generally and by general equitable principles; (b) the execution, delivery and performance of this Agreement have been duly authorized by all necessary action on the part of JDRF and its directors; (c) the individual executing this Agreement on behalf of JDRF is duly authorized to do so; and (d) no provision contained in this Agreement violates any other agreement to which JDRF is bound or otherwise subject.

ARTICLE XI MISCELLANEOUS PROVISIONS

11.1 Governing Law. This Agreement shall be governed by and construed in accordance with the internal laws of the State of Delaware without regard to any conflict of laws principles thereof that would cause the application of the laws of a different jurisdiction.

11.2 Dispute Resolution.

(a) In the event of any dispute, claim or controversy arising out of, relating to or in any way connected to the interpretation of any provision of this Agreement, the performance of either Party under this Agreement or any other matter under this Agreement, including any action in tort, contract or otherwise, at equity or law (a "Dispute"), either Party may at any time provide the other Party written notice specifying the terms of such Dispute in reasonable detail. As soon as practicable after receipt of such notice, the Chief Executive Officers, or their respective designees, of both JDRF and Sangamo shall meet at a mutually agreed upon time and location for the purpose of resolving such Dispute. The Chief Executive Officers, or their respective designees, shall engage in good faith discussions and/or negotiations for a period of up to thirty (30) days to resolve the Dispute or negotiate an interpretation or revision of the applicable portion of this Agreement which is mutually agreeable to both Parties without the necessity of formal dispute resolution procedures relating thereto. During the course of such discussion and/or negotiation, the Parties shall reasonably cooperate in order that each of the Chief Executive Officers, or their respective designees, may be fully informed with respect to the issues in the Dispute.

(b) In the event any Dispute is not resolved by the Chief Executive Officers, or their respective designees, pursuant to Section 11.2(a), then the Parties shall resolve such Dispute by final and binding arbitration. Arbitration shall be held in New York, NY, according to the then-current JAMS' Commercial Rules of Arbitration ("JAMS' Rules"), except to the extent such rules are inconsistent with this Section 11.2. The arbitration will be conducted by one (1) arbitrator who shall be reasonably acceptable to the Parties and who shall be appointed in accordance with JAMS' Rules. If the Parties are unable to select an arbitrator, then the arbitrator shall be appointed in accordance with JAMS' Rules. Any arbitrator chosen hereunder shall have educational training and industry experience sufficient to demonstrate a reasonable level of relevant scientific, financial, medical and biotechnology industry knowledge. Within twenty (20) days of the selection of the arbitrator, each Party shall submit to the arbitrator a proposed resolution of the Dispute that is the subject of the arbitration (the "Proposals"). The arbitrator shall thereafter select one of the Proposals so submitted as the resolution of the Dispute, but may not alter the terms of either Proposal and may not resolve the Dispute in a manner other than by selection of one of the submitted Proposals. If a Party fails to submit a Proposal in accordance with the terms of this Section 11.2(b), the arbitrator shall select the Proposal of the other Party as the resolution of the Dispute. The arbitrator shall agree to render its opinion within thirty (30) days of the final arbitration hearing. No arbitrator shall have the power to award punitive damages under this Agreement regardless of whether any such damages are contained in a Proposal, and such award is expressly prohibited. The proceedings and decisions of the arbitrator shall be confidential, final and binding on all of the Parties. Judgment on the award so rendered may be entered in a court having jurisdiction thereof. The Parties shall share the costs of arbitration according to the decision of the arbitrator. Nothing in this Section 11.2(b) will preclude either Party from seeking equitable relief in accordance with Section 11.3 or interim or provisional relief from a court of competent jurisdiction, including a temporary restraining order, preliminary injunction or other interim equitable relief, concerning a dispute either prior to or during any arbitration if necessary to protect the interests of such Party or to preserve the status quo pending the arbitration proceeding.

11.3 Equitable Relief. The Parties acknowledge and agree that, in the event of a breach or a threatened breach by either Party of this Agreement for which there is no adequate remedy at law, the other Party may suffer irreparable damage and accordingly, shall be entitled to seek injunctive and other equitable remedies to prevent or restrain such breach or threatened breach, in addition to any other remedy such Party might have at law or at equity.

11.4 Waiver. No provision of this Agreement may be waived except in writing by both Parties hereto. No failure or delay by either Party hereto in exercising any right or remedy hereunder or under applicable law will operate as a waiver thereof, or a waiver of any right or remedy on any subsequent occasion.

11.5 Force Majeure. Neither Party will be in breach hereof by reason of its delay in the performance of or failure to perform any of its obligations hereunder, if that delay or failure is caused by strikes, acts of God or the public enemy, riots, incendiaries, interference by civil or military authorities, compliance with governmental priorities for materials, or any fault beyond its reasonable

control. In such event Sangamo or JDRF, as the case may be, shall immediately notify the other Party of such inability and of 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. To the extent possible, each Party shall use reasonable efforts to minimize the duration of any force majeure.

11.6 Severability. Should one or more provisions of this Agreement be or become invalid, then the Parties hereto shall attempt to agree upon valid provisions in substitution for the invalid provisions, which in their economic effect come so close to the invalid provisions that it can be reasonably assumed that the Parties would have accepted this Agreement with those new provisions. If the Parties are unable to agree on such valid provisions, the invalidity of such one or more provisions of this Agreement shall nevertheless not affect the validity of the Agreement as a whole, unless the invalid provisions are of such essential importance for this Agreement that it may be reasonably presumed that the Parties would not have entered into this Agreement without the invalid provisions.

11.7 Assignment. This Agreement may not be assigned or otherwise transferred by either Party without the prior written consent of the other Party; provided, however, that either Party may assign this Agreement, without the consent of the other Party, (i) to any of its Affiliates, if the assigning Party guarantees the full performance of its Affiliate's obligations hereunder; (ii) in connection with such Party's merger, consolidation or transfer or sale of all or substantially all of the assets of such Party; or (iii) to any Third Party to whom Sangamo grants an exclusive or co-exclusive license to develop the Product in the Field, provided, that in the case of (ii) or (iii) hereunder, the successor, surviving entity, purchaser of assets, transferee, or Third Party, as applicable, expressly assumes in writing such Party's obligations under this Agreement. Any purported assignment in contravention of this Section 11.7 shall, at the option of the non assigning Party, be null and void and of no effect. No assignment shall release either Party from responsibility for the performance of any accrued obligation of such Party hereunder. This Agreement shall be binding upon and enforceable against the successor to or any permitted assignees from either of the Parties hereto.

11.8 Counterparts. This Agreement may be executed in duplicate, each of which shall be deemed to be original and both of which shall constitute one and the same Agreement.

11.9 No Agency. Nothing herein contained shall be deemed to create an agency, joint venture, amalgamation, partnership or similar relationship between JDRF and Sangamo. Notwithstanding any of the provisions of this Agreement, neither Party to this Agreement shall at any time enter into, incur, or hold itself out to Third Parties as having authority to enter into or incur, on behalf of the other Party, any commitment, expense, or liability whatsoever, and all contracts, expenses and liabilities in connection with or relating to the obligations of each Party under this Agreement shall be made, paid, and undertaken exclusively by such Party on its own behalf and not as an agent or representative of the other.

11.10 Notice. All communications between the Parties with respect to any of the provisions of this Agreement will be sent to the addresses set out below, or to such other addresses as may be designated by one Party to the other by notice pursuant hereto, by prepaid, certified mail (which shall be deemed received by the other Party on the fifth (5th) business day following deposit in the mails), or by facsimile transmission, or other electronic means of communication (which shall be deemed received when successful transmission is confirmed), with confirmation by first class letter, postage pre-paid, given by the close of business on or before the next following business day:

if to JDRF, at:

Richard Insel, M.D.
Executive Vice President for Research
Juvenile Diabetes Research Foundation International
120 Wall Street, 16th Floor
New York, NY 10005-4001
Tel.: (212) 785-9500
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with a copy to:

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Fax: (202) 424-7647
Email: kenneth.schaner@bingham.com

if to Sangamo, at:

Sangamo BioSciences, Inc.
501 Canal Boulevard, Suite A100
Richmond, CA 94804
Attention: Chief Executive Officer

with a copy to:

Marya Postner, Ph.D.
Cooley Godward, LLP
5 Palo Alto Square
3000 El Camino Real
Palo Alto, CA 94306

11.11 Headings. The paragraph headings are for convenience only and will not be deemed to affect in any way the language of the provisions to which they refer.

11.12 Entire Agreement. This Agreement contains the entire understanding of the Parties relating to the matters referred to herein, and may only be amended by a written document, duly executed on behalf of the respective Parties.

[Remainder of Page Intentionally Left Blank.]

IN WITNESS WHEREOF, the undersigned have executed this Agreement as of the date first Written above.

Sangamo BioSciences, Inc.

By: /s/ EDWARD O. LANPHIER

Name: EDWARD O. LANPHIER

Title Chief Executive Officer

Juvenile Diabetes Research Foundation International

By: /s/ Richard A. Insel

Name: Richard A. Insel

Title: Executive Vice President for Research

Exhibit A

Research Plan

Exhibit B

Research Funding and Milestones

I. Payment Schedule for Research Funding: Up to an aggregate amount of Three Million Dollars ($3,000,000), payable as follows:

Milestones	Payment Amount($)
1. Upon the Effective Date, if FDA acceptance of phase 2 plan (102 patients in two treatment groups) has occurred; or upon FDA acceptance of such Phase 2 plan, if such acceptance has not yet occurred as of the Effective Date	$500,000
2. Enrollment of the first Qualified Subject	$500,000
3. Enrollment of the 25th Qualified Subject	$500,000
4. Enrollment of the 50th Qualified Subject	$500,000
5. Enrollment of the 100th Qualified Subject	$500,000
6. Receipt by JDRF of the final report of the Primary Statistical Analysis	$500,000

II. Payments pursuant to this **Exhibit B** shall be paid by JDRF to Sangamo within forty-five (45) days following JDRF's receipt from Sangamo of a written certification setting forth Sangamo's achievement of the applicable Milestone unless the JRAC determines, in a meeting held within such forty-five (45) day period, that such Milestone was not achieved. If JRAC's vote on such matter during such meeting is not unanimous, then JDRF shall make the applicable payment within forty-five (45) days following resolution of such dispute in Sangamo's favor.

Exhibit C

JDRF Policies and Conditions Regarding
Funding of Research Involving Human Clinical Trials

JDRF will fund research involving human clinical trials only if the Sponsor of the trial can assure JDRF, with a reasonable degree of certainty, that the following conditions will be met:

- The research will be conducted in accordance with basic ethical principles as reflected in the Nuremburg Code, the World Medical Association Declaration of Helsinki and the Belmont Report;
- The research will comply with governmental regulatory requirements and guidance, as applicable;
- The research will be reviewed and approved by an institutional review board to assure that risk is minimized and reasonable in relation to anticipated benefits, that voluntary informed consent is given, and that the rights, safety and welfare of the subjects are maintained;
- The investigators will be qualified by training, education and experience to assume responsibility for the proper conduct of the trial and to comply with good clinical practices;
- A qualified physician will be responsible for all trial-related medical decisions. During and following a subject's participation in the trial, the investigator will arrange for adequate medical care to be provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial;
- Conflicts of interest will be disclosed and appropriate action taken;
- Safety reporting, including serious adverse event reports, will be made in a timely fashion and in accordance with applicable regulatory requirements;
- The Sponsor of the trial will implement and maintain quality assurance and quality control systems with written standard operating procedures in order to conduct the trial, generate data and document compliance with the protocol, good clinical practices and applicable regulatory requirements;
- The clinical trial will be registered in a public registry acceptable to JDRF, if applicable; and
- The investigators conducting the research, the responsible institutional review board and the Sponsor will engage in ongoing compliance and review activity to promote and assure the integrity of the research.

Exhibit D

Press Release

4.

Exhibit 10.2

FIRST AMENDMENT TO
RESEARCH, DEVLEOPMENT AND COMMERCIALIZATION AGREEMENT
BETYWEEN SANGAMO BIOSCIENCES, INC. ("SANGAMO") AND JUVENILE
DIABETES RESEARCH FOUNDATION INTERNATIONAL ("JDRF")

This First Amendment (this "First Amendment") to the Agreement of October 24, 2006 is made as of this 8th day of January 2010 (the "First Amendment Effective Date") by and between Sangamo and JDRF. Capitalized terms used but not defined herein shall have the definition provided in this Agreement.

WHEREAS, the Parties entered into the Agreement; and

WHEREAS, the Parties now desire to amend the Agreement so that JDRF may support Sangamo's SB-509-901 clinical trial which is entitled "A Phase 2b Repeat Dosing Clinical Trial of SB-509 in Subjects with Moderately Severe Diabetic Neuropathy".

NOW THEREFORE, in consideration of the foregoing, the receipt and sufficiency of which is hereby acknowledged, the Parties agree as follows:

1. Confirmation of Terms.

Except as provided in this First Amendment, the Agreement shall remain in full force and effect.

2. Acknowledgement.

The Parties hereby acknowledge that, prior to the First Amendment Effective Date, Sangamo fulfilled its obligations under the Agreement to perform the Research Plan as described in Exhibit A and to achieve the Milestones set forth in Exhibit B as it existed prior to the First Amendment Effective Date, and JDRF fulfilled its obligations under the Agreement to pay to Sangamo the amounts set forth in Exhibit B as it existed prior to the First Amendment Effective Date.

3. Amendment to Agreement.

The following amendments shall be made to the Agreement:

(a) The term "Award" as defined in Section 1.5 of the Agreement shall be amended to substitute "Six Million Dollars ($6,000,000")" in lieu of "Three Million Dollars ($3,000,000)" previously specified therein:

(b) The definiton of "Research Plan" as set forth in Section 1.54 of the Agreement shall be replaced with the following: "Research Plan" means (a) the written protocol for Sangamo's Phase II Repeat Dosing Clinical Trial of SB-509, that shall be attached to this Agreement as **Exhibit A** upon approval by the FDA, which protocol was based on the Application, includes the JDRF Studies, and has been accepted 'y the FDA, as modified from time to time by Sangamo in consultation with the FDA and in accordance with Section 2.4 and (b) the written protocol for Sangamo's SB-509-901 clinical trial that is attached to the First Amendment as **Exhibit C**, which Exhibit will be updated to reflect any amendments to such protocol that are agreed upon by Sangamo and the FDA."

(c) Section 3.1.2(a) shall be amended by increasing "Three Million Dollars ($3,000,000)" to "Six Million Dollars ($6,000,000)";

(d) Section 7. 7 (Insurance) of the Agreement is hereby deleted in its entirety and is replaced with the following provision:

Insurance. Sangamo shall maintain at its own expense, with a reputable insurance carrier reasonably acceptable to JDRF, coverage for Sangamo, its Affiliates, and their respective employees written on a per occurrence basis commensurate with a reasonable assessment of the risks associated with the research efforts being conducted by Sangamo, the following policies:

(a) Comprehensive general liability insurance for claims relating to the performance and lack of performance of Sangamo's obligations under this Agreement;

(b) Comprehensive general liability insurance for claims for damages, including, damages as a result of bodily injury (including death) and damages to property, arising out of acts or omissions of a Sangamo Party;

(c) Products liability insurance for claims for damages, including, damages as a result of bodily injury (including death) and damages to property, arising out of the acts or omissions of a Sangamo Party; and

(d) Clinical trials liability insurance for damages, including, damages as a result of bodily injury (including death) and damages to property, arising out of any clinical trials conducted by Sangamo in connection with its obligations under the Agreement, or arising out of the acts or omissions of a Sangamo Party. This insurance shall specifically include coverage for obligations and liabilities of Sangamo under any clinical trial agreement or protocol that is a part of clinical trials conducted by Sangamo under the Agreement and for liability arising as a result of allegations of the insufficiency or other defects in the informed consent provided to participants in the clinical trials.

All insurance policies required hereunder shall name JDRF as an additional insured, be specifically endorsed to cover Sangamo's indemnification obligations under this Article VII and be written with coverage limits approved by JDRF. Maintenance of such insurance coverage will not relieve Sangamo of any responsibility under this Agreement for damage in excess of insurance limits or otherwise. On or prior to the First Amendment Effective Date, Sangamo shall provide JDRF with an insurance certificate from the insurer(s) evidencing each insurance coverage and the insurer's agreement to notify JDRF at least sixty (60) days in advance of any cancellation or material modification of such insurance coverage. At its request, JDRF may review Sangamo's insurance coverage with relevant Sangamo officials from time to time.

In the event that the lnterruption License becomes effective pursuant to Section 9.5, JDRF shall comply with the foregoing insurance requirements and shall maintain such insurance for as long as necessary to cover any claims that may arise from JDRF's activities during the effectiveness of the Interruption License.

(e) Section 11 .10 shall be amended to replace the notice address for JDRF with the following:

Richard Insel, MD
Chief Scientific Officer
Executive Vice President, Research
Juvenile Diabetes Research Foundation International
26 Broadway, 14th Floor
New York, NY 10004
Tel.: 212-479-7604
Email: rinsel@ jdrf.org

(f) Exhibit B shall be replaced with the Exhibit B attached to this First Amendment; and

(g) Exhibit C attached to this First Amendment shall be added to the Agreement.

[Signatures on next page]

IN WITNESS WHEREOF, the undersigned have executed this First Amendment as of the First Amendment Effective Date.

Sangamo BioSciences, Inc.
By: /s/ Edward O. Lanphier
Name: Edward O. Lanphier
Title: President and Chief Executive Officer

Juvenile Diabetes Research Foundation International
By: /s/ Alan J. Lewis, Ph.D.
Name: Alan J. Lewis, Ph.D.
Title: President and Chief Executive Officer

EXHIBIT B

RESEARCH FUNDING AND MILESTONES

I. Payment Schedule for Research Funding: Up to an aggregate amount of Six Million Dollars ($6,000,000), payable as follows:

Milestones	Payment Amount ($)
1. Upon the Effective Date, if FDA acceptance of Phase 2 plan (102 patients in two treatment groups) has occurred; or upon FDA acceptance of such Phase 2 plan, if such acceptance has not yet occurred as of the Effective Date	$500,000
2. Enrollment of the first Qualified Subject	$500,000
3. Enrollment of the 25th Qualified Subject	$500,000
4. Enrollment of the 50th Qualified Subject	$500,000
5. Enrollment of the 100th Qualified Subject	$500,000
6. Receipt by JDRF of the final report of the Primary Statistical Analysis	$500,000
7. Initiation of patient screening for SB-509-901	$250,000
8. First patient for SB-509-901 randomized by assignment of randomization number	$250,000
9. 76th patient, or 50% of the then planned number of patients for SB-509-901, whichever occurs first, randomized by assignment of randomization number	$500,000
10. 150th patient, or the last planned patient for SB-509-901, whichever occurs first, randomized by assignment of randomization number	$500,000
11. Submission to JDRF of day 180 data analysis for SB-509-901	$500,000
12. Submission to JDRF of day 360 data analysis for SB-509-901	$500,000
13. Submission to JDRF of draft clinical study report for SB-509-901	$500,000

II Payments pursuant to this **Exhibit B** shall be paid by JDRF to Sangamo within forty-five (45) days following JDRF's receipt from Sangamo of a written certification setting forth Sangamo's achievement of the applicable Milestone unless the JRAC determines, in a meeting held within such forty-five (45) day period, that such Milestone was not achieved. If JRAC's vote on such matter during such meeting is not unanimous, then JDRF shall make the applicable payment within forty-five (45) days following resolution of such dispute in Sangamo's favor.

Clinical Study Protocol

A Phase 2b Repeat Dosing Clinical Trial of SB-509 in Subjects with Moderately Severe Diabetic Neuropathy

Protocol Number SB-509-0901

BB-IND 12189

Sponsor Sangamo BioSciences, Inc.
Point Richmond Tech Center II
501 Canal Blvd., Suite A100
Richmond, CA 94804
Phone: (510) 970-6000
Fax: (510) 970-6009

Medical Monitor Ely Benaim, M.D.

Phone: (510) 970-7868
Fax: (510) 970-6009

Original Date August 18, 2009

Amendment 1 Date October 9, 2009

Sangamo BioSciences, Inc.

Clinical Approval Signature Page

Protocol Number: **SB-509-0901**

Protocol Title: **A Phase 2b Repeat Dosing ClinicalTrial of SB-509 in Subjects with Moderately Severe Diabetic Neuropathy**

Version: **Amendment 1**

Date: **October 9, 2009**

/s/Ely Benaim, M.D. 10/09/2009
Ely Benaim, M.D. Date
Vice Preseident, Clinical Affairs

/s/Shelley Wang, MS. M.D. 10/09/2009
Shelley Wang, MS. M.D. Date
Associate Director, Clinical Development

TABLE OF CONTENTS

PROTOCOL SYNOPSIS

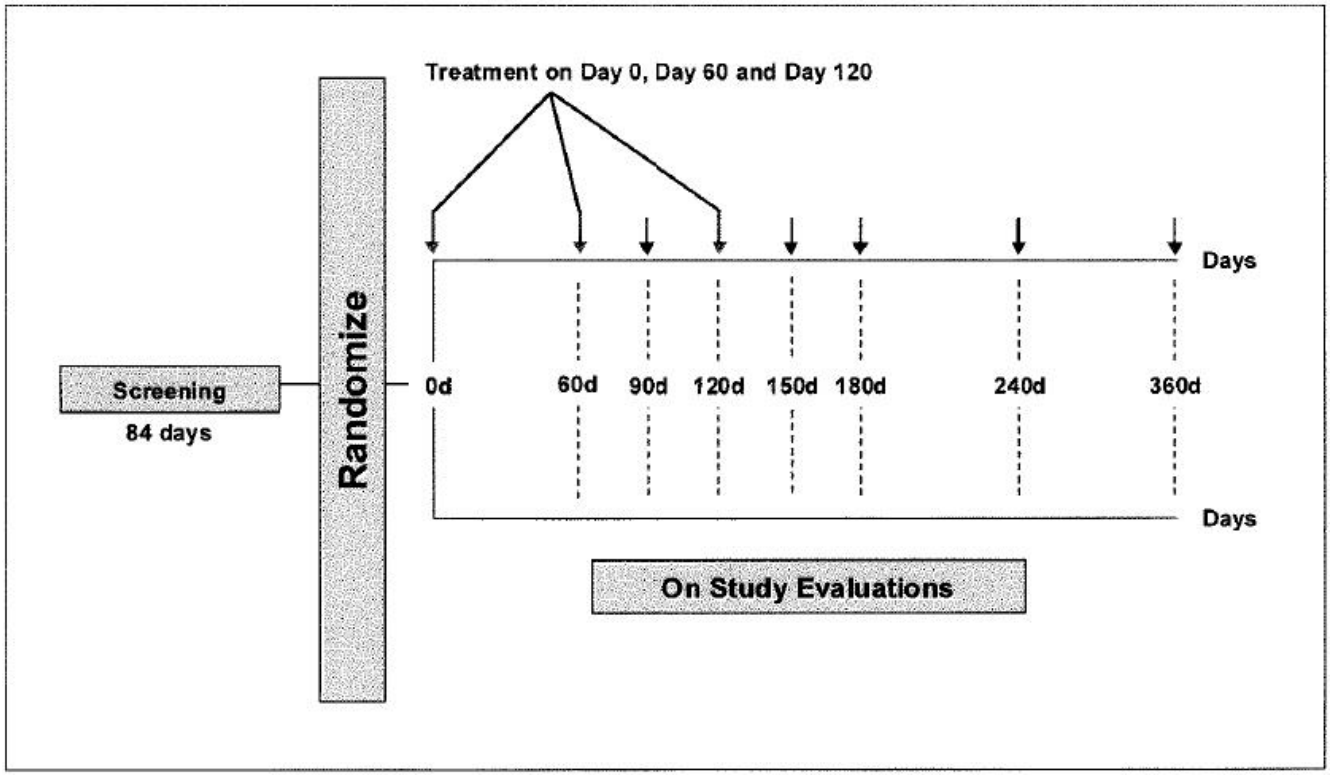
Title	A Phase 2b Repeat Dosing Clinical Trial of SB-509 in Subjects with Moderately Severe Diabetic Neuropathy
Sponsor	Sangamo BioSciences, Inc.
Investigational Products	SB-509

Objectives	**Primary:**
	To compare the effect of SB-509 versus placebo in subjects with moderately severe diabetic neuropathy (DN) on sural Nerve Conduction Velocity (NCV) at six-months
	
	Secondary:
	· To compare in subjects with moderately severe diabetic neuropathy the effect of SB-509 versus placebo on the following endpoints:
	  · Neuropathy Impairment Score - Lower Limb (NIS-LL)
	  · Motor Nerve Conduction Velocity (NCV)
	  · Quantitative Sensory Testing (QST)
	  · lntraepidermal Nerve Fiber Density (IENFD)
	  · Lower Extremity Neurological Sensory Exam
	  · Visual Analog Scale for Pain Intensity (VASPI)
	  · Neuropathy Total Symptom Score (NTSS-6)
	  · Quality of Life: NeuroQoL and SF-36
	  · Global Assessment
	· To compare the effect of SB-509 versus placebo in subjects with moderately severe diabetic neuropathy using a multi-endpoint analysis that includes Neuropathy Impairment Score - Lower Limb (NIS-LL), Sural Nerve Conduction Velocity (NCV) and lntraepidermal Nerve Fiber Density (IENFD), as detailed by O'Brien (1984)
	· To evaluate the safety of SB-509 as compared to placebo in subjects with moderately severe diabetic neuropathy

Subject Population	A total of 150 subjects with moderately severe diabetic neuropathy as defined by mean sural NCV ≤ 45 m/s,IENFD ≤ 18 fibers/mm, NIS-LL ≥ 3 points, sICAM ≥ 200 ng/ML, with measurable lower extremity nerves (sural NCV amplitude must be > 1.0 μ*V)* will be enrolled in this trial.
Study Design	Phase 2b, randomized, double-blind, placebo-controlled, multicenter study.
Treatment Plan	150 subjects will be randomized in a 1:1 ratio to treatment with SB-509 or placebo: 1) SB-509 treatment: 60 mg of SB-509 on Day 0, Day 60 and Day 120. 2) Placebo on Day 0, Day 60 and Day 120. 30 mg of SB-509 or an equal volume of placebo will be injected intramuscularly (IM) into each lower limb for a total dose of 60 mg. Each subject will receive a total of three treatments, two months apart.

Duration of Participation	The duration of participation will be approximately 15 months: 12 weeks for screening, 5 months for treatment (includes one month after the last dose), and 7 months for follow-up after the treatment period.
Randomization	Subjects will be randomized in a 1:1 ratio to SB-509 or placebo stratified by study site and screening IENFD ($< 9, \geq 9$).
Sample Size and Analyses	A sample size of 150 subjects provides 93% power to detect a mean improvement of 2.2 units on the sNCV in a comparison between the SB-509 and placebo arms, assuming a standard deviation of 4. The statistical test used will be a two-sided Wilcoxon Rank-Sum test, with a Type I error rate of 5%. Primary Efficacy Analyses The Day 180 change from baseline sNCV will be compared by treatment group using the Wilcoxon Rank-Sum test at an alpha level of 0.05 Secondary Efficacy Analyses The Day 180 change from baseline sNCV will be compared by treatment group using the Cochran-Mantel-Haenszel test stratified by IENFD < 9 and ≥ 9 at an alpha level of 0.05 For the following measures, the Day 180 change from baseline measures will be compared by treatment group using the Wilcoxon Rank-Sum test. · Neuropathy Impairment Score - Lower Limb (NIS-LL) · Lower Extremity Neurological Sensory Exam · Motor Nerve Conduction Velocity (NCV) · Quantitative Sensory Testing (QST) · lntraepidermal Nerve Fiber Density (IENFD) · Neuropathy Total Symptom Score (NTSS-6) · Visual Analog Scale for Pain Intensity (VASPI) · Quality of Life (QOL)- NeuroQoL and SF-36 · Global assessment The effect of SB-509 versus placebo in subjects with moderately severe diabetic neuropathy will be compared using a multi-endpoint analysis that includes Neuropathy Impairment Score - Lower Limb (NIS-LL), Sural Nerve Conduction Velocity (NCV) and lntraepidermal Nerve Fiber Density (IENFD), as detailed by O'Brien (1984). Safety Safety assessment will occur on all subjects who received any study medication. Terminations/premature withdrawals, adverse events, concomitant medications, and laboratory data will be tabulated. Adverse events will be coded to a standard set of terms using the MedDRA dictionary. Frequency of adverse events will be compared using Fisher's exact test.

SCHEMA


Treatment on Day 0, Day 60 and Day 120
Days
Screening
84 days
Randomize
0d
60d
90d
120d
150d
180d
240d
360d
Days
On Study Evaluations

ABBREVIATIONS

32Ep65	Engineered ZFP-TF
ACS	American Cancer Society
ADA	American Diabetes Association
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ARI	Aldose reductase inhibitors
AST	Aspartate aminotransferase
BMI	Body mass index
BOCF	Baseline observation carried forward
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
cm	Centimeter
CPK	Creatinine phosphokinase
CPKmb	Creatinine phosphokinase, mb fraction
CRF	Case report form
CTCAE	Common terminology criteria for adverse events
DN	Diabetic neuropathy
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ENFD	Epidermal nerve fiber density
ENFDR	Epidermal nerve fiber density regeneration
FDA	Food and Drug Administration
FOBT	Fecal occult blood test
HBV	Hepatitis B virus
HCV	Hepatitis C virus
Hg	Mercury
HIV	Human Immunodeficiency Virus
HPV	Human papillomaviurs
ICH	International Conference on Harmonization
IBC	Institutional Biosafety Committee
ICAM	Intracellular Adhesion Molecules
IEC	Institutional Ethics Committee
IENFD	lntraepidermal Nerve Fiber Density
IM	Intramuscular
INR	International normalized ratio
IRB	Institutional Review Board
Kb	Kilobase
kg	Kilogram
L	Liter
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LOCF	Last observation carried forward
mg	Milligram
mL	Milliliter
mm	Millimeter
mM	Millimolar
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NCS	Nerve conduction studies
NCV	Nerve conduction velocity
NF	National Formulary
NTSS-6	Neuropathy Total Symptom Score
ng	Nanogram
NGF	Nerve growth factor

NIH	National Institute of Health
NIS-LL	Neuropathy Impairment Score - Lower Limb
NLS	Nuclear localization sequence
NOAEL	No observed adverse effect level
NSAIDs	Non-steroidal anti-inflammatory drugs
P188	Poloxamer 188
PCR	Polymerase chain reaction
PSA	Prostate-specific antigen
PT	Prothrombin time
PTT	Partial prothrombin time
pV-32Ep65	Plasmid; the active drug substance in SB-509
QOL	Quality of Life
QST	Quantitative sensory testing
RNA	Ribonucleic acid
SAE	Serious adverse event
SB-509	Plasmid formulation containing the 32Ep65 expression cassette, an engineered transcription factor that induces expression of VEGF-A
sNCV	Sural Nerve Conduction Velocity
STZ	Streptozotocin
SV40	Simian Virus 40
TF	Transcription factor
TSH	Thyroid Stimulating Hormone
Tris-HCI	Tris-(hydroxymethyl)-aminomethane hydrochloride
U	Unit
µm	Micrometer (micron)
USP	United States Pharmacopoeia
VPT	Vibration Perception Threshold
VASPI	Visual Analog Scale for Pain Intensity
VEGF	Vascular endothelial growth factor
VEGF-A	Vascular endothelial growth factor-A
WBC	White blood cell
WHO	World Health Organization
ZFP	Zinc finger protein
ZFP-TF	Zinc finger protein transcription factor

1. INTRODUCTION

VEGF-A is well known as a potent angiogenic factor, but it has also been shown to be a potent neurotrophic and neuroprotective factor. Studies have shown that plasmid-mediated delivery of hVEGF-A can reverse neuropathy in diabetic animals (Schratzberger *et al*. 2001). Another study showed that gene transfer of an engineered transcription factor promoting expression of VEGF-A protects against experimental diabetic neuropathy (Price *et al*. 2006). A Phase 1 clinical trial testing hVEGF-A165 cDNA suggests that this approach may be beneficial (Simovic *et al*.2001).

The VEGF-A mRNA is alternatively spliced to express three major protein isoforms, VEGF-A189, VEGF-A165, and VEGF-A121 Recent studies suggest that the combination of all three isoforms provides a more potent angiogenic response than any of the isoforms alone (Whitlock *et al*. 2004). The same may be true for the neurotrophic and neuroprotective effects of VEGF-A.

Sangamo BioSciences has developed a plasmid SB-509 that expresses an engineered transcription factor (TF) that binds the endogenous VEGF-A promoter and activates transcription of the endogenous VEGF-A gene. The transcript produced undergoes alternative splicing, naturally producing the three major protein isoforms. This TF is based on the Cys2-His2 zinc finger DNA binding domain. Treatment of disease via localized gene delivery may mimic local autocrine/paracrine mechanisms by which VEGF-A works. It has been shown, in side-by-side comparisons, that activation of the endogenous VEGF-A gene, using engineered TFs, produces non-leaky vasculature with normal vessel architecture (Rebar *et al*. 2002) in contrast to vessels produced in response to a single isoform, which leak and have defective architecture (Elson *et al*. 2001).

SB-509 is an investigational product that has not been approved or marketed in any country.

1.1. Background

Epidemiology and Treatment of Diabetic Neuropathy

It is estimated that diabetes affects nearly 23.6 million patients in the United States, of which 5.7 million are undiagnosed (CDC 2007 National Diabetes Fact Sheet). The incidence of diabetic peripheral neuropathy ranges from 10% at the time of diagnosis of diabetes to 50% after 25 years of living with diabetes (Poncelet 2003). The severity of neuropathy in diabetes is related to the duration of disease, glucose control, hypertension, and hyperlipidemia (Feldman *et al*. 1999; Stratton *et al*. 2000; Malik 2000). In addition, neuropathy is an independent risk factor for further morbidity in diabetes due to foot ulcerations and limb amputation (McNeely *et al*. 1995; Potter *et al*. 1998). The pathogenesis is related to hyperglycemia, which affects both small and large nerve fibers. The WHO definition of diabetic neuropathy (DN) is “A disease characterized as a progressive loss of nerve fibers leading to sensation loss, foot ulceration, and amputation.” Symptoms and signs are directly related to the type of nerve fiber damage. Thinly myelinated small nerve fibers mediate pain and altered cold, heat, and light touch. Large myelinated fibers mediate vibration and proprioception. Symptoms and signs include the stocking and glove distribution of sensory loss, pain and eventually motor loss resulting in weakness of the muscles in the feet and are directly related to the type of nerve fiber damage (Thomas and Tomlinson 1993).

There is no treatment for diabetic neuropathy that has been shown to modify disease onset or progression; current treatments are limited to the relief of select symptoms (i.e. pain). Intensive glucose control can stabilize or improve diabetic neuropathy (DN) (UKPDS 33 1998). Medical treatment for pain symptoms associated with diabetic neuropathy includes anti-depressants, anti-convulsants, opiates, anti-arrhythmics, and topical agents (Poncelet 2003). Duloxetine and pregabalin have recently received FDA approval for the symptomatic treatment on Diabetic Neuropathy pain (Argoff *et al*. 2006). Additional treatment strategies have included attempts to protect or regenerate neurons and thus interfere with the primary disease process in neuropathy. Aldose reductase inhibitors (ARI) and growth factors such as Nerve Growth Factor (NGF) have been evaluated in clinical trials. Phase 3 trials with these agents have proved unsuccessful in detecting significant improvement in neurologic endpoints and have been limited by side effects (Boulton *et al*. 2004). These studies did provide significant insight into the natural course of progression of DN and the need for a composite endpoint combining measurements of the signs and symptoms of DN, neurological examination, and electrophysiological testing (Feldman 2002). Epalrestat (Kinedak™, Ono Pharmaceuticals, Osaka, Japan), approved in Japan in 1992, is the only ARI currently available commercially.

1.2. Rationale

1.2.1. Pre-clinical Data

The biological activity of the 32Ep65 transcriptional activator (also known as VZ+434) was evaluated in both in vitro multiple cell lines and in vivo in multiple species. In vitro studies demonstrated that the transcriptional activator can 1)upregulate the major

isoforms VEGF-A mRNA and conserve their relative proportions and 2) increase VEGF-A protein and 3) the secreted protein can protect neuronal-derived cells from growth arrest in response to serum starvation. The therapeutic potential of SB-509 was assessed in a validated experimental model of diabetic neuropathy in streptozotocin (STZ)-induced diabetic rats (Schratzberger et al. 2001; Calcutt *et al*. 2003; Biessels *et al*. 1999, Price *et al* 2006). Single and repeat administration of the formulated plasmid encoding 32Ep65 (SB-509) showed a significant and dose-related protection against losses in both motor and sensory nerve conduction velocities. Please refer to the **SB-509 DN Clinical Investigator's Brochure.**

Single administration pre-clinical toxicology and biodistribution studies of SB-509 were designed to support the Phase 1 dose-escalation clinical trial of a single treatment of SB-509 in subjects with diabetic neuropathy. Single administration toxicology studies included both toxicology and biodistribution studies in rats and rabbits. The single intramuscular injection treatment of SB-509 was, in general, well-tolerated, with no treatment-related effects or biologically significant differences among treatment groups for body weights, clinical observations, laboratory tests, and microscopic histological evaluation. SB-509 plasmid persisted up to 30 days and was localized to the injection site. A NOAEL of 1.0 mg/kg SB-509 was determined from the study

A repeat SB-509 administration study in rats was designed to support the Phase 2 repeat administration clinical trial in subjects with diabetic neuropathy. Rats received monthly SB-509 intramuscular administration for three months. In general, rats tolerated three doses of SB-509 given at monthly intervals at up to 1.0 mg/kg/dose SB-509 without any toxic effects. Specific ocular histopathology revealed no evidence of retinal arterial proliferation or other lesions related to SB-509 treatment. Proteinuria was observed at 5.0 mg/kg/dose SB-509 at Study Day 60 in 1/5 males and at Study Day 90 in 1/5 females. Proteinuria was also observed at a similar incidence at Study Day 120 for both the low (1.0 mg/kg) and high (5.0 mg/kg) dose groups in both male (1/5) and female (1/5) groups. This finding was not supported by protein serum changes in creatinine and blood urea nitrogen levels or by histological changes in the kidney. The only microscopic histology findings were local inflammation and muscle damage at the injection site. The incidence of these findings generally correlated with the volume administered and was a transient effect. No significant changes in body weight gain were observed during dosing (Study Days 0-60); however, during the recovery period (Study Days 60-120), males and females in the 5.0 mg/kg dose groups showed significant changes in body weight gains and were considered to insignificant and were not toxicologically relevant. One mortality was observed in a PCR (biodistribution) satellite group (5 mg/kg/dose SB-509), and the cause of death was undetermined. At all study time points (Study Days 30, 60, 90, and 120), plasmid DNA was detected at the injection sites in all rats given SB-509 at 5 mg/kg/dose. SB-509 plasmid was not found in heart or gonads at Study Days 30, 60, 90, and 120. The NOAEL was 1.0 mg/kg/dose for repeat administration of SB-509. For additional information, please refer to the **SB-509 DN Clinical Investigator's Brochure.**

1.2.2. Clinical Rationale

Clinical trials of SB-509 in subjects with mild, moderate, or severe diabetic peripheral neuropathy have identified the following effects of SB-509: improvement in sensory and motor nerve conduction velocity, improvement in quantitative sensory testing, decrease in the neuropathy impairment score-lower limb, and a strong trend for re growth of nerve fibers in the skin. Subgroup analyses by baseline disease severity show that subjects with more advanced disease (i.e., low nerve conduction velocity, low intraepidermal nerve fiber density and poor vibration perception) tend to respond better to SB-509, as indicated, for example, by a greater decrease in the neuropathy impairment score. Thus, this protocol will be conducted in subjects with advanced diabetic neuropathy who have a mean sural nerve conduction velocity of ≤ 45 m/s, NIS-LL ≥ 3, an intraepidermal nerve fiber density ≤ 18 fibers/mm, and serum Intracellular Adhesion Molecule (ICAM) ≥ 200 ng/ml.

Further information is provided in the **SB-509 DN Clinical Investigator's Brochure**.

2. OBJECTIVES

The primary objective is:

To compare the effect of SB-509 versus placebo in subjects with moderately severe diabetic neuropathy on the sural Nerve Conduction Velocity (sNCV) endpoint at sixmonths

The secondary objective is:

- To compare in subjects with moderately severe diabetic neuropathy the effect of SB-509 versus placebo on the following endpoints: Neuropathy Impairment Score - Lower Limb (NIS-LL), motor Nerve Conduction Velocity (NCV), Quantitative Sensory Testing (QST), lntraepidermal Nerve Fiber Density (IENFD), Lower Extremity Neurological Sensory Exam, Visual

Analog Scale for Pain Intensity (VASPI), Neuropathy Total Symptom Score (NTSS-6), NeuroQoL, SF-36, and Global Assessment

- To compare the effect of SB-509 versus placebo in subjects with moderately severe diabetic neuropathy using a multi-endpoint analysis that includes Neuropathy Impairment Score - Lower Limb (NIS-LL), Sural Nerve Conduction Velocity (NCV) and lntraepidermal Nerve Fiber Density (IENFD), as detailed by O'Brien (1984)
- To evaluate the safety of SB-509 as compared to placebo in subjects with moderately severe diabetic neuropathy

3. STUDY DESIGN

The Phase 2 trial is a randomized, double-blind, placebo-controlled, multi-center study of SB-509 given by intramuscular injections into the lower limbs in 150 subjects with moderately severe diabetic neuropathy.

150 subjects will be randomized in a 1:1 ratio to treatment with SB-509 or placebo stratified by study site and screening IENFD (<9 fiber/mm, ≥ 9 fiber/mm):

1) SB-509 treatment: 60 mg of SB-509 on Day 0, Day 60 and Day 120.

2) Placebo on Day 0, Day 60 and Day 120.

30 mg of SB-509 or an equal volume of placebo will be injected (IM) into each lower limb for a total dose of 60 mg. Each subject will receive a total of three treatments.

The duration of participation will be approximately 15 months: 12 weeks for screening, 5 months for treatment (includes one month after the last dose), and 7 months for follow-up after the treatment period.

4. SUBJECT SELECTION

4.1. Inclusion Criteria

1. Written informed consent signed and dated by study subject
2. Male or female between the ages of 18 and 70, inclusive
3. Clinical diagnosis of Diabetes Mellitus Type I or II for at least 12 months. A past history of Diabetes Mellitus and/or the use of anti-diabetic medications for the treatment of Diabetes Mellitus are sufficient.
4. Clinical signs and symptoms of moderate to severe diabetic sensori motor polyneuropathy of the lower extremities for at least 6 months that are not otherwise attributed to an etiology other than diabetes, as determined by a an internist with neuropathy experience, neurologist or endocrinologist and excluding subjects with only diabetic autonomic neuropathy or mononeuropathy.
5. Mean sural nerve conduction velocity ≤ 45 m/s as confirmed by the Neurological Core Laboratory
6. Measurable sural response (amplitude equal or greater than 1.0 μv) and a measurable peroneal response (amplitude equal to or greater than 500 μV) bilaterally
7. Neuropathy Impairment Score Lower Limb (NIS-LL) must be ≥ 3 points
8. lntraepidermal Nerve Fiber Density ≤ 18 fibers per mm
9. Serum Intracellular Adhesion Molecule level (ICAM) ≥ 200 ng/mL
10. Hemoglobin level ≥ 10 g/dL
11. HgbA1c level ≤ 9%. Subjects should be treated according to ADA guidelines and goals for dietary intervention and/or glucose control therapy and have stable glycemic control for 3 months, as determined by the investigator
12. WBC count ≥ 3,000/mm^3, an absolute granulocyte count ≥ 1,500/mm^3, and a platelet count ≥ 100,000/mm^3
13. Serum creatinine < 1.5 mg/dL
14. Total bilirubin ≤ 1.5 times the upper limit of normal
15. AST and ALT ≤ 2 times the upper limit of normal

16. INR < 1.5 times the upper limit of normal or PTT < 1.5 times the upper limit of normal
17. Normal or elevated serum levels of vitamin B12
18. Normal thyroid function (as determined by normal TSH and free T4 levels). For subjects on thyroid hormone replacement therapy, an elevated TSH level that is no higher than 7 mU/L is acceptable if the investigator feels the subject is clinically euthyroid.
19. Random urine sample albumin/creatinine ratio ≤ 300 µg/mg creatinine. Normal urinalysis, with the exception of glucose and protein. If other abnormalities are present, the urinalysis may be repeated within the screening period at the discretion of the investigator.
20. If subject is female and of childbearing potential, she agrees to use a medically acceptable physical barrier method contraceptive during the treatment phase through 30 days after the last dose and have a negative serum pregnancy test prior to study entry.

    A female subject is considered to be of childbearing potential if she is postmenarchial, has an intact uterus and at least 1 ovary, and is less than 2 years postmenopausal. A male subject must agree to use a medically acceptable physical barrier method contraceptive during the treatment phase through 30 days after the last dose. The following are acceptable physical barrier methods: Male condom, Female condom, Diaphragm, Cervical cap.
21. Subject must not be breastfeeding. Subjects who become pregnant during treatment must inform the investigator of their pregnancy, be withdrawn from treatment, and agree to provide follow-up information at time of delivery.
22. Complete screening tests for malignancies of the colon, breast (females only), cervix/uterus (females only), and prostate (males only) at the time of screening based on the American Cancer Society's current recommended guidelines (see **Appendix 3**). Documented evidence of negative screening tests is sufficient. Any subject found to have cancer by these screening tests is excluded from the trial.
23. Negative mammogram, if female and over age 40
24. Have a PSA (<4 ng/mL), if male and over age 45
25. Normal Pap smear documented within a year of screening, if female, unless the subject has had a hysterectomy
26. Be willing and able to participate in the study as an outpatient, make the required visits to the study center during the treatment and post treatment periods, and comply with study requirements
27. LDL cholesterol ≤ 130 mg/dL. Subjects with hyperlipidemia should be treated by diet or medications according to ADA guidelines and goals. Modification of treatment during the screening period is allowed at the discretion of the investigator. Subjects with elevated LDL in spite of adequate stalin therapy (at least 3 months) or intolerant to statins, will be discussed with the FDA for eligibility approval.
28. Blood pressure ≤ 140/90 mm Hg. Subjects with hypertension should be treated according to ADA guidelines and goals, as determined by the investigator.
29. Subjects should have a body mass index (BMI) ≤ 38 and should be receiving medical care, education, and counseling for obesity according to ADA guidelines and goals, as determined by the investigator. BMI is obtained by dividing the body weight (in kilograms) by the height squared (in meters squared).

$$\text{BMI} = \frac{\text{weight (kg)}}{\text{height (m)} \times \text{height (m)}}$$

4.2. Exclusion Criteria

1. Unable to comply with the protocol evaluation requirements
2. Require surgical intervention within 4 weeks of treatment
3. Moderate to severe ischemic heart disease or any history of congestive heart failure, or have had a myocardial infarction within the previous 6 months
4. Evidence of cardiac enlargement and/or congestive heart failure.
5. Current diabetic foot or leg ulcer, gangrene in the lower extremity, or any amputation of the lower extremity

5. Bleeding diathesis (e.g., hemophilia due to Factor VIII or IX deficiency) or require treatment with warfarin 2 weeks prior to and including the dosing period (up to 24 hours after dosing)
6. Hemorrhagic stroke
7. Gastrointestinal hemorrhage
8. Any other condition that, in the opinion of the clinical investigator or sponsor, might compromise any aspect of this trial
9. Participation in another clinical trial concurrently or have participated in such a trial within 30 days of screening
10. Received gene transfer agents within 6 months of screening
11. History of malignancy, except for the following: adequately treated basal cell or squamous cell skin cancer, superficial bladder cancer, adequately treated Stage 1 or 2 cancer currently in complete remission, or any other cancer that has been in complete remission for at least 5 years
12. Inflammatory angiopathy (e.g., Buerger's disease, etc.)
13. Have an active infection requiring systemic or oral antibiotics. Subjects with prior infection must have discontinued such treatments at least 2 weeks prior to administration of the investigational agent.
14. Be expected to require immunosuppressants (such as methotrexate, cyclophosphamide, or cyclosporine) for 30 days prior to, during, and for 30 days following administration of the investigational drug product
15. Known immune or immunodeficiency disorders (e.g., HIV positive, sarcoidosis, tuberculosis, rheumatoid arthritis, autoimmune disorders – e.g. psoriasis)
16. Chronic active viral hepatitis (HBV, HCV) or other active liver disease
17. History of clinically significant hypersensitivity reactions to any component of SB-509
18. Current history (within 12 months of start of study) of alcohol or chemical dependency (excluding nicotine), as assessed by the investigator.
19. History of or current proliferative retinopathy, macular edema or retinal neovascularization based on a dilated retinal examination with fluorescein angiography and retinal photographs performed by an ophthalmologist
20. Pre-cancerous conditions (e.g. Barrett's Esophagus, dysplasias) or benign tumors which have the potential for clinically significant growth due to VEGF stimulation.
21. History of or current benign colon polyps that have been removed that meet the following criteria: 3 or more adenomas, any adenoma ≥ 1cm, any adenoma with villous features, high-grade dysplasia or sessile adenomas.
22. Family history of inherited neuropathy (e.g. Charcot Marie Tooth, Hereditary Predisposition to Pressure Palsy).
23. Known or suspected spinal pathology such as spinal stenosis, or a history suspicious of claudication (neurogenic and/or vascular).

5. INFORMED CONSENT

Prior to entering the study, the investigator or designated assistant will explain to each subject the nature of the study, its purpose, the procedures, the expected duration, alternative therapies available, and the benefits and risks involved in study participation. Subjects will be given an information and consent document, will have the opportunity to ask questions, and will be informed of their right to withdraw from the study at any time without prejudice. After this explanation and before any studyspecific procedures have been performed, the subject will voluntarily sign and date the informed consent document.

If a subject is re-screened for study participation, the subject should be re-consented if outside of the acceptable screening window. The subject will receive a copy of the re-signed and dated written informed consent form and any other written information provided to the subject.

6. AUTHORIZATION TO USE AND DISCLOSE MEDICAL INFORMATION

Under federal law, subject study records cannot be used or disclosed for research purposes unless an authorization to use and disclose medical information is signed by each subject prior to participation in the study. The investigator or designated assistant will explain

to each subject the purpose of the subject authorization, and the disclosures will be agreed to by signing the authorization document. Subjects will be given an authorization document and will have the opportunity to ask questions. The subject must also be informed of the following:

1. They may not participate in the study unless the authorization is signed; however, they have the right to revoke this authorization (in writing) at any time.
2. If subject discontinues from the study, they need not revoke the authorization to use and disclose their medical information.
3. If subject discontinues from the study and does decide to revoke their authorization to use and disclose their medical information, the information that has already been collected in their study records may be used and disclosed as necessary to protect the integrity of the research project.

After this explanation and before any study-specific procedures have been performed, the subject will voluntarily sign and date an authorization document.

Prior to participation in the study, the subject will receive a copy of the signed and dated written authorization.

7. STUDY METHODOLOGY

The following sections describe in detail all study procedures. A detailed flow chart of all study procedures is presented in the Schedule of Events (**Appendix 1**).

STUDY VISIT PROCEDURES

7.1. Screening Visit

The objective of the screening visit procedures is to identify subjects who meet the stated inclusion and exclusion criteria and who are willing and able to participate in the study. The following screening information and procedures must be obtained and completed within 12 weeks prior to administering the first treatment.

Blood tests including CBC with WBC differential and platelet count, Coagulation tests PT/INR and PTT and Serum chemistry: electrolytes (Na, K, CO_2 , Cl), CPK, CPKmb, troponin, creatinine, BUN, glucose, uric acid, total bilirubin, ALP, ALT (or SGPT), AST (or SGOT), LDH, albumin, calcium, vitamin B12, T4/TSH, direct LDL, and total protein must be performed and reviewed for eligibility within 12 weeks prior to administering the first treatment.

Procedures that were performed as standard care (e.g., chest X-ray and ECG) may be done prior to written informed consent and may be used for screening eligibility, but they must be completed within 12 weeks prior to administering the first treatment. Sigmoidoscopies or colonoscopies and pap smears may be used for screening eligibility if these procedures have been completed within a year of screening. Mammograms may also be used for screening eligibility if the procedure has been completed within 3 months of screening.

A summary table of the study procedures can be found in the Schedule of Events, **Appendix 1**. The following study procedures will be performed at the screening visit:

1. Obtain a signed and dated subject informed consent form and authorization document to use and disclose medical information prior to performing any study-specific procedures
2. Assign a subject number
3. Review the inclusion and exclusion criteria
4. Collect subject demographic information
5. A complete medical history; and perform a general physical examination, including evaluation of lower extremity edema, height, weight, vital sign measurements (temperature, blood pressure [systolic and diastolic], and pulse rate), assessment of concomitant medications and **a digital rectal exam for male subjects only**. If the subject is not normally seen at the study center and reports having a condition listed in the exclusion criteria, it may be necessary to obtain medical records to confirm study eligibility (i.e., document stability of a clinically significant abnormality or disease)

6. CBC with WBC differential and platelet count
7. Coagulation tests PT/INR and PTT
8. Serum chemistry: electrolytes (Na, K, C02 , Cl), CPK, CPKmb, troponin, creatinine, BUN, glucose, uric acid, total bilirubin, ALP, ALT (or SGPT), AST (or SGOT), LDH, albumin, calcium, total protein, and vitamin B12
9. T4/TSH
10. Direct LDL cholesterol (subject should be fasting from midnight on)
11. HgbA1c levels
12. HIV serology
13. Serum pregnancy test if female subject is of childbearing potential
14. Urinalysis - test for presence of glucose, protein, bilirubin, blood, pH, and specific gravity
15. Spot urine test for microalbumin/creatinine
16. Blood sample collection: 6 mL blood (3 mL plasma) sample for PCR assay and 10 mL blood (5 mL serum) sample for serum Intracellular Adhesion Molecule (ICAM) level, cytokine assay, immunogenicity testing and detection of inflammatory markers, which should be collected and stored frozen until ready to be shipped to the laboratory. Collection, handling, and shipping instructions will be provided in the **Study Reference Manual**.
17. Lower extremity neurological examination for NIS-LL and Lower Extremity Neurological Sensory Exam testing. (See **Appendix 5 and Appendix 6** for details).
18. Electrophysiological testing of the sural and peroneal nerves (See **Appendix 7** and the **Study Reference Manual** for details of testing requirements)
19. Review of waveforms for nerve conduction velocity by the Neurological Core Laboratory.
20. Quantitative sensory testing (QST) of bilateral lower extremities (**Appendix 8**)
21. 3 mm skin biopsy to determine lntraepidermal Nerve Fiber Density (IENFD) (See **Appendix 9**)
22. Neuropathy Total Symptom Score (NTSS-6) (See **Appendix 10**)
23. Visual Analog Scale for Pain Intensity (VASPI) (See **Appendix 11**)
24. Neuro-QoL(lSee **Appendix 12**)
25. SF-36 (See **Appendix 13**)
26. Electrocardiogram (ECG)- standard 12-lead
27. Chest X-ray (2 views anterior-posterior and lateral)
28. Retinal examination with fluorescein angiography and fundus photos, performed by an ophthalmologist
29. PSA blood test for male subjects 45 years of age and older
30. Mammogram for female subjects 40 years of age and older; A mammogram performed within 3 months of screening can be used for screening eligibility.
31. Pap smear for females who have not had a procedure within a year of screening
32. Flexible sigmoidoscopy for subjects 50 years of age and older; A sigmoidoscopy or colonoscopy performed within a year of screening can be used for screening eligibility. Subjects with a history of benign colon polyps removed that do not meet exclusion criteria, must have documented evidence of a normal colonoscopy within the last 12 months. Subjects who have benign colon polyps removed during a sigmoidoscopy performed in the screening period that do not meet exclusion criteria need to have a colonoscopy performed and any additional polyps removed.
33. Fecal Occult Blood Test (FOBT) for subjects 50 years of age and older; (Note: It is acceptable to perform the FOBT test without altering the subject's anti-platelet medication. If the subject tests positive, anti-platelet medications should be stopped for 3 days and the test should be repeated.) *Note: Only a sigmoidoscopy is required at screening, however if a colonoscopy is performed during screening, the FOBT test is not required.*

7.2. Subject Enrollment Procedures

For the subject to be enrolled, the clinical site must fax all required documentation, signed by the investigator, to Sangamo BioSciences at (510) 970-6009. The Medical Monitor will review the enrollment form and supportive clinical documentation to confirm eligibility. If the subject meets the enrollment criteria, the subject will be approved for entry into the treatment phase of the protocol and will be randomized to one of the two treatment groups. A product kit number will be assigned to the subject. Please refer to the **Study Reference Manual** for additional details.

7.3. Baseline Duplicate Assessments

After a subject is enrolled and randomized into the study, baseline duplicate measurements will be performed within 14 days prior to the Day 0 visit.

NOTE: Duplicate assessments cannot be performed on the same day (there must be a minimum of 1 day and a maximum of 14 days from the other assessment).

The following duplicate assessments must be performed in enrolled and randomized subjects within 14 days prior to the Day 0 visit.

1. Electrophysiological testing of the sural and peroneal nerves
2. Quantitative sensory testing (QST)
3. Lower extremity neurological examination

7.4. Schedule for Treatment Period

7.4.1 Day 0 - Baseline Evaluations (to be completed prior to treatment)

1. Review eligibility (inclusion and exclusion criteria)
2. Vital signs: blood pressure (systolic and diastolic), pulse, and temperature
3. Weight
4. Assessment for ischemic ulcers (present, absent, location, number, size), gangrene (present, absent), and lower extremity edema
5. CBC with WBC differential and platelet count
6. Coagulation tests PT/INR and PTT
7. Serum chemistry: electrolytes (Na, K, CO_2, Cl), CPK, CPKmb, troponin, creatinine, BUN, glucose, uric acid, total bilirubin, ALP, ALT (or SGPT), AST (or SGOT), LDH, albumin, calcium, and total protein
8. Urine pregnancy test – must be negative prior to drug administration
9. Spot urine test for microalbumin/creatinine
10. Blood sample collection - 6 mL blood (3 mL plasma) sample for PCR assay and 10 mL blood (5 mL serum) sample for serum Intracellular Adhesion Molecule (ICAM) level, cytokine assay, immunogenicity testing and detection of inflammatory markers
11. Electrophysiological testing of the sural and peroneal nerves
12. Quantitative sensory testing
13. Lower extremity neurological examination, including gait
14. 3 mm skin biopsy
15. Neuropathy Total Symptom Score (NTSS-6)
16. Visual Analog Scale for Pain Intensity (VASPI)
17. NeuroQoL
18. SF-36

19. Assessment of concomitant medications
20. Subjects counseled to remain compliant with ACS guidelines and followup
21. Drug administration

7.4.2 Day 0 – 2 hours post-treatment

1. AE query and appropriate medical evaluation if positive
2. Blood sample collection. 6 mL blood (3 mL plasma) sample for PCR assay and 10 mL blood (5 mL serum) sample for cytokine assay, immunogenicity testing and detection of inflammatory markers.

7.4.3 Day 60 - Evaluations to be completed prior to treatment (visit window may be ± 7 days)

1. Vital signs: blood pressure (systolic and diastolic), pulse, and temperature
2. Weight
3. Assessment for ischemic ulcers (present, absent, location, number, size), gangrene (present, absent), and lower extremity edema.
4. CBC with WBC differential and platelet count
5. Serum chemistry: electrolytes (Na, K, CO_2, Cl), CPK, CPKmb, troponin, creatinine, BUN, glucose, uric acid, total bilirubin, ALP, ALT (or SGPT), AST (or SGOT), LDH, albumin, calcium, and total protein
6. Spot urine test for microalbumin/creatinine
7. Blood sample collection: 6 mL blood (3 mL plasma) sample for PCR assay and 10 mL blood (5 mL serum) sample for cytokine assay, immunogenicity testing and detection of inflammatory markers.
8. Global assessment
9. AE query and appropriate medical evaluation if positive
10. Assessment of concomitant medications
11. Drug administration

7.4.4 Day 60 – 2 hours post-treatment

1. AE query and appropriate medical evaluation if positive
2. Blood sample collection. 6 mL blood (3 mL plasma) sample for PCR assay and 10 mL blood (5 mL serum) sample for cytokine assay, immunogenicity testing and detection of inflammatory markers.

7.4.5 Day 90 (visit window may be ± 7 days)

1. Vital signs: blood pressure (systolic and diastolic), pulse, and temperature
2. Weight
3. Assessment for ischemic ulcers (present, absent, location, number, size), gangrene (present, absent), and lower extremity edema.
4. CBC with WBC differential and platelet count
5. Serum chemistry: electrolytes (Na, K, CO_2 , Cl), CPK, CPKmb, troponin, creatinine, BUN, glucose, uric acid, total bilirubin, ALP, ALT (or SGPT), AST (or SGOT), LDH, albumin, calcium, and total protein
6. HgbA1c
7. Spot urine test for microalbumin/creatinine
8. Blood Sample collection: 6 mL blood (3 mL plasma) sample for PCR assay and 10mL blood (5 mL serum) sample for cytokine assay, immunogenicity testing and detection of inflammatory markers.
9. Electrophysiological testing of the sural and peroneal nerves

10. Quantitative sensory testing (QST) of bilateral lower extremities
11. Lower extremity neurological examination
12. Neuropathy Total Symptom Score (NTSS-6)
13. Visual Analog Scale for Pain Intensity (VASPI)
14. NeuroQoL
15. Global assessment
16. AE query and appropriate medical evaluation if positive
17. Assessment of concomitant medications

7.4.6 Day 120 - Evaluations to be completed prior to treatment (visit window may be ± 7 days)

1. Vital signs: blood pressure (systolic and diastolic), pulse, and temperature
2. Weight
3. Assessment for ischemic ulcers (present, absent, location, number, size), gangrene (present, absent), and lower extremity edema.
4. CBC with WBC differential and platelet count
5. Serum chemistry: electrolytes (Na, K, CO_2 , Cl), CPK, CPKmb, troponin, creatinine, BUN, glucose, uric acid, total bilirubin, ALP, ALT (or SGPT), AST (or SGOT), LDH, albumin, calcium, and total protein
6. HgbA1c
7. Spot urine test for microalbumin/creatinine
8. Blood sample collection: 6 mL blood (3 mL plasma) sample for PCR assay and 10 mL blood (5 mL serum) sample for cytokine assay, immunogenicity testing and detection of inflammatory markers.
9. Global assessment
10. AE query and appropriate medical evaluation if positive
11. Assessment of concomitant medications
12. Drug administration

7.4.7 Day 120 – 2 hours post-treatment

1. AE query and appropriate medical evaluation if positive
2. Blood sample collection. 6 ML blood (3 mL plasma) sample for PCR assay and 10 mL blood (5 mL serum) sample for cytokine assay, immunogenicity testing and detection of inflammatory markers.

7.4.8 Day 150 (visit window may be ± 7 days)

1. 3 mm skin biopsy
2. Global assessment
3. AE query and appropriate medical evaluation if positive
4. Assessment of concomitant medications

7.5. Schedule for Follow-Up Period

7.5.1 Day 180 (visit window may be ± 7 days)

1. Vital signs: blood pressure (systolic and diastolic), pulse, and temperature
2. Weight

3. Ischemic ulcers (present, absent, location, number, size)
4. Gangrene (present, absent)
5. Assessments for lower extremity edema.
6. CBC with WBC differential and platelet count
7. Serum chemistry: electrolytes (Na, K, CO_2, Cl), CPK, CPKmb, troponin, creatinine, BUN, glucose, uric acid, total bilirubin, ALP, ALT (or SGPT), AST (or SGOT), LDH, albumin, calcium, and total protein
8. HgbA1c
9. Spot urine test for microalbumin/creatinine
10. Urine pregnancy test
11. Blood sample collection: 6 mL blood (3 mL plasma) sample for PCR assay and 10 mL blood (5 mL serum) sample for serum Intracellular Adhesion Molecule (ICAM) level, cytokine assay, immunogenicity testing and detection of inflammatory markers.
12. Electrophysiological testing of the sural and peroneal nerves
13. Quantitative sensory testing (QST) of bilateral lower extremities
14. Lower extremity neurological examination, including gait
15. 3 mm skin biopsy
16. Neuropathy Total Symptom Score (NTSS-6)
17. Visual Analog Scale for Pain Intensity (VASPI)
18. NeuroQoL
19. SF-36
20. Global assessment
21. Retinal examination with fluorescein angiography and fundus photos, performed by an ophthalmologist **(Visit window for the retinal examination is ±14 days)**
22. AE query and appropriate medical evaluation if positive
23. Assessment of concomitant medications

7.5.2 Day 180 ± 14 days: The following **duplicate** assessments must be performed ± 14 days of the Day 180 visit. Duplicate assessments cannot be performed on the same day (there must be a minimum of 1 day and a maximum of 14 days from the other assessment).

1. Electrophysiological testing of the sural and peroneal nerves
2. Quantitative sensory testing
3. Lower extremity neurological examination

7.5.3 Day 240 (visit window may be ± 7 days)

1. Vital signs: blood pressure (systolic and diastolic), pulse, and temperature
2. Weight
3. Assessment for ischemic ulcers (present, absent, location, number, size), gangrene (present, absent), and lower extremity edema.
4. CBC with WBC differential and platelet count
5. Serum chemistry: electrolytes (Na, K, CO_2, Cl), CPK, CPKmb, troponin, creatinine, BUN, glucose, uric acid, total bilirubin, ALP, ALT (or SGPT), AST (or SGOT), LDH, albumin, calcium, and total protein
6. HgbA1c

7. Spot urine test for microalbumin/creatinine
8. Blood sample collection: 6 mL blood (3 mL plasma) sample for PCR assay and 10 mL blood (5 mL serum) sample for cytokine assay, immunogenicity testing and detection of inflammatory markers.
9. Global assessment
10. AE query and appropriate medical evaluation if positive
11. Assessment of concomitant medications

7.5.4 Day 360 (visit window may be ± 14 days)

1. General physical examination for all subjects, including a digital rectal exam for male subjects only.
2. Vital signs: blood pressure (systolic and diastolic), pulse, and temperature
3. Weight
4. Assessment for ischemic ulcers (present, absent, location, number, size), gangrene (present, absent), and lower extremity edema.
5. CBC with WBC differential and platelet count
6. Coagulation tests PT/INR and PTT
7. Serum chemistry: electrolytes (Na, K, CO_2, Cl), CPK, CPKmb, troponin, creatinine, BUN, glucose, uric acid, total bilirubin, ALP, ALT (or SGPT), AST (or SGOT), LDH, albumin, calcium, and total protein
8. HgbA1c
9. Direct LDL cholesterol (subject should be fasting from midnight on)
10. Spot urine test for microalbumin/creatinine
11. Urine pregnancy test
12. Blood sample collection: 6 mL blood (3 mL plasma) sample for PCR assay and 10 mL blood (5 mL serum) sample for serum Intracellular Adhesion Molecule (ICAM) level, cytokine assay, immunogenicity testing and detection of inflammatory markers.
13. Electrophysiological testing of the sural and peroneal nerves
14. Quantitative sensory testing (QST) of bilateral lower extremities
15. Lower extremity neurological examination, including gait
16. 3 mm skin biopsy
17. Neuropathy Total Symptom Score (NTSS-6)
18. Visual Analog Scale for Pain Intensity (VASPI)
19. NeuroQoL
20. SF-36
21. Global assessment
22. ECG – standard 12-lead
23. Retinal examination with fluorescein angiography and fundus photos, performed by an ophthalmologist
24. PSA blood test for male subjects 45 years of age and older
25. Mammogram for female subjects 40 years of age and older
26. FOBT for subjects 50 years of age and older
27. Subject counseled to remain compliant with ACS guidelines and followup
28. AE query and appropriate medical evaluation if positive

29. Assessment of concomitant medications

7.5.5 Day 360 ± 14 days: The following **duplicate** assessments must be performed ± 14 days of the Day 360 visit. Duplicate assessments cannot be performed on the same day (there must be a minimum of 1 day and a maximum of 14 days from the other assessment).

1. Electrophysiological testing of the sural and peroneal nerves
2. Quantitative sensory testing
3. Lower extremity neurological examination

8. CRITERIA FOR WITHDRAWAL FROM THE STUDY

8.1. Discontinuation from Study Treatment and Follow-up of Subjects

Subjects will be strongly encouraged to continue with follow-up safety evaluations if they withdraw consent from the study. If a subject discontinues from the study a conference between the investigator and medical monitor will take place to ensure that all subjects will comply with the follow-up safety evaluations of the protocol. Participation in this study will not prejudice the subject's future medical care.

Subjects will be assessed for treatment-related adverse events and disease status.

Subjects who discontinue during the post-treatment follow-up period will not be replaced; therefore, study centers are encouraged to carefully select subjects who would be likely to complete all study procedures.

9. ADMINISTRATION OF STUDY DRUG

9.1. Product Description

The SB-509 drug product is a clear, colorless, and sterile liquid supplied in single use glass vials. Each 3 mL glass vial is filled with 2.2 mL of drug product that contains 2 mg/mL of pV-32Ep65 DNA plasmid, 2 mM Tris, 150 mM sodium chloride and 5% (w/v) poloxamer 188 at pH 8.0. It is intended for intramuscular administration.

9.2. Description and Manufacturer of Drug Substance

The drug substance containing the active ingredient, plasmid pV-32Ep65, is manufactured under cGMP at Althea Technologies, Inc., San Diego, CA.

pV-32Ep65 is a typical eukaryotic expression vector bearing the CMV immediate early enhancer/promoter and a polyadenylation site from the bovine growth hormone gene. The vector backbone, pVAX-1 (3.0 kb), has been specifically designed for use in the development of DNA vaccines.

pV-32Ep65 is a 4106 base-pair DNA plasmid that encodes an engineered ZFP-TF. The therapeutic gene encodes a 3-finger DNA binding ZFP with a transactivation domain and nuclear localization signal (NLS) and was cloned into a pVAX-1 vector backbone. The ZFP-TF is a 378 amino acid protein that is composed of:

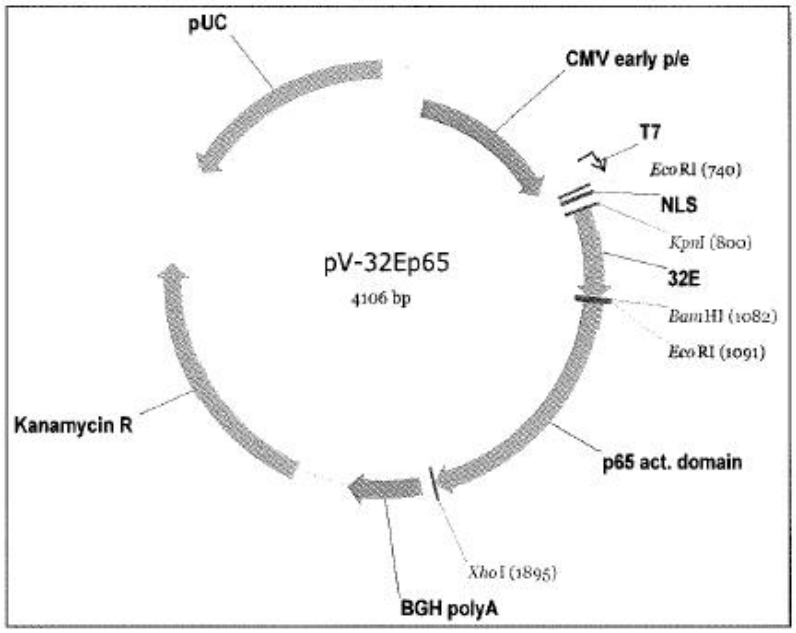
a) the NLS of the long T antigen of SV40

b) a designed 3-finger ZFP (32E) that binds to a 9 base pair target present in the human VEGF-A promoter region (GGGGGTGAC)

c) the transactivation domain from the p65 subunit of the human transcription factor NF-KB

The key features of pV-32Ep65 are illustrated in the plasmid map shown in **Figure 5**.

Figure 5. Circular Plasmid Map of pV-32Ep65



9.3. SB-509 and Placebo Study Drug Composition

SB-509 is a purified, double-stranded bacterial DNA plasmid. It is formulated as a sterile, injectable solution and is filled 2.2 mlin 3-mL vials. The drug product composition is described in **Table 1**. It consists of pV-32Ep65 DNA plasmid (2 mg/ml), Poloxamer 188 (5% w/v), NaCI (150 mM), 2 mM Tris-HCI, pH 8.0, and sterile water for injection.

Table 1. Composition of SB-509

Component	Unit Formula (mg/mL)
pV-32Ep65 (plasmid DNA)	2 mg
Sodium chloride, USP (150mM NaCI)	8.76 mg
Poloxamer 188, NF (5%w/v)	50 mg
Tromethamine, pH 8.0, USP (2 mM Tris-HCI)	0.242 mg
Sterile Water for Injection, USP	q.s. to 1.0 mL

The final drug product is tested for appearance, identity, potency, concentration, purity, pH, conductivity, endotoxin, and sterility.

Normal saline (0.9% NaCI) will be provided in identical 3-mL vials and will serve as the placebo.

9.4. Inventory, Storage, and Handling of the Drug Product

Labeled product will be stored at Fisher Clinical Services for distribution to the clinical sites. Sangamo BioSciences requires its sponsored investigators to maintain adequate drug inventory and security at all times (Appendix 4). Therefore, SB-509 and placebo will be supplied as a frozen liquid "to deliver"

2.0 ml. Upon receipt of labeled product, the investigator or designated individual (e.g., pharmacist) will check the details of the supplies and document receipt. As a double-blind controlled trial, the clinical supplies will be in a blinded packaging configuration containing 18 vials per kit. One kit will be assigned for each dose.

The investigator will store both SB-509 and the placebo in a locked –20°C freezer and will monitor and maintain a log of the temperature. Immediately before use, vials will be thawed at room temperature and allowed to equilibrate to room temperature for at least 10 minutes. Once thawed, vials will not be reused on subsequent days.

Empty vials and any remaining product in the used vials will be stored at room temperature at the clinical sites and must be kept with original carton. Vials should not be discarded until the Sangamo BioSciences monitor reviews the drug accountability log.

Accessibility to labeled product should only be to those individuals authorized by the investigator to dispense this study drug.

The investigator or designated individual will maintain an inventory. A drug accountability log will be provided to the pharmacist. This inventory will include the description and quantity of labeled product received during the course of this study, as well as a record of the labeled product that is dispensed. This inventory record shall indicate the quantity and description of labeled product on hand at any time during the course of this study. A Sangamo BioSciences monitor will review this inventory during interim monitoring visits.

At the conclusion or termination of this study, return or destruction of all drug supplies must be coordinated with Sangamo BioSciences. Please see the Study **Reference Manual** for additional details.

The investigator agrees not to supply labeled product to any person other than study personnel and subjects in this study.

In accordance with Good Clinical Practice, it is Sangamo BioSciences policy always to investigate suspected cases of fraud.

16.11 Termination of the Study

Sangamo BioSciences retains the right to terminate the study and remove all study materials at any time. Specific instances that may precipitate such termination are as follows:

- Completion of the study at an investigational site
- Unanticipated adverse medical experiences in this or other studies indicating a potential health hazard caused by the investigational drug
- Significant protocol deviation and/or lack of compliance and cooperation on the part of the investigator; such as failure to obtain signed informed consent prior to initiating study-related procedures, unsatisfactory subject enrollment with regard to quality or quantity, deviation from protocol requirements without prior approval from Sangamo BioSciences, or inaccurate and/or incomplete data recording on a recurrent basis
- Investigator withdrawal from participation in the study
- Withdrawal of investigational drug from investigational use
- Termination of this study by Sangamo BioSciences

16.12 Record Retention

The investigator should retain essential documents according to 21 CFR 312.62(c) and ICH Guidelines for Good Clinical Practices (E6), until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with Sangamo BioSciences. It is the responsibility of Sangamo BioSciences to inform the investigator as to when these documents no longer need to be retained.

Records to be retained by the investigator include, but are not restricted to, protocols; amendments; investigator's brochure; Investigator agreement (including financial agreement); IRB/IEC/IBC applications; approvals and composition; copies of the Form FDA 1572; pre-study and follow-up financial disclosure; completed, signed, and dated informed consents; subject medical records; case report forms;

monitoring log; serious adverse event reports; IRB notifications; subject screening/enrollment log; study personnel signature log; drug accountability record and logs; clinical laboratory normal ranges and accreditation certificate; and all correspondence between study monitor, study sponsor, and IRB/IEC/IBC.

Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution, or private practice, but not less than 15 years.

16.13 Confidentiality

Subject medical information obtained for the purpose of this trial is confidential, and disclosure to third parties, other than those noted below, is prohibited. Upon the subject's request and receipt of written permission, medical information may be given to his/her personal physician or other appropriate medical personnel responsible for the subject's welfare.

Data generated for this study must be available for inspection upon request to representatives of the FDA, other national or local health authorities, Sangamo BioSciences, and the associated IRB/IEC/IBC.

Release of research results or data that reveal subject names or other identifiers, such as photographs, audiotapes, or videotapes, must be carried out in accordance with the Department of Health and Human Services' proposed Standards for Privacy of Individual Health information, 45 CFR 164.508. Written authorization must be obtained from the subject and the IRB/IEC/IBC prior to the release of such information. Identifiable subject data may not be used for the purpose of promoting the study drug.

16.14 Publication Statement

It is intended that the results of the study be published in scientific literature. Results may also be used in submissions to regulatory authorities. The following conditions are to protect commercial confidential materials (e.g., patents), not to restrict publication.

All information concerning the labeled product under study (such as patent applications, formulae, basic scientific data, or formulation information supplied to the investigator and not previously published) is considered confidential by Sangamo BioSciences and shall remain the sole property of Sangamo BioSciences.

It is understood by the investigator that the results of this clinical trial may be used by Sangamo BioSciences in registration documents for regulatory authorities in the U.S. or abroad, or for public dissemination in the form of papers, abstracts, posters, or other informational materials to be presented at scientific meetings, or published in professional journals, or as a part of an academic thesis by an investigator.

All proposed publications, papers, abstracts, or other written materials related to the study, or an outline of any proposed oral presentations, shall be submitted to

Sangamo BioSciences for approval at least 45 days prior to (1) submission for publication or (2) any proposed oral disclosure to a third party. Sangamo BioSciences shall have the right to review and comment on such written material or outline, and to confirm the accuracy of the data described therein by comparison with that collected during the course of this study. In the event that Sangamo BioSciences determines that an enabling description of patentable subject matter is contained in such written material or outline, it shall notify the clinical site(s) within 1 month after receipt by Sangamo BioSciences, and Sangamo BioSciences will have an additional 90 days for review.

In the event of publication of multi-center data, the number of subjects enrolled by each investigator will usually determine the order of participation, unless otherwise agreed upon by the investigators and Sangamo BioSciences.

17 STUDY FUNDING

The costs necessary to perform the study will be agreed to by the investigator and/or the management of the study facility and will be documented in a separate financial agreement. All financial agreements will be signed by the investigator and Sangamo BioSciences.

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APPENDIX 1:SCHEDULE OF EVENTS

Visit Number	VO	VI/V2		V3		V4	V5		V6	V7/V8	V9	V10/11
		Dose 1		Dose 2			Dose 3					
Visit	Day-84 Screening	Day 0	Day 0 (2 hours post-tx)	60	Day 60 (2 hours post-tx)	90	120	Day120 (2 hours post-tx)	150	180	240	360n
Informed consent	X											
Eligibility	X	X										
Medical history	X											
Physical exam[a]	X											X
Vital signs[b]	X	X		X		X	X			X	X	X
Height	X											
Weight	X	X		X		X	X			X	X	X
Ischemic ulcers/Gangrene		X		X		X	X			X	X	X
Lower extremity edema	X	X		X		X	X			X	X	X
CBC with WBC differential and platelet count	X	X										X
PT/INR and PTT	X	X		X		X	X			X	X	X
Serum chemistry[c]	X					X	X			X	X	X
HgbA1c	X											
HIV serology	X											
Serum pregnancy test	X											
Urine pregnancy test[d]		X								X		X
Urinalysis[e]	X											
Spot urine test for microalbumin/creatinine	X	X		X		X	X			X	X	X
Blood sample[f]	X	X	X	X	X	X	X	X		X	X	X
Drug administration		X		X			X					
Electrophysiological testing (sural and peroneal nerves)[g]	X	**XX***				X				**XX***		**XX***
QST[g]	X	**XX***				X				**XX***		**XX***
Lower extremity neurological examination	X	**XX***				X				**XX***		**XX***
3 mm skin biopsy (IENFD)	X	X							X	X		X
NTSS-6	X	X				X				X		X
VASPI	X	X				X				X		X
Neuro-QoL	X	X				X				X		X
SF-36	X	X								X		X
Global assessment				X		X	X		X	X	X	X
12-lead ECG[h]	X											X
Chest X-ray[h]	X											
Retinal examination and photos	X									X		X
PSA[i]	X											X
Mammogram[i]	X											X
Pap Smear[k]	X											

Visit Number	VO	VI/V2		V3		V4	V5		V6	V7/V8	V9	V10/11
		Dose 1		Dose 2			Dose 3					
Visit	Day-84 Screening	Day 0	Day 0 (2 hours post-tx)	60	Day 60 (2 hours post-tx)	90	120	Day120 (2 hours post-tx)	150	180	240	360n
FOBT[l]	X											X
Sigmoidoscopy[l]	X											
AEs[m]			X	X	X	X	X	X	X	X	X	X
Assessment of concomitant medications	X	X		X		X	X		X	X	X	X
Subject counseled to remain compliant with ACS guidelines and follow-up		X										X

* **Duplicate assessments (XX) must be performed in enrolled and randomized subjects within14 days prior to the Day 0 visit, or performed within ± 14 days of the projected visit day (Day 180 and Day 360).**

[a] Physical examination for all subjects to include a digital rectal examination for male subjects only.

[b] Vital signs to include systolic/diastolic pressure, pulse, and temperature.

[c] Serum chemistry: electrolytes (Na, K, C02, Cl), CPK, CPKmb, troponin, creatinine, BUN, glucose, uric acid, total bilirubin, ALP, ALT (or SGPT), AST (or SGOT), LDH, albumin, calcium, and total protein; In addition: On screening day: vitamin B12, T4/TSH, direct LDL; On Day 360: direct LDL

[d] Urine pregnancy test: result must be negative prior to drug administration on Day 0.

[e] Urinalysis: test for the presence of glucose, protein, bilirubin, blood, pH, and specific gravity.

[f] Blood samples will be used for PCR assay, cytokine assay, immunogenicity testing, ICAM assay, and detection of inflammatory markers.

[g] The screening (Day -84) disease activity assessments may be done in stages, but they must be completed prior to Day 0.

[h] If none available in the preceding 12 weeks.

[I] PSA blood test for male subjects age 45 years or older.

[j] Mammogram: for females older than 40 years of age. A mammogram performed within 3 months of screening can be used for screening eligibility.

[k] Pap smear for females who have not had a procedure within a year of screening.

[l] FOBT for subjects 50 years of age or older. Only a sigmoidoscopy is required at screening, however if a colonoscopy is performed during screening, an FOBT is not required. Sigmoidoscopy for subjects 50 years of age or older. A sigmoidoscopy or colonoscopy performed within a year of screening may be used for screening eligibility.

[m] Query for AEs and appropriate medical evaluation if positive.

[n] Day 360 or early termination.

9.5. SB-509 Administration

9.5.1. Overview

150 subjects will be randomized in a 1:1 ratio stratified by study site and screening IENFD (<9, ≥9) to treatment with SB-509 or placebo:

1) SB-509 treatment: 60 mg of SB-509 on Day 0, Day 60 and Day 120.

2) Placebo on Day 0, Day 60 and Day 120.

30 mg of SB-509 or an equal volume of placebo will be injected (IM) into each lower limb for a total dose of 60 mg. Each subject will receive a total of three treatments. The drug will be supplied in 3-mL vials and will be injected in 0.5 or 1 mL volumes each injection in the lower leg and thigh, respectively. See **Appendix 4** for detailed pharmacy preparation and subject injection instructions.

Injection Procedure

The injection site in the muscle will allow the deposit of 0.5 mL and 1.0 mL doses of study drug by inserting a needle along the long axis of the muscle fiber (i.e., parallel with the femoral artery) up to its hub (the needle's full insertion point) and depositin 0.5 mL doses to the lower leg injection sites or 1.0 mL doses to the thigh injection sites.

9.5.2. Injection Needles and Volumes for Each Injection Site

Needles (25 gauge; 1- to 1.5-inch or 27 gauge; 1.25 inch) with 1 mL syringes are to be used. Care should be taken to avoid injection into any area of skin ulceration.

9.6. Precautions

SB-509 is an investigational drug, and there is a possible risk of anaphylaxis. SB-509 should be administered in a setting where emergency treatment is available for anaphylaxis. If any serious allergic or anaphylactoid reaction occurs, administration should be immediately discontinued and appropriate therapy initiated. Subjects must remain in the clinic for 2 hours after administration of SB-509.

9.7. Premedications

NSAIDs or acetaminophen may be taken prior to or after injections for pain. Diphenhydramine, oral or topical, may be used for pruritus.

9.8. Dose Modifications

No dose modifications will be allowed.

10. SAFETY

10.1. Potential Risks

10.1.1. SB-509

SB-509 has been administered to a total of 164 subjects with diabetic peripheral neuropathy in four clinical trials. Twenty-seven subjects received SB-509 as a single treatment; 75 subjects as a repeat dosing (Days 0, 60, and 120), and 30 subjects as a repeat dosing (Days 0 and 90). For the single treatment, separate groups received increasing doses of 1 mg, 5 mg, 15 mg, 30 mg, or 60 mg. For the repeat dosing, the dose was 60 mg. The length of follow-up was 180 days after the single dose, and 360 days after the first dose of the repeat dosing schedule.

SB-509 was well-tolerated. Most of the AEs were injection site reactions, which were mild to moderate in severity. There were no drug-related SAEs, dose-limiting toxicities, deaths, or discontinuations of study drug because of AEs. Immunogenicity was not triggered by SB-509. There was no evidence of retinal neovascularization or tumorigenesis.

Further information is provided in the **SB-509 DN Clinical Investigator's Brochure**.

10.1.2. Vascular Endothelial Growth Factor

SB-509 induces the production of all isoforms of VEGF. Clinical studies have been performed with recombinant human VEGF and VEGF plasmid DNA gene therapy. A review of the previous human experience with VEGF is in the **SB-509 DN Clinical Investigator's Brochure**. The major potential risk is the augmentation of growth of tumors and a reversible leg edema with VEGF plasmid DNA gene therapy.

10.1.3. Poloxamer 188

Poloxamer 188 is being used as a delivery enhancer in SB-509. It is a complex polymer that is commonly used in stool softeners and foods. It has an effect on red blood cell elasticity and has been used parenterally for the treatment of Sickle Cell Crisis. A review of the previous human experience is in the **SB-509 DN Clinical Investigator's Brochure**. The major risk is an idiosyncratic allergic reaction that would be associated with any component of the formulation.

10.1.4. Gene Transfer

There is a risk that people who receive gene transfer may develop new tumors. This risk is primarily associated with viral gene transfer vectors that integrate into the cellular DNA and may induce carcinogenesis. This risk with plasmid DNA gene transfer is extremely low.

10.1.5. Skin Biopsy

Skin biopsies will be obtained during the trial for the analysis of intraepidermal nerve fiber density to see if treatment with SB-509 will affect the number of epidermal nerve fibers in the skin. The size of the biopsies is 3 mm in diameter. Side effects include pain, bleeding, low rates of infection (1/500 biopsies), and, rarely, depigmented skin at the healed biopsy site.

11. EFFICACY

11.1. Potential Benefits

It is likely that the subjects receiving this treatment will not derive any benefit from their participation in this trial. However, based on the results to date, subjects receiving SB-509 treatment may have improvements in nerve conduction velocities and vibration perception threshold.

11.2. Efficacy Criteria

11.2.1. Clinical Evaluation

A neurological evaluation, electrophysiological test, and quantitative sensory testing will be performed at screening, on Day 0 pre-treatment, on Days 90, 180, and 360. Duplicate measurements will be completed within 14 days prior to the Day 0 visit, and ±14 days of Day180 and Day 360 visits. **Note**: Neurological evaluation must be performed by a qualified medical doctor

11.2.2. Disease Assessment

Diabetic peripheral neuropathy will be evaluated by using the following scales and modalities based on the neurological examination data, electrophysiological testing data, skin biopsy data, subject neurological questionnaire, subject pain assessment, and Quality of Life questionnaires.

- Electrophysiological testing using nerve conduction velocity (NCV) studies (**Appendix 7**)
- Signs using Neuropathy Impairment Score – Lower Limb (NIS-LL) (**Appendix 5**)
- Lower Extremity Neurological Sensory Exam (**Appendix 6**)
- Quantitative sensory testing (QST) with the Vibratron II instrument (**Appendix 8**)
- lntraepidermal Nerve Fiber Density (IENFD) (**Appendix 9**)
- Neuropathy Total Symptom Score (NTSS-6) (**Appendix 10**)
- Visual analog scale for pain intensity (VASPI) (**Appendix 11**)

- Neuro-Qo(**Appendix 12**)
- SF-36 (**Appendix 13**)
- Global Assessment (**Appendix 14**)

12. CONCOMITANT MEDICATIONS

The investigator will record all concomitant medications, including those given for treatment of adverse events on the concomitant medication page in the subject's case report form. Any medication taken by the subject from screening throughout the course of the study, including over-the-counter medicinal products, dietary supplements, and herbal medications, should be recorded on this form. Medications may be adjusted as needed throughout the course of the study.

Subjects will be evaluated for pain, and use of pain medications will be recorded from the time of the first treatment throughout the course of the study.

If required after Day 0, antibiotics must be completed at least 2 weeks prior to the dose and the subject must be asymptomatic prior to dosing.

13. ADVERSE EVENTS

13.1. Adverse Event Reporting Period

The screening period is defined as starting with screen procedures and ending with the first treatment. The treatment period is defined as starting with the first treatment and ending 4 weeks after the last treatment. The follow-up period is defined as starting 4 weeks after the last treatment until the Day 360 visit.

During the screening period, study procedural related adverse events will be reported. During both the treatment and follow-up periods, subjects will be queried and events will be assessed at each clinic visit. All adverse events will be reported. Subjects will be reminded to immediately report any Serious Adverse Event to the investigator.

13.2. Definitions

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject that is temporally related to protocol procedures, including the administration of a labeled product at any dose, but which does not necessarily have a causal relationship with the treatment.

The term adverse event also applies to laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant (e.g., that required unscheduled diagnostic procedures or treatment measures, or resulted in withdrawal from the study).

An adverse drug reaction (ADR) occurring in a clinical study is an untoward medical occurrence in a patient or clinical investigation subject that is possibly or probably causally related to the administration of a labeled product. Such ADRs are a subset of the adverse events defined above.

The term “adverse event” could include any of the following events which develop or increase in severity during the course of the study. Examples include:

- Any sign, symptom, or physical examination finding that worsens in nature, severity, or frequency compared to baseline. Whether thought to be related or unrelated to the condition under study
- Any clinically significant laboratory abnormality or laboratory abnormality that requires medication or hospitalization
- All reactions from study drug, including those occurring as a result of an overdose, abuse, withdrawal phenomena, sensitivity, or toxicity to study drug
- Concurrent illness
- Injury or accident

A pre-existing condition is one that is present prior to or at the start of the study and is to be reported as part of the subject's medical history. It should be reported as an adverse event only if the frequency, intensity, or the character of the condition worsen during study treatment.

An unexpected adverse event is one not identified in nature, severity, or frequency in the current protocol or the **SB-509 DN Clinical Investigator's Brochure.**

13.3. Recording of an Adverse Event

The principal investigator is responsible for evaluating all adverse events, obtaining supporting documents, and determining that documentation of the event is adequate. He/she is responsible for determining the severity and relationship to the investigational drug. The principal investigator may delegate these duties to sub investigators and must assure that these sub-investigators are qualified to perform these duties under the supervision of the principal investigator.

All adverse events will be recorded in the subject's case report form (CRF). The detailed description of the event will include appropriately graded severity of the adverse event and its relationship to the study drug.

Severity will be categorized by toxicity grade according to the revised NCI Common Terminology Criteria for Adverse Events v4.0 (CTCAE) (**Appendix 2**).

Adverse events not listed in the NCI CTCAE will be evaluated by using the following criteria:

- *Grade 1, Mild*: Subject is aware of signs and symptoms, are easily tolerated; usually transient and requiring no special treatment; does not interfere with usual daily activities
- *Grade 2, Moderate*: May be ameliorated by simple therapeutic measures; sufficient to restrict; should not prevent usual daily activities
- *Grade 3, Severe*: Incapacitating; inability to perform usual daily activities
- *Grade 4, Life-threatening/Disabling*: Subject was at risk of death or significant disability at the time of the event

The relationship of the adverse event to the investigational drug will be determined by the principal investigator and will be categorized as:

- *Not Related*: The adverse event is clearly related to other factors, such as the subject's clinical state, environmental factors, or other modes of therapy or concomitant drugs administered to the subject.
- *Related*: The adverse event is temporally associated with the use of the study drug, and/or a causal relationship between the study drug and the adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

All Grade 3 and 4 clinical laboratory results that represent an increase in severity from baseline will be reported as adverse events. A Grade 1 or 2 clinical laboratory abnormality should be reported as an adverse event only if it is considered clinically significant by the investigator.

In the event of death, the cause of death should be recorded as the adverse event and reported as an SAE (see **Section 14**). "Death" is not the adverse event; "death" is an outcome. A copy of the death certificate should be obtained. Because the long-term effects of gene transfer are not known, the NIH would like an autopsy in the event of death. If an autopsy is performed, a copy of the autopsy report should be obtained.

14. SERIOUS ADVERSE EVENT

14.1. Serious Adverse Event Reporting

"Serious" events, whether or not unexpected or considered to be associated with the use of the labeled product, must be communicated to Sangamo BioSciences upon discovery of the event, either by telephone or fax within 24 hours.

Medical Monitor:	Ely Benaim, M.D
Phone Number:	(510) 970-7868
	(510) 621-8533, mobile
Fax Number:	(510) 970-6009

The investigator is responsible for promptly notifying the Institutional Review Board (IRB) or Independent Ethics Committee (IEC), in accordance with local regulations, of all serious adverse events.

The National Institutes of Health (NIH) requires that all investigators participating in gene transfer research report all drug related serious adverse events immediately to the FDA, NIH, and Institutional Biosafety Committee (IBC). Sangamo BioSciences will assume responsibility for NIH and FDA reporting.

All "serious" events must be followed with appropriate medical management until resolved or stabilized.

14.2. Definitions

A "Serious" Adverse Event (SAE) is defined as any event that suggests a significant hazard, contraindication, side effect, or precaution. An SAE is also any adverse event or adverse drug reaction that, at any dose, results in the following outcomes:

- death
- life-threatening condition
- in-patient hospitalization or prolongation of an existing hospitalization
- persistent or significant disability/incapacity
- congenital anomaly/birth defect in the offspring of an exposed subject

An important medical event that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, it jeopardizes the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

A life-threatening adverse event is defined as any adverse experience that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

14.3. Recording of a Serious Adverse Event

Serious Adverse Events reported by telephone must be recorded on a written Serious Adverse Event Report Form, provided by Sangamo BioSciences. The SAE report form must be faxed to the medical monitor within 24 hours.

The medical monitor will then advise the investigator regarding the nature of any further information or documentation that is required. Follow-up reports must be submitted in a timely fashion as additional information becomes available.

15. STATISTICAL METHODS AND DATA ANALYSIS

15.1. Sample Size

The results from SB-509-601 showed a treatment effect of SB-509 in patients with baseline serum ICAM > 200 ng/mL. The change from baseline in sural NCV for treated patients showed an increase in m/s of 1.06 compared to a decrease in placebo of -1.18. With 150 patients (75 per group) the power to detect a similar difference with a standard deviation of 4 and alpha=0.05 is 93%, using Wilcoxon's rank-sum test.

15.2. Randomization

150 subjects will be randomized in a 1:1 ratio to treatment with SB-509 or placebo stratified by study site and screening IENFD (<9, ≥9):

1) SB-509 treatment: 60 mg of SB-509 on Day 0, Day 60 and Day 120.
2) Placebo on Day 0, Day 60 and Day 120.

15.3. Statistical Methods/Data Analysis

The statistical analyses will be reported using summary tables, figures, and data listings. Statistical tests will be two-sided at the alpha =0.05 significance level. All analyses and tabulations will be performed using SAS® or SPLUS. Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. Categorical variables will be summarized by counts and by percentages of subjects in corresponding categories. All raw data obtained from the case report forms as well as any derived data will be included in data listings.

All efficacy analyses will be performed on the intent-to-treat population. All safety analyses will be performed on all subjects that received any study medication.

All tables will report summary results by treatment and dose group.

15.4. Intent-to-Treat Population

All subjects enrolled and randomized will be included in the intent-to-treat population and analyzed by the treatment received at Day 0.

15.5. Subject Disposition

Summaries will include the number of randomized subjects, the number of subjects receiving study medication, the number of subjects completing the study, and the reasons for discontinuation.

15.6. Demographics

Demographic variables include age, sex, and race. Other baseline characteristics include medical history, physical exam, duration of diabetes, duration of neuropathic pain, resting ankle-brachial systolic pressure index, and baseline assessments of diabetic neuropathy by symptoms, by neurological examination, by lower extremity electrophysiological testing and by quantitative sensory testing.

15.7. Efficacy

The primary measurement of efficacy is:

· Sural Nerve Conduction Velocity (NCV)

The secondary measurements of efficacy are:

· Neuropathy Impairment Score-Lower Limb (NIS-LL)
· Lower Extremity Neurological Sensory Exam
· Motor Nerve Conduction Velocity (NCV)
· Quantitative Sensory Testing (QST)
· lntraepidermal Nerve Fiber Density (IENFD)
· Neuropathy Total Symptom Score (NTSS-6)
· Visual Analog Scale for Pain Intensity (VASPI)
· Quality of Life (QOL)- NeuroQoL and SF-36
· Global assessment

Primary Efficacy Analyses

The Day 180 change from baseline sural NCV measurements will be compared by treatment group using the Wilcoxon Rank-Sum test at an alpha level of 0.05

Secondary Efficacy Analyses

The Day 180 change from baseline sNCV will be compared by treatment group using the Cochran-Mantel-Haenszel test stratified by IENFD < 9 fiber/mm and ≥ 9 fiber /mm at an alpha level of 0.05.

For the following measures, the Day 180 change from baseline measures will be compared by treatment group using the Wilcoxon Rank-Sum test.

- Neuropathy Impairment Score-Lower Limb (NIS-LL)
- Lower Extremity Neurological Sensory Exam
- Motor Nerve conduction velocity (NCV)
- Quantitative Sensory Testing (QST)
- lntraepidermal Nerve Fiber Density (IENFD)
- Neuropathy Total Symptom Score (NTSS-6)
- Visual Analog Scale for Pain Intensity (VASPI)
- Quality of Life (QOL)- NeuroQoL and SF-36
- Global assessment

The effect of SB-509 versus placebo in subjects with moderately severe diabetic neuropathy will be compared using a multi-endpoint analysis that includes Neuropathy Impairment Score - Lower Limb (NIS-LL), Sural Nerve Conduction Velocity (NCV) and lntraepidermal Nerve Fiber Density (IENFD), as detailed by O'Brien (1984).

Exploratory

The efficacy variables will be organized by clinically meaningful groups of 4 or fewer endpoints and analyzed by treatment and dose group with a multiple endpoint analysis defined by O'Brien (1984). For each grouping of endpoints, subjects will be ranked separately by each component of the multiple endpoint and the sum of the ranks will be obtained for each subject. The sums of ranks by treatment group will be compared with a Wilcoxon Rank-Sum test.

15.8. Baseline Values

The baseline value for each variable is the last value recorded before the start of dosing. For NCV, QST, NIS-LL, and the lower extremity neurological sensory exam, the two measurements prior to dosing will be averaged for the baseline value.

15.9. Missing Data

Physically undetectable NCV measures will be imputed with the 1st percentile value of all measurable observations by nerve. For all other measures, no imputations for missing data will be made.

15.10. Safety

Safety assessment will occur on all subjects who received any study medication. Terminations/premature withdrawals, adverse events, concomitant medications, and laboratory data will be tabulated. Adverse events will be coded to a standard set of terms using the MedDRA dictionary. Frequency of adverse events will be compared using Fisher's exact test.

15.11. Laboratory Data

Laboratory data will be summarized for each time-point that specimens are collected. Change-from-baseline values may be calculated for selected laboratory parameters. (Baseline refers to blood drawn prior to the first study treatment.) Shift tables (change-from-baseline relative to the normal range) may be constructed for selected laboratory parameters.

16. STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

The investigator will ensure that the study is conducted in compliance with the protocol and according to ICH Guidelines for Good Clinical Practices (E6), the Declaration of Helsinki, and all regulatory and institutional requirements, including those for subject privacy, informed consent, IRB or IEC approval, and record retention.

A final study report will be prepared as part of Sangamo BioSciences' commitment to Good Clinical Practice.

16.1. Institutional Review Board/Institutional Ethics Committee

An Institutional Review Board should safeguard the rights, safety, and well being of all study subjects. In performing this study, both the investigator and sponsor endorse, as a minimum, the standards for conduct of clinical research activities as set forth in the Declaration of Helsinki and local country regulations. As such, this study must have the approval of a properly constituted IRB or IEC, with the investigator responsible for providing the IRB or IEC with all necessary documents for review.

This study will only be undertaken or investigational drug supplies shipped when full approval has been obtained from the appropriate IRB or IEC and a copy of the IRB or IEC approval letter has been received by Sangamo BioSciences. The approval letter must contain sufficient information to identify the version of both the protocol and subject information/informed consent, the date of the committee's approval, the chairperson's signature, and identify all study documents reviewed.

Protocol amendments must also be reviewed and approved by the IRB or IEC and must be received by Sangamo BioSciences before implementation.

Until written approval by the IRB or IEC has been received by the investigator, no subject may undergo any procedures solely for the purpose of determining eligibility for this study.

16.2. Informed Consent

According to 21 CFR Part 50.20, no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject or the subject's legally authorized representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative.

Sangamo BioSciences will provide the investigator with a template for the consent form. State and local laws and/or institutional requirements may require the disclosure of additional information in the informed consent. The proposed consent form must be submitted to Sangamo BioSciences prior to submission to the IRB or IEC to ensure that it meets Sangamo BioSciences' standards for consent forms.

The IRB or IEC must approve the consent form. A copy of the approved form must be submitted to Sangamo BioSciences prior to the initiation of the study. Prior to the initiation of any procedures or treatment relating to the study, informed consent shall be documented by the use of a written consent form approved by the IRB and signed and dated by the subject or the subject's legally authorized representative at the time of consent. A copy of the signed informed consent will be given to the person signing the form. The investigator must keep each subject's signed consent form on file for inspection by a regulatory authority at any time.

16.3. Study Amendments

Any changes to this protocol will be initiated by Sangamo BioSciences. Approval of the amendment by the investigator's IRB must be obtained before implementation, with the following exception:

- When necessary to eliminate apparent immediate hazard to the subject

All amendments must be signed and dated by Sangamo BioSciences. Sangamo BioSciences will notify other investigators using this protocol.

16.4. Study Drug Accountability

The investigator must ensure that subjects receive study drug only from personnel who fully understand the procedures for dosing and administering the drug.

The investigator or designated individual will maintain an inventory. A drug accountability log will be provided to the pharmacist or designated personnel. This inventory will include the description and quantity of labeled product received during the course of this study, as well as a record of the labeled product that is dispensed. This inventory record shall indicate the quantity and description of labeled product on hand at any time during the course of this study. Empty vials and any remaining product in the used vials will be stored at room temperature at the clinical sites and will be kept in the original carton. Vials should not be discarded until the Sangamo BioSciences monitor reviews the drug accountability log. A Sangamo BioSciences monitor will review this log during interim monitoring visits.

Drug accountability records must be readily available for inspection by representatives of Sangamo BioSciences and are open to inspection by regulatory authorities at any time.

Return or destruction of all drug supplies must be coordinated with Sangamo BioSciences. Please see the **Study Reference Manual** for additional details.

16.5 Study Personnel

The investigator should maintain a list of appropriately qualified persons who are delegated to perform significant study-related studies. In addition, the investigator should maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on the case report forms.

The investigator is responsible for informing the subject's primary care physician that the subject is participating in a clinical study. This should only be done after agreement from the subject.

16.6 Monitoring the Study

Sangamo BioSciences, as sponsor of this study, is responsible to regulatory authorities for ensuring the proper conduct of the study as regards protocol adherence and validity of the data recorded on the case report forms presented to the regulatory authorities. Sangamo BioSciences has therefore assigned a clinical monitor and a medical monitor to this study. Their duties are to aid the investigator and, at the same time, Sangamo BioSciences in the maintenance of complete, legible, well-organized, and easily retrievable data. In addition, a Sangamo BioSciences study monitor will explain, interpret, and ensure the investigator's understanding of all applicable regulations concerning the clinical evaluation of a labeled product (whether licensed or unlicensed) and ensure an understanding of the protocol, reporting responsibilities, and the validity of the data.

In order to perforrn their roles well, the Sangamo BioSciences monitors must be given direct access to primary subject data (source documents) that support data entered onto the case report forms (e.g., hospital and general practice charts, appointment books, original laboratory records). The investigator must exercise judgment regarding information in a subject's chart that is not relevant to the performance, observation, or conduct of this study. The investigator must make available such records to Sangamo BioSciences, Quality Assurance, Institutional Review Board, and Regulatory personnel for inspection and copying. Because this enters into the realm of subject confidentiality, this fact must be included in the information signed by the subject.

The investigator or designated person should agree, as a minimum requirement, to record the following information in the subject notes:

- Protocol identification number, brief description or title of study
- Date and statement that subject has given written informed consent
- All visit dates
- All Adverse Events
- All concomitant medications
- Primary efficacy details (as defined by the protocol)
- All labeled product accountability information

Entries in the subject notes must contain the signature or initials of the person making the entries.

The clinical study monitor will perform source data verification at each monitoring visit.

A Sangamo BioSciences representative will monitor individual sites at appropriate intervals. The frequency of interim monitoring visits may vary depending on enrollment rate and the quality of data collected. Telephone contact will be made with each site Study Coordinator to keep abreast of subject status and to answer study-related questions.

16.7 Completion and Return of Case Report Forms

The investigator is responsible for the quality of the data recorded on the case report form. The data recorded should be a complete and accurate account of the subject's record collected during the study.

The investigator and Sangamo BioSciences study monitor will identify any data that will be recorded directly on the case report form and considered as source data (i.e., no prior written or electronic record of the data). The Sangamo BioSciences monitor will document this on the study initiation report and document the use of case report forms as source documents as necessary during the course of the study.

Detailed instructions for case report form completion will be provided in the **Study Reference Manual.**

The investigator agrees to complete case report forms in a timely fashion, and make them available to the Sangamo BioSciences study monitor for full inspection. In addition, all data queries should be resolved promptly.

Before acceptance, the Sangamo BioSciences study monitor will review the case report forms for completeness and adherence to the protocol.

16.8 Deviation from Protocol for Individual Subjects

Digressions from a written protocol for individual subjects are inherent to clinical research and will be categorized by Sangamo BioSciences as deviations.

Examples of protocol deviations include the following:

- Informed consent improperly obtained
- Violation of inclusion/exclusion criteria
- Error in product randomization
- Major drug injection errors that may compromise subject safety or efficacy assessments
- Administration of an excluded concomitant medication or treatment during the course of the study
- Vital signs were not measured at study visit

- Missed, delayed, or rescheduled visit
- Missing laboratory results

Investigators are encouraged to adhere to protocol procedures in that the deviation does not affect the evaluation of the data for the subject or compromise statistical analysis.

When a significant deviation occurs, the investigator should contact the study or medical monitor by telephone. The medical monitor will decide whether the subject is to continue on study.

16.9 Quality Assurance Procedures

Quality Assurance activities undertaken during this study include monitoring and source data verification by the study monitor. It is possible that Sangamo BioSciences personnel or their agents may audit this study center.

16.10 Sangamo BioSciences Policy on Fraud in Clinical Studies

APPENDIX 2: CTCAE

Sangamo BioSciences, Inc. will provide the Common Terminology Criteria for Adverse Events (CTCAE) v.4.0 to the clinical site.

APPENDIX 3: AMERICAN CANCER SOCIETY (ACS) CANCER DETECTION GUIDELINES

The following cancer screening guidelines are recommended for those people at average risk for cancer (unless otherwise specified) and without any specific symptoms.

People who are at increased risk for certain cancers may need to follow a different screening schedule, such as starting at an earlier age or being screened more often. Those with symptoms that could be related to cancer should see their doctor right away.

Cancer-related Checkup

For people aged 20 or older having periodic health exams, a cancer-related checkup should include health counseling, and depending on a person's age and gender, might include exams for cancers of the thyroid, oral cavity, skin, lymph nodes, testes, and ovaries, as well as for some non-malignant (non-cancerous) diseases.

Special tests for certain cancer sites are recommended as outlined below.

Breast Cancer

- Yearly mammograms are recommended starting at age 40 and continuing for as long as a woman is in good health.
- Clinical breast exam (CBE) should be part of a periodic health exam, about every 3 years for women in their 20s and 30s and every year for women 40 and over.
- Women should know how their breasts normally feel and report any breast change promptly to their health care providers. Breast self-exam (BSE) is an option for women starting in their 20s.
- Women at high risk (greater than 20% lifetime risk) should get an MRI and amammogram every year. Women at moderately increased risk (15% to 20% lifetime risk) should talk with their doctors about the benefits and limitations of adding MRI screening to their yearly mammogram. Yearly MRI screening is not recommended for women whose lifetime risk of breast cancer is less than 15%.

Colon and Rectal Cancer

Beginning at age 50, both men and women at *average risk* for developing colorectal cancer should use one of the screening tests below. The tests that are designed to find both early cancer and polyps are preferred if these tests are available to you and you are willing to have one of these more invasive tests. Talk to your doctor about which test is best for you.

Tests that find polyps and cancer

- flexible sigmoidoscopy every 5 years*
- colonoscopy every 10 years
- double contrast barium enema every 5 years*
- CT colonography (virtual colonoscopy) every 5 years*

Tests that mainly find cancer

- fecal occult blood test (FOBT) every year*,**
- fecal immunochemical test (FIT) every year*,**
- stool DNA test (sDNA), interval uncertain*

*Colonoscopy should be done if test results are positive.

**For FOBT or FIT used as a screening test, the take-home multiple sample method should be used. A FOBT or FIT done during a digital rectal exam in the doctor's office is not adequate for screening.

People should talk to their doctor about starting colorectal cancer screening earlier and/or being screened more often if they have any of the following colorectal cancer risk factors:

- a personal history of colorectal cancer or adenomatous polyps
- a personal history of chronic inflammatory bowel disease (Crohns disease or ulcerative colitis)
- a strong family history of colorectal cancer or polyps (cancer or polyps in a first degree relative [parent, sibling, or child] younger than 60 or in 2 first-degree relatives of any age)
- a known family history of hereditary colorectal cancer syndromes such as familial adenomatous polyposis (FAP) or hereditary non-polyposis colon cancer (HNPCC)

Cervical Cancer

- All women should begin cervical cancer screening about 3 years after they begin having vaginal intercourse, but no later than when they are 21 years old. Screening should be done every year with the regular Pap test or every 2 years using the newer liquid-based Pap test.
- Beginning at age 30, women who have had 3 normal Pap test results in a row may get screened every 2 to 3 years. Another reasonable option for women over 30 is to get screened every 3 years (but not more frequently) with either the conventional or liquid-based Pap test, plus the HPV DNA test. Women who have certain risk factors such as diethylstilbestrol (DES) exposure before birth, HIV infection, or a weakened immune system due to organ transplant, chemotherapy, or chronic steroid use should continue to be screened annually.
- Women 70 years of age or older who have had 3 or more normal Pap tests in a row and no abnormal Pap test results in the last 10 years may choose to stop having cervical cancer screening. Women with a history of cervical cancer, DES exposure before birth, HIV infection or a weakened immune system should continue to have screening as long as they are in good health.
- Women who have had a total hysterectomy (removal of the uterus and cervix) may also choose to stop having cervical cancer screening, unless the surgery was done as a treatment for cervical cancer or precancer. Women who have had a hysterectomy without removal of the cervix should continue to follow the guidelines above.

Endometrial (Uterine) Cancer

The American Cancer Society recommends that at the time of menopause, all women should be informed about the risks and symptoms of endometrial cancer, and strongly encouraged to report any unexpected bleeding or spotting to their doctors. For women with or at high risk for hereditary non-polyposis colon cancer (HNPCC), annual screening should be offered for endometrial cancer with endometrial biopsy beginning at age 35.

Prostate Cancer

The American Cancer Society (ACS) does not support routine testing for prostate cancer at this time. ACS does believe that health care professionals should discuss the potential benefits and limitations of prostate cancer early detection testing with men before any testing begins. This discussion should include an offer for testing with the prostatespecific antigen (PSA) blood test and digital rectal exam (DRE) yearly, beginning at age 50, to men who are at average risk of prostate cancer and have at least a 10-year life expectancy. Following this discussion, those men who favor testing should be tested. Men should actively take part in this decision by learning about prostate cancer and the pros and cons of early detection and treatment of prostate cancer.

This discussion should take place starting at age 45 for men at high risk of developing prostate cancer. This includes African American men and men who have a first-degree relative (father, brother, or son) diagnosed with prostate cancer at an early age (younger than age 65).

This discussion should take place at age 40 for men at even higher risk (those with several first-degree relatives who had prostate cancer at an early age).

If, after this discussion, a man asks his health care professional to make the decision for him, he should be tested (unless there is a specific reason not to test).

References

American Cancer Society. *Cancer Facts & Figures 2009.* Atlanta, Ga: American Cancer Society; 2009.

Levin B, Lieberman DA, McFarland, et al. Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps, 2008: A Joint Guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Published online March 5, 2008. *CA Cancer J Clin.* 2008;58.

Saslow D, Boetes C, Burke W, et al for the American Cancer Society Breast Cancer Advisory Group. American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography. *CA Cancer J Clin.* 2007;57:75-89.

Last Revised: 05/21/2009

APPENDIX 4: SB-509 DRUG PRODUCT AND PLACEBO DESCRIPTION AND INSTRUCTIONS FOR STORAGE, HANDLING, ADMINISTRATION AND DISPOSAL

Product Description

SB-509 is a bacterial DNA plasmid (pV-32Ep65) that encodes an engineered zinc finger protein transcription factor (32Ep65) that up-regulates endogenous VEGF-A gene transcription. SB-509 is formulated as a liquid in 5% poloxamer 188. Sterile injectable saline (0.9% NaCl) serves as the placebo.

They are supplied in 3 mL glass vials filled with 2.2 mL of product, to deliver 2.0 mL. The SB-509 drug product is supplied at a concentration of 2.0 mg/mL. Each vial is prepared as a direct injectable.

Refer to the **SB-509 DN Clinical Investigator's Brochure** for additional information on SB-509 and the placebo.

Storage and Administration

SB-509 and placebo are shipped to the clinical site by air courier on dry ice. Upon receipt at the clinical site, the vials should be immediately transferred to a locked -20°C or below freezer. Accurate accounting logs of all investigational drug received, dispensed, destroyed, and/or returned to Sangamo should be maintained at the clinical site.

Injection Preparation

At the time of injection, the vials are removed from the freezer, allowed to thaw at room temperature at least 10 minutes. First draw the study drug into 1 mL syringes with **19 gauge, 1½ inch needles**. Syringes will be filled with either **0.5 mL** or **1.0 mL** according to the table shown on the next page. Once the syringes are filled, replace the **19 gauge needle** with a **25 gauge needle**, with either **1 inch** or **1½ inch** needles, as indicated in the table. A **27 gauge 1¼ inch** needle may also be used for the lower leg and thigh injections. Follow the same injection technique as described on the following page. Additional syringes may be filled as back-up if necessary. The syringes are then released to the appropriate medical personnel for intramuscular injection and kept at room temperature until the drug is administered. All injections should be given the same day the study drug is thawed.

Injection Volumes
Lower leg (injection 1-14): 0.5 mL
Thigh (injections 15-22): 1.0 mL

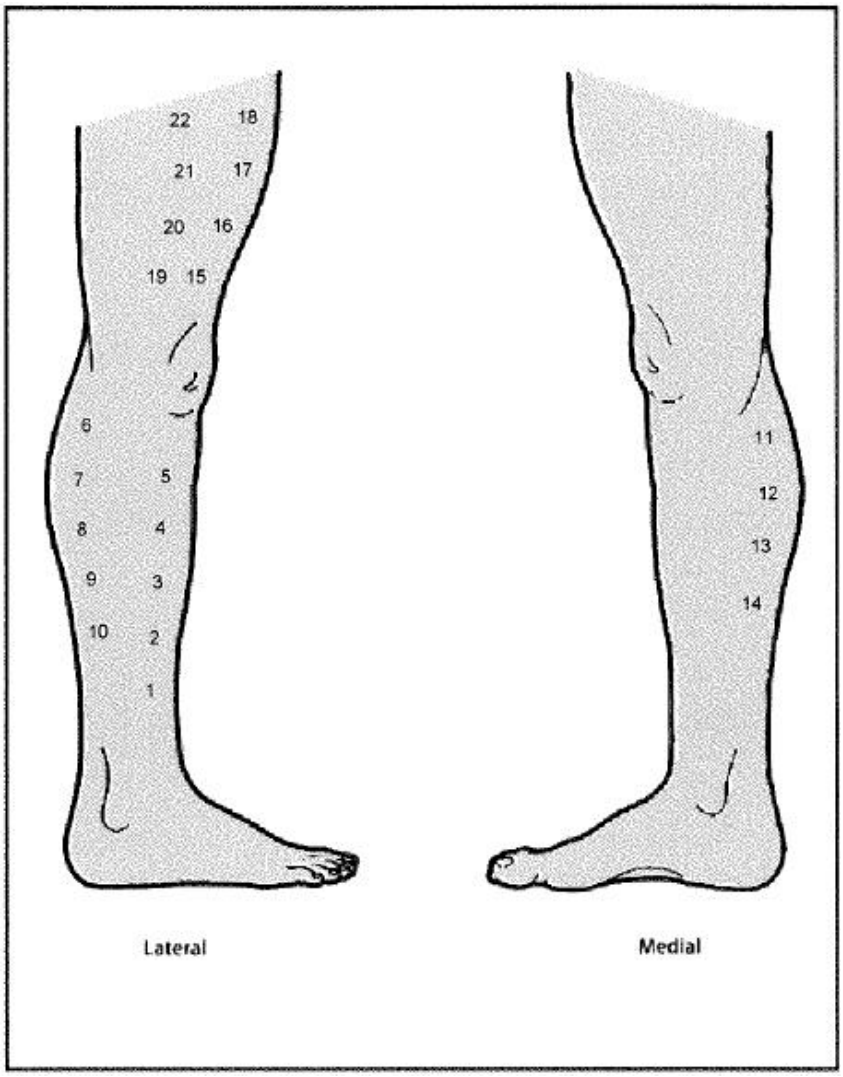
Injection Technique

Use standard aseptic technique for preparation of the skin at the injection site. Cleaning of the sites with alcohol wipes, with a second alcohol swipe at the site prior to injection is recommended. Administer 0.5 mL and 1.0 mL doses of study drug by inserting a needle along the long axis of the muscle fiber (i.e., parallel with the femoral artery) up to its hub (the needle's full insertion point) and depositing 0.5 mL for the 0.5 mL volume in the lower leg or 1.0 mL volume in the anterior and lateral thigh. The needle will be pointed toward the foot and inserted at an approximate 30° angle to the surface of the skin. Needles (25 gauge) with 1 mL syringes are to be used as follows: 1-inch needle for the lower leg and a 1½-inch needle for the thigh. If a 27 gauge needle is used, use the 1 ¼ inch needle for both the lower leg and thigh injections.

Injection Site Summary

- **Dose level: 60 mg (30 mg per leg)**
- **Total volume: 30 mL(15 mL per leg)**

	Syringe Fill	Needle Gauge & Length	Number of Syringes per Leg*	Total Number of Syringes	Muscle Injection Sites	Peripheral Nerve
Lower leg	0.5 mL	25 gauge: 1 inch or 27 gauge: 1 ¼ inches	14	28	1-14	peroneal, sural, tibial
Thigh	1.0 mL	25 gauge: 1 ½ inches or 27 gauge: 1 ¼ inches	8	16	15-22	sciatic and femoral



Dose Level Injection Instructions

Lower leg injections

- **Anterior leg injections**

Identify the bony landmarks of the anterior tibia and the fibula in the anterior lower leg. The muscle between these bones is the tibialis anterior. Identify Injection site 1 as the distal tibialis anterior muscle, 2-3 inches above the lateral malleolus of the ankle.

Beginning at site 1 as described above, identify 5 ascending injection sites in the tibialis anterior separated by at least one inch. Inject 0.5 mL into injections 1-5 (see **figure**).

- **Lateral leg injections**

Palpate the lateral fibular head and then extending inferiorly to the lateral malleolus, the peroneus longus muscle. Inject five, 0.5 mL at least one inch apart, moving inferiorly along the leg for injections 6-10 (see **figure**).

- **Medial leg injections**

Palpate the medial gastrocnemius muscle. At the top of the medial muscular portion of the muscle inject 4, 0.5 mL injections at least one inch apart moving inferiorly along the medial curve of the gastrocnemius for injections 11-14 (see **figure**).

Thigh injections

The upper leg or thigh injections will use syringes filled with 1.0 mL and will **deliver one dose of 1.0 mL at maximum needle length** (needle's full insertion point).

- **Anterior thigh**

Palpate the body of the rectus femoris muscle above the patella approximately 5-6 inches above the knee. Injections 15-18 (see **figure**) should be placed at least one inch apart, extending superiorly along the rectus femoris.

- **Lateral thigh**

Palpate the body of the muscles of the lateral quadriceps, anterior and superior to the iliotibial band at approximately 5-6 inches above the knee. Injections 19-22 (see **figure**) should be placed at least one inch apart, extending superiorly along the lateral quadriceps.

APPENDIX 5: NEUROPATHY IMPAIRMENT SCORE- LOWER LIMB (NIS-LL)

Adapted from Bril, Eur. Neural. (1999). 41 (supp. 1):8-13

A. Muscle Group Testing

Groups Tested

The following muscle groups are tested for power (bilaterally):

- Hip Flexion
- Hip Extension
- Knee Flexion
- Knee Extension
- Ankle Dorsiflexion
- Ankle Plantar Flexion
- Toe Extension
- Toe Flexion

Scoring

Each muscle group is scored according to the following scale:

Muscle Power	NIS-LL Score
Normal	0
25% Weak	1
50% Weak	2
75% Weak	3
Paralysis	4

Muscles groups are scored between 0 and 4 points per side per group (bilaterally) for a maximum total of 64 points.

B. Sensory and Reflex Testing

Sensory Testing

The following sensory modalities are tested:

- Touch pressure
- Pin Prick
- Vibration
- Joint position

Reflex Testing

Deep tendon reflex testing is done at the following sites (bilaterally):

- Quadriceps (patellar)
- Ankle (Achilles)

Scoring

Sensory testing and reflex testing is scored according to the following scale:

Sensory/Reflex Activity Grading	NIS-LL Score
Normal	0
Decreased	1
Absent	2

Sensory modalities are scored between 0 and 2 points per modality (bilaterally) for a maximum total of 16 points. Reflexes are scored between 0 and 2 points per reflex (bilaterally) for a maximum total of 8 points.

APPENDIX 6: LOWER EXTREMITY NEUROLOGICAL SENSORY EXAM

The Lower Extremity Neurological Sensory Exam includes distal to proximal examinations to evaluate sensory changes.

Pin Prick, Vibration and Touch Pressure will be evaluated at the Toe, Mid-Foot, Ankle, Mid-calf, Knee and Above Knee locations. At each location and for each leg, the sensory testing is scored according to the following scale:

Sensory Grading	Score
Normal	0
Decreased	1
Absent	2

Sensory modalities are scored between 0 and 2 points per modality (bilaterally) for a maximum total of 24 points per modality and 72 points overall.

APPENDIX 7: ELECTROPHYSIOLOGICAL STUDIES

Nerve conduction studies (NCS) will be done at the sural and peroneal motor nerves. All NCS studies will be done bilaterally using standard surface recording techniques. Procedures for the recording of NCS are briefly outlined below and presented in full detail in an accompanying **Study Reference Manual** for NCS Studies.

The temperatures at the beginning and the end of the NCS will be recorded. Hard copies of all nerve conduction studies will be printed and saved (see **Study Reference Manual** for details).

Sural Sensory Nerve
Conduction velocity and sensory amplitudes will be measured using antidromic procedures. Surface electrodes will be placed adjacent to the lateral malleolus of the ankle (active recording electrode); the stimulating cathode will be applied to a more proximal segment of the nerve (12-14 cm distance).

Peroneal Motor Nerve
Motor nerve conduction velocity, distal and proximal baseline-to-peak compound muscle action potential amplitudes will be measured using orthodromic procedures. The active recording electrode will be placed over the extensor digitorum brevis muscle; the distal stimulation cathode will be placed at the ankle. The fibular head will be used as a proximal stimulation point.

APPENDIX 8: QUANTITATIVE SENSORY TESTING (QST)

1.0 SCHEDULE

See **Appendix 1, Schedule of Events.**

2.0 DEFINITION OF TERMS

THRESHOLD - minimal energy required before a subject can just detect a stimulus - in the present study, the last correctly identified intensity.

TWO ALTERNATIVE FORCED CHOICE PROCEDURE - VPT testing algorithm in which two potential stimuli are presented in each trial and the subject must select which stimulus is actually vibrating.

3.0 EQUIPMENT

The Vibratron II, manufactured by Physitemp Instruments, Inc. (Clifton N.J), is a QST device to quantify the ability of human subjects to detect vibratory stimuli at the distal extremes of their upper and lower limbs. It consists of a controller and two vibrating posts. The frequency of vibration is fixed at 120 Hz. The power supply, switches and digital meter are encased as one unit, while the vibrating rods are located in separate units with adjoining cables. Each vibrating rod protrudes through a metal case and can be contacted by either the hands or the feet. The tandem vibrating surfaces are manufactured from hardened rubber and are identical in appearance. Vibration is achieved by driving the transducers with a variable voltage source. A dual position switch connected in series with the vibrating units, controls which rod vibrates, while a "dummy" switch is used to imitate the sounds and motions of switching. The amplitude of vibration is proportional to the square of the applied voltage and is continuously available on a digital display accurate to the nearest 0.1 units. A switch sets the maximal level of the vibration, which ranges from 0- 6.5 vibration units or 6.5 - 20 vibration units.

4.0 TESTING PROCEDURE

4.1 Methodology

Thresholds should be measured bilaterally, on the great toes. The methodology of testing is a "two alternative forced choice procedure." For each trial the subject is required to determine which of the two rods is actually vibrating. The position of vibration is under experimental control, determined by a randomization sequence. The intensity sequence is similarly under the control of the experimenter and is determined by a testing algorithm (see **Section 4.6**).

4.2 Temperature Control

Prior to testing, each subject should be seated in a comfortable chair and allowed an adaptation period of approximately 10 minutes, during which time they can become acclimated to room temperature. Subjects should then remove all footwear, including pantyhose. A surface thermometer should be used to determine skin temperature at the arch of the foot. Skin temperature at this site must be at least 30°C, otherwise the subject should be warmed using a circulating water bath, an insulated thermal wrap or a heating pad. Radiant heaters should not be used.

4.3 Adaptation Period

After the subject is warmed, they should be given an opportunity to become familiar with the testing apparatus and with the expected vibratory sensations. During this period, the experimenter can instruct the subject as to the appropriate length and force with which to contact the vibrating rod. An ideal duration for contact is approximately one second and the force should be the minimum necessary to detect vibration. This adaptation period will also allow the experimenter to determine the appropriate voltage level at which to begin testing. A number of vibration intensities should be set and sampled by the subject. For the initial trial, the experimenter should set the intensity at a level detectable by that subject 100% of the time. For many subjects in the 20

to 50 year age range, an initial intensity setting of 10-12 units is sufficient. This level should be increased for older subjects. For each trial, both the intensity setting and the subject's choice should be recorded in the appropriate columns on the data sheet.

4.4 Foot Support

Throughout testing, the subject should rest his/her feet on the elevated platform provided by Physitemp. Thus, the subject should only be required to pivot his/her foot to contact each vibrating rod.

4.5 Instructions

At the beginning of each testing session, the subject should be issued the following instructions:

> "Please press your toe lightly against each rod in sequence for approximately one second. During each trial you will be allowed to touch the rods only once. Only one of the rods will be vibrating; please decided which rod (A or B) is vibrating or please let us know if you no longer can tell the difference. The task will become increasingly more difficult."

4.6 Testing Algorithm

The starting intensity, in vibration units (vu), should be entered on the left hand column of the worksheet. The location of the stimulus (A or B rod) is indicated by the first column in the A/B matrix. If the subject correctly identifies which rod is vibrating, circle the "A" or "B" - then decrease the intensity for the next presentation by approximately 10%. If the subject incorrectly identifies the vibrating rod, cross out the "A" or "B" on the sheet with an "X" and increase the intensity for the next presentation by approximately 10% (ie., return to the level immediately prior to the error). The A/B matrix should be followed diagonally to the right (up one level and to the right one column).Testing is complete when a subject responds that there is "no difference" (mark with a single line on the A/B matrix) **OR** if the subject makes two errors before responding "no difference." The final lowest "correct" intensity is entered as the VPT value. Ideally, the subject should have at least 10 correct responses before they report "no difference" or make their first error. If the subject reports "no difference" or if there is an error in the first 10 trials, the test must be restarted at a higher initial intensity level. If the test was started at 20 vibration units (vu), simply report the last score correctly identified. If the subject reports "no difference" or makes an error at the 20 vu level, check the circle "intensity >20" on the worksheet. For sample worksheet see **Study Reference Manual**.

5.0 TECHNICAL CONCERNS

To determine accurate vibration thresholds, the experimenter must be concerned with the following details:

5.1 The subject should be consistent in the location and duration of touch, as well as in the approximate force applied to the vibrating surface. Instructions such as “please don’t press so hard” can be issued during testing to ensure trial-to-trial consistency.

5.2 Throughout testing, the sounds and motions associated with changing the stimulus position should be presented between each trial. For the conditions where the stimulus position remains unaltered, the "dummy" switch must be used. Both the active and "dummy" switches can be used between trials to mask the actual positioning of the stimulus.

5.3 The rods should be visually inspected prior to every test to ensure that they are "free-standing" and not in contact with the metal covering.

5.4 The subject must take care not to contact the metal casing around the vibrating rods during the trials.

5.5 The subject should be carefully screened from viewing the instrument settings or the data sheet.

5.6 All testing should be conducted in a quiet room with minimal distractions.

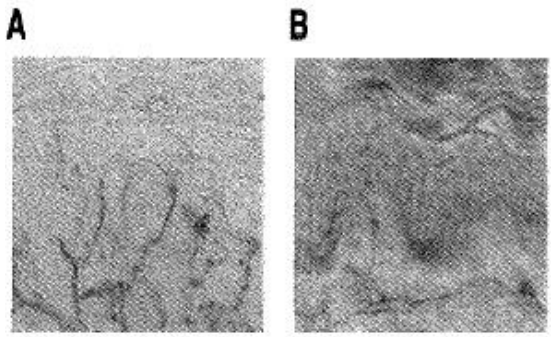
5.7 Each Vibratron II should be factory calibrated at an interval appropriate for the study.

APPENDIX 9: SKIN BIOPSY

1.0 INTRODUCTION

Rationale
3 mm skin biopsy punches will be obtained for the evaluation of intra-epidermal nerve fiber density (IENFD). Epidermal nerve fibers are C and A-sigma small caliber unmyelinated nerve fibers that are relevant to diabetic neuropathy. These fibers are not directly assessed by conventional testing measures such as nerve conduction velocity, amplitude, or most forms of quantitative sensory testing.

In the figure below, epidermal nerve fiber axons can be seen extending to the dermis in a normal subject (panel A). Decreased numbers of epidermal nerve fiber axons are evident in a skin biopsy from a diabetic subject (panel B).



Skin section (50 μm) stained for PGP9.5+ IENFDs in a nondiabetic subject (A) and in a subject with established neuropathy (B). Original magnification X600 (Quattrini et al. 2008).

3.0 SCHEDULE AND GENERAL PROCEDURES

The schedule for skin biopsy collection is located in **Appendix 1: Schedule of Events**. The method for obtaining this analysis requires a 3 mm skin biopsy on the distal lateral thigh. The sample will then be processed with fixative and shipped to Johns Hopkins University. The samples will then be further processed by the laboratory and analyzed to determine intraepidermal nerve fiber density.

A manual with detailed instructions will be provided to you in the **Study Reference Manual** for obtaining, processing and shipping the biopsy samples. In addition, each investigator will be provided with a video clip presentation on CD that will further illustrate the specific procedures.

APPENDIX 10: NEUROPATHY TOTAL SYMPTOM SCORE (NTSS-6)

Bastyr, Clinical Therapeutics (2005) 27:1278-1294

Instructions for the Health Care Professional (HCP)

1. Each of the 6 questions is scored by marking an X in the box on the grid corresponding to the symptom frequency and intensity.
2. Grading of the symptom frequency and intensity should be according to the definitions provided below for each category level.
3. The symptom evaluated should be due to diabetic peripheral neuropathy in the feet or legs, in the opinion of the administering HCP. The symptom question should be evaluated taking into consideration what would be normal for a healthy person of comparable age and sex.
4. Symptoms are graded based on the experience of the patient during the past 24 hours.
5. Each symptom question can be assigned a maximum score of 3.66 points. The NTSS-6 total score is the sum of the 6 individual symptom scores and has a maximum of 21.96 points.
6. The HCP scores the symptom question based on the patient's response to the question and the definitions of symptom frequency and intensity provided to the HCP (see below).

Definitions for Grading

Frequency

- ***Never or occasional*** means that the symptom does not occur; occurs a normal amount; not beyond normal; not noticeable.
- ***Occasional, but abnormal*** means that the symptom occurs or is present less than a third of the time, either in total frequency or duration. It also applies to symptoms that may have a duration of only seconds and occur only during a portion of the day and/or night.
- ***Often*** means that the symptom occurs for one third to two thirds of the time, either in total frequency or duration. It may also apply to symptoms that may have a duration of only seconds and occur throughout the day and/or night.
- ***Almost continuous*** means that the symptom occurs for more than two thirds of the time, either in total frequency or duration. It may also apply to symptoms that may have a duration of only seconds and occur throughout the day and/or night.

Intensity

- ***Not present*** means no symptoms noted.
- ***Mild*** means that the patient notices the pain or other symptom but it does not interfere with or restrict daily activities, and the patient does not need any treatment to control it.
- ***Moderate*** means that the pain or other symptom sometimes interferes with or restricts ≥1 of the patient's sleep, work, social, or family activities, or the patient needs treatment to control the pain or symptom.
- ***Severe*** means that the pain or other symptom usually interferes with or restricts ≥1 of the patient's sleep, work, social, or family activities, even if the pain or symptom is treated.

Symptoms and Questions Evaluated by the NTSS-6

- Aching pain: "Do you experience a deep, aching, tightness, boring, pulling, or squeezing pain in your feet or legs?"
- Allodynia: "Do you experience unusual sensitivity or tenderness when your feet are touched or are used in activities such as walking?"
- Burning pain: "Do you experience burning pain in your feet or legs?"
- Lancinating pain: "Do you experience sharp, stabbing, or shooting pain, electrical shock-like pain, or surges of pain that last seconds to minutes in your feet or legs?"

- Numbness: "Do you experience numbness, lost sensation, or a ‘dead feeling’ like an anesthetic, without prickling in your feet or legs?"
- Prickling sensation: "Do you experience a prickling or tingling feeling, with or without an ‘asleep’ feeling, in your feet or legs?"

NTSS-6 Sample Scoring Sheet

	Symptom Intensity			
Symptom Frequency	Not Present	Mild	Moderate	Severe
Never or occasional (normal amount)	0.00	0.00	0.00	0.00
Occasional but abnormal (less than 1/3 of the time)	0.00	1.00	2.00	3.00
Often (1/3 to 2/3 of the time)	0.00	1.33	2.33	3.33
Almost continuous (more than 2/3 of the time)	0.00	1.66	2.66	3.66

APPENDIX 11: VISUAL ANALOG SCALE FOR PAIN INTENSITY (VASPI)

Please rate your pain by circling the one number that best describes your pain from diabetic neuropathy in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Possible Pain

APPENDIX 12: NEURO-QOL

Vileikyte, Diabetes Care (2003) 26:2549-2555

NEUROPATHY-SPECIFIC QUALITY OF LIFE

Questionnaire Instructions (UK Version)

- These questions ask about the effect your FOOT PROBLEMS may have on your daily life and well-being. By foot problems we mean lost or reduced feeling in your extremities, pain, discomfort and/or ulcers (open sores) on your feet and, in some cases unsteadiness while walking or standing.
- Please note that many questions have two parts. Answer every question by ticking one box for each part (tick two boxes per line). Please make sure you answer all questions.
- Please concentrate on how you have felt IN THE PAST 4 WEEKS for all of the questions.
- There are no right or wrong answers. If you are unsure about how to answer a question, you can ask the person who gave you the questionnaire. Please DO NOT ask a relative or friend to help you.
- All of your responses will be held strictly confidential.

In the past 4 weeks how often have you experienced the following symptoms?	All the time	Most of the time	Some of the time	Occa-sionally	Never	**How much bother did this cause you?** Very much	Some bother	None
1. Burning in your legs or feet								
2. Excessive heat or cold in your legs or feet								
3. Pins and needles in your legs or feet								
4. Shooting or stabbing pain in your legs or feet								
5. Throbbing in your legs or feet								
6. Sensations in your legs or feet that make them jump								
7. Irritation of the skin caused by something touching your feel, such as bedsheets or socks								

A. Have these **painful symptoms** reduced your quality of life?	Very much	Quite a lot	Some what	A little	Not at all

In the past 4 weeks how often have you experienced the following symptoms?	All the time	Most of the time	Some of the time	Occa-sionally	Never	**How much bother did this cause you?** Very much	Some bother	None
8. Numbness in your feet								
9. Inability to feel the difference between hot and cold with your feet								
10. Inability to feel objects with your feet								

B. Have these **last three symptoms** reduced your quality of life?	Very much	Quite a lot	Some what	A little	Not at all

In the past 4 weeks how often have you experienced the following symptoms?	All the time	Most of the time	Some of the time	Occa-sionally	Never	**How much bother did this cause you?**		
						Very much	Some bother	None
11. Weakness in your hands								
12. Problems with balance or unsteadiness while walking								
13. Problems with balance or unsteadiness while standing								

C. Have these **last three symptoms** reduced your quality of life?	Very much	Quite a lot	Some what	A little	Not at all

The following questions ask about how your FOOT PROBLEMS affect your daily activities, relationships and feelings.

Are you in <u>PAID WORK</u>?	Yes	No	If **YES** please go to Question 14. If **NO** please go to Question 15.

In the past 4 weeks, HOW MUCH have your foot problems interfered with your:	Very much	Quite a lot	Some what	A little	Not at all	**How important is this aspect of your life to you?**		
						Very much	Some what	Not at all
14. Ability to perform your paid work?								
15. Ability to perform tasks around the house or garden?								
16. Ability to take part in leisure activities?								

D. Have these changes in **daily activities** as a result of your foot problems reduced your quality of life?	Very much	Quite a lot	Some what	A little	Not at all

In the past 4 weeks:	**How important is this aspect of your life to you?**

	Very much	Quite a lot	Some what	A little	Not at all	Very much	Some what	Not at all
17. How much have your foot problems interfered with your relationships with people close to you?								
18. Have you felt more physically dependent than you would like to be on people close to you as a result of your foot problems?								
19. Have you felt more emotionally dependent than you would like to be on people close to you as a result of your foot problems?								
20. Has your role in the family changed as a result of your foot problems?								

E. Have these changes in **relationships with other people** as a result of your foot problems reduced your quality of life?	Very much	Quite a lot	Some what	A little	Not at all

						How much bother did this cause you?		
How much do you agree with the following statements:	Completely agree	Partly agree	Neither agree or	Partly disagree	Completely disagree	Very much	Some bother	None
21. People treat me differently from other people as a result of my foot problems.								
22. I feel older than my years as a result of my foot problems.								
23. My self - confidence is affected as a result of my foot problems.								
24. My foot problems make my life a struggle.								
25. I generally feel frustrated because of my foot problems.								
26. My foot problems cause me embarrassment.								

27. I feel depressed because of my foot problems								
F. Have these **feelings about yourself** as a result of your foot problems reduced your quality of life?	Very much	Quite a lot		Some what	A little		Not at all	
	Very much	Quite a lot		Some what	A little		Not at all	
28. Overall, I would say problems with my feet reduced my Quality of Life:								
	Excellent	Very good		Good	Fair		Poor	
29. Overall, I would rate my quality of life as:								

APPENDIX 13: SF-36

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. *Thank you for completing this survey!*

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
q	q	q	q	q
☐1	☐2	☐3	☐4	☐5

2. **Compared to one year ago, how would you rate your health in general now?**

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
q	q	q	q	q
☐1	☐2	☐3	☐4	☐5

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, Limited a lot	Yes, Limited a little	No, not Limited at all
	q	q	q
a Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	……☐1……	……☐2……	……☐3
b Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	……☐1……	……☐2……	……☐3
c Lifting or carrying groceries	……☐1……	……☐2……	……☐3
d Climbing several flights of stair	……☐1……	……☐2……	……☐3
e Climbing one flight of stairs	……☐1……	……☐2……	……☐3
f Bending, kneeling, or stooping	……☐1……	……☐2……	……☐3
g Walking more than a mile	……☐1……	……☐2……	……☐3
h Walking several hundred yards	……☐1……	……☐2……	……☐3
i Walking one hundred yards	……☐1……	……☐2……	……☐3
j Bathing or dressing yourself	……☐1……	……☐2……	……☐3

4. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	q	q	q	q	q
[a] <u>Cut down on the amount of time</u> you spent on work or other activities	…..☐1…..	…..☐2…..	…..☐3…..	…..☐4…..	…...☐5
[b] <u>Accomplished less</u> than you would like	…..☐1…..	…..☐2…..	…..☐3…..	…..☐4…..	…...☐5
[c] Were limited in the <u>kind</u> of work or other Activities	…..☐1…..	…..☐2…..	…..☐3…..	…..☐4…..	…...☐5
[d] Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	…..☐1…..	…..☐2…..	…..☐3…..	…..☐4…..	…...☐5

5. During the <u>past 4 weeks</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	q	q	q	q	q
[a] <u>Cut down on the amount of time</u> you spent on work or other activities	…..☐1…..	…..☐2…..	…..☐3…..	…..☐4…..	…...☐5
[b] <u>Accomplished less</u> than you would like	…..☐1…..	…..☐2…..	…..☐3…..	…..☐4…..	…...☐5
[c] Did work or other activities <u>less carefully than usual</u>	…..☐1…..	…..☐2…..	…..☐3…..	…..☐4…..	…...☐5

6. During the <u>past 4 weeks</u>, to what extent has your <u>physical health or emotional problems</u> interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
q	q	q	q	q
☐1	☐2	☐3	☐4	☐5

7. How much <u>bodily</u> pain have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very Severe
q	q	q	q	q	q
☐1	☐2	☐3	☐4	☐5	☐6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderate	Quite a bit	Extremely
q	q	q	q	q
☐1	☐2	☐3	☐4	☐5

9. These questions are about how you feel and how things have been with you <u>during the past 4 weeks</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past 4 weeks</u>….

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
	q	q	q	q	q
[a] Did you feel full of life?	…..☐1…..	…..☐2…..	…..☐3…..	…..☐4…..	…...☐5
[b] Have you been very nervous?	…..☐1…..	…..☐2…..	…..☐3…..	…..☐4…..	…...☐5
[c] Have you felt so down in the dumps that nothing could cheer you up?	…..☐1…..	…..☐2…..	…..☐3…..	…..☐4…..	…...☐5
[d] Have you felt calm and peaceful?	…..☐1…..	…..☐2…..	…..☐3…..	…..☐4…..	…...☐5
[e] Did you have a lot of energy?	…..☐1…..	…..☐2…..	…..☐3…..	…..☐4…..	…...☐5
[f] Have you felt downhearted and depressed?	…..☐1…..	…..☐2…..	…..☐3…..	…..☐4…..	…...☐5
[g] Did you feel worn out?	…..☐1…..	…..☐2…..	…..☐3…..	…..☐4…..	…...☐5
[h] Have you been happy?	…..☐1…..	…..☐2…..	…..☐3…..	…..☐4…..	…...☐5
[i] Did you feel tried?	…..☐1…..	…..☐2…..	…..☐3…..	…..☐4…..	…...☐5

10. During the <u>past 4 weeks</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
q	q	q	q	q
☐1	☐2	☐3	☐4	☐5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
	q	q	q	q	q
[a] I seem to get sick a little easier than other people	…..☐1…..	…..☐2…..	…..☐3…..	…..☐4…..	…...☐5
[b] I am as healthy as anybody I know	…..☐1…..	…..☐2…..	…..☐3…..	…..☐4…..	…...☐5
[c] I expect my health to get worse	…..☐1…..	…..☐2…..	…..☐3…..	…..☐4…..	…...☐5
[d] My health is excellent	…..☐1…..	…..☐2…..	…..☐3…..	…..☐4…..	…...☐5

APPENDIX 14: GLOBAL ASSESSMENT

The following question will be asked of the subject according to the schedule outlined in **Appendix 1: Schedule of Events:**

How have you felt since your last visit?

- ☐ Better
- ☐ Same
- ☐ Worse

Exhibit 31.1

CERTIFICATION

I, Edward O. Lanphier II, certify that:

1. I have reviewed this quarterly report on Form 10-Q of Sangamo BioSciences, Inc. ("registrant")

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:

   (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: April 28, 2015

/s/ Edward O. Lanphier II
Edward O. Lanphier II
President and Chief Executive Officer

Exhibit 31.2

CERTIFICATION

I, H. Ward Wolff, certify that:

1. I have reviewed this quarterly report on Form 10-Q of Sangamo BioSciences, Inc. ("registrant")

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:

   (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: April 28, 2015

/s/ H. Ward Wolff
H. Ward Wolff
Executive Vice President and Chief Financial Officer
(Principal Financial and Accounting Officer)

Exhibit 32.1

Certification Pursuant to 18 U.S.C. §1350, as Adopted Pursuant to §906 of the Sarbanes-Oxley Act of 2002

Each of the undersigned hereby certifies pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002 in his capacity as an officer of Sangamo BioSciences, Inc. (the "Company"), that:

(1) the Quarterly Report of the Company on Form 10-Q for the quarterly period ended March 31, 2015, as filed with the Securities and Exchange Commission (the "Report") fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; 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/ Edward O. Lanphier II
Edward O. Lanphier II
President and Chief Executive Officer
(Principal Executive Officer)

Date: April 28, 2015

/s/ H. Ward Wolff
H. Ward Wolff
Executive Vice President and Chief Financial Officer
(Principal Financial and Accounting Officer)

Date: April 28, 2015