# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**22-341**

# SUMMARY REVIEW

# Summary Basis for Regulatory Action

| | |
|---|---|
| **Date** | January 25, 2010 |
| **From** | Curtis J. Rosebraugh, MD, MPH<br>Director, Office of Drug Evaluation II |
| **Subject** | Summary Review |
| **NDA/BLA #**<br>**Supp #** | NDA 22-341 |
| **Applicant Name** | NOVO Nordisk |
| **Proprietary / Established (USAN) Names** | Victoza<br>Liraglutide (rDNA origin) Injection |
| **Dosage Forms / Strength** | Injectable solution (6mg/mL)<br>0.6 mg, 1.2 mg, and 1.8 mg |
| **Proposed Indication(s)** | Treatment of Type 2 Diabetes Mellitus |
| **Action:** | *Approval* |

**Introduction**

This review will be a brief summary of the basis for the regulatory action regarding liraglutide. Please refer to the reviews in the action package for a more detailed discussion. Liraglutide is a glucagon-like peptide-1 (GLP-1) analogue. GLP-1 is an intestinal peptide released in response to food ingestion that has an enhancing effect on insulin secretion when serum glucose is elevated and also has an inhibitory effect on glucagon (thereby inhibiting hepatic glucose synthesis) as well as slowing gastric emptying. GLP-1 has minimal, if any, effect on insulin secretion when glucose is normal or low and therefore GLP-1 analogues, by themselves, have less hypoglycemia as compared to some of the other agents used to treat diabetes. Intrinsic GLP-1 is degraded in minutes by dipeptidyl peptidase IV (DPP-4) which limits its clinical use; however, the analogues have prolonged pharmacokinetic profiles which allow a practical dosing interval.

The Agency has recently approved one other GLP-1 analogue, Byetta (exenatide) which is administered twice-daily as a subcutaneous injection. In addition, several others are in various stages of development.

As an overview, the efficacy of this drug is not in question. However, there are preclinical and clinical safety concerns that have led to differing opinions among the reviewers within the division as to whether liraglutide should be approved for marketing.

Preclinical rodent studies demonstrated C-cell hyperplasia (considered a pre-neoplastic lesion for medullary thyroid cancer in rodents) and C-cell tumor findings in two different rodent species (both sexes) at clinically relevant doses. Deciding on a course of action in regard to this finding is new territory for the agency. As we have yet to encounter this, we have not determined what this finding may mean in regard to human use and the concern is that it may be an indication that use of this drug will place humans at risk for medullary thyroid cancer

(MTC). MTC is a very rare tumor in humans, with about 600 cases a year. Therefore, the question in regard to this preclinical finding, while probably only applying to a very small population, is what is the strength of uncertainty and whether or not the clinical benefit/utility would justify marketing in the face of uncertainty. If we were to allow marketing, this then brings into question what type of monitoring would we consider (if any) for what is a very rare event in humans. It should also be noted that the decision made in this regard does not affect just liraglutide, as Dr. Bruno-Davis has noted that data under review from other GLP-1 receptor agonists with longer half-lives as well as sustained-release formulations of short-acting analogues suggest that they all have this effect in rodents and that it is probably related to persistent receptor activation. It is interesting to note that a sustained-release formulation for exenatide, also seems to exhibit this findings while the immediate-release form did not, although as I will discuss below, the preclinical studies for the immediate-release form did not reflect the frequent dosing interval used in humans.

While the pre-clinical findings are the main concern with this application, there are also cardiovascular and pancreatic clinical issues that need consideration.

Regarding cardiovascular issues, control of hyperglycemia by hypoglycemic drugs has consistently demonstrated benefits in microvascular outcomes (retinopathy, neuropathy, renal function) but not so for macrovascular events (stroke, myocardial infarct). This is not a new finding, as sulfonylurea drugs have carried labeling indicating that they may increase cardiovascular mortality up to 2.5 times that of patients treated with diet alone. However, in the last two to three years, there have been increasing concerns that other anti-diabetic drugs may also increase cardiovascular events. This has led to debate regarding the adequacy of cardiovascular risk assessment during development programs. This is important as cardiovascular disease is very common in the general population and patients with diabetes have an additional 2 to 4 times increase risk compared to matched non-diabetic populations. Therefore, from a population health standpoint, if a drug increases cardiovascular risks it would affect a very large number of patients. These issues were discussed at an Advisory Committee meeting in July of 2008, where the panel recommended that glycemic control agents for type 2 diabetes coming before the agency should at a minimum have some type of screening pre-approval cardiovascular assessment, with further, definitive, post-approval testing. After much internal deliberation and consideration of the recommendations we received from AC panel members, we issued a final guidance that incorporated recommendations from that meeting. This guidance, in accord with the recommendations we received, allows for two 'step-wise' assessments of potential cardiovascular risk during drug development. Step-one occurs during the development program before marketing, and requires making a determination that the investigational agent has an upper bound of a two-sided 95 percent confidence interval for the estimated risk ratio of less than/equal to 1.8 compared to a control group (with a point estimate near unity). This would assure that at a minimum, the drug does not double the risk of cardiovascular disease. Demonstration that less than a 1.8 increase exists allows marketing while a longer and larger outcome study is conducted. The concept is that any further or more definitive pre-approval testing would be too burdensome to drug development, but this level of definition described above would be feasible/practical and would provide some assurances while further testing was underway. Further testing would be accomplished by a larger outcome study that must demonstrate that

the investigational agent has an upper bound of a two-sided 95 percent confidence interval for the estimated risk ratio of less than/equal to 1.3 (rule out a 30% increase, smallest amount of difference felt to be generally practical) compared to a control group in order for continued marketing to occur.

These principles incorporate recommendations from the advisory committee. The details of this approach are outlined in the guidance[1], but of relevance is that at the time of issuance of the guidance, three NDAs were in review. We concluded that recommendations should apply to all ongoing programs including those with applications pending with the agency at the time of guidance issuance. Although not totally in alignment with the guidance, liraglutide as well as saxagliptin seemed to, in spirit, fulfill 'step-one' and both were presented at a subsequent advisory committee meeting for discussion. The majority of the panel at that meeting voted that liraglutide (and saxagliptin) had fulfilled step-one requirements which would allow for marketing while awaiting the results of a definitive study.

Pancreatitis has been identified in post-marketing reporting with the use of incretin-based therapies. We have received reports for both exenatide (Byetta) and sitagliptin (Januvia-a dipeptidyl-peptidase IV inhibitor) and these reports also included cases of hemorrhagic/necrotizing pancreatitis. While the preclinical animal studies and pre-marketing clinical development program for exenatide and sitagliptin did not detect a signal, a recent publication[2] in a transgenic rat model that expresses human islet amyloid polypeptide (IAPP or amylin) did note that rats exposed to sitagliptin increased pancreatic ductal cell turnover, demonstrated metaplasia of these cells and one animal had pancreatitis (hemorrhagic). While further exploration of these findings is necessary, this does provide a possible mechanistic hypothesis for pancreatitis in regard to drugs that exert there effects through the incretin system. The published report referred to above along with the post-market reports gives us great concern and will lead us to have further studies in animal models that are a closer approximation to the disease state of Type 2 diabetes.

The preclinical evaluation for liraglutide did note increased pancreatic organ weight, but treatment-related microscopic pathology, overt pancreatitis or pancreatic cancer was not identified. Other studies conducted in a variety of animal models that give a closer approximation to Type 2 diabetes (insulin deficiency but not resistance as noted in Dr. Parks memo), did not reveal any serious gross pancreatic pathology although none of these models display the complete clinical presentation of diabetes and were not performed as toxicology studies so they did not include careful histopathology evaluations. However, there were several cases of pancreatitis in subjects during the liraglutide clinical development program, with a greater number associated with the use of liraglutide than controls, even after correcting for exposure. This adds to the body of evidence that is accumulating that incretin-based therapies may have some type of detrimental effect in the pancreas.

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[1] Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, December 2008, Clinical/Medical.

[2] Matveyenko AV, Dry S, Cox HI, Beneficial endocrine but adverse exocrine effects of sitagliptin in the human islet amyloid polypeptide transgenic rat model of type 2 diabetes: interactions with metformin. Diabetes. 2009 Jul; 58(7):1604-15

I will discuss these issues as well as provide an overview of the efficacy findings below.

Efficacy

This has been thoroughly discussed in Drs. Derr, Yanoff, Joffe and Parks reviews and I agree with their conclusions. The following table from Dr. Parks review (Page 17), summarizes the important randomized trials.

**Table 7.1 Summary of Pivotal Phase 3 Studies**

| Study # | Treatment Groups | Background Therapy | Mean Baseline HbA1c | Mean Duration of Diabetes (yrs) |
|---|---|---|---|---|
| **Monotherapy** | | | | |
| Study 1573 | Lira 1.2 mg<br>Lira 1.8 mg<br>Glimepiride 8 mg | Diet and exercise | 8.2 | 5.4 |
| **Add-on to Single OAD (Dual Therapy)** | | | | |
| Study 1572 | Lira 0.6 mg + met 2g<br>Lira 1.2 mg + met 2g<br>Lira 1.8 mg + met 2g<br>Metformin 2g<br>Glimepiride 4mg + metformin 2g | Metformin | 8.4 | 7.4 |
| Study 1436 | Lira 0.6 mg + glim 4mg<br>Lira 1.2 mg + glim 4mg<br>Lira 1.8 mg + glim 4mg<br>Glimepiride 4 mg<br>Rosiglitazone 4 mg + glim 4mg | Glimepiride | 8.4 | 7.9 |
| **Add-on to Two OADs (Triple Therapy)** | | | | |
| Study 1574 | Lira 1.2 mg + met 2g + rosi 8 mg<br>Lira 1.8 mg + met 2g + rosi 8 mg<br>Metformin 2g + rosi 8 mg | Metformin + rosiglitazone | 8.5 | 9.0 |
| Study 1697 | Lira 1.8 mg + glim 4 mg + met 2g<br>Glim 4 mg + met 2 g<br>Insulin glargine + glim 4 mg + met 2g | Metformin + glimepiride | 8.3 | 9.4 |

The primary endpoint was change from Baseline of HbA1c either after 52 weeks (Study 1573) or 26 weeks (remaining studies). The review team concluded that the 0.6 mg dose demonstrated minimal efficacy compared to the 1.2 mg and 1.8 mg doses. The following table from Dr. Joffe's review (Page 17) summarizes the findings from these trials.

**Table 3. Change from baseline in HbA1c (%)**
**(intent-to-treat population with last-observation-carried-forward)**

| | N | Baseline±SD | Adjusted mean change±SE | Change with lira relative to change with placebo | | Change with lira relative to change with comparator | |
|---|---|---|---|---|---|---|---|
| | | | | Mean difference (95% CI) | p-value | Mean difference (95% CI) | p-val |
| **Monotherapy (Study 1573) – 52 weeks** | | | | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ra 1.2 mg | 236 | 8.2±1.1 | -0.8±0.1 | | | -0.3 (-0.5, -0.1) | 0.001 |
| a 1.8 mg | 234 | 8.2±1.1 | -1.1±0.1 | N/A | | -0.6 (-0.8, -0.4) | <0.0001 |
| Glimep 8 mg | 241 | 8.2±1.1 | -0.5±0.1 | | | | |
| **Add-on to metformin (Study 1572) – 26 weeks** | | | | | | | |
| Lira 0.6 mg | 239 | 8.4±0.9 | -0.7±0.1 | -0.8 (-1.0, -0.6) | <0.0001 | +0.3 (0.1, 0.5) | <0.001 |
| Lira 1.2 mg | 232 | 8.3±1.0 | -1.0±0.1 | -1.1 (-1.3, -0.9) | <0.0001 | 0.0 (-0.2, 0.2) | 0.88 |
| Lira 1.8 mg | 236 | 8.4±1.0 | -1.0±0.1 | -1.1 (-1.3, -0.9) | <0.0001 | 0.0 (-0.2, 0.2) | 0.86 |
| Placebo | 120 | 8.4±1.1 | 0.1±0.1 | | | | |
| Glimep 4 mg | 234 | 8.4±1.0 | -1.0±0.1 | | | | |
| **Add-on to glimepiride (Study 1436) – 26 weeks** | | | | | | | |
| Lira 0.6 mg | 224 | 8.4±1.0 | -0.6±0.1 | -0.8 (-1.1, -0.6) | <0.0001 | -0.2 (-0.4, 0.0) | 0.09 |
| Lira 1.2 mg | 223 | 8.5±1.1 | -1.1±0.1 | -1.3 (-1.5, -1.1) | <0.0001 | -0.6 (-0.8, -0.5) | <0.0001 |
| Lira 1.8 mg | 226 | 8.5±0.9 | -1.1±0.1 | -1.4 (-1.6, -1.1) | <0.0001 | -0.7 (-0.9, -0.5) | <0.0001 |
| Placebo | 107 | 8.4±1.0 | 0.2±0.1 | | | | |
| Rosi 4 mg | 224 | 8.4±1.0 | -0.4±0.1 | | | | |
| **Add-on to metformin+rosiglitazone (Study 1574) – 26 weeks** | | | | | | | |
| Lira 1.2 mg | 174 | 8.5±1.2 | -1.5±0.1 | -0.9 (-1.1, -0.8) | <0.0001 | | |
| Lira 1.8 mg | 177 | 8.6±1.2 | -1.5±0.1 | -0.9 (-1.1, -0.8) | <0.0001 | N/A | |
| Placebo | 167 | 8.4±1.2 | -0.5±0.1 | | | | |
| **Add-on to metformin+glimepiride (Study 1697) – 26 weeks** | | | | | | | |
| Lira 1.8 mg | 224 | 8.3±0.9 | -1.3±0.1 | -1.1 (-1.3, -0.9) | <0.0001 | -0.2 (-0.4, -0.1) | <0.01 |
| Placebo | 110 | 8.3±0.9 | -0.2±0.1 | | | | |
| rgine | 225 | 8.2±0.9 | -1.1±0.1 | | | | |

I would like to make a few observations regarding these results. Study 1573 was the only monotherapy evaluation of liraglutide. More patients in the glimepiride group (10.1%) withdrew due to reasons of ineffective therapy compared to the liraglutide groups (3.6 and 6%). As noted above, there was a dose-ordered increase in LS Mean Change from Baseline for HbA1c in the liraglutide groups that were substantially greater than the glimepiride 8-mg group. It would appear that liraglutide had greater reductions in HbA1c than the comparator (and less withdrawals due to ineffectiveness) in a 'fair fight' as the maximal labeled dose of glimepiride was used.

Study 1572, which added glimepiride 4-mg and various doses of liraglutide onto metformin therapy demonstrated that comparisons between the glimepiride vs. liraglutide had non-inferiority (as opposed to superiority). This would indicate that over a 26 week period, liraglutide would not offer any difference in HbA1c reduction over glimepiride as add-on therapy to metformin. This should be viewed with some caution, as this study did not include glimepiride using an 8-mg dose. So it is unknown if glimepiride may have actually had superior results. The results of this study seem to somewhat contradict those of Study 1573, or at least demonstrate that there may be a difference in efficacy between these two drugs dependant upon whether they are used as monotherapy or are added on to another therapy.

Study 1436 demonstrated that liraglutide added on to glimepiride had additional benefits compared to add-on rosiglitazone therapy. However, rosiglitazone was given at only half the

maximal approved dose, so these results may be somewhat misleading and would need to be supported by trials in which rosiglitazone is given at its maximal dose.

Study 1697 offered an interesting insight into what may happen if patients were begun on insulin therapy instead of a GLP-1 inhibitor. While it must be viewed with caution as the insulin titration may not have been as aggressive as what may occur in practice, it did appear that liraglutide at least held its own with an additional benefit of weight loss (-1.81 kg) compared to weight gain (+1.62) as noted in the insulin group. I would also point out that aggressive insulin titration may result in more hypoglycemia, which may be somewhat less of a concern with liraglutide therapy (although hypoglycemia is still a concern when incretin therapy is used in conjunction with insulin secretagogues).

Dr. Parks has observed how the results noted above compare to other placebo-subtracted HbA1c changes seen with recent approvals in other trials. These are not head-to-head comparisons, but does give a sense of how liraglutide might 'stack-up' with other treatments and are summarized in the table below.

| Drug group | Placebo Subtracted HbA1c change |
|---|---|
| sitagliptin and saxagliptin | 0.5-0.8% |
| colesevelam and bromocriptine | 0.4-0.6% |
| Exenatide | 0.5-0.7% |
| Liraglutide | 0.94-1.36% |

The clinical trials demonstrate that liraglutide use provides an important reduction in HbA1c, and for the most part, when added to already established therapy (usually metformin), has effects that are either the same (or better?) than other diabetic agents (at least the ones tested above). The weight loss associated with use and less profound effects on hypoglycemia (probable) are important considerations in therapy. This of course would need to be weighed against the inconvenience of the drug only being available as an injectable and the safety considerations discussed below.

Safety

Drs. Parola and Davis-Bruno have recommended not approving liraglutide because of the findings of thyroid C-cell hyperplasia, adenoma and carcinoma in rats and mice. These findings seem to be occurring through a non-genotoxic mechanism. Their evaluation concluded that the human relevance of these tumors is unknown, but that there is not a mechanistic explanation of this phenomenon that would preclude its importance to humans. Dr. Paul Brown agrees with the evaluation of findings from Drs. Parola and Davis-Bruno, but gives options for possible actions including not approving until further pre-clinical study has occurred, or, if clinical benefit is considered great enough, to allow marketing with postmarketing requirements for further animal testing to try to better define a mechanism.

While liraglutide has been negative in a series of genetic toxicity studies, it has demonstrated dose-related carcinogenic potential in both genders of rats and mice in life-time treatment carcinogenic studies occurring at clinically relevant exposures. Drs. Parola and Davis-Bruno

are also concerned because in shorter duration studies, rodents have demonstrated thyroid C-cell focal hyperplasia which is felt to be a marker for possible evolution into C-cell carcinoma in rodents. The ultimate concern is that these findings in rodent may be a marker for risk in humans for the formation of MTC. Noted during the life-time study was C-cell adenomas (non-malignant) in mice and rats at 10x exposures (both genders) and 0.5-2x exposures (depending on gender), respectively. Also, excess carcinomas were noted in female mice (but not male) and male rats (but not female) at 8x and 45x exposures, respectively. The carcinomas were noted after 60-70% life exposure, depending on species, although the malignancies were not a cause of death. The two tables below from Dr. Parks review (pages 9, 11) summarize the carcinogenicity studies.

**Table 4.3. Thyroid Histopathology Results in Rat Carcinogenicity Study**

| Thyroid Gland Findings | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| | Control N=50 | LD N=49* | ID N=50 | HD N=50 | Control N=50 | LD N=49* | ID N=49* | HD N=50 |
| Follicular Cell Adenoma (benign) | 0 | 2 | 1 | 2 | 1 | 0 | 2 | 0 |
| Follicular Cell Carcinoma (malignant) | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| Focal C-cell hyperplasia | | | | | | | | |
| Minimal | 3 | 0 | 2 | 3 | 6 | 1 | 2 | 4 |
| Mild | 6 | 7 | 8 | 9 | 7 | 7 | 14 | 11 |
| Moderate | 2 | 3 | 6 | 4 | 1 | 5 | 6 | 4 |
| Marked | 0 | 4 | 4 | 8 | 0 | 1 | 5 | 5 |
| Ttl incidence | 11 (22%) | 14 (29%) | 20 (40%) | 24 (48%) | 14 (28%) | 14 (29%) | 27 (55%) | 24 (48%) |
| Diffuse C-cell hyperplasia | | | | | | | | |
| Minimal | 1 | 1 | 0 | 0 | 2 | 0 | 0 | 0 |
| Mild | 2 | 2 | 1 | 3 | 3 | 2 | 2 | 2 |
| Moderate | 0 | 2 | 1 | 2 | 0 | 4 | 1 | 0 |
| Marked | 0 | 1 | 1 | 2 | 1 | 2 | 0 | 1 |
| Ttl incidence | 3 (6%) | 6 (12%) | 3 (6%) | 7 (14%) | 6 (12%) | 8 (16%) | 3 (6%) | 3 (6%) |
| C-cell adenoma (benign) | 6 | 8 | 21 (42%) | 23 (46%) | 5 | 13 (27%) | 16 (33%) | 28 (56%) |
| C-cell carcinoma (malignant) | 1 | 4 | 3 | 7 (14%) | 0 | 0 | 2 | 3 |

LD = low dose (0.075 mg/kg/d); ID = intermediate dose (0.25 mg/kg/d); HD = high dose (0.75 mg/kg/d)
*Note that some thyroid glands were autolysed in animals found dead and no histopath could be performed. No abnormal gross pathology were listed for these animals.

**Table 4.6 Thyroid Histopathology Results in Mouse Carcinogenicity Study**

| | Males | | | | | Females | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Dose (mg/kg/day)** | **0** | **0.03** | **0.2** | **1** | **3** | **0** | **0.03** | **0.2** | **1** | **3** |
| **Human exposure multiple[a]** | **-** | **0.2** | **1.8** | **10.0** | **45.0** | **-** | **0.2** | **1.8** | **10.0** | **45.0** |
| **N** | 79 | 66 | 65 | 67 | 79 | 75 | 66 | 67 | 66 | 76 |
| Focal hyperplasia (rare)[b] | 0 | 0 | 1 (2%) | 11 (16%) | 30 (38%) | 0 | 0 | 7 (10%) | 10 (15%) | 22 (29%) |
| C-cell adenoma (rare)[c] | 0 | 0 | 0 | 9 (13%) | 15 (19%) | 0 | 0 | 0 | 4 (6%) | 15 (20%) |
| C-cell carcinoma (rare)[c] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (3%) |
| C-cell adenoma or carcinoma (rare)[c] | 0 | 0 | 0 | 9 (13%) | 15 (19%) | 0 | 0 | 0 | 4 (6%) | 17 (22%) |

a=based on area under the time-concentration curve relative to the 1.8 mg dose
b=Diffuse C-cell hyperplasia cannot be adequately assessed without specialized staining
c=tumor considered common or rare based on incidence in historical control groups of >1% or <1%, respectively
statistically significant differences from control identified in bold/red font

Mechanistic studies to date have not been able to determine that this finding is limited to rodents only. Diffuse and focal hyperplasia and adenomas are common findings in aging rats (but not mice), however carcinoma is a rare finding (<1%). As stated above, the carcinomas were not discovered until after 60-70% of the rodent life-span (depending on species) but C-cell hyperplasia was noted in mice exposed to 88x exposure compared to humans within 4 weeks, which would correspond to 3-4% of their lifespan. However, data also indicates that the hyperplasia mostly reverses after a 15 week recover period (one animal had not reversed yet) as is demonstrated in the table below.

**Table 2** **NN204338. Incidence focal C-cell hyperplasia in mice dosed with liraglutide for 9 weeks followed by a 6 week (9+6wk) or 15 week (9+15wk) recovery period (30-34/group/time, sexes combined).**

| Time point | No. of animals with focal C-cell hyperplasia / total number in group | | |
|---|---|---|---|
| Dose mg/kg/day | 0 | 0.2 | 5 |
| 9 weeks dosing | 0 / 32 | 2 / 32 | 7 / 32 |
| 9 + 6 week recovery | 0 / 34 | 0 / 32 | 5 / 33 |
| 9 + 15 week recovery | 0 / 32 | 0 / 34 | 1 / 30 |

The treatment-related increase is seen in focal C-cell hyperplasia after 9 weeks of dosing, shows reversibility after 6 and 15 weeks of recovery.

Monkey studies have not shown proliferative thyroid C-cell lesions following liraglutide treatment up to 20 months (5% of their lifespan) at > 60x human exposure. This must be viewed with some caution as GLP-1 receptors have also not been demonstrated in monkey thyroid tissue and as Dr. Davis-Bruno observes, there were a limited number of animals (n=40), limited life-time exposure and immunogenic response in monkeys that may have neutralized the effects in monkeys. Dr. Parks notes that the immunogenic response was only noted in 3 animals receiving the highest dose and was expressed only after 52 weeks of exposure. To complete the picture of GLP-1 receptors in thyroid tissue, Dr. Parola has done an extensive search and has located only one paper[3] where autoradiography detected GLP-1 binding in 12/12 normal thyroid samples from rats, 3/5 normal thyroid samples from mice, and

[3] Korner M, et al. GLP-1 receptor expression in human tumors and human normal tissues: potential for in vivo targeting. Jn Nucl Med. 2007; 48:736-43.

1/18 normal human thyroid samples from surgical resection, with 5/18 surgical resection samples from subjects with MTC demonstrating binding. The sponsor submitted a summary of an autoradiographic ligand binding study during the review cycle where they were unable to duplicate the above results in humans (while they could in rats) but has not submitted the study for review. I think it is hard to draw final conclusions on what the true binding in normal human thyroid tissue may be without further study, but this may be an indication that there are GLP-1 receptors in the thyroid of humans, although it does not locate whether the binding occurs in follicular cells or C-cells.

For clinical considerations, calcitonin is synthesized and secreted from C-cells and is used clinically as a screening tool and prognostic biomarker for MTC. Therefore, a great deal of the clinical safety analysis for this application is focused on measuring calcitonin and what trends the levels may have exhibited during the clinical trials. Normal levels for females and males are 5.0 ng/L and 8.4 mg/L respectively and levels of 50 ng/L or greater are considered clinically important warranting further evaluation. The sponsor has provided data with up to 600 liraglutide-treated subjects after 2 years of treatment. Dr. Joffe has a very thorough and complete outline regarding the limitations of the data, including limitations on blinding for extension data beyond six months and such, but I would agree with him that calcitonin is an objective measure and does provide insight into serum calcitonin trends during treatment. I would note that the safety reviews of Drs. Mahoney, Joffe and Parks have very thorough analyses and discussion that go into great detail regarding whether or not there are trends that may indicate dose-related shifts of calcitonin levels, whether there are imbalances of the percentage of liraglutide exposed subjects with any upward shifts compared to the overall population, and other forms of exploratory analyses along with their interpretations of what the results demonstrated. However, to put this in a broader context, all these analysis involve very small changes in serum calcitonin, from below the level of quantification (LOQ), which is 0.7 ng/L, to around 1 ng/L. I think, considering that levels of 50 ng/L are considered the point at which it is important to consider cancer, and that there is usually a lot of variability involved in measurements that are around the LOQ, trying to draw conclusion regarding trends of values that are less than one is giving more credibility to an imprecise measure than is warranted. Dr. Joffe has the table below that gives a summary of the six month controlled data (page 38).

**Table 14. Repeated measures analysis for calcitonin for the five major phase 3 trials**

| | **Week 12 calcitonin (ng/L) LS mean (95% CI)** | **Week 26/28 (ng/L) LS mean (95% CI)** |
|---|---|---|
| Liraglutide 0.6 mg | 0.78 (0.72, 0.84) | 0.96 (0.90, 1.04) |
| Liraglutide 1.2 mg | 0.78 (0.73, 0.83) | 0.99 (0.94, 1.05) |
| Liraglutide 1.8 mg | 0.76 (0.72, 0.81) | 1.01 (0.95, 1.06) |
| Active comparator | 0.70 (0.66, 0.74) | 0.97 (0.91, 1.02) |
| Placebo | 0.67 (0.63, 0.73) | 0.89 (0.83, 0.95) |

Considering that the LOQ is 0.7 ng/L, and that the upper level of normal is 5 for females and 8.4 for males, this table indicates to me that there is not an important effect of liraglutide on serum calcitonin. Below are several other figures from Dr. Joffe's review that demonstrate data from longer periods of evaluation during open-label extension phases of the clinical trials.

**Figure 2. Geometric mean calcitonin values over 2 years in the monotherapy trial (Week 0-52 is blinded; Week 52-104 is the open-label, voluntary extension)**

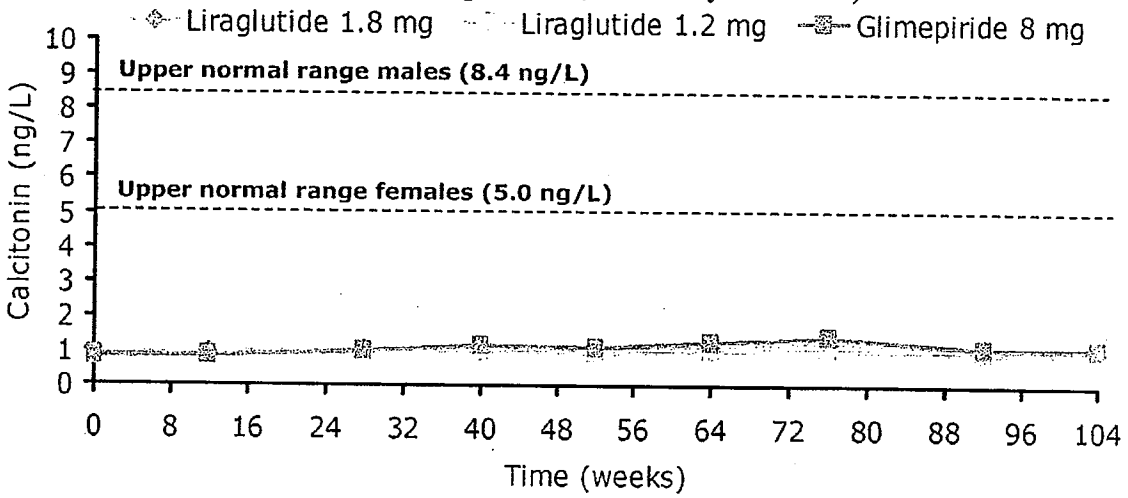



**Figure 3. Geometric mean calcitonin values over 2 years in the add-on to metformin trial (Week 0-26 is blinded; Week 26-104 is the open-label, voluntary extension)**

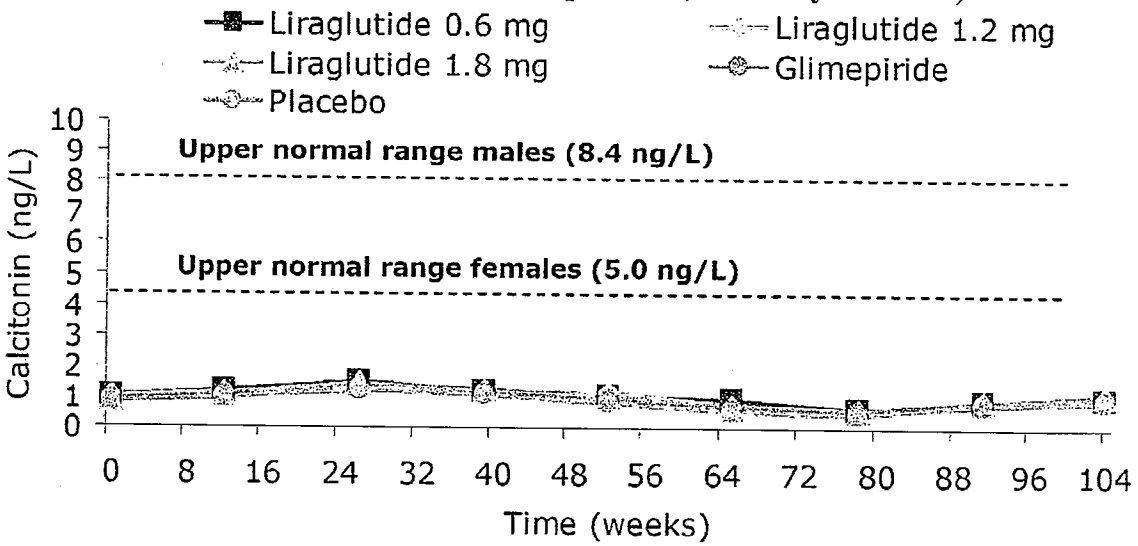
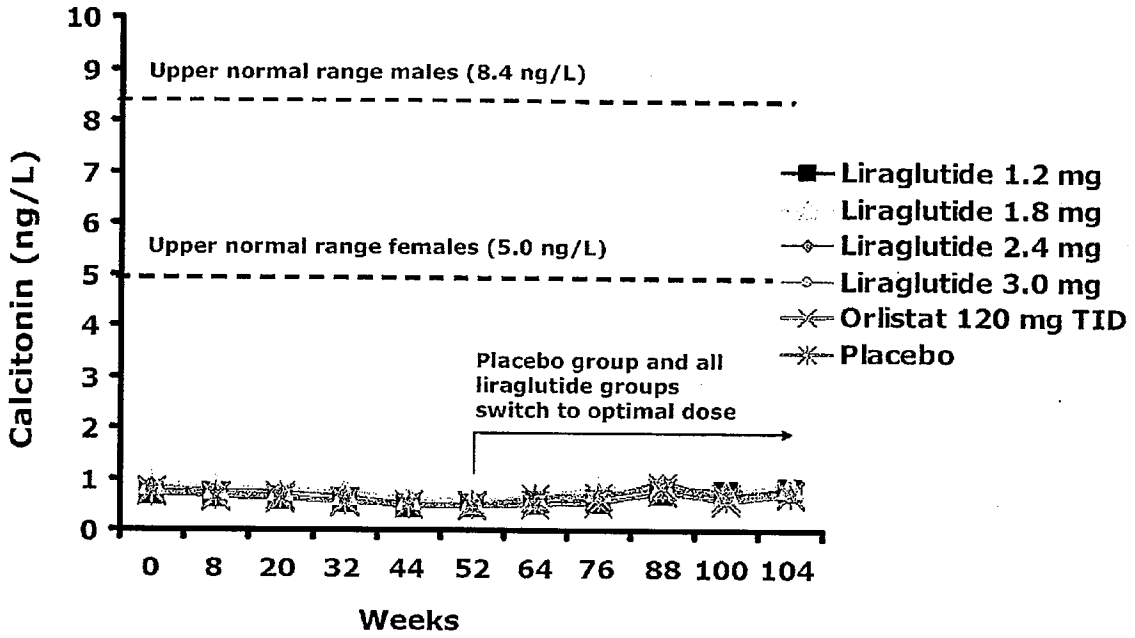



**Figure 4. Geometric mean calcitonin values over 1 year in the obesity trial (at Week 52, patients on liraglutide and placebo were switched to liraglutide 2.4 mg and subsequently uptitrated to 3.0 mg)**




The results presented in these tables give me comfort that liraglutide is not causing a mean change in calcitonin levels compared to other drugs or placebo, and is not even approaching the upper normal range in females or males, at least up to a two year time interval. Dr. Joffe details 17 subjects who have at least one. I refer the reader to his very thorough analysis, but I agree with his conclusion that there is not an imbalance in treatment-emergent serum calcitonin ≥20 ng/L between the liraglutide treated subjects vs. comparators. Dr. Joffe notes that the two thryoidologists sitting on the Advisory Committee panel had a split vote regarding approval based on the thyroid findings. I note that the thyroidologist voting no during his discussion stated that if he had data from a 6-12 month extension study documenting that calcitonin levels did not continually raise, he would feel assuaged (page 219, AC transcript). The tables above would seem to fulfill that criterion.

Dr. Joffe has a very thorough review of the likelihood that additional clinical data would feasibly define human risk. As the table below from his review (page 59) demonstrates, given the rarity of the tumor, there would have to be at a minimum 100-fold increase in the incidence of the cancer for detection. This seems highly unlikely (even the rodent models did not have carcinomas above baseline rates at doses approximating human exposures) and also indicates that this is not likely a question to be answered by a clinical trial.

**Table 22. Sample sizes needed for a single-arm trial to detect 2-fold to 100-fold increases over the background rate in the risk for non-familial medullary thyroid carcinoma (from Drs. Derr and Sahlroot, FDA biostatisticians)**

| Power | Increase in risk for medullary thyroid carcinoma | | | | |
|---|---|---|---|---|---|
| | 2-fold | 5-fold | 10-fold | 20-fold | 100-fold |
| **3-year treatment period** 80% | 1,888,050 | 229,783 | 62,383 | 31,183 | 3,353 |

| | | | | | |
|---|---|---|---|---|---|
| 90% | 2,578,783 | 278,383 | 110,850 | 40,517 | 4,793 |
| **5-year treatment period** | | | | | |
| 80% | 1,132,830 | 137,870 | 37,430 | 18,710 | 2,012 |
| 90% | 1,547,270 | 167,030 | 66,510 | 24,310 | 2,876 |
| **10-year treatment period** | | | | | |
| 80% | 566,415 | 68,935 | 18,715 | 9,355 | 1,006 |
| 90% | 773,635 | 83,515 | 33,255 | 12,155 | 1,438 |
| Power calculations from StatXact, 1-sided alpha 0.05 | | | | | |

In regards to the cardiovascular safety evaluation, please see Dr. Parks review for a comprehensive discussion with which I am in agreement. The filing of this application predated Agency guidance regarding cardiovascular safety evaluation for drugs used in glycemic control in diabetes. As such, this program did not have pre-specified definitions or prospective adjudication of major cardiovascular endpoints and any evaluation was retrospective in nature. Therefore the cardiovascular event data were evaluated in many different ways. I believe the most pertinent aspect of this is that for the most part, no matter how the data are 'sliced and diced', the point estimate for cardiovascular events is less than one, and when all categories are considered such that there are enough events to have any meaning, the upper bound of the confidence interval is less than the 1.8 goal-post (bearing in mind all the caveats inherent in any type of unplanned, retrospective analysis on an endpoint that was not originally identified as something of interest and where only a small number of events occurred). This does give us some reassurance that liraglutide will not have a negative cardiovascular impact and while not a perfect analysis, does fulfill the spirit of our guidance and the Advisory Committee voting reflected this view point as well. I believe that due to this being an unplanned analysis, retrospective in nature, and with limited events, labeling should not include this analysis and should only have the standard labeling that we use for diabetic agents noting no conclusive evidence of cardiovascular benefit with any anti-diabetic drug. I believe to do otherwise would be misleading, would misrepresent our degree of comfort with the data, and would create an unfair playing field for other agents.

I do note that the Advisory Committee Panel, with a clear majority voting that there was enough cardiovascular data to allow marketing, was not as overwhelming positive for this drug as it was for saxagliptin that was discussed on the previous day of the 2-day meeting. Comments at the time of those voting not to approve reflect the limited number of events upon which to draw conclusions. I find this somewhat curious, as this program had approximately the same number of events as saxagliptin, and one could speculate that having more time to consider things had caused some members to rethink their position. In any regard, I note as Dr. Parks has that some subgroup analyses resulted in a confidence interval that exceeded 1.8, but, I feel that the application provides the same level of confidence regarding cardiovascular safety as that provided by the saxagliptin analysis (which was approved) and should therefore, for this issue, be allowed to market with a commitment to perform a large post-marketing study.

Regarding pancreatitis, it is widely felt that patients with diabetes have up to a 3-fold[4] increased rate compared to matched controls just by virtue of their underlying diabetic disease. It is also felt that about 20% of patients reporting with acute pancreatitis will have a severe form such as hemorrhagic/necrotic which has up to a 30% mortality rate.[5] We have cases of pancreatitis, including hemorrhagic/necrotic, identified in the AERs database associated with use of both sitagliptin and exenatide. Both of these drugs manifest their glucose lowering effects through the incretin system. Considering that the baseline rate of pancreatitis for patients with diabetes is probably elevated and occurs frequently, it is difficult to tease out whether the reported events represent increase risk above baseline and are associated with incretin-based therapies or are just a consequence of having diabetes. In any event, we are quite concerned that incretin-based therapies may be associated with pancreatitis and have made our concerns public in communications and labeling. For the GLP-1 analogues, it is particularly important that clinicians have heightened awareness of the possibility of pancreatitis as these drugs are associated with high rates of nausea and vomiting, which may mask the diagnosis of pancreatitis if physicians are not vigilant in regard to a complete differential diagnosis.

Liraglutide has increased my concern in this regard, as they have a numeric imbalance of pancreatitis cases. There were 8 cases reported with liraglutide use compared to 1 in comparator groups. When considering exposure, this gives a rate of 2.2 and 0.6 per 1000 pt-years for liraglutide and comparator respectively, or about a 4-fold increase. Noted in Dr. Joffe's review is that the application for exenatide did not have an imbalance compared to placebo although I note that the rate for exenatide of 2.3 events per 1000 patient-years is about the same as that seen for liraglutide (2.3 events and 2.7 events per 1000 patient-years for exenatide and placebo respectively- exposures 3065 and 2434 patient-years for exenatide and liraglutide respectively). There were too few cases of pancreatitis in the safety database, and this small number of events is too fragile to determine if there is any causative effect, or to determine if there is a greater risk of pancreatitis with liraglutide compared to other diabetic drugs that work through the incretin system. However, given our prior concerns with drugs in this class and the new animal data reported in the literature that I mentioned earlier, this cannot be minimized or dismissed. I believe that future trials should include prospective evaluation for pancreatitis with amylase/lipase measurement routinely and also for cases where subjects have nausea and vomiting that occurs outside of routine measurements. While routine screening may help to gather further data to define some of the unknowns above, I am also cognizant that it may also be confusing as there are also data to suggest that asymptomatic patients with diabetes have abnormal (elevated) serum amylase and lipase levels such that currently recognized 'normal' levels for amylase and lipase may not apply.[6] In any regard, obtaining the data above in a trial setting should be useful to try to make a more thorough assessment of what 'normal' lipase/amylase levels in asymptomatic patients with diabetes are so that they can be applied to define asymptomatic elevations and also define what percentage of patients with nausea and vomiting actually have pancreatitis. All this information should be

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[4] Noel RA, Braun DK, Patterson RE, Bloomgren GL. Increased risk of acute pancreatitis and biliary disease observed in patients with type 2 diabetes: a retrospective cohort study. Diabetes Care. 2009 May; 32(5):834-8
[5] Whitcomb DC. Acute Pancreatitis. May 18, 2006 NEJM. 354;20:2142-2150
[6] Bastyr, EJ, Cheng C, Hall N. Frequent pancreatic lipse and amylase elevations in Type 2 diabetes mellitus. Diabetes. June 2009; 58 Supplement 1:A136

applicable to the clinical setting and will aid clinicians in making treatment decisions. Our concern regarding pancreatitis, and the findings from the liraglutide database, should be relayed in the label.

Approximately 10% of liraglutide recipients form anti-drug antibodies, of which approximately 50% cross-react with native GLP-1 and approximately 10% demonstrate neutralizing activity in cell-based assay. A consult was obtained with the Division of Pulmonary and Allergy Products (DPAP) to evaluate this finding. Dr. Porter from DPAP noted that efficacy and safety did not seem to be affected by antibody formation, but that sampling was not done uniformly which may bias results toward false negative misclassification and regression toward the mean (for both safety and efficacy). As such, they recommend further post-marketing evaluation.

**Conclusions and Recommendations**

I respect the professionalism and dedication that each reviewer has brought to this very challenging application. While it should not be surprising that in an application of this complexity there are a variety of opinions internally as to what the appropriate course of action should be (also reflected in the Advisory Committee voting and advice obtained at an internal Regulatory Briefing were there was a mixture of opinions), I also appreciate that many of the reviewers have indicated that their recommendations are based on their review of an isolated aspect and that judgments regarding final action decisions need to incorporate factors from the other reviews in order to form a complete picture upon which to make conclusions.

Trying to evaluate how to factor in preclinical data into human relevance can be very difficult. I do not think that additional preclinical data will resolve the uncertainty of the relevance of rodent C-cell tumor findings to humans, at least not in the short term. In discussions with Dr. Jacobson-Kram, he posits that mechanistic studies often raise as many questions as they answer. In coming to my conclusion regarding what action to take, I am struck that the actual malignant tumors themselves (as opposed to non-malignant tumors or focal hyperplasia) in rodents were very few in number, were not detected until treatment of over 50% of the animal's lifespan, did not occur in both sexes, and occurred only at levels that were several-fold above human exposures. I think this constellation of features should give us some comfort. I agree with Drs. Joffe and Parks that the proposals set forth by the pharmacology/toxicology team will not provide us with reassurance, but such studies could inform labeling for clinicians, and I am in favor of requiring the sponsor to perform them.

Medullary thyroid carcinoma is a very rare tumor with approximately 600 cases per year. Since this is a very rare occurrence, it is highly unlikely that any clinical trial will ever answer the question of whether liraglutide increases the risk of this cancer. I also note that we do not have a signal of malignancy in the database, unlike other drugs such as pioglitazone where despite only having a relative small exposure, there was a signal for bladder cancer in the application database and again in one published clinical trial[7], yet it continues to receive

[7] Dormandy JA, Charbonnel B, Ecland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (Prospective pioglitazone clinical trial in macrovascular events) : a randomised controlled trial. Lancet. 2005 Oct 8; 366(9493):1279-89

support by practicing physicians. I also am reassured that the use of liraglutide was not associated with increase levels of serum calcitonin in over 2 years of therapy. As mentioned above in the rodent studies, there was a lack of formation of actual medullary cancer in lifetime animal exposure of male mice and cases in female mice only occurred with 45x human exposure (noting the opposite in rats where there were not excessive cases of carcinoma in females and male excess cases occurring at 8x human exposure).

I also am not convinced that the concerns we have with liraglutide should not extend to the presently approved exenatide as I am have trouble reconciling that exenatide is any safer as intravenous dosing and the extended release form seems to give a similar signal. I suspect we probably have a false sense of security that the presently marketed exenatide does not have the same cancer concerns because it did not have a rodent signal in its application, but that conclusion may be misleading because the immediate release form of exenatide was dosed only once a day to rodents instead of twice a day as it is with humans. While this dosing interval for rodent studies may have seemed appropriate at the time, as it provided a similar exposures based on AUC in the rodents as that expected in the humans, our current evidence would seem to suggest that exposure based on AUC alone may not explain the animal findings, and that other factors such as length of time of receptor activation, which may not be reflected in AUC, are at play.

As noted by the Advisory Committee split vote, this is a complex issue. Some of the hesitation that individuals may have is in questioning whether liraglutide offers a unique benefit to other therapies. I would agree that its main advantage compared to exenatide is in regard to decreasing dosing from twice a day to once a day (although some indirect evidence indicates it may have some additional HbA1c lowering) and one could question whether that is important. However, our internal data indicates that the preclinical findings are not unique to liraglutide but will probably extend to all the 'extended' GLP-1 agents. So to condemn liraglutide would be to condemn them all. Some of the agents in development will offer patients the advantage of even less frequent dosing, perhaps to only once a week or even less frequent such as once a month, and I would portend that this is a unique benefit to patients. I am not willing to keep such medications from patients for years while we await the results of mechanistic studies that may not even actually answer the question of human relevancy.

I am also cognizant that this is not the first time the agency has had to face an issue where a drug has caused cancer in both sexes of two different rodent species. Rat or/and mouse studies for statins were noted to cause liver carcinoma with various agents. Simvastatin, an early but not the first in class statin, caused hepatic carcinoma in mice (4-8x human exposure-both sexes) and rats (15-25x human exposure-both sexes) at human exposure multiples similar to those seen for MTC in rodents with liraglutide. I also note that lovastatin, the first approved statin caused liver carcinoma in both sexes in mice, but only in male rats, yet this seemingly safer pre-clinical profile finding did not preclude the approval of simvastatin which seemed to have a stronger signal causing hepatic carcinoma in rats in both sexes. While we approved these medications and were willing to tolerate the unknown risk because of the clinical benefit we felt they may have, it wasn't until years later that the mechanism was defined to demonstrate that this effect did not have relevance to humans.

I agree with Dr. Brown's comments in his review that if the clinical benefit is considered great enough, postmarketing pharmacology/toxicology requirements can assess the relevance. These studies should be completed within 3-5 years, which is a very minor exposure time-frame relative to that required in the rodent studies to demonstrate cancer formation. I believe the level of risk for MTC in humans is de minimis especially for this time frame of exposure.

I am not in favor of routinely obtaining ultrasonography or serum calcitonin for patients that may be placed on liraglutide. I believe that the consequence of unnecessary thyroidectomy would far outweigh any potential benefit of routine screening. As noted by Dr. Joffe, serum calcitonin has a positive predictive in the single digits for levels between 20 and 50 ng/L which would lead to excess unnecessary medical evaluation for a very rare tumor. I do agree that a case series registry might help us to identify a possible signal, and agree that it should continue through many years as we would expect a prolong latency should cancer actually occur because of liraglutide use.

I am concerned that the incretin based therapies may cause pancreatitis. However, even if we do eventually discover that they do, we most likely would not remove them from the market (depending on the magnitude of increase risk and severity of pancreatitis), but encourage awareness and early diagnosis. I do not think that we have evidence that liraglutide is any worse offender in this regard than the other agents.

It is fair to ask of what benefit the GLP-1 analogues have as we have many classes of diabetic drugs. They have less hypoglycemia concerns when used as single agents, may have weight loss instead of gain as seen in some other diabetic drug classes and may have a very convenient dosing schedule especially for future products. Liraglutide itself does seem to indicate in cross-study comparisons that it offers comparable or even increased HbA1c reduction compared to some other agents and seems well tolerated by patients with renal and liver disease. One also has to note that most of the other classes of anti-diabetic agents including the most commonly used ones have their own concerns. Sulfonylurea agents are currently labeled for increased cardiovascular mortality and we are also exploring several signals of potential association with hepatotoxicity. Rosiglitazone is under investigation for potential cardiovascular risks, pioglitazone as mentioned above may have a bladder cancer signal (that potentially would affect a greater number of patients than the MTC risk, if present, for liraglutide) and both can cause heart failure. Insulin itself given at super-physiologic doses has been questioned of potentially being associated with cardiovascular events and is a pro-growth factor giving concerns of a cancer potential. While metformin seems immune to some of the concerns with other agents, as beta-cell function declines over time eventually multiple therapies are required and it cannot be used in those with renal compromise. As such, it would seem there is not a perfect agent and the key is to recognize the risks, and manage them as is appropriate for the individual patient.

Dr. Parks has recommended the restriction of second-line therapy be placed in the label, so that this drug is slowly introduced into clinical practice giving us an opportunity to gain clinical experience gradually. I agree with this philosophy for this drug. While many sponsors may responsibly introduce a drug into marketing, theirs is a profit-based business and the pressures to generate revenue are strong. Also, with most classes of drugs, there are similar

drugs in development from competitors which places even more pressure to generate profit before there is more competition. Limitations placed on labeling will help in assuring prudence with a drug that has unknowns and may help to motivate the sponsor to complete animal studies with the goal of liberalizing labeling.

I recommend approval.

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22341 | ORIG-1 | NOVO NORDISK INC | VICTOZA (LIRAGLUTIDE) |

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

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/s/

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CURTIS J ROSEBRAUGH
01/25/2010

# Summary Review for Regulatory Action

| | |
|---|---|
| **Date** | January 22, 2010 |
| **From** | Mary H. Parks, M.D. |
| **Subject** | Division Director's Memo |
| **NDA/BLA #**<br>**Supplement #** | 22-341 |
| **Applicant Name** | Novo Nordisk |
| **Date of Submission** | May 23, 2008 |
| **PDUFA Goal Date** | March 23, 2009 |
| **Proprietary Name / Established (USAN) Name** | Victoza/Liraglutide (rDNA origin) Injection |
| **Dosage Forms / Strength** | Injectable solution (6 mg/mL)<br>0.6 mg, 1.2 mg, and 1.8 mg |
| **Proposed Indication(s)** | Treatment of Type 2 Diabetes Mellitus |
| **Action/Recommended Action for NME:** | Approval |

| **Material Reviewed/Consulted**<br>OND Action Package, including: | **Names of discipline reviewers** |
|---|---|
| Medical Officer Review | Lisa Yanoff, M.D. (efficacy)<br>Karen M. Mahoney, M.D. (safety) |
| Statistical Review | Janice Derr, Ph.D.<br>Todd Sahlroot, Ph.D. |
| Pharmacology Toxicology Review | Anthony Parola, Ph.D.<br>Karen Davis-Bruno, Ph.D. |
| CMC Review/OBP Review | Joseph Leginus, Ph.D., Suong Tran, Ph.D., Ali Al Hakim, Ph.D., Christine Moore, Ph.D. |
| Microbiology Review | Brian Riley, Ph.D., James McVey, Ph.D. |
| Clinical Pharmacology Review | Manoj Khurana, Ph.D., Ritesh Jain, Ph.D., Wei Qiu, Ph.D., Rajanikanth Madabushi, Ph.D., Christoffer Tornoe, Ph.D., Sally Choe, Ph.D. |
| DDMAC | |
| DSI | Susan Leibenhaut, M.D., Constance Lewin, M.D.<br>Xikui Chen, Ph.D., C.T. Viswanathan, Ph.D., Sriram Subramaniam, Ph.D. |
| CDTL Review | Hylton V. Joffe, M.D., M.M.Sc. |
| OSE/DMEPA | Walter Fava, R.Ph., Kellie Taylor, M.P.H., Pharm.D., Denise Toyer, Pharm.D., Carol Holquist, R.Ph., |
| OSE/DEPI | Diane Wysowski, Ph.D., Gwen Zomberg, M.D., Solomon Iyasu, M.D. |

| | |
|---|---|
| OSE/DRISK | Kendra Worthy, Pharm.D., Mary Dempsey, Claudia Karwoski, Pharm.D. |
| Other | CDRH: Sajjad Syed<br>QT-IRT : Joanne Zhang, Ph.D., Christine Garnett, M.D., Rajnikanth Madabushi, Ph.D., Suchitra Balakrishnan, Ph.D., Norman Stockbridge, M.D., Ph.D. |

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DEPI= Division of Epidemiology
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

# Division Director's Review

## 1. Introduction

Liraglutide is a glucagon-like peptide 1 (GLP-1) analogue under development as an anti-diabetic agent for type 2 diabetes mellitus (T2DM) and as a weight-loss drug. For this application, Novo Nordisk has submitted data in support of an indication to improve glycemic control in adults with T2DM.

GLP-1 is an incretin hormone that increases insulin secretion in response to an ingested meal. Unlike other anti-diabetic therapies, which control hyperglycemia through stimulation of insulin release from the pancreas (e.g. sulfonylureas or glinides), incretin-based therapies control hyperglycemia through a glucose-dependent manner thereby mitigating the risk of hypoglycemia. Because human GLP-1 is rapidly degraded by the serine protease, dipeptidyl peptidase IV (DPPIV), it has limited clinical use.

The half-life of liraglutide is prolonged due to a slowed absorption after subcutaneous injection, as a result of self-association into heptamers, and extensive albumin-binding providing some resistance against DPPIV degradation. Pharmacokinetic profile support once-daily dosing. Currently, the only approved GLP-1 analogue is Byetta® (exenatide) which is administered as twice-daily subcutaneous injections.

Novo Nordisk has submitted an extensive and complex NDA requiring the input of multiple review disciplines within CDER, with additional consultation to CDRH. Throughout my memo, the reader is referred to specific primary reviews to appreciate the scope of regulatory and scientific matters considered in the overall recommendation of this application.

## 2. Background

Over the past two to three years, concerns regarding the cardiovascular safety profile of certain anti-diabetics have resulted in much debate within the scientific and regulatory community on the adequacy of the development programs for anti-diabetic therapies to ensure that these drugs do not contribute to excess cardiovascular mortality and morbidity in a patient population that is already at 2- to 4-fold risk of dying from heart disease.

On July 1 and 2, 2008, the FDA convened a public advisory committee meeting to discuss the role of CV assessment in the pre- and postmarket settings. The pivotal question raised to the panel members was:

> *It should be assumed that an anti-diabetic therapy with a concerning CV safety signal during Phase 2/3 development will be required to conduct a long-term cardiovascular*

*trial. For those drugs or biologics without such a signal, should there be a requirement to conduct a long-term cardiovascular trial or to provide other equivalent evidence to rule out an unacceptable cardiovascular risk. (vote yes/no requested).*

The outcome was 14 "yes" and 2 "no" votes.

Following this advisory committee meeting, the FDA issued a Final Guidance to Industry in December 2008 titled, *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes.* With its release, the FDA also publicly announced that the recommendations in this guidance will be applied to all ongoing diabetes development programs and marketing applications pending before the agency. In order to gain approval, applicants must compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8.

At the time of its issuance, the FDA had three NDAs under review: alogliptin (Nesina), saxagliptin (Onglyza), and liraglutide (Victoza). Saxagliptin and liraglutide were each presented at a public advisory committee meeting on April 1 and 2, 2009, respectively. Alogliptin was not presented before an advisory committee panel because it was deemed deficient for approval. Because none of these 3 NDAs were conducted with knowledge of these new recommendations, the review division applied a uniform approach to assessing risk for these NDAs. This approach is clearly described by the clinical and statistical reviewers in their finalized review of this NDA and also in the advisory committee briefing materials. I have summarized the targeted CV risk assessment and my conclusions of the findings under Section 8.0 of this memo.

In addition to CV safety assessment, the advisory committee meeting for liraglutide also focused only on thyroid neoplasms, particularly C-cell neoplasms. This specific safety concern for liraglutide arose from pre-neoplastic and neoplastic C-cell findings in the rat and mouse carcinogenicity studies. Under Sections 4.0, 8.0 and 13.0, I discuss these findings and how they have shaped the differing opinions on approvability of this application by the advisory committee panel and FDA review staff.

## 3. CMC/Device

*Please see the following finalized reviews for a complete discussion of CMC/Device issues:*

- *Initial Quality Assessment by Dr. Suong Tran, dated July 2, 2009*
- *CMC Review #1 by Dr. Joseph Leginus, dated December 29, 2008*
- *CMC Review #2 by Dr. Joseph Leginus, dated April 17, 2009. A CDRH review dated February 13, 2009, is appended to this review*
- *CDRH review by Dr. Sajjad Syed*

**Drug Substance**

Liraglutide is a fragment of the native human glucagon-like peptide 1 (GLP-1) sequence position 7-37. Its precursor Arg34 GLP-1[7-37] is produced by recombinant DNA technology

from yeast Saccharomyces cerevisiae, and the precursor is subsequently modified by addition of a glutamic acid-spaced palmitic acid to the ε-amino group of lysince at position 26 to yield liraglutide. A shelf life of 24 months is recommended for the drug substance when stored at -18°C±2°C/ambient relative humidity or at lower temperature.

**Drug Product**

The drug product is a sterile solution for subcutaneous administration. It is supplied in pre-filled — cartridges that are pre-assembled in disposable, multi-dose pen injectors. Initially upon review by DMEPA, recommendations were made and accepted by the applicant to market only one pen which can deliver 3 proposed doses of 0.6, 1.2 and 1.8 mg. Each vial contains 3 mL at a protein concentration of 6 mg/mL b(4)

described in the CMC review. The drug product is photo-labile for which the pen-injector provides adequate protection from degradation due to light. A long-term expiry of 24 months is recommended for the drug product when stored under refrigerated conditions of 2 to 8°C and an in-use expiry of 32 days is recommended for the drug product when stored at room temperature of 28 to 32°C.

The device was reviewed by Center for Device and Radiologic Health (CDRH). Based on a Human Factors Study conducted by the applicant and submitted part way through the review process, the CDRH reviewer Sajjad Syed has found the data supporting use of the device acceptable.

Office of Compliance has issued an acceptable recommendation for the GMP status of all manufacturing and testing facilities.

## 4. Nonclinical Pharmacology/Toxicology

*Please see the following finalized reviews for a complete discussion of Nonclinical Pharmacology/Toxicology issues:*

- *Carcinogenicity Assessment Committee (CAC/CAC-EC) Report and FDA-CDER Rodent Carcinogenicity Database Factsheets for Mouse and Rat dated September 13 and 15, 2008*
- *Pharmacology/Toxicology Review by Dr. Anthony Parola dated February 12, 2009*
- *Pharmacology/Toxicology Review by Dr. Anthony Parola dated July 10, 2009*
- *Supervisory Pharmacology/Toxicology Review by Dr. Karen Davis-Bruno dated July 13, 2009*

**General Toxicology Findings**

The overall toxicology program involved studies in several different species, across a wide range of doses and over different durations of drug exposure. Dosing in animals is typically expressed as some multiple of human exposure. For the most part, the nonclinical dosing is described as multiples of human exposure calculated as the ratio of plasma liraglutide $AUC_{0-24h}$ in animals divided by $AUC_{0-24h}$ in humans at maximum recommended human dose (MRHD) of 1.8 mg/day. With exception for the 2-year carcinogenicity studies, the longest study duration was an 87-week mechanistic study in monkeys.

Aside from the nonclinical C-cell tumor finding which will be discussed under a separate subsection, liraglutide was well-tolerated in the acute and general toxicity studies. Below are summary findings of some of the toxicology studies.

*Mice* – in single sc or iv-dosed studies the main side effect was decreased food consumption and weight loss, reversible within 3 days of dosing. There were no treatment-related deaths or macroscopic necropsy findings. Similar findings were noted in a 4-wk, repeat sc-dosed study with exception for mild anemia. In a 13-wk, repeat sc-dosed study involving doses which achieve multiples of human exposures at 2-, 19-, and 85-fold, no treatment-related unscheduled deaths occurred. Transient decreased food consumption and weight loss, and mild anemia were again noted. In both the 4-wk and 13-wk studies, the thyroid was the only target organ of note.

*Rats* – Single-dose studies yielded unremarkable findings. Repeat-dose studies of 7-day, 28-day, 13-week, and 26-week duration were conducted at doses of 0, 0.1, 0.25, or 1 mg/kg/day. The 7-day study also employed 0.4, 2 and 10 mg/kg/day dose group. Animals in the 2 and 10 mg/kg/day dose groups were sacrificed on Study Days 2 and 3 due to clinical signs of toxicity (piloerection, rolling/high stepping gait, hunched posture, dark extremities, and thin appearance). There were no treatment-related unscheduled deaths in the other repeat-dose studies. The maximum tolerated dose (MTD) was 1 mg/kg/day (~8 to 14-fold human exposure multiple) in these other studies. Similar toxicities observed in the mice studies were noted (mild anemia, transient decreased food consumption, and weight) along with injection site reactions and CPK elevations. Unlike the mice studies, no target organs of note were identified. Specifically, liraglutide did not cause cell proliferation in the pancreas or thyroid C-cells by staining for proliferating cell nuclear antigen (PCNA) and no proliferative thyroid C-cell lesions were noted.

*Monkeys* – Studies included a 3-day rising tolerability study, a 14-day tolerability study, a 28-day repeat dose study, a 13-week repeat dose study, and a 52-week dose toxicity study. The range of doses evaluated was 0.05 to 5 mg/kg/day. There were no unscheduled deaths in any of these studies. The monkey studies employed dosing which provided the highest human exposure multiple for the longest duration. The 52-week dose toxicity study included exposures of 73-fold the maximum recommended human dose of 1.8 mg/day.

Because the 52-week monkey study is the longest duration for the highest human exposure multiple, I will highlight some of the findings from this study, particularly in light of thyroid C-cell abnormalities in rodents.

**52-Week Subcutaneous Toxicity Study in Cynomolgus Monkeys with 4-Week Recovery Period** (Please see pages 152-163 of Dr. Parola's review for details)
A total of 40 animals (males and females) were studied across the following treatment groups: 0 (vehicle), 0.05 mg/kg/day (1x human exposure multiple), 0.5 mg/kg/day (9x human exposure multiple), and 5 mg/kg/day (73x human exposure multiple). In addition, 8 animals were evaluated in a 4-week recovery period.

Recurring findings of mild anemia, weight loss in males, transient decreased food consumption and one animal with CPK elevation were noted. The anemia reversed during the recovery period. Injection site reactions appear to be more prevalent in the monkey studies establishing a NOAEL below the lowest dose (0.05 mg/kg/day) tested in the 13-week and 52-week studies. Reactions were described as subcutaneous thickening with macroscopic findings of reddening and microscopic findings of fasciitis and hemorrhage; however, no animals required treatment discontinuation as a result of these findings.

Despite the high human exposure multiple in this one-year study, no unscheduled deaths occurred. Four animals did require veterinary treatment due to liquid feces (2 animals), infection (1 animal), and a tail wound as well as liquid feces (1 animal). The latter animal required an 8-day hold of treatment due to dehydration secondary to the persistent liquid feces. These events occurred at the lowest and intermediate dose groups of liraglutide.

ECG recordings were obtained prior to treatment and during treatment on Day 2, Weeks 26 and 52 and during recovery Week 4. It was reassuring that no treatment-related findings on ECG were noted.

This and the 87-week mechanistic monkey study were the only nonclinical studies in which anti-liraglutide antibodies which cross-reacted with native GLP-1 were detected. Three high dose animals were found to be Ab-positive; one at Week 52 and the other two at the end of the recovery period. It is unknown whether these antibodies are neutralizing but their finding is unlikely to invalidate this toxicology study.

There was a dose-dependent increase in pancreatic organ weight which appeared to be due to increased mass of exocrine cells and pancreatic ducts. There was no increased in pancreatic beta-cell mass.

Liraglutide administration in cynomolgus monkeys had no effect on plasma calcitonin, thyroid C-cell proliferation, or calcium homeostasis parameters. This also included plasma calcium and iPTH levels in studies up to 87 weeks. Although these studies included dosing at > 70 x human exposure, Dr. Davis-Bruno notes that these monkey studies are not designed to assess carcinogenicity risk given the small sample size (e.g., 40 animals total vs >500 in each of the rodent studies) and duration of exposure. The rodent carcinogenicity studies are designed to assess cancer risk over the lifespan of the animals whereas the 52-week duration in this monkey study only approximates 5% of the monkey's lifespan. It is interesting to note that focal C-cell hyperplasia was observed as early as 4 weeks in mice exposed to 88 x the clinical exposure and that this also represents 3-4% of the mouse's lifespan. Therefore it might be an auspicious finding that at a similar time point in monkeys exposed to similar high multiples of drug, C-cell abnormalities are not observed.

**Rodent Carcinogenicity Studies**

The primary deficiency identified by the pharmacology/toxicology reviewers is the inadequate data presented to conclude that C-cell tumors observed in both rats and mice at clinically relevant exposures are rodent-specific. As a result of this deficiency, Drs. Parola and Davis-Bruno can not be assured that these carcinogenicity findings do not represent a clinical risk for

this chronically administered drug. They have both recommended against approval of this NDA.

The findings from these 2 rodent studies have been extensively reviewed and discussed in Dr. Parola's review and succinctly summarized in Dr. Davis-Bruno's supervisory memo and Dr. Joffe's CDTL memo. I will briefly summarize the findings below.

**Rat Carcinogenicity Study (See Appendix B, page 348 of Dr. Parola's review)**
This was a 104-week study in which approximately 400 male and female Sprague Dawley rats were administered vehicle or liraglutide 0.075, 0.25, or 0.75 mg/kg/day subcutaneously. Estimated human exposures for the liraglutide doses were 0.5x, 2x, and 8x the MRHD of 1.8 mg/day. Table 4.1 describes the treatment assignments.

**Table 4.1 Treatment Groups in Rat Carcinogenicity Study**

| Group 1 | Treatment | Human Exposure Multiple | Animal Numbers | |
|---|---|---|---|---|
| | | | Males | Females |
| 1 | Control (vehicle) | -- | 1-50 | 201-250 |
| 2 | Low Dose 0.075 mg/kg/day | 0.5x | 51-100 | 251-300 |
| 3 | Intermediate Dose 0.25 mg/kg/day | 2x | 101-150 | 301-350 |
| 4 | High Dose 0.75 mg/kg/day | 8x | 151-200 | 351-400 |

There were no treatment-related effects on mortality (Table 4.2). A similar, if not higher percentage of animals on the liraglutide groups survived until scheduled necropsy. There was no dose-related trend in the mortality data.

**Table 4.2 Mortality Data in Rat Carcinogenicity Study (Sample Size of 50 in each group)**

| Group | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | Premature Sacrifice | Found Dead | Scheduled Necropsy | Premature Sacrifice | Found Dead | Scheduled Necropsy |
| 1 (control) | 42% | 12% | 46% | 42% | 2% | 56% |
| 2 (LD) | 44% | 8% | 48% | 48% | 2% | 50% |
| 3 (ID) | 34% | 8% | 58% | 54% | 4% | 42% |
| 4 (HD) | 44% | 4% | 52% | 36% | 6% | 58% |

LD = low dose (0.075 mg/kg/d); ID = intermediate dose (0.25 mg/kg/d); HD = high dose (0.75 mg/kg/d)

Animals that were prematurely sacrificed or found dead were also necropsied.

Gross pathology findings related to the thyroid are notable for the following:

- Masses were noted only in the treated animals: 1 male in Group 2; 1 male in Group 4; 1 female in Group 4
- Enlarged thyroid glands were noted only in the treated animals at intermediate or higher doses in both males and females

Histopathology findings related to the thyroid are notable for the following:

**Table 4.3. Thyroid Histopathology Results in Rat Carcinogenicity Study**

| Thyroid Gland Findings | Males | | | | Females | | | |
|---|---|---|---|---|---|---|---|---|
| | Control N=50 | LD N=49* | ID N=50 | HD N=50 | Control N=50 | LD N=49* | ID N=49* | HD N=50 |
| Follicular Cell Adenoma (benign) | 0 | 2 | 1 | 2 | 1 | 0 | 2 | 0 |
| Follicular Cell Carcinoma (malignant) | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 |
| Focal C-cell hyperplasia | | | | | | | | |
| Minimal | 3 | 0 | 2 | 3 | 6 | 1 | 2 | 4 |
| Mild | 6 | 7 | 8 | 9 | 7 | 7 | 14 | 11 |
| Moderate | 2 | 3 | 6 | 4 | 1 | 5 | 6 | 4 |
| Marked | 0 | 4 | 4 | **8** | 0 | 1 | **5** | 5 |
| Ttl incidence | 11 (22%) | 14 (29%) | 20 (40%) | **24 (48%)** | 14 (28%) | 14 (29%) | **27 (55%)** | 24 (48%) |
| Diffuse C-cell hyperplasia | | | | | | | | |
| Minimal | 1 | 1 | 0 | 0 | 2 | 0 | 0 | 0 |
| Mild | 2 | 2 | 1 | 3 | 3 | 2 | 2 | 2 |
| Moderate | 0 | 2 | 1 | 2 | 0 | 4 | 1 | 0 |
| Marked | 0 | 1 | 1 | 2 | 1 | 2 | 0 | 1 |
| Ttl incidence | 3 (6%) | 6 (12%) | 3 (6%) | 7 (14%) | 6 (12%) | 8 (16%) | 3 (6%) | 3 (6%) |
| C-cell adenoma (benign) | 6 | 8 | **21 (42%)** | **23 (46%)** | 5 | **13 (27%)** | **16 (33%)** | **28 (56%)** |
| C-cell carcinoma (malignant) | 1 | 4 | 3 | **7 (14%)** | 0 | 0 | 2 | 3 |

LD = low dose (0.075 mg/kg/d); ID = intermediate dose (0.25 mg/kg/d); HD = high dose (0.75 mg/kg/d)
*Note that some thyroid glands were autolysed in animals found dead and no histopath could be performed. No abnormal gross pathology were listed for these animals.

From Table 4.3, there are follicular cell tumors (non-medullary thyroid tumors) noted; the majority being benign adenomas. One follicular cell carcinoma was noted in a male LD and male ID group. There are too few cases to formulate any conclusions from these findings.

The incidence of C-cell tumors (benign and malignant) was significantly higher in the liraglutide-treated groups than control (bold/red font cells). There was a significantly higher incidence of focal C-cell hyperplasia in the HD male and ID female groups compared to controls. According to Dr. Parola, focal C-cell hyperplasia is considered a pre-neoplastic tumor.

- For C-cell adenomas (benign), significant increases were noted in males dosed at ≥ 0.25 mg/kg/day (human exposure multiple of 2x or higher) and in females dosed at ≥ 0.075 mg/kg/day (human exposure multiple of 0.5x or higher).

- For C-cell carcinoma (malignant), significant increases were noted in males dosed at ≥ 0.25 mg/kg/day (human exposure multiple of 2x or higher) only, However, C-cell carcinoma is a rare tumor in rats and its incidence exceeded concurrent and historical controls at all doses in males (≥ 0.075 mg/kg/day) and at ≥ 0.25 mg/kg/day in females.

**Mouse Carcinogenicity Study (See Appendix A, page 298 of Dr. Parola's review)**
This was a 104-week study in which approximately 700 male and female CD1 mice were administered vehicle or liraglutide 0.03, 0.2, 1.0, or 3.0 mg/kg/day subcutaneously. Estimated human exposures for the liraglutide doses were 0.2x, 1.8x, 10x, and 45x the MRHD of 1.8 mg/day. Similar to the rat carcinogenicity study, 50 animals/sex/dose were planned for the main study. Additional animals were studied in all treatment groups for a planned interim sacrifice at Week 78. However, due to high mortality in the main study control female groups (Table 4.4), treatment in the animals originally assigned to interim sacrifice was extended to 104 weeks.

**Table 4.4 Percentage Survival for Scheduled Necropsies from Main Study (sample size 50 in all treatment groups/sex)**

| Treatment Group | Males | Females |
|---|---|---|
| Group 1 (control) | 50% | 28% |
| Group 2 (0.03 mg/kg/d) | 58% | 22% |
| Group 3 (0.2 mg/kg/d) | 56% | 38% |
| Group 4 (1.0 mg/kg/d) | 62% | 38% |
| Group 5 (3.0 mg/kg/d) | 38% | 38% |

Unlike the rat study, mice found dead or sacrificed moribund were necropsied at the discretion of the pathologist, with the intent of determining a cause of death. If there were a substantial number of early decedents with missing necropsy data, there would be incomplete data ascertainment which may impact the overall conclusions of this study. In discussing this observation further with Drs. Parola and Davis-Bruno, Dr. Parola pointed out that the number of animals contributing to the histopathology results closely approximated the expected numbers from the combined main study and Week 78/104 group. Animals that died early in the study were replaced and were not examined; however, these animals were only dosed for a short duration (2 weeks) and would unlikely contribute much relevant information regarding the carcinogenic potential of liraglutide. Both female mice with C-Cell carcinoma died prior to study termination (Week 64 and 92), but only one had C-cell carcinoma listed as a cause of death. Fibrosarcoma on the dorsal surface was listed as a cause of death in 9/47 decedents (19.1%) in the high dose male treatment group.

It appears that there were differences in opinion in some of the thyroid tissue readings requiring resolution by consensus diagnosis. The following table reproduced from Dr. Parola's review summarizes these cases.

**Table 4.5 Discrepant Readings of Thyroid Tissues – Resolved by Consensus**

| Animal #/treatment grp | Reviewing Pathologist's opinion | Study Pathologist's opinion | Consensus |
|---|---|---|---|
| 75/male 0.03 | Follicular cell adenoma, undifferentiated, with solid pattern | Follicular cell adenoma | Follicular cell adenoma with unusual features |
| 158/male 1.0 | C-cell adenoma | Follicular cell adenoma | C-cell adenoma |
| 163/male 1.0 | C-cell adenoma + C-cell hyperplasia | 2 C-cell hyperplasia (on 1st section) | C-cell adenoma + C-cell hyperplasia |
| 452/female 3.0 | C-cell adenoma (autolysed section) | Follicular cell adenoma | C-cell adenoma |
| 371/female 0.2 | C-cell hyperplasia | -- | C-cell hyperplasia |
| 213/male 3.0 | C-cell hyperplasia | -- | C-cell hyperplasia |
| 665/female0.2 | C-cell hyperplasia | -- | C-cell hyperplasia |

Among the tissue samples in which there were differences in opinion (Table 4.5), there were no cases of C-cell carcinoma identified. However, there were only two C-cell carcinoma cases identified in the high-dose female treatment groups at 45 x human exposure multiples. They alone were not statistically significant findings in this carcinogenicity study. The predominant tumor contributing to the statistically significant finding for total C-cell tumors was C-cell adenoma (see Table 4.6).

**Table 4.6 Thyroid Histopathology Results in Mouse Carcinogenicity Study**

| | Males | | | | | Females | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Dose (mg/kg/day)** | **0** | **0.03** | **0.2** | **1** | **3** | **0** | **0.03** | **0.2** | **1** | **3** |
| **Human exposure multiple[a]** | **-** | **0.2** | **1.8** | **10.0** | **45.0** | **-** | **0.2** | **1.8** | **10.0** | **45.0** |
| **N** | 79 | 66 | 65 | 67 | 79 | 75 | 66 | 67 | 66 | 76 |
| Focal hyperplasia (rare)[b] | 0 | 0 | 1 (2%) | **11 (16%)** | **30 (38%)** | 0 | 0 | **7 (10%)** | **10 (15%)** | **22 (29%)** |
| C-cell adenoma (rare)[c] | 0 | 0 | 0 | **9 (13%)** | **15 (19%)** | 0 | 0 | 0 | **4 (6%)** | **15 (20%)** |
| C-cell carcinoma (rare)[c] | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 (3%) |
| C-cell adenoma or carcinoma (rare)[c] | 0 | 0 | 0 | **9 (13%)** | **15 (19%)** | 0 | 0 | 0 | **4 (6%)** | **17 (22%)** |

a=based on area under the time-concentration curve relative to the 1.8 mg dose
b=Diffuse C-cell hyperplasia cannot be adequately assessed without specialized staining
c=tumor considered common or rare based on incidence in historical control groups of >1% or <1%, respectively
statistically significant differences from control identified in bold/red font

From Table 4.5 there were 3 cases of C-cell adenoma adjudicated by a consensus opinion: 2 occurred in the male 1.0 mg/kg/day group and 1 in a female treated at 3.0 mg/kg/day. It is unclear how these discrepant histopathologic diagnoses affect the overall findings but as there were no C-cell adenomas noted in control or lower dose groups, elimination of these cases may only alter slightly the statistical significance of the overall results.

I also note that there were treatment-related skin and subcutis fibrosarcomas in the mouse carcinogenicity study (males only) that were not observed in the rat study. Dr. Parola has identified this finding as another concerning signal of carcinogenic potential and further comments that the local toxicity assessment may have been inadequate in the general toxicology studies due to a more dilute concentration of drug administered to animals than evaluated in the clinical program. I concur with ECAC that the clinical relevance of the skin tumor findings is questionable given that it was isolated to male mice only. Regarding the issues surrounding the local toxicity observed in some of the repeat-dose toxicology studies, I believe that the issue of lower concentrations evaluated can be evaluated by the clinical program in which the to-be-marketed formulation and formulations with similar drug concentrations were assessed.

Dr. Parola has extensively and completely reviewed the nonclinical development program. These data were also presented before the agency's Executive Carcinogenicity Assessment Committee (ECAC) which deemed that both rodent studies were adequately designed and executed to permit an assessment of carcinogenic potential of liraglutide. The applicant had conducted several mechanistic studies to establish a mode-of-action for the C-cell tumor findings which were considered evidence that these tumors are rodent-specific. Their proposal that the tumors were due to activation of GLP-1 receptors on thyroid C-cells which resulted in persistent calcitonin synthesis and secretion which then resulted in C-cell hyperplasia and tumor was rejected by the pharmacology/toxicology reviewers and ECAC. In addition, an overwhelming number of advisory committee panel members (12 vs 1) were not convinced that the rodent tumor findings were not relevant to humans. The applicant has since abandoned its position and agrees that the originally proposed mode-of-action can not be relied upon to dismiss potential clinical risk.

I will not elaborate further on the prior mode-of-action and the results of the mechanistic studies conducted to support this hypothesis and refer the reader to Appendix C (page 379) of Dr. Parola's review for a detailed discussion.

As stated earlier, both Drs. Parola and Davis-Bruno are recommending against approval. A tertiary review from Dr. Paul Brown, associate director for pharmacology/toxicology in Office of Drug Evaluation II, is pending. Dr. Parola's states the following in his review:

*"Based on the nonclinical data, this application is not approvable because there is insufficient nonclinical information about liraglutide to determine if it is safe for chronic use."*

This statement is presumably based *primarily* on the 2-year carcinogenicity studies because it is followed by the following:

*"In 2-year lifetime exposure carcinogenicity studies, liraglutide caused thyroid C-cell tumors in mice and rats at clinically relevant exposures. The human relevance of liraglutide-induced rodent C-cell tumors is unknown, and mechanistic studies performed by the applicant did not mitigate this risk."*

I emphasize that his statement is based *primarily* on the carcinogenicity data because I acknowledge that there are other GLP-1 analogues in development which have similar C-cell tumor findings suggesting a drug class effect for which this signal can not be dismissed.

In his Executive Summary, Dr. Parola has proposed 3 items for the applicant to address prior to approval. In brief they are: 1) determine a mode-of-action for liraglutide-induced rodent C-cell tumors and evaluate the human relevance of rodent C-cell tumors based on this mode-of action; 2) provide evidence that local toxicity after repeat subcutaneous injection with liraglutide was adequately assessed in nonclinical studies; and 3) evaluate the *in vitro* genetic toxicity of liraglutide impurities at impurity levels consistent with drug substance and drug product acceptance criteria.

In her supervisory pharmacology/toxicology memo, Dr. Davis-Bruno concurs with Dr. Parola's overall recommendation based on the rodent C-cell tumor findings. She did not identify the skin findings, local toxicity, and impurity profile as deficiencies which should be included in her basis for recommending against approval.

**Pancreatic Pathology**

Recently, several safety concerns related to the pancreas have been identified with the use of two approved incretin-based therapies, exenatide (a GLP-1 analogue) and sitaglitpin (a dipeptidyl-peptidase IV inhibitor or DPP4-inhibitor). Pancreatitis, including several cases of hemorrhagic and/or necrotizing pancreatitis, has been reported for both these drugs in spontaneous postmarketing adverse event reports. The pre-marketing clinical development program for both these drugs did not detect such a signal whereas liraglutide had a higher number of patients experiencing pancreatitis than controls, even after correcting for differential exposures. In April of this year, results from a 12-week study in a transgenic rat model of type 2 diabetes noted increased pancreatic ductal turnover and ductal metaplasia in sitagliptin-treated animals and pancreatitis in one sitagliptin-treated animal.[1]

In the nonclinical development program for liraglutide, increased pancreatic organ weight was noted in several repeat-dose studies but no treatment-related microscopic pathology was observed in the pancreas. In a 13-week study in Sprague-Dawley rats, a higher incidence of mild acinar cell atrophy was noted in the exocrine pancreas and there was a dose-related increase in incidence of minimal focal inflammation in female rats. Overt pancreatitis was never noted in all of the toxicology studies. Furthermore, pancreatic cancer was not identified in either of the rodent carcinogenicity studies.

Although the extensive nonclinical development programs for the incretin-based therapies have not identified any serious pancreatic pathology, it has been suggested that utilizing an animal disease model that correlates with the clinical disease would be provide greater sensitivity for detecting safety concerns such as pancreatitis and pancreatic cancer. To date, only the human IAPP transgenic rat (HIP) has been studied in this capacity. A variety of

[1] Matveyenko AV et al. Beneficial endocrine but adverse exocrine effects of sitagliptin in the human islet amyloid polypeptide transgenic rat model of type 2 diabetes rat model of type 2 diabetes: interactions with metformin. *Diabetes*. 2009 Jul;58(7):1604-15. Epub 2009 Apr 29)

studies were performed in other animal models of Type 2 diabetes and obesity/hyperphagia in the liraglutide program. Dr. Parola describes these studies and their findings in detail under Section 2.6.2.2 of his review (pages 29-42). None of these animal models displays the complete clinical presentation of type 2 diabetes (e.g., some are insulin-deficient but not resistant). More importantly though, these studies were conducted to evaluate several pharmacodynamic endpoints attributed to liraglutide's overall efficacy results (e.g., effects on food consumption, weight loss, pancreatic beta-cell mass). These studies were not toxicology studies and careful histopathology evaluations of pancreatic exocrine and ductal cells were not performed.

The pharmacology/toxicology review team and the Office of Testing and Research (OTR) in CDER are evaluating use of other animal disease models to directly study the effects of incretin-based therapies on the pancreas.

**Cardiovascular Safety**
Safety pharmacology studies evaluating the effects of liraglutide on the CV system included *in vitro* hERG channel studies, *ex vivo* studies in isolated rabbit heart, and *in vivo* studies in conscious telemetered male Sprague Dawley rats and male cynomolgus monkeys. Based on the hERG channel and isolated rabbit heart study, liraglutide was not expected to have a proarrhythmogenic effect which was confirmed in the TQT study discussed under Section 5. In the rat study (single bolus sc injection), liraglutide increased arterial blood pressure and heart rate and decreased body temperature whereas in the monkey study (single bolus sc study), liraglutide had no significant effect on systolic, diastolic, or mean arterial blood pressure, heart rate, ECG intervals or body temperature. Aside from these findings, no adverse effects of liraglutide or correlative histopathology findings on the CV system were noted in the nonclinical CV safety program comprised of healthy animals.

# 5. Clinical Pharmacology/Biopharmaceutics

*Please see the following finalized reviews for a complete discussion of Clinical Pharmacology/Biopharmaceutics issues:*

- *Clinical Pharmacology/Pharmacometrics Review by Drs. Khurana, Jain, Qiu, Madabushi, and Tornoe dated April 22 2009*
- *DSI memos by Dr. Subramaniam dated February 18, 2009 and Dr. Capron dated March 9, 2009*
- *Memo to File by Drs. Khurana and Choe dated August 13, 2009*

**PK Characteristics**
In a study evaluating single, ascending doses administered subcutaneously in healthy male subjects, maximum concentrations across the 9 different doses (range 1.25 to 20 ug/kg) studied were achieved between 9 to 12 hrs. The elimination half-life ranged from 11 to 15 hrs and liraglutide exposure increased proportionally with increasing doses (See Section 2.2.1 of OCP review). These PK characteristics were similar between the Phase 3 formulations tested and the to-be-marketed formulation. In a multiple-dose study, liraglutide $AUC_{0-24}$ increased by approximately 1.5-fold from Day 1 to Day 11.

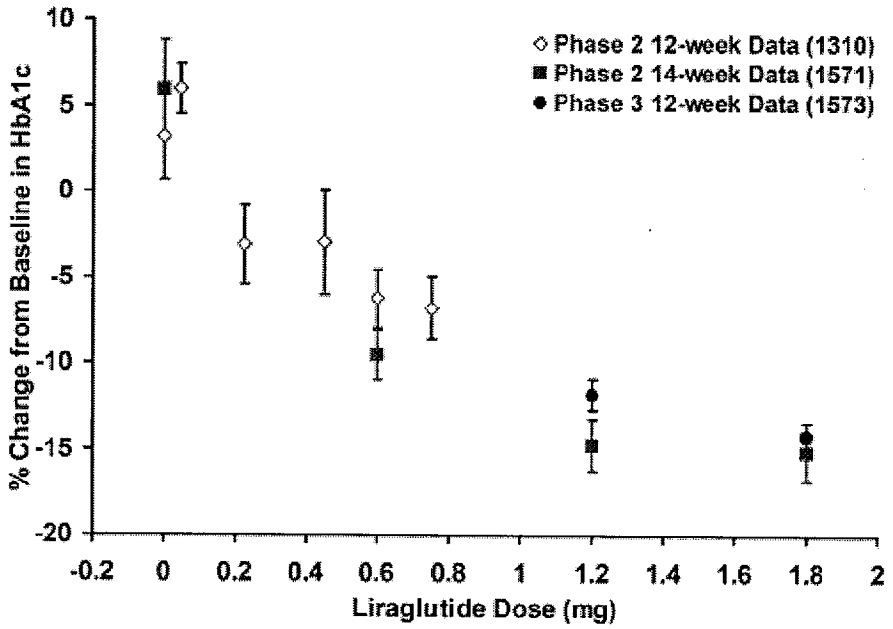
The relative bioavailability of liraglutide after s.c. injection at three different sites (thigh, upper arm, and abdomen) was evaluated and AUCs were lower in the thigh and upper arm relative to abdomen. Injection in the thigh appeared to provide the lowest exposures of liraglutide; however, OCP has concluded that the difference is not clinically meaningful. Of note, the Phase 3 clinical trials allowed for patients to rotate the sites of injection.

Overall, the PK characteristics support once-daily dosing of liraglutide.

**PD Findings Supporting Dose Selection**

The pharmacometrics review from OCP details the exposure-response relationship of liraglutide in the type 2 diabetic population and concludes that the doses selected for Phase 3 and marketing are appropriate. Since maximal HbA1c reduction is achieve by Week 12, data at this timepoint in a Phase 3 monotherapy study were compared with a 12 to 14-week Phase 2 trial and graphically represented in the figure below (obtained from FDA pharmacometrics review conducted by Drs. Khurana and Madabushi).

**Figure 2. Dose dependent increase in effectiveness of liraglutide based on Mean(±SE) %change from baseline in HbA1c from 12-week Phase 2 trial (1310), 14-week Phase 2 trial (1571), and 12-week data from the 52-week Phase 3 confirmatory trial (1573)**




As concluded by Drs. Khurana and Madabushi, there was a dose-dependent reduction in HbA1c from Baseline across the 3 doses proposed for marketing. The numerical advantage of 1.8 mg over 1.2 mg cited by the OCP reviewers is barely discernable in the above figure. The clinical and statistical reviews of the pivotal Phase 3 studies further show that any greater mean reduction of 1.8 mg over 1.2 mg is accompanied by overlap in the confidence intervals between these two doses.

**Metabolism/Elimination**
Liraglutide is fully metabolized in the body by the ubiquitous serine protease enzyme, dipeptidyl peptidase IV, and by neutral endopeptidases. No unchanged liraglutide is detected in urine or feces.

**Thorough QT Evaluation (See Section 2.2.3 of OCP Review)**
A Thorough QT study was conducted with liraglutide 1.2 and 1.8 mg doses and no significant effect on QT prolongation was noted with either doses. Of note, supraphysiologic doses of liraglutide were not studied due to tolerability issues. Because there is little potential for any drug-drug interaction due to CYP P450 inhibition and exposures are lower in certain special populations of clinical relevance in diabetes (e.g., renal impaired patients), it can be concluded that the TQT study appropriately evaluated the potential for QT prolongation and torsades for liraglutide.

**Potential for Drug-Drug Interactions**
Based on *in vitro* studies using human liver microsomes, liraglutide is not expected to cause any drug-drug interactions via the cytochrome P450 pathway.

Since liraglutide has an effect on gastric motility, DDI studies were conducted with several compounds representative of the different Biopharmaceutics Classification Systems (BCS) categories I-IV (paracetamol, atorvastatin, griseofulvin, lisinopril, and digoxin). For the most part, AUC of these drugs, given under steady state conditions of liraglutide, remained unchanged but Cmax was decreased and Tmax was delayed. Griseofulvin Cmax increased 37% and digoxin Cmax and AUC decreased by 31% and 16%, respectively. The results of these DDI studies are summarized in Table 20 in the OCP review.

The effect of liraglutide on oral contraceptives was also evaluated in a study involving ethinylestradiol and levonorgestrel. Cmax of both these components were lowered slightly (12 and 13%, respectively), AUC of ethinylestradiol remain unchanged while levonorgestrel AUC was increased by 18%.

No recommendations for dose adjustments or timing of co-administration of drugs were made based on findings from these DDI studies.

**Use in Special Populations**
*Renal impairment*
The renal PK study evaluated a single dose (0.75 mg) of liraglutide in patients with normal renal function or mild, moderate, severe, or end-stage renal impairment (based on GFR estimated by Cockcroft-Gault equation). Liraglutide exposure across the 4 different stages of renal impairment, relative to patients with normal renal function, was approximately 19-35% lower. OCP is not recommending any special dosing in patients with renal impairment although labeling recommendations are that caution be used in patients with renal impairment due to the sparse number of patients with renal disease evaluated in the clinical development program.

*Hepatic impairment*
The pharmacokinetics of liraglutide were evaluated in patients with mild, moderate or severe hepatic impairment compared to healthy volunteers. Lower Cmax and $AUC_{0\text{-}inf}$ were observed across the spectrum of hepatic impaired patients relative to healthy individuals. No special dosing is recommended in patients with hepatic impairment although labeling will recommend caution when using liraglutide in these patients due to the limited data from the clinical development program.

*Weight*
Body weight was found to be a significant predictor of apparent clearance of liraglutide wherein increasing body weight is associated with increasing clearance and decreasing exposure of liraglutide. In contrast, BMI did not have any effect on liraglutide clearance. The OCP reviewers concluded that these findings are not clinically significant and no weight-based dose adjustements are necessary over the range of 40 to 160 kg. Their conclusions are based on drug concentration levels observed in patients with body weight 160kg which were above the concentration levels needed to achieve maximal HbA1c reduction. As noted by Dr. Joffe, the analyses of the Phase 3 trials showed no difference in efficacy based on baseline weight.

**Conclusions/Recommendations from OCP/DCP-2**
The final conclusion from the Office of Clinical Pharmacology/Division of Pharmacology 2 is that the submitted in support of this NDA is acceptable. No postmarketing commitements or requirements were requested.

# 6. Clinical Microbiology

Drs. Riley and McVey conducted the microbiology review for this application and have identified no deficiencies precluding approval. Please see their review dated March 10, 2009.

# 7. Clinical/Statistical-Efficacy

*Please see the following finalized reviews for a complete discussion of Clinical/Statistical Efficacy issues:*

- *Clinical efficacy review by Dr. Lisa Yanoff dated August 13, 2009*
- *Statistical reviews by Dr. Janice Derr dated May 20, 2009 and August 14, 2009*
- *Cross-discipline team leader memo by Dr. Hylton Joffe dated October 9, 2009*

Please see the primary medical review of efficacy prepared by Dr. Lisa Yanoff, the statistical review prepared by Dr. Janice Derr, and the CDTL memo by Dr. Hylton Joffe, for a complete discussion of the clinical trial designs, conduct, and efficacy findings. This section of my memo will provide the overview of these trials, key efficacy findings, and whether any additional studies are necessary to better characterize the effectiveness of liraglutide in the treatment of T2DM.

Conclusions on efficacy are based primarily on 5 pivotal Phase 3 trials. Dr. Yanoff has described the Phase 2 studies in her review and Section 5 in this memo has also briefly

described these studies which were relied upon for selection of doses studied in Phase 3. I will only focus on the 5 pivotal Phase 3 trials in this section of my memo.

Table 7.1 summarizes these 5 studies. All 5 studies were randomized, controlled, and double-blind. The controls varied as described in the table below. Except for Study 1573, which had a treatment period of 52 weeks, all others were 26-week trials. Several of these studies had open-label extensions which will not be discussed under the efficacy section of this memo.

**Table 7.1 Summary of Pivotal Phase 3 Studies**

| Study # | Treatment Groups | Background Therapy | Mean Baseline HbA1c | Mean Duration of Diabetes (yrs) |
|---|---|---|---|---|
| **Monotherapy** | | | | |
| Study 1573 | Lira 1.2 mg<br>Lira 1.8 mg<br>Glimepiride 8 mg | Diet and exercise | 8.2 | 5.4 |
| **Add-on to Single OAD (Dual Therapy)** | | | | |
| Study 1572 | Lira 0.6 mg + met 2g<br>Lira 1.2 mg + met 2g<br>Lira 1.8 mg + met 2g<br>Metformin 2g<br>Glimepiride 4mg + metformin 2g | Metformin | 8.4 | 7.4 |
| Study 1436 | Lira 0.6 mg + glim 4mg<br>Lira 1.2 mg + glim 4mg<br>Lira 1.8 mg + glim 4mg<br>Glimepiride 4 mg<br>Rosiglitazone 4 mg + glim 4mg | Glimepiride | 8.4 | 7.9 |
| **Add-on to Two OADs (Triple Therapy)** | | | | |
| Study 1574 | Lira 1.2 mg + met 2g + rosi 8 mg<br>Lira 1.8 mg + met 2g + rosi 8 mg<br>Metformin 2g + rosi 8 mg | Metformin + rosiglitazone | 8.5 | 9.0 |
| Study 1697 | Lira 1.8 mg + glim 4 mg + met 2g<br>Glim 4 mg + met 2 g<br>Insulin glargine + glim 4 mg + met 2g | Metformin + glimepiride | 8.3 | 9.4 |

The primary efficacy endpoint in all these trials was change from Baseline in HbA1c after 52 weeks of treatment (Study 1573 only) or 26 weeks of treatment (remaining 4 trials). The inclusion and exclusion criteria have been summarized by Dr. Yanoff in her review. The range of HbA1c allowed for study enrollment was similar across the 5 trials. These Phase 3 studies evaluated use of liraglutide as monotherapy and as add-on to another OAD or two other OADs. As such, the mean duration of diabetes at Baseline varied across these trials with the shorter duration noted in the patients eligible for monotherapy whereas the triple therapy studies enrolled patients with more severe disease and the longest duration of diabetes (See Table 7.1)

Three doses of liraglutide were studied in the Phase 3 trials: 0.6, 1.2, and 1.8 mg. The clinical and statistical reviewers have concluded that the 0.6 mg dose demonstrates minimal efficacy and is being proposed for marketing to enable titration to the more effective doses of 1.2 and

1.8 mg. I will not present the efficacy findings of 0.6 mg and refer the reader to the primary reviews for these data. The titration scheme for liraglutide is also described in Dr. Yanoff's review. I will only point out that the scheme proposed by the applicant was designed for a rapid progression to the 1.2 or 1.8 mg doses to enable their evaluation in parallel treatment study designs. Upward titration in this program was based solely on tolerability; there are no data to inform us how long to treat at liraglutide 1.2 mg before proceeding to the 1.8 mg dose due to lack of efficacy. This observation is not a deficiency precluding approval but will be addressed under the labeling discussion in Section 12.

**Study 1573**

Study 1573 was the only monotherapy Phase 3 study in this development program. It also differed in that it had the longest double-blind controlled period of 52 weeks compared to 26 weeks with all other Phase 3 trials. This was a multicenter study which randomized 746 patients with T2DM 1:1:1 to liraglutide 1.2 mg qd (n=247), liraglutide 1.8 mg qd (n=251), or glimepiride 8 mg qd (n=248). 36.5% of the patients were on diet and exercise only at Baseline and 63.5% were being treated with a single oral agent for at least two months. All previous anti-diabetic therapies were discontinued prior to randomization but there was no washout period. The mean Baseline HbA1c was 8.2 with approximately 30% of patients with values ≤ 7.5% at Baseline. This high proportion of patients with reasonably controlled diabetes at Baseline may reflect the absence of a washout period and the carry-over effect of prior OADs or a population that had a shorter duration and less severe disease.

65.3% of the randomized population completed the 52-week trial. More patients in the glimepiride group (10.1%) withdrew due to the reason "ineffective therapy" compared to the liraglutide groups (3.6 and 6%). This observation is considered supportive of liraglutide's greater efficacy over glimepiride in this study population. Table 7.2 summarizes the primary efficacy findings from this trial.

**Table 7.2 Study 1573 - Primary Efficacy Results (LOCF, ITT population)**

| Treatment Group | N | LS Mean Chg from Baseline (SEM) | LS Mean Treatment Difference (95% CI) | p-value |
|---|---|---|---|---|
| Liraglutide 1.2 mg | 236 | -0.84 (0.080) | -0.33 (-0.53,-0.13) | 0.0014 |
| Liraglutide 1.8 mg | 234 | -1.14 (0.081) | -0.62 (-0.83,-0.42) | <0.0001 |
| Glimepiride 8 mg | 241 | -0.51 (0.077) | | |

Both clinical and statistical reviewers have concluded that both doses of liraglutide, 1.2 and 1.8 mg, provide superior efficacy compared to glimepiride 8 mg with respect to HbA1c reduction. I concur with their conclusions.

**Study 1572**

Study 1572 evaluated the efficacy of liraglutide added on to metformin 1.5 to 2 g compared to placebo or glimepiride 4 mg. Prior to study enrollment, patients could have been treated with a single agent (35.3%) or combination therapy (64.7%) for at least 3 months. After screening, patients entered a forced metformin titration period followed by 2-week double-blind titration of liraglutide or glimepiride then a 24-week double-blind maintenance period (See Figure 6.3 from Dr. Yanoff's review). A total of 1,091 patients were randomized to liraglutide 0.6 plus met (n=242), lira 1.2 plus met (n=241), lira 1.8 plus met (n=242), metformin only (n=122) or

metformin plus glimepiride (n=244). In practical terms, this study might inform practitioners on what efficacy can be expected in patients not adequately controlled on metformin monotherapy if the patient:

1. remains on metformin monotherapy;
2. has glimepiride added-on to metformin; or
3. has one of three doses of liraglutide added-on to metformin.

Mean Baseline HbA1c was 8.4. Approximately 86% of patients completed this trial with discontinuation due to lack of efficacy highest in the placebo group (23.8%) followed by liraglutide 0.6 mg (7.9%) and similar rates in the two higher doses of liraglutide (3.3% and 5.4%) and glimepiride (3.7%).

The primary objective of this trial was to demonstrate that combination therapy of liraglutide and metformin provided greater glycemic control than metformin monotherapy and was non-inferior to combination therapy of glimepiride and metformin. Dr. Derr has described under Section 3.1.5 of her review the applicant's approach towards controlling for multiple comparisons. Table 7.3 summarizes the primary efficacy findings from this trial.

**Table 7.3 Study 1572 – Primary Efficacy Results (LOCF, ITT population)**

| Treatment Group | N | LS Mean Chg from Baseline (SEM) | Lira or Glim vs Pbo LS Mean Treatment Difference (95% CI) | Lira vs Glim LS Mean Treatment Difference (95% CI) |
|---|---|---|---|---|
| Lira 0.6 + metformin | 239 | -0.70 (0.067) | -0.78 (-0.99, -0.57) | 0.29 (0.12, 0.46) |
| Lira 1.2 + metformin | 232 | -0.97 (0.069) | -1.06 (-1.27, -0.85) | 0.01 (-0.16, 0.19) |
| Lira 1.8 + metformin | 236 | -1.00 (0.066) | -1.09 (-1.30, -0.88) | -0.02 (-0.19, 0.15) |
| Metformin only | 120 | 0.08 (0.090) | -- | -- |
| Glimepiride + metformin | 234 | -0.99 (0.068) | -1.07 (-1.28, -0.86) | -- |

All three doses of liraglutide added on to metformin provided greater efficacy than metformin alone as noted in the 4th column of Table 7.3 in which the 95% CIs all excluded zero. Comparison of liraglutide to glimepiride using a non-inferiority margin of 0.4 revealed that the liraglutide 1.2 and 1.8 mg doses were non-inferior to glimepiride as the upper bound of the 95% CI excluded 0.4. Liraglutide 0.6 mg was not non-inferior to glimepiride, with the results showing inferiority.

Dr. Yanoff noted that the highest dose of glimepiride (8 mg) was not studied in this trial; however, as she also pointed out, maximal efficacy is typically achieved with the 4 mg dose.

The applicant was able to achieve the primary objective of this trial. My clinical interpretation of these results is that the addition of liraglutide 1.2 or 1.8 mg to metformin in patients who have no achieved adequate glycemic control will afford greater efficacy than continuing therapy with metformin alone. This is not an unexpected finding as greater efficacy is often seen when two OADs with different mechanisms of action typically confer greater HbA1c reductions than the single agent. However, these data would also lead me to conclude that choosing glimepiride over liraglutide would not result in any difference in efficacy, and that the decision here should be based on individual safety concerns, tolerability concerns (including oral versus injectable drug) and costs.

**Study 1436**

Similar to Study 1572, Study 1436 was designed to evaluate the efficacy of liraglutide added-on to glimepiride compared to placebo or rosiglitazone 4 mg/day. After screening, eligible patients who have received treatment with OADs for at least 3 months were discontinued from these prior therapies and entered a forced glimepiride titration period to achieve a dose of 4 mg/day, if tolerated. This was followed by a titration period for liraglutide dosing. A total of 1,041 patients were randomized to liraglutide 0.6 mg plus glimepiride 4 mg (n=233), lira 1.2 mg plus glim 4 mg (n=228), lira 1.8 mg plus glim 4 mg (n=234), glimepiride monotherapy (n=114), glimepiride 4 mg plus rosiglitazone 4 mg (n=232). In practical terms, this study might inform practitioners on what efficacy can be expected in patients not adequately controlled on glimepiride monotherapy if the patient:

1. Remains on glimepiride monotherapy
2. Has rosiglitazone added on to glimepiride therapy
3. Has one of three doses of liraglutide added on to glimepiride monotherapy

Mean Baseline HbA1c was 8.4. Approximately 86% of the randomized population completed the trial. Discontinuation due to lack of efficacy was highest in placebo (17.5%) followed by rosiglitazone (6.9%) and liraglutide 0.6 mg (5.2%). Three to 3.5% of patients in the two higher dose groups of liraglutide discontinued due to lack of efficacy.

**Table 7.4 Study 1436 – Primary Efficacy Results (LOCF, ITT population)**

| Treatment Group | N | LS Mean Chg from Baseline (SEM) | Lira or RSG vs Pbo LS Mean Treatment Difference (95% CI) | Lira vs RSG LS Mean Treatment Difference (95% CI) |
|---|---|---|---|---|
| Lira 0.6 + glimepiride | 224 | -0.60 (0.071) | -0.83 (-1.07, -0.60) | -0.16 (-0.35, 0.02) |
| Lira 1.2 + glimepiride | 223 | -1.08 (0.072) | -1.31 (-1.54, -1.08) | -0.64 (-0.82, -0.45) |
| Lira 1.8 + glimepiride | 226 | -1.13 (0.072) | -1.36 (-1.60, -1.13) | -0.69 (-0.88, -0.51) |
| Glimepiride only | 107 | 0.23 (0.100) | -- | -- |
| Glimepiride + rosiglitazone | 224 | -0.44 (0.071) | -0.67 (-0.90, -0.44) | -- |

All three doses of liraglutide added on to glimepiride resulted in significantly greater HbA1c reduction than glimepiride alone, as evidenced by the confidence interval around the mean treatment difference excluding zero. When liraglutide was compared to rosiglitazone 4 mg, the liraglutide 1.2 and 1.8 mg doses achieved statistically significantly greater HbA1c reductions than rosiglitazone and the 0.6 mg dose had a greater mean reduction with the upper bound of the 95% CI around the treatment difference suggesting non-inferiority. However, both Drs. Yanoff and Derr emphasized that only half the maximal approved dose of rosiglitazone was studied in this trial. Consequently, labeling should not allow a claim of superiority of liraglutide over rosiglitazone and it may be better to not include the results summarized in the last column in Table 7.4 in labeling.

Similar to Study 1572, I interpret the results from Study 1436 as evidence that liraglutide will provide improved glycemic control if prescribed to patients who have failed to achieve adequate control with glimepiride monotherapy. Choosing liraglutide over rosiglitazone as add-on therapy in this situation may not necessarily provide greater efficacy since the 8 mg

dose of rosiglitazone was not studied. In the absence of such data, it can not be concluded that the two agents would provide comparable efficacy either.

**Study 1574**

Study 1574 evaluated the effect of adding liraglutide 1.2 or 1.8 mg on to two other OADs, metformin 2 g daily and rosiglitazone 8 mg daily, compared to the dual combination of metformin and rosiglitazone. Patients could have received OADs and/or exenatide for at least 3 months prior to screening; approximately 83% of patients were on combination OAD prior to enrollment. After discontinuation of prior therapies, patients entered a forced titration period. All patients had a 6-week maintenance period with rosiglitazone 8 mg and metformin 2 g prior to randomization at Week 0. 533 patients were randomized to liraglutide 1.2 mg plus met/rosi combination (n=178), liraglutide 1.8 mg plus met/rosi combination (n=178) or placebo plus met/rosi combination (n=177). A total of 76.4% of patients completed this 26-week trial. Discontinuation due to ineffective therapy was highest with the placebo treatment (16.4%) compared to 1.7% with each of the liraglutide treatment groups.

**Table 7.5 Study 1574 – Primary Efficacy Results (LOCF, ITT population)**

| Treatment Group | N | LS Mean Chg from Baseline (SEM) in HbA1c | LS Mean Treatment Difference (95% CI) |
|---|---|---|---|
| Lira 1.2 + Met2g/rosi8mg | 174 | -1.48 (0.078) | -0.94 (-1.12, -0.76) |
| Lira 1.8 + Met2g/rosi8mg | 177 | -1.48 (0.075) | -0.94 (-1.12, -0.75) |
| Met 2g /rosi8mg | 167 | -0.54 (0.080) | -- |

The addition of liraglutide 1.2 or 1.8 mg to metformin 2g daily and rosiglitazone 8mg daily achieved significantly greater HbA1c reduction than the dual combination therapy. Unlike the other trials which were able to demonstrate a numerically greater effect with the liraglutide 1.8 mg dose over the 1.2 mg dose (albeit not significantly different from one another), this trial essentially showed identical response of the two doses.

This trial did not have a concurrent active control group.

**Study 1697**

Study 1697 also evaluated the effect of liraglutide as an add-on therapy to two OADs, metformin and glimepiride. However, unlike Study 1574, only one dose of liraglutide was tested (1.8 mg). In addition to the placebo-control arm, this study included insulin glargine in an active comparator arm. Practically all of the patients enrolled in this study (94.3%) received prior combination therapy which was discontinued at screening and a force-titration period of metformin and glimepiride was initiated to achieve a 2 g daily and 4 mg daily dose, respectively.

581 patients were randomized to liraglutide 1.8 mg plus met/glim (n=232), placebo plus met/glim (n=115), or insulin glargine plus met/glim (n=234). Approximately 90% completed the trial with the highest discontinuation rate due to ineffectiveness observed in the placebo group (11.3%) followed by similar low rates in lirgalutide (n=2; 0.9%) and glargine (n=1; 0.4%).

Patients randomized to the glargine treatment arm could adjust their insulin dose 2 times weekly based on self-measured fasting plasma glucose levels and following a titration guideline (See Table 6.6, page 53 from Dr. Yanoff's review). The FPG goal was ≤ 100 mg/dL with incremental increases in insulin dose for values > 100 and > 120. Only approximately 40% of patients on the glargine treatment arm achieved a FPG at Wk 26 of < 120 mg/dL and even fewer patients (~20%) achieved a goal of ≤ 100 mg/dL.

**Table 7.6 Study 1697 Primary Efficacy Results (LOCF, ITT population)**

| Treatment Group | N | LS Mean Chg from Baseline (SEM) in HbA1c | Lira vs Placebo LS Mean Treatment Difference (95% CI) | Lira vs Glargine LS Mean Treatment Difference (95% CI) |
|---|---|---|---|---|
| Lira 1.8 mg + met/glim | 224 | -1.33 (0.088) | -1.09 (-1.28, -0.90) | -0.24 (-0.39, -0.08) |
| Metformin + glim | 110 | -0.24 (0.106) | -- | -- |
| Glargine + met/glim | 225 | -1.09 (0.090) | -- | -- |

As summarized in Table 7.6, the addition of liraglutide 1.8 mg daily to the dual combination of metformin 2 g daily and glimepiride 4 mg daily provided significantly greater reductions in HbA1c than the dual combination alone. The efficacy results also show significantly greater reductions in HbA1c with liraglutide compared to insulin glargine. The absolute treatment difference is more modest (-0.24) between liraglutide and glargine and it did not appear that many patients randomized to glargine received maximal upward titration in their insulin dose to meet a targeted FPG of < 100 mg/dL. Given these findings, any conclusion of superiority over insulin should be made with caution. Although I would note that the liraglutide treatment group had a mean weight change of -1.81 kg whereas the glargine treatment group had a +1.62 kg change from Baseline. The difference between the two treatment groups was statistically significant. The favorable effect on weight loss may make liraglutide a more desirable treatment option over insulin.

Each of the pivotal studies also evaluated several secondary efficacy endpoints. Dr. Yanoff has described these in detail in her review, including changes in body weight. I would note that the applicant has a separate clinical development program for liraglutide as a weight-loss drug. Dr. Derr has summarized the changes in body weight across the 5 trials in Exhibitis 1-5 of her review.

Overall, liraglutide provides a greater average weight loss compared to the active comparators, rosiglitazone, glimepiride, and glargine. With exception for Study 1574, the placebo (refers to background treatment group) treatment groups display an average weight loss throughout the study duration but the reductions were of a lesser degree than the liraglutide 1.8 mg dose group. In Study 1574, background therapy involved metformin 2g and rosiglitazone 8mg, which may have accounted for the weight gain observed in this placebo arm. These findings alongside the HbA1c efficacy results summarized earlier would support the conclusion that the selection of liraglutide over another anti-diabetic therapy may result in similar glycemic control. However, the choice of the other anti-diabetic therapies in these studies were all associated with weight gain of 1-2 kg, as opposed to weight reductions ranging between 0.2 to 2.8 kg with liraglutide. Although these findings are suggestive of an advantage of liraglutide over the tested comparators, not every patient treated with liraglutide experienced weight loss.

# 8. Safety

*Please see the following finalized reviews for a complete discussion of Clinical Safety issues:*

- *Clinical Safety Review by Dr. Karen Mahoney dated August 6, 2009*
- *Addendum to Dr. Mahoney's review dated August 14, 2009*
- *Cross-Discipline Team Leader Memo by Dr. Hylton Joffe dated October 9, 2009*

In this section of my memo I will focus primarily on safety findings which have contributed to the final recommendation of non-approval by Dr. Mahoney. In addition, I will summarize events that are evolving safety concerns with the incretin-based therapies. Please see Dr. Mahoney's review for this NDA for a complete presentation of the safety evaluation and other findings for this NDA not highlighted in my memo. Please also refer to Dr. Joffe's CDTL memo which provides a very succinct overview of the clinical safety findings for liraglutide.

**Cardiovascular Safety**

"Inadequate data to assess the risk of major adverse cardiovascular events in humans" was one of two reasons cited by Dr. Mahoney in her Executive Summary for not recommending approval of this application. Under Section 7.1.3.3.1.8 (page 108), Dr. Mahoney summarizes her observations regarding major adverse CV events in this program, which I have interpreted as contributing to her recommendation. Specifically, it appears that the following were relevant to her recommendation: the liraglutide program was not prospectively designed and lacked a pre-defined adjudication plan to evaluate CV risk; the population enrolled was at low risk for a CV event with a resultant low number of MACE events; the development program was not designed to facilitate a proper meta-analysis of many Phase 2 and 3 trials; there were inconsistent results in the CV risk analyses depending upon the choice of comparator (placebo or active control); and the overall vote from the advisory committee with emphasis on the 'no' vote by the only two cardiologists on the panel as well as the biostatistician.

As stated in the Background section of this memo, the FDA issued a Guidance to Industry in December 2008, which requested a dedicated assessment of cardiovascular risk for all therapeutics developed for the treatment of Type 2 diabetes. The FDA stated that this guidance would apply to all therapies in development, including those with marketing applications pending before the agency at the time the guidance was issued. The basis for inclusion of pending applications under this new regulatory environment was because there were already 10 classes of anti-diabetic therapies available for the treatment of T2DM and that introduction of any new molecular entities (NME) to the market should not carry similar CV safety concerns raised in recent years with other approved agents.

It is important to point out that guidances represent the Agency's current thinking on a particular topic. As stated upfront in every guidance document, "You can use an alternative approach if the approach satisfies the requirements of the applicable statues and regulations." This newly-issued guidance is neither a regulation nor a part of any statute. As stated by Dr. Curtis Rosebraugh before the advisory committee panel members, this guidance is not a requirement. Indeed, it would have been an *unjust* requirement on FDA's part to mandate every aspect of this new guidance to the 3 NDAs under review during this time period. Not only were the Phase 2 and 3 trials designed to support the approval of these drugs completed prior to December 2008, but these programs were conducted with the guidance of the FDA and

submitted to the FDA in advance of the issuance of this guidance. And to this extent, recommendations in the guidance for a planned program that enables the performance of a meta-analysis across the different clinical trials, establishing an independent CV endpoints committee for prospective adjudication of events in a blinded fashion, and enrollment of selected patients at higher risk for CV events would have been unreasonable expectations for which the companies would have all failed to meet.

It should not be construed, however, that FDA disregarded the importance of this guidance in considering these three applications. In fact, one of the three NDAs was deemed deficient in meeting a critical recommendation from this guidance and received a Complete Response action letter with an expectation that a dedicated CV safety trial be conducted before consideration for approval. This critical recommendation was the following, excerpted from the guidance:

- *Sponsors should compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8. This can be accomplished in several ways. The integrated analysis (meta-analysis) of the phase 2 and phase 3 clinical trials described above can be used. Or, if the data from all the studies that are part of the meta-analysis will not by itself be able to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8, then an additional single, large safety trial should be conducted that alone, or added to other trials, would be able to satisfy this upper bound before NDA/BLA submission. Regardless of the method used, sponsors should consider the entire range of possible increased risk consistent with the confidence interval and the point estimate of the risk increase. For example, it would not be reassuring to find a point estimate of 1.5 (a nominally significant increase) even if the 95 percent upper bound was less than 1.8.*

- *If the premarketing application contains clinical data that show that the upper bound of the two-sided 95 percent confidence interval for the estimated increased risk (i.e., risk ratio) is between 1.3 and 1.8, and the overall risk-benefit analysis supports approval, a postmarketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3. This can be achieved by conducting a single trial that is adequately powered or by combining the results from a premarketing safety trial with a similarly designed postmarketing safety trial. This clinical trial will be a required postmarketing safety trial.*

As noted in the reviews of Drs. Mahoney and Joffe, the FDA recognized that the meta-analysis conducted by these NDAs "caught in the middle" of a change in regulatory guidance would be fraught with methological challenges. However, the review division applied a consistent approach to identifying clinically relevant CV events which might be considered MACE events to provide a level playing field in the review of these three applications. Dr. Mahoney has described this approach in detail under Section 7.1.3.3.1.3 (page 50) of her review and this

"FDA Custom MACE" was discussed publicly at the April 1 and 2, 2009, advisory committee meeting for this NDA and the recently approved NDA for Onglyza® (saxagliptin). For all three applications, FDA considered the primary analysis for CV safety would be based on FDA Custom MACE events occurring during the controlled portions of the completed Phase 2 and 3 clinical trials. For this reason, I will focus primarily on the findings based on FDA Custom MACE events observed in Population A (controlled portions of completed Phase 2/3 liraglutide trials). Because there are not marked differences between the FDA's and applicant's analyses, I will present the FDA analyses and refer the reader to Tables 7.1.3.3.1.3.2 through 7.1.3.3.1.3.7 in Dr. Mahoney's review for a summary of the applicant's analyses.

In her review of CV safety, Dr. Janice Derr from the FDA's Office of Biometrics calculated the incidence ratio based on the percentage of patients with events in liraglutide versus the percentage of patients with events in the comparator group. Calculation of the 95% CI surrounding this incidence ratio was based on two different statistical methods: an exact analysis or a fixed-effects Mantel-Haenszel analysis with continuity correction for 0 events. Both methods stratified by study. The different methods were selected to evaluate the sensitivity of the upper bound of the 95% CI.

Data were presented by the following categories by choice of comparator:

1. Liraglutide vs Total Comparator (placebo and active control)
2. Liraglutide vs Placebo
3. Liraglutide vs Active Control

As noted above, the guidance does not specify what the control group is comprised of (i.e., placebo or active control) and more importantly, it does not require the applicant meet the specified upper 95% CI boundary for subgroups. Regardless, the following tables summarize the FDA findings for all three categories.

**Table 8.1 FDA Analyses (Exact Method) of FDA Custom MACE Endpoint in Completed Phase 2 and 3 Controlled Trials (adapted from Dr. Janice Derr's review)**

| Choice of Comparator | # of studies included in the analysis (with at least 1 event in the comparator group) | % of cases excluded from analysis (studies with 0 events in comparator group) | Actual Number of Events | | Incidence Ratio (95% CI) |
|---|---|---|---|---|---|
| | | | Liraglutide | Comparator | |
| Liraglutide vs Pbo | 5 of 12 | 25.6% | 9 | 3 | 0.78 (0.19, 4.76) |
| Liraglutide vs. Active Control | 7 of 9 | 1.9% | 12 | 10 | 0.68 (0.26, 1.83) |
| Liraglutide vs. Ttl Comparator | 8 of 15 | 18.1% | 13 | 13 | 0.72 (0.30, 1.74) |

**Table 8.2 FDA Analyses (Fixed-Effects Method) of FDA Custom MACE Endpoint in Completed Phase 2 and 3 Controlled Trials (adapted from Dr. Janice Derr's review)**

| Choice of Comparator | # of studies included in the analysis (with at least 1 event in the comparator group) | % of cases excluded from analysis (studies with 0 events in comparator group) | Actual Number of Events | | Incidence Ratio (95% CI) |
|---|---|---|---|---|---|
| | | | Liraglutide | Comparator | |
| Liraglutide vs Pbo | 12 of 12 | 0% | 9 | 3 | 0.52 (0.21, 1.25) |
| Liraglutide vs. Active Control | 9 of 9 | 0% | 12 | 10 | 0.60 (0.27, 1.31) |
| Liraglutide vs. Ttl Comparator | 15 or 15 | 0% | 13 | 13 | 0.63 (0.32, 1.24) |

Overall, the actual number of events was small with only 26 MACE events noted in both liraglutide and total comparators. The upper bound of the 95% CI was affected by the different statistical methods used in estimating risk. In the exact method, studies with zero events were excluded and the upper bound of the 95% CI exceeded 1.8 in the two subgroup comparisons of liraglutide vs placebo and liraglutide vs active control (red font in Table 8.1) but just fell below this goal post in the comparison to total comparators. In the fixed-effects method, all studies contributed data in the analysis because studies with zero events in one or both groups were assigned a continuity correction of 0.5. This resulted in the upper bound of the 95% CI falling below 1.8 in every category of comparator group.

I concur with Dr. Mahoney that the shifting upper bounds of the CI likely reflected the low event rates; however, I do note that in all FDA analyses of the population of primary interest, the point estimates are below 1.0. Dr. Mahoney does discuss analyses in which point estimates are > 1.0 (but with CIs including 1.0) but these are analyses including the open-label extension studies (referred to as Population B by the applicant) or the Broad SMQ endpoint. A finding of a point estimate exceeding 1.0 was confined only to the liraglutide vs placebo comparison. In three of these scenarios, the point estimate was 1.02 to 1.04. One analysis using the exact method noted a point estimate of 1.10 with an accompanying 95% CI of 0.56-2.31 (See Table 7.1.3.3.1.3.12 in Dr. Mahoney's review). None of these results signify excess CV risk.

In all analyses (FDA's and Novo Nordisk's) of liraglutide vs total comparator, the results yielded point estimates below 1.0 with the upper bound of the 95% CI falling below 1.8 (some below 1.3). Table 8.3 summarizes these findings. Analyses of liraglutide vs total comparator in both Population A and B using the Broad SMQ endpoint also yielded point estimates below 1.0 with the upper bound of the 95% CI below the 1.8 cut-point.

**Table 8.3 Incidence Ratio (95% CI) using Different Statistical Analyses Comparing Liraglutide vs. Total Comparator in Both Population A and B on FDA Custom Endpoint**

| Statistical Method | Population A | Population B |
|---|---|---|
| Asymptotic Mantel-Haenszel (applicant) | 0.72 (0.32-1.61) | 0.79 (0.41-1.54) |
| Exact method (FDA) | 0.72 (0.30-1.74) | 0.80 (0.39-1.64) |
| Fixed-effects meta-analysis (FDA) | 0.63 (0.32-1.24) | 0.71 (0.39-1.30) |

Dr. Mahoney discusses the individual advisory committee member votes under Section 8.5 of her review. It is apparent that many of the committee members had concerns surrounding the low event rates despite some of these same members voting the day before that another anti-diabetic had provided appropriate evidence of CV safety and that perhaps the 'no' votes on the following day were swayed by the analyses by subgroups (Drs. Konstam, Teerlink and Proschan) whereas the other diabetes program had consistent results with the upper bound of the 95% CI clearly excluding 1.8 in all analyses.

Although there are limitations to the CV safety database for this NDA, I recognize that many of these limitations are due to a program that was developed with FDA guidance issued at that time but is now being judged by FDA using a different guidance document. I also find it problematic that so much weight is being placed on a subgroup analysis wherein the CV events are reduced by half of the total number. While some have concluded that this program is inadequate to rule out an unacceptable CV risk, I am reassured that for every analysis conducted there was not an excess risk observed in which the CI excluded 1.0. Furthermore, except for situations in which Population B and/or the Broad SMQ endpoints were considered and limited only to the liraglutide vs placebo analysis, all the point estimates were below 1.0. I am further reassured by the nonclinical program which did not identify a serious CV safety signal despite exposures far exceeding the maximum recommended human dose, including the lifespan carcinogenicity studies.

In my opinion, this NDA has sufficiently demonstrated an acceptable CV risk profile premarketing. However, as the applicant was not able to rule-out an upper bound of the 95% CI of 1.3, it will be required to conduct a dedicated CV safety trial as a post-marketing required study under FDAAA.

**Clinical Findings Related to C-Cell Tumor Risk**

"A strong signal in animals of C-cell tumors of the thyroid gland, with inadequate duration of controlled study in humans to adequately assess the human risk" was the other reason for which Dr. Mahoney is recommending against approval of this NDA. I have already discussed the animal findings of C-cell tumors under Section 4.0. Under this section, I will highlight the results of calcitonin screening in the clinical development program. I will also discuss the impact of calcitonin screening in the setting of clinical uncertainty regarding the animal findings.

Medullary thyroid cancer (MTC) is a neuroendocrine tumor, derived from the parafollicular or C-cells of the thyroid. MTC comprises about 3-10% of all thyroid neoplasms. Approximately 75-80% of the MTC cases occur sporadically while 20-25% are associated with the multiple endocrine neoplasia (MEN) syndromes or are of the familial form (FMTC). Medullary thyroid

cancer within the MEN syndromes and nearly all of the FMTC cases are due to activating germ-line mutations of the rearranged during transfection (RET) proto-oncogene, but up to 6% of sporadic forms of MTC may have this mutation. Somatic RET mutations have been estimated to occur in 20-50% of the sporadic MTC form. There were no cases of MTC observed in the liraglutide treatment group in this clinical development program; however, given the rarity (~600 cases reported per year) of this type of cancer and its long latency period, it is not expected that any typical drug development program would observe a case. The one case of MTC observed in the active-comparator group was likely pre-existing given the elevated calcitonin levels at baseline.

As clinical cases of MTC were not expected to be detected in this program, the applicant implemented calcitonin monitoring, including calcium stimulation testing performed in a subset of the study population. Calcitonin is synthesized and secreted from the C-cells and has been used as a screening and prognostic biomarker for MTC. In Section 7.1.3.3.2.4 of her review, Dr. Mahoney provides a very thorough overview of this biomarker, its clinical utility and factors which impact the specificity of this test in detecting MTC (e.g., chronic renal failure, use of proton pump inhibitors, other thyroid diseases, smoking, and other neoplasms). There is less experience in the use of calcitonin screening for detection of sporadic forms of MTC and no experience with its use for detecting potential drug-induced C-cell tumors. By extension, there is no experience with use of other biomarkers (procalcitonin, CEA) for this purpose.

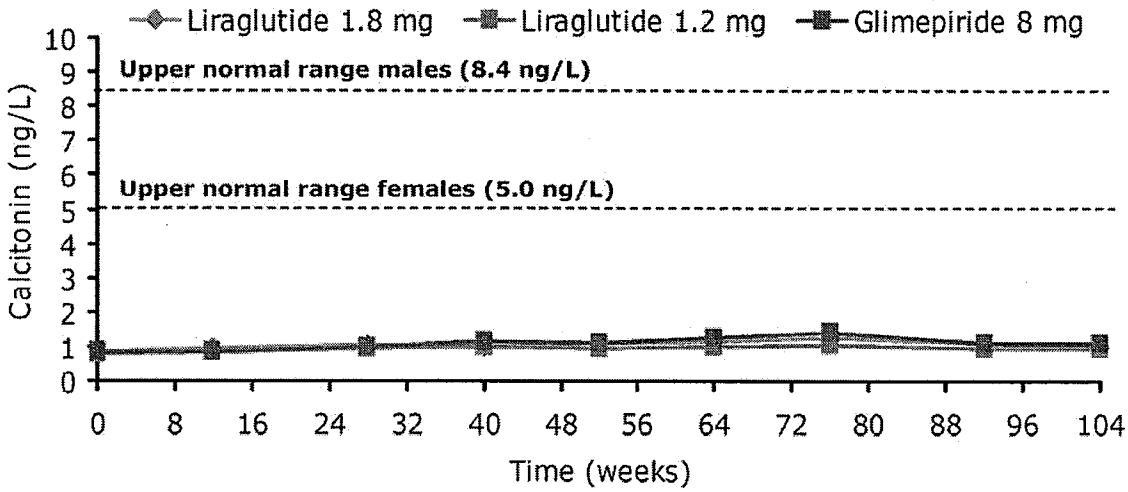
In this development program, the calcitonin assay used had a lower limit of quantification (LLOQ) of 0.7 ng/L, an upper limit of normal (ULN) of 5.0 ng/L for women and 8.4 ng/L for men. In this program, 85% of women and 30% of men had baseline calcitonin levels below the LLOQ.

Dr. Mahoney presented the percentage of patients who had any upward shift in calcitonin levels from baseline to Weeks 26/28 in the 5 Phase 3 trials. She noted a dose-dependent increase in women but not in men, although the highest percentage of upward shift occurred at the 1.8 mg dose in both genders (Table 7.1.3.3.2.4.2 of Dr. Mahoney's review). Similar trends of increasing calcitonin levels in the liraglutide groups versus comparators are noted in different analyses, including a repeated measures analysis performed by the applicant. In this analysis (See Table 7.1.3.3.2.4.5 from Dr. Mahoney's review), the LS Mean calcitonins were higher in the liraglutide groups than active control or placebo at Week 12, and higher than placebo at Week 26. The relative difference between liraglutide and the comparators were accompanied by significant p-values at Week 12. At Week 24, the relative differences between the 3 liraglutide doses and placebo were significant, as was the difference between active control and placebo ($p<0.05$). Not only should these analyses be considered exploratory, but the clinical relevance of these findings is highly questionable given that the majority of mean calcitonins are below 1.0 ng/L with a few hovering around 1.0 ng/L, within the normal reference range for both genders.

I concur with Dr. Mahoney that the duration of the studies in this NDA program are inadequate to fully assess the potential for drug-induced C-cell tumor but there were also calcitonin data beyond Weeks 26/28 which did not show any difference between liraglutide

and comparators. Dr. Mahoney recommends applying caution in interpreting these data as they include extension periods in which there are differential drop-outs and discontinuations resulting in a much lower sample size. However, even at Week 104, there are data in over 500 liraglutide-treated patients and 200 active-control patients (See Table 13 from Dr. Joffe's memo). It is particularly reassuring that the majority of these patients receiving therapy beyond 1 (some over 2 years) have mean calcitonins within the range of 1 to 2 ng/L. In Dr. Joffe's memo, he presented 3 figures provided by the applicant which illustrate the long-term calcitonin data in 3 different clinical trials. I have included one of those figures for illustrative purposes below. In the setting of no clinically meaningful change in calcitonin, the absence or reduced number of controls is less of a concern.

**Figure 8.1 Geometric mean calcitonin values over 2 years in the monotherapy trial Week 0-52 is blinded; Week 52-104 is the open-label, voluntary extension)**




Depending upon the case-series, calcitonins exceeding 30-50 ng/L increase the likelihood of MTC with values exceeding 100 ng/L highly predictive of cancer.[2] In this NDA there were a few patients with calcitonins > 20 ng/L (11 liraglutide, 5 active control, 1 placebo). Dr. Joffe has summarized the clinical details for all these patients. One liraglutide-treated patient had a final calcitonin of 22.4 ng/L with no follow-up data after he was discontinued due to nausea and diarrhea. In the remaining liraglutide-treated patients, calcitonins were either below 20 ng/L at last clinic visit despite continued therapy (n=4) or remained below 30 ng/L (range 20.2 to 25.8 ng/L). The patient with the highest calcitonin (25.8 ng/L) had Hashimoto's thyroiditis, a condition which has been associated with mild elevations in calcitonin. This patient had a normal thyroid ultrasound.

One 1.8 mg liraglutide-treated patient had a serum calcitonin > 50 ng/L at Week 26. Upon request from the FDA, the applicant has furnished additional follow-up data on this patient. Subject 530002 is a 46-year old male who was treated with liraglutide 1.8 mg for

[2] Iacobone M et al. Can sporadic medullary thyroid carcinoma be biochemically predicted? Prospective analysis of 66 operated patients with elevated serum calcitonin levels. *World J Surg* 2002;26:886-890.

approximately 6 months (July 24, 2006 through January 21, 2007). Calcitonin levels during the course of the trial were 10.7 ng/L (Week 0), 30.7 ng/L (Week 12), and 53.5 ng/L at Week 26. Principal Investigator notes of physical exam performed on October 10, 2009 did not report any abnormalities but there was no specific mention of a neck exam. Serum calcitonin performed on that date was 22.3 ng/L (ref range < 8.4 ng/L). Concomitant medications included simvastatin, aspirin, ramipril, clopidigrel, and metformin. Renal impairment noted with an estimated GFR of 56 mL/min. In conclusion, this patient's elevated serum calcitonin declined after study discontinuation but still remained above baseline and ULN nearly two years after liraglutide was discontinued. Contributing factors to this elevation include mild renal impairment. The applicant has recommended that the subject be referred to an endocrinologist for further evaluation of the elevated calcitonin level.

Overall, the calcitonin findings in this NDA were not of great clinical concern. Perhaps the detailed analyses and extensive interpretation of the upward shifts from below the LLOQ to within the range of quantification were a consequence of the nonclinical carcinogenicity findings. In the absence of such animal data, the calcitonin findings in this clinical program would unlikely be considered a potential signal of cancer risk. However, the animal findings of tumor exist and the calcitonin monitoring may have an unintended consequence of thyroidectomies that would have otherwise not been performed.

Under Section 7.1.3.3.2.2.1.2, Dr. Mahoney summarizes the 6 cases of papillary thyroid cancer in the liraglutide-treated patients versus one case in the comparator group. As noted by her, all of the patients underwent surgery because of calcitonin or ultrasound findings performed as part of the clinical trial monitoring. Two of these patients had documented pre-operative calcitonins of 19.4 or 22.3 ng/L, levels for which the likelihood of detecting MTC is low.

Some of these patients along with 3 additional ones discussed separately in Dr. Mahoney's review had pathological findings of diffuse C-cell hyperplasia, focal C-cell hyperplasia, or MTC in situ (one each in liraglutide and contol group). There was a numeric imbalance of C-cell hyperplasia not favoring liraglutide but the relevance of this histopathological finding to the development of MTC is debatable.

Dr. Mahoney points out that while all thyroid tumors were detected through clinical trial monitoring of calcitonin and/or thyroid ultrasounds, she stated that the scheduled calcitonin assessments were per protocol and should have resulted in a similar rate of thyroidectomies in a blinded, randomized trial. However, it is possible that GI-related symptoms (the most common AE reported for liraglutide which exceeded that of control groups) could have led the investigator to assume assignment to liraglutide which then influenced management (e.g., f/u ultrasound, biopsy and surgery) subsequent to the mild calcitonin elevation. The experience from this monitoring program might serve to inform us on how practitioners, particularly those who are not familiar with managing thyroid conditions, might inappropriately interpret mild calcitonin elevations should monitoring be recommended in labeling.

The advisory committee panel was asked to comment on the numerical imbalance of reports of papillary thyroid cancer in the clinical trials. From the minutes cleared by the Chair of the committee, Dr. Kenneth Burman, the following summary was provided:

*The committee felt that papillary cancer is related to ascertainment bias. The risk of this agent causing or mediating medullary thyroid cancer or C-cell hyperplasia seems relatively low. There does not seem to be a physiological, pathophysiological or oncogenic basis for the development or propagation of papillary cancer.*

The panel was also asked to vote whether these papillary thyroid cancer findings would still allow marketing of liraglutide. The majority (12 yes, 0 no, 1 abstain) did not feel that these findings should prevent approval.

**Pancreatitis**

Acute pancreatitis with some severe cases of hemorrhagic and necrosis has been reported in the postmarketing setting for exenatide, the only approved GLP-1 analogue. This has prompted two FDA safety alerts and labeling changes. More recently, cases of pancreatitis including two severe cases have also been described with sitagliptin use in the postmarketing setting. It remains unclear whether these adverse events represent a risk associated with GLP-1 analogues or the incretin-based therapies (GLP-1 analogues plus DPP4-inhibitors) or that these postmarketing reports merely represent an elevated risk of pancreatitis in patients with T2DM in which 15-20% may present as hemorrhagic or necrotizing.

Unique to liraglutide is a numeric imbalance of pancreatitis in its premarketing application that was not observed premarketing with either exenatide or sitagliptin. Section 7.1.3.3.3 (page 139) of Dr. Mahoney's review provides a detailed summary of the pancreatitis cases. There were 8 cases reported in liraglutide-treated patients versus 1 in the comparator group, yielding a rate per 1000 pt-years of 2.2 and 0.6, respectively. A fatality occurred in the liraglutide group wherein acute pancreatitis with features suggesting necrolysis was described post-mortem. Both Drs. Mahoney and Joffe have summarized the pathologist's reports for this case which was confounded by possible post-mortem autolysis of the gland. In reviewing the narrative summaries provided by Dr. Mahoney, I note that in three liraglutide-treated patients, the study drug was continued. However, there was one other case (Patient 514014) involving a 71-year old woman which appeared to have features of necrotizing pancreatitis.

Overall, there is an imbalance in the incidence of pancreatitis not favoring liraglutide. This finding along with the evolving issues surrounding the other approved incretin-base therapies will at a minimum require inclusion of this risk in labeling under the Warnings and Precautions section and postmarketing required studies which will better inform us of this risk and determine if additional communications or regulatory action are necessary.

**Other Adverse Events of Interest**

Other clinical adverse events of interest have been extensively documented in both reviews by Drs. Mahoney and Joffe. These include but are not limited to hypersensitivity reactions, injection site reactions, hypoglycemia, and neoplasms. In addition, elevated serum creatinines without evidence of renal deterioration were observed more in the liraglutide-treated patients than control. I do not believe that any of these adverse events are of sufficient magnitude to preclude approval of this NDA. However, findings on all the adverse events of interest will be discussed in labeling and will be further evaluated in selected postmarketing required trials.

Overall, there is a low risk of hypoglycemia with liraglutide use. Howevere, there were some differences in the discussion of hypoglycemia presented by Drs. Mahoney and Joffe in their separate reviews. Different terminologies describing hypoglycemic events were used by each of them. In her review, Dr. Mahoney defined serious hypoglycemia as "one in which the patient requires the assistance of another person in order to treat the hypoglycemia". Dr. Joffe defined major hypoglycemia as "if the patient was unable to self-treat (i.e., required another person to administer food, glucagon, or intravenous glucose". In essence, they are describing the same adverse event. Both reviewers identified 9 patients meeting their respective definitions, all liraglutide-treated patients. Dr. Mahoney stated that 6 of the 9 patients received concomitant sulfonylureas. Dr. Joffe confirmed this but provided additional information in the remaining three patients which could have contributed to the "major" hypoglycemic episode (co-administration of insulin or hospitalization for intracranial bleed with unknown fasting duration). I have sought clarification from both reviewers and was made aware of additional information provided by the applicant on the 3 other patients after Dr. Mahoney's review had been finalized. Consequently, I would conclude that while serious hypoglycemia (I prefer this terminology because it does convey the greater need for external assistance than major hypoglycemia) can occur with liraglutide, it appears that this is more likely in the setting of insulin use or use of an insulin-secretagogue. There was a similar finding in the NDA review for exenatide. Labeling for liraglutide should therefore include this risk of hypoglycemia under Warnings and Precautions with a recommendation that dose reduction may be needed with the insulin secretagogue.

## 9. Advisory Committee Meeting

This NDA was presented before the Endocrinology and Metabolism Advisory Committee (EMDAC) on April 2, 2009. The following four questions were posed to the panel members. The final votes are provided after each question.

1. Based on the preceding discussion, has the applicant provided appropriate evidence of cardiovascular safety to conclude that liraglutide rules out unacceptable excess cardiovascular 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?

   Yes: 8; No: 5: Abstain: 0

2. Has the applicant provided adequate data on the animal thyroid C-cell tumor findings to demonstrate that these findings are not relevant to humans?

   Yes: 1; No: 12; Abstain: 0

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

   Yes: 6: No: 6; Abstain: 1

4. Assuming the remainder of the risk:benefit data are acceptable, do the available data on papillary thyroid cancer permit marketing of liraglutide?

Yes: 12; No: 0; Abstain: 1

Drs. Mahoney and Joffe have each opined on these votes. In Section 8.5 of her review, Dr. Mahoney has provided excerpts from the transcripts.

I believe the votes from this advisory committee on Question 1 and 3 reflect the difficulty in assessing risk vs benefit in this application and that even this panel of experts (the two thyroidologists voted differently on question 3) struggled with the data presented before them. For questions 2 and 4, there was little to no equivocation. After reading the extensive clinical and pharmacology/toxicology reviews, I would conclude there is alignment within the FDA with the advisory committee panel on the issues of nonclinical mode-of-action and risk of papillary thyroid cancer.

# 10. Pediatrics

Please see Dr. Joffe's memo. A PK/PD study will first be conducted to explore lower dosing in children ≥ 10 years of age with type 2 diabetes. This will be followed by an efficacy and safety trial. The timelines for submission of the PK/PD study is in advance of the protocol submission date for the efficacy/safety trial to allow FDA time to review before allowing the larger study to proceed in the setting of ongoing safety concerns.

# 11. Other Relevant Regulatory Issues

**Division of Scientific Investigations**
DSI inspected two clinical sites. As discussed in Dr. Yanoff's review, these two sites were selected because one enrolled a large number of patients relative to other participating sites and the second was selected because there was disclosable financial information submitted by the principal investigator. No regulatory violations were noted in the inspection report.

**Financial Disclosures**
Please see Dr. Yanoff's review. No notable findings to preclude approval.

**Tradename Consult**
Victoza® was found acceptable by the Division of Medication Error Prevenation and Analysis (DMEPA).

## 12. Labeling

Extensive internal and external labeling negotiations are ongoing at this time. Liraglutide will be approved with a Medication Guide and a Risk Communication Plan. The professional labeling will have a boxed warning which will describe the nonclinical C-cell tumor finding and the potential clinical risk. In addition, liraglutide will be contraindicated in patients with a personal history of MTC or those from families with known familial MTC or MEN2 syndromes.

Of debate is whether labeling should recommend routine calcitonin and/or thyroid ultrasound monitoring to detect early evidence of C-cell tumor as only early surgical resection is considered curative for MTC. The clinical trial experience suggests that routine calcitonin or ultrasound monitoring might increase the likelihood for thyroidectomies without the detection of any serious thyroid pathology. I do not recommend such monitoring be included in labeling but would recommend that any patient prescribed liraglutide undergo a thorough neck exam before initiating therapy and periodically thereafter.

I would consider a recommendation for Baseline calcitonin prior to initiating liraglutide only to ensure that the prescriber and patient more carefully consider the potential risks for C-cell tumors with liraglutide use in the setting of a patient with calcitonins > 20-50 ng/L. I am cognizant that such monitoring in the clinical trials did result in thyroidectomies for which no serious thyroid disease was found on surgical pathology so any recommendation for Baseline calcitonin monitoring should include available information on sensitivity and specificity of calcitonin as a screening biomarker and a recommendation for referral to a thyroid specialist. The intent is to reduce the likelihood that patients undergo surgery for mild elevations in calcitonin.

## 13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Approval

- Risk Benefit Assessment

In coming to my decision to recommend approval, I have considered all the primary and secondary reviews. While my final recommendation does not align with that of several reviewers, I acknowledge their arguments and in this section will attempt to explain how I have reached a conclusion that the overall risk-benefit assessment favors approval with certain restrictions on marketing while the applicant collects additional safety data from postmarketing required trials/studies under FDAAA.

Benefits/Advantages

A discussion of the benefits of this drug is necessary before delving into the risks because no risk can be tolerated with a drug which has not established benefit. Across 5 Phase 3 trials, liraglutide has demonstrated itself to be an effective anti-glycemic agent resulting in statistically significant reductions in HbA1c when initiated as monotherapy and in combination with one or two other oral anti-diabetic agents. Compared to placebo, liraglutide 1.2 to 1.8 mg daily injection provided a mean HbA1c reduction of 0.94 to 1.36 (See Table 8 from Dr. Janice Derr's statistical review). In the past 4 years, the FDA has approved four active ingredients for the treatment of T2DM (sitagliptin, colesevelam, bromocriptine, saxagliptin). The placebo-subtracted HbA1c reduction expected with these products ranges from 0.5-0.8 for the two DPP4-inhibitors (sitagliptin and saxagliptin) and is more modest with colesevelam and bromocriptine (0.4-0.6). While there were no head-to-head comparisons of liraglutide with these agents, given the consistent efficacy results for each of these agents across multiple trials, I would anticipate that comparative efficacy trials between liraglutide and the DPP4-inhibitors, colesevelam, or bromocriptine, would favor liraglutide. I note that a head-to-head study of liraglutide vs exenatide has been completed by the applicant. This study should be submitted to the agency as part of the listed required studies.

A unique feature of this program was the use of active-control arms enabling the assessment of efficacy relative to other approved therapies. The active controls used in this program were glimepiride, rosiglitazone, and insulin glargine. With exception for the monotherapy study comparing liraglutide to glimepiride, the other studies did not provide convincing evidence that liraglutide added-on to other oral anti-diabetics is superior to the active control in the particular study. In Study 1572, the addition of liraglutide to metformin background therapy was non-inferior to the addition of glimepiride. Although Study 1436 showed superior efficacy with the addition of liraglutide to background glimepiride therapy than the addition of rosiglitazone, the use of half the maximum approved dose of rosiglitazone precludes any claim of superiority. Similarly, in Study 1697, the addition of liraglutide to background glimepiride and metformin therapy was superior to the addition of insulin glargine, but the low percentage of insulin users achieving protocol-defined target goals suggests less-than-ideal insulin titration.

Although the data do not support a conclusion that liraglutide provides greater glycemic efficacy than a thiazolidenedione, sulfonylurea or insulin in the setting of add-on therapy, these trials do provide information on other benefits of liraglutide which might favorably influence its use over these other agents. As stated above, rosiglitazone and insulin glargine were not used at maximally effective doses. However, even at these less efficacious doses the agents exhibited greater weight gain than liraglutide. Obesity and weight gain are several factors contributing to the development or worsening of T2DM. In Study 1436, approximately 47% of the liraglutide-treated patients (at 1.2 and 1.8 mg doses) experienced up to a 5% weight reduction from Baseline compared to 22.7% in the rosiglitazone group. In contrast, about 21% of the rosiglitazone-treated patients experienced between 5 and 10% weight increase from Baseline compared to 5 to 5.6% in the liraglutide-treated group. Similarly, in Study 1697, only 2.2% of the liraglutide-treated patients experienced a 5 to 10% weight gain versus 11.5% in the insulin glargine group. The following graphs provided by Dr. Janice Derr illustrate the weight changes in these two studies. Similar patterns were noted in all 5 Phase 3 trials.

**Figure 13.1 Study 1436 – Body Weight Change at Week 26 (ITT/LOCF) – prepared by Dr. Janice Derr**

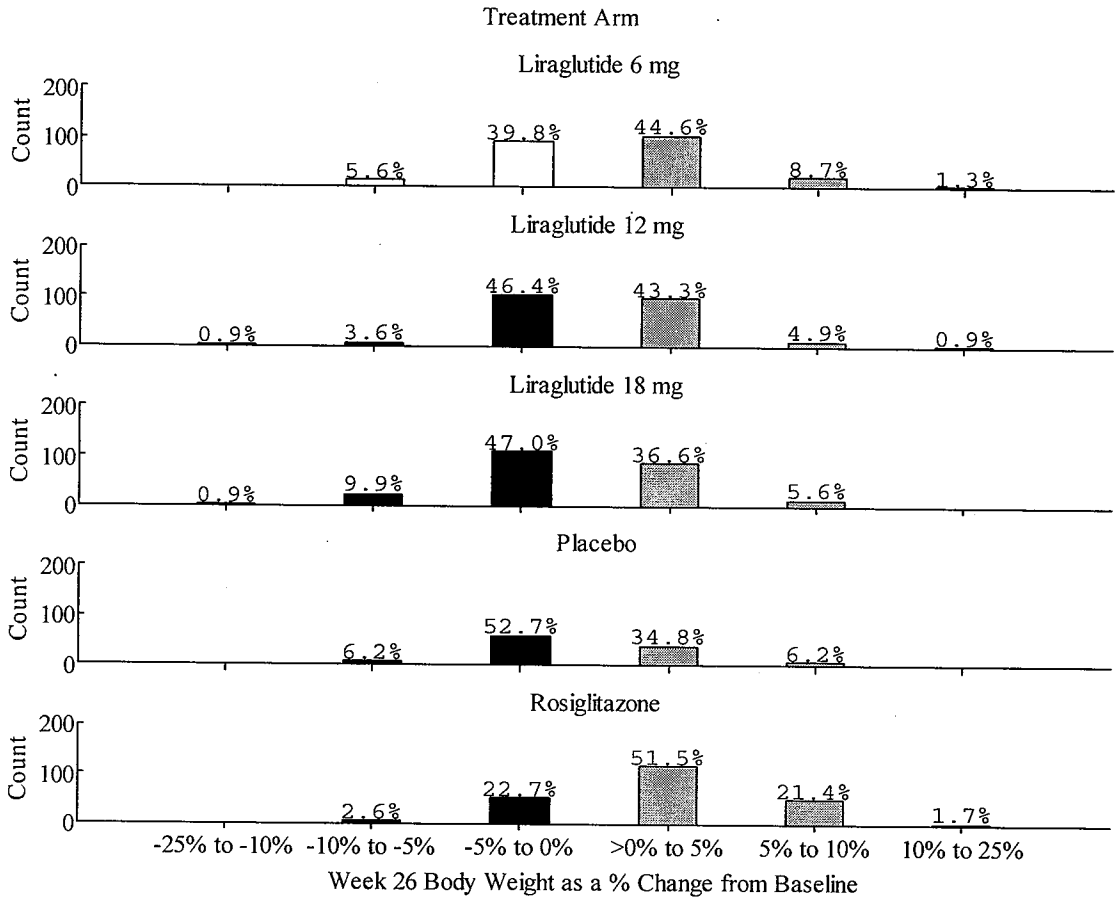
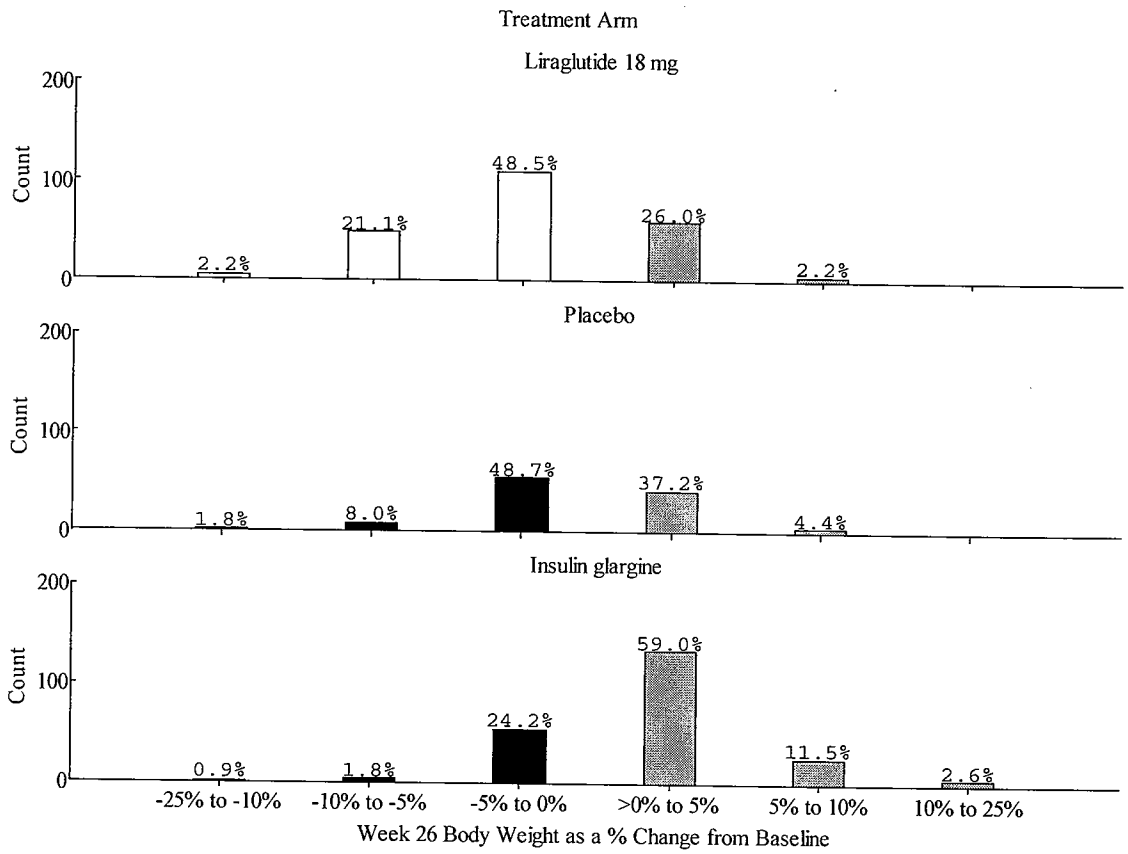


**Figure 13.2 Study 1697 – Body weight Change at Week 26 (ITT/LOCF) – prepared by Dr. Janice Derr**




Another advantage of liraglutide over currently available therapies is the low likelihood for drug-drug interactions via the cytochrome P450 pathway. And in contrast to the currently marketed GLP-1 analogue, exenatide, there will be no recommendation for adjustment in dosing schedule with certain drugs. Unlike metformin, which is contraindicated in patients with renal impairment, and most other anti-diabetics with lower dosing regimens recommended for worsening renal function, there is no recommendation for dosage adjustment with liraglutide for renal impairment (or hepatic impairment).

Risks/Disadvantages

Like any drug, liraglutide carries risks and disadvantages which must be weighed against the benefits/advantages. In this clinical development program, the most common adverse event that should be considered a disadvantage is the high rate of gastrointestinal adverse events including nausea, vomiting, and diarrhea which contributed to the higher rate of discontinuation. However, GI-related adverse events are not unique to this agent (e.g., metformin, pramlintide, exenatide) and these events are rarely serious. Many cases abate over time.

Another disadvantage of liraglutide is the parenteral route of administration. Injection site reactions may limit use. Again, this is not unique to this agent as two other approved agents for the treatment of hyperglycemia in T2DM are administered by sc injection (e.g., pramlintide and exenatide), not to mention insulin therapy. In the liraglutide NDA, the incidence of treatment-emergent injection site events was higher in the liraglutide 1.2 and 1.8 groups (1.8% and 2.4%, respectively) than the placebo (1.5%) and active-control (1.2%) groups (except for the insulin glargine group, comparators received placebo injections along with the assigned oral agents). None of these events was reported as serious and of all discontinuations, only 4% were due to injection site reactions. The head-to-head study against exenatide will be informative with respect to efficacy and safety data.

In my opinion, the primary safety concerns which set liraglutide apart from other currently approved drugs are pancreatitis and nonclinical C-cell tumors. I have already discussed the CV risk assessment under Section 8.0 of my memo and I do not believe there is evidence of excess CV risk that places liraglutide at a disadvantage over other therapies (N.B. the applicant will be required to conduct a CV outcomes trial). Although pancreatitis has been reported with exenatide and sitagliptin, there was a clear numeric imbalance of pancreatitis cases in this pre-marketing application that was not present with exenatide or sitagliptin. Whether this signifies a greater risk of this drug than the other incretin-based therapies is uncertain given the small number of events and the absence of head-to-head comparison. In reviewing the narratives of each of the liraglutide cases, I do not consider these events of such magnitude to preclude approval. Regardless, the findings will clearly need to be placed under Warnings and Precautions with postmarketing required studies/trials to further investigate this risk and if necessary, refine labeling and risk communications.

The single safety concern which was commonly identified by reviewers not recommending approval was the C-cell tumor finding in rats and mice. I agree with them on the rodent carcinogenicity findings and that the monkey studies have limitations for dismissing the cancer signal. Furthermore, I agree that the initially proposed mode-of-action in which liraglutide activates GLP-1 receptors on rodent C-cells with subsequent calcitonin secretion driving the development of hyperplasia and tumor development, is not applicable to both animal models. Therefore, I cannot conclude that these findings are rodent-specific and not clinically relevant. I am less convinced that the greater upward shifts in calcitonin signify a clinical risk and believe that the imbalance in both thyroid papillary neoplasm and C-cell hyperplasia may be a result of the calcitonin monitoring plan implemented in the trials.

I agree with Drs. Mahoney, Parola and Davis-Bruno that inadequate data have been provided to reassure us that no clinical risk exists. However, I am in agreement with Dr. Joffe that none of the proposals set forth by them will provide us of that degree of reassurance. Drs. Parola and Davis-Bruno have recommended studies to explore further the mode-of-action for liraglutide-induced C-cell tumors. Some suggestions (some of these are in the primary pharm/tox reviews; others have been raised in subsequent internal discussion by the review team) include:

1. Evaluating the effect of liraglutide on RET-signaling in rodent C-cells
2. Evaluating GLP-1 receptor expression in normal, focal hyperplastic, and neoplastic C-cells in liraglutide-treated mice
3. Evaluating the role of GLP-1 receptor in tumor induction (focal C-cell hyperplasia) through studies of liraglutide in GLP-1 knockout mice or studies of GLP-1 receptor antagonists in normal mice

The first proposal may have some clinical relevance since activation of RET proto-oncogene is responsible for nearly all the familial forms of MTC. Somatic RET mutations have also been observed in a large proportion of sporadic MTC cases; however, this can only be detected via thyroid tissue samples, not via peripheral white blood cells. Should liraglutide cause activation of RET-signaling pathways and there are still advantages to having this drug available for T2DM, this information would unlikely change my recommendation for risk assessment at present other than emphasis on regular and thorough neck examinations and palpation for detecting thyroid nodules. The study results, however, may impact recommendations on other forms of monitoring (e.g., biomarker screening or thyroid ultrasound).

The second proposal would determine if GLP-1 receptor expression occurs in normal, preneoplastic (focal C-cell hyperplasia), or neoplastic C-cells. Since a published study showed only 60% of mice express GLP-1 receptor in their thyroid, the proposed study would also determine if liraglutide-induced C-cell focal hyperplasia/neoplasia only occurs in thyroid GLP-1 receptor positive mice.

Should the third proposal reveal that the tumor induction in mice to be specific to GLP-1 receptor activation (e.g., GLP-1 receptor knockout mice do not develop C-cell hyperplasia), this may be reassuring in that data appear to support the presence of this receptor on rodent thyroid cells and not on human thyroid samples. However, there remain some debate on these data and such an established mode-of-action would not obviate the need for post-marketing vigilance proposed with this approval. Similarly, the inability to link tumor induction to the activation of GLP-1 receptors would only underscore the situation we are currently in: established C-cell tumor findings in rodents with unknown mode-of-action not enabling us to dismiss clinical relevance of such findings.

During the October 2009 NDA Wrap-Up Meeting, Drs. Parola and Davis-Bruno presented a fourth nonclinical study to determine if liraglutide increases lifetime C-cell tumor incidence in mice treated long enough to induce focal C-cell hyperplasia, but terminating treatment before tumors develop. This last proposal would inform us if limited exposure to liraglutide increases the lifetime risk of C-cell tumor induction even after liraglutide treatment has been discontinued in animals. This has clinical relevance in that the short-term exposure to liraglutide may still place a patient at risk years later even in the absence of continued exposure to drug. A study in mice showed that focal C-cell hyperplasia (considered pre-neoplastic lesions in rodents) induced after 9-weeks of liraglutide treatment were not fully reversed after a 15-week recovery period. However, in the setting of continued, lifetime exposure in the two carcinogenicity studies, malignant tumors were not detected until after more than 1 year of treatment (> 50% of the animal's lifespan). Given the available

information, I would consider the clinical risk of limited exposure to liraglutide inducing malignant MTC to be low while awaiting these animal data. However, these findings will still be informative and may dictate some limitation on duration of clinical use.

In all, I do not believe the proposed non-clinical studies will provide data to alter my current risk-benefit assessment. However, I do believe these studies will be informative and may further refine risk communication and/or modify the limitations of clinical use. As such, additional non-clinical studies should be required post-marketing studies under FDAAA. The pharmacology/toxicology reviewers and supervisors are currently discussing which studies will be included in the action letter as PMRs under FDAAA.

Dr. Mahoney is recommending the applicant initiate their proposed 9000-patient CV outcomes trial and include in that trial, multiple biomarkers to assess C-cell activation. These data can be submitted to the agency after 3 years of double-blinded controlled follow-up. However, she acknowledges that she does not expect any cases of MTC to be detected in this trial. Dr. Joffe provided in his memo Table 22 (see below) in which Drs. Derr and Sahlroot have calculated the sample size necessary for a single-arm trial to detect a 2-fold, 5-fold, 10-fold, 20-fold, or 100-fold risk.

**Table 22. Sample sizes needed for a single-arm trial to detect 2-fold to 100-fold increases over the background rate[a] in the risk for non-familial medullary thyroid carcinoma (from Drs. Derr and Sahlroot, FDA biostatisticians)**

| Power | Increase in risk for medullary thyroid carcinoma | | | | |
|---|---|---|---|---|---|
| | 2-fold | 5-fold | 10-fold | 20-fold | 100-fold |
| **3-year treatment period** | | | | | |
| 80% | 1,888,050 | 229,783 | 62,383 | 31,183 | 3,353 |
| 90% | 2,578,783 | 278,383 | 110,850 | 40,517 | 4,793 |
| **5-year treatment period** | | | | | |
| 80% | 1,132,830 | 137,870 | 37,430 | 18,710 | 2,012 |
| 90% | 1,547,270 | 167,030 | 66,510 | 24,310 | 2,876 |
| **10-year treatment period** | | | | | |
| 80% | 566,415 | 68,935 | 18,715 | 9,355 | 1,006 |
| 90% | 773,635 | 83,515 | 33,255 | 12,155 | 1,438 |

Power calculations from StatXact, 1-sided alpha 0.05
[a]Background rate refers to an estimated 480 cases of non-familial MTCs diagnosed annually/estimated U.S. population of 300 million

From the animal carcinogenicity studies, it is highly unlikely that liraglutide, should it cause MTC, would do so at 100-fold risk thereby confirming the conclusion that the proposed CV outcomes trial (which would have approximately 4500 patients exposed to liraglutide) will unlikely detect any case of MTC. In addition, patients enrolled in this CV outcomes trial may succumb to a CV-related fatality which will further reduce the ability to detect a cancer with a long latency period.

Dr. Mahoney's proposal to replace the clinical cancer endpoint with biomarker screening would only be an exploratory study as there are no data on the utility of calcitonin,

procalcitonin, or CEA as a screening tool for drug-induced MTC. It would therefore appear that awaiting the submission of 3-year controlled data would address her requirement for longer term data but there is no evidence that it would address her other requirement that the data adequately assess the human risk of MTC.

In Dr. Mahoney's review she states that there are already 11 classes of drugs approved for glycemic control in type 2 diabetes, including one other in this class, such that there is no urgency in approving liraglutide in the setting of uncertainty in risks. She is correct that we have many therapeutic options to treat T2DM. But we have also approved many of these therapeutic options in the setting of more certainty in some other risks than what we are challenged with in this NDA. Some of these other established risks are serious, including drug-related fatalities (e.g., hypoglycemia, lactic acidosis, congestive heart failure).

In 2007, the agency took the position that the oral anti-diabetic, rosiglitazone, should remain on the market because there remained uncertainty in the risk of myocardial ischemia from the meta-analysis of 42 controlled clinical trials. In June 2009, four epidemiologic studies were published online in *Diabetologia* suggesting an increased risk of cancer with insulin glargine. The agency issued an early communication on July 1, 2009 which placed these findings in perspective of the type of trial design which detected this signal, with a recommendation that patients *not* stop taking insulin therapy while additional data were reviewed or requested of the firm. These decisions, made in the setting of uncertain risk, took into consideration the potential benefit of the drugs, their indicated use, the risks associated with other available therapies, and what additional data could be obtained for these drugs to provide more clarity on these safety signals.

As noted in their primary reviews, there are no known FDA-approved drugs with findings of C-cell tumors in two species. However, this finding alone does not represent a regulatory policy that no drugs would be approved if cancers are identified in multiple species. More than likely, companies discontinue their drug development plans (e.g., PPAR-agonists) prior to submission of their marketing application and the question of risk versus benefit of the drug is not asked of the agency for that particular drug. Many of these discontinued applications had not only a single tumor finding in both species but multiple tumors (bladder cancer, hemangiosarcoma, fibrosarcoma) observed in multiple organs (fat, spleen, liver, GI tract), with some individual animals exhibiting these multiple-tumor, multiple-organ findings. It is clear that the potential to cause aggressive tumors was much greater with these compounds than observed in the carcinogenicity studies with lirgalutide.

FDA has been faced with consideration of carcinogenic compounds in the approval process previously. During the advisory committee meeting and in several internal discussions for liraglutide, the Forteo® (teriparitide) case has been raised as an example of how the agency managed uncertain risk and clinical relevance of animal cancer findings. Although the malignant osteosarcomas of Forteo® were observed only in male and female rats (at 3 to 60x the human therapeutic exposure), the carcinogenicity studies with that drug showed decreased survival in both male and female rats (significant in females). This finding persisted even after excluding deaths due to neoplasms. As stated previously, survival was not affected by

liraglutide treatment in both rat and mouse carcinogenicity studies and there was only one death attributed to C-cell carcinoma in a female mouse at 45x the MHRD.

Forteo® was ultimately approved in 2002 not because the applicant was able to demonstrate a mode-of-action to conclude rat-specific carcinogenic potential (monkey study was negative), but because the agency felt that the drug offered a benefit not available with other approved agents. However, to ensure that the product would be marketed and used in only those patients for whom the expected benefit would outweigh the potential risks, the FDA placed restrictions on the indications and duration of use (< 2 years). In addition, the company was told to establish a post-approval case-series study of 10-years duration as a post-marketing commitment (PMC). This approval pre-dated the Food and Drug Administration Amendments Act (FDAAA) in which postmarketing safety assessments were enforceable. In July 2009, the FDA approved a supplement for Forteo® which expanded its indication to men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture. This supplement was approved in the setting of postmarketing reports of osteosarcoma in patients treated with Forteo®. However, the agency again felt the benefit in this patient population outweighed the risk but under FDAAA deemed that a Risk Evaluation Mitigation Strategies (REMS) was necessary with this approval. The details of the elements of this REMS can be obtained at Drugs@FDA[3] under NDA 21-318/S012 but it included a Medication Guide and a Communication Plan (Dear HCP Letter, Direct Mail Letter, and Highlighted Information for Prescribers). In addition, the original PMC study was converted to a postmarketing required study expanded to 15-years of follow-up and a registry was established.

I have summarized the Forteo® approval history as a case example that can be applied to the approval of liraglutide. Liraglutide should be approved with a REMS and several postmarketing required studies and trials under FDAAA. These items are discussed further below.

Although I concur with Dr. Joffe that liraglutide has a risk/benefit profile which can still fill an unmet niche in the treatment of T2DM, I do have concerns that prescribers will not fully comprehend the challenging safety issues that have resulted in split approval decisions by an advisory committee panel of experts including diabetologists and thyroidologists, and more importantly, the split approval decisions by FDA review staff who are more keenly aware of the details and nuances of the data submitted in this application. On this matter, I am not in full agreement with Dr. Joffe, as I am not optimistic that liraglutide can be made "available and *left* to the discretion of healthcare providers and their patients" to interpret whether the uncertain risk of MTC outweighs the benefits of the drug while awaiting additional data under FDAAA. And to this end, I believe liraglutide should be approved with limitations on its use and labeling which would circumscribe marketing and promotional practices until completion of several studies/trials under FDAAA.

The applicant has demonstrated that treatment with liraglutide significantly reduces HbA1c and the magnitude of this effect appears to be greater than many recently approved agents. But this alone should not prompt the use of this agent as first-line therapy in newly-diagnosed

[3] http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021318s012rems.pdf

or treatment-naïve patients who have failed diet and exercise. In fact, a very small proportion of patients (6.8%, n=272) in the Phase 3 program were treatment-naïve. Until additional long-term, controlled data are available, other therapeutic options with established efficacy and safety profiles (e.g., metformin) should be considered before initiating liraglutide.

I would not impose a restriction in duration of use because the nonclinical carcinogenicity data do not suggest early cancer development (carcinomas appeared after 60% of mouse lifespan and 70% of rat lifespan). Use of liraglutide as second-line therapy after approval will be, at most, 3 years of clinical exposure before data from the required CV outcomes trial and additional nonclinical studies enable further refinement of the label, including any restriction on duration of use.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

In order to ensure that the benefits of the drug outweigh the risks, this NDA should be approved with a REMS which would include the following:

1. Medication Guide
2. Communication Plan including letters to healthcare providers and the dissemination of information through professional societies about the REMS, safety concerns with this drug, and limitations on its use.

I do not believe an ETASU (Elements to Assure Safe Use formerly referred to as restricted distribution) is necessary with this approval but welcome the applicant's _____ _____ I believe labeling which recommends against first-line therapy (or alternatively limits to second-line use only) will place limits on promotional practices and remind prescribers to carefully consider the risks-benefits of this drug prior to prescribing it for T2DM or possible off-label use as a weight-loss agent. b(4)

- Recommendation for other Postmarketing Requirements and Commitments

At present the following have been determined to be PMRs to be included in the action letter. There are no post-marketing studies which will be listed as PMCs.

1. CV outcomes trial
2. i3 Aperio epidemiology study
3. MTC case-series registry
4. Pediatric studies

Given the premarketing imbalance in pancreatitis with liraglutide, I would also list the head-to-head study between liraglutide and exenatide as a PMR with an expected date for submission of these trial results. This study would further enable the agency to determine whether liraglutide has any unique advantage or disadvantage over the currently marketed GLP-1 analogue.

Other PMRs should include:

1. Mechanistic studies in animals regarding the development of C-cell tumor and determining the relevance of the mechanism in humans

2. Studies which further explore the role of GLP-1 receptor in the development of C-cell tumors in animals and the relevance to clinical risk
3. Studies to evaluate whether pre-neoplastic events progress after drug discontinuation which will inform us on duration of clinical use
4. Nonclinical studies to evaluate the effect of liraglutide on pancreatitic pathology including pancreatitis and pancreatitc cancer

Finally, the evolving safety signals in the incretin-based therapies may warrant consideration for a class REMS and PMRs. Given that the non-clinical signal for C-cell tumor does not appear limited to liraglutide but is observed with other GLP-1 analogues with sustained pharmacokinetic profiles, the agency should consider recommending that all companies pursuing a marketing application for a GLP-1 analogue work together to conduct a case-series registry which will more than likely require 15+ years of follow-up.

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|---|---|---|---|
| NDA-22341 | ORIG-1 | NOVO NORDISK INC | VICTOZA (LIRAGLUTIDE) |

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/s/

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MARY H PARKS
01/22/2010