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

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): March 28, 2023

Biomea Fusion, Inc.
(Exact name of registrant as specified in its charter)

Delaware	**001-40335**	**82-2520134**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

900 Middlefield Road, 4th Floor **Redwood City, California**	**94063**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: 650 980-9099

Not Applicable
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

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

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 par value	BMEA	The NASDAQ Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☒

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

Item 7.01 Regulation FD Disclosure.

On March 28, 2023, Biomea Fusion, Inc. (the "Company") issued a press release announcing initial clinical data from the Phase II portion of COVALENT-111, the Company's clinical trial of its lead product candidate, BMF-219, in type 2 diabetes. A copy of the press release is furnished herewith as Exhibit 99.1 to this Current Report on Form 8-K.

The Company also hosted a conference call and live webcast to discuss the interim clinical data on March 28, 2023 at 8:30 a.m. E.T. The Company has made available a slide presentation to accompany the call, a copy of which is furnished herewith as Exhibit 99.2 to this Current Report on Form 8-K.

The information in this Item 7.01, including Exhibit 99.1 and Exhibit 99.2 attached hereto, is intended to be furnished and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended (the "Securities Act"), or the Exchange Act, except as expressly set forth by specific reference in such filing.

Item 8.01 Other Events.

On March 28, 2023, the Company reported topline initial clinical data from the Phase 2 portion of COVALENT-111. 40 subjects were enrolled in the first three cohorts of COVALENT-111, with the first cohort comprising 16 healthy volunteers (HVs) exposed to 100 mg BMF-219 once daily for two weeks. In Cohorts 2 and 3, subjects with Type 2 diabetes mellitus (T2DM) (n=12 per cohort with ten subjects treated with BMF-219 and two subjects on placebo) received BMF-219 once daily for four weeks with or without food, respectively. In the two diabetes cohorts, enrolled patients had T2DM diagnosed for ≤15 years, were ages 18 to 65, had a body mass index (BMI) ≥25 and ≤40 kg/m^2, and had uncontrolled diabetes with HbA1c ≥7.0% and ≤10% despite being on up to three standard-of-care diabetes therapies. At baseline, patients enrolled in Cohorts 2 and 3 had a median A1c of 7.9% and 7.8%, respectively.

Active treatment Cohort 3 (BMF-219 without food) compared to Cohort 2 (BMF-219 with food) showed a positive dose-response pharmacokinetics relationship demonstrated by about a threefold median increase in C_{max} (ng/ml) and AUC (ng x h/ml) when BMF-219 was administered without food. This increase in BMF-219 systemic exposure was in line with the differences seen in the response rates between the two cohorts. Specifically, the change in HbA1c at four weeks for Cohort 3 patients (n=9) on BMF-219 (100 mg, without food) showed a median A1c reduction of -1.0% and a 89% (8/9) response rate at four weeks, with 78% of subjects achieving a ≥0.5% reduction in A1c and 56% achieving a ≥1.0% reduction in A1c. Cohort 2 patients (n=10) on BMF-219 (100 mg, with food) showed a median A1c reduction of -0.3% and a 70% (7/10) response rate at four weeks, with 30% of subjects achieving a ≥0.5% to ≤1.0% reduction in A1c. Placebo patients (n=4) showed a median and mean A1c reduction between -0.1% and -0.15%.

The Company also reported on the tolerability profile of BMF-219 observed in Cohorts 1, 2, and 3 of COVALENT-111. During the HV portion of the study, in Cohort 1 (n=16), the Company observed minor Grade 1 Treatment Emergent Adverse Events (TEAEs) and no TEAEs were considered related to BMF-219. During the dosing of diabetes patients in Cohorts 2 and 3, all TEAEs observed were Grade 1, except for an asymptomatic laboratory finding of Grade 2 elevated lipase in a single subject that was considered unrelated to BMF-219. In summary, BMF-219 was generally well-tolerated.

Cautionary Note Regarding Forward Looking Statements

This Current Report on Form 8-K and certain of the materials filed or furnished herewith contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, without limitation, statements regarding the Offering, and expectations regarding our cash runway, use of capital, expenses and other future financial results. The words "may," "might," "will," "could," "would," "should," "expect," "plan," "anticipate," "intend," "believe," "expect," "estimate," "seek," "predict," "future," "project," "potential," "continue," "target" and similar words or expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Any forward-looking statements, such as those related to the clinical and therapeutic potential of the Company's product candidates and

development programs, including BMF-219, the potential of BMF-219 as a treatment for various types of cancer and diabetes, the Company's research, development and regulatory plans, including its pursuit of BMF-219 in metabolic diseases, the Company's plans to continue the evaluation of BMF-219 for type 2 diabetes in its COVALENT-111 study and the availability of future data from the Phase II portion of the study, are subject to a number of risks, uncertainties and important factors that may cause actual events or results to differ materially from those expressed or implied by any forward-looking statements contained in this Current Report on Form 8-K or the materials furnished or filed herewith, including, without limitation, uncertainties related to the risks that initial results may not be indicative of final results in later clinical trials, the Company may encounter delays or unforeseen results in preclinical development, IND-filing and acceptance, patient enrollment and in the initiation, conduct and completion of its ongoing and planned clinical trials and other research, development and regulatory activities. These and other risks and uncertainties are described in greater detail in the section entitled "Risk Factors" in the Company's most recent Annual Report on Form 10-K or Quarterly Report on Form 10-Q, as well as any subsequent filings with the Securities and Exchange Commission. In addition, any forward-looking statements represent the Company's views only as of today and should not be relied upon as representing its views as of any subsequent date. The Company explicitly disclaims any obligation to update any forward-looking statements. No representations or warranties (expressed or implied) are made about the accuracy of any such forward-looking statements.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits.

Exhibit Number	Description
99.1	Press release titled "Biomea Fusion Announces Positive Data from Initial Cohorts of Ongoing Phase II Study (COVALENT-111) of BMF-219 in Patients with Type 2 Diabetes; 100 mg Cohort 3 Demonstrated an 89% Response Rate and 1% Median Reduction in HbA1c at Day 28," issued by Biomea Fusion, Inc. on March 28, 2023, furnished herewith.
99.2	Corporate presentation titled "COVALENT-111: Phase II First Data Readout of Initial Healthy Volunteer (HV) and Type 2 Diabetes Mellitus (T2DM) Cohorts," dated March 28, 2023, furnished herewith.
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURES

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

Biomea Fusion Inc.

Date: March 28, 2023

By: /s/ Thomas Butler
Thomas Butler
Principal Executive Officer

Exhibit 99.1

Biomea Fusion Announces Positive Data from Initial Cohorts of Ongoing Phase II Study (COVALENT-111) of BMF-219 in Patients with Type 2 Diabetes; 100 mg Cohort 3 Demonstrated an 89% Response Rate and 1% Median Reduction in HbA1c at Day 28

- In Cohort 3, after 4 weeks of once-daily 100 mg dosing with the investigational, oral covalent menin inhibitor, BMF-219, 89% of patients achieved a reduction in A1c, 78% of patients achieved at least a 0.5% reduction in A1c, and 56% achieved at least a 1% reduction in A1c.
- Initial observations of continued glycemic control were seen in follow up visits in patients that had already reached week 8 in the study (4 weeks after the last BMF-219 dose) at the time of this publication.
- BMF-219 demonstrated a well-tolerated safety profile. No patients on BMF-219 discontinued dosing and all patients completed 4 weeks of treatment.
- Biomea continues dose escalation of BMF-219 in COVALENT-111 and plans to explore additional dosing periods greater than 4 weeks in order to evaluate the optimal duration of glycemic control.
- Biomea plans to explore the potential clinical utility of BMF-219 in other diabetic patient populations, including type 1 diabetes.
- Biomea to host conference call on Tuesday, March 28th at 8:30 AM EDT.

REDWOOD CITY, Calif., March 28, 2023 (GLOBE NEWSWIRE) – Biomea Fusion, Inc. (“Biomea”) (Nasdaq: BMEA), a clinical-stage biopharmaceutical company dedicated to discovering and developing novel covalent small molecules to treat and improve the lives of patients with genetically defined cancers and metabolic diseases, today announced initial positive topline data for the first two cohorts of patients with type 2 diabetes mellitus (T2DM) enrolled in the Phase II portion of its ongoing Phase I/II clinical study (COVALENT-111) of BMF-219, the company’s novel, investigational covalent menin inhibitor.

Beta cell loss has been observed to be a critical component of the etiology and pathogenesis of both type 2 and type 1 diabetes; menin is thought to be a key inhibitory regulator that limits beta cell recovery in the pancreas. Using its proprietary FUSION™ System, Biomea designed BMF-219 to specifically inhibit menin to release the brakes on beta cells, and potentially enable their regeneration, reactivation, and preservation. This is the first clinical observation of patients with diabetes having a robust glucose-lowering response driven by an investigational menin inhibitor with a potentially disease-modifying mechanism of action, which may allow for continued glycemic control for prolonged periods even after treatment is stopped.

“Our goal with BMF-219 is to deliver the first disease-modifying treatment for patients with diabetes by addressing the root biological cause of the disease and its inevitable progression: the loss of insulin-producing beta cells. Today, we are seeing indications that we are achieving that goal and that BMF-219 may indeed be capable of regenerating, preserving, and reactivating healthy, functional beta cells. Moreover, we are seeing this impact and high level of glycemic control after just 4 weeks of treatment, a remarkably short timeframe, and at the first dose level, with highly favorable safety and tolerability,” said Thomas Butler, Biomea Fusion’s Chief Executive Officer and Chairman of the Board. “More than 50% of the 27 million patients in the US diagnosed with type 2 diabetes have an A1c higher than 7%, indicating that their current treatments are not able to control their disease and their increased sugar levels may lead to harming their organs. With BMF-219, we believe we have the potential to radically transform the treatment of type 2 diabetes and help millions of patients – and these initial data certainly support that belief and excitement.”

Mr. Butler continued, “We are now exploring the various dose levels in the escalation portion of the study and will select the two most promising dose levels, to investigate the treatment length and with the goal of optimizing treatment responses and durability for the majority of diabetes patients. Importantly, these initial data also give us the confidence to continue our plans to move forward with evaluating BMF-219 as a potential treatment for patients with type 1 diabetes. This is an exciting day for the Biomea team, but most importantly an exciting day for patients with diabetes.”

Dr. Jose E. Rodriguez, Internal Medicine & Medical Director at the Southwest General Healthcare Center (Fort Myers, Florida), a treating physician in COVALENT-111, added, “My patients had great benefits being included in COVALENT-111. The study drug showed hardly any side effects and was easily accepted. My patients are seeing positive health improvements, and I can literally say they are generally feeling better, overall happy and are enthusiastic, with more energy than they had before they started the study.”

Preliminary Clinical Data

40 patients were enrolled in the first three cohorts of COVALENT-111, with the first cohort (Cohort 1) comprising 16 healthy volunteers (HVs); 12 HVs were exposed to 100 mg BMF-219 once daily (QD) for two weeks and 4 HVs were exposed to placebo. In Cohorts 2 and 3, T2DM patients (n=12 per cohort with 10 patients treated with BMF-219 and 2 patients on placebo) received BMF-219 once daily for 4 weeks with or without food, respectively. In the two active treatment cohorts, enrolled patients had T2DM diagnosed for $\leq$15 years, were between the ages of 18 to 65, had been treated with

lifestyle management together with up to three anti-diabetic medications, with a stable dose for at least two months prior to screening, had a BMI ≥25 and ≤40 kg/m^2, and had poorly controlled diabetes (HbA1c ≥7.0% and ≤10%). At baseline, diabetic patients enrolled in the two active treatment cohorts, Cohorts 2 and 3, had a median A1c of 7.9 and 7.8%, respectively.

A negative food effect was seen between active treatment Cohort 3 (BMF-219 dosing without food) and Cohort 2 (BMF-219 dosing with food), which decreased the exposure significantly. Patients in active treatment Cohort 3 (taken without food) saw about a three-fold median increase in C_{max} (ng/ml) and AUC (ng x h/ml) compared to Cohort 2 (taken with food).

Additional Clinical Observations:

- Cohort 3: Patients on BMF-219 demonstrated a median A1c reduction: -1.0% and an 89% response rate at 4 weeks
  - 78% of patients achieved a ≥0.5% reduction in A1c
  - 56% achieved a ≥1.0% reduction in A1c
- Cohort 2: Patients on BMF-219 had a median A1c reduction: -0.3% and a 70% response rate at 4 weeks
  - 30% of patients achieved a ≥0.5% to ≤1.0% reduction in A1c
- Placebo: 4 diabetic patients on placebo had a median A1c and mean A1c reduction between -0.1% to -0.15%

In COVALENT-111 all patients are being assessed for changes in plasma glucose, HOMA-B, HOMA-IR, C-peptide, fasting insulin, oral glucose tolerance testing, key metabolic and lipid parameters, including weight, triglycerides, cholesterol, and for durability of response after BMF-219 treatment has completed. Further analysis and a detailed data summary will be presented at an upcoming major medical meeting.

Initial Tolerability Data

BMF-219 was generally well tolerated; all patients completed the 4-week treatment, and all patients continue in follow-up to assess the durability of the treatment effect. There were no dose reductions, serious adverse events, or severe adverse events. In the active treatment Cohorts 2 and 3 (100 mg QD, n=24) 7 of 20 patients treated with BMF-219 showed mild (Grade 1) Treatment Emergent AEs (TEAEs), 1 of 20 patients treated with BMF-219 showed a moderate (Grade 2) TEAE and 2 of 4 patients treated with placebo showed mild (Grade 1) TEAEs. No patients showed symptomatic hypoglycemia and no other TEAEs were observed.

In the healthy volunteer Cohort 1 (100 mg QD, n=16), 2 of 12 subjects treated with BMF-219 and 1 of 4 subjects treated with placebo showed mild (Grade 1) TEAEs. No other TEAEs were observed.

Conference Call and Webcast Details

Webcast, and related presentation, of Biomea's investor update on Tuesday, March 28th at 8:30 am ET will be available to registered attendees under the Investors and Media section of the company's website at https://investors.biomeafusion.com/news-events/events. A replay of the presentation will be archived on Biomea's website following the event.

Participants who want to join the call and ask a question may register here to receive the dial-in numbers and unique PIN to seamlessly access the call. Otherwise please access the listen-only webcast available at https://investors.biomeafusion.com/news-events/events.

COVALENT-111

COVALENT-111 is a multi-site, randomized, double-blind, placebo-controlled Phase I/II study. In the completed Phase I portion of the trial, healthy subjects were enrolled in single ascending dose cohorts to ensure safety at the prospective dosing levels for type 2 diabetic patients. Phase II consists of multiple ascending dose cohorts and includes adult patients with type 2 diabetes uncontrolled by current therapies. Additional information about the Phase I/II clinical trial of BMF-219 in type 2 diabetes can be found at ClinicalTrials.gov using the identifier NCT05731544.

About Menin's Role in Diabetes

Loss of functional beta cell mass is a core component of the natural history in both types of diabetes — type 1 diabetes (mediated by autoimmune dysfunction) and type 2 diabetes (mediated by metabolic dysfunction). Beta cells are found in the pancreas and are responsible for the synthesis and secretion of insulin. Insulin is a hormone that helps the body use glucose for energy and helps control blood glucose levels. In patients with diabetes, beta cell mass and function have been observed to be diminished, leading to insufficient insulin secretion and hyperglycemia. Menin is thought to act as a brake on beta-cell turnover and growth, supporting the notion that inhibition of menin could lead to the regeneration of normal, healthy beta cells. Based on these and other scientific findings, Biomea is exploring the potential for BMF-219-mediated menin inhibition as a viable therapeutic approach to potentially halt or reverse progression of type 2 diabetes.

About Type 2 Diabetes

Diabetes is considered a chronic health condition that affects how the body turns food into energy and results in too much sugar in the bloodstream. Over time, this can cause serious health problems and damage vital organs. Most people with diabetes have a shorter life expectancy than people without this disease. The CDC estimates about 2 in 5 of the adult population in the USA are now expected to develop diabetes during their lifetime. More than 37 million people of all ages (about 11% of the US population) have diabetes today. 96 million adults (more than 1 in 3) have pre-diabetes, blood sugars that are higher than normal but not high enough to be classified as diabetes. Diabetes is also one of the largest economic burdens on the United States health care system with $1 out of every $4 in US health care costs being spent on caring for people with diabetes. Despite the current availability of many diabetes medications, there remains a significant need in the treatment and care of patients with diabetes.

About Biomea Fusion

Biomea Fusion is a clinical stage biopharmaceutical company focused on the discovery and development of covalent small molecules to treat patients with genetically defined cancers and metabolic diseases. A covalent small molecule is a synthetic compound that forms a permanent bond to its target protein and offers a number of potential advantages over conventional non-covalent drugs, including greater target selectivity, lower drug exposure, and the ability to drive a deeper, more durable response.

We are utilizing our proprietary FUSION™ System to discover, design and develop a pipeline of next-generation covalent-binding small molecule medicines designed to maximize clinical benefit for patients with various cancers and metabolic diseases, including diabetes. We aim to have an outsized impact on the treatment of disease for the patients we serve. We aim to cure.

Visit us at biomeafusion.com and follow us on LinkedIn, Twitter and Facebook.

Forward-Looking Statements

Statements we make in this press release may include statements which are not historical facts and are considered forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the "Securities Act"), and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). These statements may be identified by words such as "aims," "anticipates," "believes," "could," "estimates," "expects," "forecasts," "goal," "intends," "may," "plans," "possible," "potential," "seeks," "will," and variations of these words or similar expressions that are intended to identify forward-looking statements. Any such statements in this press release that are not statements of historical fact, including statements regarding our cash runway, the clinical and therapeutic potential of our product candidates and development programs, including BMF-219, the potential of BMF-219 as a treatment for various types of cancer and diabetes, our research, development and regulatory plans, including our pursuit of BMF-219 in metabolic diseases, our plans to continue the evaluation of BMF-219 for type 2 diabetes in our COVALENT-111 study, that initial results may not be indicative of final results in later clinical trials, the availability of future data from the Phase II portion of the study, and the timing of such events, may be deemed to be forward-looking statements. We intend these forward-looking statements to be covered by the safe harbor provisions for forward-looking statements contained in Section 27A of the Securities Act and Section 21E of the Exchange Act and are making this statement for purposes of complying with those safe harbor provisions.

Any forward-looking statements in this press release are based on our current expectations, estimates and projections only as of the date of this release and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements, including the risk that we may encounter delays or unforeseen results in preclinical development, IND-filing and acceptance, patient enrollment and in the initiation, conduct and completion of our planned clinical trials and other research, development and regulatory activities. These risks concerning Biomea Fusion's business and operations are described in additional detail in its periodic filings with the U.S. Securities and Exchange Commission (the "SEC"), including its most recent periodic report filed with the SEC and subsequent filings thereafter. Biomea Fusion explicitly disclaims any obligation to update any forward-looking statements except to the extent required by law.

Contact:

Sasha Blaug
SVP Corporate Development
sb@biomeafusion.com

Exhibit 99.2

COVALENT-111: Phase II

First Data Readout of Initial Healthy Volunteer (HV) and Type 2 Diabetes Mellitus (T2DM) Cohorts

March 28, 2023

biomea FUSION

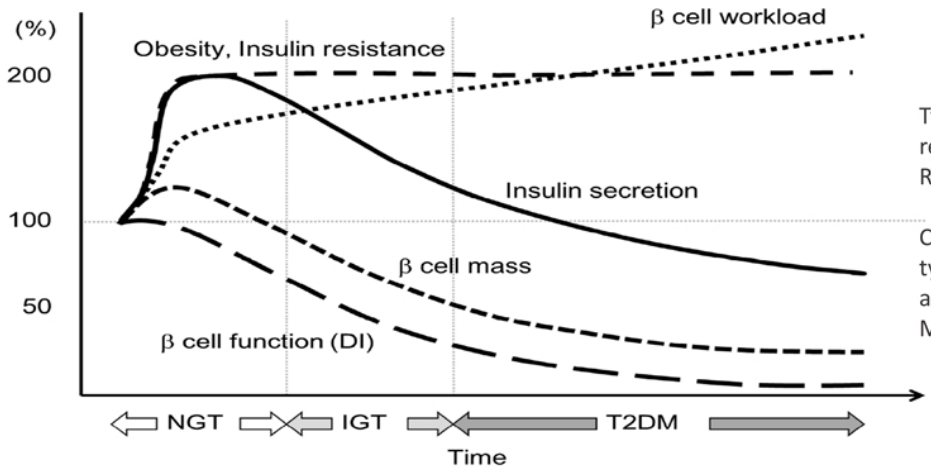
Legal Disclaimer & Forward-Looking Statements

Certain statements in this presentation and the accompanying oral commentary are forward-looking statements. These statements relate to future events or the future business and financial performance of Biomea Fusion, Inc. (the "Company") and involve known and unknown risks, uncertainties and other factors that may cause the actual results, levels of activity, performance or achievements of the Company or its industry to be materially different from those expressed or implied by any forward-looking statements. In some cases, forward-looking statements can be identified by terminology such as "may," "will," "could," "would," "should," "expect," "plan," "anticipate," "intend," "believe," "estimate," "predict," "potential" or other comparable terminology. All statements other than statements of historical fact could be deemed forward-looking, including any projections of financial information or profitability, the initiation, timing and results of pending or future preclinical studies and clinical trials, the actual or potential actions of the FDA, the status and timing of ongoing research, development and corporate partnering activities, any statements about historical results that may suggest trends for the Company's business; any statements of the plans, strategies, and objectives of management for future operations; any statements of expectation or belief regarding future events, potential markets or market size, or technology developments, unfavorable global economic conditions, including inflationary pressures, market volatility, acts of war and civil and political unrest, and other factors affecting the Company's financial condition or operations. The Company has based these forward-looking statements on its current expectations, assumptions, estimates and projections. While the Company believes these expectations, assumptions, estimates and projections are reasonable, such forward-looking statements are only predictions and involve known and unknown risks and uncertainties, many of which are beyond the Company's control. For a discussion of these and other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in our most recent annual report on Form 10-K filed with the Securities and Exchange Commission, as well as discussions of potential risks, uncertainties, and other important factors in our other subsequent filings with the Securities and Exchange Commission. The forward-looking statements in this presentation are made only as of the date hereof. Except as required by law, the Company assumes no obligation and does not intend to update these forward-looking statements or to conform these statements to actual results or to changes in the Company's expectations. This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

Agenda

Introduction	Ramses Erdtmann *Chief Operating Officer & Co-Founder of Biomea*
Diabetes Background & Overview	Dr. Juan Frias *Medical Director & Principal Investigator of Velocity Clinical Research, Scientific Advisory Board Member of Biomea*
Diabetes & Beta Cell Function	Dr. Rohit Kulkarni *Senior Investigator and Professor of Medicine of Harvard Medical School, Faculty Member, Joslin Diabetes Center, Scientific Advisory Board Member of Biomea*
COVALENT-111 First Study Results	Dr. Steve Morris *Chief Medical Officer of Biomea*
Executive Summary & Outlook	Thomas Butler *Chief Executive Officer, Chairman of the Board & Co-Founder of Biomea*

Type 2 Diabetes Progression is Driven by Loss of Beta Cell Mass



Type 1 and Type 2 Diabetes both result in Beta Cell Loss and Reduction in Beta Cell Mass

Current Diabetes Therapies are typically **not** observed to address the decrease in Beta Cell Mass and Beta Cell Health

Normal Glucose Tolerance (NGT) followed by Impaired Glucose Tolerance (IGT) followed by Type 2 Diabetes Mellitus (T2DM) Insulin Resistance has been observed to lead to an increase in Beta Cell Workload which may ultimately lead to Beta Cell Failure and Death, and the Progression of Type 2 Diabetes.

*Int. J. Mol. Sci. 2016, 17, 744; doi:10.3390/ijms17050744

Menin – Downregulated by Prolactin during Pregnancy

Allowing for beta cell expansion and prevention of gestational diabetes

- Stanford researchers have observed that during pregnancy, maternal pancreatic islets grow to match dynamic physiological demands.
- Menin has been found to control islet growth in pregnant mice. Pregnancy stimulates proliferation of maternal pancreatic islet beta-cells, an effect accompanied by reduced beta-cell levels of menin and its targets.
- Prolactin, a hormonal regulator of pregnancy, represses beta-cell menin levels and stimulates beta-cell proliferation.
- Transgenic expression of menin in maternal beta-cells prevented islet expansion and led to hyperglycemia and impaired glucose tolerance, hallmark features of gestational diabetes.

REPORTS

Menin Controls Growth of Pancreatic β-Cells in Pregnant Mice and Promotes Gestational Diabetes Mellitus

Satyajit K. Karnik,[1] Haiman Chen,[1]* Graeme W. McLean,[1]* Jeremy J. Heit,[1]* Xueying Gu,[1] Andrew Y. Zhang,[1] Maggi Fontaine,[2] Michael H. Yen,[1,2] Seung K. Kim[1,3]†

2 NOVEMBER 2007 VOL 318 SCIENCE www.sciencemag.org

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Karnik et al. Science, (2007), 801-806, 318(5851)

Summary of Results

	Cohort 2		Cohort 3	
	BMF-219	**Placebo**	**BMF-219**	**Placebo**
Number of Subjects	10	2	10	2
Exposure: C_{max} (ng/mL)/ AUC (hr*ng/mL)	34.8 / 84.3	-	94.2 / 224	-
Median (Mean) HbA1c % at Baseline	7.9 (8.0)	8.4 (8.4)	7.8 (8.1)	7.8 (7.8)
Median (Mean) Change in HbA1c % at Week 4	**-0.3 (-0.25)**	-0.1 (-0.1)	**-1.0 (-0.81)**	-0.15 (-0.15)

Note: **Cohort 2** – 100 mg BMF-219 or placebo daily for 4 weeks taken with food
Cohort 3 – 100 mg BMF-219 or placebo daily for 4 weeks taken without food

COVALENT-111: A Phase 1/2 Randomized, Double-Blind, Placebo-Controlled Single and Multiple Ascending Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of BMF-219, an Oral Covalent Menin Inhibitor, in Healthy Adult Subjects and in Adult Subjects with Type 2 Diabetes Mellitus (NCT05731544)

Phase 1 (SAD)

SAD C1 to SAD C4 (HVs)
Total N=40
Dose [100, 200, 400, and 600 mg]

Phase 2 (MAD)

MAD C1 (HVs)
Total N = 16

MAD C2 to MAD C8 (T2DM)
Total N=108

Dose [100, 200, 300, 400, 600 mg]

In Phase 2, COVALENT-111 is enrolling subjects with an HbA1c of 7-10% despite being on standard of care (up to three T2DM agents).

Study Treatment: BMF-219

- A covalent small molecule menin inhibitor, administered orally daily in 28 day cycles

Primary Objective:

- Evaluate safety and tolerability of BMF-219

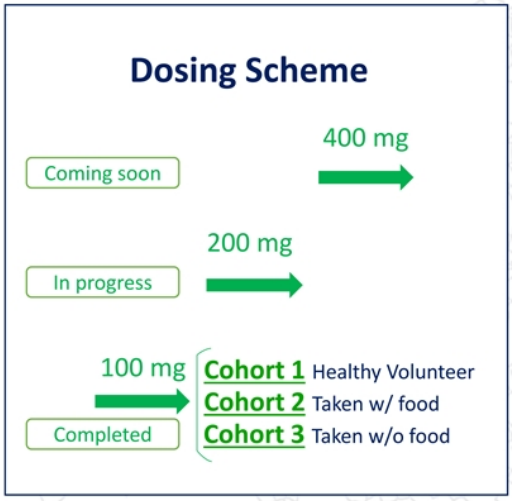
Secondary Objectives:

- Evaluate PK of BMF-219
- Evaluate the effect on BMF-219 on glycemic parameters (HbA1c, PG) and few additional parameters using OGTT, 7-day CGM
- Evaluate the changes in beta cell function
- Evaluate impact on lipid parameters, body weight etc.

Exploratory Objectives:

- To assess the durability of response to glycemic parameters

Dose Escalation Phase (Oral, Daily Dosing X 28 days)

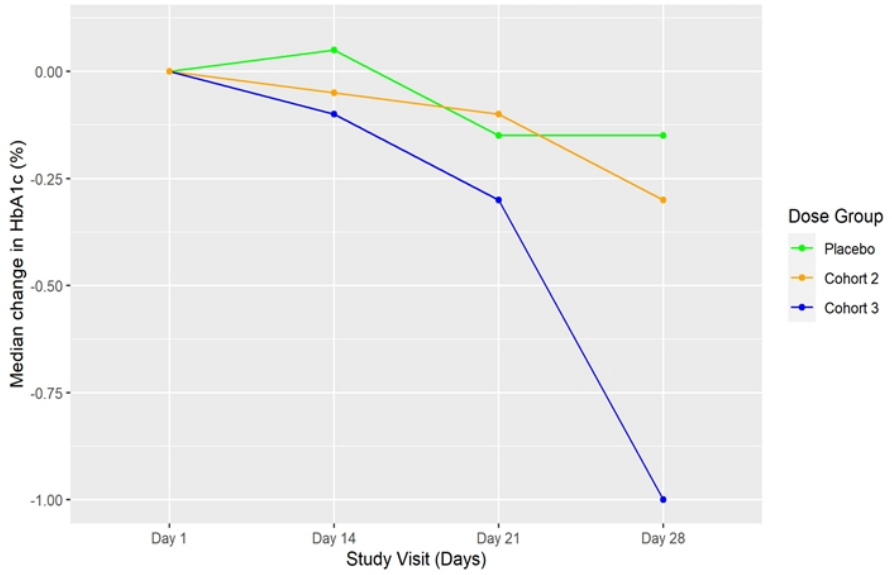


- Dose Escalation Phase (Total N) = 60 Type 2 Diabetes
  - Each dose cohort [N=10 active, 2 placebo]
  - Key Inclusion criteria: HbA1c= 7-10%; Time since diagnosis within 15 yrs. on stable anti-diabetic regimen (up to 3 agents) for at least 2 months prior to enrollment.
  - (H.V.) Study treatment duration – once daily dosing for 14 days
  - (T2DM) Study treatment duration – once daily dosing for 28 days
  - Follow-up duration – 5 months post completion of study treatment
- Dose Expansion Phase at two dose levels (Total N) = 24 Type 2 Diabetes

COVALENT-111 Baseline Patient Characteristics

	Cohort 2		Cohort 3	
	BMF-219	**Placebo**	**BMF-219**	**Placebo**
Number of Subjects	10	2	10	2
Age (min, max)	35, 60	40, 53	38, 63	35, 61
Sex (M, F)	7, 3	2, 0	6, 4	2, 0
Time since T2DM diagnosis (min, max)	4 yrs, 14 yrs	~1 yrs, 5 yrs	6 mo, 9 yrs	9 mo, 9 yrs
Concurrent Medications for T2DM	▪ Metformin (7/10) ▪ Janumet (1/10) ▪ Jardiance [Metformin + Empagliflozin] (1/10) ▪ Synjardy [Metformin + Empagliflozin] (1/10)	▪ Metformin alone (1/2) ▪ Janumet [Metformin + Sitagliptin] (1/2)	▪ Metformin alone (9/10) ▪ Janumet and Farxiga [Dapagliflozin] (1/10)	▪ Metformin (2/2)

Observed HbA1c Lowering of BMF-219



Cohort 2

Response Rate

70% of patients responded to BMF-219

HbA1c (all pts)

Median Baseline: 7.9%

Median Δ: - 0.3% (at week 4)

Cohort 3

Response Rate

89% of patients responded to BMF-219

HbA1c (all pts)

Median Baseline: 7.8%

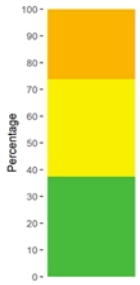
Median Δ: - 1.0% (at week 4)

COVALENT-111 HbA1c Summary Results at Week 4

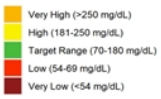
	Cohort 2		Cohort 3	
	BMF-219	**Placebo**	**BMF-219**	**Placebo**
Number of Subjects	10	2	10	2
HbA1c (%) at Baseline	7.1 – 9.1		7.0 – 9.8	
Median HbA1c (Mean) (%) at Baseline	7.9 (8.0)	8.4 (8.4)	**7.8 (8.1)**	7.8 (7.8)
Number of Subjects with Reduction in HbA1c at week 4	7/10 (70%)	1/2	**8/9 (89%)***	1/2
≥0.5% Reduction in HbA1c at Week 4	3/10 (30%)	1/2	**7/9 (78%)***	0
≥1% Reduction in HbA1c at Week 4	0	0	**5/9 (56%)***	0
Median Change in HbA1c at Week 4 (Mean) (%)	-0.3 (-0.25)	-0.1 (-0.1)	**-1.0 (-0.81)**	-0.15 (-0.15)

*Note: The active group denominator in Cohort 3 is 9 because the week 4 sample for one patient was unable to process.

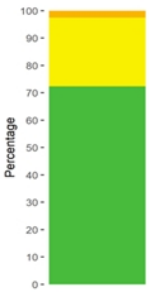
Case Report Cohort 3 Patient Results (Patient A): Glycemic Parameters



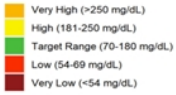
Continuous Glucose Monitoring
Baseline



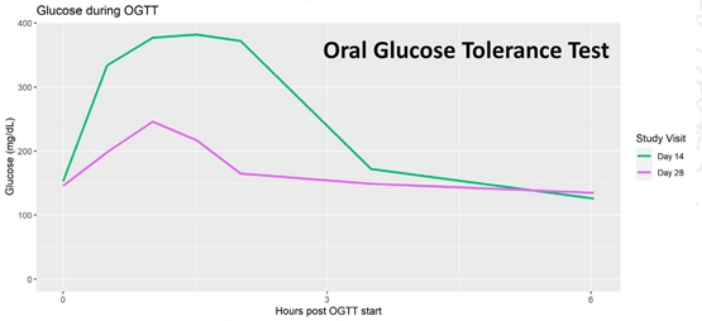
- Average glucose 205 mg/dL
- 37% time in Target Range

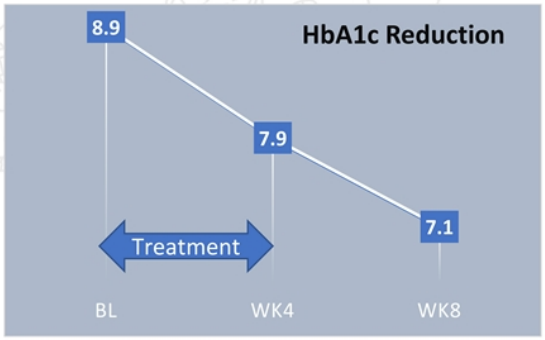


Continuous Glucose Monitoring
Week 4

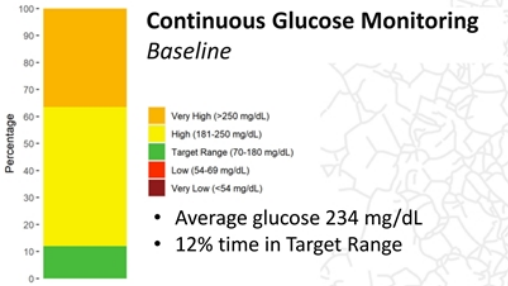


- Average glucose 169 mg/dL
- 72% time in Target Range



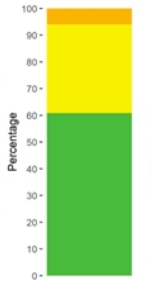


Case Report Cohort 3 Patient Results (Patient B): Glycemic Parameters



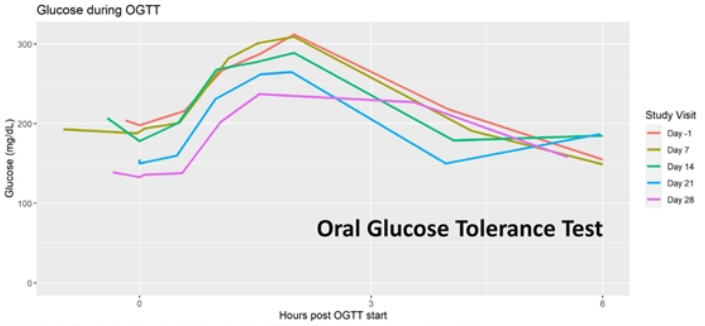
Continuous Glucose Monitoring
Baseline

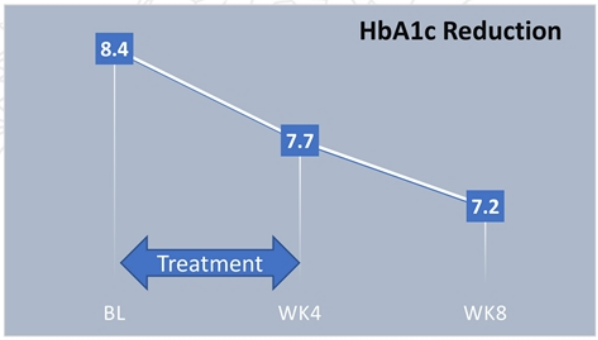
- Average glucose 234 mg/dL
- 12% time in Target Range



Continuous Glucose Monitoring
Week 4

- Average glucose 174 mg/dL
- 60% time in Target Range





COVALENT-111 Cohort 1 All Treatment Emergent Adverse Events (TEAEs) (Healthy Volunteers, n=16; *100 mg once daily for 14 days*)

Preferred Term for TEAE	BMF-219 (N=12)	Placebo (N=4)	Total (N=16)
Subjects with ≥1 TEAE	2 (16.7%)	1 (25%)	3 (18.8%)
Headache	1 (8.3%)	1 (25%)	2 (12.5%)
Sharp left eye pain	1 (8.3%)	0	1 (6.3%)

*All TEAEs were Grade 1

COVALENT-111 Cohort 2 & 3 All TEAEs
(Type 2 Diabetes n=24; 100 mg once daily dosing X 4 weeks)

Preferred Term for TEAE	BMF-219 (N=20)	Placebo (N=4)	Total (N=24)
Subjects with ≥1 TEAE	7 (35%)	2 (50%)	9 (38%)
Abdominal bloating	2 (10%)	0	2 (8.4%)
Elevated pancreatic polypeptide in plasma	0	2 (50%)	2 (8.4%)
Cough	1 (5%)	1 (25%)	2 (8.4%)
Elevated GGT	1 (5%)	0	1 (4.2%)
Elevated AST	1 (5%)	0	1 (4.2%)
Elevated ALT	1 (5%)	0	1 (4.2%)
Sore throat	1 (5%)	0	1 (4.2%)
Non-specific GI symptoms	1 (5%)	0	1 (4.2%)
Decreased interleukin-6	1 (5%)	0	1 (4.2%)
Swollen lymph nodes	0	1 (25%)	1 (4.2%)
Elevated lipase	1 (5%)	0	1 (4.2%)
Intermittent headaches	1 (5%)	0	1 (4.2%)
Contact dermatitis	1 (5%)	0	1 (4.2%)

All TEAEs are Grade 1 except Elevated Lipase (Grade 2)

Summary of Data

Safety

- BMF-219 demonstrated a well-tolerated safety profile
- No dose discontinuations
- All 20 subjects completed 4 weeks of treatment and continue in 5-month follow-up period
- No severe or serious TEAEs were observed
- No episodes of symptomatic hypoglycemia occurred in any patients

Efficacy

Cohort 3 highlights

- 89% pts achieved a reduction in HbA1c
- 78% pts achieved ≥ 0.5% reduction in HbA1c
- 56% pts achieved ≥ 1% reduction in HbA1c
- Positive trend in OGTT and CGM parameters

Q & A

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