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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	3/15/2011
From	Ilan Irony, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	201280 Original Submission
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc.
Date of Submission	July 2, 2010
PDUFA Goal Date	May 2, 2011
Proprietary Name / Established (USAN) names	Tradjenta (under DMEPA review) / linagliptin
Dosage forms / Strength	5 mg oral tablet
Proposed Indication(s)	1. Treatment of Type 2 Diabetes Mellitus
Recommended:	*Approval*

1. Introduction

This is the Cross Discipline Team Leader review of linagliptin, the fourth drug in the class of dipeptidyl peptidase IV (DPP4) inhibitors submitted for review under a 505 (b)(1) New Drug Application (NDA). Two drugs in the class have been approved and are currently marketed in the US: sitagliptin since 2006 and saxagliptin since 2009. A third, vildagliptin, is marketed in various countries outside the US, having received an "Approvable" letter in 2007. The application for alogliptin has received a Complete Response letter in September 2009 and trials to support a resubmission are ongoing.

The clinical development of this drug was conducted under IND 70963. (b) (4)

This document will briefly cover the review of all discipline teams, but will focus particularly on the clinical and statistical reviews.

2. Background

The incretin effect in the homeostasis of blood glucose levels is primarily based on the action of two gastrointestinal hormones, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). GLP-1 and GIP are secreted following oral intake of nutrients, and stimulate insulin release in a glucose-dependent fashion. GLP-1 also suppresses glucagon, slows gastric emptying and induces satiety, all beneficial effects in patients with T2DM. The plasma half-life of GLP-1 and GIP is limited to a few minutes because of rapid proteolytic degradation by the enzyme DPP4. Therefore, inhibition of DPP4 prolongs the half-life and the anti-hyperglycemic effect of these incretin hormones.

DPP4 inhibitors tend to have relatively modest efficacy but these medications appear to be generally well-tolerated with neutral effects on body weight and a low risk for hypoglycemia.

Potential class risks for all incretin-based drugs (DPP4 inhibitors and GLP-1 receptor agonists) include pancreatitis, and specific monitoring for this adverse event is implemented in investigational as well as approved products.
Linagliptin is a selective (>10,000-fold selectivity for DPP4 compared to the closely related enzymes DPP8 and DPP9), competitive, reversible inhibitor of human DPP4.
The clinical development started in September 2004. The clinical program comprised 24 Phase 1 trials, four Phase 2 trials, and 9 Phase 3 trials including an open-label extension trial of the pivotal trials.
No major issues were identified in the IND milestone meetings (End of Phase 2 and Pre-NDA meetings), with the possible exception of the linagliptin requirement to demonstrate its safety profile regarding major adverse cardiovascular events (MACE). In December 2008 FDA issued a final guidance, recommending "*To establish the safety of a new antidiabetic therapy to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk*." Like other applicants with recently approved antidiabetic drugs, the linagliptin IND sponsor had not planned or conducted a dedicated trial to establish the magnitude of cardiovascular (CV) risk of linagliptin during the then ongoing Phase 3 program; similar to the clinical development of saxagliptin and liraglutide (a GLP-1 receptor agonist), the linagliptin applicant conducted an independently blinded and adjudicated metanalysis of the Phase 3 trials to assess its relative risk of MACE. Therefore, most of the discussions concentrated on the metanalysis plan for the NDA submission as well as the overall plan to demonstrate that the upper bound of the 95% confidence interval in the hazard ratio of CV risk associated with linagliptin will not exceed 1.3 post-approval.

3. CMC/Device

Please refer to Dr Markofsky's CMC review for details. Please refer to Dr. Stephens' review of issues related to Quality by Design.

Drug Substance: Linagliptin is manufactured by Boehringer Ingelheim Pharma GmbH & Co. KG in Germany. The chemical designation is 1H-Purine-2, 6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7- (2-butyn-1-yl)-3, 7-dihydro- 3 methyl-1-[(4-methyl-2- quinazolinyl) methyl] – and the molecular formula is $C_{25}H_{28}N_8O_2$. Linagliptin is crystalline white to yellowish solid, which has been found to exist (b) (4) Boehringer Ingelheim classifies this drug substance as a Class III compound according to the Biopharmaceutical Classification System (BCS) because of its high solubility and low bioavailability. Linagliptin shows high solubility (> 1 mg/ml) in aqueous media up to pH 8. Satisfactory stability data were provided to support a retest date of (b) (4) for the drug substance for storage at 25°C / 60 % relative humidity.

Drug Product: The linagliptin dosage form is a 5 mg immediate release film-coated tablet that is light red, round, biconvex, bevel-edged with one side debossed with the Boehringer Ingelheim company symbol and the other side debossed with 'D5'. The proposed market packages for the 5 mg tablets are 60 cc HDPE bottles containing 30 or 90 tablets and 375 cc

HDPE bottles containing 1,000 tablets (intended for dispensing at mail order pharmacies). All of the bottles are equipped with a child resistant, senior friendly closure with an induction foil seal liner, and silica gel desiccant packets. Physician samples are aluminum/aluminum push-through blisters containing 7 tablets. Besides linagliptin, the drug product contains the following inactive ingredients: mannitol, pregelatinized starch, corn starch, copovidone, and magnesium stearate. In addition, the film coating contains the following inactive ingredients: hypromellose, titanium dioxide, talc, polyethylene glycol, and red ferric oxide. All of the inactive ingredients are compendial.

The stability studies support an expiration-dating period of 30 months for linagliptin 5 mg tablets when stored at controlled room temperature [25°C (77°F)], with excursions permitted between 15°C and 30°C packaged in all of the proposed commercial container closure systems. Consequently, a 30-month expiry is granted.

CMC had a number of information requests to the applicant, and these were adequately addressed in an amendment submitted January 6, 2011.

The applicant requested a Categorical Exclusion (waiver) from the preparation of an Environmental Assessment under 21CFR§25.31(b), since the estimated concentration of linagliptin at the point of entry into the aquatic environment will be below 1 part per billion. The waiver was granted.

The ONDQA/Biopharmaceutics team has also found the NDA acceptable.

Dr. Stephens identified risk Quality by design items for consideration under a manufacturing site inspection, but no inspection took place, since this was deemed unnecessary.

4. Nonclinical Pharmacology/Toxicology

For details, please refer to Drs. Carlson and Bourcier reviews of the pharmacology and toxicology issues.

A comprehensive battery of nonclinical studies was conducted to support development of linagliptin for chronic use. Two DPP4 inhibitors have been approved for diabetes treatment and the toxicity profile of linagliptin is similar to that of these drugs. All pivotal studies with linagliptin were conducted in compliance with current GLP standards.

All pivotal nonclinical studies were conducted using oral administration of drug, which is the clinical exposure route. Toxicity studies in healthy, non-diabetic animals were sufficient to identify NOAEL exposures for comparison to clinical exposure.

Safety margins to expected human exposure were estimated C_{max} = 11 nM and AUC_{0-24} = 158 nM*h plasma exposure in diabetic subjects (PK/PD Study 1218.2 and population PK) at the proposed maximum recommended human dose (MRHD) of 5 mg linagliptin. Linagliptin is not highly metabolized and is excreted largely unchanged. A single major human metabolite, CD 1790 (13% linagliptin exposure), was monitored and qualified in nonclinical studies.

Linagliptin pharmacology was assessed in a variety of in vitro and in vivo animal models to investigate DPP4 inhibition and glycemic effects. Linagliptin and other DPP4 inhibitors have been shown to reduce blood sugar and HbA1c in vivo in healthy and diabetic animal models. Linagliptin achieves efficacy at relatively low drug concentrations despite having comparable inhibitory potency to other DPP4 inhibitors. This may be in part a result of linagliptin exhibiting high affinity binding to DPP4 in plasma and tissues which results in a very long plasma terminal half-life of up to 100 hours in animals and humans. Linagliptin binds to and

saturates DPP4 expressed in the kidney, liver, lung, and other DPP4-containing tissues. Drug is released slowly over several days from these DPP4- expressing tissues. Studies with DPP4-deficient and DPP4-knockout rodents confirmed the absence of tissue accumulation in animals lacking tissue DPP4. There is no apparent toxicity associated with accumulation of linagliptin in kidney, liver or other DPP4-expressing tissues, at doses close to the recommended human dose. In the blood and at therapeutic drug concentrations (~10 nM), linagliptin binds to and saturates plasma DPP4 with high affinity, while excess drug binds to other plasma proteins with lower affinity. As drug concentration increases further, as it did in the toxicology studies, linagliptin continues to bind with low affinity to other plasma proteins. As a result, the free fraction of drug continues to increase as the drug concentration increases. The sustained and high affinity binding of linagliptin to the DPP4 enzyme both in tissues and in the blood likely contribute to achieving efficacy at drug concentrations only 2- to 3-fold higher than the in vitro IC50 inhibitory potency for DPP4 activity (3.6 nM).
Linagliptin showed high selectivity for inhibiting DPP4, with >10,000-fold selectivity for DPP4 compared to the closely related cytoplasmic dipeptidyl peptidases DPP8 and DPP9, which are differentially expressed in skeletal muscle, heart, liver, and activated T-cells.
Skin, immune, and GI-related toxicity have been observed with some DPP4 inhibitors and, based on the similar toxicity profile with selective DPP8 and/or DPP9 inhibition, some toxicity attributed to DPP4 inhibition may be due to off-target inhibition of DPP8/9. Specifically, edema and necrotic skin lesions have been seen with several DPP4 inhibitors, which may be due to off-target inhibition of DPP8 and/or DPP9. No skin lesions were seen in monkeys or other species treated with linagliptin.
Linagliptin was generally well tolerated in healthy and diabetic animals. Irreversible and/or non-monitorable toxicity typically occurred only at very high exposure multiples (> 90-times the MRHD). Linagliptin produced a pseudoallergy-type, hypersensitivity response in dogs and minipigs after oral dosing and in monkeys only after very high intravenous exposures (> 600-times clinical exposure). The toxicity presented as facial flushing/reddening and edema, but was tolerable even at high doses of linagliptin. The pseudoallergy reaction has been shown to involve systemic histamine release but there was no evidence of an IgE-mediated allergic response. This reaction was not seen in human healthy volunteers exposed to the same plasma linagliptin concentrations as the dogs.
Investigative studies showed linagliptin was not an irritant or hemolytic.

Reviewer comment: [redacted] (b) (4) *is a DPP4 substrate, and it has been speculated that these allergic-type, or generally termed "hypersensitivity" reactions are related to increased* [redacted] (b) (4) *off-target effects of DPP4 inhibitors. Similar effects in nonclinical studies with sitagliptin were not reported in clinical trials, but appeared postmarketing and have been appropriately labeled. With saxagliptin, these effects were seen also in the clinical trials. The risk for these events is largely unknown, due to potential underreporting of transient or mild events in the clinical trials and in the postmarketing environment. It is conceivable that certain patients may be more prone to hypersensitivity reactions such as urticaria, flushing, angioedema based on the interaction between a particular DPP4 inhibitor and their genomic make up or their use of certain concomitant medications (such as angiotensin converting enzyme inhibitors) that may exacerbate these reactions. As I describe under the Clinical Review section of this document, there was no imbalance in cases of hypersensitivity in the linagliptin clinical trials (versus placebo or glimepiride), after adjusting for exposure.*

Target organs were identified only at very high exposure multiples with NOAELs > 30- times clinical exposure in chronic toxicity studies. Kidney, liver, lung, stomach, and testes toxicity occurred at > 90-times the MRHD. Toxicities included: kidney tubular degeneration, necrosis/apoptosis, and increased plasma and urine biomarkers; liver increased organ weight and cytoplasmic rarefaction (glycogen accumulation), centrilobular hypertrophy, and plasma ALT biomarker; stomach erosion and necrosis; testes gross changes (decreased size, prominent tubules) and germ cell depletion, mineralization, and epididymal dilatation; and, lung increased alveolar macrophages suggestive of phospholipidosis. Toxicity suggestive of phospholipidosis in lung was seen in short term rat studies and chronic lifetime treatment with > 400-times the MRHD caused lung cholesterol cleft granulomata. The clinical risk of phospholipidosis is considered minimal based on the large safety margin relative to the clinical dose.

Linagliptin and several drug substance impurities were not genotoxic in a standard battery of in vitro and in vivo assays.

Carcinogenicity was assessed in chronic, lifetime oral gavage studies in mice and rats at doses that provided several hundred-fold higher exposure than experienced clinically, with protocols agreed upon by the executive carcinogenicity assessment committee. Linagliptin caused drug-induced lymphomas in female mice at 287 times the MRHD. No other drug-related tumors were seen in mice or rats. The NOAEL for drug-related tumors in female mice provided a 34-fold margin over expected human exposures. Linagliptin poses minimal carcinogenic risk to humans based on high exposure multiples at the NOAEL for drug-related tumors (34X) and very high exposure multiples (287X) at the tumorigenic (lymphomas) dose in female mice. In addition, no drug-related tumors were found in rats exposed to over 400-times the MRHD. The very high exposure multiples achieved in rodents reflect the limited toxicity of linagliptin at the doses tested in the clinical trials.

Reproductive and developmental toxicity were assessed in fertility, early embryonic development, and pre- and post-natal development studies. Linagliptin was not teratogenic at up to 30 mg/kg in rat (49X MRHD) and 150 mg/kg in rabbit (1943X MRHD). Very high, maternally toxic doses in rats (1000X MRHD) resulted in slightly decreased number of corpora lutea and embryofetal survival, increased late resorptions, and a slight 3-4% increase in rib malformations (flattened and thickened) above the historical range. There were no treatment-related fetal malformations in rabbits. Rabbit fetal variations of small gallbladder / hypoplasia and increased lumbar ribs were increased at high doses (> 1000-times MRHD) compared to concurrent and historical controls. Treatment with 240 mg/kg (> 800X MRHD) in male and female rats prior to mating did not have any apparent effect on fertility. Rats dosed during pregnancy (F0) and throughout lactation (F1) with 300 mg/kg linagliptin (> 1000X MRHD) resulted in offspring with lower birth weight that persisted to adulthood, delays in several physical and learning/memory developmental endpoints, and a reduced number of viable offspring (F2) after mating. No functional, behavioral, or reproductive toxicity was observed in offspring of rats exposed to 49 X the clinical dose.

Summary of nonclinical issues relevant to clinical use:

1. Hypersensitivity / pseudoallergy may occur in susceptible individuals in the clinical population based on the findings in dogs and minipigs. The evidence suggests that this is not an IgE-mediated allergic response.
2. The overall non-clinical toxicity profile suggests minimal target organ risks in humans. However, since DPP4 cleaves substrates other than the targeted incretin hormones, inhibition of DPP4 may have unintended consequences with prolonged dosing that were not evident in the nonclinical program. As noted in the Januvia review "Effects on human immunity, specifically recall responses to antigens and immune cell trafficking, may be adversely affected by DPP4 inhibition. This risk is an unavoidable characteristic of…the drug class."
3. Pancreatitis has arisen as a safety concern for GLP1 targeted therapeutics, including the DPP4 inhibitors. Linagliptin did not cause histological changes in the pancreas of animals indicative of pancreatitis or pancreatic injury, despite long-term exposure to very high doses of drug. A limitation to extrapolating these studies to the intended diabetic clinical population is that toxicity studies are conducted in normoglycemic healthy animals.
4. Linagliptin readily crosses the placenta and is secreted in milk in rats at approximately 4-times higher concentrations than maternal plasma. Fetal exposure was confirmed in rats and rabbits and assumed in nursing rats based on good overall oral bioavailability and the absence of evidence that linagliptin would be retained in milk and not absorbed in nursing pups. No specific risks from reproductive toxicity studies are predicted for fetuses, neonates, or nursing infants at clinical exposures; nevertheless, animal data support a conclusion that human fetuses and nursing infants will be exposed to linagliptin from maternal drug use. The pharmacology / toxicology team agrees with the designation of Category B in Section 8.1 (Use in Pregnancy) of the linagliptin label.

5. Clinical Pharmacology/Biopharmaceutics

Please refer to Drs. Jain's, Earp's, Garnett's and Choe's Clinical Pharmacology and Pharmacometrics reviews for details.

Dose-Response

Two 12-week dose-response trials were conducted:

- Trial 1218.5 tested 0.5 mg, 2.5 mg and 5 mg PO qd X 12 weeks in drug naïve subjects with T2DM against placebo and metformin up to 100 mg bid. Each cohort had 54 – 63 subjects. Reduction in mean HbA1c for the 2.5 and the 5 mg doses was comparable after 12-week monotherapy with linagliptin (-0.4% vs. 0.5%, placebo-adjusted).
- Trial 1218.6 tested 1 mg, 5 mg or 10 mg PO qd X 12 weeks in subjects with T2DM not adequately controlled on metformin therapy, against placebo and glimepiride. Cohort sizes were similar to Trial 1218.5. Results are shown in Table 1.

Table 1. Adjusted means for HbA1c change from baseline to Week 12 (Full Analysis Set)

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)	0.25 (0.10)	–0.15 (0.10)	–0.48 (0.11)	–0.42 (0.10)
Difference to placebo (SE) 95% CI p-value		–0.40 (0.14) (–0.68, –0.12) 0.0055	–0.73 (0.14) (–1.01, –0.44) <.0001	–0.67 (0.14) (–0.95, –0.39) <.0001

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

- The 5 mg dose was more likely to achieve > 80% inhibition of DPP-4 at steady-state compared to the 2.5 mg dose.
- Dr. Jain points out in his review that the criteria for dose selection in Phase 3 trials (80% inhibition of DPP4 activity in > 80 % of subjects treated with linagliptin at any particular dose, in addition to optimal HbA1c reduction) may not correspond to the effect on the efficacy endpoint, namely, HbA1c after 6 months, so that the dose of 2.5 mg could have been evaluated in Phase 3 trials.

Exposure-Response

A relationship was established between linagliptin exposure and HbA1c response by using the predicted steady-state exposures for 1 to 10 mg linagliptin doses. In the Phase 2 trials 1218.5 and 1218.6 (described above), doses of 0.5 mg, 1 mg, 2.5 mg, 5 mg and 10 mg were used daily for 12 weeks, with trough PK samples and glycemic parameters assessed. Changes in HbA1c from baseline (Δ HbA1c) increased with increasing exposure (steady state $AUC_{\tau,ss}$) and reached plateau at exposures greater than approximately 100 nM·h, achieved with the 5 mg dose. Overlap in the range of simulated exposures for different dose levels was likely due to non-linear PK. As a result, the exposure quartiles in exposure-response relationship do not exclusively represent only one dose level. Therefore, it is not possible to relate the exposure-response relationship with the dose of linagliptin. Nevertheless, the simulated exposure for 5 mg dose overlaps with the exposure quartiles resulting in maximum reduction in HbA1c. Exposure response regarding adverse events is less clear: across Phase 2 and Phase 3 trials, there was a small increase in rate of arthralgias and back pain when the 5 mg dose cohorts are compared to the single 10 mg dose cohort; a similar tendency was observed for bronchitis and cataract, but the number of events is very small to establish a conclusive dose- or exposure-relationship.

Pharmacodynamics

- The extent of DPP4 inhibition increased with increases in doses from 1 to 10 mg. Average steady-state DPP4 inhibition at 24 hours after the last dose were 62.5%, 76.9%, 85%, and 89.4% for 1 mg, 2.5 mg, 5 mg, and 10 mg dose groups, respectively (Trial 1218.2).
- The GLP-1 concentrations 30 minutes after a mixed meal test increased by about 3-fold for linagliptin doses ranging from 2.5 to 10 mg (4-week treatment) compared to placebo in

Trial 1218.3, but approximately 1/3 of the samples had GLP-1 below the limit of detection of the assay.

Pharmacokinetics

- Linagliptin followed non-linear PK for doses ranging from 1 mg to 600 mg. Increases in exposures were less than dose proportional for the dose range of 1 mg to 10 mg, more than dose proportional for the dose range of 25 mg to 100 mg, and almost dose proportional for the dose range of 100 mg to 600 mg.
- The non-linearity in dose range of 1 to 10 mg and long half-life of linagliptin (i.e., >100 hours) may be explained by concentration dependent binding to DPP4. At concentrations of 1 nM, almost 99% of drug remains bound to DPP4; binding is reduced to 70-80% at concentrations of about 100 nM.
- The absolute bioavailability of linagliptin after oral administration of a 10 mg dose is approximately 30%. Data from non-clinical studies and drug-drug interaction studies suggest that linagliptin is a P-gp substrate. T_{max} is reached between 0.5 to 3 hours, but the rate of absorption was reduced when linagliptin was given with food (median t_{max} increased from 1 to 3 hours and C_{max} was reduced by about 15% with no food effect on the extent of absorption.
- The accumulation half-life of linagliptin ranged from 8 - 12 hours.
- Metabolism is a minor pathway of elimination for linagliptin. The majority of drug is eliminated unchanged in feces (~85%) and a minor proportion in urine (~4.5%). Enterohepatic circulation contributes to linagliptin elimination.
- The predominant metabolite, CD1790 (formed by CYP3A4), is therapeutically inactive.
- According to population PK, the between-subject variability on clearance was low (i.e., CV% of 24%).

Specific Population

- Renal function affected linagliptin exposure, based on results from a single-/multiple-dose PK study 1218.26. Linagliptin steady-state exposure increased by 8% and 71% in non-diabetic subjects with mild and moderate renal impairment compared to that of non-diabetic subject with normal renal function. In subjects with T2DM, severe renal impairment group had 42% higher steady-state exposures compared to the group with normal renal function. On average $AUC_{\tau, ss}$ were relatively higher for creatinine clearance <60 mL/min. No dose-adjustments are recommended for subjects with renal impairment.
- In addition, no dose-adjustments are recommended for subjects with hepatic impairment.
- Age, weight, BMI, and gender had no clinically meaningful effect of linagliptin PK.
- Linagliptin exposures in subjects with Japanese and Chinese ethnicity were ~25-30% higher than that of Caucasian subjects. This small change was not expected to be clinically meaningful.

Drug-Drug Interaction

- Linagliptin is a substrate and weak inhibitor of P-gp and a substrate of CYP3A4.

- No dose adjustments of linagliptin are recommended for coadministration with P-gp and CYP 3A4 inhibitors.
- Linagliptin coadministration with P-gp and CYP 3A4 inducers may reduce its efficacy because of lower linagliptin exposures: 39 % decrease in $AUC_{\tau, ss}$ and 44% in C_{max} (a 5 mg daily dose would have an expected glycemic effect of a 1 mg dose, approximately); therefore, it is strongly recommended to use the alternative treatments when it is to be co-administered with P-gp or CYP3A4 inducers (e.g., rifampicin). The Clinical Pharmacology team made labeling recommendations to address this drug-drug interaction issue.

Effect on QTc interval

In a randomized, placebo-controlled, active-comparator, 4-way crossover study, 36 healthy subjects were administered a single oral dose of linagliptin 5 mg, linagliptin 100 mg (20 times the recommended dose), moxifloxacin, and placebo. No increase in QTc was observed with either the recommended dose of 5 mg or the 100 mg dose. At the 100 mg dose, peak linagliptin plasma concentrations were approximately 380-fold higher than the peak concentrations following a 5 mg dose.

6. Clinical Microbiology

Not applicable. Linagliptin is not an antimicrobial product.

7. Clinical/Statistical- Efficacy

The overall clinical development program for linagliptin, as described in the NDA, included 24 Phase 1 trials (2 of them conducted in subjects with T2DM), four Phase 2 trials, and nine Phase 3 trials.
This section will focus on the efficacy results from the controlled, phase 2/3 clinical trials of 12 weeks in duration or longer. Please see Dr. Somya Dunn's clinical review and Dr. Wei Liu's statistical review for further details.
Like similar antidiabetic drug programs, linagliptin's efficacy has been characterized in multiple settings: dose ranging Phase 2 trials to select optimal doses for Phase 3, monotherapy (treatment naïve), add-on to different background medications, and active-controlled trials.
The applicant also conducted an open label extension trial for the long term safety follow up of completers in some of the trials described below.
Dr. Dunn has used in her integrated review of efficacy some of the same trial groupings used by the applicant (see below), while Dr. Wei included in his statistical review separate results of the seven trials that are described under the Clinical Studies section in the linagliptin prescribing information.

Grouping of Trials for the purpose of integrated analyses of efficacy (Table 2)
The applicant numbered the trials as Study 1218.X or 1218.XX, where X or XX denotes the specific trial. In this review, I will refer to the specific trial only by the applicant's last digit(s) after the period (X or XX).

Table 2. Applicant's trial groupings for the integrated analyses of efficacy

Shorthand	Trial characteristics	Treatment duration	Study
EFF-1	Pivotal double-blind placebo-controlled 24-week efficacy trials (pooled)	24 weeks	1218.15 1218.16 1218.17 1218.18
EFF-2	Double-blind active-controlled efficacy trial	52 weeks [a]	1218.20
EFF-3	Double-blind controlled short-and midterm efficacy trials (not pooled; linagliptin 5 mg, placebo, and double-blind active comparator included)	12 weeks 12 weeks 18 weeks 18 weeks [b] 24 weeks 24 weeks 24 weeks 24 weeks 26 weeks 52 weeks [a]	1218.5 1218.6 1218.35 1218.50 1218.15 1218.16 1218.17 1218.18 1218.23 1218.20
EFF-4	Double-blind trials without background medication (not pooled; linagliptin 5 mg and placebo included)	12 weeks 12 weeks 18 weeks [b] 24 weeks	1218.5 1218.23 1218.50 1218.16
EFF-5	Double-blind trials with metformin background (not pooled; linagliptin 5 mg, placebo, and double-blind active comparator included)	12 weeks 24 weeks 52 weeks [a]	1218.6 1218.17 1218.20
EFF-6	Double-blind trial with metformin plus SU background	24 weeks	1218.18
EFF-7	Double-blind trial with SU background	18 weeks	1218.35
EFF-8	Double-blind trial with initial combination with TZD	24 weeks	1218.15
EFF-9	Double-blind placebo-controlled trials with MTT (pooled)	24 weeks 24 weeks	1218.16 1218.17
EFF-10	Double-blind, placebo-controlled trials with more than one linagliptin dose level (not pooled; all linagliptin doses and placebo included)	12 weeks 12 weeks 12 weeks [c]	1218.5 1218.6 1218.23
EFF-11	Trials to assess long-term efficacy (not pooled; data from study 1218.40 combined with data from initial studies)	52 weeks [a] 52 weeks 102 weeks [d]	1218.20 1218.23 1218.40/EFF-1

a Duration for interim analysis (total treatment duration: 104 weeks)
b Duration for interim analysis, i.e. duration of placebo-controlled treatment (was followed by 34 weeks active-controlled treatment with linagliptin vs. glimepiride)
c Duration of both placebo-controlled and active-controlled treatment (was followed by 14 weeks active-controlled treatment with linagliptin vs. voglibose, followed by a 26-week extension period with linagliptin 5 mg and 10 mg)
d Planned total treatment duration in the initial studies (EFF-1; treatment duration: 24 weeks) and the 78-week open-label extension (study 1218.40). Since study 1218.40 is still ongoing, interim data from this study were included, providing efficacy data over up to 90 weeks.

EFF-1 (applicant's Proof of Principle trials or Dr. Dunn's Pivotal Trials) comprises the four large pivotal Phase 3 trials, of 24 weeks duration each: 15, 16, 17 and 18.
Trial 15 was conducted in treatment naïve subjects, randomized to initial therapy with pioglitazone alone or to linagliptin 5 mg and pioglitazone. Placebo was used in both arms for the purpose of masking.
Trial 16 tested linagliptin 5 mg in treatment naïve subjects (monotherapy).
Trial 17 tested linagliptin 5 mg in subjects receiving metformin background therapy.
Trial 18 tested linagliptin 5 mg in subjects on metformin and sulfonylurea background therapy.
Since these trials had the same design and duration and comparable eligibility criteria, the data from these trials were pooled to provide supportive evidence of efficacy and to provide the basis for the evaluation of efficacy in subgroups.

EFF-2 includes only Trial 20, an active-controlled double-blind trial designed to compare linagliptin with glimepiride over a total of 104 weeks of treatment, of which 52 weeks of interim data were submitted (interim analysis was prespecified).

EFF-3 includes all trials where the 5 mg dose of linagliptin was tested (efficacy data from other doses used were excluded from EFF-3). Since the included trials differed in their design and duration of treatment (12 to 52 weeks), the data from these trials were not pooled, but the results of the individual trials are summarized and compared. The following trials are included:
Trial 5 is a Phase 2, 12-week, dose ranging (0.5, 2.5 and 5 mg), placebo- and metformin–controlled.
Trial 6 is a Phase 2, 12-week, dose-ranging (1, 5 and 10 mg), placebo- and glimepiride-controlled.
Trial 35 tested linagliptin 5 mg in subjects on sulfonylurea background therapy for 18 weeks.
Trial 50 tested linagliptin 5 mg in subjects for whom metformin was contraindicated or who were intolerant to metformin in an 18-week, placebo controlled phase followed by a 34-week glimepiride-controlled phase. Only the 18-week, placebo-controlled data were reported in this submission.
Trial 23 tested linagliptin 5 and 10 mg doses among Japanese subjects in a 12-week placebo- and voglibose-controlled phase, followed by a 14-week voglibose-controlled phase, with a 26-week open label extension with linagliptin dosed at 5 or 10 mg qd. Voglibose is an alpha-glucosidase inhibitor (same class as acarbose) not approved or marketed in the US.
Trials 15, 16, 17 and 18 (as in EFF-1, see above)
Trial 20 (also in EFF-2, above)

Groupings EFF-4, EFF-5, EFF-6, EFF-7 and EFF-8 are additional efficacy trial groupings created to evaluate the efficacy of linagliptin with the different relevant background medications.
EFF-4 includes all trials that tested linagliptin 5 mg in monotherapy versus placebo for 12 to 24 weeks (trials 5, 16, 23 and 50).
EFF-5 includes all trials in subjects taking metformin background therapy (trials 6, 17 and 20) with data from subjects who received linagliptin 5 mg, placebo, or active comparator in a double-blind design; data from the open-label active comparator arm of study 6 were not included.
EFF-6 tested linagliptin as add-on therapy to metformin plus sulfonylurea (trial 18)
EFF-7 tested linagliptin as add-on therapy to sulfonylurea (trial 35)
EFF-8 tested linagliptin as initial combination with a thiazolidinedione (trial 15).
EFF-9 tested linagliptin effects on post-prandial parameters (trial 16 and 17): subgroup of subjects who underwent mixed meal tolerance test only.
EFF-10 includes trials that tested more than one linagliptin dose level (no data on the active comparators used in the trials are included). Trials in this grouping include 5, 6 and 23. Due to the differences in study design, the data from these trials were not pooled, but the individual trial results are summarized and compared.
EFF-11 was designed to demonstrate persistence of efficacy, including up to 90 weeks of data in EFF-1 and their combined open label extension (trial 40), trial 20 (treatment duration for

interim analysis: 52 weeks) and trial 23, which consisted of a 26-week double-blind controlled treatment period followed by a 26-week extension period.

As depicted in Table 3, 4278 subjects were exposed to any dose of linagliptin in the 11 Phase 2 and Phase 3 trials of 12 weeks or longer duration, and of these, 3872 were treated with the 5 mg dose.

Table 3. Number of subjects randomized to linagliptin, placebo or active comparator in the 11 Phase 2 or Phase 3 trials

Study characteristics	Study number	Number of patients, N (%)				
		Total	Placebo	Linagliptin total	Linagliptin 5 mg	Active comparator
Pivotal double-blind placebo-controlled efficacy studies	1218.15	389 (100.0)	130 (33.4)	259 (66.6)	259 (66.6)	0 (0.0)
	1218.16	503 (100.0)	167 (33.2)	336 (66.8)	336 (66.8)	0 (0.0)
	1218.17	701 (100.0)	177 (25.2)	524 (74.8)	524 (74.8)	0 (0.0)
	1218.18	1058 (100.0)	265 (25.0)	793 (75.0)	793 (75.0)	0 (0.0)
Double-blind active-controlled efficacy study	1218.20	1560 (100.0)	0 (0.0)	779 (49.9)	779 (49.9)	781 (50.1)
Additional double-blind placebo-controlled efficacy studies	1218.35	245 (100.0)	84 (34.3)	161 (65.7)	161 (65.7)	0 (0.0)
	1218.50	227 (100.0)	76 (33.5)	151 (66.5)	151 (66.5)	0 (0.0)
Double-blind efficacy studies with more than one linagliptin dose level	1218.5	302 (100.0)	67 (22.2)	170 (56.3)	55 (18.2)	65 (21.5) [a]
	1218.6	333 (100.0)	71 (21.3)	197 (59.2)	66 (19.8)	65 (19.5) [b]
	1218.23 [c]	561 (100.0)	80 (14.3)	319 (56.9)	159 (28.3)	162 (28.9)
Open-label long-term extension study	1218.40 [d]	2122 (100.0)	0 (0.0)	2122 (100.0) [e]	2122 (100.0) [e]	0 (0.0)
Overall total		5879 (100.0)	1117 (19.0)	4278 (72.8)	3872 (65.9)	1073 (18.3)

a Metformin open-label arm for sensitivity analyses
b Glimepiride open-label arm for sensitivity analyses
c Patients initially randomised to placebo were randomised to linagliptin 5 mg or 10 mg after 12 weeks of treatment; patients initially randomised to active comparator (voglibose) were randomised to linagliptin 5 mg or 10 mg after 26 weeks of treatment. Therefore, the total number of patients in study 1218.23 is smaller than the sum of patients in the individual treatment groups.
d Extension of the pivotal placebo-controlled studies (studies 1218.15, 1218.16, 1218.17, 1218.18). Thus, the total number of patients who participated in study 1218.40 is not included in the overall total.
e A total of 1533 patients in study 1218.40 had received linagliptin already in the pivotal placebo-controlled studies and they are therefore not included in the overall total.

Source: Applicant's Table 1.1:2 in the Summary of Clinical Efficacy

As shown in Table 3, the randomization ratio in Trial 20 was 1:1, in Trials 15, 16, 35 and 50 was 2:1 favoring linagliptin, and in Trials 17 and 18 was 3:1 favoring linagliptin.

Endpoints

The primary efficacy variable in all trials was the concentration of HbA1c. The samples for all trials were analyzed in central laboratories that held a National Glycohemoglobin Standardization Program Level I certificate.
The concentration of fasting plasma glucose (FPG) was an important secondary efficacy variable. In some trials (trials 16, 17, and 20), a meal tolerance test (MTT) was performed in a subgroup of patients at selected visits. The most important MTT variable was postprandial

glucose, determined at 2 h after intake of a standardized meal (2 h-postprandial glucose, 2h PPG).

Statistical Analyses

To ensure a homogeneous distribution of subjects with more severe hyperglycemia across treatment groups, randomization was stratified by the HbA1c value at the beginning of the placebo run-in period (<8.5% versus ≥8.5%) in most of the trials, with the exception of trials 5, 6, and 23. Randomization was also stratified by the number of oral antidiabetic drugs (OADs) at the time of enrolment in most of the trials, except for trials 5, 6, 18, and 23.
The primary endpoint in all trials except for the open-label extension trial (trial 40) was the change in HbA1c from baseline to the last on-treatment visit. It was analyzed using an analysis of covariance (ANCOVA) with treatment and baseline HbA1c as covariates. In the trials that comprised stratified randomization by the number of prior OADs, the number of previously used OADs was used as a fixed factor. HbA1c measurements were regarded as 'on-treatment' if they were taken after the first dose of study medication and up to 7 days after the last dose of study medication had been administered. Missing HbA1c and FPG data were handled by the "last observation carried forward" (LOCF) imputation approach, with other sensitivity analyses conducted. The primary analysis was always conducted in the full analysis set, or FAS (a modified intent to treat that included all randomized subjects who received ≥ one dose of study drug, had a baseline HbA1c, and had ≥ one on-treatment HbA1c measurement).
In the placebo- or active-controlled trials that were intended to demonstrate superiority of linagliptin using one dose, the change from baseline in HbA1c was tested at the level of a = 0.05 (2-sided test). For the superiority studies with more than one linagliptin dose (trials 5, 6, and 23), superiority of linagliptin was tested sequentially from the highest to the lowest dose, using a closed stepwise procedure. Each hypothesis was tested at alpha = 0.025 (1-sided).
For the glimepiride-controlled trial 20, confirmatory analyses are performed both after 52 weeks of treatment (pre-specified interim analysis; these results were reported in this NDA submission) and after 104 weeks of treatment (at end of study). To adjust for the multiple testing after 52 weeks and 104 weeks, a Bonferroni correction was applied.

Unlike the applicant's method for the primary analysis, Dr. Wei applied the mixed model for repeated measures (MMRM) method with an additional fixed effect 'visit week' to the general model on the actually observed data, the OC population. Dr. Wei performed sensitivity analyses on per-protocol (PP), last observation carried forward (LOCF) populations, and the FAS-completers using the MMRM method. All MMRM analyses examined the contrast at the last time point.
Due to the consistency of results using different population sets and analytical methods, I will discuss only summary findings and tests based on ANCOVA tests conducted in FAS population sets.

Secondary and other endpoints

The change in FPG from baseline to the last on-treatment visit was investigated as secondary endpoint in all studies. Other endpoints were proportion of subjects who reached a target HbA1c of 7% (or 6.5%) or less, changes in HbA1c and FPG over time, proportion of subjects

requiring glycemic rescue therapy under protocol pre-specified thresholds, 2h PPG, changes in body weight, and other exploratory endpoints (HOMA, disposition index, etc).

Eligibility

All trials supporting the analysis of efficacy used similar inclusion and exclusion criteria. Male or female subjects had to be diagnosed with T2DM, were to have insufficient glycemic control, had to have a BMI of ≤ 40 kg/m^2 and were to be between 18 and 80 years of age (for trials 5 and 6, subject age was 21 to 75 years; for trial 23, subject age was 20 to 80 years). Most trials included subjects with HbA1c between 7 or 7.5% and 10% (after washout of prior medications, if applicable). The exception was Trial 15, where the range of HbA1c acceptable for eligibility was 7.5 to 11%, since both groups would be actively treated. Canadian sites participating in multiple protocols had a stricter criterion for HbA1c: up to 9% at the start of the 2-week placebo run-in.
As I will emphasize again upon discussion of linagliptin cardiovascular safety, the population participating in the linagliptin trials was healthier than the make up of the overall diabetic population in the US. The applicant excluded patients with a myocardial infarction, stroke, or transient ischemic attack within 6 months prior to enrollment. The number of patients with renal dysfunction who could participate was relatively small, due to a large proportion of subjects who entered trials under metformin background therapy or certain limitations regarding severe renal failure and use of TZDs or sulfonylureas.

Results

As described above, a total of 11 trials are included in this CDTL memo. The trials are arranged according to their importance for the principle proof of efficacy: The four pivotal double-blind placebo-controlled trials (15, 16, 17 and 18) are described first, followed by the double-blind active-controlled efficacy trial 20 and the two additional double-blind placebo-controlled efficacy trials (35 and 50). Thereafter, the double-blind efficacy trials with more than one linagliptin dose level are presented (trials 5, 6 and 23), followed by the open-label extension trial 40.

Disposition

Approximately 40% of subjects initially screened were not randomized, most of them due to not meeting HbA1c range criteria. This is common in diabetes drug development trials. Of subjects randomized in the EFF-1 grouping trials, 94% completed the 24 weeks of treatment period: 5.2 % of linagliptin-treated versus 8.2% of placebo-treated subjects discontinued prematurely, mostly due to administrative reasons (non-compliance with protocol, lost to F/U or withdrawal of consent). Similar disposition characteristics were reported in the larger EFF-3 trial grouping (which includes all four pivotal trials, but also the large glimepiride-controlled trial 20).

Baseline characteristics

Baseline HbA1c, FPG, time since diagnosis of T2DM and number of OADs at the time of enrollment were balanced across the treatment groups in EFF-1 and also in Trial 20. It is noteworthy that the mean HbA1c at baseline has been in the range 8.0 to 8.2% (SD 0.9) for the majority of the trials, except for Trial 15 (lina + pio vs. pio alone as initial therapy), where the HbA1c was 8.6% (SD 0.9). Also consistent with other diabetes drug programs, the majority of subjects in monotherapy trials who were either treatment naïve or on a single OAD prior to washout were diagnosed < 5 years prior to enrollment (75%), in contrast with Trial 18 (on background of both metformin and sulfonylurea), where the majority of subjects (75%) had been diagnosed with T2DM > 5 years prior to enrollment.

The development program (Phase 2 and Phase 3 combined) enrolled sufficient numbers of patients with mild and moderate renal impairment: 944 subjects with mild (60 to < 90 mL/min) and 112 subjects with moderate (30 to < 60 mL/min) renal impairment were treated with linagliptin, but only included two subjects with severe renal impairment (<30 mL/min), based on the Modification of Diet in Renal Disease staging, MDRD. The 4-Month Safety Update included an interim report on Trial 43, conducted in patients with severe renal impairment, as had been agreed upon at the time of the Pre-NDA meeting.

Demographic characteristics (Table 4 and Table 5)

Demographic characteristics were generally well balanced across individual trials and in the overall pooled groups. It is noteworthy that Blacks (including African Americans) are clearly underrepresented (0.5% in EFF-1 and 2.4% in the large glimepiride-controlled trial) in the trials of linagliptin, compared to the proportion of Blacks with T2DM in the US population. This has been a recurrent problem in the development of newly approved antidiabetic drugs, as more trials are being conducted in countries with little representation of, or trial access to Black subjects. Nonetheless, subgroup analyses did not show any deviation from the overall efficacy of linagliptin or other DPP4 inhibitors which would preclude an extrapolation of the efficacy findings.

Another point of interest is the higher proportion of male subjects (well balanced between the treatment groups) in Trial 15. A DSI inspection at one of the Japanese sites conducting Trial 15 (initial therapy with linagliptin + pioglitazone versus pioglitazone alone) revealed that only 2 female subjects were enrolled out of 59 subjects. Dr. Matsuoka, the PI, stated that, when he was provided with a list of potentially eligible subjects from the clinical site's database, he implemented an additional (undocumented) sorting process that removed any subjects that were experiencing edema at the time of the screening visits and removed subjects that had a BMI > 30 because of the cautions in the Japanese label for pioglitazone regarding the side effect of edema occurring more frequently in women. The issue concerning edema in women was also discussed with the local IRB and the sponsor, who allowed for this variation on screening criteria as covered by the exclusion criterion concerning investigator judgment. Therefore, this observation was not cited as a violation, and we did not consider this as affecting the overall efficacy findings according to gender.

Table 4. Key demographics in EFF-1 (pivotal placebo-controlled trials) - FAS

Study/ treatment group	Number of patients	Age, mean (SD) [years]	Male gender, N (%)	Race, N (%)			BMI, mean (SD) [b] [kg/m^2]
				White	Black [a]	Asian	
1218.15/							
Placebo	128	56.8 (10.0)	85 (66.4)	95 (74.2)	0 (0.0)	33 (25.8)	29.76 (4.87)
Linagliptin	252	57.6 (9.7)	147 (58.3)	186 (73.8)	0 (0.0)	66 (26.2)	28.71 (4.86)
1218.16/							
Placebo	163	54.7 (10.1)	75 (46.0)	90 (55.2)	0 (0.0)	73 (44.8)	29.18 (4.85)
Linagliptin	333	56.4 (10.0)	162 (48.6)	178 (53.5)	0 (0.0)	155 (46.5)	29.04 (4.79)
1218.17/							
Placebo	175	56.6 (11.0)	101 (57.7)	138 (78.9)	2 (1.1)	35 (20.0)	30.07 (5.03)
Linagliptin	513	56.6 (10.0)	273 (53.2)	388 (75.6)	6 (1.2)	119 (23.2)	29.85 (4.85)
1218.18/							
Placebo	262	57.6 (9.7)	127 (48.5)	115 (43.9)	2 (0.8)	145 (55.3)	28.17 (4.53)
Linagliptin	778	58.3 (9.9)	364 (46.8)	369 (47.4)	6 (0.8)	403 (51.8)	28.37 (4.80)
EFF-1 pool/							
Placebo	728	56.6 (10.2)	388 (53.3)	438 (60.2)	4 (0.5)	286 (39.3)	29.13 (4.84)
Linagliptin	1876	57.4 (10.0)	946 (50.4)	1121 (59.8)	12 (0.6)	743 (39.6)	28.94 (4.86)

a or African American
b baseline value

Source: Applicant's Table 3.1.2.1 in the Summary of Clinical Efficacy

Table 5. Key demographics in Trial 20 - FAS

Study/ ***initial study***/ treatment group	Number of patients	Age, mean (SD) [years]	Male gender, N (%)	Race, N (%)			BMI, mean (SD) [b] [kg/m^2]
				White	Black [a]	Asian	
1218.20 /							
Linagliptin	766	59.7 (9.4)	454 (59.3)	649 (84.7)	19 (2.5)	98 (12.8)	30.21 (4.73)
Glimepiride	761	59.8 (9.4)	465 (61.1)	644 (84.6)	17 (2.2)	100 (13.1)	30.33 (4.58)

Source: Adapted from the applicant's Table 3.1.2.1 in the Summary of Clinical Efficacy

Primary Efficacy Endpoint – HbA1c

EFF-1 (Four 24-week pivotal trials)

In the EFF-1 grouping, all trials were placebo-controlled and 24-weeks in duration.
As shown in Table 6, the changes in HbA1c from baseline to week 24 were consistent across the trials in the grouping, the most robust support for the efficacy of linagliptin as an antidiabetic drug.

Table 6. Change from baseline in HbA1c (%) at Week 24 in pivotal trials in EFF-1 grouping - FAS population with LOCF imputation

Study/ treatment group	Number of patients	Baseline HbA_{1c}, mean (SD)	Change from baseline in HbA_{1c}		Difference from placebo		
			Mean (SD)	Adjusted mean (SE)	Adjusted mean (SE)	95% CI	p-value
1218.15/[a]							
Placebo	128	8.58 (0.87)	-0.75 (1.21)	-0.56 (0.09)			
Linagliptin	252	8.60 (0.79)	-1.25 (1.07)	-1.07 (0.06)	-0.51 (0.10)	(-0.71, -0.30)	<0.0001
1218.16/[a]							
Placebo	163	8.00 (0.86)	0.22 (1.07)	0.25 (0.07)			
Linagliptin	333	8.00 (0.87)	-0.46 (0.81)	-0.44 (0.05)	-0.69 (0.08)	(-0.85, -0.53)	<0.0001
1218.17/[a]							
Placebo	175	8.02 (0.88)	0.10 (1.00)	0.15 (0.06)			
Linagliptin	513	8.09 (0.86)	-0.56 (0.83)	-0.49 (0.04)	-0.64 (0.07)	(-0.78, -0.50)	<0.0001
1218.18/[b]							
Placebo	262	8.14 (0.84)	-0.10 (0.87)	-0.10 (0.05)			
Linagliptin	778	8.15 (0.80)	-0.72 (0.86)	-0.72 (0.03)	-0.62 (0.06)	(-0.73, -0.50)	<0.0001
EFF-1 pool/[c]							
Placebo	728	8.16 (0.88)	-0.09 (1.06)	-0.03 (0.03)			
Linagliptin	1876	8.17 (0.85)	-0.70 (0.91)	-0.64 (0.02)	-0.61 (0.04)	(-0.69, -0.54)	<0.0001

a Model includes baseline HbA_{1c}, number of prior OADs, and treatment
b Model includes baseline HbA_{1c} and treatment
c Model includes baseline HbA_{1c}, washout, treatment, study, and treatment-by-study interaction

Source: Applicant's Table 3.2.1.1:1 in the Summary of Clinical Efficacy

As shown in Drs. Dunn and Wei clinical and statistical review, the favorable efficacy findings persist with sensitivity analyses (among completers only and among observed cases [rescue therapy values computed in the analysis]). The effect also persisted in analyses of subgroups based on baseline characteristics relevant for the outcome and based on demographic characteristics. Dr. Wei pointed out that in Trial 15, the linagliptin effect on HbA1c was not significant for women (HbA1c difference between groups of -0.2% [CI: -0.6, 0.1]) but this was the trial where there was under enrollment of women (see above), and the trial was likely not adequately powered for the analysis within this subgroup.

EFF-2 – Glimepiride-controlled, 52-week trial (trial 20)

Summary results of a pre-specified unblinded 52-week interim analysis of the active-controlled trial 20, which investigates the efficacy of linagliptin (5 mg) versus glimepiride (1 to 4 mg) as add-on therapy to metformin over a total of 104 weeks, are presented here.
In the interim analysis after 52 weeks of treatment, three confirmatory hypotheses were tested:

- Non-inferiority of linagliptin versus glimepiride in terms of change in HbA1c from baseline (non-inferiority margin: 0.35%, using an ANCOVA with treatment and number of prior OADs as fixed effects and baseline HbA1c as a covariate.);
- Superiority of linagliptin versus glimepiride in terms of change in body weight from baseline;

- Superiority of linagliptin versus glimepiride in terms of occurrence of hypoglycemic events.

These hypotheses were ordered hierarchically and tested in a fixed sequence at alpha = 0.025. After 52 weeks of treatment, a mean HbA1c decrease from baseline after 52 weeks was observed in both treatment groups (Table 7). The reduction of HbA1c was numerically greater in the glimepiride group (-0.6%) than in the linagliptin group (-0.4%), resulting in an adjusted mean difference in HbA1c between linagliptin and glimepiride of 0.2%. Nevertheless, the 2-sided 97.5% CI (0.1%, 0.3%) for the treatment difference excluded the pre-specified non-inferiority margin of 0.35%, and the 1-sided p-value for the non-inferiority test (p = 0.0007) was below alpha = 0.0125. The applicant concluded that linagliptin was non-inferior to glimepiride with regard to the change from baseline in HbA1c after 52 weeks of treatment.

Table 7. Change from baseline in HbA1c at week 52 in the glimepiride-controlled trial 20 (EFF-2, FAS population, LOCF imputation)

Study/ treatment group	Number of patients	Baseline HbA_{1c}, mean (SD)	Change from baseline in HbA_{1c}		Difference from glimepiride		
			Mean (SD)	Adjusted mean (SE) [a]	Adjusted mean (SE) [a]	97.5% CI	p-value [b]
1218.20/							
Linagliptin	766	7.69 (0.88)	-0.43 (0.82)	-0.38 (0.03)	0.22 (0.04)	(0.13, 0.31)	0.0007
Glimepiride	761	7.70 (0.87)	-0.65 (0.88)	-0.60 (0.03)			

a Model includes baseline HbA_{1c}, number of prior OADs, and treatment
b Non-inferiority test (non-inferiority margin 0.35%)
Source: Applicant's Table 3.2.2.1:1 in the Summary of Clinical Efficacy

These results were consistent when tested in different analyses sets (completers and per-protocol).
As Dr. Dunn pointed out in her review, linagliptin was statistically non-inferior to glimepiride, but, judged solely from the standpoint of glycemic control, is clinically somewhat inferior. In addition, the maximum dose of glimepiride allowed in this trial was 4 mg qd, with most subjects taking 3 mg, when the maximum recommended dose in the glimepiride US label is 8 mg qd. On the other hand, linagliptin was superior to glimepiride in the other pre-specified endpoints, which are relevant in the treatment of patients with T2DM: rates of hypoglycemia (41 of 778 [5.3%] subjects in the linagliptin group versus 249 of 781 [31.9%] subjects in the glimepiride group) and changes in body weight (see below).

EFF-3 (all trials testing linagliptin 5 mg)

This grouping involves most trials in the Phase 2 and Phase 3 program, and showing all individual trial results will incur in unnecessary overlap with results in other groupings described previously or others that follow EFF-3. Therefore, I will focus on the following trial results, in order to discuss specific aspects of the program: Trials 5, 6, 23, 35 and 50.

Comparison between linagliptin and other antidiabetic drugs

Trial 20 was the only Phase 3, active-controlled trial in the development program. It was adequately designed and powered to achieve its objective. In Trial 20, the efficacy of

linagliptin was shown to be slightly worse than that of glimepiride, even though it met the pre-defined statistical non-inferiority margin.
But the linagliptin effects against glimepiride seen in Trial 20 are consistent with results from a smaller and shorter Phase 2 trial (Trial 6). Trial 6 was a dose-ranging, 12-week trial where three different dose levels of linagliptin were compared to placebo in subjects not adequately controlled on metformin therapy. Dose levels of 1, 5 and 10 mg of linagliptin taken daily were compared to placebo, in a treatment period lasting 12 weeks. In that trial, an additional cohort of subjects was randomized to open label glimepiride the applicant used the term "glimepiride reference"). In the primary analysis of Trial 6, the three dose levels of linagliptin were compared to placebo (Table 8).

Table 8. Changes from baseline in HbA1c (%) at week 12 in Trial 6 (FAS set, LOCF imputation)

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)	0.25 (0.10)	–0.15 (0.10)	–0.48 (0.11)	–0.42 (0.10)
Difference to placebo (SE) 95% CI p-value		–0.40 (0.14) (–0.68, –0.12) 0.0055	–0.73 (0.14) (–1.01, –0.44) <.0001	–0.67 (0.14) (–0.95, –0.39) <.0001

Means are adjusted based on a model with baseline HbA1c, treatment
Source: Applicant's Table 11.4.1.1.1:1 in the report BI Trial No.: 1218.6

But the applicant also conducted a separate analysis of the changes in HbA1c between placebo and glimepiride. Investigators were instructed to start glimepiride at 1 mg qd X 4weeks, and then "follow the labeled instructions". The results are shown in Table 9.

Table 9. Changes from baseline in HbA1c at week 12 in Trial 6: glimepiride versus placebo (FAS set, LOCF imputation)

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
Source: Applicant's Table 11.4.1.1.2:3 in the report BI Trial No.: 1218.6

Unlike the doses of glimepiride used in the active-controlled, non-inferiority trial 20, in Trial 6 almost 30/65 of subjects randomized to glimepiride took only 1 mg daily, 12/65 took 2 mg daily and 23/65 subjects took 3 mg daily of glimepiride. And despite these lower than maximally effective glimepiride doses, the mean change in HbA1c at week 12 was greater with glimepiride than with linagliptin, either at 5 or at 10 mg daily.

Another "unintended" active-controlled trial was the small, 12-week Phase 2 dose-ranging trial (Trial 5). In that trial linagliptin at dose levels of 0.5, 2.5 and 5 mg were compared to placebo, in subjects who were treatment naïve. But a parallel cohort taking open label metformin was also randomized in the Trial 5 (the applicant calls the cohort "metformin reference").
The change in HbA1c among the different dose levels of linagliptin versus placebo is shown in Table 10.

Table 10. Change in HbA1c from baseline at week 12 in Trial 5 (FAS set)

	Placebo	BI 1356 0.5mg	BI 1356 2.5 mg	BI 1356 5 mg
Number of patients	63	57	55	54
HbA1C [%]				
Adjusted Mean (SE)	0.18 (.10)	0.04 (.10)	-0.24 (.10)	-0.28 (.10)
HbA1C difference to Placebo [%]				
Adjusted Mean (SE)		-0.14 (.14)	-0.42 (.14)	-0.46 (.14)
95% CI		(-0.41, 0.14)	(-0.69, -0.14)	(-0.74, -0.18)
P-value		0.3271	0.0032	0.0012

Note: The above results are based on analysis that includes BI 1356 doses, Metformin and Placebo data
Source: Applicant's Table 11.4.1.1.1:1 in Study Report BI Trial No.: 1218.15

Table 11 shows the change in HbA1c from baseline to week 12 in the placebo and the metformin arms in Trial 5.

Table 11. Change from baseline in HbA1c (%) at week 12: comparison between placebo and open label metformin in Trial 5 (FAS)

	Placebo	Metformin
Number of patients	63	65
HbA1C [%]		
Adjusted Mean (SE)	0.18 (.10)	-0.68 (.09)
HbA1C difference to Placebo [%]		
Adjusted Mean (SE)		-0.85 (.13)
95% CI		(-1.1, -0.59)
P-value		<0.0001

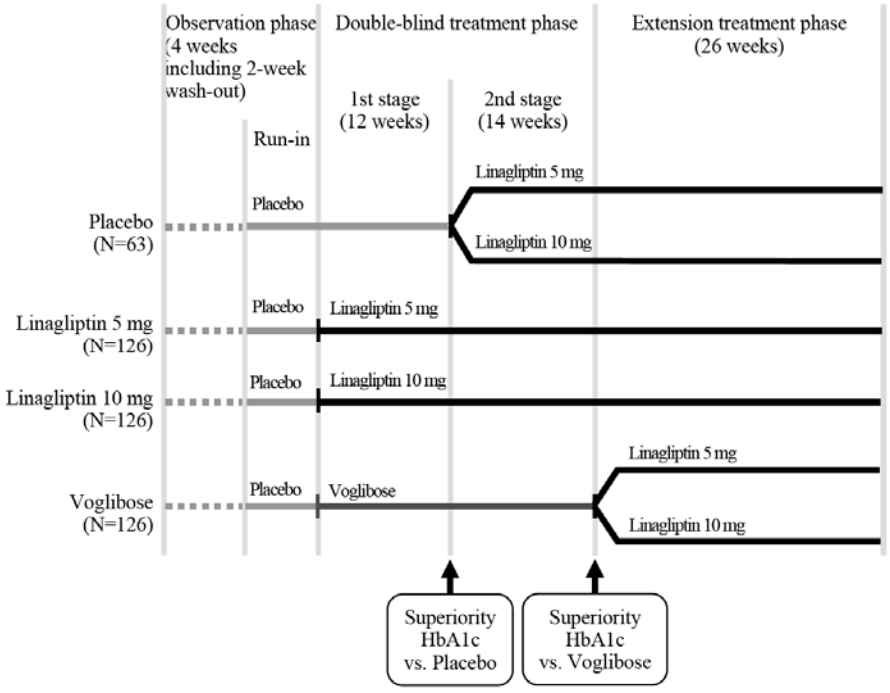
Note: The above results are based on analysis that includes BI 1356 doses, metformin and placebo data
Source: Applicant's Table 11.4.1.4:1 in Study Report BI Trial No.: 1218.5

So, from trials 5 and 6, we may conclude that 5 mg of linagliptin is as effective as 10 mg; as Drs. Dunn and Jain have concluded, the applicant chose an optimal linagliptin dose to take to market (5 mg).

But the other aspect not yet discussed by the other reviewers is how linagliptin compares to other medications in the oral diabetes armamentarium. These findings from Trials 5 and 6, comparing 12-week data between linagliptin and other commonly used antidiabetic medications, are not robust to make any conclusive determinations of comparative efficacy: they are short term trials (linagliptin reaches its maximum placebo-adjusted effect only after 12 weeks), they are underpowered, the active medications are used in open label fashion, and there is no pre-established non-inferiority margin or pre-planned comparisons to metformin (Trial 5) or glimepiride (Trial 6). But they give some evidence that, within the setting of randomized subjects in the same trial, linagliptin performs slightly worse than either metformin or glimepiride.
As suggested by the applicant, a health care provider selecting a treatment for his/her patient with T2DM need not only look at the placebo-adjusted glycemic control achieved in randomized controlled trials, but at the overall risks and benefits provided by each drug or class of drugs. And clearly the class of DPP4 inhibitors can provide glycemic benefits in patients who cannot take either metformin or sulfonylureas.

In addition to the comparison to metformin or to a commonly used sulfonylurea, the applicant also provides a comparison between linagliptin and a drug in another class of antidiabetic agents: alpha glucosidase inhibitors. Trial 23 was a placebo-controlled trial of 12 weeks duration against linagliptin at dose levels of 5 and 10 mg, but was also an active-controlled, 26 week duration trial between linagliptin (at 5 and 10 mg) versus voglibose, an alpha glucosidase inhibitor marketed in Japan. This was a multicenter trial conducted in Japanese sites only in treatment-naïve subjects. Figure 1 shows the complex trial design.

Figure 1. Design of Trial 23



So the trial served to help inform dose selection for marketing and for a comparison to voglibose used at a dose of 0.2 mg three times daily (0.6 mg daily dose).

The placebo-adjusted change in HbA1c for both the 5 mg and 10 mg dose levels of linagliptin was better than in other trials, at least in part due to substantial worsening of glycemia among subjects in the placebo group. The absolute change in HbA1c in the linagliptin groups with the magnitude of effect in Trials 5 and 6, also after the same 12-week treatment period (Table 12).

Table 12. Change in HbA1c (%) from baseline to week 12 in Trial 23 (FAS set, LOCF imputation)

	Linagliptin 5 mg	Linagliptin 10 mg	Placebo
Number of patients	159	160	80
Number of patients with baseline and on-treatment results	159	157	80
Baseline			
Mean (SE)	8.07 (0.05)	7.98 (0.05)	7.95 (0.07)
Change from baseline			
Mean (SE)	-0.49 (0.06)	-0.50 (0.05)	0.39 (0.10)
Adjusted[1)] mean (SE)	-0.24 (0.06)	-0.25 (0.06)	0.63 (0.08)
Comparison vs. placebo (difference: Linagliptin - Placebo)			
Adjusted[1)] mean (SE)	-0.87 (0.09)	-0.88 (0.09)	
95% confidence interval	(-1.04, -0.70)	(-1.05, -0.71)	
p-value	<0.0001	<0.0001	

1) Model includes treatment, baseline HbA1c and number of previous antidiabetic medication
Source: Applicant's Table 11.4.1.1.1.1.:1 in Study Report BI Trial No.: 1218.23

The other objective of the trial was to compare two dose levels of linagliptin against voglibose (Table 13). The mean effect of linagliptin, at either dose, was better than that observed with voglibose. Since this was designed as a superiority trial, the applicant demonstrated the superiority of linagliptin to voglibose.

Table 13. Change in HbA1c (%) from baseline to week 26 in Trial 23 (FAS set, LOCF imputation)

	Linagliptin 5 mg	Linagliptin 10 mg	Voglibose
Number of patients	159	160	162
Number of patients with baseline and on-treatment results	159	157	162
Baseline			
Mean (SE)	8.07 (0.05)	7.98 (0.05)	8.02 (0.06)
Change from baseline			
Mean (SE)	-0.44 (0.07)	-0.48 (0.06)	-0.10 (0.08)
Adjusted[1)] mean (SE)	-0.13 (0.07)	-0.19 (0.07)	0.19 (0.07)
Comparison vs. placebo (difference: Linagliptin - Voglibose)			
Adjusted[1)] mean (SE)	-0.32 (0.09)	-0.39 (0.09)	
95% confidence interval	(-0.49, -0.15)	(-0.56, -0.21)	
p-value	0.0003	<0.0001	

1) Model includes treatment, baseline HbA1c and number of previous antidiabetic medication
Source: Applicant's Table 11.4.1.1.1.2.:1 in Study Report BI Trial No.: 1218.23

We cannot compare voglibose to the alpha glucosidase inhibitor acarbose, approved and marketed in the US under the trade name Precose. A small and short trial (30 subjects with

T2DM treated for 8 weeks) between these two alpha glucosidase inhibitors conducted in Thailand indicated a similar degree of change in HbA1c (Table 14).

Source: Vichsyanrat A, Ploybuth S, Tunkalit M, et al. Efficacy and safety of voglibose in comparison with acarbose in type 2 diabetic patients. Diabetes Research and Clinical Practice (55): 99-103, 2002.

If this is indeed the case, these data suggest that linagliptin is at least as effective, if not more, than alpha glucosidase inhibitors.

Trials of linagliptin as add-on to sulfonylureas or in patients cannot use metformin

Trial 35 was an 18-week placebo-controlled trial of linagliptin 5 mg added on to sulfonylurea as background therapy. Patients on any drug in the class of sulfonylurea could be eligible, as long as the dose had been at least half of the maximally effective dose and stable.
Table 15 shows the HbA1c results reported in Trial 35.

Table 15. Changes in HbA1c (%) from baseline at week 18 in Trial 35 (FAS set, LOCF imputation)

	Placebo	Linagliptin
Number of patients	82	158
Number of patients with baseline and on-treatment results	82	158
Baseline		
Mean (SE)	8.60 (0.08)	8.61 (0.07)
Change from baseline		
Mean (SE)	-0.11 (0.08)	−0.58 (0.07)
Adjusted[1] mean (SE)	−0.07 (0.10)	−0.54 (0.07)
Comparison vs. placebo (difference linagliptin - placebo)		
Adjusted[1] mean (SE)		−0.47 (0.12)
95% Confidence interval		−0.70, −0.24
p-value		<0.0001

[1] Model includes continuous baseline HbA_{1c}, number of prior antidiabetic drugs, and treatment. SE = Standard error
Source data: Table 15.2.1.1: 2

Source: Applicant's table 11.4.1.1.1.:1 in Study Report BI Trial No.: 1218.35

The last trial in this grouping is Trial 50, an 18-week, placebo-controlled, efficacy and safety trial of linagliptin 5 mg, followed by a 34-week double extension period (placebo subjects were switched to glimepiride) in subjects with insufficient glycemic control for whom metformin therapy is inappropriate (intolerability or contraindication). Only the 18-week placebo-controlled phase results are reported in this interim report. Superiority of linagliptin over placebo was demonstrated for the primary endpoint of change in HbA1c from baseline at Week 18. The treatment difference between linagliptin and placebo, calculated as the adjusted mean change in HbA1c from baseline at Week 18, adjusted for the stratification factors and

baseline HbA1c, was -0.6% (95% confidence interval -0.9, -0.3; p< 0.0001; FAS set, LOCF imputation).
The interesting aspect of this trial is that the applicant sought to identify a population of subjects who could be followed long term without the use of the most commonly prescribed medication for T2DM: metformin, to evaluate durability of effect of linagliptin against a sulfonylurea. The trial is ongoing, so we have no 52-week results at this time.

Trial 43 in the 4-Month Safety Update – diabetics with severe renal insufficiency

As mentioned earlier in this document, the applicant provided an interim report on the safety and efficacy of linagliptin in patients with severe renal impairment (eGFR < 30 mL/min, based on MDRD). This is a multicenter, Phase 3 trial being currently conducted in subjects with background insulin or insulin and other antidiabetic drugs to determine the safety and efficacy of linagliptin 5 mg qd over a 52-week treatment period. Sixty eight subjects were randomized to linagliptin and 65 to placebo.
There were 62 subjects of the placebo group and 66 subjects of the linagliptin group included in the FAS. All efficacy analyses were based on the FAS. The primary endpoint in this interim report was the change from baseline in HbA1c to week 12 of treatment. The treatment difference between linagliptin (n=66) and placebo (n=62), calculated as the adjusted mean change in HbA1c from baseline at Week 12, was -0.6 % (95% CI -0.9, -0.3), demonstrating superiority of linagliptin over placebo (p=0.0001) in the reduction of HbA1c. Sensitivity analyses confirmed the results observed for the primary endpoint.

Secondary endpoint – Fasting Plasma Glucose

In EFF-1 – Placebo-controlled 24-week pivotal trials (Table 16)

Table 16. Change from baseline in fasting plasma glucose (mg/dL) at Week 24 in pivotal placebo-controlled trials (EFF-1, FAS population set, LOCF imputation)

Study/ treatment group	Number of patients [a]	Baseline FPG, mean (SD)	Change from baseline in FPG		Difference from placebo		
			Mean (SD)	Adjusted mean (SE)	Adjusted mean (SE)	95% CI	p-value
1218.15/[b]							
Placebo	122	186.43 (39.77)	-21.35 (37.12)	-18.52 (2.99)			
Linagliptin	243	188.36 (42.14)	-36.28 (38.24)	-32.77 (2.18)	-14.25 (3.51)	(-21.16, -7.35)	<0.0001
1218.16/[b]							
Placebo	149	165.72 (37.69)	13.28 (42.84)	14.86 (2.98)			
Linagliptin	318	163.86 (41.58)	-8.53 (37.43)	-8.48 (2.03)	-23.34 (3.59)	(-30.40, -16.29)	<0.0001
1218.17/[b]							
Placebo	159	163.81 (39.30)	10.79 (47.86)	10.46 (2.80)			
Linagliptin	495	168.98 (43.03)	-12.69 (37.99)	-10.68 (1.65)	-21.13 (3.14)	(-27.30, -14.96)	<0.0001
1218.18/[c]							
Placebo	248	162.60 (37.20)	6.86 (38.87)	8.07 (2.38)			
Linagliptin	739	159.20 (36.54)	-4.21 (41.97)	-4.61 (1.38)	-12.69 (2.75)	(-18.09, -7.28)	<0.0001
EFF-1 pool/[d]							
Placebo	678	167.86 (39.19)	4.12 (43.38)	5.37 (1.48)			
Linagliptin	1795	166.67 (41.15)	-11.65 (40.91)	-12.61 (1.00)	-17.98 (1.69)	(-21.29, -14.66)	<0.0001

a Patients in the FAS with a baseline FPG value and at least 1 on-treatment FPG value
b Model includes baseline HbA_{1c}, baseline FPG, number of prior OADs, and treatment
c Model includes baseline HbA_{1c}, baseline FPG, and treatment
d Model includes baseline HbA_{1c}, baseline FPG, washout, treatment, study, and treatment-by-study interaction

Source: Applicant's Table 3.2.1.2:1 in the Summary of Clinical Efficacy

Although all trials in EFF-1 showed FPG changes favorable to linagliptin, the magnitude of mean placebo-adjusted effect was lower in Trials 15 and 18 (mean -14 mg/dL and -13 mg/dL, respectively) compared to Trials 16 and 17 (mean -23 mg/dL and -21 mg/dL, respectively). It is unclear why, in view of such consistent HbA1c results, there was a discrepancy in FPG among the trials in this pivotal grouping.

Neither trial 15 nor trial 18 assessed effects of linagliptin on PPG. Trial 18 tested linagliptin in subjects maximally treated with glimepiride and metformin, so it is possible that in this setting glimepiride was providing near-maximal insulin stimulation in the fasting state, and there was not much additional effect from linagliptin. Therefore, most of the effect of linagliptin to account for the same overall effect on HbA1c was due to the suppression of postprandial glucose ("the incretin effect"). The Trial 18 FPG results are similar to the results reported in Trial 35, where linagliptin was tested in subjects treated with background sulfonylurea for 18 weeks. In Trial 35 the placebo-adjusted change in HbA1c at week 18 was -0.5% (95% CI: -0.7, -0.2) whereas the mean placebo-adjusted change in FPG was only -6 mg/dL (95% CI: -17, 4). The applicant did not address the results in Trial 15, but speculated that the lesser decline in fasting plasma glucose in the subjects treated with linagliptin with an overall HbA1c decline in par with the other pivotal trials was due to a greater effect in postprandial glucose. This cannot be confirmed, as Trial 15 did not evaluate the effect of linagliptin on postprandial glucose.

In EFF-2 – Trial 20 – Active controlled against glimepiride for 52 weeks

Consistent with the HbA1c decrease from baseline, a mean reduction in FPG after 52 weeks was observed in both treatment groups. The mean decrease in FPG was more pronounced for glimepiride than for linagliptin, and a statistically significant treatment difference in the adjusted mean FPG change of 7 mg/dL (p <0.0001) was seen (Table 17). This result indicates that glimepiride provided a greater reduction in FPG levels than linagliptin after 52 weeks of treatment, although small in magnitude.

Table 17. Change in fasting plasma glucose (mg/dL) from baseline at week 52 in Trial 20 (FAS population set, LOCF imputation)

Study/ treatment group	Number of patients [a]	Baseline FPG, mean (SD)	Change from baseline in FPG		Difference from glimepiride		
			Mean (SD)	Adjusted mean (SE) [b]	Adjusted mean (SE) [b]	97.5% CI	p-value [c]
1218.20/							
Linagliptin	736	164.10 (42.94)	-8.29 (35.04)	-8.59 (1.24)	7.62 (1.68)	(3.86, 11.38)	<0.0001
Glimepiride	731	166.63 (42.33)	-17.26 (40.23)	-16.21 (1.25)			

a Patients in the FAS with baseline value and at least 1 on-treatment value for FPG
b Model includes baseline HbA_{1c}, baseline FPG, number of prior OADs, and treatment
c Superiority test

Source: Applicant's Table 3.2.2.3:1 in the Summary of Clinical Efficacy

However, the analysis of 2h PPG over time showed that the mean change from baseline in 2h PPG was comparable for linagliptin and glimepiride both after 28 weeks and after 52 weeks of treatment (Table 18).

Table 18. Change in 2-hour post prandial glucose (mg/dL) from baseline at Week 28 and Week 52 in Trial 20 (MTT set – all subjects in FAS with MTT at baseline and ≥ one valid on-treatment MTT)

Time point	Linagliptin			Glimepiride		
	Number of patients	Mean	SD	Number of patients	Mean	SD
Baseline	286	273.27	81.72	287	273.89	79.13
Change from baseline at Week 28	180	-38.72	65.23	188	-38.16	71.74
Change from baseline at Week 52	146	-32.92	65.13	143	-36.16	69.65

Source: Applicant's Table 5.6.2:1 in the Summary of Clinical Efficacy

Secondary Endpoint- Proportion of subjects reaching HbA1c < 7%

The proportion of subjects reaching target values of HbA1c < 7.0% was a secondary endpoint in all studies in EFF-1. Treatment with linagliptin brought a higher percentage of patients to target than treatment with placebo in all 4 studies in EFF-1.

When the data from the subjects in the four studies in EFF-1 were pooled, the overall proportion of subjects with an on-treatment HbA1c < 7.0% after 24 weeks was 31.4% in the linagliptin group and 14.8% in the placebo group. As for the individual studies, the odds of achieving HbA1c < 7.0% after 24 weeks were significantly higher for linagliptin than for placebo, with an odds ratio of 3.49 (logistic regression).

In EFF-2 (comprised of Trial 20 only, the active controlled, 52 week trial of linagliptin versus glimepiride in subjects not controlled on metformin therapy), the proportion of subjects who

reached HbA1c < 7% in the linagliptin group was 39.6% (303/766) and in the glimepiride group was 44.7% (340/761). The proportion of subjects reaching HbA1c < 6.5% was slightly lower in the linagliptin group: 18.4% versus 23.9 % for glimepiride.

Secondary Endpoint – Change in body weight (Table 19)

Table 19. Change from baseline in body weight at week 24 in the pivotal trials (EFF-1, FAS- observed cases)

Study/ treatment group	Number of patients [a]	Baseline body weight, mean (SD)	Change from baseline in body weight		Difference from placebo		
			Mean (SD)	Adjusted [b] mean (SE)	Adjusted [b] mean (SE)	95% CI	p-value
1218.15/							
Placebo	102	82.72 (15.83)	1.23 (3.94)	1.27 (0.29)			
Linagliptin	228	78.43 (16.13)	2.36 (3.65)	2.34 (0.19)	1.07 (0.34)	(0.40, 1.74)	0.0017
1218.16/							
Placebo	124	79.08 (15.48)	-0.31 (2.04)	-0.27 (0.26)			
Linagliptin	288	77.89 (16.04)	-0.02 (2.14)	0.00 (0.17)	0.27 (0.31)	(-0.33, 0.88)	0.3711
1218.17/							
Placebo	133	83.89 (16.41)	-0.46 (3.31)	-0.34 (0.25)			
Linagliptin	452	82.33 (16.51)	-0.40 (3.34)	-0.31 (0.14)	0.03 (0.28)	(-0.53, 0.58)	0.9231
1218.18/							
Placebo	222	77.39 (16.86)	-0.06 (2.46)	0.05 (0.21)			
Linagliptin	714	76.61 (16.90)	0.27 (2.43)	0.37 (0.14)	0.32 (0.22)	(-0.11, 0.75)	0.1402
EFF-1 pool/							
Placebo	581	80.17 (16.48)	0.02 (2.95)	0.18 (0.13)			
Linagliptin	1682	78.61 (16.70)	0.32 (2.97)	0.60 (0.08)	0.42 (0.15)	(0.14, 0.71)	0.0036

a Patients in the FAS with a baseline value and at least 1 on-treatment value for body weight
b Model includes baseline HbA_{1c}, baseline weight, washout, treatment, study, and treatment-by-study interaction
Source: Applicant's Table 3.2.1.4:1 in the Summary of Clinical Efficacy

Based on the pooled data from the four trials in EFF-1, the mean baseline weight of subjects treated with linagliptin was 78.6 kg and of subjects receiving placebo 80.2 kg. After 24 weeks of treatment, the adjusted mean change in body weight was 0.6 kg in the linagliptin group and 0.2 kg in the placebo group. Thus, there was a small, but significant difference in the adjusted mean change in body weight between linagliptin and placebo (0.4 kg; p = 0.0036), which was driven by the results of Trial 15. This magnitude of weight gain in the linagliptin-treated subjects is not likely to be clinically relevant.

EFF-2 – Trial 20- Glimepiride-controlled 52-week trial (Table 20)

After 52 weeks of treatment, a decrease in mean body weight was noted for the subjects treated with linagliptin (adjusted mean change -1.1 kg), as opposed to a mean weight gain in the patients receiving glimepiride (1.4 kg). Linagliptin was shown to be superior to glimepiride in regard to the change from baseline in body weight after 52 weeks of treatment, with a treatment difference of -2.5 kg (p <0.0001).

Table 20. Change in body weight from baseline at week 52 in Trial 20 (FAS, LOCF)

Study/ treatment group	Number of patients [a]	Baseline body weight, mean (SD)	Change from baseline in body weight		Difference from glimepiride		
			Mean (SD)	Adjusted mean (SE) [b]	Adjusted mean (SE) [b]	97.5% CI	p-value [c]
1218.20/							
Linagliptin	736	86.00 (17.45)	-1.02 (3.62)	-1.13 (0.14)	-2.49 (0.19)	(-2.92, -2.07)	<0.0001
Glimepiride	730	86.93 (16.69)	1.46 (3.70)	1.36 (0.14)			

a Patients in the FAS with baseline value and at least 1 on-treatment value for body weight
b Model includes baseline HbA_{1c}, baseline body weight, number of prior OADs, and treatment
c Superiority test

Source: Applicant's Table 3.2.2.2:1 in the Summary of Clinical Efficacy

Linagliptin, as other members of the class of DPP4 inhibitors, is weight neutral.

In summary, the efficacy of linagliptin in lowering HbA1c and fasting plasma glucose is similar to other drugs in the DPP4 inhibitor class. The data are robust, in that a large number of subjects participated in the trials, in different settings reflective of how the drug will be used post-approval. The data withstood different sensitivity analyses, with consistent evidence of glycemic benefit.
I concur with both the statistical review team and the medical officer reviewing this application that the applicant was able to demonstrate efficacy of linagliptin in the proposed indication (treatment of adults with T2DM).

8. Safety

Datasets for review

My discussion of the general safety of linagliptin is based on:
1. The large grouping of placebo-controlled trials (the applicant calls this SAF-2)
2. The large Trial 20 (SAF-4 for the applicant).

For details on the safety in other datasets comprising the NDA submission (see Table 21), please refer to Dr. Dunn's review.

Table 21. Grouping of trials for the analysis of safety

Shorthand	Characteristics of grouping (categories of analysis)	Treatment durations	Studies (without preceding '1218')	Number of patients treated*
SAF-1	All trials with linagliptin in patients (linagliptin 5 mg vs. linagliptin all doses)	12 days to 104 weeks	.2, .3, .5, .6, .12, .15, .16, .17, .18, .20, .23, .35, .37, .40, .50 (pooled analysis)	n=4687
SAF-2	All placebo-controlled trials with linagliptin 5 mg in patients (Placebo vs. linagliptin 5 mg)	12 days to 52 weeks	.2, .3, .5, .6, .15, .16, .17, .18, .23, .35, .37, .50 (pooled analysis)	n=3749
SAF-3	Pivotal placebo-controlled trials with linagliptin 5 mg in patients (Placebo vs. linagliptin 5 mg)	24 weeks	.15, .16, .17, .18 (pooled analysis)	n=2647
SAF-4	Long-term safety in an active-controlled trial in patients (linagliptin 5 mg vs. glimepiride)	≥52 weeks	.20 (by-study analysis)	n=1559
SAF-5	Long-term safety in controlled and uncontrolled trials in patients (linagliptin 5 mg)	52 to ≤102 weeks	.20, .23, .40 (pooled analysis)	n=3436
SAF-6	Placebo-controlled trials with more than one linagliptin dose level in patients (Placebo, linagliptin ≤2.5 mg, 5 mg, 10 mg)	12 days to 52 weeks	.2, .3, .5, .6, .12, .23 (pooled analysis)	n=1100
SAF-7	Phase I trials in healthy subjects (linagliptin total)	1 to 21 days	.1, .4, .7, .8, .9, .10, .11, .13, .25, .28, .29, .30, .31, .32, .33, .34, .44, .45, .58, .67 (pooled analysis)	n=453
SAF-8	Trials in patients with renal and hepatic impairment (renal: without vs. mild vs. moderate vs. severe vs. ESRD; hepatic: without vs. mild vs. moderate vs. severe)	1 to 10 days	.26, .27 (by-study analysis)	n=84

* Numbers are based on the treated set

Source: Applicant's Report on Summary of Clinical Safety, Section 1.1.3

I have reviewed also the 4-Month Safety Update submitted by the applicant on 11/2/2010, and concluded that the overall safety profile of linagliptin has not changed with the updated information provided. Therefore I will not include data from the 4-Month Safety Update in this memorandum.

Dr. Dunn's review of the general safety of linagliptin included an analysis of the deaths, serious adverse events (SAEs) and AEs leading to discontinuation from the trials, as well as a review of the common AEs and lab values, vital signs and other parameters. In addition to these, which are common to all medical reviews of safety in the Office of New Drugs, the applicant submitted, upon our pre-NDA agreement, an analysis of AEs of special interest for diabetes and for the drug class: hypoglycemia, hypersensitivity reactions, renal events (including laboratory evaluations), hepatic events (including laboratory evaluations), severe cutaneous adverse reactions, and pancreatitis.

In addition, linagliptin is a new oral drug intended to treat T2DM; as such, linagliptin is subject to the requirement to "demonstrate that it will not result in an unacceptable increase in cardiovascular (CV) risk". For the purposes of the December 2008 Guidance, this means that

the upper bound of the 95% CI in the hazard ratio of major cardiovascular events in the linagliptin group compared to control must not exceed 1.8 at the time of the NDA submission and review. I will review and comment briefly on the results of these analyses. For further detail, please refer to Dr. Dunn's medical review and to Drs. Ding and Soukup statistical review of the metanalysis conducted to estimate this risk.

Exposure

In order to weigh in on the adequacy of the overall exposure to linagliptin in clinical trials, the most appropriate dataset pooled by the applicant is SAF-1. SAF-1 is the safety grouping that includes all trials in subjects with T2DM, and constitutes the largest analysis set (Table 22).

- 6198 subjects with T2DM were randomized in the clinical trial program
- Out of these, 4687 subjects were treated with linagliptin (any dose)
- 4040 subjects received linagliptin 5 mg. In addition, 21 subjects with T2DM were randomized in trial 26 (comprising diabetics and non-diabetics with renal impairment) and treated with linagliptin 5 mg, therefore in total 4061 subjects with T2DM received linagliptin 5 mg.

This exposure is adequate for a development program in T2DM, and is in line with other recently FDA-approved drugs for this indication.

Table 22. Exposure to study drug for SAF-1 and SAF-2

	SAF-1		SAF-2	
	Linagliptin 5 mg	Linagliptin	Placebo	Linagliptin 5 mg
Number of patients, N (%)	4040 (100.0)	4687 (100.0)	1183 (100.0)	2566 (100.0)
Exposure categories, N (%)				
≥1 day	4040 (100.0)	4687 (100.0)	1183 (100.0)	2566 (100.0)
≥2 weeks	4000 (99.0)	4612 (98.4)	1152 (97.4)	2535 (98.8)
≥4 weeks	3981 (98.5)	4583 (97.8)	1139 (96.3)	2518 (98.1)
≥12 weeks	3811 (94.3)	4274(91.2)	1007 (85.1)	2360 (92.0)
≥24 weeks	3430 (84.9)	3692 (78.8)	647 (54.7)	1679 (65.4)
≥52 weeks	2390 (59.2)	2474 (52.8)	0 (0.0)	0 (0.0)
≥78 weeks	536 (13.3)	536 (11.4)	0 (0.0)	0 (0.0)
Duration of treatment exposure [days]				
Mean (±SD)	364.7 (165.5)	336.0 (176.2)	133.9 (51.5)	148.2 (42.4)
Median (minimum, maximum)	400 (1, 685)	364 (1, 685)	168 (1, 213)	169 (1, 214)
Overall patient years	4034.2	4311.4	433.8	1041.4

Source: Applicant's Table 1.2.1:1 in the Summary of Clinical Safety

The applicant conducted Study 40 as an open label, 78-week uncontrolled extension to the 24-week pivotal trials 15, 16, 17 and 18. Over 2000 subjects were followed on linagliptin 5 mg qd. However, an uncontrolled extension is relatively uninformative regarding the effects of a particular drug on common AEs, either in the general population or in the diabetic population.

Disposition

SAF-2

In SAF-2 (placebo-controlled trials), 3754 subjects were randomized to receive treatment with either placebo (n = 1185) or linagliptin 5 mg (n = 2569). Of the 3754 randomized subjects, 3749 were treated and received at least one dose of study medication. Of the 3749 subjects treated with randomized study medication, more subjects in the placebo group (11.2%) than in the linagliptin 5 mg group (7.1%) discontinued prematurely. The most frequent reasons for discontinuation were due to AEs (2.3% total) and refusal to continue trial medication (2.1% total), both having comparable percentages between treatments. More subjects in the placebo group (2.9%) than in the linagliptin 5 mg group (0.5%) discontinued due to lack of efficacy. An overview of the patient disposition of SAF-2 is given in Table 23.

Table 23. Disposition of subjects in the placebo-controlled trials (SAF-2)

	SAF-2		
	Placebo N (%)	Linagliptin 5 mg N (%)	Total N (%)
Randomised	1185	2569	3754
Treated[a]	1183 (100.0)	2566 (100.0)	3749 (100.0)
Not prematurely discontinued	1051 (88.8)	2384 (92.9)	3435 (91.6)
Prematurely discontinued	132 (11.2)	182 (7.1)	314 (8.4)
Adverse event	31 (2.6)	56 (2.2)	87 (2.3)
Worsening of disease under study	10 (0.8)	6 (0.2)	16 (0.4)
Worsening of other pre-existing disease	3 (0.3)	10 (0.4)	13 (0.3)
Other AE	18 (1.5)	40 (1.6)	58 (1.5)
Lack of efficacy[b]	34 (2.9)	13 (0.5)	47 (1.3)
Non-compliance to protocol	13 (1.1)	26 (1.0)	39 (1.0)
Lost to follow-up	11 (0.9)	17 (0.7)	28 (0.7)
Refused to continue trial medication	28 (2.4)	52 (2.0)	80 (2.1)
Other reason	15 (1.3)	18 (0.7)	33 (0.9)

[a] 'Treated' refers to treatment with randomised trial medication.

[b] Includes patients who discontinued due to hyperglycaemia.

Source: Applicant's Table 1.2.3:2 in the Summary of Clinical Safety

SAF-4

Trial 20 randomized 1560 subjects in a 1:1 ratio to receive treatment either with linagliptin 5 mg (n = 779) or glimepiride (n = 781). Of these, all but one subject in the linagliptin group were treated and received at least one dose of study medication. Of the 1559 subjects treated with randomized study medication, 1274 subjects (81.7%) completed at least 52 weeks of treatment (interim analysis; 82.0% linagliptin 5 mg and 81.4% glimepiride). In total, 285 subjects (18.3%) prematurely discontinued trial medication, the percentages being comparable between both groups: 18.0% in the linagliptin group and 18.6% in the glimepiride group. The most frequent reasons for discontinuation were due to AEs, with more patients withdrawing in the glimepiride group (9.9%) than in the linagliptin 5 mg group (5.8%). Discontinuations due to lack of efficacy were higher in the linagliptin 5 mg group (3.7%) than in the glimepiride group (1.2%). An overview of patient disposition of the SAF-4 is given in Table 24, below.

Table 24. Disposition of randomized subjects in SAF-4 (Trial 20)

	SAF-4		
	Linagliptin 5 mg N (%)	Glimepiride N (%)	Total N (%)
Randomised	779	781	1560
Treated[a]	778 (100.0)	781 (100.0)	1559 (100.0)
Not prematurely discontinued[c]	638 (82.0)	636 (81.4)	1274 (81.7)
Prematurely discontinued	140 (18.0)	145 (18.6)	285 (18.3)
Adverse event	45 (5.8)	77 (9.9)	122 (7.8)
Worsening of disease under study	6 (0.8)	5 (0.6)	11 (0.7)
Worsening of other pre-existing disease	4 (0.5)	5 (0.6)	9 (0.6)
Other AE	35 (4.5)	67 (8.6)	102 (6.5)
Lack of efficacy[b]	29 (3.7)	9 (1.2)	38 (2.4)
Non-compliance to protocol	9 (1.2)	4 (0.5)	13 (0.8)
Lost to follow-up	6 (0.8)	15 (1.9)	21 (1.3)
Refused to continue trial medication	24 (3.1)	21 (2.7)	45 (2.9)
Other reason	27 (3.5)	19 (2.4)	46 (3.0)

[a] 'Treated' refers to treatment with randomised trial medication.

[b] Includes patients who discontinued due to hyperglycaemia.

[c] Including patients who were still on study drug at the time of the data cut-off for the interim analysis.

Source: Applicant's Table 1.2.3:4 in the Summary of Clinical Safety

Deaths

SAF-2 (All placebo-controlled trials)

There were 2 deaths in this safety grouping: 2 subjects (0.1%) in the linagliptin 5 mg group died during the randomized treatment period. Patient 50630 died due to cardio-respiratory arrest and patient 55591 died due to myocardial infarction.

SAF-4 (Trial 20)

Two subjects died in the linagliptin group and three subjects died in the glimepiride group. The subjects in the linagliptin group died due to cardio-respiratory arrest (patient 29071) and sudden cardiac death (patient 20995). The subjects in the glimepiride group died due to abdominal infection (patient 21411), sudden cardiac death (patient 20971), and MI (patient 26005).

Due to the very small number of deaths in these two groupings (SAF-2 and SAF-4), we turned to the entire clinical trial database in patients with T2DM (SAF-1) to look for imbalances or any particular causes of deaths that could signify an emerging signal. The incidence rate of death in the linagliptin-treated subjects in the overall development program was not increased, compared to active controls or placebo groups (Table 25).
The review of fatal cases did not demonstrate any imbalance against the comparators (placebo or active controls).

Table 25. Estimates of death incidence rates per 1000 patient-years exposure during controlled Phase 3 trials and uncontrolled extension trial (trial 40)

BI trials	Treatment	Number of patients	Exposure [years]	Number of patients with fatal AE	Time at risk [years]	Incidence rate [per 1000 years at risk]
Controlled Phase III trials[a]	Linagliptin 5 mg	3319	2059.6	4	2072.9	1.9
	Combined comparator	1920	1372.2	3	1378.7	2.2
	Placebo	977	421.8	0	427.1	0.0
	Active comparator	943	950.3	3	951.6	3.2
Uncontrolled extension trial[b]	Linagliptin 5 mg	2121	1887.1	3	not de-termined	≤1.6

[a] BI trials 1218.15, 1218.16, 1218.17, 1218.18, 1218.20, 1218.23, 1218.35, and 1218.50
[b] BI trial 1218.40

Source: Applicant's Table 2.1.2:1 in Study Report Summary of Clinical Safety

Serious Adverse Events

SAF-2

Overall, the number of subjects with SAEs was low and the frequencies were comparable between treatments: 29 subjects (2.5%) in the placebo group and 69 subjects (2.7%) in the linagliptin group. The frequency of SAEs on the preferred term level was below 1% in each treatment group with no clear trends towards certain system organ classes (SOCs) or preferred terms in either treatment group (Table 26).

Table 26. Serious adverse events (N/%) per treatment group in SAF-2

SOC	Placebo	Linagliptin
	N (%)	N (%)
Number of patients	1183 (100.0)	2566 (100.0)
Total with SAEs	29 (2.5)	69 (2.7)
Blood and Lymphatic disorders	0 (0)	1 (0)
Cardiac Disorders	4 (0.3)	14 (0.5)
Eye Disorders	2 (0.2)	3 (0.1)
Gastrointestinal Disorders	2 (0.2)	5 (0.2)
General disorders and admin. Site conditions	1 (0.1)	3 (0.1)
Hepatobiliary disorders	1 (0.1)	4 (0.2)
Infections and infestations	5 (0.4)	10 (0.4)
Injury, poisoning & procedural complications	5 (0.4)	10 (0.4)
Investigations	1 (0.1)	0 (0)
Metabolism and nutrition disorders	1 (0.1)	3 (0.1)
Musculoskeletal & connective tissue disorder	4 (0.3)	5 (0.2)
Neoplasms benign, malignant & unspecified	2 (0.2)	1 (0)
Nervous system disorders	2 (0.2)	4 (0.2)
Renal and urinary disorders	2 (0.2)	6 (0.2)
Reproductive systems and breast disorders	1 (0.1)	0 (0)
Respiratory, thoracic & mediastinal disorders	0 (0)	3 (0.1)
Skin & subcutaneous tissue disorders	0 (0)	2 (0.1)
Surgical and medical procedures	0 (0)	1 (0)
Vascular disorders	1 (0.1)	10 (0.4)

The only small imbalance was reported in the SOC of vascular disorders, reported by one subject (0.1%) in the placebo group (hypertension) and 10 subjects (0.4%) in the linagliptin 5 mg group (circulatory collapse, hypertension, hypertensive crisis, hypotension, temporal arteritis, varicose vein). But the spread of preferred terms does not point to a particular risk associated with linagliptin.

SAF-4

The number of subjects reporting SAEs was similar in the two groups (12.0% in the linagliptin group and 14.6% in the glimepiride group) (Table 27). The only differences of note between the groups was a higher incidence of nervous system disorders (particularly cerebrovascular accident and cerebral infarction) in the glimepiride group, and a higher incidence of renal and urinary disorders in the glimepiride group.

Table 27. Frequency of patients with SAEs occurring at an incidence of >2 subjects in either treatment group at the preferred term level, sorted by SOC and preferred term

System Organ Class/ Preferred Term	Linagliptin N (%)	Glimepiride N (%)
Number of patients, N (%)	778 (100.0)	781 (100.0)
Number of patients with SAEs, N (%)	93 (12.0)	114 (14.6)
Infections and infestations	11 (1.4)	15 (1.9)
Pneumonia	3 (0.4)	1 (0.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	13 (1.7)	10 (1.3)
Prostate cancer	5 (0.6)	1 (0.1)
Nervous system disorders	6 (0.8)	19 (2.4)
Cerebrovascular accident	0 (0.0)	5 (0.6)
Cerebral infarction	0 (0.0)	3 (0.4)
Transient ischaemic attack	1 (0.1)	3 (0.4)
Cardiac disorders	17 (2.2)	18 (2.3)
Myocardial infarction	3 (0.4)	5 (0.6)
Coronary artery disease	4 (0.5)	2 (0.3)
Angina pectoris	1 (0.1)	3 (0.4)
Cardiac failure	3 (0.4)	0 (0.0)
Hepatobiliary disorders	5 (0.6)	3 (0.4)
Cholelithiasis	3 (0.4)	2 (0.3)
Musculoskeletal and connective tissue disorders	11 (1.4)	14 (1.8)
Osteoarthritis	3 (0.4)	5 (0.6)
Renal and urinary disorders	4 (0.5)	10 (1.3)
Nephrolithiasis	2 (0.3)	3 (0.4)
Renal colic	1 (0.1)	3 (0.4)

Source: Applicant's Table 12.3.2:1 in the Study Report BI Trial No.: 1218.20 Interim Analysis

There was a small imbalance in the incidence of prostate cancer (5 subjects [0/6%] in the linagliptin group and one subject [0.1%] in the glimepiride group). Of note, a concern about inhibition of DPP4 and metastatic prostate cancer was raised after a publication of in vitro, cellular data[1]. But this small imbalance in a single trial was not seen in other datasets, and could be a spurious finding with relatively small numbers, under an exposure time typically insufficient to allow detection of cancer or metastatic disease.

Discontinuation due to Adverse Events

SAF-2

The number of subjects with AEs leading to discontinuation was higher in the placebo group (43 subjects, 3.6%) compared to the linagliptin 5 mg group (58 subjects, 2.3%). In any of the

[1] Sun YX, Pedersen EA, Shiozawa Y, et al. CD26/dipeptidyl peptidase IV regulates prostate cancer metastasis by degrading SDF-1/CXCL12. Clin Exp Metastasis. 2008; 25(7):765-76

SOCs, the frequencies of AEs leading to discontinuation were smaller than 1% (in any treatment group on preferred term level) and overall no clear trend could be observed.

SAF-4

Fewer subjects were reported with AEs leading to discontinuation in the linagliptin 5 mg group (45 subjects, 5.8%) compared to the glimepiride group (77 subjects, 9.9%). The most frequent AE leading to discontinuation was hypoglycemia, which occurred at a higher frequency in the glimepiride group (2.3%), compared to the linagliptin group (0.3%). All other AEs leading to discontinuation occurred with a frequency of less than 1% (on preferred term level).

Common Adverse Events

SAF-2

Overall, the percentages of subjects with AEs were comparable between treatments (53.8% placebo, 55.0% linagliptin 5 mg). The most frequently reported AEs in both treatment groups were in the SOCs gastrointestinal disorders (10.7% placebo, 10.5% linagliptin 5 mg), infections and infestations (20.6% placebo, 19.1% linagliptin 5 mg), metabolism and nutrition disorders (17.6% placebo, 15.9% linagliptin 5 mg), and musculoskeletal and connective tissue disorders (8.6% placebo, 10.3% linagliptin 5 mg).

The SOCs in which AEs were reported with a higher frequency (difference of at least 1% between treatments) in the linagliptin 5 mg group than in the placebo group were:

- Musculoskeletal and connective tissue disorders (8.6% placebo; 10.3% linagliptin 5 mg)
  - PTs: arthralgia (1.8% both treatments), back pain (2.5% placebo; 1.9% linagliptin 5 mg), and pain in extremity (0.9% placebo; 1.3% linagliptin 5 mg)
- Respiratory, thoracic and mediastinal disorders (2.2% placebo; 4.0% linagliptin 5 mg)
  - cough (0.8% placebo; 1.8% linagliptin 5 mg)
- Skin and subcutaneous tissue disorders (2.6% placebo; 4.0% linagliptin 5 mg)
  - hyperhidrosis (0.2% placebo; 0.6% linagliptin 5 mg), pruritus (0.6% placebo; 0.9% linagliptin 5 mg), and rash (0.3% placebo; 0.4% linagliptin 5 mg)
- Vascular disorders (2.4% placebo; 3.6% linagliptin 5 mg)
  - hypertension (1.9% placebo; 2.3% linagliptin 5 mg)

The observed imbalance in vascular disorders was mainly brought about by trial 16, likely due to imbalance in baseline characteristics not favoring the linagliptin group. The imbalance observed for vascular disorders was predominantly due to differences in hypertension (1.9% vs. 2.3%) and hypertensive crisis (0.1% vs. 0.4%) which were more frequent in linagliptin-treated subjects. The imbalance in the overall analysis of SAF-2 is mainly brought about by trial 16, where imbalances in baseline characteristics were reported. In that trial, overall exposure in the two treatment groups differed substantially (placebo 74.9 PY, linagliptin 155.0 PY) and the incidences of vascular disorders (placebo 24.0%, linagliptin 26.5%), hypertension (20.4% vs. 21.7%) and essential hypertension (0% vs. 1.2%) at baseline differed. Furthermore, the use of antihypertensive medication at baseline was not balanced (placebo 61.1%,

linagliptin 56.0%). Thus, the linagliptin group comprised more subjects with vascular disorders and hypertension but substantially fewer subjects were treated for these conditions. Furthermore, in trial 16, no clinically relevant changes in mean systolic blood pressure (SBP) and mean diastolic blood pressure (DBP) were observed.

SAF-4

Overall, fewer subjects were reported with AEs in the linagliptin 5 mg group (611 subjects, 78.5%) than in the glimepiride group (662 subjects, 84.8%). The most frequently reported AEs in both treatment groups were in the SOCs gastrointestinal disorders (21.6% linagliptin 5 mg, 22.7% glimepiride), infections and infestations (39.2% linagliptin 5 mg, 41.1% glimepiride), metabolism and nutrition disorders (13.8% linagliptin 5 mg, 35.9% glimepiride), musculoskeletal and connective tissue disorders (25.2% linagliptin 5 mg, 22.3% glimepiride), and nervous system disorders (14.7% linagliptin 5 mg, 18.3% glimepiride).
Musculoskeletal and connective tissue disorders (25.2% linagliptin 5 mg, 22.3% glimepiride) was the SOC in which AEs were reported with a higher frequency (difference of at least 1% between treatments) in the linagliptin 5 mg group than in the glimepiride group, with back pain (6.4% linagliptin 5 mg, 5.2% glimepiride) being the most commonly reported preferred term.
Within metabolism and nutrition disorders (13.8% linagliptin 5 mg, 35.9% glimepiride), hypoglycemia (5.3% linagliptin 5 mg, 30.3% glimepiride) was the most commonly reported PT and mainly accounted for the large difference between the 2 treatment groups. This was a pre-specified endpoint in the trial; the difference between the groups was statistically significant ($p<0.0001$) in favor of linagliptin.

Adverse Events of Special Interest

The analysis of the AEs of special interest was based on narrow SMQs and not on investigator-reported significant AEs to cover the medical concepts for hypersensitivity reactions, renal events, hepatic events, severe cutaneous adverse reactions, and pancreatitis in a more complete way.
Details on the selected narrow SMQs (MedDRA version 12.1) are provided below.

- Hypersensitivity reactions: Analysis was performed based on the following narrow SMQs: 'anaphylactic reaction' (20000021), 'angioedema' (20000024), and 'asthma-bronchospasm' (20000025). In addition, the system organ classes were checked for skin reactions that could potentially indicate hypersensitivity.
- Renal AEs: Analysis was performed based on the narrow SMQ 'acute renal failure' (20000003) in addition to the overall analysis of adverse events in the SOC 'Renal and urinary disorders'. Changes in renal function were evaluated by categorizing the estimated glomerular filtration rate (eGFR) at baseline and last value on treatment according to the modification of diet in renal disease (MDRD) staging and additionally based on estimated creatinine clearance rate based on Cockcroft-Gault.
- Hepatic events: the following narrow SMQs were used for this analysis: 'liver-related investigations, signs and symptoms' (20000008), 'choleastasis and jaundice of hepatic origin' (20000009), 'hepatitis, non-infectious' (20000010), and 'hepatic failure, fibrosis, cirrhosis, and other liver damage-related conditions' (20000013). To support the analyses

of liver-related adverse drug effects, potential Hy's law cases and additional analyses were evaluated in the laboratory analyses.

- Severe cutaneous adverse reactions: the respective MedDRA system organ classes were screened for severe cutaneous adverse reactions, in addition the following narrow SMQ was used for this analysis: 'severe cutaneous adverse reaction' (20000020).
- Pancreatitis: the following narrow SMQ was used for this analysis: 'acute pancreatitis' (20000022).

SAF-2

The numbers of subjects with AEs of special interest were comparable between treatments. Hypersensitivity reactions were reported by 6 subjects (0.5%) in the placebo group and 18 subjects (0.7%) in the linagliptin 5 mg group. Renal events were reported by two subjects (0.2%) in the placebo group and three subjects (0.1%) in the linagliptin 5 mg group. Hepatic events were reported by 14 subjects (1.2%) in the placebo group and 25 subjects (1.0%) in the linagliptin 5 mg group. Severe cutaneous adverse reactions and pancreatitis were only reported in the linagliptin 5 mg group by one subject each.

SAF-4

There were no subjects with severe cutaneous adverse reactions or pancreatitis in SAF-4. Hypersensitivity reactions were reported by 10 subjects (1.3%) in the linagliptin 5 mg group and by 14 subjects (1.8%) in the glimepiride group. Renal events were only reported in the glimepiride group (6 subjects, 0.8%). Hepatic events were reported by 21 subjects (2.7%) in the linagliptin 5 mg group and by 26 subjects (3.3%) in the glimepiride group.

A particular concern for incretin-based therapies (including both GLP-1 receptor agonists and DPP4 inhibitors) is the possible increased risk of pancreatitis. In the entire linagliptin program, a total of 8 cases were identified (Table 28).

Table 28. AEs of pancreatitis in all subjects treated with linagliptin

Study #	Patient #	Brief Description of Case	Duration and Dose of Treatment at Event Onset
40	96363	57 year old woman with history of chronic pancreatitis was hospitalized for 4 days for exacerbation.	Linagliptin 5 mg x 14 months
40	90963	66 year old woman, hospitalized for 7 days for acute pancreatitis.	Linagliptin 5 mg x 11 months
40	94364	34 year old woman, hospitalized for 2 weeks for acute pancreatitis. Serum amylase was not elevated, but urine amylase was elevated. Patient also had fever and abdominal pain.	Linagliptin 5 mg x 11 months
40	96346	55 year old woman with recent influenza, diagnosed with chronic pancreatitis. Event was reported for 9 day duration.	Linagliptin 5 mg x 1 year
20	28310	70 year old man diagnosed with myocardial infarction and pulmonary edema. Linagliptin was stopped and two days later on CT scan, pancreatitis was found and described as chronic pancreatitis. Patient did not have symptoms and amylase was not elevated.	Linagliptin 5 mg x 4 months
18	85360	68 year old woman with a 20 year history of chronic pancreatitis had exacerbation of chronic condition. She had abdominal pain for about one month. Labs were not done at that visit. Amylase was normal at the prior and post visit.	Linagliptin 5 mg x 1 month
5	4411	65 year old man with abdominal pain and hematuria. He was diagnosed with acute and chronic pancreatitis and hospitalized three times over three months. There were several concomitant medical problems (i.e. renal cyst and calculi).	Linagliptin 2.5 mg x 1 month
6	9106	42 year old man with abdominal pain and elevated amylase. He also concurrently had influenza. He was not hospitalized.	Linagliptin 5 mg x 1 month

Source: Dr. Dunn's medical review of NDA 201280, Table 83

In SAF-2, amylase was reported to have increased from baseline more often in the linagliptin group than on placebo (2.2% in placebo, 2.8% in linagliptin). But the magnitude of these changes is likely not clinically relevant.
Based on the summary narrative of these few cases, it is possible that the majority had chronic pancreatitis prior to treatment with investigational agent. Adjusting for exposure, the incidence of pancreatitis reported in the linagliptin group was 1 per 538 person-years versus zero in 433-person-years for comparator. Thus, the question about increased pancreatitis risk with either linagliptin, with the class of DPP4 inhibitors, with incretin-based therapies or with the background of T2DM itself remains unanswered.

Of the laboratory changes, mean uric acid increased in the linagliptin group (change of 0.11 mg/dL from baseline to week 24) compared to placebo (change of -0.19 mg/dL from baseline to week 24). This was also found in my review of the sitagliptin NDA, the first DPP4 inhibitor approved in the US. The mean increase with sitagliptin was 0.2 mg/dL, while the mean increase in placebo was 0.02 mg/dL in the pooled Phase 3 trials.
This increase in uric acid was mostly driven by a few outliers, and they were not associated with increased number of glut or gout arthritis exacerbations.

Saxagliptin was found to be associated with mean small decreases in absolute lymphocyte counts and platelets. These lab changes were not seen in the linagliptin clinical trials.

Cardiovascular Safety

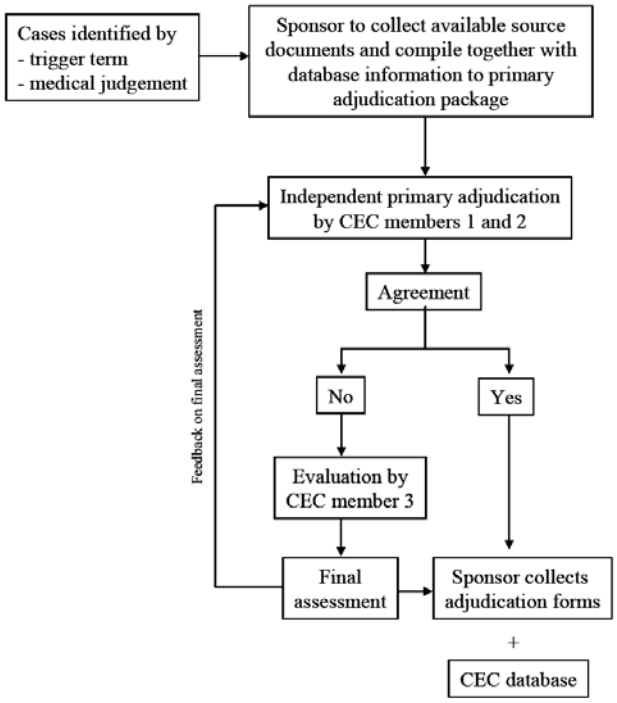
As discussed previously, FDA has requested that applicants of new OADs demonstrate that these treatments do not result in an unacceptable increase in cardiovascular (CV) risk. The 2008 guidance on this topic[2] asks sponsors to do the following during the planning stage of their drug development programs for therapies for type 2 diabetes:

• Establish an independent CV endpoints committee to prospectively and blindly adjudicate major CV events (MACE) during phase 2 and 3 clinical trials.
• Ensure that the phase 2 and 3 clinical trials are appropriately designed so that a pre-specified meta-analysis of MACE can reliably be performed.
• To enroll patients at increased CV risk, such as elderly patients and those with renal impairment.

The guidance states that to support approvability from a CV standpoint, the applicant should compare the incidence of major cardiovascular events with the investigational agent to the incidence of major cardiovascular events occurring with a control group and show that the upper bound of the two-sided 95 percent CI for the estimated risk ratio is less than 1.8 with a reassuring point estimate. If this upper bound is between 1.3 and 1.8 and the overall risk-benefit analysis supports approval then a postmarketing CV trial generally will be needed to definitively show that this upper bound is less than 1.3. If the premarketing data show that this upper bound is less than 1.3 and the overall risk-benefit analysis supports approval then a postmarketing cardiovascular trial generally may not be necessary.
For the linagliptin Phase 3 trials, all reported treatment-emergent fatal events and events suspected of stroke or myocardial ischemia (including myocardial infarction [MI]) were reviewed in a blinded fashion by an independent Clinical Event Committee (CEC). The CEC consisted of the CEC Cardiology and the CEC Neurology. The CEC Cardiology reviewed all fatal events (without stroke events) and events suspected of myocardial ischemia; it consisted of 3 cardiologists (b) (4) The CEC Neurology was responsible for the adjudication of events suspected of stroke (fatal and non-fatal strokes); it was composed of 3 neurologists (b) (4) .
Based on clinical documentation provided by the applicant, the CEC evaluated whether pre-specified definitions for cardiovascular death, stroke, or myocardial ischemia were met. A graphical overview of the adjudication process is given in Figure 2 below.

[2] Diabetes Mellitus – Evaluating Cardiovascular Risks in New Anti-diabetic Therapies to Treat Type 2 Diabetes

Figure 2. Process flow for the CEC adjudication of MACE in the linagliptin Phase 3 program



The applicant conducted a metanalysis to assess the CV risk in patients with T2DM treated with linagliptin in comparison to placebo or active control. The metanalysis was performed on the combined controlled trials of the Phase 3 program. With the beginning of the Phase 3 program, the CEC was implemented, which adjudicated selected CV and neurologic events. The primary endpoint was a composite endpoint consisting of cardiovascular death (including fatal stroke and fatal MI), non-fatal MI, non-fatal stroke, and hospitalization due to unstable angina. The CV risk ratio was assessed by the following approaches: 1) hazard ratio based on Cox regression, 2) risk ratio based on Poisson regression, 3) odds ratio based on exact test, and 4) incidence ratio based on a stratified Cochran-Mantel-Haenszel method. All analyses were stratified by trial and 95% confidence intervals (CIs) were provided. Secondary endpoints were 1) a composite endpoint consisting of cardiovascular death (including fatal stroke and fatal MI), non-fatal MI, and non-fatal stroke; 2) a composite endpoint consisting of all adjudicated events (cardiovascular death [including fatal stroke and fatal MI], non-fatal MI, non-fatal stroke, hospitalization due to unstable angina, stable angina pectoris, TIA); and 3) endpoint of MACE. Tertiary endpoints were each of the following adjudicated events: cardiovascular death (including fatal stroke and fatal MI), non-fatal MI, non-fatal stroke, hospitalization due to unstable angina, unstable angina with or without hospitalization, stable angina, and TIA.

Metanalysis results according to the applicant

Eight trials (15, 16, 17, 18, 20, 23, 35, and 50) with a total of 5239 subjects with T2DM were included in the CV metanalysis. Out of these, 3319 subjects were treated with linagliptin (3159 subjects receiving 5 mg and 160 subjects receiving 10 mg), 977 subjects were treated with

placebo, and 943 subjects were treated with an active comparator (either glimepiride with n = 781 or voglibose with n = 162).
One hundred forty two potential events were identified for adjudication, by searching all AEs from a pre-specified list of trigger events (SMQs for Ischaemic Heart Disease and Cerebrovascular Disorders). The independent CEC then adjudicated all potential events prospectively. In total, **11 primary events** were observed in the linagliptin group and a total of **23 primary events occurred in the comparator group** (with 3 primary events in the placebo group, 20 primary events in the glimepiride group, and none in the voglibose group), resulting in incidence event rates (per 1000 patient-years of exposure) for the primary endpoint of 5.3 for linagliptin and 16.8 for the total comparators. Linagliptin treatment was not associated with an increase in cardiovascular risk, and the primary endpoint for linagliptin was significantly lower compared to the total comparators (upper bound of the 95% CI in each analysis is shown in **bold and underlined font type**) whether it was expressed as Cox regression hazard ratio (HR) **0.34 (95% CI 0.16; 0.70)**, Poisson regression risk ratio (RR) 0.34 (95% CI 0.15; **0.74**), exact test for stratified 2x2 tables odds ratio (OR) 0.34 (95% CI 0.15; **0.75**) or stratified Cochran-Mantel-Haenszel (CMH), with treatment arm continuity correction, RR 0.39 (95% CI 0.19; **0.80**).
The CV risk for all secondary endpoints was significantly lower for linagliptin versus the total comparators, i.e. with all upper 95% CI being < 1.0, with linagliptin HR, RR or OR for the first secondary endpoint (composite of all adjudicated events) being 0.55 to 0.59, the second secondary endpoint (composite of cardiovascular death, non-fatal MI and non-fatal stroke) being 0.36 to 0.42, and the third secondary endpoint (custom MACE) being 0.34 to 0.39. The only exception was the RR for all adjudicated events when evaluated with CMH method, in this case the upper 95% CI equaled 1.0.

The applicant concludes from the metanalysis that treatment with linagliptin was not associated with an increased CV risk compared to a pooled comparator group (placebo, glimepiride, and voglibose), but rather showed a risk reduction. The applicant realizes that the estimates and confidence intervals, although favorable to linagliptin, are likely unstable due to the very small number of MACE reported and adjudicated by the CEC.

Metanalysis results according to the FDA statistical reviewers

In contrast to the applicant primary analyses methods (exact stratified odds ratio and the CMH relative risk), FDA chose to use the Mantel-Haenszel risk difference and the associated 95% confidence interval as the primary analysis method. This method makes use of all trials including trials with no events of interest. The unit of analysis was the subject and the stratification factor was the trial. For trials with more than two arms, arms that were part of the same comparison group (linagliptin versus comparator) were combined. Confidence intervals of risk difference for individual trials were based on exact method. The FDA statisticians used the applicant's methods assessing risk ratios and their 95% CI as sensitivity analyses, but excluded trials with no events from the metanalyses. FDA also preferred the stratified log-rank test and the stratified Cox regression for time-to-event as they require fewer assumptions and are more robust than the Cox regression and Poisson model used by the applicant. The primary comparison for the FDA statisticians was between linagliptin and all-comparator in the safety

population of these 8 trials, but FDA also conducted a sensitivity analysis comparing linagliptin to placebo.

Drs. Ding and Soukup point out that, within each of the eight randomized phase 3 trials, the baseline CV risk factors were well balanced between linagliptin and comparator (Table 29 for Framingham scores) but expressed concern that the pooled Framingham risk scores at baseline were quite different among the eight randomized phase 3 trials: subjects from the two trials involving active comparator (Trials 20 and 23) had higher Framingham risk scores compared to subjects from the other 6 placebo-controlled trials.

Table 29. Baseline Framingham Risk by Study and Treatment Group (Safety Population)

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: Dr. Ding's statistical review

The meta-analysis results for the primary composite endpoint were heavily driven by Trial 20 (Table 30). Among the total of 23 events of the primary composite endpoint reported in the pooled all comparator group, 20 occurred in the glimepiride arm in Trial 20.

Table 30. Summary of Events of Primary Endpoint by Trial and Treatment Group (Safety Population)

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)

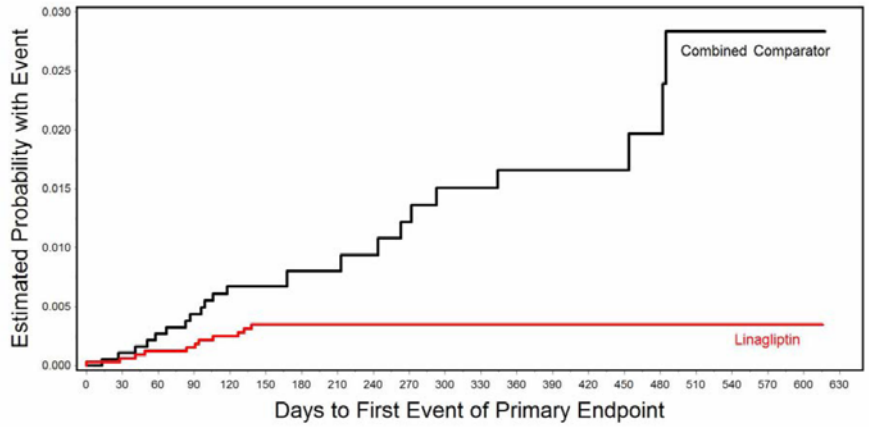
* UA with Hosp – Hospitalization due to unstable angina

Source: Dr. Ding's statistical review

The incidence of CV related events was found to be statistically significantly lower in the linagliptin group than in the all comparator group. The M-H risk difference between linagliptin and all comparator was -0.69% with a 95% CI of (-1.17%, -0.21%). Similarly, the M-H relative risk ratio between linagliptin and all comparator was 0.34 with a 95% CI of (0.15, 0.74), and the exact stratified odds ratio between linagliptin and all comparator was 0.36 with a 95% CI of (0.16, 0.78).

Based on the Kaplan Meier method using safety information from the eight randomized phase 3 trials, the cumulative probability of developing a CV related event as measured by the primary composite endpoint is shown in Figure 3. MACE occurred earlier and more often in the combined comparator group, compared to the linagliptin group. Based on the stratified log-rank test stratified by trial, the onset time of event was statistically significantly different between the linagliptin group and the comparator group (p-value=0.003). The stratified Cox proportional hazard ratio (HR) of linagliptin compared to combined comparator was 0.35 with a 95% CI of (0.17, 0.73).

Figure 3. Time to Event Analysis of the Primary Composite Endpoint (Safety Population, Double-Blind Treatment Phase)



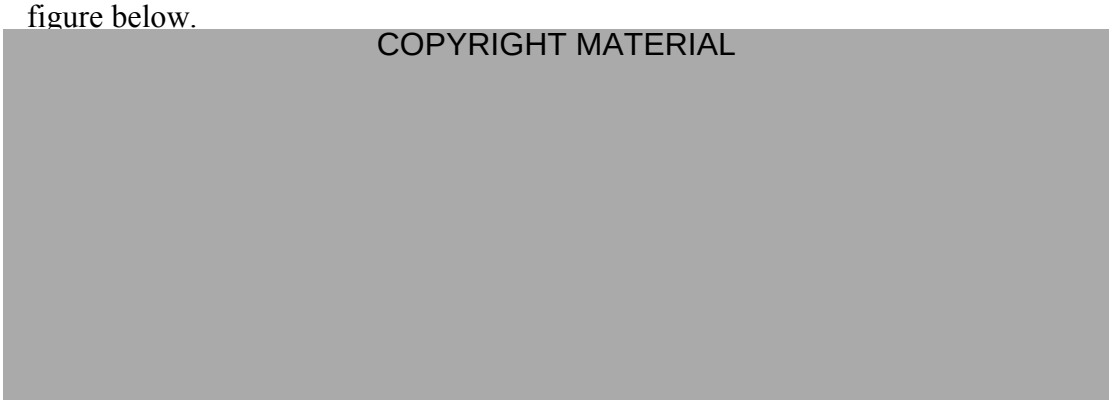
Source: Dr. Ding's statistical review

Drs. Ding and Soukup expressed concern about the interpretability of the metanalysis results when Trial 20 weighs so heavily with its contribution of MACE endpoint events. They argue that Trial 20 is the only glimepiride-controlled trial, the only non-inferiority trial, and had the longest duration, and the participating subjects had the highest CV risk at baseline compared to other trials. These factors prompted the reviewers to conduct an ad-hoc sensitivity analysis excluding the effect of Trial 20 to assess the robustness of the metanalysis results.
Without Trial 20, the incidence of the primary composite endpoint was 0.31% (8 events out of 2541 subjects) in the linagliptin group, as compared to 0.26% (3 events out of 1139 subjects) in the all comparator (placebo + voglibose) group, for a total of 11 events. In the safety population with the exclusion of Trial 20, the incidence of CV related events was not statistically significantly different between the linagliptin group and the all comparator group. The M-H risk difference between linagliptin and all comparator was 0.06% with a 95% CI of (-0.34%, 0.46%). The corresponding M-H relative risk ratio between linagliptin and all comparator was 1.21 with a 95% CI of (0.35, 4.26), and the exact stratified odds ratio was 1.23 with a 95% CI of (0.29, 7.27).
They also conducted a sensitivity analysis, only with the placebo-controlled subset of the safety population. A total of 9 events occurred in the placebo-controlled subset of the safety population, with 6 reported in the linagliptin group and 3 reported in the placebo group.
In the placebo-controlled subset of the safety population, the incidence of CV related events was not statistically significantly different between the linagliptin group and the placebo group (Table 12). The M-H risk difference between linagliptin and placebo was - 0.04% with a 95% CI of (-0.45%, 0.37%). Compared to placebo, the M-H relative risk ratio of linagliptin was 0.86 with a 95% CI of (0.23, 3.26), and the exact stratified odds ratio of linagliptin was 0.85 with a 95% CI of (0.18, 5.32).

In response to these valid concerns, I offer the following comments:

1. For a typical safety database (considered by the Division as generally adequate) such as the linagliptin clinical program, the number of pre-defined MACE events was indeed low (n = 34). But this incidence is in line with other recent development programs for drugs intended to treat T2DM. In a recent presentation, Dr. Mary Parks cited four recent drugs

developed and approved with similar, if not lower, numbers of MACE events, seen in the figure below.



Source: Dr. Parks presentation at Drug Information Association, Washington DC, September 23-24, 2009

This reflects the reality of clinical trials in diabetes prior to issuance of the CV guidance. Applicants chose to enroll lower risk subjects, and the safety data obtained through clinical trials had limited capability for extrapolation to the general population. In order to address the problem, the guidance encourages enrollment of subjects with higher CV risk. The linagliptin example validates the importance of the requirements in the CV risk guidance.

2. The relative risk of composite MACE estimated through these eight trials is indeed heavily dependent on one single trial (Trial 20). Part of the reason for this is that this is by far the largest trial, and the longest trial. The intended goal of the trial was to show the non-inferiority of linagliptin to glimepiride in terms of glycemic efficacy: the fact that this is a non-inferiority trial with a tight NI margin in itself requires a larger sample size than a placebo-controlled superiority trial. In addition, the applicant had the intention to show the comparative durability of the linagliptin effect compared to a sulfonylurea, based on published reports from animal models showing that DPP4 inhibitors exert beneficial effects on preservation of beta cell function. So this trial was extended from the typical duration (24 weeks) of a placebo-controlled trial to 52 weeks (for this interim analysis) and eventually to 104 weeks. The much higher number of subjects and the longer trial duration would be reasons enough to expect higher numbers of CV events. In addition, this was an active-controlled trial, and the HbA1c range for eligibility was higher than in other trials, since no subject would be treated with placebo long term; and subjects with higher HbA1c tend to be older and have diabetes for a longer duration, so the Framingham risk scores may have been higher for these reasons. But the fact that the CV risk at baseline was balanced between the treatment groups, not only in Trial 20, but through all eight trials is reassuring in that we can interpret the metanalysis results.

3. It is also true that the conclusion of linagliptin statistical superiority, regarding CV risk, is invalid when Trial 20 is excluded from the metanalysis. But the applicant's goal was not to show or claim superiority based on this metanalysis: was simply to meet a regulatory requirement to get linagliptin on the US market to treat diabetics, without the unacceptable higher CV risk. The applicant understands that further assurance of CV safety is required, and they will be conducting a dedicated CV safety trial as a postmarketing requirement, to demonstrate that the upper bound of the 95% CI of the risk ratio of linagliptin against a

comparator is less than 1.3. We are reviewing the protocol for such trial at the time of this writing.

4. One may criticize the choice of a comparator. Glimepiride is a sulfonylurea, and the class has been tainted since the 1970's University Group Diabetes Program Trial[3], which suggested first generation sulfonylureas were associated with higher CV risk. In fact, the glimepiride label, as others in the class, carries a bolded warning about "Increased Risk of Cardiovascular Mortality". These issues have been extensively discussed with the applicant. The applicant argued that sulfonylureas are widely used in the US and in Europe, second perhaps only to metformin. The trial was conducted as add-on to metformin, so metformin could not be used as a comparator. Furthermore, recent literature[4, 5] suggests that risks of sulfonylureas, (at least the third generation drugs with higher receptor specificity to the pancreas), are not increased when compared to some other antidiabetic drugs. In addition, as a practical manner, it is relevant and informative for a health care provider to compare the risk of cardiovascular events associated with linagliptin with those conferred by a commonly and widely used medication.

5. Finally, the time to event analysis (through Kaplan Meyer) provides reassuring evidence that the CV risks associated with linagliptin do not increase over time, compared mainly to glimepiride, but also to placebo and to voglibose.

Vital signs and ECG changes

In both safety groupings (SAF-2 and SAF-4) there were no clinically meaningful changes in vital signs. In both groupings there was a trend for a small decline in systolic blood pressure, compared to placebo and glimepiride (mean < 1 mmHg), that started at about 8 weeks and persisted for 2 years. There were no notable ECG changes or trends in the linagliptin program. There was no evidence of QTc prolongation either (with either the proposed 5 mg or the supratherapeutic dose of 100 mg).

9. Advisory Committee Meeting

This NDA was not taken to an Advisory Committee meeting. Linagliptin is the third drug in the class of DPP4 inhibitors, and our reviews have not identified safety or efficacy concerns or complex regulatory issues requiring input from an external advisory panel.

[3] Diabetes, 19 supp. 2: 747-830, 1970
[4] Zeller M, Danchin N, Simon D, et al. Impact of Type of Preadmission Sulfonylureas on Mortality and Cardiovascular Outcomes in Diabetic Patients with Acute Myocardial Infarction. J Clin Endocrinol Metab, November 2010, 95(11)
[5] United Kingdom Prospective Diabetes Study (UKPDS) Group 1998 Intensive blood-glucose control with sulphonylureas or insulin com-pared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 352:837–853

10. Pediatrics

The applicant proposed a pediatric plan which includes a waiver for children younger than 10 years of age, and a deferral of trials for children between age 10 and younger than 17 years. The trials proposed are:
Trial 1: A 12-week, randomized, double-blind, placebo-controlled, parallel dose-finding trial evaluating at least 2 dose levels (e.g. 1 mg and 5 mg) of linagliptin monotherapy compared to placebo.
Trial 2: A randomized, double-blind, 12-week efficacy and safety trial comparing linagliptin monotherapy, metformin, and placebo in a 2:1:1 ratio, followed by a 40 week extension (52 weeks total) during which the patients previously treated with placebo will be randomized to treatment with linagliptin or metformin in a 2:1 ratio for the remaining 40 weeks of the trial.

FDA will revise this proposal to require the assessment of the safety and efficacy of linagliptin in the pediatric population also when added on to metformin therapy in subjects who cannot achieve adequate glycemic control with metformin. This is consistent with recent PREA-related PMRs for antidiabetic drugs approved in our Division.

The plan above, with our revision, was discussed in the PeRC meeting of March, 16th, 2011, and was deemed acceptable. PeRC only recommended that we emphasize to the applicant the important of adequate sample sizes to allow analyses in subgroups based on important characteristics of children (Tanner stage, race/ethnicity, etc).

11. Other Relevant Regulatory Issues

Six clinical investigator sites and the applicant were inspected in support of this NDA. The primary endpoint data were verified. Inspection of Drs. Inoue, Matsuoka, and Thomas' sites noted violations that did not appear to be systemic or widespread in nature and no significant violations were noted at the other three clinical sites. The sponsor conducted an additional audit at the Thomas site. Data that were previously unreported to the applicant were discovered concerning administration of rescue medication, adverse events, concomitant medications and baseline data; this was subsequently provided to DSI and forwarded to the review division. Except for the unreported rescue medication, the other issues were minor. The significance of the unreported rescue for the three subjects in each protocol is considered minor. Although some regulatory violations were noted as per above, these are considered isolated occurrences and are unlikely to significantly impact the integrity of primary efficacy and safety data overall. The data are considered reliable in support of the application.
Note: The final classification for the inspection of the applicant is pending.

12. Labeling

The proprietary name Tradjenta is under review at the time of this writing. Labeling negotiations are ongoing. The product will carry a PPI, but we do not consider necessary to

impose a Medication Guide, as we have not identified particular safety issues to be mitigated through patient education.

13. Recommendations/Risk Benefit Assessment

In agreement with the reviewers in all discipline teams, I recommend approval of linagliptin 5 mg for the treatment of adult patients with T2DM.

Throughout this review, I showed summary data demonstrating a favorable risk benefit profile for this drug. The glycemic effects are modest, but similar in magnitude to the other approved drugs in the same class, and the safety profile did not indicate any important issue to the public health or to specific subgroups of patients.

I do not recommend imposing any Postmarketing Risk Evaluation and Management Strategies (REMS) or a Medication Guide.

The postmarketing requirements for linagliptin agreed upon internally at FDA and being discussed with the applicant are the PREA-related pediatric development program, as summarized above (Section 10 of this review), and the conduct of a cardiovascular safety trial well designed and powered to rule out an upper bound of 1.3 in the 95% CI of the cardiovascular risk ratio associated with linagliptin therapy.

In addition to the two postmarketing requirements, we also plan to obtain a postmarketing commitment from the applicant to continue the two ongoing trials in the renally impaired diabetic subjects and submit complete reports under an agreed upon timeline.

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/s/

ILAN IRONY
04/03/2011

MARY H PARKS
04/04/2011
Please see DD memo