Closer Look

MEMORANDUM

FDA publishes briefing documents for upcoming review of Novo Nordisk's insulin degludec and degludec/aspart - November 7, 2012

Executive Highlights

- The FDA posted briefing documents on its website pertaining to the November 8 advisory committee meeting for insulin degludec and degludec/aspart, including a list of six questions for the committee.
- The advisory committee meeting will focus on the insulins' CV risk, as well as their potential for flexible dosing and their possible hypoglycemia benefit compared to glargine.
- The emphasis on CV risk is based on two unexpected meta-analyses showing an increased CV risk with degludec. We believe the committee will favor at minimum post-marketing cardiovascular surveillance and that a CV outcomes trial is certainly possible but contingent on how the meta-analysis is assessed. The timing of a potential CVOT (pre-approval vs. post-approval) is unclear, although we imagine there is not enough evidence to justify pre-approval.

Yesterday, the FDA published briefing documents on its website for the upcoming November 8 Endocrinologic and Metabolic Drugs Advisory Committee meeting on Novo Nordisk's insulin degludec (brand name Tresiba; IDeg) and insulin degludec/aspart (Ryzodeg; IDegAsp). The documents include an agenda, meeting roster, briefing information, and questions for the committee to consider (see http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/E... tabolicDrugsAdvisoryCommittee/ucm285142.htm). The questions (listed below) confirm that the meeting will focus heavily on the increased CV risk shown by two meta-analyses of phase 3 data for IDeg and IDegAsp: an original and updated meta-analysis found a 10% and a 30%, respectively, increased risk of unstable angina, myocardial infarction, stroke, and CV death with IDeg/IDegAsp vs. comparators. However, the 95% confidence intervals surrounding both hazard ratios were large - 0.68-for the original analysis and 0.88-1.93 for the updated analysis - and both cross one. Thus, animportant role of the committee, as detailed in the questions, will be to evaluate the reliability of the CV meta-analyses. The FDA documents ask the committee members to discuss the clinical significance of the CV signal and to vote on whether the FDA should require a cardiovascular outcomes trial - the key question for committee members is whether the outcomes trial should be conducted pre- or post- approval (below, we break down individual panelists and past votes). If post-approval, another critical question will be defining degludec's label (i.e., hypoglycemia superiority, flexible dosing), which will have important implications for marketing against glargine, pricing, and adoption. We note that meta- analysis use will also likely come up as a serious issue to address, given that it's a significantly lower number of people than were actually in the degludec trials.

The FDA also asks the committee to evaluate the hypoglycemia benefit of IDeg and IDegAsp relative to insulin glargine, and to discuss the clinical relevance of the results of a hypoglycemia meta-analysis (details below). The Agency previously mentioned that a hypoglycemia benefit would be weighed against the excess cardiovascular risk, though we suspect that no advantage in hypoglycemia could outweigh an increased CV risk. What value the meta-analysis provides is, of course, a major question that will also be debated. The panelists will also likely discuss the validity and possible clinical benefits of being able to dose IDeg at different times of day ("flexible dosing"). We note that we've heard that degludec offers patients a greater stability - while this wouldn't affect A1c per se, it would certainly affect the percentage of time that patients are in their "target zone" - a measure we expect to continue to hear more about, though granted it's not one that receives great attention today.

Novo Nordisk has previously noted that the safety data provided to the FDA is the same as that given to the regulatory agencies in the EU and Japan; we assume that the favorable opinions given by these respective agencies will hold some weight with panelists and will increase their relative confidence in the CV safety of IDeg and IDegAsp. As a reminder, Novo Nordisk received an approval for both insulins in Japan in September and received a positive opinion from the EMA's Committee for Medicinal Products for Human Use (CHMP) in October, with a final decision from the European Commission expected by the end of 2012. Both regulatory bodies received the same meta-analyses.

Looking forward, we expect that panelists will consider the nuanced cardiovascular and hypoglycemia data in the larger context of how IDeg and IDegAsp could improve diabetes care and set precedence for future insulin development, given how great the need is for improved adherence among patients - presumably, better products would increase adherence among patients and use among HCPs. We're especially interested in how a longer-acting and more stable insulin such as degludec could be combined with mealtime insulin or a GLP-1 (in the case of Novo Nordisk's degludec/liraglutide combination) to provide more reliable glycemic control and the convenience of a single device for administration. Furthermore, given the heavy financial burden and additional time associated with pre-approval CV outcomes studies, we hope that the panelists consider how their decisions could influence the incentive to invest in improved diabetes therapies.

MEETING AGENDA AND ROSTER

- **Both Novo Nordisk and the FDA will give presentations focused on cardiovascular (CV) risk.** Following an early 7:30 AM start time, Novo Nordisk will present on the rationale behind the development of insulin degludec, followed by a review of degludec's clinical development program. Dr. Anne Philips, MD (Clinical Development, Medical and Regulatory Affairs, Novo Nordisk) will then discuss the CV safety of IDeg and IDegAsp, followed by cardiologist Dr. Steve Marso's (University of Missouri, Kansas City, MO) talk on "Assessing CV Risk with Insulin Degludec." FDA's four presentations will focus on: 1) clinical safety; 2) the cardiovascular meta-analysis; 3) the hypoglycemia meta-analysis; and 4) the clinical perspective of hypoglycemic analysis and results. As a reminder, the meeting will be broadcast live via webcast, and details are available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM327013.pdf.
- **The draft roster includes 12 voting panelists, including six endocrinologists, three cardiologists, and one statistician.** For comparison, the most recent EMDAC meeting (for Arena's Belviq [lorcaserin]) included 23 voting members. Interestingly, a previous document posted by the FDA noted that of the invited thirteen diabetologists and endocrinologists, only four were able to attend the advisory committee. Six were unable to attend "because of conflicts" (we assume this means conflicts of interest) and three could not attend "because they are unavailable." Broadly speaking, it continues to be challenging to find advisory committee members with no experience advising academic or commercial drug development. If the FDA were to temper its conflict-of-interest policy, the additional expertise gained from KOLs that have advised industry certainly may outweigh the potential for bias decision marking. Below, we have enclosed a panelist-by-panelist review, including relevant historical votes and biographical information.
- **Panelists' voting histories from previous advisory committees broadly suggest: 1) positive sentiments towards novel therapies, given the patient need; 2) preference for post-approval studies; and 3) some consideration of the effects of FDA requirements on drug development.** Overall, the panelists noted below have mostly voted in favor of new therapies, including lorcaserin (4 yes, 0 no), Qnexa/Qsymia (3 yes, 0 no), dapagliflozin (2 yes, 1 no), Contrave (3 yes, 0 no), and liraglutide (1 yes, 0 no, 1 abstention). Advisors have favored post-approval studies in virtually all cases, including a 4-2 margin against blanket CV guidelines for obesity drugs at the March 2012 advisory committee. A number of the panelists have raised the negative effect CVOTs can have on drug development..
    - **Chair: Dr. Kenneth Burman, MD** (Washington Hospital Center Washington, DC): We remember Dr. Burman as an extremely valuable chair at the 2010 Avandia advisory

committee. Dr. Burman was staunchly in favor of holding the data to rigorous standards-standards he did not feel the Avandia data met. We were struck by the depth he could cover during the brief moments he allowed himself to justify his vote and the fact that he was capable of doing this while also directing the (unruly) panel. He voted in favor of Qnexa's (Qsymia's) approval in 2012, turning around his vote against approval in 2010, when he was looking for more data.

- **Dr. Erica Brittain, PhD** (National Institutes of Health, Bethesda, Maryland): At the Obesity CV Guidance Advisory Committee in March, Dr. Brittain voted in favor of additional CV safety assessment (a two-staged approach) because obesity drugs will be used by a large population. At the advisory committee for Arena's lorcaserin, she voted "yes" in favor of approving the drug, though was not happy about the abundant missing data - she felt this compromised the integrity of randomized comparisons of efficacy and safety. She also expressed some concern about the feasibility of conducting placebo-controlled trials post-marketing. Notably, at the Qnexa (Qsymia) panel in March, she voted in favor of approval "not without trepidation," especially with regards to cardiovascular risk. She voted against the approval of dapagliflozin, emphasizing that primarily, she wanted to get more information on the safety of dapagliflozin, and that the timing of the collection of such data was somewhat a secondary concern. Dr. Brittain suggested that the proposed CV outcomes trial could be monitored as it progresses for cancer and hepatotoxicity risks, and that information could be used to change whatever decision is made.
- **Dr. Ed Hendricks, MD** (Center for Weight Management, Roseville and Sacramento, California): Dr. Hendricks voted in favor of approving lorcaserin, voicing support for a post-marketing CV study. At the obesity CV guidance advisory committee, he voted against requirements, arguing that a blanket CV assessment should not be required for drugs without a CV safety signal because of the impact it would have on drug development. He voted in favor of dapagliflozin's approval on the basis of clinical relevance and suggested that a "post- marketing study would settle the safety issues". He was a strong supporter of Orexigen's Contrave throughout the 2010 meeting and voted in favor of approval. In his view, even if a post-approval trial revealed an increased CV risk, he was optimistic that it would also suggest populations where the risk-benefit profile is favorable.
- **Dr. Ellen Seely, MD** (Harvard Medical School, Boston, MA): At the Obesity CV Guidance Advisory Committee, Dr. Seely voted against additional requirements. She thought that additional CV safety assessment requirements would reduce the number ofobesity drugs that become available, and would perhaps overemphasize CV safety at the expense of other safety concerns. She voted for approval of dapagliflozin, citing the need for additional treatments in the diabetes armamentarium, especially ones that are weight neutral or promote weight loss. She also voted for approval of Contrave, and was in favor of a pre-approval study due to concerns about the drug's effects on heart rate and blood pressure. Dr. Seely expressed confidence that a large trial with an interim analysis could safely determine the ideal population for Contrave.
- **Dr. Robert Smith, MD** (Brown University East Providence, Rhode Island): Dr. Smith voted for approval of lorcaserin and thought the FDA should require post-approval cardiovascular (CV) outcome studies to assess CV risk. He was comfortable recommending a drug that showed clinically significant benefits in only a subgroup of patients. Dr. Smith also voiced a strong yes for Vivus' Qnexa (Qsymia) - cardiovascular data were a "plus/minus" in his assessment, but he said that the drug's impressive efficacy (albeit known "only for a limited time") outweighed the possibility of adverse CV events. He stated that the FDA should require rapid completion of postmarketing studies to truly resolve the CV risk-benefit question.

- **Dr. William Hiatt, MD** (University of Colorado School of Medicine, Aurora, CO): Dr. Hiatt voted in favor of approving lorcaserin, noting that the cancer risks had been defined and could be monitored post-marketing. To him, the biggest safety concerns from a clinical perspective - the valvulopathy and cardiovascular risks - could be addressed with a REMS program and a post-marketing cardiovascular outcomes trial (CVOT). At the Obesity CV Guidance Advisory Committee, he voted against additional requirements - Dr. Hiatt felt that if the FDA decided to impose a blanket CV requirement for anti-obesity drugs, then the Agency should be consistent and impose a similar requirement for all symptomatic drugs across all indications. He indicated that imposing such a requirement on drugs without a CV signal "just made no sense" to him. However, he stated that his threshold for a signal would be quite low. It will be very telling to see how this is interpreted in this setting. Second, he noted that while he was very uncomfortable with the notion of requiring a dedicated CV outcomes study for all of these drugs (given the cost and duration of these studies), he would be comfortable with a required meta- analysis of phase 2/3 data to help generate any potential signal. Again, it will be very interesting to see how he assesses this meta-analysis. At the Contrave panel meeting, Dr. Hiatt voted for approval and noted that "a study pre-approval would likely kill development of the drug, and I'm just wrestling with what the message will be to the wider community. Requiring a 10,000-patient trial before approval in the future would be a steep hill to climb."
- **Dr. Marvin Konstam, MD** (Tufts University School of Medicine Boston, MA): At the Obesity CV Guidance Advisory Committee, Dr. Konstam voted in favor of imposing pre- and post- approval cardiovascular safety assessment requirements for obesity therapeutics similar to those for diabetes drugs. He was not convinced that adopting such standards would be excessively onerous to the development of anti-obesity medications. He was in favor of withdrawing Avandia from the market in 2010 and actually abstained from voting on whether to approve liraglutide in 2009. However, he did want tighter confidence intervals on liraglutide to show that there was not unacceptable risk. He was in favor of a post-marketing study for saxagliptin.
- **Rebecca Killion (Patient Representative):** At the 2008 FDA Advisory Committee on the CV Safety of Diabetes Drugs, Ms. Killion voted against requiring all new type 2 diabetes drugs to demonstrate cardiovascular safety in a hard outcomes clinical trial or by other means, even if no concerning cardiovascular signal is observed in phase 2/3. She was in favor of approving liraglutide in 2009 and thought that the cardiovascular risk could be safely managed. In 2008, she was in favor of a post-marketing trial for saxagliptin. Ms. Killion has been a very recognized strong voice for improving the therapy options for patients; it is positive for Novo Nordisk that she is on the panel.
- **We do not have any previous voting history on any diabetes or obesity- related advisory committee in the last four y**strong>e**ars for four of the or four panelists:** Dr. David Cooke, MD (Johns Hopkins University School of Medicine, Baltimore, MD); Dr. Brendan Everett, MD, MPH (Harvard Medical School, Boston, MA); Dr. Charles Stanley, MD (Children's Hospital of Philadelphia, PA); and Dr. Thomas Weber, MD (Duke University Medical Center, Durham, NC). They may well have voted on some but we are not aware of which ones. It will be interesting to hear from Dr. Stanley, who received a waiver in order to participate on the panel.

CARDIOVASCULAR META-ANALYSIS

- **The briefing documents acknowledge that the FDA and Novo Nordisk previously agreed that the clinical programs for IDeg and IDegAsp would not be powered to rule out a pre-specified margin of CV risk** - this information is consistent with previous comments from Novo Nordisk management. The FDA documents do state that at the end-of- phase 2 meeting, the FDA requested that Novo Nordisk collect, analyze, and adjudicate CV data from the clinical

trials, using the process outlined in the FDA's 2008 guidance on assessing CV risk for diabetes drugs (details of the guidance are available in our July 2, 2012 *Closer Look* at http://www.closeconcerns.com/knowledgebase/r/ac8baf71).

    - **Novo Nordisk has previously noted that the safety data provided to the FDA is the same as that given to the regulatory agencies in the EU and Japan;** we assume that the favorable opinions given by these respective agencies demonstrates the agencys' confidence in the CV safety of IDeg and IDegAsp. As a reminder, Novo Nordisk received an approval for both insulins in Japan in September and received a positive opinion from the EMA's Committee for Medicinal Products for Human Use (CHMP) in October, with a final decision from the European Commission expected by the end of 2012**.**

- **The FDA briefing documents describe the design of the CV meta-analyses for insulin degludec (IDeg) and insulin degludec/aspart (IDegAsp).** At the time of the original NDA filing, Novo Nordisk submitted a CV meta-analysis that included 16 phase 3 trials (11 for IDeg and five for IDegAsp) with data from ~9,000 patients and 5,400 person-years exposure (PYE). According to the FDA, "Results from the initial analysis of the CV safety suggested the potential for an increase in CV risk, though a statistically significant finding could not be determined," prompting the agency to request additional information to perform an updated meta-analysis. The updated analysis included the 16 original trials plus six extension trials (of ongoing phase 3 studies) and one new phase 3 trial - the second analysis evaluated data from a similar number of participants (~9,000; this is expected given that only one new trial was added), but included a 40% increase in PYE (now ~7,700). The primary endpoint was a composite of major adverse cardiovascular events consisting of acute coronary syndrome (including unstable angina pectoris), myocardial infarction, stroke, and CV death - collectively referred to as "MACE+".

Novo Nordisk also conducted an analysis with a stricter endpoint definition consisting only of myocardial infarction, stroke, and CV death - collectively called "MACE". Information on CV events was censored either seven days or 30 days after treatment discontinuation.

- **At first glance, both the original and updated meta-analyses suggest an increased CV risk with IDeg and IDegAsp though we aren't sure how to weight (or even interpret) the data given the confidence intervals and given that many fewer patients are included in this analysis compared to the entire set of trials.** Based on the MACE+ primary endpoint and data censorship after seven days, the original analysis found a 10% increase in CV risk with IDeg/IDegAsp compared to active comparators. Notably, however, the 95% confidence interval around the point estimate was extremely wide and indicated that IDeg/IDegAsp's true CV effects could range from a 32% risk reduction to a 77% risk increase. The updated analysis showed a less-favorable outlook, indicating a 30% increase in CV risk with IDeg/IDegAsp compared to comparators. The 95% confidence internal was again quite large, indicating that the insulins' true CV effects could range from a 12% risk reduction to a 93% risk increase. A similar statistical analysis based on the MACE endpoint found an increase in CV risk with IDeg/IDegAsp of 39% in the original analysis (95% CI: 0.76-2.57) and of 67% in the updated analysis (95% CI: 1.01-2.75).

Table 1: Cox proportional hazards analysis results for MACE+ endpoint based on original and updated meta-analyses

	Original Analysis		**Updated Analysis**	
	IDeg/IDegAsp	**Comparator**	**IDeg/IDegAsp**	**Comparator**
Censoring after seven days				
MACE + Events	53	27	95	37

MACE + HR (95% CI)	1.10 (0.68, 1.77)	_____	1.30 (0.88, 1.93)	_____
Censoring after 30 days				
MACE + Events	56	27	99	39
MACE + HR (95% CI)	1.17 (0.73, 1.87)	_____	1.29 (0.88, 1.89)	_____

Table 2: Cox proportional hazards analysis results for MACE endpoint based on original and updated meta-analyses

	Original Analysis		**Updated Analysis**	
	IDeg/IDegAsp	**Comparator**	**IDeg/IDegAsp**	**Comparator**
Censoring after seven days				
MACE Events	39	15	70	21
MACE	1.39 (0.76, 2.57)	_____	1.67 (1.01, 2.75)	_____
HR (95% CI)				
Censoring after 30 days				
MACE Events	42	15	74	23
MACE HR (95% CI)	1.50 (0.82, 2.75)	_____	1.61 (1.00, 2.61)	_____

- **The high degree of additional CV risk observed with IDeg/IDegAsp would be concerning if based on studies that were designed to assess cardiovascular safety and risk; we'll be very interested to see how the advisory committee views these results given the large confidence intervals and depending what studies were and were not included, etc**. While we presume that the degree of acceptable risk is higher with a life-saving drug such as insulin, the important question is whether the advisory committee will find the incremental benefit of insulin degludec (over insulin glargine and detemir) significant enough to balance the potentially increased CV risk. While it is of course difficult to imagine any benefit in hypoglycemia or flexible dosing that would outweigh a true ~30% increase in CV risk, as indicated by the updated meta-analysis (the additional risk rises to 67% when only strict MACE events are considered), we don't know, of course, how the meta-analysis will be perceived. As a reminder, for all diabetes drugs but insulins, the FDA requires that the upper limit of the 95% confidence interval fall below 1.8 pre-approval and below 1.3 post-approval. Interestingly, insulin degludec nearly meets this pre-approval criteria in the MACE+ analysis (upper limits of 1.77 and 1.93 for the original and update analyses, respectively), but falls well above the limit for the perhaps more important MACE analysis (upper limits of 2.57 and 2.75 for the original and updated analyses, respectively.
- **FDA changed the meeting time from 8 am to 7:30 am, which suggests that FDA expects a great deal of discussion on a great number of topics. The meta-analysis results will undoubtedly prompt panelists to discuss the meta-analysis itself, what was included,**

how it was designed, and what it showed, and to characterize the extent to which it should be used to discuss whether a CV outcomes trial should be performed. Following the discussion of the meta-analysis, we assume that discussion will center on whether an outcomes trial should be required and whether it should be performed before or after approval. This decision, as noted, will hinge largely on how panelists view the ability of the meta-analyses to accurately characterize CV risk. The first draft question asks the panelists to evaluate the reliability of the meta-analyses and consider the endpoints chosen, the adjudication process, the patient population, and the design of the clinical program. The documents do clearly state the FDA's conclusion: "While various scenarios resulted in different values of the HR and RD point estimates, a consistent trend was observed - IDeg/IDegAsp was shown to be associated with an increase in CV risk."**The FDA conducted a sensitivity analysis evaluating the CV risk of IDeg/IDegAsp compared to insulin glargine** (IGlar). Of the 17 phase 3 trials included in the updated meta- analysis, 12 used insulin glargine as the active comparator. Results based only on these 12 trials are shown below. Based on the MACE+ primary endpoint and data censorship after seven days, IDeg/IDegAsp was associated with a 54% increase in CV risk compared to insulin glargine, with a 95% confidence internal of 0.99 to 2.40. Based on the MACE endpoint, IDeg/IDegAsp was associated with an 82% increase in CV risk compared to insulin glargine, with a wider (andstatistically significant) 95% confidence internal of 1.03 to 3.19. In the briefing document, the FDA noted that compared to insulin glargine, the lower bounds of the 95% confidence intervals are near or above 1.00 for both the MACE and MACE+ endpoints.

Table 3: Cox proportional hazards analysis results for MACE+ and MACE endpoints based on the updated meta-analysis including only IGlar-controlled trials.

	MACE +		**MACE**	
	IDeg/IDegAsp (n=4,397)	**IGlar** (n=2,540)	**IDeg/IDegAsp** (n=4,397)	**IGlar** (n=2,540)
Censoring after seven days				
Events (%)	87 (2.0%)	27 (1.1%)	62 (1.4%)	16 (0.6%)
HR (95% CI)	-----	1.54 (0.99, 2.40)	-----	1.82 (1.03, 3.19)

- **Additional sensitivity analyses indicated a higher CV risk with IDegAsp than with IDeg; for both treatments, the point estimate was higher for the MACE endpoint vs. the MACE+ endpoint.** Eleven of the 17 phase 3 trials included in the updated meta-analysis evaluated IDeg alone and showed that IDeg was associated with a 29% increased CV risk (95% CI: 0.83-2.02) for the MACE+ and a 59% increased CV risk (95% CI: 0.89-2.83) for MACE. Analysis of the remaining six trials investigating IDegAsp revealed a hazard ratio of 1.33 (95% CI: 0.59- 2.99) for MACE+ and a hazard ratio of 1.91 (95% CI: 0.72-5.08) for MACE.
- **Cardiovascular event rates were generally lower among people with type 1 diabetes vs. those with type 2 diabetes.** Of the 17 trials included in the updated analysis, four were conducted in patients with type 1 diabetes (with the remaining 13 conducted in patients with type 2 diabetes). Sensitivity analysis showed that in people with type 1 diabetes (and with a seven day censoring window), IDeg/IDegAsp provided a similar - if not slightly better - rate of CV events compared to comparators for MACE+ (HR: 0.96 [95% CI: 0.30-3.09]). However, IDeg/IDegAsp was associated with an increased CV risk compared to comparators in the more strict MACE analysis, though with a very large 95% confidence interval (HR: 1.30 [95% CI: 0.27-6.29]). In people with type 2 diabetes, IDeg/IDegAsp was associated with a 35% increase in CV risk for MACE+ (95% CI: 0.89-2.04) and a 71% risk increase for MACE (95% CI: 1.01-2.90).

- **We first learned about the FDA's focus on IDeg/IDegAsp's cardiovascular (CV) risk** when the FDA recently published a conflict of interest waiver for pediatric endocrinologist Dr. Charles Stanley (Children's Hospital of Philadelphia, PA). Specifically, the waiver disclosed the reason for the advisory committee meeting in the "additional facts" section, stating: "this meeting will focus on the cardiovascular safety of two products, insulin degludec/aspart and insulin degludec, as meta-analyses of several clinical trials suggest an excess risk for cardiovascular events with this insulin over comparators." The manner in which this news was disclosed was quite surprising to us, as it was written on the second page of a conflict of interest waiver rather than through an open and transparent announcement from the FDA.
    - **From a broader perspective, this method of revealing information illustrates how, despite efforts to open communication channels, the FDA's intentions and actions still remain fairly opaque and unpredictable**. From a patient perspective, we hope that the FDA puts greater focus on more open communication with companies and the public, as progress would benefit both the agency (who would receive more specific data from sponsors) and companies (who would get a more concrete idea of the FDA's expectations, allowing them to more wisely invest in drug development).

HYPOGLYCEMIA META-ANALYSIS

- **Novo Nordisk performed a hypoglycemia meta-analysis** that included seven phase 3 studies comparing IDeg/IDegAsp to insulin glargine (IGlar) that enrolled a total of roughly 4,300 participants. The primary endpoint was "confirmed hypoglycemia," which Novo Nordisk defined as the sum of severe hypoglycemia (where the patient requires help from another person) and minor episodes with plasma glucose <56 mg/dl or with whole blood glucose <50 mg/dl. As an interesting side note, the cardiovascular meta-analysis included 12 phase 3 trials with IGlar as the active comparator (vs. only seven included in the hypoglycemia meta-analysis)- perhaps the discrepant five studies completed after the sponsor conducted the hypoglycemia meta-analysis.
- **Data from the meta-analysis suggest that the hypoglycemia advantage of IDeg relative to insulin glargine differs by diabetes type.** Across all trials, insulin degludec provided a 9% smaller risk of confirmed hypoglycemia compared to glargine (rate ratio = 0.91 [95% CI: 0.83-0.99]). However, a subanalysis including only the two trials with type 1 patients (total n = 1,000) found a 11% increased risk of confirmed hypoglycemia with IDeg vs. glargine (95% CI: 0.94-1.31). However, IDeg did provide a hypoglycemia benefit in a subanalysis including the five studies with type 2 patients (total n = 3,300; rate ratio: 0.84 [95% CI:0.76-0.93]). The FDA noted that Novo Nordisk submitted additional subgroup analyses by gender, age, and race, the results of which were consistent with the findings discussed above. However, subgroup analyses by country of randomization showed that among patients in the US, insulin glargine and degludec led to similar rates of confirmed hypoglycemia in both type 1 and type 2 diabetes (rate ratio for type 1 diabetes = 0.99 [95% CI: 0.81-1.20]); rate ratio for type 2 diabetes = 0.97 [95% CI: 0.81-1.15]). Only in participants randomized outside the US was the risk of confirmed hypoglycemia higher with degludec in people with type 1 diabetes (rate ratio: 1.28 [95% CI: 0.96- 1.71]) and lower with degludec in those with type 2 diabetes (rate ratio: 0.79 [95% CI: 0.69-0.90]).
- **Based on the meta-analysis, we would not be surprised if the FDA did not include a general hypoglycemia benefit in degludec's label.** In its draft questions, the FDA asks the committee members to consider the clinical relevance of the hypoglycemia findings, taking into account the difference in hypoglycemic risk between types of diabetes, as well as between geographic areas. As a reminder, degludec's Japanese label does include an advantage for nocturnal hypoglycemia with insulin degludec, based on trials comparing degludec to glargine in Asian patients with type 2 diabetes.

DRAFT QUESTIONS TO THE COMMITTEE

1. **As agreed with the FDA, the degludec and degludec/aspart programs were not designed to rule out a pre-specified margin of cardiovascular (CV) risk. However, at the end-of- phase**

2 meeting, FDA informed the applicant that this program was still required to collect and analyze CV data from clinical trials as outlined in the December 2008 Guidance for Industry. Based on the information provided in the briefing package and the presentations at today's meeting, please comment on the reliability of the CV risk assessment with respect to:

a. The CV endpoints included in the primary analysis for CV risk

b. The adjudication process in the CV meta-analysis

c. The patient population included in the CV risk assessment

d. The design of the clinical program (e.g., open-label nature) and the impact, if any, this may have had on reporting, collecting, and interpreting the results of the CV meta-analysis.

e. The original meta-analysis of the 16 clinical trials versus the updated meta-analysis of 17 clinical trials including the extension phases of six trials in the original meta-analysis.

2. Based on your response to question 1, please discuss whether the CV safety signal identified in the degludec and degludec/aspart program represents a clinical concern in the management of type 1 and type 2 diabetes mellitus (DM). In your discussion, please consider the background CV risks of patients requiring insulin for the management of their diabetes.

Information for Question 3:

The applicant performed several pre-specified secondary analyses of hypoglycemia data across several trials in the degludec and degludec/aspart programs and a pre-planned meta-analysis to compare the risk of "confirmed hypoglycemic events" between insulin degludec and insulin glargine.

In these analyses "confirmed hypoglycemic episodes," represent the sum of "severe episodes" and "Novo Nordisk minor episodes."

a. A severe episode was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.

b. A Novo Nordisk minor episode was defined as an episode not requiring third party assistance where a plasma glucose <56 mg/dl or whole blood glucose <50 mg/dl was recorded (i.e., with or without presence of hypoglycemic symptoms).

Other definitions of hypoglycemia and their rates have been presented.

3. Based on the information provided in the briefing package and the presentations at today's meeting, please discuss the following:

a. The clinical relevance of the results of the pre-planned meta-analysis of hypoglycemia relying on the Novo Nordisk definition of "confirmed" hypoglycemic episodes.

b. The clinical relevance of difference in hypoglycemic risk between types of diabetes (type 1 vs. type 2) observed in the meta-analysis of hypoglycemia.

c. The clinical relevance of differences in hypoglycemic risk between geographic regions (US vs. non-US) observed in the meta-analysis of hypoglycemia.

d. In the overall program, comment on the clinical relevance of the hypoglycemic event findings. Please consider in your discussion the following:

i. The relative importance of "confirmed" nocturnal episodes versus "confirmed" episodes over the entire 24-hour period.

ii. The time frame used to define the nocturnal period.

iii. The differences between degludec and comparator in regards to timing injection as well as insulin pharmacokinetic and pharmacodynamics properties.

iv. How the primary efficacy findings and how insulin dose differences between groups observed at end of trial impact interpretation of the hypoglycemia results.

4. Please comment on the long duration of action of degludec with respect to its dosing regimen and what clinical relevance this may have to patients with type 1 or type 2 diabetes.

5. Based on the results from the CV meta-analysis, should a cardiovascular outcomes trial be conducted for degludec and degludec/aspart?

a. If you voted "Yes", please provide your rationale.

b. If you voted "No", please provide your rationale.

6. Based on the information included in the briefing materials and presentations today, has the applicant provided sufficient efficacy and safety data to support marketing of degludec and degludec/aspart for the treatment of type 1 and type 2 diabetes?

a. If you voted "Yes", please provide your rationale and whether you recommend any additional studies post-approval.

b. If you voted "No", please provide your rationale and discuss what additional data are necessary to potentially support approval.

Close Concerns Questions

Q: Will the FDA require cardiovascular outcomes trials for all new insulins? Q: What will the implications be for biosimilars following this meeting?

Q: Will the FDA define a new cardiovascular safety cut-point specifically for insulins, and if so what would be considered an acceptable risk for a life-saving drug?

-- by Nina Ran, Jessica Dong, Adam Brown, and Kelly Close