MEMORANDUM

Biodel F3Q14- Positive phase 2 results for ultra-rapid-acting BIOD-531 - August 14, 2014

Executive Highlights

- Biodel reported positive topline phase 2 data on BIOD-531 (U400 ultra-rapid-acting human insulin); results showed superior postprandial control and better time in range compared to Lilly's Humalog Mix 75/25 and Lilly's Humulin R 500.
- A phase 1 trial of the dual-chamber Glucagon Emergency Management (GEM) rescue device is expected to begin in 4Q14; NDA submission is still expected in late 2015.

Biodel reported F3Q14 financial results on Monday in a call led by CEO Dr. Errol de Souza. The vast majority of the call was focused on newly released phase 2 data for BIOD-531, the company's concentrated ultra-rapid-acting insulin candidate. Below, we include the top six highlights of the call, followed by a pipeline summary and Q&A.

1. Biodel announced positive topline results from a phase 2 trial of BIOD-531 (U400 ultra-rapid-acting human insulin); results demonstrated superior postprandial glucose control and improved time-in-range with BIOD-531 (delivered both pre- and post-meal) compared to Lilly's Humalog Mix 75/25 and Lilly's Humulin R U500. Further phase 2 data in severely insulin resistant patients is expected in 4Q14, along with FDA feedback on the development program.

2. Management did not provide updates on its ultra-rapid-acting human insulin, BIOD-123 (phase 3 ready, but awaiting a partnership).

3. Similarly, there was no update on the ultra-rapid-acting formulations of insulin aspart and insulin lispro.

4. Biodel plans to begin a phase 1 trial of its Glucagon Emergency Management (GEM) rescue device in 4Q14; an NDA submission is still expected in late 2015, consistent with prior timelines.

5. Biodel is testing several stable liquid glucagon formulations in animal models for use in the ultra-portable BD Uniject rescue device. Stability work also continues on formulations for the artificial pancreas.

6. As of June 30, Biodel had cash and cash equivalents of $25 million. With the help of two additional funding vehicles deployed in F3Q14, management believes financial resources will last through the filing of an NDA for the GEM device in late 2015.

Table of Contents

TOP SIX HIGHLIGHTS

1. Biodel announced positive topline results from a phase 2 meal study of BIOD-531 (U400 ultra-rapid-acting human insulin). The single-blind, four-arm crossover study (ClinicalTrials.gov Identifier: NCT02212951) enrolled 12 patients with type 2 diabetes (11 completed the study) whose daily insulin requirement was 50-200 units per day; the average baseline A1c was 9% and the average BMI was 33.5 kg/m². Participants received a single 0.6 U/kg dose of BIOD-531 immediately before breakfast, Lilly's Humalog Mix 75/25 immediately before breakfast, Lilly's Humulin R U500 immediately before breakfast, or BIOD-531 20 minutes after breakfast. Visits were separated by 7-21 day washout periods. Glucose levels were monitored every five minutes for 12 hours after dosing, and patients were not given additional insulin with lunch. More detailed results are posted here and presentation slides are posted here.

- **Pre-meal and post-meal BIOD-531 led to superior postprandial glycemic control and higher time in range vs. Humalog Mix and Humulin R U500.** BIOD-531 also provided better extended coverage compared to the two marketed products: both the average blood glucose concentration and the percentage of blood glucose readings within the target range were significantly higher with BIOD-531 than with either comparator throughout the entire 12-hour monitoring period - slide two illustrates this quite well.

	Average Postprandial Glucose (0-5.5 hrs)	**Time in range** (70-180 mg/dl; 0-5.5 hrs)	**Estimated A1c** (baseline 9.0%)
Pre-meal BIOD-531	168 mg/dl*	53%*	7.8%
Post-meal BIOD-531	173 mg/dl*	49%	7.8%
Humalog Mix 75/25	205 mg/dl	28%	9.5%
Humulin R U500	193 mg/d	34%	8.5%

*p<0.05 vs. Humalog Mix or Humulin U500

- **It was particularly notable to see that the postprandial benefits of BIOD-531 were maintained with administration 20 minutes after breakfast.** This has long been a downside of current rapid-acting insulins, as they control postprandial glucose most optimally when taken 20 minutes before a meal. As management emphasized during Q&A, this is very clinically relevant, as post-meal administration of prandial insulin aligns more closely with how patients often behave in a real-world setting.
- **"We could not be more enthusiastic about these results. They confirm our earlier assessment that BIOD-531 is an important asset within Biodel's expanding portfolio."** Management's excitement was palpable in this call, and given the product's potential market, we would not disagree. We thought the data looked very strong and really substantiated the multi-pronged benefits of this concentrated insulin - better post-meal coverage and better daytime coverage than both premixed insulin and Lilly's concentrated U500 insulin.
- **A second phase 2 study evaluating BIOD-531 in highly insulin-resistant type 2 patients is expected to complete in calendar 4Q14.** The trial will have essentially the same design as the completed trial, except that it will enroll patients who use >200 units of insulin per day, administer two doses of prandial insulin (one at breakfast and one at dinner), and monitor blood glucose for 24 hours.
- **Biodel is "working with the FDA to define a clinical development program" for BIOD-531; feedback is expected in early calendar 4Q14.** The company learned in F2Q14 that the FDA will not require a CVOT for Biodel's ultra-rapid-acting recombinant human insulin BIOD-123, and we assume that would likely be the case this product as well. The call emphasized

Biodel's plans to market BIOD-531 as an alternative to both premixed insulin (e.g., Lilly's Humalog 75/25 and Novo Nordisk's Novolog 70/30) and concentrated insulin (Lilly's Humulin R U500). Management has said in previous updates that Biodel could likely commercialize the severe insulin resistance opportunity on its own, as marketing to endocrinologists is possible with a small sales force, but the company would likely pursue a partnership for the larger group of patients with type 2 diabetes and moderate degrees of insulin resistance (i.e., mostly in the primary care setting). In Q&A, management was optimistic about the potential for the label to include language around a faster onset of action - this is not in the initial Afrezza label, so we would note that this is not a given.

- **Biodel has also conducted preclinical insulin pump studies of BIOD-531 through an NIH SBIR grant.** Results presented at ADA demonstrated that the rate of absorption and onset of action of BIOD-531 is faster than Humulin U500 and similar to Lilly's Humalog. In the past management had discussed potential for an artificial pancreas application of BIOD-531, though this call specifically mentioned pumps for type 2 diabetes. This was not a surprise, as we had assumed the pharmacodynamic profile of BIOD-531 (fast-in/slow-out) was not ideal for the closed-loop (fast-in/fast-out).

2. Management did not provide updates on the phase 3 ready BIOD-123 (ultra-rapid-acting recombinant human insulin). Given the updates on BIOD-531 and the glucagon program, management said that the call did not offer enough time to share updates on this compound and analog-based candidates (see below) - we might also speculate that their status has been deprioritized in favor of the programs discussed on the call. It might also be that partnership discussions are ongoing and there is nothing formal to share at this point in time.

- **Biodel received detailed feedback from the FDA on a proposed phase 3 program for BIOD-123 in F2Q14, but trials will not begin until Biodel finalizes a partnership deal**. The company has expressed hope that such a deal could encompass development of the analog-based ultra-rapid-acting insulin portfolio as well. Management has said that it is ideally looking for a "pharma company with adequate resources to commercialize BIOD-123 for type 1 and type 2 diabetes," and we assume that only established insulin players like Sanofi or Lilly would meet this criterion (Novo Nordisk does not typically partner and has its own ultra-rapid-acting version of insulin aspart in phase 3). Given Sanofi's partnership to license MannKind's Afrezza, we assume Lilly is one of the most likely candidates at this point.
- **Biodel presented somewhat inconclusive phase 2 data on BIOD-123 at ADA.** Overall, BIOD-123 produced non-inferior A1c reductions compared to Humalog (0.17% treatment difference in favor of Humalog), though the 95% confidence interval barely met the non-inferiority threshold of 0.4%. Ten-point profiles and CGM did not demonstrate consistent differences in postprandial glucose between BIOD-123 and Humalog, despite a clear postprandial benefit (~15 mg/dl) observed during a liquid meal challenge test. Interpretation of these results was challenging due to large baseline group imbalances in gender, differences in basal insulin doses, and an open-label design.

3. Similarly, management also did not provide updates on ultra-rapid-acting versions of insulin aspart (Novo Nordisk's Novolog) and insulin lispro (Lilly's Humalog). As of F2Q14, Biodel had identified viable ultra-rapid-acting lispro formulations with sufficient stability for clinical trials and was in active discussions to source supplies of lispro. As a reminder, the company reported phase 1 results for two such formulations, BIOD-238 and BIOD-250, in January 2013; both exhibited a faster-on, faster-off profile relative to Humalog.

- **In April, Biodel signed a research supply and technology agreement with China-based HEC Pharm to source insulin aspart for its analog-based ultra-rapid-acting insulin program.** Under the terms, HEC will supply Biodel with insulin aspart, and Biodel will add its proprietary ingredients for ultra-rapid-acting formulations (including EDTA, citrate, and magnesium sulfate). We saw the news as a positive for Biodel, as an API source of lispro/aspart was a gating factor to advancing the analog-based ultra-rapid-acting insulin program.

- **Development of these ultra-rapid-acting insulin analogs would likely follow the 505(b)(2) regulatory pathway**, which would allow referencing of existing data on Novolog and Humalog and potentially moving directly from phase 1 to phase 3. To our knowledge, Humalog's US patent expired in June 2014, and Novolog's is due to expire in 2017.

4. Biodel has filed an Investigational New Drug (IND) application for its Glucagon Emergency Management (GEM) rescue device and plans to begin a phase 1 trial of the device in 4Q14. An NDA submission for the dual-chamber, auto-reconstitution device is still expected in late 2015, consistent with previous timelines. The six-arm, crossover, phase 1 trial is expected to enroll 12 healthy volunteers who will receive either an intramuscular or subcutaneous injection of BIOD-961 (Biodel's glucagon formulation), or Lilly or Novo Nordisk's marketed glucagon formulations. The goal is to demonstrate pharmacokinetic (PK) and pharmacodynamics (PD) bioequivalence between BIOD-961 and the marketed formulations and to select one of the marketed products as a comparator for a subsequent pivotal trial in 30 healthy volunteers (expected to complete in 3Q15).

- **A recent human factors study collected positive usability data on the GEM device.** All subjects successfully triggered auto-reconstitution, delivered a complete injection, and engaged the automatic needle retraction mechanism in less than one minute, regardless of whether they had received training on the device. In addition, all subjects replicated the results in a second dosing attempt. Management concluded that the GEM device is more intuitive and would therefore be more effective in a hypoglycemic emergency than currently marketed glucagon kits. Future human factors studies will directly compare the usability of the GEM device to existing glucagon kits, and the final study is expected to complete in 3Q15.
- **Biodel has a supply chain arrangement in place to scale up production for the NDA submission and commercialization.** Management is working with Unilife and Emergent BioSolutions to facilitate manufacturing of the GEM device, and the company is "on track" to begin manufacturing six registration lots for clinical trial initiation in late 4Q14 and to complete manufacturing in 3Q15.
- **As a reminder, the GEM device (pictures here) contains a lyophilized cake of glucagon, which can be delivered in three steps:** 1) remove a cover and twist (reconstitutes the glucagon and unlocks the front needle cover; 2) remove the needle shield; 3) push plunger to give dose (the needle automatically retracts into the barrel following completion of a full dose). The device is expected to have two-year dating and come in 1 mg and 0.5 mg (children) doses. See our detailed coverage of Biodel's Luncheon at ADA 2014 for more information on this device.

5. Biodel has "made solid progress" and continues to test several "promising" stable liquid glucagon formulations in animal models for use in the ultra-portable, low-cost BD Uniject device (prefilled multipacks that last four months each) for severe hypoglycemia. Management has not provided a specific timeline update for this product since F1Q14, when the hope was to develop a formulation by the second half of 2014. As a reminder, this novel approach to stable glucagon lowers the hurdle for room temperature stability from two years to four months, as patients could simply take a new Uniject out of the refrigerator every four months without the need for a new prescription. For more detailed information on the Uniject program, see our Biodel F4Q13 report.

- **Biodel is also continuing to develop stable glucagon formulations for use in insulin pumps/artificial pancreas.** These efforts are being funded by an NIH SBIR grant; management did not provide a specific timing update.

6. As of June 30, Biodel had cash and cash equivalents of $24.5 million, reflecting a cash burn of $4.2 million in F3Q14. The company has put in place two financing vehicles for the sale of up to $14 million of the company's common stock and an equity purchase commitment for an additional $15 million of the company's common stock. In July, the company raised approximately $2.9 million through these vehicles. Management did not give a specific financial runway, but has previously indicated that current resources are sufficient to fund operations until at least the end of 2Q15. These additional funding vehicles are expected to fund the GEM development program "through the filing of an NDA" (i.e., late 2015).

PIPELINE SUMMARY - INSULIN

Ultra-Rapid-Acting Insulin Candidate	Key Advantages	Status
BIOD-531 (U400 concentrated recombinant human insulin)	Ultra-rapid profile and long duration of action; phase 2 results suggest superior postprandial glucose control vs. Lilly's Humulin R U500 and Lilly's Humalog Mix 75/25.	Topline phase 2 results reported on August 11. More phase 2 results and FDA feedback on phase 3 program expected in 4Q14.
BIOD-123 (recombinant human insulin)	A1c non-inferiority vs. Humalog in phase 2, with trends toward less hypoglycemia, better postprandial glucose control, and a weight advantage.	Partnership desired before moving to phase 3. FDA feedback on phase 3 design shared in 1Q14. Phase 2 results presented at ADA 2014.
Analog-based formulations (lispro and aspart)	More rapid absorption and faster decline from peak concentration vs. Humalog	Partnership discussions ongoing. Identified viable lispro-based ultra-rapid-acting formulations to move into the clinic; in active discussions to source GMP supplies of lispro. Initiated aspart program following signing of a research supply and technology development agreement with China-based HEC Pharm in April.

PIPELINE SUMMARY - GLUCAGON

Glucagon Product	Indication	Room Temp Stability	Key Advantages/ Market Segment	Status
GEM Device (dual-chamber, auto-reconstitution device)	Rescue (severe hypoglycemia)	Two years	Simpler than current glucagon kits. Offers needle-stick protection. Long-term room temp stability. Targeted at parents/caregivers, institutions, emergency responders.	IND filed. Phase 1 trial will begin in 4Q14; pivotal trial will begin upon phase 1 completion. NDA submission expected in late 2015.

BD Uniject device (stable liquid glucagon-filled multipacks)	Rescue (severe hypoglycemia)	Four months	High portability, small device, no reconstitution needed. Lower bar of four months for room temp stability. Appealing to active patients and parents of children with diabetes.	Following GEM device. Formulation and stability work ongoing.
Stable liquid glucagon for artificial pancreas	24/7 use in dual-chambered pump	Not disclosed	Tighter glucose control, less hypoglycemia as part of an artificial pancreas.	Following GEM device. Formulation and stability work ongoing.

COMPETITIVE LANDSCAPE OVERVIEW - GLUCAGON

Company*	**Details**	**Stage****
Locemia (AMG Medical)	Intranasal formulation for severe hypoglycemia.	Phase 3 studies ongoing in children and adults.
Xeris	G-Pen (stabilized glucagon auto-injector for severe hypoglycemia) G-Pen Mini (mini-dosing for mild/ moderate hypoglycemia) G-Pump glucagon (pumpable)	Phase 3 to start in 4Q14 (n=30); FDA submission in mid-2015. Phase 2 - first patient dosed Phase 2 - first patient dosed
Biodel	Auto-reconstitution, dual-chamber pen (GEM Device) Liquid glucagon multipacks for severe hypoglycemia (BD Uniject device) Pumpable glucagon (artificial pancreas)	Pivotal study to start in 4Q14; late 2015 NDA submission Following GEM Device. Following GEM Device.
Zealand	ZP-GA 1: liquid glucagon analog.	Data presented at ADA 2014 in late-breaking poster 390-P
Latitude	Aqueous glucagon formulation for use in pumps. Six-month stability at room temperature.	Clinical testing to begin in 2014. JDRF partnership announced at ADA 2013.
Zosano Pharma	Glucagon Microneedle Patch for Severe Hypoglycemia	Second phase 1 study to begin in 3Q14; see coverage of S-1 Form filing to go public
Dr. Ken Ward et al., OHSU	"A Novel, Stable Formulation of Glucagon for Bihormonal, Closed-Loop Treatment of Type 1 Diabetes"	Oral #236 at ADA 2014
Enject	Automated reconstitution device (lyophilized glucagon)	???

Arecor	Aqueous formulation requiring refrigeration.	???
PhySci (Marcadia)/ Roche	Glucagon analogs	To our knowledge, this program has been discontinued.

QUESTIONS AND ANSWERS

Q: On BIOD-531, do you think it would be feasible to get language about administration after a meal in a product label?

A: I think the answer is yes. In fact, some of the prandial insulins currently have in their label approval before or after meals. I believe that applies to Humalog and Apidra. So yes, that is an achievable goal.

Q: Would your aim be to get any kind of time frame around that, meaning the number of minutes before vs. after the meal?

A: Yes. That kind of language does exist in those labels. When you're talking about before the meal, for example, Humalog is approved to be used anywhere from zero to 15 minutes before the meal. The current labeling is not so specific after the meal. But certainly, I think our labeling would be consistent with how we've conducted this trial and any future trials. The way we dosed it in this trial was within two minutes, which to me is equivalent to immediately before the meal. And in this case, we dosed 20 minutes after the start of the meal for the post-meal arm. So I suspect that if the final labeling needs that kind of precision, we would have that kind of instruction.

To me, the time frames we used in this trial are what's clinically relevant because that's when patients are willing to take prandial insulins - either right before the meal, or some patients do prefer to take it right after the meal. The U500 label recommends a 30-minute time interval between the injection of U500 and then subsequently eating a meal. And I can tell you, in the real world of patient care, that's a very difficult thing for patients to comply with every day. So to me, the most clinically relevant time frames are the ones we tested in this study - immediately before the meal or just after the meal.

Q: For the GEM product, can you talk about what amount of stability data or duration of stability data you expect to need for submission of the NDA and what data you have today?

A: That is a negotiation that we'll have with the FDA in our pre-NDA meeting or post-pivotal trial meeting, which will be around sort of the middle of next year. And we are planning to put the lots for stability toward the end of this year, so we might have close to 12 months of data for the filing of the NDA. One of the things we're doing is tracking BIOD-961 head-to-head vs. Lilly's glucagon. We've got several months' worth of data and we look at least as good as the Lilly formulation that's out there. So that's the stability data. We are very confident that the stability of BIOD-961 will be at least equivalent to the marketed products. But exactly how much stability data we'll put into the NDA will be a point of dialogue that we'll have with the FDA, because we can always supplement with additional data while the NDA is being reviewed.

Q: These look like some very positive results you've reported for phase 2. Based on these results and the prior phase 1, it seems to me that there are two potential markets you can go after with BIOD-531: the market for patients with a good amount of insulin resistance that need a higher concentration of product and then also patients that are using the mixed products to provide a postprandial and basal insulin. Could you talk a little bit about what you think is needed from a regulatory point of view, potential clinical trials that you would need to do for either or both of those settings?

A: I think the clinical development program here would be very similar to new insulin clinical development programs in general, in the sense that the primary goal of all new insulins is to show at least as good A1c control - in other words, non-inferior A1c control with no excess hypoglycemia in that setting. That's what's necessary for regulatory approval without any unexpected or new safety problems, of course. So I think that's what it would take for approval. Now with this candidate BIOD-531, I would hope that we could actually show

more attractive features than just those. But that requires multi-dose trials to do. I think the standard non-inferiority insulin trial is a parallel group trial where patients are treated for six months. Oftentimes there are some extensions there, but again, I wouldn't see anything radically different about the design of those kinds of pivotal trials.

This is a question that we have actually posed to the FDA so that we're not second-guessing what they would require for approval of these products, and we anticipate receiving their feedback probably in about six weeks or so if they hold to their timelines. But if you think about the utility of this program, let's go after the large indication. You could do a trial vs. Humalog 75/25 and, as was demonstrated in this profile, it would be a non-inferiority trial on A1c. But then we've got superiority on two other fronts in terms of better prandial coverage, which the current trial demonstrated, and lower volumes of injection and a better duration even with a second meal. So that's why we're excited about this trial we just reported on, which gives us the confidence to go head-to-head against the best-selling mix that's out there.

Now, the second trial that's ongoing that we'll get the data for toward the end of the year, that's the severely insulin-resistant patients that we're going after. And our suggestion to the FDA is that we would do one trial in diabetes patients that use over 200 units of insulin a day. And I can tell you, that is a growing population. If you listen to Lilly's last call, most of what they're reporting in Humulin sales in the US are from U500. Ex-US, it's the other Humulin U100. But in the US, this is the major product. That's increasing, and we know from at least the moderate insulin-resistant patients that we look better. We'll have the other trial.

So we think that those trials would be what we would need. The other kinds of questions that we have asked the FDA is to give us clarity on the toxicology package that we would need and the kinds of additional safety data in terms of extension trials. Once we have that, then we can come back. We are very excited about this product and chomping at the bit to move forward, but we don't want to second-guess the FDA in terms of what the requirements are.

Q: Could you also talk a little bit about the injection tolerability that you observed in this study?

A: We measured that using the 100 mm visual analog scales, and all the results were quite low. They were a little higher in the BIOD-531 treatments vs. the comparators, but we're still talking about a mean level of five and below out of 100. These were also scaled on an absolute severity scale, where the patient describes it as mild, moderate, or severe. And again, the mean results are in the mild range. So I believe that this is a well-tolerated formulation just like the others, and I suspect we would see good toleration in the multi-dose trial.

-- by Emily Regier, Adam Brown, and Kelly Close