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by Lynne Peterson

Quick Pulse

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Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com
TrendsInMedicine@aol.com

FDA Advisory Committee Says One Diabetes Drug is Safe but Another Needs More Study

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The FDA's Endocrinological and Metabolic Drugs Advisory Committee reviewed the safety of two diabetes drugs, Bristol-Myers Squibb's Onglyza (saxagliptin) on April 1 and Novo Nordisk's Victoza (liraglutide) the next day. The panel voted 10 to 2 that saxagliptin does not pose a cardiovascular (CV) safety risk, clearing the way for probable FDA approval, but the panel also unanimously agreed that the company must do long-term postmarketing studies in higher-risk patients, and Bristol-Myers Squibb (BMS) pledged to do those trials. The panel was less convinced of the CV safety of liraglutide, and the panel basically said the thyroid safety of liraglutide needs more study. The panel actions and comments by FDA officials during the two sessions suggested that the path has gotten tougher for some other diabetes drugs in development.

Under new FDA rules imposed in December 2008, ***all*** new diabetes drugs must conduct long-term CV trials or provide other equivalent evidence to rule out an unacceptable cardiovascular risk. Both saxagliptin and liraglutide were submitted to the FDA prior to implementation of the new rules. Therefore, their development plans did not include the types of patients, endpoints, etc., that are now required. Since the FDA changed the rules of the game after the submissions, the Agency asked both companies to do a post hoc analysis of CV events in the Phase II and III trials, using FDA-designated definitions of MACE (SMQ MACE and Custom MACE).

Like Merck's Januvia (sitagliptin), saxagliptin is an oral, once-daily dipeptidyl peptidase (DPP)-4 inhibitor that stimulates glucose-dependent insulin release, slows gastric emptying, inhibits inappropriate post-meal glucagon release, and reduces food intake. BMS is seeking approval of saxagliptin 5 mg as monotherapy; as add-on therapy to metformin, sulfonylureas, and TZDs; as an initial combination with metformin as an adjunct to diet and exercise to improve glycemic control in patients with Type 2 diabetes. Saxagliptin was discovered and developed by BMS, which entered into a partnership with AstraZeneca on further development and commercialization.

Like Lilly/Amylin's Byetta (exenatide, the only FDA-approved GLP-1 analog so far), liraglutide is a glucagon-like peptide (GLP)-1 analog that is resistant to DPP-4 degradation. Byetta is dosed twice daily whereas liraglutide is dosed once daily. Novo Nordisk is seeking approval of liraglutide as an adjunct to diet and exercise to improve glycemic control in patients with Type 2 diabetes. Liraglutide is a once-daily subcutaneous injection, starting at a dose of 0.6 mg, with titration to

1.2 mg SQ once daily after at least one week and up-titration to 1.8 mg SQ once daily possible after at least one week at 1.2 mg/day.

The panel for saxagliptin was comprised of 13 members – 3 endocrinologists, 2 cardiologists (one a heart failure specialist), 2 statisticians, an NIH diabetes expert, a diabetes researcher, a pharmacologist, a health science professor (the consumer representative), a patient advocate, and a non-voting industry representative (Schering-Plough). For the liraglutide panel, an additional endocrinologist (a thyroid cancer expert from Memorial Sloan Kettering Cancer Center) was added.

In addition, the panel was asked to provide the FDA with more general guidance on CV safety issues:

- *Do low CV event rates permit a reliable assessment of CV safety?* **No**, but if the point estimate of the odds ratio is very low, it is somewhat reassuring.
- *Do the FDA recommended endpoints and post hoc analyses permit a reliable assessment of CV safety?* **Yes**, to a degree and when there is consistency among the analyses.
- *What improvements to the endpoints and analyses should be applied to Phase III programs that were completed or were near completion when the new FDA guidance on CV safety was issued in December 2008?* The sponsors should do multiple analyses and try to study all of the requested endpoints to the best of their ability.
- *Is the statistical method for measuring the sensitivity of these rules to the analytical method adequate?* Generally, **yes**.

*Asked about a timetable for a guidance document on **marketed** diabetes drugs*, Dr. Mary Parks, director of the FDA's Division of Metabolism and Endocrinology Products (DMEP), Center for Drug Evaluation and Research (CDER), indicated that isn't coming anytime soon. She said the FDA has begun discussing it internally, but her comments suggested it may not be forthcoming this year.

REGULATORY BACKGROUND

On July 1-2, 2008, the Endocrinological and Metabolic Drugs Advisory Committee voted 14 to 2 that an anti-diabetic therapy with a "concerning" CV safety signal during Phase II/III trials should be required to conduct a long-term CV trial and that drugs/biologics without such a signal should also be required to conduct a long-term CV trial ***or to provide other equivalent evidence to rule out an unacceptable CV risk***.

Then, in December 2008, the FDA's Division of Metabolism and Endocrinology Products imposed new trial requirements for diabetes drugs that clearly meant it would be harder and would take longer to get new drugs approved. The Agency announced that ***effective immediately***, companies developing drugs to treat Type 2 diabetes would be required to conduct longer clinical trials and include very specific patient populations in order to ensure cardiovascular safety. The new guidance applied to new drug applications (NDAs) and biologic license applications (BLAs) that had already been submitted to the FDA as well as all ongoing and planned trials.

For diabetes drug trials, the new rules mean that sponsors must:

- **Enroll patients at higher risk of CV events** than in the past – older patients, patients with more advanced Type 2 diabetes, and patients with kidney impairment.
- **Change the design of ongoing Phase II and Phase III trials** to bring them in accordance with this guidance.
- Use **predefined definitions of and criteria for cardiovascular events** in trials. The FDA believes this will increase the reliability of the events the Agency will be analyzing.
- Use an **independent, outside cardiovascular endpoint committee** made up of experts who will review CV events in a blinded fashion.
- Make the protocols of all Phase II and Phase III trials amenable to a **meta-analysis** – not exactly a pooled analysis but more an "aggregate" analysis – by the FDA.
- **Have longer follow-up**, a minimum of "more than a year" for both the drug arm and the control arm. Apparently, many trials run the drug arm for a year but stop the control at 6 months, and this is no longer acceptable. The FDA believes this will provide not only better safety data but also information about the glycemic durability of the new drug.
- **Enroll more patients.** How much sizes would have to be increased depends on the patient population enrolled. Trials aimed at younger and healthier patients likely would require a "substantial" number of patients. If the trial is in patients at higher risk or more advanced disease, it might not need as many more patients.
- **Discuss with the FDA the re-design of trials.**
- **Show comparability in the findings when a study is repeated.** The FDA is using a 95% confidence interval standard, and the Agency wants the event ratio between 2 trials of similar populations to be "very close to 1.0," though in some cases 1.3 would be acceptable and in others 1.8 would be acceptable. However, an FDA official emphasized that a 1.5 ratio would be concerning to the FDA.

For companies who have already submitted a new drug application (NDA), the FDA requested post hoc analyses of CV events, including:

- An analysis of the randomized, controlled periods for all completed Phase II and III clinical trials.
- An analysis of blinded, controlled data from treatment periods that extended beyond the timepoint of the primary efficacy endpoint for glycemic control.

BRISTOL-MYERS SQUIBB'S ONGLYZA (saxagliptin), a DPP-4 Inhibitor

The FDA's action date (the PDUFA) for saxagliptin is April 30, 2009, and it looks likely that the FDA will approve it.

Most panel members were fairly positive about saxagliptin, with some even suggesting it may become a blockbuster drug. Some were very encouraged about the possibility that it could have a lower rate of hypoglycemia, though that has not been proven.

Was the CV safety issue the last hurdle for saxagliptin at the FDA? Dr. Parks would only say, "The review is still ongoing."

Asked if approval of saxagliptin would be softening the guidance on CV safety requirements that the FDA issued in December, Dr. Parks said, "I know we applied the 1.8 and 1.3 goalposts to all diabetes therapies going forward, whether an NDA was in house or arrived afterwards…I would find it a little unusual that we would require (a new trial) of all products that have already undergone their clinical development program…There are many ways you can get to the goalpost…I am emphatic on the goalpost, but there are may ways you can establish that kind of CV risk assessment. It doesn't have to be in the exact same fashion as Drug X, Drug Y, etc." Dr. Curtis Rosebraugh, director of the FDA's Office of Drug Evaluation II, added, "In reality, what they need to study is people who will have events…And the events tend to happen in people with diabetes a long time, older patients. What we have tried to emphasize to sponsors is they have to have enough events to make some sort of decision...(saxagliptin) had a very favorable point estimate but few events, and we needed help with (balancing) that."

Asked about what the postmarketing trial will look like, Dr. Rosebraugh said, "It is early in the ballgame, and we haven't had time to talk (with BMS) about it, but most postmarketing trials now are large, multiyear, in populations that reflect the general population that will get the drugs…and a lot of interim analyses."

In a statement after the panel meeting, Bristol-Myers Squibb and AstraZeneca indicated they "are encouraged by the Committee's recommendations. We will review the information leading to the Committee's decision and continue to work closely with the FDA to support the review of Onglyza. Bristol-Myers Squibb and AstraZeneca are committed to helping patients and physicians manage Type 2 diabetes."

THE FDA PERSPECTIVE ON ONGLYZA (Saxagliptin)

At the time that saxagliptin was submitted to the FDA, there were 26 completed Phase I and II trials, but these were not included in the CV risk assessment because they were uncontrolled, conducted in healthy subjects, not randomized, or of short duration. Eleven Phase IIb/III studies have been completed or are ongoing, but three of these are ongoing Phase IIIb studies for which data have not yet been given to the FDA. Thus, the CV analysis is based on 2 Phase IIb trials and 6 Phase III trials.

The studies that could be analyzed for CV events were: two studies with 12-week treatment periods and six studies with 24-week treatment periods (including, 4 monotherapy studies in patients largely naïve to previous anti-diabetic treatment, 3 studies of add-on therapy, and one fixed dose study of saxagliptin plus metformin).

The problems with the saxagliptin data included:

- No patients at higher risk of CV events.
- No follow-up more than 1 year on drug.
- No CV data adjudication.
- Too few patients. And the patients in the trials were generally younger and healthier.

The FDA reviewers found that all the saxagliptin MACE results met the guidance criterion of an upper bound on the 95% confidence interval (CI) of the odds ratio of <1.8. The MACE results also showed upper bounds for the confidence interval to be <1.3. The key points the reviewers made in briefing documents prepared for the panel about these studies were:

1. **The analysis was post hoc**, though that was at the FDA's request.
2. There was **no signal of cardiotoxicity in preclinical studies** in multiple animal models – rats, mice, dogs, and monkeys – though the number of animals studied was relatively small, and they were healthy (without comorbidities).
3. None of the trials in the CV analysis had a patient population considered by the FDA to be at **high risk** for CV events.
4. The studies were **not long-term.** Initially, 2,642 subjects took saxagliptin for ≥24 weeks and 1,937 for ≥52 weeks.
5. **Major adverse cardiac events (MACE) were generally low**, and there was no evidence of a dose response in individual studies or for a pooled analysis. The FDA defined MACE two ways and did analyses based on both: Custom MACE and SMQ MACE. (**NOTE:** Bristol-Myers Squibb used different MACE definitions than Novo Nordisk did for liraglutide, so the FDA imposed the same new definitions for both products.) Overall, the comparator had a higher MACE rate (0.6% or 1.4%, depending on the MACE definition) than all saxagliptin-treated subjects (0.1% or 0.7%). Cardiac disorders were also more frequent with the comparator (0.4%) than saxagliptin (<0.1%). There was no difference in MACE among population subgroups, though the gender results were borderline significant. The low MACE rate in control suggested that these were low CV-risk patients.

6. ~74% of patients in the Phase III studies completed the short-term treatment period. In all studies the **completion rate** for U.S. sites was ~20% lower than for the non-U.S. sites.
7. There were 10 **deaths** with saxagliptin, 8 with placebo, and 5 with metformin.

Dr. Naomi Lowy, a medical reviewer from the FDA's Division of Metabolism and Endocrinology Products, described the Agency's analysis of the CV safety of saxagliptin.

Dr. Hylton Joffee, the FDA's Diabetes Clinical Team Leader in DMEP, CDER, concluded:

- The patient populations were comparable across the studies, with low event rates (<2% annual rate for Custom MACE).
- Consistent results for Custom MACE and SMQ MACE when excluding PT "increased CPK."
- ST + LT results were consistent with the ST results.
- MACE results were not dependent on the statistical method used.
- Analyses of all endpoints yielded estimates of common odds ratio <1 and upper bounds for 95% CI <1.8.

MACE Summary

Measurement	Comparator n=1,251	Saxagliptin n=3,356	Common odds ratio stratified on study (95% CI)
BMS MACE short- and long-term	0.5%	1.0%	0.5 (0.1, 1.2)
Custom MACE ST	0.1%	0.6%	0.21 (0.04, 0.8)
Custom MACE ST + LT	0.7%	1.3%	0.52 (0.3, 1.0)
SMQ MACE ST	1.8%	2.0%	0.90 (0.6, 1.5)
SMQ MACE ST + LT	3.1%	34.2%	0.96 (0.7, 1.4)

Saxagliptin MACE by Different FDA Analyses

Measurement	Comparator	Saxagliptin 2.5 mg	Saxagliptin 5 mg	Saxagliptin 10 mg
Custom MACE				
Short-term (ST)	0.6%	0.1%		
Short- and long-term (LT)	1.4%	0.7%		
Cardiac disorders	0.4%	0	0	0.1%
General disorders	<0.1%	0	0	0
Nervous system disorders	<0.1%	<0.1%	<0.1%	0.1%
Acute MI	<0.1%	0	0	0
Cardiac failure	<0.1%	0	0	0
MI	0.2%	0	0	0.1%
CVA	<0.1%	<0.1%	0.1%	<0.1%
Hemorrhagic stroke	0	0	0	0.1%
Broad (SMQ) MACE				
ST overall	2.0%	1.7%	1.4%	1.9%
		1.7%		
ST + LT overall	3.3%	3.0%	2.9%	3.0%
		3.0%		
Cardiac disorders	0.4%	0	0	0.1%
General disorders	<0.1%	0	0	00
Nervous system disorders	0.4%	<0.1%	<0.1%	0.2%
Vascular disorders	0	0.1%	0	0.1%
Investigations	1.1%	1.5%	1.3%	1.6%
Blood CPK increased	1.5%	2.0%	2.2%	1.7%
EKG ST segment abnormal	0	0	<0.1%	0
Blood CPK-MG increased	0	0	0	0.1%

BMS Presentation on Onglyza (saxagliptin)

Dr. Robert Wolf, a BMS vice president and development lead for saxagliptin, told the panel that there is an unmet need for saxagliptin, noting that many patients are not at goal or suffer safety/tolerability issues. He said there are drawbacks to the other key classes of diabetic medications:

- GI effects with metformin.
- Weight gain, hypoglycemia, and cardiac effects with sulfonylureas.
- Weight gain, edema, and a CHF contra-indication for TZDs – GlaxoSmithKline's Avandia (rosiglitazone) and Takeda's Actos (pioglitazone).

He emphasized these properties of saxagliptin:

- ≥2 orders of magnitude selectivity for DPP-4 vs. other proteases.
- Once-daily dosing.
- May be taken without regard to meals.
- Predictable and dose-proportional pharmacokinetics (PK) similar in healthy and diabetic patients.
- Clearance via metabolism, renal, and non-renal routes.

Dr. Roland Chen, BMS group director for cardiovascular/metabolics, reviewed the saxagliptin clinical program.

Dr. Wolf then discussed the CV safety of saxagliptin. He said that there was no microscopic evidence of cardiotoxicity with saxagliptin in any non-clinical species; no indication of adverse CV effects during *in vitro* or *in vivo* studies of rats, dogs, or monkeys; and no adverse effect on lipid parameters, blood pressure, heart rate, or QTc in Phase I studies. He also pointed out that there are "no meaningful differences" between saxagliptin and Januvia in terms of incidence rates of cardiac-related or ischemia-related adverse experiences.

The Kaplan-Meier curve for time to onset of first Primary MACE (which Dr. Wolf contended is comparable to the FDA's Custom MACE) showed saxagliptin to have a lower

rate than control at all timepoints out to 128 weeks. He said, the data in this do not indicate a problem in either short-term or long-term phases of saxagliptin studies. He also showed an analysis of the pooled Phase II/III trial data indicating that the point estimate for the incidence rate of Primary MACE favored saxagliptin in every comparison. Looking at subgroups, the Primary MACE rate was lower with saxagliptin in every subgroup.

Dr. Wolf said BMS analyzed multiple CV endpoints using multiple analytic techniques as well as CV endpoints in pooled Phase IIb/III populations by subgroup and by study, and "the results are consistent with the FDA criteria for excluding an unacceptable CV risk." He then concluded that saxagliptin provides meaningful benefits in glycemic control, provides a favorable safety and tolerability profile, and offers a new treatment option with a favorable risk:benefit profile for Type 2 diabetics.

Dr. Brian Daniels, BMS senior vice president for global development and medical affairs, reviewed the company's plans for post-approval studies. This includes:

- Spontaneous reporting with additional targeted questionnaires.
- Analysis of FDA's adverse event reports (AERS) database "as needed."
- Pharmacoepidemiology studies utilizing large U.S. and European databases and comparing saxagliptin with oral anti-diabetic agents.

Saxagliptin Efficacy and Safety

Measurement	Comparator	Saxagliptin 2.5 mg	Saxagliptin 5 mg	Saxagliptin 10 mg
Change in HbA1c at Week 24				
Monotherapy studies	+0.19%	-0.43%	-0.46%	-0.54%
Combination with metformin (MET)	+0.1%	-0.59%	-0.69%	-0.56%
Combination with TZD	-0.3%	-0.66%	-0.94%	---
Combination with glimepiride (Sanofi-Aventis's Amaryl)	+0.08%	- 0.54%	-0.64%	---
Safety in pooled database				
≥1 adverse event	70.6%	72.0%	72.2%	76.7%
Deaths	0.3%	0.2%	0	0
≥1 serious adverse event	3.4%	3.5%	3.4%	2.5%
Discontinuations due to adverse events	1.8%	2.2%	3.3%	3.9%
Hypoglycemia				
Reported with monotherapy	4.1%	4.0%	5.6%	8.2%
Confirmed with monotherapy	0	0	0	0
Reported as add-on to metformin	5.0%	7.8%	5.2%	3.9.%
Confirmed as add-on to metformin	0.6%	0.5%	0.5%	0.6%
Reported as add-on to sulfonylurea (SU)	10.1%	13.3%	14.6%	---
Confirmed as add-on to SU	0.7%	2.4%	0.8%	---
Reported as add-on to TZD	3.8%	4.1%	2.7%	---
Confirmed as add-on to TZD	0	0.5%	0	---
Reported initial combination with MET	4.0%	3.4%	5.0%	1.5%
Confirmed initial combination with MET	0.3%	0	0.6%	0

Saxagliptin Cardiac Safety

Measurement	Clinical components	Saxagliptin patients with a cardiac event
Acute CV events (sponsor-defined)	Acute ischemic events	61
Primary MACE (sponsor-defined)	CV death, non-fatal MI, non-fatal stroke	41
Custom MACE (FDA-defined)	CV death, non-fatal MI, non-fatal stroke	40
SMQ MACE (FDA-defined)	CV death, non-fatal MI, non-fatal stroke	141

- Phase IIb and Phase IV clinical trials with independent adjudication of CV events.
- A large, randomized, event-driven, controlled trial to:
  - Characterize long-term benefits.
  - Further develop the CV profile using prospective adjudication and analysis.
  - Study a population at elevated risk for CV events.
  - Provide another mechanism for the continued assessment of the clinical profile of saxagliptin.

PANEL QUESTIONS FOR COMPANY EXPERTS AND THE FDA ON ONGLYZA (saxagliptin)

The panel had a variety of questions for these experts.

Applying the FDA guidance to specific drugs

Panel members asked the FDA for guidance on how to apply the FDA's guidance document on CV risk and diabetes drugs to drugs in the pipeline already like saxagliptin. Dr. Marvin Konstam, a cardiologist from Tufts Medical Center, said, "We are sort of in between with an NDA that came long prior to the document. Dr. Rosebraugh said his sense of the panel's recommendations in July 2008 on the CV issue were that they wanted "some comfort there won't be a cataclysmic MI resulting from a drug, recognizing that definitive data would take 5-7 years …To have enough events so we know there is a balance such that this drug won't create a great risk and then can be approved for marketing…Did they (the drug) hit the first stage where we can say we don't see something cataclysmic, and we can let them on the market until we get the evidence from the outcomes study…The guidance document doesn't mean you have to do (something), but it is guidance on what you have to do to make us happy."

Dr. John Teerlink, a heart failure specialist from San Francisco VA Medical Center, said he is "struggling" with applying the FDA's CV guidance document to saxagliptin. He asked FDA officials, "If we…believe the population in which the drug is studied doesn't have relevance to the question of CV risk, how are we to apply data from the database to the issue of CV risk? ...Are you suggesting we apply a different standard of public health of protecting people from these (CV) events (for drugs already in the pipeline when the guidelines were issued)?" The FDA's Dr. Rosebraugh responded, "What we are asking you folks (the panel) to help with is: Is having an MI in someone who had diabetes for 3-5 years different than an MI in someone who had diabetes for 10 years?"

What do this panel's deliberations on saxagliptin – and the upcoming liraglutide panel – mean for these and other drugs in the pipeline? The FDA's Dr. Parks said, "When the guidance was published in December (2008), it was also decided that this requirement to assess CV risk…(would be applied) to any NDA coming before the FDA, including the ones in house. That is what will be uniform for all these programs. What becomes more complicated are the companies caught in the middle. The line has been drawn in the sand, and they stood before that line…The decisions here will also apply to other programs in Phase II and III…(The question is if the efficacy) benefit has been established for us (the FDA), whether or not the quality of the data here address the CV risk goalpost (a point estimate of 1.3-1.8)."

Lack of data in high-risk patients

Dr. Teerlink expressed concern several times about the lack of data in high-risk patients or in patients who have had diabetes >10 years. He said, "The risk of increased CV events doesn't increase (in diabetics) until they have had the disease for at least 10 years…There are almost no patients who had diabetes for >10 years in the entire (saxagliptin) development program." Dr. Peter Savage, a diabetes expert from NIH, agreed that the patient population studied with saxagliptin appears to be a relatively low-risk group.

Duration of Type 2 Diabetes in Saxagliptin Patients

Years	Saxagliptin 2.5 mg	Saxagliptin 5 mg	Saxagliptin 10 mg	Comparator
≥5 years	41.2%	31.5%	19.3%	31%
≥10 years	16.4%	14.6%	14.6%	N/A

MACE analyses

Panel members asked for an explanation for the FDA's choice of the Custom MACE endpoint. The FDA's Dr. Joffee said, "SMQ MACE and Custom MACE were both defined before we looked at any of the data…There was concern in looking at broad SMQ MACE that some of the events that are included in that endpoint, though consistent with a CV event, may not actually represent an event in some patients. So, to try to pare that down, (our) reviewers looked through the terms and picked out those most likely to represent a CV event…And that was the analysis the FDA asked of the company."

The panel had a problem understanding and applying the FDA's point estimates of 1.3 and 1.8. Michael Proschan, PhD, an NIH biostatistician said, "Ruling out something as harmful at 1.8 isn't saying much. That is still allowing something pretty harmful to get in…I think this idea of ruling out a 1.8 and feeling somehow confident of that is really not saying a whole lot." Dr. Katherine Flegal, a CDC statistician, wanted to know what a "reassuring" point estimate would be, and the FDA's Dr. Joffee said "close to 1.0."

Hypoglycemia

Dr. Konstam challenged the company on its suggestion that saxagliptin has a lower potential for hypoglycemia than other diabetes therapies, saying that has not yet been proven. A BMS official said a head-to-head trial of saxagliptin vs. SU is underway and should help answer the question, but currently the company can only say the hypoglycemic events are lower than placebo.

CK elevations

The panel discussed the saxagliptin patients with CK elevations – are they really MI patients or not? Dr. John Alexander, a Duke University cardiologist who was asked by BMS to review the CV data on saxagliptin, said, "The isolated CK values…in my judgment, are hard to conclude are CV events." The cardiologists on the panel – Dr. Konstam and Dr. Teerlink – didn't agree. Dr. Konstam said, "No, you can't say that...It is a concern…You could not say with only CPK that it is not an MI…You could say it is not specific for MI, and there are other things that could cause it…I wouldn't say it means little. It is a concern and a possible MI." Dr. Kathleen Wyne, a diabetes researcher from Methodist Hospital in Houston, said that in practice diabetes doctors probably would look at an asymptomatic patient with a CK elevation and assume it is due to something other than an MI.

Postmarketing studies

BMS's Dr. Daniels emphasized that the company is committed to postmarketing studies. He said, "We have a great desire to do an appropriate, large outcomes study – after approval if possible…The commitment is there. It is real. It may seem a little unformed, but that is because we want to have the right discussion with FDA and other regulatory and academic groups on the design."

High sensitivity C-reactive protein (hsCRP)

A panel member wanted to know if there is any impact on hsCRP with saxagliptin, and a BMS official said no.

Labeling

Jessica Henderson, PhD, a health science professor from Western Oregon University and the consumer representative on the panel, said, "I would encourage the label to say there are not enough data on subgroups."

CV safety of other DPP-4s

At the request of a panel member, a BMS official presented data on the cardiac safety of Merck's Januvia. He added, that the point estimates for cardiovascular serious adverse events with Novartis's Galvus (vildagliptin), which does not have FDA approval, are to the left of unity, "Our interpretation of these data is that we have not seen evidence of cardiac harm from other members of the class where there are published data."

CV Safety of Januvia

Measurement	Januvia	Non-exposed patients
Carotid disorder adverse events	4.0%	3.9%
Carotid disorder serious adverse events	1.2%	1.5%
Ischemic adverse events	2.0%	2.0%
Serious ischemic adverse events	1.1%	1.5%

Skin cancer

A BMS official said the company did two long-term (preclinical) carcinogenicity studies, "We saw no signals, including skin cancers…We looked at the experience with skin cancer in the clinic, and we saw no evidence of an increase in skin cancer among saxagliptin-exposed patients."

Creatinine clearance

In response to a panel member's question, BMS offered data on baseline creatinine clearance with saxagliptin.

Baseline Creatinine Clearance in Saxagliptin Trials

Creatinine clearance	Saxaglipt in 2.5 mg	Saxagliptin 5 mg	Saxaglipt in 10 mg	Comparator
<50	1.2%	1.2%	1.2%	1.3%
<80	16.9%	19.1%	14.7%	19.0%

PUBLIC WITNESS ON ONGLYZA (saxagliptin)

There was only one public witness, Kelly Close, editor-in-chief of ***diaTribe***, a newsletter on products and research in diabetes and a Type 1 diabetic herself. She told the panel new treatments are needed, "We are not achieving goals. Our success rates are very low…Only 7% of patients reach glucose, lipid, and blood pressure goals…Most are out in one of these…(And) prevalence is up. We need new drugs so people can get earlier and more aggressive therapy that they will take…We continue to need alternate options, and I would like to live in a system where innovation is encouraged not discouraged, even passively…While I support assuring the safety of all drugs...I encourage the FDA not to put excessive barriers in place."

FDA DISCUSSION POINTS FOR THE PANEL ON ONGLYZA (saxagliptin)

The following four topics were discussed by the panel, but no vote was taken on any discussion point.

DISCUSSION POINT #1. Discuss whether the low CV event rate in the saxagliptin clinical trials permits a reliable assessment of cardiovascular safety.

The panel chair summarized the sense of the panel: "The studies only examined patients with low CV risk for a relatively short period of time, which may not be applicable to higher-risk patients, but, nevertheless, it appears there was an acceptable CV risk. There is a question whether this risk will apply to patients with a higher risk, and it seems the majority think the risk from a statistical standpoint of missing significant CV events is low."

Panel member comments included:

- *Statistician:* "Analyzing it many different ways is an advantage, and it shows the results don't change very much as you change your methodology, which is important. It is true there are not a lot of events…I found it reassuring that the different analyses came out with similar conclusions by and large."
- *Dr. Konstam, cardiologist:* He said there are two issues: (1) the confidence that can be garnered from the low number of events, and (2) whether it is likely that the risk will be different in different patient populations, "On the first issue, it reassures me that a lot of the point estimates are to the better side of unity. The other issue we can't deal with, though I must challenge myself to see if I know of another drug that has two directional effects – one that drives the point estimate in a good direction in a low-risk population and in a bad direction in a high-risk patient. I don't know of a drug that does that."
- *Dr. Teerlink, another cardiologist:* "I think the data do give us a good picture of the CV risk in the patients studied, but…I just have no idea what happens if you give this (saxagliptin) to someone with coronary disease or long-term diabetes with risk factors for coronary disease."
- *Dr. Lynne Levitsky, a pediatric endocrinologist from Massachusetts General Hospital:* "My attitude is the biology suggests there won't be adverse outcomes with this drug but I don't think we have the data to say that… But, on the other hand, I don't think we can say this drug needs a 20-year study before it can get out on the market." Asked if it should be broadly approved, Dr. Levitsky said, "Probably for all patients with very careful surveillance (of the database)."

DISCUSSION POINT #2. The recent guidance regarding evaluation of CV risk for diabetes therapies, ongoing and future diabetes drug development programs will be required to conduct pre-planned adjudication of CV events and to collect all data necessary for such adjudication. However, the saxagliptin development program was already complete by the time the guidance was issued. For saxagliptin, neither pre-planned nor post hoc adjudication occurred, and full data were not available to permit meaningful assessment of many CV events. The MACE endpoints were defined post hoc for a drug development program that was not designed to prospectively measure CV risk associated with saxagliptin. **Please discuss whether these endpoints and the post hoc analyses permit a reliable assessment of CV safety. Please offer suggestions for improvements to the endpoints and analyses that may be applied to other diabetes programs that have already completed or had ongoing Phase III programs at the time the final guidance was issued.**

The panel chair summarized the sense of the panel: "All of us are uncomfortable with post hoc adjudication, but the company is caught in between there. Both the company and the FDA have done a great job trying to work out a system to figure out if there is an increased CV risk. All of us are uncomfortable with the data, but under the circumstances, the thinking is that this is the best job that could be done."

Panel member comments included:

- *Dr. Konstam:* "The FDA did a great job…They described it well. I'm reassured that the Custom MACE data seem pretty similar to the company's Primary MACE…The absence of adjudication and pre-specification are substantial limitations…(That) makes the confidence around the statistical test questionable, and maybe you need to widen the confidence interval around the 'true estimate' in some way…that doesn't make it real data…It just makes the estimate a bit more difficult."
- *Dr. Teerlink:* "The FDA and sponsor all did a great job analyzing the data we have…(In the future) the sponsor needs to (collect) as much of the information as possible and gear up to do as much adjudication as possible prior to breaking the database lock or codebreak. If they are beyond that point, then go on as this sponsor tried to do… Send it off to Duke, but give them more than four weeks (to analyze the data), and try to do (the analysis) as close to the guidance document as possible."
- *Industry representative:* "I think the FDA did a wonderful job looking at the Custom MACE concept…but if you have an adjudicated CV database…you can possibly accurately compare adjudicated vs. the customized approach ...and I suspect that will be very close."

DISCUSSION POINT #3. The saxagliptin trials included a 24-week, short-term, double-blind period followed by a long-term, double-blind period. Patients entered the long-term period if they completed the short-term period or if they were discontinued from the short-term period due to inadequate glycemic control. Patients who entered the long-term period because of inadequate glycemic control during the short-term period were administered open-label rescue medication. **Please discuss whether this trial design affects interpretation of CV results for the short-term period and for the combined short-term and long-term periods.**

The panel chair summarized the sense of the panel: "It seems the consensus of the panel is that this, given the issues we discussed before, is an appropriate summary and does give us significant information on the CV risk of this drug. And we wondered if there is a relationship between rescue and higher events and that doesn't seem so. And it seemed the longer the patient was followed the greater the risk of an event."

Panel comments included:

- *Panel chair, Dr. Kenneth Burman, an endocrinologist from Washington Hospital Center:* "The trials are imperfect, but in the real world seem reasonable."
- *Dr. Konstam:* "I don't have too much concern about combining long-term and short-term trials in this case (analysis). From what I understand, randomization and blinding were retained, and it was a mix between patients who continued short term and those who had glycemic rescue. I'm not seeing a major problem with combining these populations."
- *Dr. Wyne:* "I'm not concerned about lumping the events together because they are such small numbers."

DISCUSSION POINT #4. Multiple statistical methods were used to analyze cardiovascular outcomes. **Please discuss the adequacy of these methods for measuring sensitivity of the results to analytical method.**

The panel chair summarized the sense of the panel: "I think we agree they are reasonably sensitive. There could be a slight chance they are wrong, and there could be higher CV events over the longer term, but that chance is low."

Panel comments included:

- *Dr. Teerlink:* "I have this sense of unease when you deal with such small numbers. You can do multiple statistical tests on the same number, but that doesn't change the fact that there are just small numbers…How many more patients would have had to show up in the saxagliptin group to move the point estimate or CI into 1.3 or 1.8? How many would have had to move to change that…and my guess is that number would not be big."

FDA Questions for the Panel on Onglyza (Saxagliptin)

The FDA asked the panel to vote on two issues. The panel went directly to the votes, with no discussion:

Question #1. Has the applicant provided appropriate evidence of CV safety to conclude that saxagliptin rules out unacceptable excess CV risk relative to comparators, including evidence that the upper bound of the two-sided 95% confidence interval for the risk ratios/odds ratios is less than 1.8?

VOTE: 10 YES, 2 NO

The NO votes were Dr. Teerlink and Dr. Wyne.

Panel member comments about their votes included:

- *Dr. Teerlink, cardiologist:* "I want to limit how it should be labeled…It needs to be a relatively restricted patient population."
- *Dr. Wyne:* "I voted no because...the number of events are too low to provide an adequate assessment."
- *Dr. Levitsky, the consumer rep:* "I voted yes but not a full yes. I had some of the same concerns."
- *Dr. Eric Felner, a pediatric endocrinologist from Emory University School of Medicine:* "I think everything was done according to the guidelines…I think the answer is yes…A low cardiac signal does not need further investigation."
- *Panel chair, Dr. Burman, an endocrinologist:* "I think that saxagliptin was caught between the former CV requirements and the new guidelines…and any effort to assess data in such a study will intrinsically have flaws, and we have taken those into account in the best way we can."
- *Dr. Proschan, statistician:* "It definitely convinced me there is not big harm."
- *Dr. Henderson, the consumer rep:* "Yes, with labeling."
- *Dr. Konstam, cardiologist:* "This agent has promised to differentiate itself, specifically in getting glycemic control without hypoglycemia, even though the sponsor didn't show that, but there is some promise of that. The spirit of the guidance was we should know something about CV risk for these drugs. And the bar was set for approvability of ruling out excess risk of 1.8, with the caveat that we could ask the sponsor to do more postmarketing studies… I'm very reassured by how favorable the point estimate is. This might wind up being a great drug, but we don't know that yet…The sponsor did not study patients at extremely high risk, including patients with known atherosclerotic disease, so I think there should be something in the label that the safety in that population has not been investigated."

Question #2. For the Custom MACE endpoint, the upper bound of the two-sided 95% confidence interval for the risk ratio/odds ratio was less than 1.3. These data involved a total of 11 cardiovascular events in the 24-week, double-blind, short-term study periods and a total of 40 cardiovascular events in the combined short-term and long-term study periods of median 62-week exposure. **Are these data adequate to conclude that postmarketing cardiovascular safety trial(s) are unnecessary?** If no, please comment on the limitations of the completed NDA program that will require an additional postmarketing trial(s).

VOTE: Unanimously NO

The panel chair said the take-away message is: "Everyone wants good postmarketing studies."

Panel comments included:

- *Dr. Konstam, cardiologist:* "When it comes to a higher level of confidence that there could not be harm here…I don't think you can get there from here. The number of events are far too low for that…I do think additional trials should be directed to raising the confidence…And the sponsor should be extremely confident about doing those trials because if they believe their point estimate, they should have a blockbuster drug."
- *Dr. Proschan, statistician:* "There is enough uncertainty to make me feel even more like I do want a longer-term trial and perhaps it would be nice to enroll people with coronary disease so we can get evidence on that."
- *Dr. Flegal, a statistician:* "The point estimates are favorable, and that is encouraging, but there are a small number of events and lack of adjudication."
- *Panel chair:* "A postmarketing study should include longer-term and higher-risk patients and look at not only cardiovascular but also high-risk patients. Other factors, such as lymphocyte count, pancreatic function, platelet count, and skin lesions, among other things, (should be investigated)…Our primary goal is to protect the patient population, and I don't think there are enough data so far to know there is no risk to many populations."
- *Dr. Wyne, a diabetes doctor:* "I'd like to complement the sponsor and the Agency on analyzing this data…I think the (drug) has nice glucose lowering data, so I don't have any concern using it for that, but I would like to know the long-term safety…and it really needs to be (studied) in the people at highest risk which means patients with more than 7-10 years of diabetes."
- *Dr. Teerlink, cardiologist:* "I think this should be approved and be available for patients. This – as well as new therapies – needs to be made available…Clearly, all of us think new trials in high-risk patients need to be done."

- *Rebecca Killion from Bowie MD, the patient representative:* "I felt a little schizophrenic about this…There are gray areas…I think clearly we have some ongoing concern, but I want to credit the sponsor for saying they are doing additional studies…and I'm sure they will do a good job on that."
- *Dr. Peter Savage, a diabetes expert:* "It seems to me that the preliminary studies done on a drug prior to this type of thing clearly should include more data on high-risk patients in the future…We should demand that data in the relatively near future...The issue of avoiding hypoglycemia is important, and there should be more data on that…It could be this drug is safer to use in some circumstances, but there weren't enough data here or on the elderly."
- *Timothy Lesar, PharmD, Albany Medical Center:* "They particularly need to study it in high-risk patients."

NOVO NORDISK'S VICTOZA (liraglutide), a GLP-1 Agonist

On Thursday, April 2, 2009, the FDA's Endocrinological and Metabolic Drugs Advisory Committee reviewed two issues with Victoza (liraglutide): (1) cardiac safety and (2) possible thyroid tumorgenicity. The FDA appears to have accepted the efficacy of liraglutide, since there was only a cursory discussion of that at the panel.

The panel took 4 votes – 1 on the CV risk and 3 on thyroid issues. Overall, the panel sent a negative message to the FDA but with hope that liraglutide can be rescued. That is, they didn't say the FDA should kill it entirely; they just want more study and reassurances of safety before it is marketed. The FDA's action date (the PDUFA) date for liraglutide was March 23, 2009.

The cardiovascular issue. The cardiac issues were slightly different for liraglutide than for BMS's saxagliptin. Novo Nordisk did larger and longer studies, but the point values did not as clearly favor liraglutide as they did saxagliptin. And the panel wasn't as convinced of the CV safety of liraglutide as saxagliptin, voting 8 to 5 that liraglutide CV safety was sufficient.

The FDA's take-away message on CV safety, according to Dr. Parks, was: "The majority (of the panel said it was safe), but there were a lot of caveats with that, and that reflects both the quality of the data and the ability to make that goalpost of 1.8 prior to approval. And they (the panel) gave us a lot of good information…even those who voted no…That will help us not only determine how to advise companies that have not started but companies already underway in how to look at their data, and if they know ahead of time that they do not have the same design as what is being asked for of these 2 companies (Bristol-Myers Squibb and Novo Nordisk)…Some companies may be looking at their program very carefully…to see if they at least meet the same level or design."

The thyroid cancer issue. The key question for liraglutide is the thyroid toxicity. There is an increase in preclinical thyroid nodules and cancer, and the FDA reviewers could not rule out the possibility of thyroid carcinogenicity in humans, though they also did not prove it causes cancer.

Thyroid C-cell tumors (adenomas and carcinomas) were seen in animals – rats as well as mice – with liraglutide. In addition, fibrosarcomas were seen in male mice. The FDA – and the panel – did not agree with the company's theory about the mechanism of action. FDA reviewers concluded, "The weight of evidence from rodent carcinogenicity studies, mechanistic studies, and clinical data are not sufficient to conclude liraglutide-induced thyroid-cell tumors are rodent-specific...The applicability of these rat and mouse findings to humans is not fully understood. There have not been clear-cut cases of medullary thyroid carcinoma (MTC) in humans who received liraglutide."

Panel members felt the animal data could be applicable to humans, and they were split over whether the concern was sufficient to block approval. All agreed that more study is needed, that they wanted reassurance on the safety, though some felt this could be done postmarket and others suggested a 6-12 month study before approval. There was concern that screening or monitoring patients would impose both cost and safety issues on patients, and it might lead to an excess of thyroidectomies.

At the end of the day, what impression did the panel leave:

1. **Lack of conviction that the CV safety is okay.** The panel vote was mixed (8-5), and the FDA generally views that as a neutral vote, not a positive vote. It tells the FDA the panel thinks there could be a CV problem and isn't convinced there isn't a problem but also is not convinced there is.
2. **Concern over a potential increase in thyroid cancer and thyroid surgeries.** Though the risk is small and the incidence probably very low, the panel was worried that (1) the problem may not show up for years, and the drug wasn't studied long enough to know this, and (2) thyroidectomy is not a minor procedure.
3. **Concern over the need for monitoring patients for thyroid cancer.** The screening/monitoring itself (calcitonin blood tests, sonograms, etc.) is costly to patients and the healthcare system, can have side effects (ranging from MRSA infections, etc., to thyroidectomies requiring a lifetime of thyroid medication), and can scare patients and doctors (Will rising calcitonin be like rising PSA? Would there have to be guidelines for when it becomes a concern – 2xULN, 3xULN, 10xULN?). Without more data, the FDA and thyroid experts don't know how long patients will need to be monitored, but it ***appears that the monitoring will have to continue past the discontinuation of the drug***. The FDA toxicologist said that the risk remains in mice even after drug discontinuation.

4. **Skepticism about the company's mechanistic explanation.** The FDA rejected the explanation outright, and the panel wasn't convinced either.
5. **Concern whether calcitonin levels will continue to rise over time** as patients take liraglutide. Or, do they return to normal? (Is this like spiking ALT that returns to normal on a drug or ALT that leads to liver failure?)
6. **A lack of conviction by the FDA that liraglutide offers sufficient benefit to warrant the risk.** The diabetologists said there is an unmet need, and liraglutide is an advance that will benefit patients, but the FDA appeared less convinced of this, seeming to suggest it is perhaps just a more convenient product.
7. **Concern by the FDA over setting a precedent** by approving a drug with cancer signals in 2 species. The only comparable case the FDA could find was Lilly's Forteo (teriparatide), but that had very restrictive marketing and was not broadly used, at least initially. A diabetes drug likely would be very different and expose many, many more people.
8. **Concern with possible off-label use for weight loss.** This has occurred with Byetta but it might be more problematic with liraglutide because the safety is less established.
9. **Papillary thyroid cancer**, the most common form of thyroid cancer, is not a concern.

With all this in mind, it appears likely that the FDA will – at a minimum – require another 6-12 month study monitoring calcitonin levels and any thyroid problems very carefully. If the calcitonin levels spike (and not too high) but return to normal, that might be reassuring enough to let the drug on the market – provided there isn't any MTC or other thyroid cancer or any other concerning data in that study. The trial might also be a test of how onerous the monitoring would be. It may take some time for the company and the FDA to agree on trial design, and then it needs to be conducted, so this would appear to be at least a 2-year delay for liraglutide.

There also is a real possibility that the FDA will turn liraglutide down completely – either with a flat rejection or an onerous complete response letter over the thyroid toxicity. The FDA appears to have gone into this panel wanting to turn liraglutide down completely but was willing to be convinced otherwise. Three things the FDA officials repeatedly emphasized suggest that this worst case scenario is possible:

1. The FDA's history of not approving drugs with cancer signals in 2 species.
2. The Lilly Forteo experience – approval but with restrictions that meant very limited use.
3. The declaration that this is a class effect that they are seeing in the other long-acting GLP-1s in development.

And the FDA wouldn't be turning down all diabetes drugs if they approve saxagliptin, so the Agency has some "cover" with turning down liraglutide if it approves saxagliptin.

What does this mean for other GLP-1 agonists in development, including Byetta LAR? It most likely means they get delayed, too. Whatever liraglutide has to do, they will have to do as well. There is little or no chance whatsoever that the FDA would approve Byetta LAR or any other GLP-1 agonist while liraglutide continues to jump through hoops.

What precedent is there for requiring pre-screening for a mass-marketed diabetes drug? Dr. Parks said, "There are plenty of drugs…that you do prescreening for because certain risks are known to be associated with them…In our Division, the example was Forteo. There, because of concerns over the risk of osteosarcoma, and it is known that it may be much (worse) in certain patients, it is contraindicated. That is certainly not a novel concept…The question here is screening based on a biomarker and the utility of that biomarker." Panel chair Dr. Burman added, "Calcitonin levels are not recommended for screening the general population, but…the crux of the issue is whether it is the same harbinger in patients who don't have familial MTC and just have elevated calcitonin. (In familial MTC), calcitonin is a very good marker for predicting the presence and progression of C-cell hyperplasia (CCH) becoming MTC."

Asked how strong the thyroid cancer signal is with other GLP-1 agonists, Dr. Parks said she couldn't discuss anything under review more than was already done.

Asked about the apparent lack of concern with papillary thyroid cancer (another type of thyroid cancer), Dr. Burman said papillary cancer is the most common form of thyroid cancer, accounting for 80%-90% of cases, with follicular ~10%, MTC ~4%, and anaplastic ~1%. He added, "Stage 1 is highly treatable with >95% survival over 10 years; Stage 2, 85%-90% survival over 10 years; Stage 3, 75%; and Stage 4, 50%, meaning the sooner you pick it up, the more likely you will be to treat it."

Asked about the FDA's current level of concern about pancreatitis with Byetta or liraglutide, Dr. Parks said, "That is being evaluated as well in this and all GLP-1s and all the incretin-based therapies. I don't think at this point we have enough clinical experience with liraglutide to be able to compare (it to Byetta)…It hasn't been compared in an adequate trial to exenatide...What (comparative) studies have been done are short duration…Setting aside comparative studies, we don't have enough clinical exposure with liraglutide to comment on the risk of pancreatitis…The pancreatitis with Byetta is from postmarketing…I think it is safe to assume some expectation of additional data on pancreatitis (will be requested)…I'd hedge to say requirement."

Would the thyroid risk last for life if someone took liraglutide only for a short period? Dr. Parks said, "There are no data…Most of the data are from animals…with respect to evaluating C-cell tumors…All the animals were sacrificed…In the clinic we have even less information as to whether or not this drug is causing C-cell tumors…I don't think we can answer that question. It is reasonable to make an assumption. We think it is due to some pharmacology-based mechanism of the drug that if you take away the drug is no longer acting on the C-cell to continue down that path." Dr. Burman, the panel chair, said, "That (how long to monitor) is uncertain. If the drug does cause elevation of calcitonin, do those risks abrogate when the drug is stopped? No one knows." Tony Parola, PhD, a pharmacology/toxicology reviewer in the FDA's Division of Metabolism and Endocrinology Products, added, "In animal studies, animals treated for 9 weeks develop focal hyperplasia, and after a 16 week recovery period, there was still evidence in mice. It was not fully reversible in mice."

Asked whether liraglutide is likely to be used off-label for weight loss as Byetta has been, Dr. Parks said, "That is probably on everyone's mind, but we didn't discuss that because that is what we need to discuss with the company."

THE FDA PERSPECTIVE ON VICTOZA (liraglutide)

Novo Nordisk submitted data on 4,655 patients exposed to liraglutide: 2,412 for ≥24 weeks and 840 for ≥50 weeks. The liraglutide development program consists of 38 completed clinical trials and 2 ongoing open-label extension studies. This included 1 Phase II dose-finding trial, 2 Phase I trials (intranasal and pulmonary administration), 7 trials exclusively in Japanese patients, and 5 major Phase III trials. At the time of the filing, there were 6 ongoing trials.

The FDA's CV and thyroid cancer safety review included review of pooled data from these trials, from subsequently submitted cardiovascular and thyroid safety information, from a safety update submitted by the company in September 2008, from the Byetta data, and from the medical literature.

The two problems FDA reviewers identified were CV events and preclinical thyroid tumors. Across the development program, withdrawals due to adverse events were more common among liraglutide-treated patients than among comparator-treated patients. FDA reviewers attributed this excess withdrawal rate mostly to gastrointestinal (GI) events.

In his oral presentation to the panel, Dr. Joffee, lead medical officer for the FDA's Diabetes Drug Group in the Division of Metabolism and Endocrinology Products, told the panel that the liraglutide and saxagliptin programs "differ enough that cross comparisons are not appropriate." He highlighted the two key issues with liraglutide: thyroid tumors and CV safety.

Efficacy

FDA reviewers concluded that the efficacy of liraglutide 1.2 mg and 1.8 mg is supported by the comparisons to placebo and to active control comparators in a range of background anti-diabetic therapies, but the efficacy of liraglutide 0.6 mg is less well supported. They found that the Phase III trials demonstrated an average net loss in weight at 26 weeks and 52 weeks vs. background therapies, with ~50% of patients losing from 0-5% of their baseline body weight at study end.

Cardiotoxicity

The FDA reviewers conducted several different analyses of the CV data on liraglutide. Overall, cardiac and vascular system organ class events occurred with slightly numerically higher frequency for the total liraglutide-treated group than for the placebo-treated group, but with similar frequency to the active control and overall comparator group.

The terms "hypotension" and "orthostatic hypotension" occurred with slightly numerically higher frequency among liraglutide-treated patients than among comparator-treated patients. "Hypotension" occurred in 12 (0.3%) of liraglutide-treated patients and in 2 (0.1%) of comparator-treated patients. "Orthostatic hypotension" occurred in 5 (1%) of liraglutide-treated patients and in 1 (<0.1%) of comparator-treated patients.

In the long-term (Phase III) trials, liraglutide did not increase systolic blood pressure; most point estimates for liraglutide vs. comparator favored liraglutide, particularly for comparisons to other active anti-diabetic agents. Novo Nordisk reported that there was no significant effect of liraglutide on diastolic blood pressure in the Phase III trials. Liraglutide also had no significant effect on change from baseline in levels of hsCRP (high sensitivity C-reactive protein).

The FDA reviewers reported that across the liraglutide development program:

- Few major cardiovascular events occurred, limiting the ability to assess CV risk.
- Cardiovascular events did not undergo pre-planned adjudication *(as the new guidelines require)*.

Liraglutide Efficacy

Treatment	Time period	Change in HbA1c vs. comparator	Superiority
Monotherapy 1.2 mg	52 weeks	- 0.33	Yes
Monotherapy 1.8 mg	52 weeks	- 0.62	Yes
Add-on therapy	26 weeks	- 0.78 to - 1.36	Yes

Liraglutide Efficacy vs. Comparators

Comparator	Liraglutide 0.6 mg	Liraglutide 1.2 mg	Liraglutide 1.8 mg
Glimepiride 4 mg	Not non-inferior	Non-inferior	Non-inferior
Avandia (rosiglitazone) 4 mg	Non-inferior	Superior	Superior
Insulin glargine	---	---	Superior

- The program was not designed to include a large number of patients at high risk of CV events. In fact, intermediate- and long-term trials had an exclusion criterion for patients with significant CV disease, and thus a high incidence of CV events would not be expected among the population studied in the development program. *(Not in accordance with new guidelines.)*
- The program was not designed to facilitate the combination of its trials into a meta-analysis. Trials were of varying durations, and the blinded and open-label periods differed among major Phase III trials. *(Not in accordance with new guidelines.)*
- Choice of endpoint, comparator, and analysis method can alter the results of cardiovascular event analyses.
- In general, when comparing liraglutide to overall pooled comparator, the risk of MACE (CV death, MI, infarction, or stroke), using analysis methods stratified by study, the point estimates were <1, and 95% confidence intervals included 1. The upper bound of the 95% confidence interval usually exceeded 1.3. The estimates were not very sensitive to choice of estimation methodology. *(Not in accordance with new guidelines.)*
- Comparisons of liraglutide to active comparator for MACE were qualitatively similar to comparisons of liraglutide to total comparator. The estimates were somewhat sensitive to choice of estimation methodology.
- Comparisons of liraglutide to placebo for MACE sometimes resulted in a point estimate >1 (not favoring liraglutide), with the confidence intervals including 1, and an upper bound of the 95% confidence interval >1.8, depending on analysis method. Patients in placebo groups were not at lower CV risk than patients in other treatment groups, and thus lower risk was not an explanation. Estimates were sensitive to choice of estimation methodology. *(Not in accordance with new guidelines.)*
- Low event rates among placebo-treated patients (and low event rates in general) are likely to have contributed to the sensitivity to methodology.
- When considering all adverse events that were possibly CV in nature (not limited to CV death, stroke, or MI), there were few events or groups of events which appeared to occur with higher frequency among liraglutide-treated patients than among comparator-treated patients. Overall MedDRA System Organ Class events for the Cardiac Disorders and Vascular Disorders SOCs occurred with slightly numerically higher frequency for liraglutide-treated patients than for placebo-treated patients, but with similar frequency for liraglutide vs. active comparator and liraglutide vs. overall comparator.
- There were slightly numerically more patients who had events of hypotension, angina, and MI in the overall liraglutide group than in the overall comparator group, but the overall incidence of these individual events was low.
- There did not appear to be a relationship between liraglutide dose and risk of MACE.
- Overall, deaths from any cause occurred at a low rate and occurred with approximately equal frequency among liraglutide-treated patients and comparator-treated patients.

Dr. Joffee told the panel that the FDA is ***not*** asking the panel if postmarketing studies are necessary, which suggests that, if liraglutide is approved, postmarketing studies ***will*** be required. The FDA's Dr. Rosebraugh said, "(If the drug is approved,) you can rest assured they did not meet the 1.3 (odds ratio goalpost), and we will require them to do another study."

In her oral presentation to the panel, Dr. Karen Mahoney, a clinical reviewer in the FDA's Division of Metabolism and Endocrinology Products, CDER, said the FDA analysis found:

- vs. total comparators, the liraglutide point estimates were <1, and the upper bounds of 95% CI were <1.8 but usually >1.3.
- vs. active comparators (subgroup analyses), the point estimates were also <1, and most upper bound of 95% CI were <1.8 and >1.3. This was somewhat sensitive to the method of analysis.
- vs. placebo, liraglutide point estimates were often >1, and most upper bounds of 95% CI were >1.8. Again, this was sensitive to the analysis method.
- The FDA guidance does not require applications to meet the specified 95% CI boundary limits for subgroup analyses.
- There is no apparent relationship between liraglutide dose and risk of MACE.
- There was a low rate of total mortality, with no cause-specific pattern.

Why were some point estimates >1 for subgroup analyses of liraglutide vs. placebo? Dr. Mahoney said it was probably not due to lower baseline risk among the placebo-treated patients and low event rates.

Dr. Mahoney said it is "very rare for a drug that has caused tumors (of any cell type) in 2 species, in both genders, at clinically relevant exposures, to have been approved, regardless of mechanism…No drug that has caused C-cell tumor in 2 species is known to have been approved…Mechanistic studies did not definitely demonstrate that this risk is specific to rodents."

Among the points Dr. Mahoney made were:

- Medullary thyroid carcinoma (MTC) is relatively, though not always, indolent. The liraglutide clinical trial program may be too short to detect indolent tumors.
- Early complete surgical excision is probably the only curative option for MTC.

- To date there is no clearly-described association between a particular drug and known increased risk of MTC.
- In the liraglutide program, there was one case of MTC in a comparator-treated patient and two cases of medullary carcinoma *in situ* (one liraglutide-treated and one comparator-treated).
- There have been 3 additional liraglutide-related cases of CCH. All were diagnosed through clinical trial monitoring of calcitonin, and pre-operative calcitonin elevations were mild.
- Calcitonin testing in liraglutide patients did not demonstrate an associated risk of marketed elevation in calcitonin but liraglutide may have some effect on calcitonin levels.
- 6 cases of papillary thyroid cancer have been reported in liraglutide patients, mostly microcarcinomata. Three of these also had CCH (2 diffuse, 1 neoplastic).
- The use of calcitonin to screen for MTC is controversial, and there is no experience in using calcitonin to screen for drug-induced MTC. The mean changes in calcitonin were small, and the clinical significance of small changes in calcitonin are uncertain in this setting.
- Thyroid nodules are common in the general population, mostly benign. A thyroid nodule associated with an increased calcitonin level might be more likely to go to surgery. Enhanced monitoring with calcitonin or ultrasound might result in an increased rate of thyroidectomy, which has surgical and anesthetic risks.

Dr. Tuttle, the thyroid expert on the panel, pointed out that the levels of calcitonin being discussed by the FDA are clinically irrelevant. He said, "The clinical assays we use are mostly <5 or <2, so a large part of these numbers (you are showing) would, in my clinic, be (considered) undetectable."

A biostatistician on the panel pointed out that, with respect to CV safety, negative effects could be due to the background therapy – a point he made about saxagliptin as well.

Thyroid cancer

Liraglutide caused thyroid C-cell adenomas (benign) and carcinomas (malignant) in rats and mice and malignant fibrosarcomas in the dorsal skin and subcutis in male mice. However, FDA reviewers found, "Carcinogenicity studies in rats and mice, mechanistic studies of liraglutide-induced proliferative C-cell lesions, and clinical data are insufficient to conclude thyroid C-cell tumor findings in rodents are not relevant to human risk because:

1. Mechanistic studies did not adequately support the applicant's proposed novel mode of action for liraglutide-induced C-cell tumors in rats and mice.
2. After 26-28 weeks of treatment, liraglutide dose-dependently increased calcitonin in clinical study subjects, so if the proposed mode of action is correct, it may be operable in humans.

C-cell carcinoma, also called MTC, occurs when C-cell nodules or cords develop stromal or vascular invasion. Mechanistic studies aimed at determining a mode of action for liraglutide-induced thyroid tumors and their relevance to humans were performed using thyroid tissue, rat, and human C-cell lines, and *in vivo* in mice, rats, and monkeys. MTC is a relatively rare form of thyroid cancer, accounting for only ~5% of all thyroid carcinomas in the U.S. It arises from the C-cells of the thyroid gland, which normally secrete calcitonin, a hormone which is involved in calcium homeostasis. In medullary thyroid carcinoma, calcitonin is often secreted in excess. The 10-year survival rate is probably greater than 75%.

As of May 2008, four cases of papillary thyroid cancer among liraglutide-treated patients and one case among comparator-treated patients had been reported, which translates to a rate of 1.8 and 0.9 events per 1,000 patient-years, respectively. Since then, one additional case of papillary thyroid cancer was reported for a liraglutide-treated patient. Most of these cases were initially identified because of an elevated calcitonin level, rather than because of a palpable nodule, and most were very small (1-2.5 mm), with the largest 9 mm. One liraglutide-treated case had a specific report of neoplastic CCH, which is sometimes called "medullary carcinoma *in situ*," and this patient appeared to have had elevated baseline calcitonin. Complete resection is probably the only curative option for medullary thyroid carcinoma, so accurate early detection of those who are destined to develop it is highly desirable.

CCH and its pathologic classification are areas of some controversy within endocrinology – on the definition, the predictive value for malignancy, and whether the absence of CCH is reassuring. Not all individuals with CCH develop MTC.

The FDA reviewers reported:

- There are too few cases of non-malignant serious thyroid disorders to assign causality to liraglutide.
- In liraglutide trials, thyroid adverse events occurred with higher numerical frequency among liraglutide-treated patients than among comparator-treated patients.
- In four trials that were ongoing at the time liraglutide was submitted to the FDA, there was a similar imbalance of thyroid adverse events, though some data are still blinded.
- Although patient-time data are still blinded in the ongoing trials, it is known that three of the thyroid events occurred among patients treated with liraglutide 1.8 mg and two (both hypothyroidism) in Byetta (BID) patients. One of the liraglutide patients had an event of autoimmune thyroiditis and thyroid neoplasm, and two liraglutide patients had increased calcitonin.

- Events which occurred with a higher numerical frequency among liraglutide-treated patients than among comparator-treated patients included blood calcitonin increased, goitre, and thyroid neoplasm. One of the events listed under "thyroid disorder" was a case of diffuse C-cell hyperplasia.
- Thyroid ultrasound was performed at baseline and end of study in four trials, including the Japanese trial. No patient got a new nodule >10 mm in diameter or growth of an existing nodule by >10 mm. However, the longest duration of these trials was 14 weeks, which is a short observation time for the assessment of stimulation of thyroid nodule growth. In the Japanese study, the appearance of new, small thyroid nodules (<10 mm) was "common" but occurred with similar frequently among liraglutide and placebo patients. Ultrasounds were performed in the Japanese study, and the appearance of thyroid nodules was reported as an adverse event for some, but not all, patients who were found to have a nodule on ultrasound.
- Most of the reported papillary thyroid cancers were very small. Papillary microcarcinoma (<1 cm diameter) are common in the general population and are often incidental findings. However, given the relatively short duration of observation in the liraglutide trials, and the often indolent nature of many thyroid cancers (papillary thyroid cancer in general, and many medullary thyroid cancers), large tumors might not be expected in the clinical trials, even if the tumors were drug-induced.

Thyroid Adverse Events in Liraglutide Program

Measurement	Liraglutide	Non-liraglutide	Blinded
Completed trials			
Number of patients	4,211	2,272	---
Patient-years	2,241	1,139	---
Serious thyroid adverse event	7 patients 10 events (0.2%)	1 patient 1 event (<0.1%)	---
Thyroid adverse events (serious and non-serious)	61 patients 80 events (1.4%)	24 patients 25 events (1.1%)	---
Serious thyroid adverse events per 1,000 patient-years	4.5	0.9	---
Overall thyroid adverse events per 1,000 patient-years (serious and non-serious)	35.7	22.0	---
Ongoing trials at time of NDA			
Serious thyroid adverse events	1 patient 1 event (0.1%)	0 patients 0 events	1 patient 1 event (0.25)
Thyroid adverse events (serious and non-serious)	10 patients 10 events (1.4%)	2 patients 2 events (0.6%)	5 patients 6 events (1.1%)
Serious thyroid adverse events per 1,000 patient-years	1.7	0	6.1
Overall thyroid adverse events per 1,000 patient-years (serious and non-serious)	16.6	6.8	36.5

There are several possible mechanisms of action to explain the liraglutide-induced rodent thyroid C-cell tumors. FDA reviewers explored each of these but were not able to identify one positively.

- GLP-1 receptor agonists activate thyroid C-cell GLP-1 receptors.
- C-cell GLP-1 receptor activation stimulates calcitonin secretion. Calcitonin is a "pre-hyperplasia" biomarker.
- C-cell GLP-1 receptor activation increases calcitonin synthesis.
- Persistent calcitonin secretion and increased calcitonin synthesis causes C-cell hyperplasia.
- C-cell hyperplasia progresses to C-cell tumors, including progression of benign adenomas to carcinomas.

The FDA reviewers warned that approval of liraglutide would raise several issues:

- Whether baseline evaluation of thyroid nodule status or serum calcitonin is needed.
- Whether there would be a need for ongoing monitoring.
- What physicians should do if a liraglutide patient is found to have a thyroid nodule since nodules are common (2%-6% with palpation, 19%-35% with ultrasound, 8%-65% at autopsy).
- When surgery would be indicated for liraglutide-treated patients with thyroid nodules and/or elevated serum calcitonin values.
- Enhanced monitoring for thyroid nodules or elevated calcitonin could result in an increased rate of thyroidectomy, which has its own risks, including recurrent laryngeal nerve injury with vocal cord dysfunction, anesthetic complications, and hypoparathyroidism. An increased likelihood of thyroidectomy, especially in diabetics, might be considered a risk in itself.

Dr. Joffee told the panel that no FDA-approved drugs are known to cause C-cell tumors in two animal species, but ***some investigational GLP-1 agonists may.***

In his oral presentation to the panel, Dr. Parola, an FDA toxicologist, made a very concerning case for the potential carcinogenicity of liraglutide. He also suggested this is ***likely to be a class effect for long-acting GLP-1 agonists***.

Among his points were:

- Most approved drugs only cause (tumors) in rats…but liraglutide is a non-genotoxic, multi-sex, multi-species carcinogen in rodents…Byetta causes adenomas in female rats only…No approved drug causes C-cell tumors in mice.
- GLP-1 receptor mediation of C-cell proliferative effects in rats or mice has not been demonstrated.

- Rodent thyroid C-cell tumors may be a pharmacologic class effect of long-acting GLP-1 receptor agonists. No other investigational drugs cause C-cell tumors in mice.
- Mechanistic studies using subcutaneous exenatide performed by Novo Nordisk showed it causes focal CCH in mice.
- Recent final and interim toxicity reports of other long-acting GLP-1 receptor agonists show they cause focal CCH or tumors in mice and C-cell tumors in rats.
- Cinacalcet, which increases calcitonin secretion in rats, does not cause C-cell tumors in mice or rats.
- The mechanism of persistent calcitonin secretion in liraglutide-treated mice is unknown.
- Bone resorption parameters (BMD, biomarkers of bone resorption) were not measured in liraglutide patients.
- C-cell lines are not thyroid C-cells. 28% of human MTCs were GLP-1 receptor positive, so not all human C-cell lines would be expected to express the receptor.
- Plasma calcitonin in rats is age-dependent. Increased plasma calcitonin in mice is liraglutide dose- and treatment duration-dependent.

Dr. Parola said the absence of diffuse or focal CCH in liraglutide-treated monkeys is not reassuring because:

- Diffuse CCH did not occur in liraglutide-treated mice or rats, but liraglutide induced focal CCH and tumors.
- Monkey studies do not adequately assess the risk of focal CCH and C-cell tumors because of the small number of animals treated and the short period of dosing compared to their lifespan.

What is the relevance of rodent C-cell tumors to the human risk? Dr. Parola said mechanistic studies do not adequately support the mode of action for liraglutide-induced thyroid C-cell tumors in rats and mice, "Liraglutide-increased plasma calcitonin…may be operable in humans. There is a potential increase in the risk of thyroid tumors in humans treated with liraglutide."

During questioning of Dr. Parola immediately after his presentation, Dr. Michael Tuttle, an endocrinologist and thyroid cancer specialist from Memorial Sloan Kettering Cancer Center, did not appear to agree with Dr. Parola's high level of concern about the thyroid safety of liraglutide. Dr. Tuttle said, "It is not clear you can use rats to predict what happens in mice much less humans…Your (the FDA's) main conclusion is different from the mechanism of action the company proposed. You evaluated whether calcitonin secretion would cause cancer and concluded this is not what will happen which agrees with what most of us think."

Dr. Tuttle suggested the issue hinges on the mechanism of action, with the company and the FDA suggesting different mechanisms. He had an interesting exchange with another panel member:

- *Dr. Marvin Konstam, a cardiologist from Tufts:* "There is a very strong signal in rats, and when you deal with safety issues, the onus is to say the signal doesn't mean anything …You have this very strong signal (in rats) and a somewhat lesser signal in mice. Can we prove it is not relevant to humans?"
- *Dr. Tuttle:* "We always get in a tough situation when you have to prove a negative. I look at it more as whether the rat is the exception rather than the rule. The mice and monkey data are not very convincing, so we have to explain the mechanism…What I am trying to figure out is whether the method of action in rats really correlates to people or has any outcome."
- *Dr. Konstam* indicated Dr. Parola's presentation changed his mind about the thyroid safety of liraglutide: "I'm still stuck trying to take the sponsor's presentation to give me comfort the rat signal is irrelevant, and what we just heard moved me off of fully accepting some of the things the sponsor said."
- *Dr. Tuttle:* "I wouldn't say the rat data says it is not reasonable at all (that) there is a question...but I leave it there…It doesn't drive me much further."
- *Dr. Parola:* "Liraglutide is unique in causing C-cell tumors in both rats and mice at clinically relevant exposures."

THE NOVO NORDISK PERSPECTIVE OF VICTOZA (liraglutide)

Dr. John Buse, former president of the American Diabetes Association and chief of the Division of Endocrinology at the University of North Carolina School of Medicine, briefly described the rationale for developing new drugs for Type 2

Species Differences in Liraglutide Effects on Plasma Calcitonin

Measurement	Rats	Mice	Humans
Liraglutide	No durable effects on plasma calcitonin	Calcitonin increased with liraglutide dose and treatment duration	Liraglutide dose-dependently increased calcitonin
Calcitonin	Not a biomarker for liraglutide-induced focal C-cell hyperplasia/tumors	Is a biomarker for liraglutide-induced focal C-cell hyperplasia/tumors	Calcitonin being used as a biomarker for C-cell hyperplasia
Timecourse of liraglutide-induced C-cell proliferative lesions	<8 months insensitive to liraglutide effects on C-cells; increased C-cell adenomas at 30 weeks and focal CCH at 43 weeks	Focal CCH developed within 4-9 weeks with high dose; focal CCH precedes adenomas	---

diabetes. He pointed out that the lifetime risk of Type 2 diabetes is ~1 in 3, and 7.5% of the U.S. population – 23 million people – have Type 2 diabetes, with 1.5 million new cases per year.

Current treatment guidelines specify a GLP-1 agonist be added as a second tier treatment option in combination with metformin. Why? He said it is because of the limitation of current therapies – GI intolerance, hypoglycemia, weight gain, bone fracture, fluid retention – and because GLP-1 agonists have the potential to improve glycemic efficacy and have extraglycemic benefits, including weight loss, blood pressure lowering, improved insulin sensitivity, and improved beta-cell function.

Dr. Alan Moses, global chief medical office for Novo Nordisk, reviewed GLP-1 pharmacology in general and liraglutide specifically. Dr. Milan Zdravkovic, corporate vice president for GLP-1 development at Novo Nordisk, reviewed the efficacy and safety profile of liraglutide. He noted that in the clinical trials liraglutide met the primary endpoint of glycemic control as monotherapy, in combination with sulfonylurea (SU), and in combination metformin (MET).

Thyroid safety

Dr. Zdravkovic reviewed the company's preclinical carcinogenicity studies of liraglutide. His conclusion: C-cell findings are a rodent phenomenon. Among the points he made in arriving at this conclusion were:

- Lifetime bioassays in mice and rats showed no general increase in tumor incidence.
- Mice with dorsal subcutaneous sarcomas had predisposing factors present – repeated subcutaneous injections and microchip identification implants. He emphasized that this was a single species and single sex finding, with an increased incidence only at the highest doses of liraglutide, and that it was not considered of clinical relevance.
- Liraglutide is not genotoxic *in vitro* or *in vivo*.
- In contrast to the FDA suggestion, Novo Nordisk does ***not*** hypothesize that calcitonin is the cause of C-cell proliferation. "Rather, we find that calcitonin is a biomarker of C-cell activation." Calcitonin is a biomarker in rats and mice. Early calcitonin release occurred in both rats and mice, which preceded C-cell proliferation. Calcitonin response was most pronounced in mice.
- In non-human primates, there was no calcitonin release and no C-cell proliferation in a 52-week primate study or an 87-week study. Short-term exposure with calcium and vitamin D can induce C-cell proliferation in non-human primates. Long-term exposure with liraglutide did not induce C-cell proliferation in non-human primates.
- Rodent C-cell findings are GLP-1 receptor mediated. Calcitonin is a sensitive marker for C-cell GLP-1 receptor activation.
- No C-cell related findings have been found in non-human primates – no calcitonin release and no C-cell proliferation.
- A calcium stimulation test in humans failed to show any increase over time nor any apparent dose-response relationship. There also was no pattern of individual patient shifts in calcitonin values.

Dr. Gilbert Daniels, co-director of the Thyroid Clinic at Massachusetts General Hospital, reviewed the clinical perspectives on thyroid and calcitonin.

- C-cell hyperplasia occurs in up to 33% of unselected thyroids.
- In the absence of hereditary medullary thyroid carcinomas (MTC), there is no evidence that C-cell hyperplasia is a precursor of MTC.
- GLP-1 agonists do not activate C-cell in humans as evidenced by a lack of stimulation of calcitonin secretion.

Liraglutide Trial Efficacy

Measurement	Liraglutide plus				
	Monotherapy n=745	MET n=1,087	SU n=1,040	MET + TZD n=530	MET + SU n=576
Baseline demographics					
Age	5.0	56.7	56.1	55.1	57.6
Duration of diabetes	5.4 years	7.4 years	7.9 years	9.0 years	9.4 years
Efficacy					
HbA1c change from baseline	-0.8% at 1.2 mg -1.1% at 1.8 mg	-1.0% at both 1.2 mg and 1.8 mg	-1.1% at both doses	-1.5% at both doses	-1.3% at 1.8 mg
Patients with HbA1c <7%	42.8% at 1.2 mg 50.9% at 1.8 mg	35.3% at 1.2 mg 42.4% at 1.8 mg	34.5% at 1.2 mg 41.6% at 1.8 mg	57.6% at 1.2 mg 53.7% at 1.8 mg	53.1% at 1.8 mg
Minor hypoglycemic episodes per patient-year vs. comparator	0.3% vs. 2.0%	0.1% vs. 1.2%	0.5% vs. 0.1%	0.6%	1.2% vs. 1.3%
Weight change from baseline	-2.1 kg at 1.2 mg -2.5 kg at 1.8 mg	-2.6 kg at 1.2 mg -2.8 kg at 1.8 mg	+0.3 kg at 1.2 mg -0.2 kg at 1.8 mg	-1.0 kg at 1.2 mg -2.0 kg at 1.8 mg	-1.8 kg at 1.8 mg
Patients with ≥5% weight loss	22.0% at 1.2 mg 26.7% at 1.8 mg	22.5% at 1.2 mg 35.2% at 1.8 mg	4.5% at 1.2 mg 10.8% at 1.8 mg	19.3% at 1.2 mg 24.2% at 1.8 mg	23.4% at 1.8 mg

- There is no benefit in finding C-cell hyperplasia in the general population. The American Thyroid Association does not recommend routine calcitonin screening – even in patients with thyroid nodules. Only substantial calcitonin levels are an accurate predictor of clinically significant C-cell disease. There is no merit in a calcitonin screening program.
- GLP-1 agonists stimulate rodent C-cells but do not stimulate C-cells in non-human primates (NOTE: Dr. Daniels was defending all GLP-1s, not just liraglutide).
- Thyroid follicular cells are distinct from C-cell in origin, abundance, and function. They give rise to goiters, nodules, and most thyroid cancers. There is no evidence for disorders of follicular cells with liraglutide in any animal model, including humans.

The FDA has raised the question of whether liraglutide causes papillary thyroid microcarcinomas. Dr. Daniels insisted liraglutide does ***not***, "It was the screening program that lead to the diagnosis. There is no evidence that liraglutide caused these small papillary carcinomas. I believe there is no relevance of rodent C-cell findings for humans…Screening for thyroid follicular and C-cell disease is not warranted nor recommended."

Cardiovascular safety

Dr. Zdravkovic then reviewed the company's MACE analysis of liraglutide, saying that the development program "gives an extensive randomized exposure experience." He concluded that the MACE analyses were consistent across a number of different populations and outcome definitions, with all point estimates <1.0 and all upper 95% CIs <1.8.

Dr. Alan Moses summed up the company's view of the efficacy and safety of liraglutide:

- **Efficacy** – effective glycemic control, lower non-glycemic events, low risk of hypoglycemia, and ease of use (once-daily dosing unrelated to meals).

Liraglutide CV Safety

MACE analysis	Population A		Population B	
	Liraglutide	Control	Liraglutide	Control
Number of subjects experiencing a MACE event				
Custom total	13	13	21	17
Custom serious	11	12	17	15
Narrow total	22	17	35	24
Broad total	51	35	69	45
Broad serious	16	16	25	19
MACE incidence rates				
SMQ MACE broad – all	2.71	3.35	2.39	3.03
SMQ MACE broad – serious	0.85	1.53	0.87	1.28
SMQ MACE narrow – all	1.17	1.63	1.21	1.62
SMQ MACE narrow – serious	0.80	1.53	0.83	1.28
Custom MACE – all	0.69	1.24	0.73	1.14
Custom MACE – serious	0.59	1.15	0.59	1.01

- **C-cell findings** are limited to rats and mice, with no abnormalities in non-human primates and no evidence of drug-induced C-cell activation in >5,000 patients.
- **Papillary carcinoma** of the thyroid is an incidental finding based on a calcitonin screening program.
- **Pancreatitis** occurred in a small number of cases consistent with the incidence rate in a diabetes population.
- **CV safety** – no QT prolongation, no adverse effects on traditional biomarkers of CV risk, and the MACE analyses met the FDA safety criteria.

The company has an extensive Phase IIIb program underway with 1,800 additional subjects exposed or being exposed to liraglutide vs. additional diabetes comparator agents:

- Liraglutide vs. Byetta – completed.
- Liraglutide vs. Januvia – fully enrolled.
- Liraglutide + basal insulin detemir – enrolling.
- PK study in adolescents (ages 10-17).
- Safety and efficacy in pediatric population (ages 10-17).

Novo Nordisk pledged a comprehensive postmarketing program that would include:

- Labeling.
- Postmarketing pharmacovigilance.
- Postmarketing study commitments.
- Review of FDA's AERS database to assess spontaneous reports of adverse events.
- Large proactive claims safety surveillance database study: looking for rare or infrequent events, focusing on thyroid and C-cell neoplasms, CV events, and pancreatitis with reports to the FDA and European regulators for 3-5 years.
- A prospective post-approval CV outcomes study that is randomized, controlled, and international. It is a two-arm, parallel-design vs. placebo on top of standard therapy in ≥9,000 patients followed for a minimum of 3.5 years, and using a CV endpoint adjudication committee and independent data safety monitoring board. The primary endpoint would be designed to yield sufficient MACE events to exclude excess relative risk of CV death, non-fatal MI, or non-fatal stroke.

PANEL CONSIDERATION OF FDA QUESTIONS ON VICTOZA (liraglutide)

QUESTION #1. Has the applicant provided appropriate evidence of CV safety to conclude that liraglutide rules out unacceptable excess CV risk relative to comparators, including evidence that the upper bound of the two-sided 95% confidence interval for the risk ratios/odds ratios is less than 1.8?

VOTE: 8 YES, 5 NO

The NO votes were: Dr. Henderson (consumer rep), Dr. Proschan (statistician), Dr. Wyne (diabetes researcher), and both cardiologists on the panel – Dr. Konstam and Dr. Teerlink.

The panel chair summarized the sense of the NO votes: "The NOs were concerned about the low event rate, lack of adjudication, and the lack of higher-risk populations as well as a concern about the statistical analysis, especially in the placebo group."

Asked how the FDA interprets this vote, the FDA's Dr. Parks said, "The majority voted that it met the cutpoint, that it met the spirit of the guidance."

Panel comments after the vote included:

- YES – *Dr. Flegal, a CDC statistician:* "The events are small…I can't truly rule out an excess risk."
- YES - *Panel chair, Dr. Burman, an endocrinologist/ thyroid specialist:* "I think the same guidelines have to be applied to different drugs and medication, and I think the results were between 1.3 and 1.8 for the upper limit…but I think postmarketing studies need to be performed."
- YES – *Dr. Felner, a pediatric endocrinologist:* "I think (the sponsor) did everything they were supposed to do...I think this drug has great potential…I would love to treat kids early with it."
- YES – *Dr. Tuttle, endocrinologist:* "You can't change the rules in the middle of the game…It does rule out the excess CV risk in the patient population studied…I think the risk is acceptable with the understanding of additional follow-up evaluations."
- YES – *Dr. Levitsky, a pediatric endocrinologist:* "I think …it will need follow-up (studies), but the company did a great job of dealing with a retrospective look-see of their data."
- YES – *Patient representative:* "I think this particular drug was caught in the crosshairs of the gap period…Given that, the FDA and the sponsor have done a great job trying to shake the most important data out…I am excited about this class. I am concerned about the CV risk, but that is not the primary concern for a large segment of the diabetes population…and the promise of this for younger diabetics is very encouraging."
- YES – *Dr. Savage, an NIH diabetes expert:* "Yes, but with considerable reservation. More so than (with saxagliptin)…I think the design of these studies…which was no fault of the sponsor because they were playing by the old rules…was weaker than it should have been. Excluding people with CV disease for a diabetes drug is not something we should accept in the future…I think there should be some restrictions on the use of these drugs until there is more certainty of safety in high-risk CV patients…I was 1.45 if 1.5 is a NO…There is a group of relatively low-risk diabetes patients who could potentially benefit from this drug without any undue CV risk."
- YES – *Dr. Lesar, a pharmacologist:* "A troubled YES. I'm troubled by the low number of incidents, the population studied, the placebo comparator. I'm comforted somewhat by the total comparators statistics."
- NO – *Dr. Wyne, a diabetes researcher:* "I really again complement the sponsor for work they did to pull out meaningful data…Unfortunately, they just don't have the data…My vote doesn't preclude the drug from being approved…I do feel strongly it is important to do the postmarketing trial which would then answer the question of CV safety."
- NO – *Dr. Konstam, cardiologist:* "I really don't think it meets the (goals of the) guidance document...Even though I voted no, I would accept this degree of evidence if I am very convinced this represents a clinical advantage. I heard from my diabetology colleagues and (the patient representative) that it might be…I heard from the Agency some uncertainty about that…so I don't know how to come down on that…To the extent this is a major step for diabetes care, I would accept this level of risk for approvability. Going forward, ***obviously it needs another trial to assess the risk***."
- NO – *Dr. Proschan, statistician:* "I'm troubled that the relative risk vs. placebo is worse than the relative risk vs. the comparators."
- NO – *Dr. Teerlink, a cardiologist/heart failure specialist:* "This isn't fair, but…we need to be able to protect the public health, and I don't think we have the data here to protect the public adequately."

QUESTION #2a. Has the applicant provided adequate data on the animal thyroid C-cell tumor findings to demonstrate that these (medullary thyroid cancer) findings are *not* relevant to humans? If no, why not?

VOTE: 12 NO, 1 YES

The YES vote was: Dr. Flegal (the CDC statistician).

The panel chair summarized the sense of the NO votes: "The NOs were concerned about the low event rate, lack of adjudication, and the lack of higher-risk populations as well as a concern about the statistical analysis, especially in the

placebo group…The issue revolves around how applicable the rodent data are to humans, and obviously the panel was worried that the findings of carcinogenicity and neogenicity in several species is a concern…There were lower events in humans, but the question here was the possible applicability to humans."

The FDA's Dr. Parks said this vote "speaks for itself."

Panel comments after the vote included:

- *Dr. Flegal, a CDC statistician:* "The events are small…I can't truly rule out an excess risk…And there is also the increased risk of unnecessary screening."
- *Pharmacologist:* "I was not convinced of the mechanistic explanation."
- *Dr. Savage:* "I felt the animal data were worrisome, and I didn't see sufficient human data to be reassured. I also am not convinced the benefits of this – with the unknown risk – outweigh the tradeoffs."
- *Patient rep:* "We just don't know...but I have hope."
- *Dr. Levitsky:* "There is enough concern about the rodent data…though the data in humans so far doesn't support (a problem)...but that…will require some monitoring."
- *Dr. Tuttle, a thyroid expert:* "We can't rule out an effect in humans, and that is probably the bar we should set with this level of preclinical data. I wouldn't be surprised if people develop a little C-cell hyperplasia or a little MTC down the road…When you look at the risk:benefit of this drug, it is not just the risk of C-cell hyperplasia, but the risk of getting the drug, getting the screening, and the risk of the surgery. The risk of unnecessary surgery and screening has to go into this as well…That doesn't mean that for the individual patient they should not have the option for monitoring…If I were going to use (liraglutide), I would do screening CT and ultrasound and follow that yearly for a bit."
- *Dr. Felner, a pediatric endocrinologist:* "It is unanswerable…To answer the question as written, would be a NO…I don't know if looking at trends in calcitonin, then looking at the RET gene…would be another tool…since that (RET) seems to be the big player here in patients who develop MTC."
- *Panel chair Dr. Burman, a thyroid expert and President of the American Thyroid Association:* "Are calcitonin levels a harbinger for C-cell hyperplasia and ultimately MTC in RET-negative individuals? This is impossible to know at present. The progression from hyperplasia to cancer does occur in RET-positive patients, and it is (unknown) if that occurs in RET-negative individuals…It is unlikely that mild calcitonin increases are a harbinger, without more (information, we don't know)…It is important to err on the side of caution, even if the drug may be efficacious."
- *Dr. Proschan, statistician:* "I just don't know how you can be comfortable in knowing it is not relevant to humans."
- *Consumer rep Dr. Henderson:* "You can't dismiss the data from the rodents."
- *Dr. Konstam, a cardiologist:* "We are in uncharted territory on a preclinical signal without any associated clinical evidence…Even if the sponsors and the FDA agreed on the mechanism of action, it would not have reassured me this is not clinically relevant."
- *The FDA's Dr. Joffee:* "Some investigational GLP-1s have also seen similar non-clinical findings, and we are in a quandary how best to monitor for those in clinical trials."

QUESTION #2b. Assuming the remainder of the risk:benefit data are acceptable, do the available data on medullary thyroid C-cell tumors permit marketing of liraglutide?

a. If yes, why? Please comment on the need for and approach to post-approval risk management (e.g., whether baseline assessment and/or ongoing monitoring for medullary thyroid cancer is needed for liraglutide-treated patients. If so, what types of assessments should be done?

b. If no, why not? What additional data related to medullary thyroid cancer are needed to support approvability?

VOTE: 6 YES, 6 NO, 1 Abstain

The NO votes were panel chair Dr. Burman, statisticians Dr. Proschan and Dr. Flegal, cardiologist Dr. Teerlink, the NIH diabetologist Dr. Savage, and pharmacologist Dr. Lesar. The abstention was Dr. Konstam, a cardiologist.

The panel chair summarized the sense of the panel: "The YES votes thought the risk slight of MTC in humans and that it was detectable and manageable, and that this agent has especially unique and effective characteristics in the treatment of diabetes. The NO votes were concerned about the unknown effects of the agent on C-cells over a longer period of time, given the small number of patients…and they were worried about collateral effects of increased costs to the healthcare system and to patients…The NOs didn't want to exposure the entire population to the possibility of an undefined and indefinable risk…and there is the question of the effect on other tumors…It seems that even the NOs were close to the margin of voting YES and that further…premarket or post-market studies might help abrogate our worry."

The FDA's Dr. Parks said this vote "speaks to the complexity of the issue…It shows a panel of experts who vigorously debated this issue found that it was difficult to interpret but also how to convey to the Agency their best path forward… There were a lot of reservations…They said no with some

optimism that the hurdle may not be too great…but they didn't know what to require from the company that could excuse the risk entirely premarketing."

Panel comments after the vote included:

- YES – *Dr. Henderson, the consumer rep:* "Yes, because I think it is a manageable risk."
- NO – *Dr. Proschan, a biostatistician:* "No, but I'm not sure."
- YES – *Dr. Felner, a pediatric endocrinologist:* "I'd hate to miss out on getting this medication."
- YES – *Dr. Tuttle, a thyroid expert:* "I can't think of two years more data the sponsor can do to make me comfortable…I just don't see with a new class how doing more and more research studies will get me (what) I need to know...Unfortunately, the only way we are going to know the answer is to expose a large percentage of the population to this drug long term…I am reassured that it isn't causing problems early on (1-2 years)…Many patients would consider the benefits outweigh the risks…I am not a big fan of calcium stimulation testing…Its sensitivity is not good…I would do that in a subset (of patients in the postmarketing trial) – either random or a high-risk subset – but not everyone."
- YES – *Dr. Levitsky, a pediatric endocrinologist:* "I would probably want to do a CT scan and some of the other tests (the panel chair) suggested…The only way to see this through is to power a large population to make sure this really is not going to be an important event...If it doubles or triples the incidence of MTC, one won't find it out except by large scale surveillance…I am not worried about something in 6-12 months but long-term use that may pop up concerns…I'm not sure we can be sure of that with any of the agents in this class, and that troubles me." The panel chair added, "That troubles a lot of us."
- YES – *Dr. Wyne, a diabetes researcher:* "I think it is important not to prevent patients who might be more compliant (from having access)."
- NO – *Dr. Teerlink, a cardiologist:* "I was tempted to abstain…If this had only been about the natural history of thyroid cancer, I might have done that…But it is impossible to separate the process by which these patients will be screened and the potential collateral damage from the related surgeries, etc., the issue of the actual thyroid cancer…The combination of those things made me more uncomfortable. This is an opportunity for the sponsor to get your chance to say we can get a good definition of the benefit:risk (with another trial) and…we may, hopefully, not discover thyroid cancer, and we didn't cause a risk with the screening process…To my colleagues: Please take a look at the total risk:benefit. When you add that up, control of blood glucose may not be balanced by all those other events."
- YES – *Patient rep:* "I feel like my voting is likely to cause me to have whiplash…There are clearly arguments on both sides…My overall sense is the risks are manageable…and the risk management shifts to the patient and the doctor, which is probably where they should be in cases like this anyway…Even though I was a bit conflicted, I am pretty comfortable with my yes vote."
- NO – *Dr. Savage, an NIH diabetologist:* "I just don't think we have enough data to be reasonably confident of the safety in humans for long-term use. It has been mentioned that this class could be particularly useful in young patients, but those are the ones most likely to have a serious consequence if they were on this long term… The greatest risk may be being screened for this sort of thing…and that would be out of our control once it was out on the market…It also should be made clear what is the benefit of this or any other in the class with longer duration over existing drugs on the market. I know it is fewer injections. Are there other benefits? That should be made clear. It sounded like it (the thyroid issue) is a class effect for any of the longer-acting agents. I would urge people to go back and look at any population data you can get on patients taking exenatide (Byetta BID) to see if there is any information – negative information and positive information, both would be useful."
- NO – *Dr. Lesar, a pharmacologist:* "I don't believe that the data support a high risk…It is the unknown part that is a concern. It doesn't take a lot of data to switch me…I'm very concerned about the risks based on the monitoring… I also believe this class, including the short-acting agents, should be evaluated for potential risk or lack thereof…On balance, I believe the risk to patients is greater than the potential benefits."

FDA officials also asked the panel to address what the sponsor could do to monitor for MTC issue in studies.

- *Panel chair:* "My opinion is that we don't need much… Partly, it is an unanswerable question…I would feel assuaged if there were a 6-12 month extension study looking at liraglutide and documenting calcitonin levels to be sure they don't continue to rise…and if many dropped, I would (be happy) about that...You (could do) a CEA (carcinoembryonic antigen) assay and procalcitonin and occasionally a sonogram of the neck to document that this very mild calcitonin elevation is clinically insignificant and not a harbinger of MTC. I realize no short-duration study will answer definitively…All of us who voted NO were very close to saying YES, and it is an optimistic NO. We just need a little longer data, and nothing will answer the question short of many decades. Should we expose the entire population to risks, though low, and to the collateral damage of thyroidectomies and cost if we can get a little extra data on the low risk of elevated calcitonin, especially if that trends back down to normal (over time)."

- *Dr. Flegal:* "I would like to see calcitonin data – and more data, and look at it more closely."
- *Dr. Lesar:* "I agree some earlier short-term trial data would be (useful)…I wasn't far from a YES vote…(I would like to be reassured that) it won't result in an excessive cost in monitoring."
- *Dr. Savage:* "Some data may need to be longer – maybe 2 years – to make sure we are satisfied this won't change in a negative direction. And I also would suggest looking at longer-term follow-up on the drug in use, to make sure there isn't some signal they haven't picked up yet… Maybe there is something else going on we haven't noticed…So, some surveillance of maybe electronic databases from some organizations that have the ability to link together whether a patient has been diagnosed with thyroid carcinoma."
- *Dr. Teerlink:* "Screening…will be a part of this drug, and that has risk:benefits of its own…What are the risk: benefits being added?…You need to see how many drive-by thyroidectomies are being done…This drug will have a label that it might cause thyroid cancer…and I think people in the U.S. will say it is safer to look…Oops, found something there. Okay, let's take out the thyroid… I am concerned how often that might happen…I don't understand the biology of drug-induced MTC."
- *Dr. Proschan:* "These cancers will take many years to develop, and you wouldn't see them in a trial of a few years."
- *Dr. Konstam:* "I would say to the Agency: Really go back and (see if this represents) a substantial improvement in the clinical management of diabetes…I don't think we heard a good analysis on whether the data support that view…If you come away with 'this is a major clinical advance,' then I would go ahead and approve the agent with a black box warning and whatever screening you can get from thyroid experts. If you can't do that… then I would not recommend approving the drug. How would I get there? If it is not a major clinical advance, then you need enough clinical data to indicate you don't have a human problem, or I wouldn't approve it."
- *Dr. Tuttle, a thyroid expert:* "The Institute of Medicine looked at the risk of low-dose radiation in the U.S., where people were exposed to a very, very low dose of radiation and whether screening outweighed the risk of radiation. You can go through their decision analysis and put in the percentages for MTC, etc., and you can statistically get a really good feel for how many would be hurt by that decision…I don't see how if we had another year (of data, it would help)…If it is not changing (the thyroid status) in two years, I can't imagine it will change in 3-4-5 years."

QUESTION #2c. Assuming the remainder of the risk:benefit data are acceptable, do the available data on papillary thyroid C-cell tumors permit marketing of liraglutide?

VOTE: Unanimously YES

THE IMPLICATIONS FOR OTHER GLP-1 AGONISTS

The favorable saxagliptin panel suggests that diabetes drugs already in the pipeline can meet the new FDA guidelines on CV safety, but the thyroid issues raised at the liraglutide panel suggest that not only liraglutide but every other GLP-1 in development may face a delay.

FDA officials repeatedly made references to seeing thyroid issues with other GLP-1s in development. These were some but not all of the comments:

- *Dr. Mahoney:* "A similar signal is being noted in interim carcinogenicity data for some other long-acting (once-a-day and longer) GLP-1 analogues in development."
- *Dr. Joffee:* "No approved drugs are known to cause C-cell tumors in two animal species, but some investigational GLP-1 agonists may."
- Dr. Parola suggested this is likely to be a class effect for long-acting GLP-1 agonists.

The future of Amylin's Byetta LAR (exenatide long-acting, administered once-weekly) may hinge on this panel. The FDA reviewers noted that Byetta (BID, not LAR) doesn't have the same pattern of thyroid carcinogenicity as liraglutide because it is short-acting, which, of course, suggests there could be a problem with LAR if there is one with liraglutide.

AMYLIN/LILLY'S BYETTA (exenatide) – the only FDA-approved GLP-1 agonist

Last year, the FDA asked Amylin for information on all thyroid cancer cases with Byetta. Amylin responded that as of September 30, 2008, there had been no cases of thyroid cancer in clinical trials of Byetta, which included >5,500 patients and >4,600 patient-years of exposure. Calcitonin was not

GLP-1 Agonists in Development

Company	GLP-1	Status
ConjuChem	CJC-1131	Abandoned
Human Genome Sciences/ GlaxoSmithKline	Syncria (albiglutide)	Phase III
Lilly/Amylin/Alkermes	Byetta LAR (exenatide long-acting)	Phase III
Novo Nordisk	Liraglutide	Submitted to FDA
Roche	Taspoglutide	Phase III
Sanofi-Aventis	AVE-0010	Phase III
Takeda	Alogliptin	FDA rejected for insufficient CV safety data

measured in any of the Byetta trials. However, there were nine spontaneous postmarketing reports of thyroid cancer (3 papillary and 6 unspecified type), with ~7 million prescriptions filled for Byetta (an estimated cumulative exposure of 840,000 patient-years).

With respect to exenatide, the FDA liraglutide reviewers noted:

- Exenatide caused C-cell adenomas in female rats but not male rats or mice of either sex.
- Differences in potency to induce C-cell tumors are likely due to PK differences between exenatide and liraglutide.
- Exenatide has a shorter elimination half-life than liraglutide in mice and rats.
- Sustained subcutaneous infusion to pharmacologically-relevant plasma levels of exenatide increased plasma calcitonin and caused focal C-cell hyperplasia in CD-1 mice. Administering 0.25 mg/kg/day exenatide by bolus injection QD resulted in a low incidence of focal C-cell hyperplasia at 12 weeks and none at 16 weeks, but constant infusion caused a higher incidence of hyperplasia after 12 or 16 weeks. Repeat dosing with ≤1 mg/kg exenatide for ≤3 times a day for up to 13 weeks did not cause focal C-cell hyperplasia in CD-1 mice, even though it increased plasma calcitonin and thyroid calcitonin mRNA. PK/PD modeling in mice showed that sustained GLP-1 receptor activation, by daily subcutaneous injection of liraglutide or constant subcutaneous infusion of exenatide, results in persistent calcitonin secretion and focal C-cell hyperplasia. These results indicate persistent GLP-1 receptor activation induces increased plasma calcitonin and caused focal C-cell hyperplasia in mice, but to date, only liraglutide caused C-cell tumors in mice.
- Exenatide has not had any cases of thyroid cancer in clinical trials, although calcitonin measurements (which prompted further evaluation and subsequent detection of 4-5 cases of thyroid cancer in patients treated with liraglutide) were not routinely performed in the exenatide clinical trials. There have been 9 spontaneous post-marketing reports of thyroid cancer (3 papillary and 6 unspecified type) with exenatide, and there were two reported cases of thyroid serious adverse events with Byetta (BID, not LAR) in an ongoing trial.

Does the FDA plan to bring Byetta before a panel or ask Amylin/Lilly to do some new animal analysis? The FDA's Dr. Parks said, "We did look back at the Byetta clinical trial program and found no thyroid cancer…We also looked at the postmarketing experience…There were a few cases (of thyroid cancer) out of ~2.1 million prescriptions written…Right now, with the data limited, there is not a signal we can take from that."

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