CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201280Orig1s000

SUMMARY REVIEW

Division Director's Memo

Date	May 2, 2011
From	Mary H. Parks, M.D.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	201280
Applicant Name	Boehringer Ingelheim Pharmaceuticals, Inc.
Date of Submission	July 2, 2010
PDUFA Goal Date	May 2, 2011
Proprietary Name / **Established (USAN) Name**	Tradjenta/Linagliptin
Dosage Forms / Strength	5 mg tablets
Proposed Indication(s)	To improve glycemic control in adults with T2DM as an adjunct to diet and exercise
Action/Recommended Action for NME:	Approval

1. Introduction

Linagliptin is the 5th dipeptidyl peptidase-4 enzyme inhibitor (DPP4-inhibitor) to be submitted under an NDA for the treatment of T2DM. Two other DPP4-inhibitors are currently marketed in the United States. These are Januvia (sitagliptin) and Onglyza (saxagliptin), and their fixed-dosed combinations with metformin, Janumet or Kombiglyze XR, respectively.

This is a relatively new class of anti-diabetic therapy whose mechanism of action targets the impaired release and availability of the incretin hormone, glucagon-like peptide-1 (GLP-1) in patients with type 2 diabetes. GLP-1 and another incretin hormone, glucose-dependent insulinotropic polypeptide (GIP), are released from the gastrointestinal tract in response to meals to further stimulate insulin release. Because GLP-1 is rapidly degraded by the serine protease, dipeptidyl peptidase 4, an inhibitor of this enzyme will prolong the half-life of this incretin hormone allowing for a more sustained effect on glucose control.

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. GLP-1 receptor agonists are another class of incretin-based therapies. These agents are manufactured to avoid susceptibility to enzyme degradation while maintaining sufficient cross-reactivity with the GLP-1 receptor to impart similar effects on glucose control as the native hormone. Two GLP-1 receptor agonists are currently marketed: Byetta (exenatide) and Victoza (liraglutide).

2. Background

The clinical development program for linagliptin was typical for most anti-diabetic therapies approved in the past 5 years. Monotherapy trials evaluated the drug's safety and efficacy profile in treatment-naïve T2DM population or patients with fairly recent diagnosis of T2DM who could be controlled on a single drug regimen. In addition, combination therapy with linagliptin added to several approved anti-diabetic therapies was assessed in multiple trials and a single head-to-head trial comparing linagliptin to glimepiride was conducted. This latter trial provides the longest duration of controlled efficacy and safety data for linagliptin in this NDA.

All new anti-diabetic therapies are now required to provide evidence to assure FDA that the new therapy is not associated with an adverse cardiovascular profile. Guidance for Industry outlining these recent changes to diabetes drug development programs was issued in December 2008. As a result, several development programs that were in the midst of Phase 2/3 clinical trials were required to make adjustments to their CV risk assessment plans. Boehringer Ingelheim's linagliptin was among these programs and the company presented to the FDA its proposal to evaluate CV risk from its ongoing Phase 2/3 trials. Although the inception of these trials was not with the recent guidance in mind, the trials were either early in initiation or not yet initiated such that a prospective plan for CV events adjudication and a meta-analytic plan could be implemented with FDA feedback/comments. Prior to submission of the NDA the applicant notified the FDA of its preliminary findings from its meta-analysis. Although the data appeared reassuring of CV safety, the limitations of the trials and the few CV events still required the conduct of a clinical trial prospectively designed to meet the standards set forth in the December 2008 Guidance.

This memo serves to highlight the key findings of the multiple disciplines involved in review of the NDA. In addition to evaluating the efficacy and safety of this new anti-diabetic therapy, with particular scrutiny of CV safety data, other disciplines have focused on the product manufacturing process and quality, nonclinical evaluation of known class safety concerns and to identify any unique toxicities of linagliptin, and clinical evaluation of the drug's metabolism and pharmacokinetic profile under multiple scenarios of use. In addition, all such materials have been considered in the review of the drug product's label and prescribing information.

In each section of this memo, the reader is referred to specific discipline reviews for a detailed discussion of their findings.

3. CMC/Device

CMC reviewers have recommended approval of linagliptin. Please see the reviews of Drs. Markofsky and Al-Hakim dated 2 February and 7 March 2011 for details. An acceptable establishment inspection report of manufacturing and testing facilities was issued on 15 February 2011.

Linagliptin will be available as a 5-mg, immediate-release film coated tablet in the following package presentations: 60 cc HDPE bottles containing 30 or 90 tablets; 375 cc HDPE bottles

containing 1000 tablets; and physician samples as aluminum push-through blister packets containing 7 tablets. The commercial container systems have a 30-month expiry when stored at room temperature with excursions between 15-30^{o}C permitted.

Linagliptin has one chiral center with the R-enantiomer (b) (4) being the predominant enantiomer that is also considered the active ingredient. Linagliptin also exists as (b) (4) .

The commercial formulation and investigational formulations differ only in the following: (b) (4) The biopharmaceutics review considered these to be Level 1 changes in accordance with SUPAC-IR guidance and no further comparative studies (dissolution testing or BE studies) were required.

4. Nonclinical Pharmacology/Toxicology

Please see Dr. David Carlson's review dated 7 March 2011 which contains the details of the pharmacology/toxicology program for linagliptin. Dr. Todd Bourcier's secondary review dated 10 March 2011 concurs with Dr. Carlson's assessment and both have recommended approval from pharmacology/toxicology perspective.

Linagliptin, its metabolite, and impurities were adequately studied in the nonclinical program. Pivotal repeat-dose toxicity studies were conducted in rats and monkeys and provided evidence of a wide safety margin. In the 6-month rat study, histopathology findings identified the kidney, liver, lung, stomach, and thyroid to be target organs of toxicity at doses ≥ 100 mg/kg. The histopathology findings are summarized in a table on page 54 of Dr. Carlson's review. In the 12-month monkey study there was one death of a female (1/4) at the highest dose tested 100 mg/kg/day. The cause of death was deemed kidney-related. Both males and females had evidence of delayed sexual maturation at this dose, as evidenced by decrease reproductive organ weights and decreased corpora lutea (females).

Studies exceeding 6 months in rats, including the 2-year carcinogenicity study, provided safety margins exceeding 50-times clinical exposures. Three and 12-month studies in monkeys provided safety margins exceeding 40-times clinical exposures. The exposures corresponding to the above toxicities were ≥ 54,650 nM*h in the rat and 125,000 nM*h in the monkey. In contrast, clinical exposures at steady-state is approximately 158 nM*hr for the proposed daily dosing of 5 mg.

Linagliptin is not mutagenic or clastogenic. Two impurities were identified positive on Ames testing (one was also clastogenic); however, Dr. Carlson noted that human exposure estimates for the impurities are below levels that which would pose a carcinogenic risk. Carcinogenicity studies established a NOAEL for neoplasms in male and female rats at 418x MRHD and 271x MRHD for male mice and 34x MRHD for female mice. No treatment difference in survival was noted in these studies. There were no statistically significant increases in tumor incidence

between treatment and control in the rat carcinogenicity study. There was a statistically significant increase in incidence of malignant lymphoma in female mice only at the highest dose (80 mg/kg/day ~ 287x MRHD). Given that no other drug-related tumors were observed in rats and male mice and the lymphoma finding was limited only in female mice at a 34-fold safety margin, this finding is unlikely to be of clinical relevance.

Reproductive/fertility studies also established wide safety margins for linagliptin and both Drs. Carlson and Bourcier support pregnancy category B labeling. Linagliptin crosses the placenta and is secreted in breast milk. These findings will also be reflected in labeling.

Safety findings of special interest for the class of DPP4-inhibitors include: pancreatitis (signal arising from AERS reports for Januvia and a GLP-1 analog, Byetta); cutaneous lesions (from nonclinical program of vildagliptin, a DPP4 inhibitor marketed outside the U.S.); and hypersensitivity reactions which will be further discussed under the Clinical Safety section of this memo.

Overall, the nonclinical findings have identified toxicities that occur at very high exposures yielding a wide clinical safety margin. As noted by Dr. Bourcier, these safety margins would also cover the susceptible patient population that may have higher than expected drug exposures. I concur with their assessment that nonclinical findings support approval and no nonclinical postmarketing required studies are needed at this time.

5. Clinical Pharmacology/Biopharmaceutics

There were 24 Phase 1 (20 in healthy, 2 in T2DM, 1 in renal impaired, 1 in hepatic impaired), four Phase 2, and 9 Phase 3 clinical trials and several *in vitro* ADME studies conducted in support of this NDA.

Absorption of linagliptin occurs (b) (4) with Cmax ranging between 0.5 and 3 hrs post-dosing. The extent of absorption was unaffected by food but the Cmax had a clinically insignificant 14% reduction. Linagliptin is not metabolized extensively with approximately 90% excreted unchanged in the feces and 5% excreted unchanged in the urine. Non-linear pharmacokinetics is displayed with less than dose-proportional increase in exposure at doses of 1 to 10 mg and dose-proportional increase in exposure at doses exceeding 25 mg.

Dose-Response/Dose-Selection

Several doses of linagliptin were tested in Phase 1 and 2 trials resulting in the selection of the single daily dose of 5 mg for Phase 3 development and proposed marketing. In particular, two 12-week, Phase 2 studies compared linagliptin across doses of 0.5 mg, 1.0 mg, 2.5 mg, 5 mg and 10 mg to placebo. These two studies also included active comparisons to metformin or glyburide.

Study 1218.5 was a 12-wk, randomized, double-blind, placebo-controlled trial in 302 T2DM patients who were drug-naïve or were treated with one or two oral agents and who had HbA1c 7.5-10% at screening. Patients were randomized to linagliptin 0.5, 2.5, 5 mg, placebo, or metformin. The objective of this study was to compare efficacy and safety of several doses of

linagliptin to placebo. Based on a hierarchical testing procedure, a power of 85% was planned to show superiority of the highest dose of linagliptin to placebo. The metformin treatment arm was open-label and intended for sensitivity assessment. The following table summarizes only the descriptive statistics at Week 12 in the Full Analysis Set

Table 1. Mean Change from Baseline in HbA1c at Week 12 in FAS from Study 1218.5

	Placebo N=63	Lina 0.5 N=57	Lina 2.5 N=55	Lina 5 N=54	Metformin N=65
Baseline HbA1c	8.3	8.2	8.4	8.4	8.3
Mean change (SD)	0.2 (0.8)	0.1 (0.8)	-0.2 (0.8)	-0.3 (0.7)	-0.7 (0. 8)

Both the 2.5 and 5 mg dose had statistically significant reductions in HbA1c from baseline relative to placebo. The adjusted mean difference was -0.5% for the linagliptin 5 mg dose and -0.4% for the linagliptin 2.5 mg dose, with accompanying p-value of 0.0012 and 0.0032, respectively. The adjusted mean difference for linagliptin 0.5 mg was -0.1%, which was not statistically significantly different compared to placebo. Interestingly, the descriptive statistics summarized by the applicant show that metformin achieves greater glycemic control than all doses of linagliptin. The mean change in HbA1c at Week 12 in the metformin group was -0.7%, approximately twice the reduction achieved with linagliptin 5 mg.

Table 2. HbA1c in Study 1218.5 for All Treatment Groups

Table 15.2.1.1: 2 Descriptive statistics for HbA1C change from baseline at week 12 - FAS

		Placebo	BI0.5	BI2.5	BI5.0	Metformin	TOTAL
Number of patients		63	57	55	54	65	294
12 weeks							
	N	63	57	55	54	65	294
	Mean	0.19	0.06	-0.25	-0.29	-0.68	-0.20
	SD	0.81	0.76	0.79	0.67	0.78	0.82
	Min	-1.60	-2.10	-1.30	-1.90	-2.30	-3.30
	Median	0.10	0.10	-0.20	-0.40	-0.60	-0.20
	Max	3.10	1.60	1.50	1.70	1.10	3.10

Study 1218.6 was a 12-wk, double-blind, placebo-controlled trial in 669 T2DM patients who had inadequate glycemic control (HbA1c 7-10%, dependent on background therapy) on metformin therapy who were then randomized to placebo, linagliptin 1 mg, 5 mg, or 10 mg once daily, or glimepiride 1-3 mg once daily. Similar to Study 1218.5, there was a hierarchical testing procedure to show superiority of at least the highest dose of linagliptin to placebo. Glimepiride was an open-label treatment arm for sensitivity analysis.

Table 3. Glycemic Efficacy Results from Study 1218.6

Table 11.4.1.1.2: 2 Adjusted mean HbA1c change from baseline to week 12 (adjusted for antidiabetic therapy status, FAS-LOCF)

HbA1c (%)	Placebo	BI 1356 1 mg	BI 1356 5 mg	BI 1356 10 mg
Number of patients	70	64	62	66
Adjusted mean change from baseline (SE)	0.34 (0.10)	–0.05 (0.10)	–0.42 (0.10)	–0.39 (0.10)
Difference to placebo (%) 95% CI p-value		–0.39 (0.14) (–0.66, –0.12) 0.0049	–0.75 (0.14) (–1.02, –0.48) <.0001	–0.73 (0.14) (–0.99, –0.46) <.0001

Means are adjusted based on a model with baseline HbA1c, treatment, ATS

All doses of linagliptin tested showed significant reductions in HbA1c relative to placebo. Study 1218.6 also showed greater efficacy with glimepiride over placebo and the treatment difference exceeded the findings observed with all doses of linagliptin.

Table 4. Efficacy of Glimepiride vs Placebo in Phase Trial 1218.6.

Table 11.4.1.1.2: 3 ANOVA for HbA1c change from baseline at week 12; active control vs. placebo (FAS-LOCF)

HbA1c (%)	Placebo	Glimepiride
Number of patients	70	64
Adjusted mean change from baseline (SE)	0.31 (0.09)	–0.59 (0.10)
Difference to placebo (%) 95% CI p-value		–0.90 (0.13) (–1.16, –0.64) <0.0001

Means are adjusted based on a model with baseline HbA1c, treatment, ATS
p-value of effect ATS: 0.0133

The findings in the active control arms of Studies 1218.5 and 1218.6 reveal that while linagliptin can reduce HbA1c, its efficacy is less than that of two commonly prescribed anti-diabetic therapies, metformin and glimepiride, at least for the 12-week duration of these studies.

DPP4-inhibitory activity was assessed in these trials and was noted to be consistently greater than 80% at doses above 5 mg. Despite the higher DPP4 inhibition at the 10 mg dose, there was no additional reduction in HbA1c achieved with the 10 mg dose over the 5 mg dose observed in Study 1218.6. The minimal additional benefit of glycemic control was noted in another trial conducted in Japanese patients, which evaluated the 5 and 10 mg doses of linagliptin relative to placebo. After 12 weeks, the mean change from baseline in HbA1c at the 5 and 10 mg dose was identical.

Figure 1. Efficacy of Linagliptin 5 and 10 mg at 12 weeks. Figure from Dr. Lokesh Jain's review.

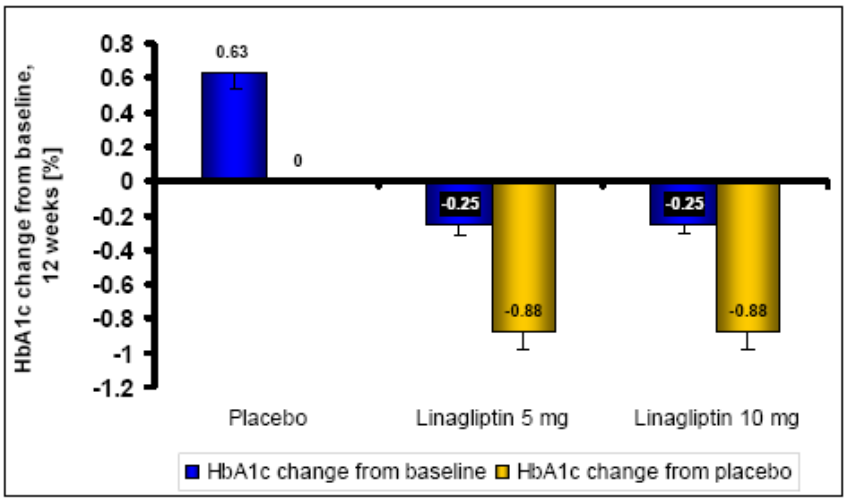


Figure 10: Adjusted means (SE) for HbA1c change from baseline and HbA1c change versus placebo after oral administration of linagliptin or placebo in monotherapy for 12 weeks in Phase 3 study 1218.23

Overall, the dose-response studies support the proposed maximal dose of linagliptin 5 mg. Although lower doses of linagliptin provided statistically greater reductions in HbA1c relative to placebo, the mean treatment differences of 0.2% and 0.4% are modest. Provided the 5 mg dose is a safe and effective dose and no vulnerable patient population has been identified necessitating a lower marketed dose, I concur that the 5 mg dose provides the maximal benefit-risk response.

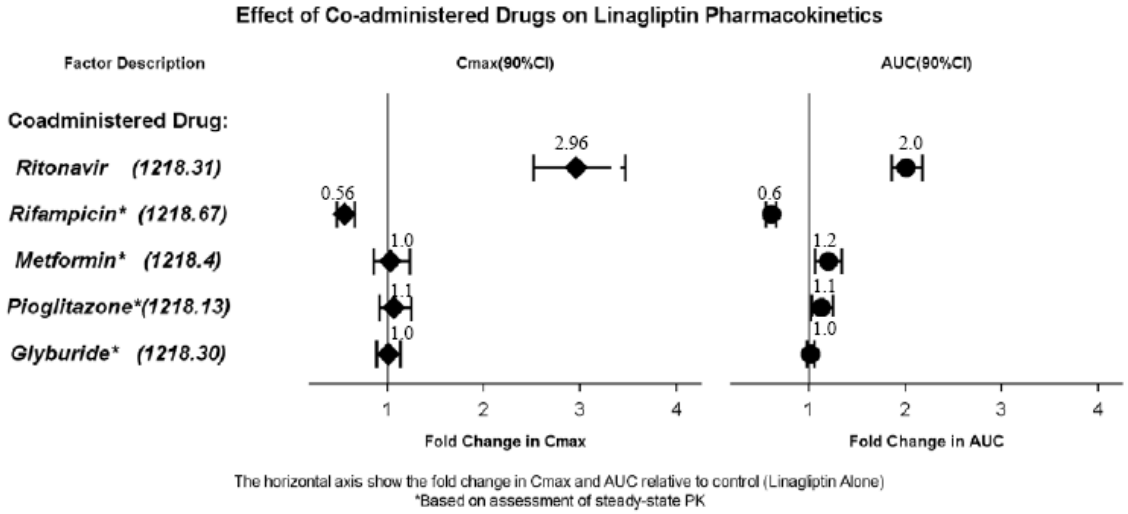
Drug-Drug Interactions

DDI studies evaluated the effect of potent inducers and inhibitors and likely co-administered drugs on the PK of linagliptin. Conversely, the effect of linagliptin on the PK of likely co-administered drugs and drugs with narrow therapeutic indices was studied in several DDI studies. Please see the review of Drs. Jain and Choe, dated 8 March 2011 for the detailed summaries of these studies. A brief summary is provided below.

Linagliptin is a CYP3A4 and P-gp substrate. The effect of CYP3A4 and P-gp inhibition on linagliptin pharmacokinetics was evaluated in a DDI study evaluating the relative bioavailability of a single dose of linagliptin 5 mg after co-administration with ritonavir 200 mg bid for 3 days compared to the bioavailability of a single dose of linagliptin 5 mg alone in a healthy male patient population. AUC and Cmax of linagliptin increased by about 2 and 3-fold, respectively. Conversely, the effect of the CYP3A4 and P-gp inducer, rifampicin, on linagliptin pharmacokinetics was evaluated and significant reduction in linagliptin exposure was noted. The bioavailability of linagliptin 5 mg daily doses was reduced to approximately the exposure expected with a 1 mg daily dosing regimen when co-administered with rifampicin.

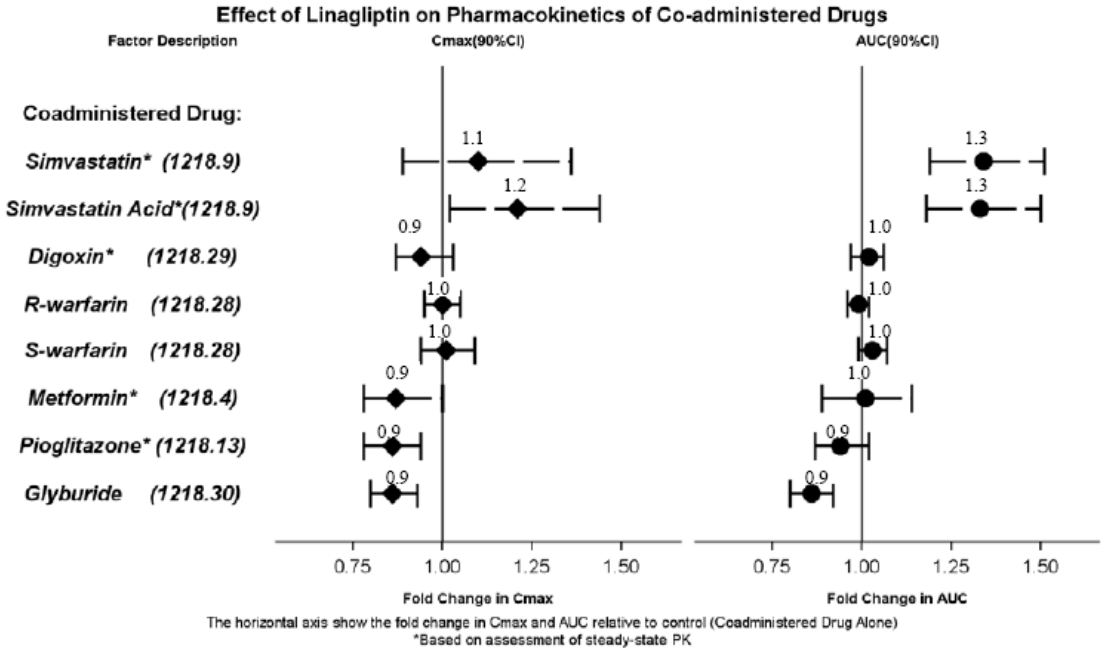
The following forest plots provide a nice summary of the different DDI studies which evaluated the effects of selected drugs on linagliptin PK and vice versa.

Figures 2 and 3. From OCP review, page 10



- There is no clinically meaningful effect of metformin, pioglitazone, and glyburide on linagiptin PK. The oral anti-diabetics were also co-administered with linagliptin in several of the Phase 3 trials.
- Co-administration with potent CYP3A4 and P-gp inhibitors is expected to increase linagliptin exposures; however, OCP reviewers are not recommending any dose adjustments based on acceptable safety data at these higher drug levels obtained in a Phase 3 trial which tested the 10 mg dose of linagliptin. I would further add that the wide safety margin identified in pharmacology/toxicology studies provide additional reassurance.
- Linagliptin drug levels will likely be reduced significantly when co-administered with a potent CYP3A4 and P-gp inducer. Given the availability of other anti-diabetic therapies including two other DPP4-inhibitors that are unaffected by 3A4 and P-gp induction, I concur with OCP recommendations that labeling should recommend the use of alternative anti-diabetic therapies in patients requiring therapies with a 3A4/P-gp inducer.

Linagliptin co-administered with simvastatin (a CYP3A4 substrate) did not result in a clinically meaningful increase in simvastatin/simvastatin acid exposures. A 30% increase in AUC is not expected to result in simvastatin exposures posing a marked increased risk for rhabdomyolysis. Linagliptin did not result in clinically meaningful increase or decreases in digoxin or warfarin. Although exposures of pioglitazone and glyburide were lowered by the co-administration with linagliptin, this should not adversely impact clinical efficacy as supported by data from several Phase 3 trials where these drugs were studied in combination.



Special Populations

This section will only summarize findings in the renal impaired patient population. The OCP review provides detailed analyses on drug exposure by gender, BMI/weight, age, race, and hepatic impairment. Overall, no clinically meaningful difference in exposures was observed by those intrinsic factors although data were sparse in certain subgroups (e.g., racial/ethnic subgroups).

Study 1218.26 was a PK study evaluating linagliptin pharmacokinetics in diabetic and non-diabetic patients with normal renal function and varying degrees of renal impairment. The study had multiple and single-dose treatment groups as summarized below:

Group 1: non-DM with normal renal function (multiple dosing; 7 days)
Group 2: non-DM with mild renal impairment (multiple dosing; 7 days)
Group 3: non-DM with moderate renal impairment (multiple dosing; 7 days)
Group 4: non-DM with severe renal impairment (single dosing)
Group 5: non-DM with ESRD (single dosing)
Group 6: T2DM with severe renal impairment (multiple dosing; 10 days)
Group 7: T2DM with normal renal function (multiple dosing; 10 days)

Sample size in each treatment group was small (n=6 except in Groups 6 and 7 which enrolled 10 and 11 patients, respectively). Across the varying degrees of renal impairment in both the non-DM and T2DM population, average linagliptin exposure was increased from 41% to 71% compared to patients with normal renal function. Cmax in all comparisons increased by 36-50%. The following scatter plot displays the individual steady state AUCs in Study 1218.26. Except for one outlier, steady state AUCs fall within the range of 100-350 nmol-hr/L.

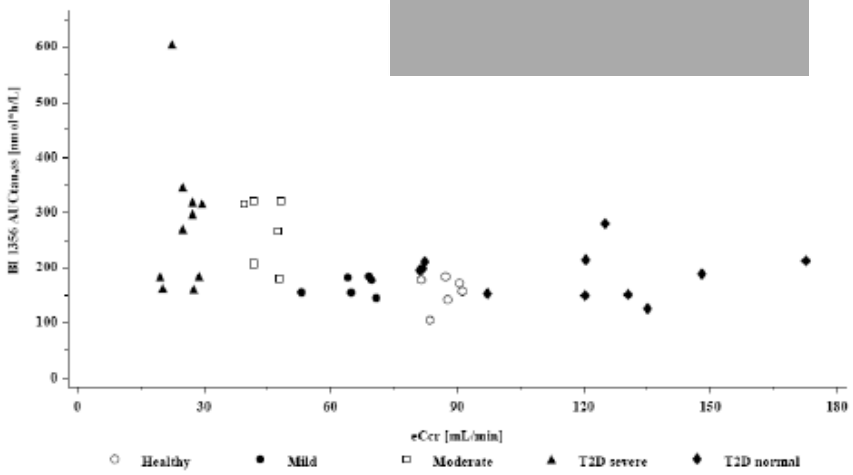


Figure 10: Scatter plot of CrCl (eCcr) and steady state $AUC_{\tau,ss}$ of linagliptin after oral administration of multiple 5 mg doses to subjects with normal renal function, patients with mild or moderate renal impairment, patients with T2DM and severe renal impairment

Clinical pharmacology reviewers are not recommending any dose adjustments based on renal function, citing the wide safety margin from nonclinical program, reassuring safety findings from a clinical trial in Japanese patients which studied linagliptin 10 mg out to 52 weeks, and the 12-week interim analysis of a 52-week trial in patients with renal impairment.

Overall, the clinical pharmacology of linagliptin has been adequately evaluated in this NDA. The Office of Clinical Pharmacology has recommended approval in its review dated 7 March 2011 without additional studies/trials required postmarketing.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

There were 9 Phase 3 trials submitted with this NDA; 7 of these were (b) (4) for efficacy and will be discussed under this section of the memo. The other two studies were reviewed in more detail by FDA for safety, including CV safety. The primary efficacy endpoint in all trials was percent change in HbA1c from baseline. Among the multiple secondary efficacy parameters were post-prandial glucose levels after meal tolerance tests (MTT) and fasting plasma glucose levels, which have been summarized in the primary reviews and will not be noted here. Please see Dr. Wei Liu's statistical review dated 11 March 2011 for a detailed discussion of trial design, statistical analysis plan, and results. I will summarize the efficacy findings of linagliptin when used as monotherapy and add-on therapy, compared to placebo or to other anti-diabetic therapies.

Linagliptin Monotherapy

The efficacy of linagliptin as a single agent for the treatment of T2DM was compared to placebo in two Phase 3 trials. Its efficacy relative to placebo was also evaluated in two dose-

response studies described under Section 5 of this memo. The Phase 3 trials included a 24-week trial in which T2DM patients who were drug-naïve or previously treated but could be washed off therapy to assess linagliptin monotherapy (Study 1218.16) and a 18-week trial in patients similar to those in Study 1218.16 plus patients who could not tolerate metformin or had contraindications to its use (Study 1218.50). This latter trial had a 2nd active-controlled, double-blind portion which will not be discussed here as it is ongoing.

Study 1218.16 was a randomized, double-blind, placebo-controlled trial in 503 T2DM patients with mean baseline HbA1c of 8%. Slightly more than half were drug-naïve (57.5%). Randomization was 2:1 (linagliptin:placebo) and stratified by HbA1c at start of run-in (< or ≥ 8.5%). The majority had HbA1c < 8.5% (70.8%). 36.1% of patients had diagnosis of T2DM of < 1 yr duration; 36.7% for 1-5 yrs; and 25.2% > 5 yrs. The short duration of disease is not unexpected for a monotherapy trial as most patients with diabetes for longer duration are on multiple drug therapy and are more appropriate candidates for add-on trials.

Different analyses were performed on the primary endpoint measure. Overall the findings across these different analyses and sensitivity analyses support the conclusion that linagliptin 5 mg daily dosing was superior to placebo in reducing HbA1c from baseline. The following table summarizes the sponsor's and FDA's primary analysis.

Table 5. Study 1218.16 Primary Efficacy Results

	Placebo	Linagliptin 5 mg
Sponsor's Analysis*		
Number of patients	163	333
Baseline mean HbA1c	8%	8%
Adjusted mean chg from baseline (SE)	+0.25 (0.07)	-0.44 (0.05)
Adjusted mean treatment difference (linagliptin-pbo) 95% CI		-0.69 (-0.85,-0.53)
FDA's Analysis**		
Number of patients	167	336
Baseline mean HbA1c	8%	8%
Adjusted mean chg from baseline (SE)	+0.26 (0.08)	-0.45 (0.05)
Adjusted mean treatment difference (linagliptin-pbo) 95% CI		-0.71 (-0.89,-0.53)

*Analysis of covariance method w/ treatment and prior anti-DM as fixed effects and baseline HbA1c as linear covariate on full analysis set
**mixed model repeated measures method with visit week as an additional fixed effect on the observed completers population

A consistent finding of greater HbA1c reduction in linagliptin compared to placebo was observed across all subgroups analyzed (e.g., baseline HbA1c, prior anti-DM therapy, gender, BMI, etc.)

Study 1218.50 was a randomized, double-blind, placebo-controlled trial in 227 T2DM patients with mean baseline HbA1c of 8%. Slightly more than half were drug-naïve (54.1%). Randomization was 2:1 (linagliptin:placebo) and stratified by HbA1c at start of run-in (< or ≥ 8.5%), previous use of anti-DM therapies; and reason for metformin ineligibility. The majority had HbA1c < 8.5% (70.8%). 22.7% of patients had diagnosis of T2DM of < 1 yr duration; 52.3% for 1-5 yrs; and 25% > 5 yrs.

Similar to Study 1218.16, different methods of analyses were performed by the applicant and FDA; however, the primary analyses and sensitivity analyses all revealed a consistent finding of linagliptin 5 mg being superior to placebo.

Table 6. Study 1218.50 Primary Efficacy Results (FDA analysis)

	Placebo	Linagliptin 5 mg
Number of patients	76	155
Baseline mean HbA1c	8.09%	8.12%
Adjusted mean chg from baseline (SE)	+0.25 (0.13)	-0.33 (0.09)
Adjusted mean treatment difference (linagliptin-pbo) 95% CI		-0.57 (-0.89,-0.26)

Dr. Wei presented efficacy results by subgroups in a forest plot in his review in Figure 3.1.8. Across all subgroups a numerically greater HbA1c reduction was observed with linagliptin although not all were statistically significant with the obvious limitation being small sample sizes in some subgroups. Metformin is considered 1st line therapy for most patients with T2DM. This study specifically enrolled patients who were ineligible or intolerant to metformin, so it of interest to see that in the subgroup of metformin ineligibles there was a mean HbA1c reduction of 0.55-0.89% relative to placebo.

In conclusion, Studies 1218.16 and 1218.50 confirm the effectiveness of linagliptin 5 mg daily dosing noted in Phase 2 trials of shorter duration. Although these Phase 3 trials would support labeling for use of linagliptin as monotherapy in T2DM, I would emphasize the observation that metformin and glimepiride provided greater glycemic control in the two Phase 2 dose-response trials over linagliptin monotherapy.

Linagliptin Add-on Therapy

Five Phase 3 trials evaluated the addition of linagliptin to other anti-diabetic therapies. Four of these trials compared linagliptin add-on to placebo add-on in patients who had not achieved adequate glycemic control on other anti-diabetic therapies or as initial therapy in a drug-naïve population. These studies were designed to show superiority of linagliptin over placebo in different add-on scenarios. There was one head-to-head comparison of linagliptin to glimepiride. The trial was designed to show non-inferiority between the two drugs.

The placebo-controlled, add-on trials all supported a conclusion of superiority of linagliptin 5 mg over placebo. This is not an unexpected finding as it is generally observed across numerous development programs that the addition of an anti-diabetic therapy of a different class to current therapies will result in better glycemic control than continuing therapy with the current regimen. The following table summarizes the findings from these four trials using FDA's analysis.

Table 7. Glycemic Control Efficacy Results in Linagliptin Add-on, Placebo-controlled Trials

		Placebo	**Linagliptin**
Study 1218.15 (24 wks)			
Compared lina+pio to pbo+pio in drug-naïve or patients wash-out of current anti-DM therapies 24-wk trial	N	130	259
	Mean baseline HbA1c (SE)	8.6 (0.08)	8.6 (0.05)
	Adjusted mean chg from baseline (SE)	-0.85 (0.09)	-1.30 (0.06)
	Adjusted mean treatment diff (95% CI)		-0.46 (-0.67, -0.24)
Study 1218.17 (24 wks)			
Compared lina+metformin to pbo+metformin in patient inadequately controlled on metformin	N	177	523
	Mean baseline HbA1c (SE)	8.0 (0.07)	8.1 (0.04)
	Adjusted mean chg from baseline (SE)	0.08 (0.07)	-0.58 (0.04)
	Adjusted mean treatment diff (95% CI)		-0.66 (-0.82,-0.50)
Study 1218.18 (24 wks)			
Compared lina + met/su to pbo + met/su in	N	263	792
	Mean baseline HbA1c (SE)	8.1 (0.05)	8.2 (0.03)

patients inadequately controlled on met/su	Adjusted mean chg from baseline (SE)	-0.11 (0.05)	-0.72 (0.03)
	Adjusted mean treatment diff (95% CI)		-0.61 (-0.73, -0.49)
Study 1218.35 (18 wks)			
Compared lina+SU to pbo+SU in patients inadequately controlled on SU	N	84	161
	Mean baseline HbA1c (SE)	8.6 (0.08)	8.6 (0.07)
	Adjusted mean chg from baseline (SE)	-0.13 (0.10)	-0.60 (0.07)
	Adjusted mean treatment diff (95% CI)		-0.47 (-0.71,-0.22)

Study 1218.20 is a long-term, active-controlled trial comparing linagliptin 5 mg daily dosing to glimepiride in T2DM previously treated with metformin or metformin plus one other oral anti-diabetic drug without changes to dosing within 10 weeks prior. Patients treated with anti-diabetic drugs other than metformin entered a 6-week washout period. In effect, this trial randomized patients in a 1:1 fashion to linagliptin + metformin vs glimepiride + metformin. Glimepiride was initiated at 1 mg. Over the course of the first 12 weeks, glimepiride could be titrated stepwise to the next dose up to 4 mg daily every 4 weeks if the home BG monitoring was > 110 mg/dL.

This trial was designed to be a 104-wk (2-yr) trial but only the interim results are presented in this NDA (52 wk data). The primary hypothesis is that linagliptin is non-inferior to glimepiride. In addition, the trial tested the superiority of linagliptin versus glimepiride with respect to body weight change and hypoglycemia. This trial is of relevance to this NDA for the following reasons:

- It contains controlled data for the longest duration of all trials reviewed in the NDA
- Long-term glycemic control of linagliptin relative to glimepiride from this trial support the observation of lower efficacy with linagliptin from a 12-wk Phase 2 trial
- It is the largest controlled trial, in terms of number of patients randomized, of all trials reviewed in the NDA
- It is an active controlled trial using the same comparator proposed in the postmarketing required trial to assess long-term CV safety
- The majority of CV events from the CV safety meta-analysis came from this trial

Mean baseline HbA1c was 7.8% in this patient population. This is in contrast to other Phase 2 and 3 trials summarized above in which the average baseline HbA1c values were 8% or higher. Approximately 53% of the population had a diagnosis of T2DM for more than 5 years and 33% of the population was ≥ 65 years of age. From Table 3.1.8 in Dr. Liu's review, one will note that other add-on trials tended to enroll fewer patient within this age category (17-27%).

The non-inferiority of linagliptin to glimepiride with regard to HbA1c reduction applied a non-inferiority margin of 0.35% as the upper bound of the 97.5% CI.

The trial randomized 1560 patients in a 1:1 fashion to linagliptin (779) and glimepiride (781) with stratification by baseline HbA1c (< vs ≥ 8.5%) and previous use of anti-diabetic drugs

(metformin monotherapy vs metformin plus one other oral anti-diabetic drug). The majority of patients (71.5%) had previous monotherapy for their diabetes.

After 52 weeks of treatment, the mean treatment difference in HbA1c from baseline of linagliptin compared to glimepiride was 0.20% (97.5% CI: 0.11, 0.30) based on the FDA analysis (note that Table 3.1.10 in Dr. Liu's review has the treatment difference reversed wherein negative values should be positive and the 97.5% boundaries are presented in reverse order – upper to lower bound).

Linaglipin 5 mg daily dosing yielded lower glycemic control than glimepiride 1 to 4 mg with the loss in efficacy potentially being as higher as 0.30%. Although the upper bound of the 97.5% CI is still below the pre-specified NI margin of 0.35%, it should also be noted that the lower bound excludes zero, indicating that linagliptin is both statistically non-inferior and inferior to glimepiride.

Although the secondary objectives of this trial included a demonstration of superiority of linagliptin over glimepiride for hypoglycemia and weight gain, these secondary objectives should not be over-emphasized in labeling such that it obscures the findings from the primary objective of this trial.

8. Safety

Please see Dr. Somya Dunn's clinical review of this NDA for details from her safety evaluation. For this NDA, there were exposure data in 4687 patients with T2DM who received linagliptin at any dose. Of those patients who received linagliptin 5 mg (n=4061), 3430 received drug for 6 months, 2390 received drug for 12 months or longer and 536 received drug for 18 months or longer. Due to unbalanced randomization in many of the trials wherein more patients were randomized to linagliptin, the number and patient-yrs of exposure were higher in linagliptin than placebo or active-control groups. For example, in the data set pooling all placebo-controlled trials, the pt-yr exposure for linagliptin 5 mg was 1041.4 versus 433.8 for placebo, approximately 2.3x higher exposure rates for linagliptin. Overall there were 4034.2 pt-yrs exposure for linagliptin 5 mg across all trials involving patients with T2DM.

My memo will focus only on CV safety and some class safety concerns of the DPP4-inhibitors/incretin mimetics.

Cardiovascular Safety

In December 2008, FDA issued a Guidance for Industry titled, "Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes". This Guidance requires sponsor to rule-out an unacceptable CV risk associated with the use of a new anti-diabetic therapy. 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. This clinical development program was already in Phase 3 at the time this Guidance was issued.

Consequently, the applicant has conducted a meta-analysis of several Phase 2 and 3 trials that were not prospectively designed to collect CV safety data to address the requirements under the December 2008 guidance. Please see the review of Drs. Xiao Ding, Mat Soukup, and Aloka Chakravarty from the Division of Biometrics VII dated 14 March 2011 for a detailed discussion of the meta-analysis.

In June 2009, the applicant provided its plans to evaluate CV safety with current clinical trial data. FDA advice/recommendations on these plans are summarized in a letter issued on 22 September 2009 under IND 70,963. Although FDA recommended that the composite endpoint of CV death, nonfatal MI, and nonfatal stroke (MACE) be specified as the primary analysis, this was not a requirement and the applicant was informed that FDA would evaluate the contribution of each component of its proposed composite endpoint to the overall findings of CV safety. The applicant has conducted a meta-analysis of 8 randomized Phase 3 trials involving data in 5,244 patients with T2DM. These studies have been discussed in earlier sections of this memo but are summarized again below with key design features:

Table 8. Trials Included in CV Meta-analysis

	Description of trials/design considered in MA	**Linagliptin**	**Placebo**	**Active Comparators**
Study 1218.15 Study 1218.16 Study 1218.17 Study 1218.18	24-wks, placebo-controlled	259 336 524 793	130 167 177 265	- - - -
Study 1218.20*	52-wks, active-control (glimepiride)	779	-	781
Study 1218.23**	12-wk, placebo-controlled 26-wk, active-controlled (voglibose)	319	80	162
Study 1218.35 Study 1218.50***	18-wks, placebo-controlled	161 151	84 76	- -
Number of patients		3322	979	943 -781 glimepiride -162 voglibose

*Trial is 104-wk long but only 52-wk interim data reviewed
**Trial has 4 treatment arms with different objectives: 12-wk comparison to pbo and 26-wk comparison to voglibose
***Trial has 2nd phase, double-blind, active control using glimepiride. Only 18wk data reviewed

Baseline characteristics of the patient populations included in the meta-analysis suggest an overall low risk population for CV events. The highest baseline risk, described as % of patients with Framingham risk > 15%, was in the active-controlled trial, 1218.20 which compared linagliptin to glimepiride. This trial also contributed the longest duration of evaluation in the overall meta-analysis. Consequently, Study 1218.20 contributed significantly to the overall results that will be discussed further below. It is also interesting to note that in the summary of baseline characteristics of the pooled studies, the active-comparator group contained a higher percentage of patients (37.8%) with Framingham risk score > 15% than the linagliptin (27.8%) or placebo (24.7%) groups (See Table 5 from DB7 review). Although the statistical reviewer made a comment that this imbalance was more likely due to differences across the studies pooled and not due to an imbalance within each trial, I note that Table 6 from his review does not support this as half of the trials had a > 5% different in Framingham risk score between treatment groups

Table 9. Baseline Framingham Risk by Study and Treatment Group (Safety Population) - Table obtained from FDA statistical reviewer

Study	Mean risk score (%) (Percentage of subjects with risk score >15%)			
	All Linagliptin	Placebo	Active Comparator	Total
1218.15	10.07 (29.0)	11.07 (36.2)	-	10.40 (31.4)
1218.16	8.63 (23.8)	7.47 (16.8)	-	8.24 (21.5)
1218.17	8.57 (22.0)	8.87 (25.4)	-	8.65 (22.9)
1218.18	9.24 (26.5)	8.67 (20.9)	-	9.10 (25.1)
1218.20	11.65 (35.9)	-	11.67 (37.9)	11.66 (36.9)
1218.23	11.09 (32.6)	11.18 (33.8)	11.32 (37.0)	11.17 (34.0)
1218.35	8.66 (21.1)	9.36 (25.0)	-	8.90 (22.4)
1218.50	7.94 (17.2)	8.72 (23.7)	-	8.20 (19.4)

Source: Created by reviewer.

There was also an imbalance in early discontinuation with more patients in the placebo/comparator groups discontinuing than linagliptin. Unlike well-designed CV outcomes trials, patients discontinued from these trials are not followed until the end of study for CV events.

The primary composite proposed by the applicant was comprised of CV death, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina. Secondary endpoints included the occurrence of each component of this composite endpoint and MACE. These events were prospectively adjudicated by a blinded endpoints committee. Please see Dr. Irony's CDTL memo for description of the adjudication process.

The statistical analytical approaches have been discussed in the FDA review from DB7. For this memo I will only summarize the results of the meta-analysis based on FDA's statistical approaches. Analyses of incidence, time-to-event, and respective sensitivity analyses were performed.

There were a total of 34 patients who had a CV death (4), NFMI (13), NF stroke (13), or hospitalization for UA (4). All but one trial had at least one of these events. The following table from the statistical review summarizes the type of event and the trial in which it occurred.

Table 10. Summary of Events of Primary Composite Endpoint by Study and Treatment Group (Safety Population) – Table obtained from FDA statistical review

Study	Arms	Sample Size	Primary Composite Endpoint n (%)	CV Death n (%)	Non-fatal MI n (%)	Non-fatal Stroke n (%)	UA with Hosp* n (%)
1218.15	linagliptin	259	1 (0.4)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
	placebo	130	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1218.16	linagliptin	336	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	placebo	167	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1218.17	linagliptin	523	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
	placebo	177	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)
1218.18	linagliptin	792	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)
	placebo	263	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
1218.20	linagliptin	778	3 (0.4)	1 (0.1)	2 (0.3)	0 (0.0)	0 (0.0)
	glimepiride	781	20 (2.6)	2 (0.3)	6 (0.8)	10 (1.3)	2 (0.3)
1218.23	linagliptin	319	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
	placebo/ ***voglibose***	242	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1218.35	linagliptin	161	2 (1.2)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.6)
	placebo	84	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
1218.50	linagliptin	151	2 (1.3)	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)
	placebo	76	1 (1.3)	0 (0.0)	1 (1.3)	0 (0.0)	0 (0.0)

* UA with Hosp – Hospitalization due to unstable angina
Source: Created by reviewer.

Overall, 0.33% of linagliptin-treated patients had a primary CV event compared to 1.2% of patients in the control groups (placebo and active combined). This yielded a risk difference of -0.69% (-1.17%, -0.21%) that was statistically significantly in favor of linagliptin. Two sensitivity analyses were conducted. As mentioned earlier, Study 1218.20 provided the predominant number of CV events in the meta-analysis with 24 of the 34 events. When Study 1218.20 was excluded, there was no significant difference between linagliptin and controls on the incidence of experiencing a primary CV event. Limiting the analysis to only placebo-controlled phases of the trials also yielded no statistically significant difference between linagliptin and placebo. The following table summarizes the overall results and the two sensitivity analyses.

Table 11. Analyses of Incidence of Primary CV Composite Endpoint in Meta-Analysis (adapted from review by Drs. Ding and Soukup)

	Linagliptin	Comparator
Overall Results		
Incidence of Events	11/3319 (0.33%)	23/1920 (1.2%)
MH Risk Difference (95% CI) MH Relative Risk Ratio (95% CI) Exact Stratified OR (95% CI)	-0.69% (-1.17, -0.21%) 0.34 (0.15, 0.74) 0.36 (0.16, 0.78)	
Excluding Study 1218.20		
Incidence of Events	8/2541 (0.31%)	3/1139 (0.26%)

MH Risk Difference (95% CI) MH Relative Risk Ratio (95% CI) Exact Stratified OR (95% CI)	0.06% (-0.34, 0.46%) 1.21 (0.35, 4.26) 1.23 (0.29, 7.27)	
Linagliptin vs Placebo Controls Only		
Incidence of Events	6/2541 (0.24%)	3/977 (0.31%)
MH Risk Difference (95% CI) MH Relative Risk Ratio (95% CI) Exact Stratified OR (95% CI)	-0.04% (-0.45, 0.37%) 0.86 (0.23, 3.26) 0.85 (0.18, 5.32)	

The Guidance states that in order for a new anti-diabetic to be approved, the applicant *must compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence of the same type of events occurring with the control group to show that the upper bound of the 2-sided 95% CI for the estimated risk ratio is < 1.8*. There is no requirement that applicants must meet this upper bound for subgroup analyses. In fact, in FDA's review of the most recently approved anti-diabetic therapy, liraglutide, the decision that the applicant had met the 1.8 regulatory threshold for approval was based on a comparison of liraglutide to total comparators in its meta-analysis of controlled clinical trials. For linagliptin, I note that the point estimates in the sensitivity analysis excluding Study 1218.20 are greater than 1.0; however, the CIs are wide and include unity. The sensitivity analyses for comparison of CV events between linagliptin and placebo yielded point estimates less than 1.0 but again, the CIs are wide and include unity. In both scenarios, these sensitivity analyses are based on very few events, single digits in each treatment group, that one cannot conclude a protective or detrimental effect of linagliptin.

With respect to the overall results, the upper bound of the 95% CI in the overall analysis not only excluded 1.8 but it also excluded 1.3. According to the Guidance, *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 less than 1.3 and the overall risk-benefit analysis supports approval, a postmarketing cardiovascular trial generally may not be necessary*. However, such a determination should really be based on robust evidence that the drug is clearly not associated with a CV risk as high as 30% over comparators. Such evidence does not exist in this NDA due to the limitations of this meta-analysis (few events, low risk population, trials not prospectively designed to evaluate CV safety, inconsistent findings on sensitivity analyses). And to that end, the applicant will be required to conduct a CV outcomes trial as a required postmarketing trial.

The applicant previously proposed an active-controlled trial of linagliptin to glimepiride in the Cardiovascular Safety of Linagliptin vs Glimepiride in Patients with T2DM at High CV Risk (CAROLINA) as its required postmarketing trial. The primary endpoint in this trial is time to first occurrence of any one of the following: CV death; nonfatal MI; nonfatal stroke; and hospitalization for unstable angina pectoris. Definitions for these endpoints are based on the ones specified by DMEP in consultation with the Division of Cardiovascular and Renal Products (DCRP).

The patient population to be enrolled in CAROLINA will include T2DM patients with established vascular disease (e.g., MI > 6 weeks prior to informed consent) or other characteristics that would put them at higher risk for a CV event during trial conduct (e.g., age ≥ 70 yrs or T2DM > 10 yrs duration plus smoking).

Patients with different background therapies for T2DM except rosiglitazone, pioglitazone, GLP-1 analogues, and DPP4 inhibitors, will be allowed to enroll (prior insulin treatment must be of limited duration) provided the same dose is maintained throughout the entire study. Patients currently on an SU or glinide will discontinue this treatment and enter a wash-out period. Only pioglitazone, metformin, or insulin will be allowed for rescue of inadequate glycemic control and their use will be based on local/regional standards of care after a patient has met the criteria requiring rescue medication. Rescued patients, including those who require discontinuation of study drug, will remain in the trial.

The trial is event driven and will randomized a minimum of 6000 patients for approximately 400 weeks beginning with randomization of the first patient. The estimated annual event rate in the glimepiride arm is 2.0%. In addition to the primary endpoint, the applicant is proposing the following key secondary endpoints to be considered in its hierarchical statistical testing for significance:

- A composite of: treatment sustainability defined as the proportion of patients that are on study treatment at study end, that at Final Visit maintain glycemic control (HbA1c ≤ 7%) without need for rescue medication (b/w Visit 6 and Final Visit) and patients w/o moderate/severe hypoglycemic episodes (b/w Visit 6 and Final Visit) and w/o > 2% weight gain at Final Visit (b/w Visit 6 and Final Visit)
- A composite of: treatment sustainability defined as the proportion of patients that are on study treatment at study end, that at Final Visit maintain glycemic control (HbA1c ≤ 7%) without need for rescue medication (b/w Visit 6 and Final Visit) and patients w/o > 2% weight gain at Final Visit (b/w Visit 6 and Final Visit)

The applicant will first test for non-inferiority on the primary CV composite endpoints (CV death, nonfatal MI, nonfatal stroke and hospitalization for UA) based on the NI margin of 1.3. If this result is significant, a test for superiority will be performed on the same primary CV composite endpoint. If superiority is demonstrated, the key secondary endpoints will be tested sequentially.

A total of 631 events will be needed to have at least 90% power to meet the 1.3 NI margin and 80% power to show superiority. However, this estimate is based on no planned interim analysis. FDA statisticians will be providing comments to the applicant on the CAROLINA protocol.

CAROLINA is unique in that it proposes a direct comparison to an active control. To date, companies have proposed a comparison to placebo plus standard of care. The concern with establishing NI to glimepiride is the absence of knowledge on glimepiride's CV safety risk relative to other available anti-diabetic therapies. Should glimepiride (or sulfonylureas as a class) be less safe than other approved therapies, establishing non-inferiority between linagliptin and glimepiride has the potential for approving a drug that carries excess CV risk

over other anti-diabetic therapies. However, a placebo-controlled non-inferiority trial to assess CV risk of a new anti-diabetic therapy does not compare it to a true placebo group, but will compare it to other therapies allowed in the trial to maintain adequate glycemic control, because the progressive nature of T2DM and the trial's long duration will necessitate initiation of drug treatment if a patient was not already prescribed one at start of the trial. As an example, the PROactive trial was a CV outcomes trial comparing pioglitazone add-on to placebo add-on to standard of care, a design not too different from what many companies are now proposing to address FDA's requirement. At the start of the PROactive trial only 4% were enrolled in the trial as true placebo-treated patients. All other patients were treated with some other anti-diabetic therapy or a combination of therapies.

Table 6.1.4.1.5 Baseline Antidiabetes Therapy

Therapy	Pioglitazone N = 2605 n (%)	Placebo N = 2633 n (%)
Metformin only	253 (9.7)	261 (9.9)
Sulfonylureas only	508 (19.5)	493 (18.7)
Metformin + sulfonylureas only	654 (25.1)	660 (25.1)
Insulin only	5 (0.2)	8 (0.3)
Insulin + metformin	456 (17.5)	475 (18.0)
Insulin + metformin + sulfonylureas	105 (4.0)	107 (4.1)
Other	306 (11.7)	305 (11.6)
Diet only	109 (4.2)	105 (4.0)

Source: Applicant's Table 10.f., pg 71, Part A, study report

As the trial progressed, the addition of rescue therapies resulted in more patients requiring insulin such that by the final visit in this 3-year trial, there were 201 patients in the pioglitazone group and 274 in placebo who required addition of insulin whereas only 5 and 8 in each of these respective groups received insulin at baseline. The balance between treatment groups at baseline for background therapies was also lost as noted in the following table. Notably, more patients in pioglitazone required the addition of a SU whereas there was a decline in SU use in the placebo group with perhaps many of those patients switched solely to insulin.

Anti-diabetic Medications by Study Visit
Full Analysis Set

	Pioglitazone N = 2605	Placebo N = 2633	Total N = 5238
Final visit - scheduled visit attended	2415	2425	4840
Metformin only	315 (13.0%)	247 (10.2%)	562 (11.6%)
Sulphonylureas only	456 (18.9%)	329 (13.6%)	785 (16.2%)
Metformin + sulphonylureas	574 (23.8%)	616 (25.4%)	1190 (24.6%)
Insulin only	201 (8.3%)	274 (11.3%)	475 (9.8%)
Insulin + metformin	409 (16.9%)	530 (21.9%)	939 (19.4%)
Insulin + sulphonylureas	150 (6.2%)	170 (7.0%)	320 (6.6%)
Insulin + metformin + sulphonylureas	106 (4.4%)	150 (6.2%)	256 (5.3%)
None	204 (8.4%)	109 (4.5%)	313 (6.5%)

These observations from PROactive should be taken into consideration as we review current proposals from applicants to address the new FDA requirements for CV risk assessment. T2DM CV trials designed to demonstrate non-inferiority to placebo (standard of care) trials will inform us on the CV safety of the new anti-diabetic therapy relative to standard of care.

In these trials one could anticipate that the placebo group will require more rescue therapies than the investigational arm and an imbalance in background therapies may result such that interpretation of CV risk would have to consider how shifting background therapies alter the risk profile in either treatment groups.

By employing an active-control arm, CAROLINA may mitigate the need for rescue therapy, or at least delay its initiation. There remains debate on which approved therapy has a neutral CV risk profile and to date, FDA has not openly specified its preference of one agent over another nor did the December 2008 Guidance make clear that a well-designed CV safety trial must compare the new agent to placebo (standard of care). Instead the Guidance has the following passage:

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.

The selection of a sulfonylurea as the comparator in CAROLINA has been problematic because of a bolded warning in all SU labels based on the United Group Diabetes Program involving tolbutamide. It remains uncertain whether the findings from this trial, which was initiated in the 1960s, hold true for other SUs, particularly those not associated with the inhibition of ATP-sensitive K+ channels. However, Boehringer-Ingelheim is also proposing a sequential testing for superiority of linagliptin over glimepiride. Based on the interim results of Study 1218.20, there may very well be a chance that linagliptin is superior to glimepiride on reducing CV risk. Using event rates based on Study 1218.20 and applying it to current CAROLINA assumptions, FDA statisticians acknowledge sufficient power to demonstrate superiority, especially if event rates in CAROLINA are similar to Study 1218.20.

A recent information request for event rates in Study 1218.20 after the 52-wk interim analysis provides continued reassurance that controlled data out to 2 years continue to favor linagliptin. Table 12 was provided by the applicant. In the 2-yr dataset, there were 13 (1.7%) MACE events in linagliptin versus 26 (3.4%) in glimperide. The majority of these events were nonfatal MI (7 vs 10) followed by nonfatal stroke (3 vs 11), with fewer events in linagliptin for both types of events. There were only 4 CV deaths, two in each treatment group and 6 hospitalizations for UA, 3 in each treatment group. These results are preliminary, as the final clinical trial report has not been completed and would therefore not be allowed in labeling.

Table 12. Response to Information Request for Updated CV Event Rates in Study 1218.20. Data below are from final 2-yr dataset with database lock of 1-26-2011. Final report pending.

Table 15.3.2: 13 Adjudication results: Frequency [N(%)] of patients with CEC confirmed events by treatment - TS

	Linagliptin	Glimepiride
Number of patients [N(%)]	776 (100.0)	775 (100.0)
Patients with TIA [N(%)]	1 (0.1)	5 (0.6)
Patients with non-fatal stroke [N(%)]	3 (0.4)	11 (1.4)
Patients with ischemic stroke [N(%)]	3 (0.4)	10 (1.3)
Patients with hemorrhagic stroke [N(%)]	0 (0.0)	1 (0.1)
Not assessable [N(%)]	0 (0.0)	0 (0.0)
Patient with non-fatal MI [N(%)]	7 (0.9)	10 (1.3)
Patients with STEMI [N(%)]	3 (0.4)	8 (1.0)
Patients with NSTEMI [N(%)]	3 (0.4)	1 (0.1)
Not assessable [N(%)]	1 (0.1)	1 (0.1)
Patients with other myocardial ischemia [N(%)]	14 (1.8)	14 (1.8)
Patients with stable angina [N(%)]	11 (1.4)	12 (1.5)
Patients with unstable angina [N(%)]	3 (0.4)	3 (0.4)
with hospitalisation [N(%)]	3 (0.4)	3 (0.4)
without hospitalisation [N(%)]	0 (0.0)	0 (0.0)
Patients with cardio-vascular death (including fatal stroke) [N(%)]	2 (0.3)	2 (0.3)
Patients with acute MI [N(%)]	0 (0.0)	0 (0.0)
Patients with sudden death [N(%)]	1 (0.1)	2 (0.3)
Patients with worsening of heart failure [N(%)]	0 (0.0)	0 (0.0)
Patients with cardio-genic shock [N(%)]	0 (0.0)	0 (0.0)
Other [N(%)]	1 (0.1)	0 (0.0)
Patients with fatal stroke [N(%)]	0 (0.0)	0 (0.0)
Patients with fatal ischemic stroke [N(%)]	0 (0.0)	0 (0.0)
Patients with fatal hemorrhagic stroke [N(%)]	0 (0.0)	0 (0.0)
Not assessable [N(%)]	0 (0.0)	0 (0.0)
Patients with cardio-vascular death, MI, stroke or unstable angina [N(%)]	13 (1.7)	26 (3.4)

The updated preliminary results from Study 1218.20 are encouraging and should be further tested in a dedicated trial of longer duration. If CAROLINA is also capable of corroborating the findings from Study 1218.20, this would yield important comparative CV safety information between linagliptin and a commonly prescribed sulfonylurea.

As the reviews for this NDA were nearing completion, the design of this ongoing trial was discussed with Drs. Jenkins and Rosebraugh. They raised concerns that an active controlled trial would not inform us of the CV risks of linagliptin relative to other available therapies outside of glimepiride. Even if CAROLINA were able to demonstrate CV risk reductions of linagliptin over glimepiride, this might result in preferential use of linagliptin because some may consider it cardioprotective when in reality, its CV risk profile may still be greater than approved therapies other than glimepiride or, perhaps, sulfonylureas as a class. The absence of a placebo treatment group in CAROLINA precludes us from making any such determination. On April 19, 2011, the applicant was notified by teleconference that it would have to conduct a trial comparing linagliptin to placebo in order to satisfy CV safety requirements under FDAAA.

<u>Safety Concerns Associated with DPP4-inhibitors/Incretin Mimetics</u>

There were several 'adverse events of special interests' identified by the applicant including hypoglycemia, hypersensitivity reactions, renal and hepatic events, severe cutaneous adverse reactions, and pancreatitis. Dr. Dunn has summarized these findings in her review and only notable events will be discussed below.

Hypoglycemia

The glucose-dependent manner in which incretin-based therapies control hyperglycemia reduces the risk for hypoglycemia with these drugs except in the setting of co-administration with other anti-diabetics that can cause hypoglycemia (e.g., insulin secretagogues or insulin). The potentiation for risk of hypoglycemia with co-administration of DPP4-inhibitors and insulin secretagogues has been observed in the currently marketed DPP4-inhibitors, and was also evident in this NDA. The overall incidence of investigator-defined hypoglycemia in the placebo-controlled trials was 8.7% in linagliptin vs 5.3% in placebo. The highest incidence occurred in the trials with sulfonylurea background treatment (1218.18 and 1218.35) in which hypoglycemia was reported from 4.8% to 23.7% of patients. When the rates were summarized by studies with or with sulfonylureas the risk of hypoglycemia was low for linagliptin administered in the absence of a SU and not appreciably different from placebo.

Table 13. Incidence of investigator-defined hypoglycemia in placebo-controlled trials presented by background use of SU (From Applicant's ISS Table 5.3.2.4)

	Placebo	Linagliptin
Studies w/ SUs	46/347 (13.3%)	197/953 (20.7%)
Studies w/o SUs	6/630 (1%)	9/1428 (0.6%)

Hypersensitivity Reactions and Immune-related AEs
Shortly after the approval of Januvia (sitagliptin), spontaneous postmarketing reports of allergic and hypersensitivity reactions were received resulting in labeling changes to the Warnings and Precautions section as follows:

> *There have been postmarketing reports of serious allergic and hypersensitivity reactions in patients treated with Januvia such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome.*

Other DPP4-inhibitors have also had clinical and nonclinical findings of hypersensitivity-like reactions. Alogliptin had hypersensitivity-like reactions in its chronic dog studies and a higher rate of similarly-coded reactions was observed with alogliptin in the clinical trials. The pre-marketing application for saxagliptin also identified a higher incidence of hypersensitivity reactions with saxagliptin over comparators as well as adverse events of urticaria.

In the pooled database of placebo-controlled trials for this NDA, 18 patients (0.7%) in the linagliptin group vs 6 (0.5%) on placebo had an adverse event reported as hypersensitivity. Urticaria was reported in 6 patients on linagliptin versus 1 on placebo). Angioedema was reported in two patients treated with linagliptin; one case occurred 11 days post-therapy. however, angioedema, facial swelling, and mouth ulcerations have also been reported. There was one report of angioedema/face swelling in a 65 yo woman who received linagliptin 1 mg in a Phase 2 study and one report in placebo group. The event in the linagliptin group was not serious and the event resolved with study drug discontinuation. In the active-controlled trial, 1218.20, there was 1 report of angioedema in a linagliptin patient versus 3 in glimepiride. Information request pending on these events

Renal Adverse Events
Dr. Dunn summarized adverse events with respect to baseline renal function and also shifts in renal impairment under Section 7.4.5 of her review. The majority of patients in the placebo-controlled trials database had no or only mild renal impairment. Only 162 patients had moderate renal impairment and 3 had severe renal impairment. No differences in AEs were noted between linagliptin and placebo for the no and mild renal impairment population whereas a slightly higher incidence of AEs was reported in the moderate renal impairment population but without any single predominant event. No signal of deteriorating renal status was noted in her assessment of shifts in renal function.

The dedicated 52-weel renal safety trial is currently ongoing; however, interim 12-wk data were submitted with this NDA.

Hepatic Adverse Events
ALT and AST increases were reported at similar frequencies between placebo and linagliptin groups in the placebo-controlled trials (0.3-0.4%). There were no cases of Hy's law. Two cases of jaundice in the linagliptin group were reported: one in a patient with pancreatic cancer and another in a patient with documented gallstones requiring ERCP.

Severe Cutaneous Adverse Reactions
Severe cutaneous adverse reactions have been noted in preclinical development programs of some DPP4 inhibitors. In one program of a DPP4 inhibitor not approved in the U.S. (vildagliptin), severe peripheral edema of the feet occurred in 5 subjects enrolled in a Phase 1 study. One individual who had severe edema of his hands and feet had CPK and AST elevations with onset occurring within 3 days of drug initiation. Unlike linagliptin, there were no safety margins for this type of adverse event with vildagliptin.

In this NDA there reports of rash and pruritus; however, there were 5 reports of exfoliative dermatitis or skin exfoliation occurring in the linagliptin group (Trials 1218.16, 1218.17, 1218.18, 1218.23, 1218.20) and only one report in control in a patient receiving glimepiride. Narratives for these cases were requested. In all but one of the cases, exfoliation, skin peeling or desquamation was noted in the hands. One patient reported exfoliation of his heels. Although all of the cases were reported as mild or moderate, one case was deemed drug related as follows:

> *Patient 81804 was a 46-year old Asian male without a medical history of allergic reactions or skin problems. He was enrolled in Study 1218.18 on 6 May 2008; started placebo run-in on 13 May 2008 and randomized to linagliptin 5 mg on 29 May 2008. Concomitant medications included metformin 2000 mg daily, glyburide 20 mg daily, and rosuvastatin 20 mg daily. On 19 August 2008 it was noted that CK levels increased from 238 u/L at baseline to 468 u/L. Rosuvastatin was discontinued on 22 August 2008; however, CK value remained elevated on 3 September 2008 at 813 u/L. On 14 September 2008, the patient noted moderate peeling of the hands, feet, and shins, and also a rash. Linagliptin was interrupted then permanently discontinued on 2 October 2008. Linagliptin was discontinued*

with a positive dechallenge; patient was not rechallenged. Patient discontinued from the trial. Most recent CK on 20 April 2009 was 295 u/L.

Although this case was not as remarkable as the ones observed in the vildagliptin program, the imbalance of reports of skin exfoliation does carry some concern that will require further pharmacovigilance and does need to be highlighted in labeling to alert practitioners to the possibility of a drug reaction necessitating discontinuation of therapy.

Pancreatitis
Spontaneous postmarketing adverse event reports for exenatide and sitagliptin and some publications from rodent models have suggested an increased risk of pancreatitis for the incretin mimetics. However, data from several observational studies of healthclaims databases have suggested no excess risk over other anti-diabetic therapies and instead have raised the possibility of increased risk of pancreatitis related to diabetes overall. Regardless, there has been a heightened assessment for this event in clinical trials of these drug classes.

In this NDA there were 8 patients, all receiving linagliptin, who were diagnosed with pancreatitis while on treatment. Drs. Irony and Dunn have reviewed the narratives of these events and it does appear that some of these cases represent patients with chronic pancreatitis. Regardless, there remains a numeric imbalance. However, this numeric imbalance must also consider that overall number of exposure and duration of treatment were heavily weighted towards linagliptin. Correcting for this imbalance reveals an incidence of pancreatitis of 1 per 538 pt-yrs in linagliptin versus 0 per 433 pt-yrs in comparator group which presents a less concerning and more appropriate representation of risk from this NDA database.

The applicant will still be required to provide post-marketing evaluation for risk of pancreatitis including prospective evaluation in its long-term CV outcomes trial and routine surveillance of postmarketing adverse event reports.

Cancer
There have been speculative reports on potential risk for thyroid and pancreatic cancer with DPP4 inhibitors. Detection of risk for developing cancer is limited in typical NDA databases. Regardless, the long-term safety trials were evaluated and one case of thyroid cancer and one pancreatic carcinoma out of 5 neoplasms were identified post-treatment. There are too few events to make any conclusions based on these observations. Routine pharmacovigiliance and prospective assessment from ongoing clinical trials will continue to assess whether there is a risk for these types of cancer associated with linagliptin use.

Thorough QT Study
Please see the QT-IRT review dated January 29, 2010. Linagliptin is not associated with any clinically relevant effect on the QT interval. The 5 mg dose and a supratherapeutic dose of 100 mg were both evaluated in a thorough QT (tQT) study. The upper bound of the 90% CI for the QTcI was well below the regulatory threshold for concern (10 ms). The study included a positive control, moxifloxacin, whose results demonstrated the expected effects of moxifloxacin on increasing the QT interval, establishing assay sensitivity of the study. The mean Cmax achieved with linagliptin 100 mg in this study was 267 nmol/L, exceeding the

Cmax anticipated under the worse-case scenario of clinical use including varying degrees of renal impairment or in the presence of a potent CYP3A4/P-gp inhibitor.

Linagliptin did not have any clinically significant effect on PR or QRS interval.

Overall, this NDA has provided sufficient CV safety data to conclude that an unacceptable CV risk does not exist for linagliptin to preclude its approval. However, as these data are derived from controlled clinical trials in relatively low risk patients for which there were few CV events, the company will be required to conduct a prospective CV safety trial to provide more conclusive evidence of CV safety. The safety review did not identify a toxicity that is unique to linagliptin and not observed with other drugs in the DPP4 inhibitor class.

9. Advisory Committee Meeting

This application was not discussed before a public advisory committee for the following reasons:

- it is not a first-in-class anti-diabetic therapy (two other DPP4-inhibitors are currently marketed);
- the indication sought is based on a well-established efficacy endpoint relied upon for approval of other drugs across the 11 classes of anti-diabetic therapies;
- clinical trials assessing efficacy and safety are typical of diabetes programs evaluated by FDA for approval of other anti-diabetic therapies;
- no unexpected safety concerns were identified in the nonclinical or clinical development program

10. Pediatrics

Please see Dr. Irony's CDTL memo which succinctly summarizes the pediatric plans for linagliptin. A meeting was held with PeRC on 16 March 2011.

11. Other Relevant Regulatory Issues

DSI

Please see DSI's clinical inspection report dated 11 February 2011 wherein it was concluded that the data are considered reliable in support of the application.

No other issues have been identified to preclude approval.

12. Labeling

The applicant originally proposed the tradename, Ondero®, which was denied by DMEPA due to orthographic and phonetic similarities to some currently marketed products. Another proposed tradename, Trajenta, was denied on January 19, 2011, as DMEPA finds it

unacceptable to include the USAN stem 'aj' in the tradename. On 8 April 2011, Tradjenta was deemed acceptable by DMEPA.

Physician labeling is still under negotiation and review. Please see the final action package for agreed-upon PI. I would note that the CV findings from the meta-analysis will not be included in this label as they have a potential for promotion of CV benefit. Although the results are reassuring enough to support approval, these data would not be considered as robust as data derived from a prospective trial(s) designed to specifically assess CV safety concerns.

Carton and container labeling was reviewed by DMEPA and recommended changes were incorporated by the applicant. No further pending issues with this aspect of labeling.

This NDA will not have an accompanying Medication Guide. A patient package insert (PPI) was submitted and a preliminary review has been conducted by DRISK and DDMAC based on the current package insert.

13. Decision/Action/Risk Benefit Assessment

Regulatory Action

Approval

Risk-Benefit Assessment
Data submitted and reviewed in this NDA support a conclusion that linagliptin is an effective anti-diabetic therapy when used as a single agent or in combination with metformin, pioglitazone, or a sulfonylurea. As a single agent, linagliptin is not as effective as well-established therapies such as metformin and glimepiride. This was evident in two Phase 2 trials comparing linagliptin to either metformin or glimepiride and one Phase 3 trial comparing linagliptin to glimepiride. However, despite its reduced efficacy the applicant provided evidence that linagliptin has a role in the diabetes armamentarium for patients who can not tolerate or have contraindications to metformin and in patients wherein weight gain or risk of hypoglycemia would be undesirable side effects of a sulfonylurea to warrant selection of linagliptin.

Although glucose-lowering efficacy of DPP4-inhibitors, like linagliptin, is modest relative to other approved therapies, no serious toxicity has been identified to offset the benefit of its availability and choice for the treatment of T2DM. Relative to the currently marketed DPP4-inhibitors, there is no dose adjustment needed for renal impairment; however, this can not be translated to any conclusion of a better safety or efficacy profile over sitagliptin or saxagliptin. At this point, this can only be viewed as a convenient dosing scheme – one dose across multiple patient populations. Safety concerns of linagliptin are similar to others in this class and will need to be noted in labeling, including the patient package insert, to allow prescribers and patients adequate information in weighing the appropriateness of this product for diabetes management.

Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
None recommended beyond routine postmarketing surveillance.

Recommendation for other Postmarketing Requirements and Commitments
The following PMRs will be included in the action letter:

- Pediatric studies required under PREA
- An epidemiology study to further investigate hypersensitivity reactions
- A dedicated CV trial designed to show that the upper bound of the 2-sided 95% CI for the estimated risk ratio for important CV events between linagliptin and comparator is < 1.3

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

/s/

MARY H PARKS
05/02/2011