CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

APPLICATION TYPE	**NDA**
APPLICATION NUMBER(S)	**201280**
PRIORITY OR STANDARD	**S**
SUBMIT DATE(S)	**JULY 2, 2010**
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DIVISION / OFFICE	**DIVISION OF METABOLISM AND ENDOCRINOLOGY PRODUCTS/OFFICE OF NEW DRUGS II**
REVIEWER NAME(S)	**SOMYA VERMA DUNN**
REVIEW COMPLETION DATE	**MARCH 11, 2011**
ESTABLISHED NAME	**LINAGLIPTIN**
(PROPOSED) TRADE NAME	

THERAPEUTIC CLASS	**DIPEPTIDYL-PEPTIDASE INHIBITOR**
APPLICANT	**BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.**
FORMULATION(S)	**ORAL TABLET**
DOSING REGIMEN	**5 MG DAILY**
INDICATION(S)	**TREATMENT OF TYPE 2 DIABETES**
INTENDED POPULATION(S)	**ADULTS**

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1 Recommendations/Risk Benefit Assessment

Linagliptin is an orally-active dipeptidyl peptidase (DPP-4) inhibitor. The applicant seeks the indication for linagliptin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). The proposed dose is 5 mg oral dose once daily. There is no proposed dosage adjustment for renal impairment.

1.1 Recommendation on Regulatory Action

According to my review of the clinical data, I recommend approval for linagliptin as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The applicant has demonstrated efficacy along with an acceptable safety profile.

1.2 Risk Benefit Assessment

The applicant has demonstrated safety and efficacy in both monotherapy and a variety of combination therapy settings. They seek approval for only one dose of linagliptin, 5 mg. This was the only dose tested in all phase III studies with the exception of one treatment arm in one study where a dose of 10 mg was also tested (study 1218.23, see Table 3 in section 5.1 *Tables of Studies/Clinical Trials*). There were a total of 9 phase III studies, four of which had a 24 week treatment period. One of these studies had data from 52 weeks of treatment with linagliptin (study 1218.20). Therefore, the data available for the 5 mg dose are sufficient to allow for a comprehensive review of this dose.

Linagliptin offers an oral, once daily therapy for T2DM that has a low risk of hypoglycemia (when not taken with a sulfonylurea). This can be used for patients either on other antidiabetic medications or in monotherapy. Efficacy has been demonstrated in two phase III monotherapy studies. It has also been demonstrated in separate phase III studies in combination with pioglitazone, metformin and a sulfonylurea. Overall, efficacy in lowering HbA1c ranges from 0.4-0.7% (placebo-subtracted) at 24 weeks. The applicant was also able to meet their predetermined non-inferiority margin in a large phase III, 52-week study against the active control glimepiride, although it was clear that glimepiride offered better glycemic control.

The safety assessment for linagliptin was also adequate and revealed a safe profile for patients with T2DM. A total of 4338 patients had exposure to 5 mg linagliptin, 3430 of these patients were treated for at least 24 weeks and at the time of NDA filing, 2390 had been treated for at least 52 weeks. Nonclinical data did not reveal skin lesions seen in other drugs of this class. Overall, animal toxicity findings were only at doses that were at high exposure multiples, indicating that human risk was minimal.

Safety issues that have arisen in this class include pancreatitis, serious allergic and hypersensitivity reactions, and more recently worsening renal function. Pancreatitis was reported in a higher number of patients treated with linagliptin than placebo or other treatments (8 patients versus 0). In view of the large denominator, the imbalance of overall randomization (2.3:1) and the very small number of events of pancreatitis, the precise incidence rate of pancreatitis associated with linagliptin treatment is uncertain. Aside from this issue, at this time, the data provided in this application show minimal concern for the other class concerns mentioned.

Linagliptin is predominantly excreted unchanged in the feces, with renal excretion being a minor pathway of elimination. Pharmacokinetic studies and the clinical pharmacologist review of these studies conclude that dosage adjustment is not necessary in patients with renal impairment. The number of patients with moderate and severe renal disease is small in the clinical program. However, the applicant submitted 12 week data from a dedicated study in subjects with moderate to severe renal impairment and has one additional study ongoing in this population. The results from these studies will shed further insight on the adverse event profile in these patients.

There were few patients of African-American origin in the linagliptin clinical program. However, at this time, pharmacokinetic/pharmacodynamic studies do not indicate that these patients should have a different safety or efficacy profile than other racial groups that were exposed to linagliptin.

The required cardiovascular meta-analysis was performed. This meta-analysis revealed that linagliptin is not associated with higher risk of predefined cardiovascular events.

Overall, linagliptin can offer benefit of glycemic control to patients with T2DM and has an acceptable safety profile.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Linagliptin, and other drugs of this class, have been found to have higher incidence of pancreatitis. The applicant will be expected to submit 15 day expedited reports with narratives for all post marketing cases of pancreatitis regardless if they are classified as serious or unexpected.

1.4 Recommendations for Postmarket Requirements and Commitments (PMRs and PMCs)

i. The applicant will be required to conduct a dedicated study to assess for increased cardiovascular risk in high risk patients. This is in line with all oral antidiabetic drugs under development or review at this time per *FDA Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* The primary objective of this trial will be to establish that the upper bound of

the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of major adverse cardiovascular events observed with linagliptin to that observed in the control group is less than 1.3. Secondary objectives must include an assessment of the long-term effects of linagliptin on pancreatitis and renal safety. For cases of pancreatitis, serum amylase and/or lipase concentrations with accompanying normal ranges and any imaging study reports should be included in the narratives. At this time, the applicant does have a protocol submitted under the Investigational New Drug application for this study and it is currently under review.
Secondary objectives in this long term study must include an assessment of the long-term effects of linagliptin on immunological reactions, hypersensitivity reactions, neoplasms, serious hypoglycemia, pancreatitis, and renal safety. For hypersensitivity reactions, especially angioedema, reports should include detailed information on concomitant use of an angiotensin-converting enzyme inhibitor or an angiotensin-receptor blocker. For cases of pancreatitis, serum amylase and/or lipase concentrations with accompanying normal ranges and any imaging study reports should be included in the narratives.

ii. Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Our agency has decided to waive the pediatric study requirement for ages 0 to 9 years because are too few children in this age range with T2DM to practically enable an adequate study for safety and efficacy. In addition we accepted the deferral of studies in patients 10 to (b) (4) because linagliptin had not been proven safe and effective in adults at the time of the request. Once approved, we will require that the applicant complete two clinical trials in pediatrics. One will be a 12-week, randomized, double-blind, placebo-controlled, parallel dose-finding study evaluating at least 2 dose levels (e.g. 1 mg and 5 mg) of linagliptin monotherapy compared to placebo. The other study will be a randomized, double-blind, 12-week efficacy and safety study 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 study. The applicant must either add an arm to this study, or conduct a third trial, with patients that were inadequately controlled on metformin (on maximum allowed doses) that has linagliptin treatment as an add treatment to metformin.

iii. At this time, a requirement for a study in moderate and severe renal impairment as a PMR is under discussion. There were very few of these patients (56 moderate impairment, 2 severe impairment) in the clinical program at the time of NDA submission. The 12 week data from a dedicated study in moderate and severe renal impairment, 1218.43—133 patients, was available at the Four Month Safety Update. The study is ongoing. There is another study in this population, 1218.64—240 patients that is

ongoing. Once completed, both will provide one year of data. In total, this number of patients and exposure time are acceptable in this population to evaluate safety and efficacy. Therefore, there is not a need to request specific patient exposure requirements in this population for the dedicated cardiovascular study as has been the case for other DPP-4 inhibitors (i.e. saxagliptin). However, in order to ensure that this data is submitted by an acceptable date, deadline/timeline requests (and/or PMR) will be sent to the applicant.

2 Introduction and Regulatory Background

2.1 Product Information

Product Description

Linagliptin is an inhibitor of plasma dipeptidyl peptidase 4 activity (DPP-4-Inhibitor) developed for the indication of type 2 diabetes mellitus (T2DM).

The drug substance linagliptin is a new chemical entity. Linagliptin is a xanthine derivative with the chemical name 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]-. The molecular formula is C25H28N8O2 and the molecular mass is 472.54 g/mol. Linagliptin is a free base and has R-configuration at the chiral carbon of the 3-aminopiperidine moiety.

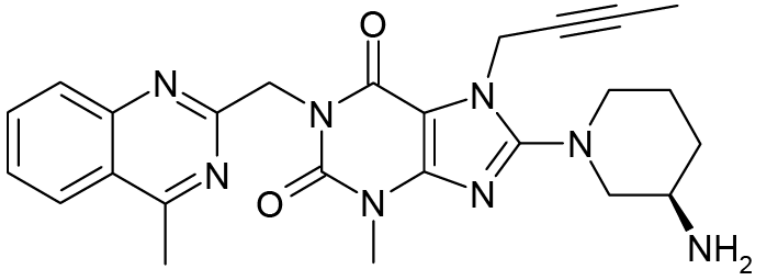

Figure 1 Molecular Structure of Linagliptin
Source Quality Overall Summary, Figure 1, page 5

Linagliptin is a small molecule drug with one chiral center. The R-enantiomer is used as active ingredient. The enantiomeric excess of the R-enantiomer accounted for (b) (4) in humans.

Established Name

Linagliptin

Proposed Trade Name

The proposed trade name for linagliptin is Tradjenta. At the time of filing of this review, the Office of Surveillance and Epidemiology is still reviewing this name.

Chemical Class

Linagliptin is a New Molecular Entity (NME).

Pharmacologic Class

Linagliptin, a DPP-4 inhibitor, belongs to a newer class of oral anti-diabetic medications known as incretin enhancers. There are currently two other marketed and approved DPP-4 inhibitors. Sitagliptin (Januvia) was approved in 2006 and saxagliptin (Onglyza) was approved in 2009. Two other DPP-4 inhibitors have been reviewed under NDA, and were not approved, vildagliptin and alogliptin.

Applicant's Proposed Indication

The applicant proposes linagliptin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Linagliptin is proposed to be used in either monotherapy or combination therapy with other treatments for T2DM.

Applicant's Proposed Dosing Regimen

The proposed clinical dose is 5 mg once daily. There is no proposed dosage adjustment for renal impairment.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 Currently Available Treatments for Type 2 Diabetes

Therapy	Example	Primary mechanism of action	Adverse Effects
Sulfonylureas	Glyburide	Increases insulin secretion	Hypoglycemia
Glitinides	Repaglinide	Increases insulin secretion	Hypoglycemia
Biguanides	Metformin	Decreases hepatic glucose output	Gastrointestinal symptoms
Alpha-glucosidase inhibitors	Acarbose	Delays gastrointestinal absorption of carbohydrates	Flatulence
Thiazolidinediones	Pioglitazone	Increases insulin sensitivity	Edema
Insulin	Lispro	Increases insulin levels	Hypoglycemia, weight gain
Amylin analogues	Pramlintide	Slows gastric emptying	Gastrointestinal symptoms
GLP-1 Analogues	Exenatide	Stimulates glucose-dependent insulin release	Gastrointestinal symptoms
DPP-4 Inhibitors	Sitagliptin	Stimulates glucose-dependent insulin release	Uncommon
Bile Acid Sequestrants	Colesevelam	Binds bile acids	Gastrointestinal symptoms
Dopamine receptor agonists	Cycloset	Unknown	Gastrointestinal

Source: Adapted from AACE Diabetes Mellitus Guidelines (2007) and Nathan D. (2002)

2.3 Availability of Proposed Active Ingredient in the United States

Linagliptin is a new molecular entity and is not marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Other DPP-IV inhibitors (including saxagliptin--Onglyza) have produced dose- and duration-dependent necrotic skin lesions in Cynomolgus monkeys. There were post marketing reports of serious allergic and hypersensitivity reactions in patients taking sitagliptin (Januvia), including anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. .

Vildagliptin, another DPP-IV inhibitor that was not approved was associated with liver aminotransferase and bilirubin elevations.

Based on post-marketing reports of acute pancreatitis with sitagliptin, including necrotizing pancreatitis, a Medication Guide-only Risk Evaluation and Mitigation Strategy (REMS) was required of the sponsor. In addition, non-clinical post marketing requirements (PMR) were also required.

Sitagliptin causes small increases in creatinine in patients with moderate renal insufficiency. In 2010, the applicant for sitagliptin has requested that "worsening renal function, including acute renal failure (sometimes requiring dialysis)" be added to the Adverse Reactions, Postmarketing Experience subsection. This label change has been very recently approved.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

End of Phase 2 (EOP2) meeting took place December 11, 2007. The clinical discussion of that meeting involved the following comments:

FDA: For sensitivity analysis, the Sponsor should consider performing the Full Analysis Set (FAS)-completers analysis instead of per protocol analysis.

This was performed by the sponsor.

FDA: (For the active control trial, study 20), the Sponsor should not perform an unblinded interim analysis on efficacy variables but keep the blind for the efficacy outcome variables until the end of the study hypothesis testing at Week 104.

The sponsor did perform an unblinded interim analysis of study 20; this was submitted with the NDA. However, the sponsor assured the agency that extensive measures were taken to maintain the integrity of the trial and only allow access of the data in a limited manner to select sponsor employees.

FDA: Sponsor should specify renal safety as an adverse event of interest, because linagliptin is concentrated in the kidney in the Sponsor's non-clinical studies and causes toxic renal effects, albeit at high exposures.

There is a separate section of the NDA submission reporting on renal safety.

FDA: The Division requests that the data from the renal impairment study ideally be available at the time of NDA filing. If the data are not available at that time, the data will likely be required as a Phase 4 commitment – in this case, the Sponsor should provide justification in the NDA for not providing the data pre-approval.

There is an ongoing study in patients with renal impairment. Twelve week data from this study (1218.43) were submitted with the NDA.

FDA: The Division stated that the proposal to study the combination of BI 1356 with insulin as a Post Marketing Commitment is reasonable.

Add on to insulin study (1218.36) was ongoing with recruitment complete at the time of the Four Month Safety Update.

Pre-NDA meeting took place on December 2, 2009. Some additional relevant clinical highlights from that meeting were as follows:

FDA: Linagliptin is a DPP-4 inhibitor and we have emerging concerns regarding pancreatitis and cutaneous skin lesions in this class of drugs. Please also include these two events in your analyses for adverse events of special interest.

This was done.

FDA: (For the cardiovascular meta-analysis) we had recommended inclusion of unstable angina as an endpoint only if hospitalization was required. You mention unstable angina alone as an endpoint. Please clarify and justify your decision.

The applicant chose to use unstable angina with hospitalization for the meta-analysis.

2.6 Other Relevant Background Information

In the United States in 2010, 25.6 million or 11.3% of all people ≥ 20 years old had a diagnosis of diabetes. The most common form of diabetes is type 2 diabetes. About 90 to 95 percent of people with diabetes have type 2. Diabetes is the leading cause of kidney failure, nontraumatic lower-limb amputations, and new cases of blindness among adults in the United States. It is the seventh leading cause of death.1

Type 2 Diabetes (T2DM) is caused by peripheral insulin resistance and impaired regulation of hepatic glucose production which leads to increased production of glucose. The disease pathophysiology also includes a decline in pancreatic ß-cell function which leads to ß-cell failure and thus inappropriate insulin secretion.

Changes to diet and an exercise regimen are first line recommended treatments for T2DM. There are also several other medical therapies available, see Table 1. However, this list of treatments while effective in lowering HbA1c to differing extents, also exposes patients to adverse events. For example, sulfonylureas, glitinides and insulin are all associated with hypoglycemia. Metformin, a biguanide, most commonly used, is associated with gastrointestinal intolerance.

Due to the large and growing population of patients with T2DM, and limitations of current therapies, new therapies for T2DM with broader safety and/or efficacy profiles

are continuously sought. The DPP-4 inhibitor class is a fairly new class of antidiabetic therapy. This class of drugs targets the incretin effect. Incretins cause insulin secretion. Both glucagon-like peptide (GLP-1) and glucose dependent insulinotropic peptide (GIP) are incretins. Their effects are limited by inactivation caused by the enzyme dipeptidyl peptidase-4 (DPP-4). DPP-4 causes proteolytic cleavage of the incretins. It is inhibition of this enzyme, in turn causing increase in incretins and thus insulin secretion that is the base for the mechanism of action in this class of drugs.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The applicant's submission was organized well and information was easily located. The applicant responded to information requests in a timely manner for any information that was not easily found in the original submission.

Inspections of the sponsor and six clinical sites were completed. Overall, at the sites that were inspected, the studies were conducted adequately, and the data generated by the clinical sites are adequate for the submission and the sought indication. There were a few protocol violations noted and most were minor. Those that were more significant are described in the following section. For additional details on site inspections, please see Dr. Susan Leibenhaut's Clinical Site Inspection Review.

3.2 Compliance with Good Clinical Practices (GCP)

All trials were conducted according to International Conference on Harmonization GCP guidelines subsequent to the review and approval of the relevant ethics committees, institutional review boards, and regulatory authorities of participating sites.

The principal trials were randomized, double-blind, placebo-controlled, parallel-group studies to maintain trial integrity. Patients were protected in the trials in several ways. All patients were consented for the trials and principal trials included a single blind run-in phase to help ensure patient compliance with the study treatment. Appropriate patient monitoring and education were in place. All principal trials also incorporated rescue procedures and limited patient enrollment by glycemic control (HbA1c).

Site Inspections

As mentioned above, site inspections were performed. One audit revealed that at Japanese site for study 1218.15 (a pivotal trial) only two female subjects out of 32 total were enrolled in the study. One female was a screen failure due to disqualifying HbA1c

value at Visit 2 and the other was discontinued by the clinical investigator (CI) due to adverse event of edema and weight gain after Visit 4. The CI was found to have implemented a sorting process that removed any subjects that were experiencing edema at screening visits and removed subjects that had a BMI >30 because of the cautions in the Japanese label for the background medication, Actos (pioglitazone) regarding the side effect of edema occurring more frequently in women. The issue concerning edema in women was also discussed with the local Institutional Review Board and the sponsor, who allowed for this variation on screening criteria as covered by the exclusion criterion concerning investigator judgment. This observation was not cited as a violation.

Reviewer' Comments
I was aware of this issue early on in my review. This imbalance in enrollment from the Japanese site did not have impact on trial integrity, or the overall efficacy or safety conclusions in women, in my review of this study.

Notable Protocol Violations

A site in India that enrolled patients for both studies 1218.16 and 1218.17 underreported data concerning rescue, concomitant medications, adverse events (AEs) and existence of baseline conditions. The rescue violations occurred when the decision to rescue was based on elevated HbA1C or elevated self-monitored glucose values. There were seven such violations and in addition, three of these were not reported to the NDA as having been rescued. The failure to report AEs and concomitant medications occurred when five subjects enrolled in Protocol 1218.17 took concomitant medications or had one or more instances of minor AEs including sore throat, urinary tract infections, epigastric tenderness, or fever that were not reported to the sponsor on the case report forms. All these subjects were in the linagliptin group.

A sponsor inspection of the site conducted after our agency's inspection found additional violations. Three subjects from each protocol were found for whom rescue was not reported. For both protocols, unreported concomitant therapy and adverse events had not been reported. None of the AEs were considered serious and none led to discontinuation of medication. Most were related to hyperglycemia and the unreported rescues. For both protocols, there were unreported baseline conditions. Most conditions were related to previous surgeries or menopause.

Reviewer's Comments
The site inspection did reveal few protocol violations. The noteworthy violations are described in this review. These violations do not have an impact on endpoint data or my overall analysis of these studies.

3.3 Financial Disclosures

The applicant submitted documentation confirming that there were no reported investigator financial disclosures that would affect data or trial integrity. These data were reviewed, and the majority of investigators, including almost all principal investigators (PIs) submitted the documentation. There were several subinvestigators that did not have submitted financial disclosure forms, but few PIs. Most of these investigators who did not have reports either did not end up participating or were no longer at the site.

Table 2 below lists all studies related to safety and efficacy considered “covered studies” for the purpose of 21 CFR 54.2. FPI stands for First Patient In and LPO means Last Patient Out.

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Table 2 Linagliptin Covered Studies for 21 CFR 54.2.

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Study Number	Protocol Title	First Patient In	Last Patient Out
1218.15	A randomised, double-blind, placebo controlled, parallel group 24 week study to assess the efficacy and safety of BI 1356 (5 mg) in combination with 30 mg pioglitazone (both administered orally once daily), compared to 30 mg pioglitazone plus placebo in drug naive or previously treated type 2 diabetic patients with insufficient glycaemic control.	15-APR-2008	19-JUN-2009
1218.16	A randomised, double-blind, placebo-controled parallel group efficacy and safety study of BI 1356 (5 mg administered orally once daily) over 24 weeks, in drug naive or previously treated (6 weeks washout) type 2 diabetic patients with insufficient glycemic control	15-FEB-2008	06-MAY-2009
1218.17	A randomised, double-blind, placebo-controlled parallel group efficacy and safety study of BI 1356 (one dose, e.g. 5 mg), administered orally once daily over 24 weeks, with an open label extension to 80 weeks (placebo paticnts switchcd to BI 1356), in type 2 diabetic patients with insufficient glycaemic control despite metformin therapy	31-JAN-2008	18-MAY-2009
1218.18	A randomised, double-blind, placebo-controlled parallel group efficacy and safety study of BI 1356 (5 mg) administered orally once daily over 24 weeks, with an open-label extension to one year (placebo patients switched to BI 1356), in type 2 diabetic patients with insufficient glycaemic control despite a therapy of metformin in combination with a sulphonylurea	25-FEB-2008	21-MAY-2009
1218.20	A randomised double-blind, active-controlled parallel group efficacy and safety study of BI 1356 (5.0 mg, administered orally once daily) compared to glimepiride over two years in type 2 diabetic patients with insufficient glycaemic control despite metformin therapy	12-FEB-2008	

1218.23	A double-blind phase III study to evaluate the efficacy of BI 1356 5 mg and 10 mg vs. placebo for 12 weeks and vs. voglibose 0.6 mg for 26 weeks in patients with type 2 diabetes mellitus and insufficient glycaemic control, followed by an extension study to 52 weeks to evaluate long-term safety	01-APR-2008	14-JAN-2010
1218.35	A randomized, double-blind, placebo-controlled parallel group efficacy and safety study of BI 1356 (5 mg administered orally once daily) over 18 weeks in Type 2 diabetic patients with insufficient glycaemic control (HbA1c 7.0-10%) despite background therapy with a sulfonylurea drug.	16-DEC-2008	14-JAN-2010
1218.5	A randomized, double-blind, placebo-controlled, five parallel group study investigating the efficacy and safety of BI 1356 BS (0.5 mg, 2.5 mg and 5.0 mg administered orally once daily) over 12 weeks in drug naive and treated patients with Type 2 diabetes with insufficient glycemic control (study includes an open-label metformin treatment arm)	19-JUN-2006	22-AUG-2007
1218.50	A randomised, db, placebo-controlled, parallel group efficacy and safety study of BI 1356 (5mg), administered orally once daily for 18 weeks followed by a 34 week double-blind extension period (placebo patients switched to glimepiride) in type 2 diabetic patients with insufficient glycaemic control for whom metformin therapy is inappropriate (intolerability or contraindication)	25-SEP-2008	
1218.6	A randomised, double-blind, placebo-controlled, five parallel groups study investigating the efficacy and safety of BI 1356 BS (1 mg, 5 mg and 10 mg administered orally once daily) over 12 weeks as add-on therapy in patients with type 2 diabetes and insufficient glycaemic control despite metformin therapy, including an open-label glimepiride treatment arm.	28-APR-2006	21-AUG-2007

Source Applicant's Financial Disclosure Report

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Please see Dr. Sheldon Markofsky's review for full details.

Linagliptin is an 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'. (b) (4) Impurity levels are well below limits allowed.

Linagliptin is a very stable compound; there is little decomposition is observed upon storage of the drug substance at high humidity or temperatures.

4.2 Clinical Microbiology

Not applicable. There was no microbiology review for linagliptin.

4.3 Preclinical Pharmacology/Toxicology

According to Dr. David Carlson nonclinical data support the safe use of linagliptin under the proposed uses. Please see Dr. Carlson's pharmacology/toxicology review for full details.

Linagliptin activity was assessed *in vitro* and *in vivo* animal models to investigate DPP4 inhibitory and effects on blood glucose. DPP4 is active in plasma, which is the target of linagliptin. DPP4 expression also occurs on the cell surface of kidney, liver, intestine, lymphocytes, and vascular endothelial cells. Linagliptin is highly selective (>10,000 fold) for DPP4 inhibition in comparison to other dipeptidyl peptidases (DPP8 and DPP9). Inhibition of DPP8/9 has been associated with animal toxicity. Skin, immune, and GI-related toxicity have been observed with some DPP4 inhibitor. 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. However, no skin lesions were seen in monkeys or other species treated with linagliptin.

A hypersensitivity response was seen in dogs and minipigs. The toxicity was evident in clinical signs of facial flushing and edema, but high dose of linagliptin were tolerated without other toxicity. These reactions involve systemic histamine release but are not IgE mediated responses that would lead to anaphylaxis.

Kidney, liver, lung, and male and female reproductive tissue toxicity occurred at > 50-times the maximum recommended human dose (MRHD). Toxicity suggestive of phospholipidosis in lung was seen in short term rat studies and chronic lifetime

treatment with >400-times the MRHD caused lung granuloma(ta). The clinical risk is thought to be minimal due to high exposure multiples.

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). In addition, carcinogenicity was assessed in chronic, lifetime oral gavage studies in mice and rats at doses that provided several hundred-fold higher exposure than expected clinically. Linagliptin caused drug-induced lymphomas in female mice at 287-times the MRHD. Linagliptin poses minimal carcinogenic risk to humans based on high exposure multiples at the NOAEL (no observed adverse effect level) for tumor incidence (34X) and very high exposure multiples (287X) at the linagliptin dose that caused tumors in a single sex in mice. In addition, no drug-related tumors were found in rats exposed to over 400-times the MRHD.

4.4 Clinical Pharmacology

Please see Dr. Lokesh Jain's review for full details on the clinical pharmacology of linagliptin.

The applicant plans to market the 5 mg dose of linagliptin, effectiveness of which was evaluated in phase 2 and phase 3 clinical trials. This is the only dose that was tested in all phase 3 efficacy trials except one phase 3 trial in Japanese patients (Trial 1218.23), which also tested a 10 mg dose. Phase 2 trials evaluated doses ranging from 0.5 to 10 mg from four to twelve weeks. Selection of 5 mg dose was based on evidence of effectiveness for primary (i.e., ΔHbA1c) and secondary (i.e., % DPP-4 inhibition and effect on GLP-1 and glucose levels) efficacy or pharmacodynamic markers. The HbA1c effect in study 1218.6 is seen in Figure 2. A statistically significant effect was observed for all tested doses of 1 mg, 5 mg, and 10 mg, which resulted in a 0.4%, 0.8%, and 0.7% placebo-corrected reduction in HbA1c, respectively. There was no added benefit for the 10 mg dose compared to the 5 mg dose.

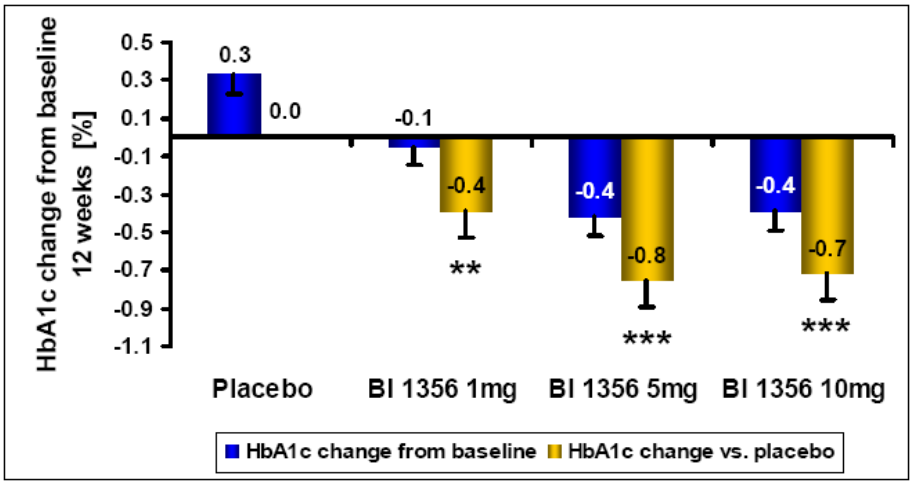

Figure 2 Adjusted mean (SE) for HbA1c change from Baseline, Study 1218.6
Source Dr. Lokesh Jain's Review

Linagliptin clinical pharmacology studies are listed here (N=number of studies):

Phase I in Healthy Volunteers

- Pharmacokinetics (PK) (N=5): Single dose, multiple dose, dose proportionality, comparison of twice daily versus once daily regimen
- Specific population PK Studies (N=5): PK in Chinese, PK in Japanese, PK in African-American (interim analysis), Renal impairment, Hepatic impairment
- Biopharmaceutics (N=3): Food effect, bioavailability and bioequivalence
- Drug-drug interaction studies (N=9): with ritonavir, rifampicin, metformin, pioglitazone, glyburide, simvastatin, warfarin, digoxin, and oral contraceptive
- QT study (N=1)

Phase I in T2DM

- Multiple dose PK (N=2) and renal impairment study included both healthy subjects and patients with T2DM

Phase II in T2DM

- Dose finding study (N=3)
- Clinical trial to assess 4 week pharmacodynamics (PD) (N=1)

PK/PD studies are all listed below in section 5.1 in Table 3 along with all studies in the clinical program.

4.4.1 Mechanism of Action

Mechanism of Action & Enzymatic Activity

Linagliptin is an orally administered DPP-4 inhibitor. The inhibition of DPP-4 prolongs the half-life of endogenous incretin hormones, GLP-1 and GIP. These two incretins are gastrointestinal hormones and stimulate the release of insulin and lower the plasma glucagon levels after meal consumption. GLP-1 activity ceases when the glucose concentration falls below 55 mg/dL. This cessation suggests that the half-life of GLP-1 by DPP-4 inhibitors do not have a high risk of causing hypoglycemia. See Figure 3.

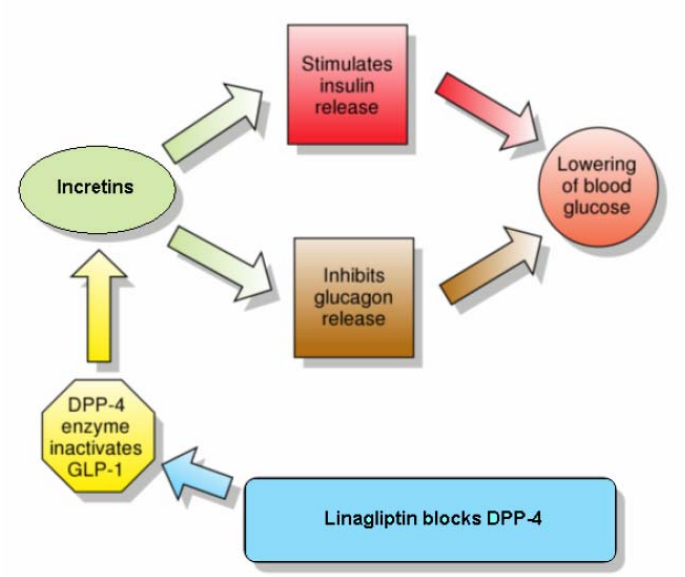

Figure 3 Linagliptin Mechanism of Action
Source Summary of Clinical Pharmacology Studies, Figure 3.5.2: 1, page 124

Linagliptin is a substrate of CYP enzymes, this was confirmed by ketaconazole inhibiton. CYP3A4 was the main human isoform metabolizing linagliptin and there was no indication for a contribution of other CYP enzymes based on *in vitro* experiments with expressed human CYPs. The predominant human metabolite is CD1790. Formation of other metabolites was very low.

Linagliptin is not an inducer of hepatic cytochrome P450.

4.4.2 Pharmacodynamics

Main PD Points for Linagliptin

- The extent of dipeptidyl peptidase-4 (DPP-4) inhibition increased with increase in doses from 1 to 10 mg. (Trial 1218.2).
- The median DPP-4 inhibition for 5 mg dose was between 81-91% in most of the dose-finding studies and DDI studies.
- The levels of GLP-1 increased by about 3 fold for linagliptin dose ranging from 2.5 to 10 mg compared to placebo (Trial 1218.3).

QT Interval Study

In healthy subjects administered a single therapeutic dose of 5 mg and a single supratherapeutic dose of 100 mg, the upper limit of the two-sided 90% confidence interval of the placebo adjusted change from baseline of the individually heart rate corrected QT interval was less than 10 ms at both dose levels and all time points. Linagliptin does not cause QT prolongation. In addition, no clinically relevant changes of the heart rate, the uncorrected QT interval or other heart rate corrected QT intervals were observed, compared with placebo. At no time during the study did any subject have a maximal QTc interval >480 ms or experienced an increase in the QTc interval from baseline that was >60 ms.

4.4.3 Pharmacokinetics

Main PK Points for Linagliptin

- Linagliptin follows non-linear PK for doses ranging from 1mg to 600 mg.
- The non-linearity and long half-life of linagliptin can be explained by concentration dependent binding to DPP-4.
- Decline in concentration of linagliptin is steeper for higher doses than lower doses indicating non-linear distribution or elimination and becomes parallel after concentrations decline to around 10 ng/mL. The terminal half-life of linagliptin was greater than 100 hrs.
- Metabolism is a minor pathway of elimination for linagliptin. 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 is CD1790 (formed by CYP3A4 isoform) which is therapeutically inactive.
- Co-administration with high-fat meal reduced linagliptin rate of absorption (i.e., C_{max}) by ~15 to 25% but had no effect on AUC

- The change is single-dose or steady-state exposure (AUC) or peak plasma concentration (C_{max}) ranged from 30 to 70% in subjects with hepatic or renal impairment. No dose-adjustments are recommended for subjects with renal or hepatic impairment.
- The effect of age, weight, and gender were evaluated in population PK analysis. The impact of these covariates on steady-state exposure was less than ±9%. Trough concentrations for patients with BMI>35 kg/m^2 and ≤35 kg/m^2 were comparable based on comparison of data from two phase 2 trials 1218.5 and 1218.6.
- Linagliptin exposures in subjects with Japanese and Chinese ethnicity were ~30% higher than that of Caucasian subjects. This small change was not expected to be clinically meaningful.

Reviewer's Comments
The efficacy and safety in Asian patients is discussed in this review and was not found to be concerning.

Of note, few black patients were (57 patients, 1.2% of the total study population) included in the clinical program for linagliptin. There was one dedicated PK study in black patients, 1218.55 that evaluated 20 patients over seven days of daily 5 mg linagliptin. This study along with the combined analysis of phase 3 trials also did not reveal any differences in efficacy and safety based on ethnicity. In addition, metabolism plays minor role in elimination of linagliptin and transporters do not appear to influence PK at therapeutic concentrations. For this reason, even with limited data it is reasonable to assume that there are no clinically meaningful differences in linagliptin based on ethnicity.

The applicant has proposed that a dosage adjustment in renal impairment is unnecessary, as mentioned above. Comparison of AUC_{0-24} after single dose demonstrated 29%, 57%, 41%, and 54% increase in subjects with mild-, moderate-, severe-renal impairment and end stage renal disease, respectively, compared to subjects with normal renal function. See Figure 4.

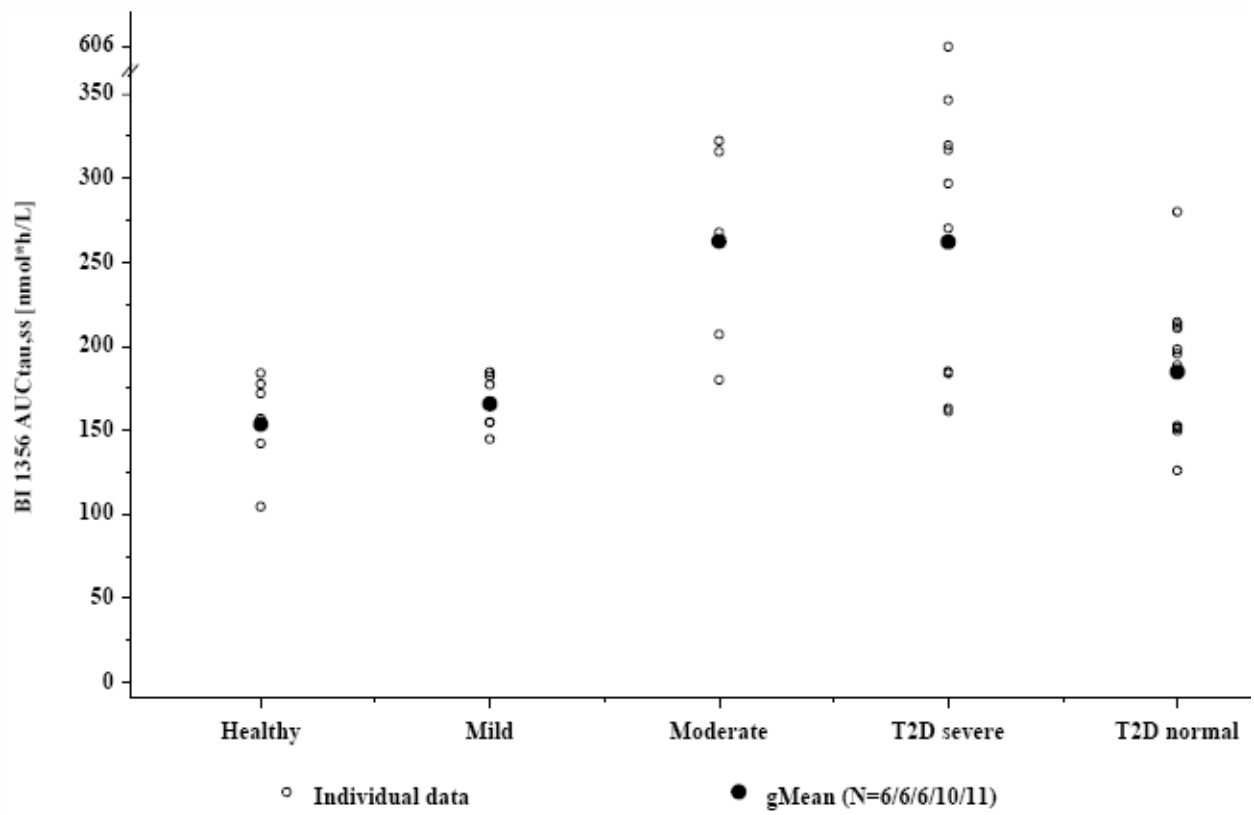

Figure 4 Steady-state AUC values of linagliptin after multiple 5 mg doses
Source Dr. Lokesh Jain's review

Drug-Drug Interaction Studies, see Figures 5 and 6

- Maximum changes in linagliptin PK were observed following co-administration with ritonavir (P-gp and CYP3A4 inhibitor) or rifampicin (P-gp and CYP3A4 inducer).
- Linagliptin co-administration with P-gp and CYP3A4 inducers may reduce its efficacy because of lower linagliptin exposures; therefore, therefore patients should use alternative treatments when linagliptin is co-adminstered with P-gp or CYP 3A4 inducers.
- No dose adjustments are recommended for co-administration of drug with P-gp and CYP3A4 inhibitors because safety of doses up to 10 mg has been established in 12-weeks dose finding studies and a long term phase 3, 52-weeks trial in Japanese patients with T2DM.
- No clinically relevant change in PK of co-administered drugs was observed following co-administration with linagliptin.

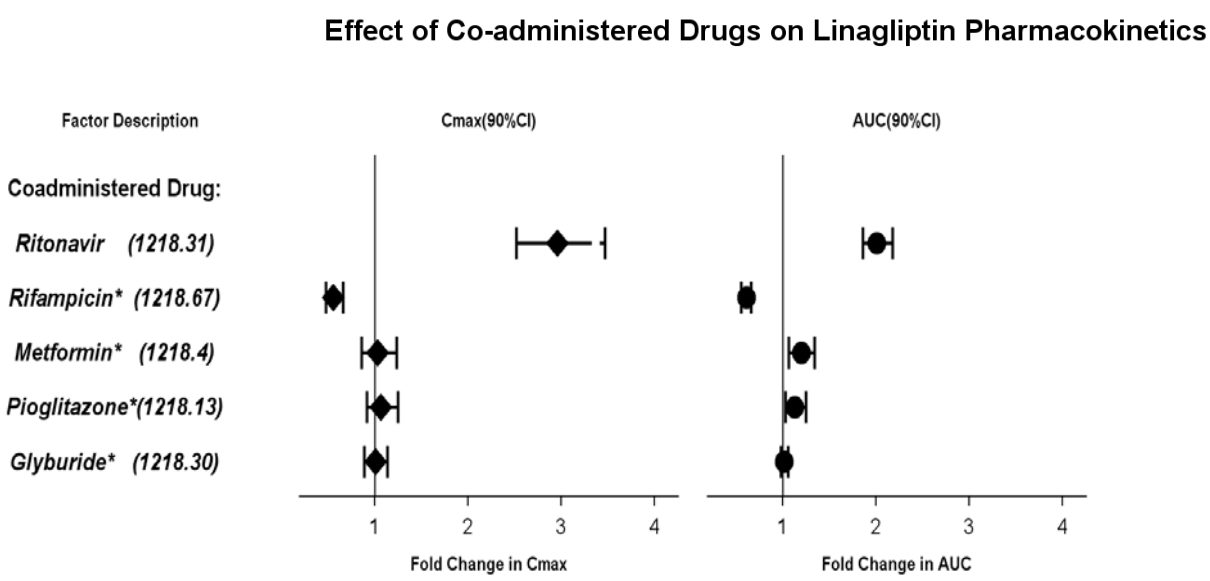

Figure 5 Drug Effect on Linagliptin
Source Dr. Lokesh Jain's review

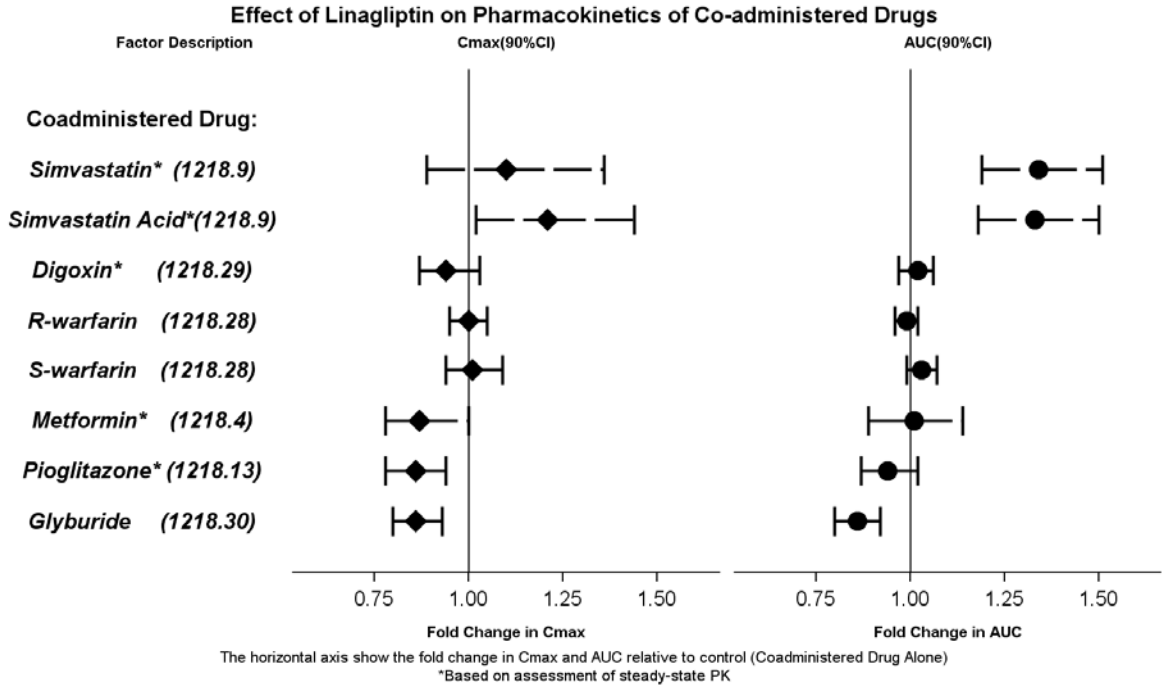

Figure 6 Linagliptin Effect on Other Drugs
Source Dr. Lokesh Jain's review

5 Sources of Clinical Data

The clinical program includes 24 phase 1, 4 phase 2, and 9 phase 3 clinical trials. The PK and PD studies were listed in both text and tabular form in Section 4.4 *Clinical Pharmacology*. The safety and efficacy studies are listed in Section 5.1 below.
The NDA was submitted in the electronic Common Technical Document format, with the following path:

\\CDSESUB1\EVSPROD\NDA201280\201280.enx

5.1 Tables of Studies/Clinical Trials

There were nine phase III trials. All trials for the clinical program of linagliptin communicated by the time of the Four Month Safety Update are included in Table 3. Study data or titles submitted at that time are at the end of the table. All studies were reviewed for safety and efficacy. Detailed review was done for all phase III studies. The *Review of Efficacy* and *Review of Safety* sections detail which studies and study pools were used for this review.

Table 3 All Studies in the Linagliptin Clinical Program

Study Category	Study Number	Study Population	Placebo (n)	Linagliptin (n)	Active Comparator (n)	Dose	Duration	Other Test Products
Phase III								
Pivotal double-blind placebo-controlled efficacy studies	1218.15	T2DM	130	259		5 mg	24 weeks	Background: Pioglitazone
	1218.16	T2DM	167	336		5 mg	24 weeks	
	1218.17	T2DM	177	524		5 mg	24 weeks	Background: Metformin
	1218.18	T2DM	265	793		5 mg	24 weeks	Background: Metformin and Sulfonylurea
Double-blind active-controlled efficacy study	1218.20	T2DM	0	779	781	5 mg	104 weeks (52 weeks completed)	Background: Metformin Comparator: Glimepiride
Additional double-blind placebo-controlled efficacy studies	1218.35	T2DM	84	161		5 mg	18 weeks	Background: Sulfonylurea
	1218.50	T2DM	76	151	76	5 mg	18 weeks 34 weeks active control	Comparator: Glimepiride
Double-blind efficacy studies with more than one linagliptin dose level	1218.23	T2DM	80	319	162	5, 10 mg	12 weeks placebo controlled 14 weeks active controlled 26 week uncontrolled extension	Comparator: Voglibose
Open-label long-term extension study	1218.40	T2DM	0	2122		5 mg	78 week extension to studies 15-18	Background: Pioglitazone Metformin Sulfonylurea
Phase II								
Double-blind efficacy studies with more than one linagliptin dose level	1218.5	T2DM	67	170	65	0.5, 2.5, 5 mg	12 weeks	
	1218.6	T2DM	71	197	65	1, 5, 10 mg	12 weeks	Comparator: Glimepiride

	1218.12	T2DM	18	65		5, 10 mg	28 days	
	1218.37	T2DM	40	40	41	5 mg	4 weeks	Comparator: Sitagliptin
Phase I								
Pharmacokinetic/ Pharmacodynamic (PK/PD)	1218.1	Healthy subjects	16	48		2.5, 5, 100 mg linagliptin solution 25, 50, 100, 200, 400, 600 mg tablets	1 dose solution 1dose tablet	
	1218.11	Healthy subjects	12	42		1, 2.5, 5, 10 mg	Single dose and 12 days of dosing	
	1218.45	Healthy subjects		16		2.5 and 5 mg	14 days (7 days each treatment)	
	1218.58	Healthy subjects		12		5 mg	1 single dose and 6 days	
PK/PD Drug Drug Interaction (DDI) studies	1218.4	Healthy subjects		16		10 mg	3 days and 6 days	Metformin for DDI
	1218.28	Healthy subjects		18		5 mg	12 days	Warfarin for DDI
	1218.29	Healthy subjects		20		5 mg	11 days	Digoxin for DDI
	1218.30	Healthy subjects		20		5 mg	6 days	Glyburide for DDI
	1218.31	Healthy subjects		12		5 mg	4 days	Ritonavir for DDI
	1218.44	Healthy subjects		18		5 mg	14-28 days	Microgynon for DDI (ethinylestradiol and levonorgestrel)

	1218.67	Healthy subjects		16		5 mg	24 days	Rifampicin for DDI
PK Absorption, Metabolism Excretion	1218.7	Healthy subjects		12		5, 10 mg	Single dose	
PK Dedicated QT study	1218.32	Healthy subjects	44	44		5, 100 mg	Single dose each	
PK in T2DM	1218.2	T2DM	12	36		1, 2.5, 5, 10 mg	12 days each dose	
	1218.3	T2DM	16	61		2.5, 5, 10 mg	28 days each dose	
	1218.26	Healthy subjects with renal impairment and T2DM patients		51		5 mg	Single dose, 7 days and 10 days	
PK Hepatic Impairment	1218.27	Healthy subjects and patients with hepatic impairment		33		5 mg	Single dose and 7 days	
PK and Bioavailability (BA)	1218.10	Healthy subjects	8	28		0.5, 2.5, 5 mg IV, 10 mg po	2 separate single doses	
PK and BA DDI	1218.9	Healthy subjects		20		10 mg	18 days	Simvastatin for DDI
	1218.13	Healthy subjects		20		10 mg	11 days	Pioglitazone for DDI
BA and food effect	1218.8	Healthy subjects		24		1, 10 mg	5 days	
	1218.34	Healthy subjects		32		5 mg	2 days	

BA	1218.25	Healthy subjects		24		5 mg (two different formulations)	3 days	
	1218.33	Healthy subjects		12		1, 2.5, 5 mg	21 days	
Reported at 4 Month Safety Update								
Phase III								
	1218.36 ONGOING	T2DM	630	630		5 mg	24 weeks with insulin 50 week extension with no insulin	Background: Insulin
	1218.43	T2DM with renal impairment	65	68		5 mg	52 weeks treatment (12 week data submitted)	
	1218.63 ONGOING	T2DM in elderly patients	80	160		5 mg	24 weeks	
	1218.64	T2DM in moderate to severe renal impairment	120	120	120	5 mg	12 weeks and 40 weeks active control	Comparator: Glimepiride
Linaglitpin/ Metformin Combination Study	1218.46	T2DM	72	428	291	2.5 bid, 5 mg	24 weeks Completed, not submitted	Comparator: Metformin
	1218.52 ONGOING	T2DM		396	171	2.5 mg bid	54 weeks	Comparator: Metformin
Phase I								
PK/PD	1218.55	African American patients with T2DM		21		5 mg	7 days	

5.2 Review Strategy

Efficacy

The review of efficacy is organized by trial groupings. The applicant has conducted four pivotal trials that are grouped as EFF-1; I have named and refer to the four studies included in this pooling as ***Pivotal Studies***. The proposed labeling is for linagliptin indicated as monotherapy and combination therapy for treatment of T2DM. Therefore, I will also discuss the two groups of studies that can support these indications in the *Review of Efficacy*. There is expected overlap between the pivotal trials and the trials used to support the indications for both monotherapy and combination therapy. I will not repeat reviews of trials that are previously discussed in other sections, and this will be noted. I will also discuss the extension study to the pivotal studies.

The applicant has presented analyses based on different population datasets. I have selected a few that I will use to guide my review. One is the **FAS (full analysis set)**. The FAS is defined as all randomized patients who received at least one dose of study medication, had a baseline HbA1c measurement, and had at least one on-treatment HbA1c measurement. This group required missing glycemic values and values obtained in subjects who initiated protocol-directed glycemic rescue to be imputed. One of the methods used by the applicant was the Last Observation Carried Forward (LOCF) method. Results from the FAS LOCF population were used frequently in my discussion. Also used for discussion is the treated set. For some study demographics, this was what was provided by the applicant and presented here. The treated set is defined as all patients who were treated with at least one dose of study medication in the randomized period of the trial. When this differed from the FAS, an explanation is provided.

The **Observed Cases group (OC)** was not one of the major analyses provided by the applicant. This population is the FAS completers with the patients that had Last Observation Carried Forward (LOCF) calculations removed. This population does not include the rescue patients, or other patients that needed imputed values. I present data from this group because analyzing the results with no imputed data included is necessary to ensure efficacy.

The estimated creatinine clearance rate (eCcr) was estimated using the Cockcroft-Gault formula; the eGFR was estimated using the MDRD formula. MDRD was used to classify the degree of renal impairment throughout the review. The eCcr was not used for this review, but mentioned in some applicant tables presented here.

Statistical Analyses

The primary endpoint in all efficacy trials discussed below except for the open-label extension trial (study 1218.40) was the change in HbA1c from baseline to the last on-

treatment visit. It was analyzed using an analysis of covariance method (ANCOVA) with treatment and baseline HbA1c as covariates. Baseline HbA1c was defined as the last available HbA1c value before the start of the study medication. Values obtained prior to the washout period were not accepted as baseline value. 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. For all other efficacy variables, measurements taken after the first dose up to one day after the last dose of study medication were regarded as on-treatment values.

5.3 Discussion of Individual Studies/Clinical Trials

Summarize and insert table for Phase 2b and 3 studies

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The applicant seeks an indication for linagliptin as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. The recommended dose of linagliptin is 5 mg once daily. Of note, no dose adjustment is recommended for patients with renal impairment.

6.1.1 Methods

Pivotal Studies

Study 1218.15
A randomized, double-blind, parallel group, 24-week study to assess the efficacy and safety of linagliptin (5 mg) in combination with 30 mg pioglitazone (both administered orally once daily), compared to 30 mg pioglitazone plus placebo in drug-naïve or previously treated type 2 diabetic patients with insufficient glycemic control

Study 1218.16
A randomized, double-blind, placebo-controlled parallel group efficacy and safety study of linagliptin (5 mg administered orally once daily) over 24 weeks, in drug naïve or previously treated (6 weeks washout) type 2 diabetic patients with insufficient glycemic control

Study 1218.17

A randomized, double-blind, placebo-controlled parallel group efficacy and safety study of BI 1356 (5 mg administered orally once daily) over 24 weeks in type 2 diabetic patients with insufficient glycemic control despite metformin therapy

Study 1218.18
A randomized, double-blind, placebo-controlled parallel group efficacy and safety study of BI 1356 (5 mg) administered orally once daily over 24 weeks in type 2 diabetic patients with insufficient glycemic control despite a therapy of metformin in combination with a sulfonylurea

General Overview and Study Design—Pivotal Studies

The development program for linagliptin included three large pivotal randomized, placebo-controlled, double-blind, parallel group, 24-week phase three trials, 1218.16, 1218.17, and 1218.18 (referred to as 16, 17 and 18 from this point). These studies shared a similar design. The main difference between the studies was background medication. The fourth pivotal trial compared the effect of linagliptin and pioglitazone to the effect of pioglitazone alone in a randomized, double-blind, parallel group, 24-week trial.

Study 15 had a thiazolidinedione (TZD) background medication—pioglitazone as part of **initial combination therapy** with linagliptin. Study 16 compared linagliptin with placebo in patients who did not receive any other antidiabetic medication. Study 17 investigated the efficacy of linagliptin versus placebo added to ongoing metformin therapy, and study 18 compared linagliptin with placebo added to ongoing combination therapy with metformin and a sulfonylurea (SU). There were few other differences that will be explained.

Studies 15, 16 and 17 all shared the same study design, see Figure 7.

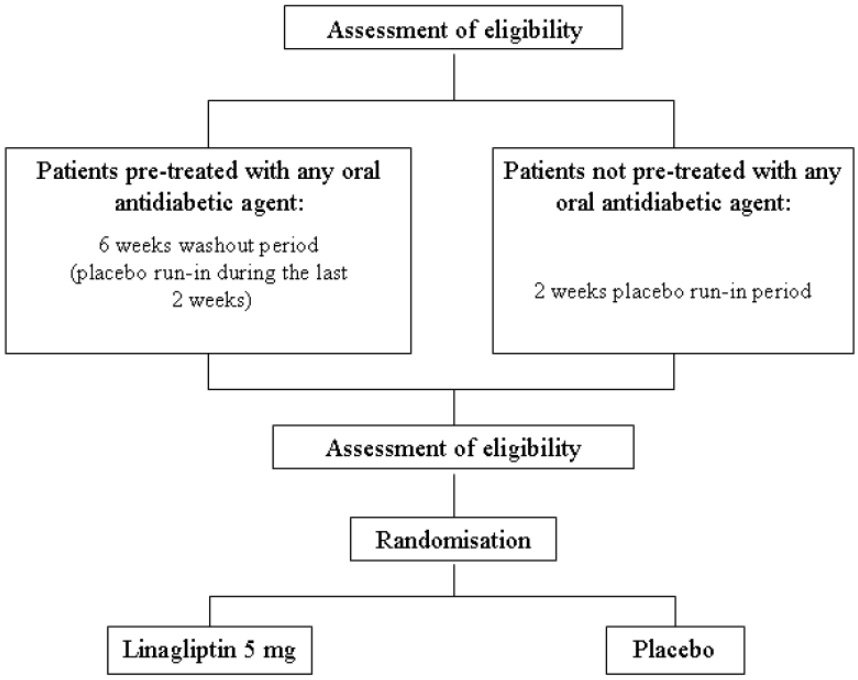

Figure 7 Study Design for Studies 15, 16 and 17
Source Figure 9.2: 1, Study Report 1218.15, page 36

For two studies (15, 16), patients stopped all their current antidiabetic treatment and underwent a 6-week washout period to enable the study treatment to mimic an initial therapy. For study 17, the washout period did not include discontinuation of metformin as metformin was ongoing therapy in this trial (10 week unchanged dose); this was an add on to metformin trial. The studies included an open-label placebo run-in period during the last two weeks of the washout period. Patients who were drug-naïve with regard to anti-diabetic medication directly entered a two-week open-label placebo run-in period. Patients who still met the eligibility criteria after the run-in period were randomized to the 24-week treatment period of the study in which they received either 5 mg linagliptin or placebo. In two studies the treatment was in addition to an oral antidiabetic drug (OAD), as described (pioglitazone in study 15 and metformin in study 17).

Reviewer's Comments
The design of study 15 is different than that of the other pivotal trials. Pioglitazone is an initial therapy for both arms; there is no ongoing treatment. The rationale was not provided in the NDA; however, on inquiry, the applicant provides an explanation. One reason given is that linagliptin and pioglitazone have complementary modes of action. This type of study offers a useful

examination of initial combination of the two medications. The applicant argues that these data would be useful and relevant in a clinical setting. They also state that there was no reason to believe that this approach would result in differences in safety or efficacy than a more traditional add on study design.

The label presents this study as it was designed; as initial therapy. This information may be useful for physicians that are considering beginning therapy with either pioglitazone or linagliptin, or both concurrently. This information will be inferred from the Clinical Studies section of the label that will describe the design of the trials.

I agree with the rationale that this study design was not likely to result in different safety or efficacy findings. Still, this nontraditional study design was considered when the study was reviewed.

Study 18 was similar to study 17 with an add on therapy design, as seen in Figure 8. It differed in that there was no six week washout as the prior medications that were allowed were continued during the study period. Patients screened and assessed to be eligible directly entered a two-week, open-label, placebo run-in period. At the end of this run-in period, patients were randomized to a 24-week treatment period in which they received either linagliptin 5 mg or placebo in addition to the background therapy of metformin in combination with SU (doses had been unchanged for 10 weeks).

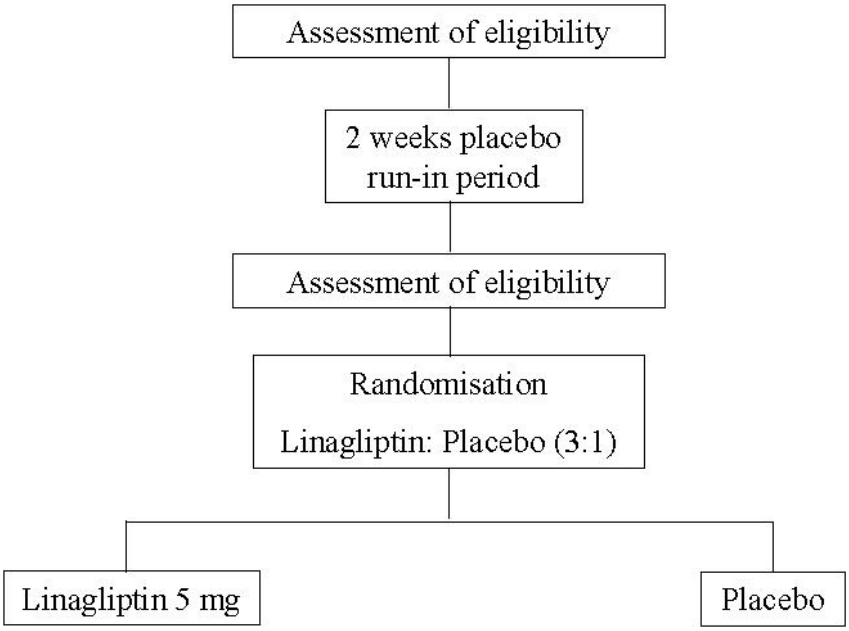

Figure 8 Study Design—Study 18
Source Figure 9.2: 1, Study Report 1218.18, page 36

Objectives—Pivotal Studies

The objectives were specific to the comparison made in each of the individual studies and were described in *General Overview and Study Design*.

Endpoints—Pivotal Studies

The primary endpoint was the change from baseline in HbA1c after 24 weeks of treatment. The term 'baseline' refers to the last observation prior to the start of randomized study treatment.

Eligibility Criteria—Pivotal Studies

Inclusion Criteria

Both male and female patients with T2DM were eligible for these studies if they met the following criteria:
• Age at screening (Visit 1a): ≥18 and ≤80 years
• Body mass index (BMI) at screening (Visit 1a) ≤40 kg/m^2

There were several criteria that differed for the studies.
For **study 15** (add on to pioglitazone as initial therapy), the HbA1c criteria were:
• **HbA1c at screening (Visit 1a):**
Patients undergoing washout of previous antidiabetic medication:
7.0%≤ HbA1c ≤9.5%
Patients not undergoing washout of previous antidiabetic medication:
7.5%≤ HbA1c ≤11.0%
• HbA1c at start of run-in (Visit 2): 7.5%≤ HbA1c ≤11.0%

For **study 16**,(monotherapy) the HbA1c criteria were:
• HbA1c at screening (Visit 1a):
Patients undergoing washout of previous antidiabetic medication:
6.5%≤ HbA1c ≤9.0%
Patients not undergoing washout of previous antidiabetic medication:
7.0%≤HbA1c ≤10%
• HbA1c **at start of run-in** (Visit 2): 7.0% ≤ HbA1c ≤10.0%

In addition, the patients in **study 16** were not to have been treated with more than one oral OAD and this therapy could not be changed for the 10 weeks prior to the informed consent date.

For **study 17** (add on to metformin), HbA1c criteria were the same as for **16** (monotherapy). These patients, however had been previously treated with metformin

and not more than one other oral antidiabetic agent. Antidiabetic therapy had to be unchanged for 10 weeks prior to the date of informed consent. A dose of ≥1500 mg/day metformin was required for inclusion into the trial and the dose needed to be stable for at least 12 weeks before randomization. Patients with a total daily dose of less than 1500 mg metformin were included only if the investigator documented them to be on their maximum tolerated dose (also in this case, the 12 week time interval applied for a stable dose).

For **study 18** (add on to metformin and SU), HbA1c criteria were the same as 16 and 17, but there were no washout criteria since there was no discontinuation of prior medications; the two prior medications that were allowed were both continued. In addition, patients who had been treated only with a stable total daily dose of preferably ≥1500 mg metformin and a dose of a SU drug that had been documented, by the Investigator, to be the individual maximum tolerated dose of that SU drug. Both the dose and dosing regimen of metformin and the SU had to be stable for 10 weeks prior to informed consent, and this was not to be changed for the duration of the trial. Again, in this trial patients with a total daily dose of less than 1500 mg metformin were included only if the investigator documented them to be on their maximum tolerated dose.

Exclusion Criteria

Patients were not eligible for the trials if they met any of the following criteria:

• MI, stroke, or transient ischemic attack (TIA) within 6 months prior to the date of informed consent
• Abnormal hepatic tests, defined as serum levels of either alanine transaminase (ALT), aspartate transaminase (AST), or alkaline phosphatase (ALP) above 3x the upper limit of normal (ULN) as determined at Visit 1a (screening)
• Alcohol or drug abuse within 3 months prior to the date of informed consent
• Pre-menopausal women not practicing an acceptable method of birth control
• Treatment with systemic steroids or change in dosage of thyroid hormones within 6 weeks prior to the date of informed consent

For **study 15** (add on to pioglitazone), additional criteria were:

• Treatment with GLP-1 analogues/agonists, insulin, or anti-obesity drugs (e.g. sibutramine, rimonabant, orlistat) within 3 months prior to the date of informed consent
• Fasting blood glucose > 240 mg/dl (>13.3 mmol/L) at screening
• Heart failure NYHA class III-IV (Class III: patients with marked limitation of activity; comfortable only at rest; Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest) or history of heart failure prior to this study
• Diabetic ketoacidosis within 6 months prior to informed consent
• Hemodialysis patients, due to limited experience with TZDs

For **study 16** (add on to placebo), an additional criterion was:

• Treatment with rosiglitazone, pioglitazone, GLP-1 analogues, insulin, or anti-obesity drugs (e.g. sibutramine, rimonabant, orlistat) within 3 months prior to the date of informed consent

For **study 17** (add on to metformin), additional criteria were:

• Treatment with rosiglitazone, pioglitazone, GLP-1 analogues, insulin, or anti-obesity drugs (e.g. sibutramine, rimonabant, orlistat) within 3 months prior to the date of informed consent
• Renal failure or renal impairment (serum creatinine ≥1.5 mg/dl as determined at Visit 1a (screening))
• Unstable or acute congestive heart failure
• Acute or chronic metabolic acidosis (present in patient history)

Study 18 had additional criteria similar to those of 17.

The following table, Table 4, clarifies the four pivotal studies and their medication eligibility criteria.

Table 4 Summary of Pivotal Study Medication Eligibility

Study	Medications Allowed Prior to Screening	Post Screening Plan for Patients with Prior OADs	Post Screening Plan for Patients without Prior OADs
15 (add on to pioglitazone)	Any OAD allowed	6 week washout	2 week run-in
16 (monotherapy)	Only one OAD allowed—(dose unchanged for 10 weeks)	6 week washout	2 week run-in
17 (add on to metformin)	Pretreated with metformin and not more than one other OAD (both unchanged for 10 weeks)	6 week washout for patients on an OAD other than metformin	2-week run in for previously treated metformin only patients
18 (add on to metformin and SU)	Pretreated with metformin and SU (both unchanged for 10 weeks)	Not Applicable	2 week run-in

Reviewer's Comments
Inclusion and exclusion criteria are acceptable for the patient population studied and differed appropriately for the conditions present in the four protocols. For example, study 15 (add on to pioglitazone) allowed for higher screening HbA1c because they were all actively treated (linagliptin plus pioglitazone versus pioglitazone alone).
Study 15, add on to pioglitazone, excluded patients undergoing hemodialysis, due to possible fluid retention in this population. In addition, in studies 17 and 18, (the add on to metformin study and add on to metformin plus SU), patients with a history of metabolic acidosis were excluded.
Overall, the criteria for entering into the studies were reasonable to ensure comprehensive assessment of linagliptin as monotherapy and as add on therapy for patients with T2DM. Data obtained from patients within the predetermined glycemic parameters can be reasonably applied to patients with HbA1c greater than 10 %. An important antidiabetic medication in the population with type 2 diabetes is insulin, but we have allowed applicants to assess the effects of their antidiabetic drugs in combination with insulin post-approval.

Randomization—Pivotal Studies

For all pivotal trials, randomization was stratified by the HbA1c value at the beginning of the placebo run-in period (<8.5% versus ≥8.5%). Randomization was also stratified by the number of oral antidiabetic drugs at the time of screening, except for study 18, which enrolled only patients with 2 prior OADs (metformin and SU).

Monotherapy

Study 1218.16—A Pivotal Study
A randomized, double-blind, placebo-controlled parallel group efficacy and safety study of linagliptin (5 mg administered orally once daily) over 24 weeks, in drug naïve or previously treated (6 weeks washout) type 2 diabetic patients with insufficient glycemic control

Study 1218.50
A randomized, double-blind, placebo-controlled, parallel group efficacy and safety study of linagliptin (5 mg), administered orally once daily for 18 weeks followed by a 34 week double-blind extension period (placebo patients switched to glimepiride) in type 2 diabetic patients with insufficient glycemic control for whom metformin therapy is inappropriate (intolerability or contraindication)

General Overview and Study Design—Monotherapy

Two studies support the monotherapy claim for linagliptin for T2DM. One is an 18-week study, 1218.50 (referred to as study 50), that was conducted on patients ineligible for metformin. The other study to support monotherapy is included in the *Pivotal Studies* analysis described in this review of efficacy. This study, study 16, was a 24 week study comparing 5 mg linagliptin to placebo treatment. Please refer to my Pivotal Studies discussion and analysis for information pertaining to this study.

Part One of study 50 tested linagliptin versus placebo over 18 weeks of treatment; the second study part had a treatment duration of 34 weeks. In Part Two, patients who received linagliptin in the first study part stayed on linagliptin, whereas those who received placebo in the first study part were switched to an SU (glimepiride). An interim data cut-off was performed to include the results from the Part One (including the analysis of the primary endpoint of the trial) in the submission; these are the data that I reviewed and are included in proposed labeling.

Part One of the study was a randomized, double-blind, placebo-controlled comparison of two groups for 18 weeks. Patients pre-treated with one OAD underwent a washout period of 6 weeks that included a placebo run-in period during the last two weeks of the washout period; patients not previously treated with an additional OAD agent performed a two- week placebo run-in period only. Part Two (not further discussed beyond this section) is the follow on double blind, active controlled, parallel group comparison of two groups (patients previously treated with placebo switch to glimepiride in a blinded fashion). See Figure 9.

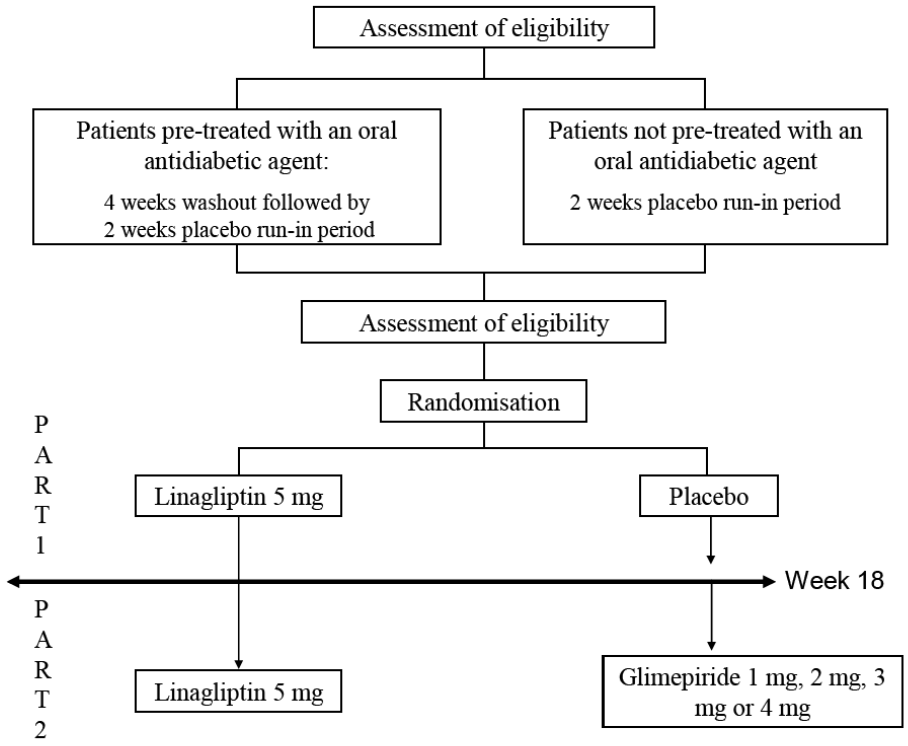

Figure 9 Study Design—Study 50
Source (b) (4) Study 1218.50, Figure 9.2: 1, page 35

Objectives—Monotherapy

The objective of this trial was to investigate the efficacy, safety and tolerability of linagliptin compared to placebo given over 18 weeks in patients for whom metformin therapy is inappropriate (intolerability, contraindication).

Endpoints—Monotherapy

The primary endpoint for the trial was the change from baseline in HbA1c after 18 weeks of treatment.

Randomization--Monotherapy

Randomization was stratified by HbA1c at Visit 2 (<8.5% versus ≥8.5%), the previous use of OADs (none, monotherapy) and reason for metformin ineligibility (gastrointestinal side effects or high serum creatinine levels).

Eligibility Criteria—Monotherapy

Inclusion Criteria

• Male and female patients with a diagnosis of T2DM, either treatment naïve (defined as either patients who had never received treatment) or patients previously on treatment who had not received antidiabetic medication (not more than one OAD) for at least 10 weeks prior to screening).
• Diagnosis of T2DM prior to informed consent.
• HbA1c at screening (Visit 1a):
    - For patients who required wash out of previous medication: HbA1c ≥6.5 and ≤9.0%
    - For patients not requiring wash out of previous medication: HbA1c ≥7.0 and ≤10.0% (HbA1c ≥7.0 and ≤9.0% in Canada; amendment made per Health Canada's request)
• HbA1c at start of run-in (Visit 2): HbA1c ≥7.0 and ≤10.0% (HbA1c ≥7.0 and ≤9.0% in Canada amendment made per Health Canada's request)
• Age at screening (Visit 1a) 18 – 80 years
• BMI at screening (Visit 1a) ≤40 kg/m^2
• Patients ineligible for metformin therapy due to contraindication according to the drug label for example:
    - Renal disease or renal dysfunction (as specified by the product information of locally approved metformin)
    - Dehydration by clinical judgment of the investigator
    - Unstable or acute congestive heart failure
    - Acute or chronic metabolic acidosis
    - Hereditary galactose intolerance
• Patients ineligible for metformin therapy due to intolerable side effects attributed to metformin for example:
    - Nausea or vomiting
    - Diarrhea
    - Intestinal gas
    - Severe abdominal discomfort

Exclusion Criteria

• MI, stroke, or TIA within six months prior to the date of informed consent
• Treatment with rosiglitazone, pioglitazone, GLP-1 analogues, insulin, or anti-obesity drugs (e.g. sibutramine, rimonabant, orlistat) within three months prior to the date of informed consent
• Impaired hepatic function, defined by serum levels of either AST, ALT or ALP above 3x ULN as determined at screening

• Severe renal impairment eGFR≤30 mL/min, calculated using MDRD formula, as determined at Visit 1a (screening)
• Treatment with systemic steroids at time of informed consent or change in dosage of thyroid hormones within six weeks prior to informed consent
• Pre-menopausal women who were not practicing an acceptable method of birth control
• Alcohol or drug abuse within three months prior to the date of informed consent

Reviewer's Comments
Study design, endpoints and eligibility criteria are appropriate for this study. The study randomization was appropriately stratified for HbA1c and metformin intolerance / ineligibility to allow better interpretability of the results. Eligibility criteria are again appropriately limited in part by metformin labeling. The upper limit of HbA1c should not change applicability of the data for patients with higher HbA1c.

Combination Therapy

Study 1218.15—a pivotal study
A randomized, double-blind, placebo controlled, parallel group, 24-week study to assess the efficacy and safety of linagliptin (5 mg) in combination with 30 mg pioglitazone (both administered orally once daily), compared to 30 mg pioglitazone plus placebo in drug-naïve or previously treated type 2 diabetic patients with insufficient glycemic control

Study 1218.17—a pivotal study
A randomized, double-blind, placebo-controlled parallel group efficacy and safety study of BI 1356 (5 mg administered orally once daily) over 24 weeks in type 2 diabetic patients with insufficient glycemic control despite metformin therapy

Study 1218.18—a pivotal study
A randomized, double-blind, placebo-controlled parallel group efficacy and safety study of BI 1356 (5 mg) administered orally once daily over 24 weeks in type 2 diabetic patients with insufficient glycemic control despite a therapy of metformin in combination with a sulfonylurea

Study 1218.20
A randomized, double-blind, active-controlled parallel group efficacy and safety study of linagliptin (5 mg, administered orally once daily) compared to glimepiride (1 to 4 mg once daily) over two years, in type 2 diabetic patients with insufficient glycemic control despite metformin therapy

Study 1218.35
A randomized, double-blind, placebo-controlled parallel group efficacy and safety study of linagliptin (5 mg administered orally once daily) over 18 weeks in Type 2 diabetic

patients with insufficient glycemic control (HbA1c 7.0-10%) despite background therapy with a sulfonylurea drug

A total of five studies in the label are cited to support the combination therapy indication. The first three studies to support the combination therapy claim are reviewed in the discussion of the pivotal studies. Study 15, where linagliptin was used with pioglitazone, study 17, where linagliptin was an add on to metformin therapy, and study 18 where linagliptin was add on to metformin plus SU, are all studies to support this and are also part of the Pivotal Studies analysis. The studies that will be discussed in this section are study 1218.20 (referred to from here as study 20), the active controlled study, and study 1218.35 (35), an 18 week add on to SU study.

General Overview and Study Design—Combination Therapy

Study 20—Active Control Study

Study 20 was a randomized, double-blind, double-dummy (each patient received an active treatment and a placebo matching the alternative treatment), active-controlled, parallel group comparison of two groups over 104 weeks. Before randomization in study 20, patients pre-treated with one additional OAD in addition to metformin underwent a washout period of 6 weeks followed by an open-label placebo run-in period of two weeks. Patients previously treated with metformin only underwent a two-week placebo run-in period. Background medication (metformin—unchanged for 10 weeks prior to informed consent/screening) was taken during the entire trial duration (including the washout and placebo run-in periods) in an unchanged dosage. See Figure 10.

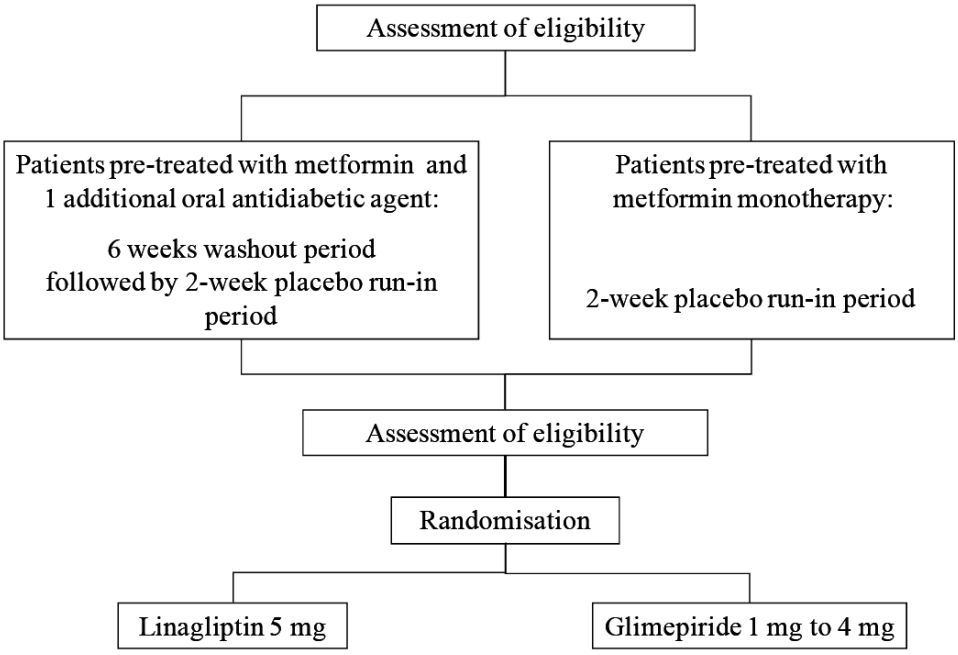

Figure 10 Study Design—Study 20
Source (b) (4) Figure 9.2: 1, page 37

Study 35—Add on to SU Study

Study 35 was a randomized, double-blind, and placebo controlled, parallel group study comparing linagliptin (5 mg) to placebo as add on therapy to the patients' anti-diabetic sulfonylurea drug over an 18-week treatment period. There was a four-week washout period followed by a two-week open-label placebo run-in period, for patients pretreated with one OAD agent in addition to a SU drug. For patients that were only pretreated with SU monotherapy, there was only a two week placebo run-in period. The treatment was 18 weeks and double-blinded and followed by one-week follow-up after study drug termination. The patients' SU drug, dose unchanged, was administered during the entire trial. See Figure 11.

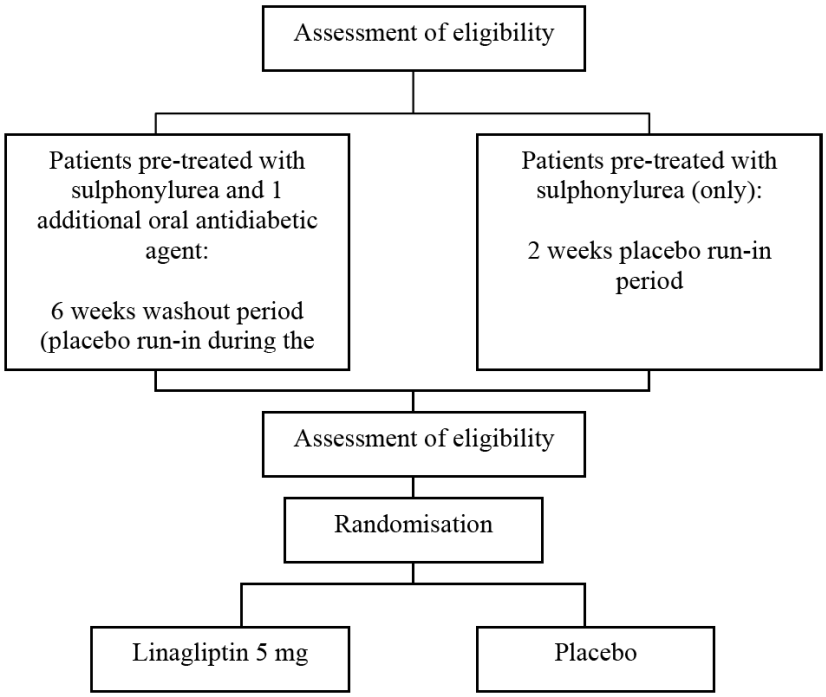

Figure 11 Study Design—Study 35
Source (b) (4) Figure 9.2: 1, page 39

Objectives—Combination Therapy

Study 20—Active Control Study

The objective of study 20 was to investigate the efficacy, safety and tolerability of linagliptin 5 mg versus glimepiride (1 mg to 4 mg) administered for 104 weeks as add-on therapy to metformin in patients with T2DM and insufficient glycemic control. The objective of the interim analysis (presented in this review) was to investigate the efficacy, safety and tolerability of linagliptin versus glimepiride over 52 weeks. The applicant planned to show non-inferiority of linagliptin to glimepiride.

Study 35—Add on to SU study

The objective of study 35 was to compare the efficacy, safety and tolerability of linagliptin (5 mg once daily) to placebo given for 18 weeks as add-on therapy to a treatment with an SU in T2DM patients with insufficient glycemic control.

Endpoints—Combination Therapy

The primary endpoint for the interim analysis was the change in HbA1c from baseline after 52 weeks of treatment in study 20, and after 18 weeks of treatment in study 35. The term 'baseline' refers to the last observation prior to the start of randomized study treatment.

Randomization—Combination Therapy

For both study 20 and study 35 randomization was stratified by HbA1c (<8.5% versus ≥8.5%) as determined from the blood sample taken at the beginning of the placebo run-in period, and the previous use of antidiabetic drugs.

Reviewer's Comments
The study design for study 20 allows only up to 4 mg of glimepiride as the active comparator. Glimepiride can be dosed up to 8 mg. This is not addressed in the NDA. On inquiry, the applicant provides the rationale that 4 mg is the most commonly administered dose worldwide. They also argue that the benefits of doses higher than 4 mg are not clear, citing a study with FPG results. Furthermore, they state that there was concern of weight gain and hypoglycemia that may result from higher doses.
This rationale is reasonable for the dose choice. However, the data reviewed will be considered in light of the less than maximal dose of glimepiride.
I reviewed the end of phase 2 (EOP2) minutes and have seen that the non-inferiority margin for the between-groups difference in LS mean HbA1c was agreed to be 0.35%.

This study supports the proposed label request of combination therapy because it is an add on to metformin study. It also offers a chance to examine controlled long term data at 52 weeks of linagliptin therapy. There are two pivotal studies that also support this, studies 17 and 18 (both 24 week studies), and one additional 18 week study described in this section, study 35.
Study 35 is also reasonable in design. This study is similar in design to those in the Pivotal Studies. It is very similar to study 18, the add on to metformin and SU study. The difference is that it is an 18 week study versus 24 weeks, and also it is *add on to SU only.*

Eligibility Criteria—Combination Therapy

Study 20—Active Control Study

Inclusion criteria

• Male and female patients with T2DM and previously treated with metformin monotherapy or metformin plus not more than one other OAD. Antidiabetic therapy had to be unchanged for 10 weeks prior to the date of informed consent. Patients had to be on a stable daily dose of ≥1500 mg metformin or ≤1500 mg metformin only if the investigator considered this was the patients' maximum tolerated dose of metformin. The dose of metformin had to remain unchanged during the course of this trial.
• **HbA1c at screening** (Visit 1a):
• Patients undergoing washout of previous antidiabetic medication:
6.0%≤HbA1c ≤9.0% (for patients in the Netherlands: 6.5%≤ HbA1c ≤8.5%)
• Patients not undergoing washout of previous antidiabetic medication:
6.5%≤HbA1c ≤10.0% (for patients in the Netherlands: 6.5%≤ HbA1c ≤8.5%)
• **HbA1c at start of run-in** (Visit 2): 6.5%≤ HbA1c ≤10.0%
• Age at screening (Visit 1a): ≥18 years, ≤80 years
• Body mass index (BMI) at screening (Visit 1a) ≤40 kg/m^2 (for patients in the Netherlands: 25 kg/m^2≤BMI ≤40 kg/m^2)
.

Exclusion criteria

• MI, stroke, or TIA within 6 months prior to the date of informed consent
• Impaired hepatic function, defined as serum levels of either ALT, AST, or ALP above 3x the ULN
• Treatment with rosiglitazone, pioglitazone, GLP-1 analogues/agonists, insulin, or anti-obesity drugs (e.g. sibutramine, rimonabant, orlistat) within 3 months prior to the date of informed consent
• Treatment with systemic steroids at the date of informed consent or change in dosage of thyroid hormones within 6 weeks prior to the date of informed consent
• Alcohol or drug abuse within 3 months prior to the date of informed consent
• Pre-menopausal who were not practicing an acceptable method of birth control

• Renal failure or renal impairment (serum creatinine >1.5 mg/dL as determined before randomization)
• The following exclusion criterion applied for patients in France only:
    • Renal failure or renal impairment: calculated creatinine clearance (calculated using Cockcroft-Gault Formula) < 60 mL/min as determined before randomization).

Study 35—Add on to SU Study

Inclusion Criteria

- Male and female patients with T2DM and previously treated with an SU drug alone and with not more than one other anti-diabetic drug
- Previous anti-diabetic therapy has to be unchanged for 10 weeks prior to informed consent SU dose of at least one-half the maximum dose (or less if documented as maximum tolerated dose of at least 12 weeks)
- **HbA1C at Visit 1a (Screening):**
- For patients undergoing washout of previous medication:
    - HbA1C ≥7.0 to ≤9.0%
- For patients not undergoing washout of previous medication:
    - HbA1C ≥7.5 to ≤10.0%
- HbA1C ≥7.5 to ≤10 % at Visit 2 **(Start of Run-in)**
- Age >18 and <80 years at Visit 1a (Screening)
- BMI (body mass index) ≤40 kg/m^2 at Visit 1a (Screening)

Exclusion Criteria

- Myocardial infarction, stroke or TIA within 6 months prior to informed consent
- Impaired hepatic function, defined by serum levels of either ALT, AST, or alkaline phosphatase above 3x ULN, or elevated total bilirubin above 3x ULN
- Known hypersensitivity or allergy to the investigational product or its excipients or the patients' SU drug or placebo
- Treatment with TZDs within 3 months prior to informed consent
- Treatment with an injectable GLP-1 analogue (e.g., exenatide) within 3 months prior to informed consent
- Chronic daily treatment with insulin within 3 months prior to informed consent
- Treatment with anti-obesity drugs (e.g., sibutramine, orlistat, rimonabant) within 3 months prior to informed consent
- Alcohol abuse or drug abuse within the 3 months prior to informed consent
- Participation in another trial with an investigational drug within 2 months prior to informed consent

- Pre-menopausal women or women of child-bearing potential not practicing an acceptable method of birth control
- Current treatment with systemic steroids at time of informed consent or change in dosage of thyroid hormones within 6 weeks prior to informed consent
- Renal failure or renal impairment (calculated GFR <30 mL/min as determined at Visit 1a/screening visit)
- Unstable or acute congestive heart failure
- Hereditary galactose intolerance
- The following in Argentina only
    - Symptoms of uncontrolled hyperglycemia
    - Patient with acute (less than 6 months), recent or unstable target organ damage must be excluded
    - Clinical history of acute diabetes complications within 12 months

Reviewer's Comments
As discussed, study 35 is similar to study 18 (pivotal study designed to be a 24 week add on to metformin and SU). In this case, add on therapy is with an SU only and treatment is for 18 weeks, not 24. The eligibility criteria are similar for both studies and appropriate for the study design and objective.

Trials with Long Term Treatment

Study 1218.20—Active Control Study

A randomized, double-blind, active-controlled parallel group efficacy and safety study of linagliptin (5 mg, administered orally once daily) compared to glimepiride (1 to 4 mg once daily) over two years, in type 2 diabetic patients with insufficient glycemic control despite metformin therapy

Study 1218.40
A 78 week open-label extension trials assessing the safety and efficacy of linagliptin (5 mg) as monotherapy or in combination with other antidiabetic medications in type 2 diabetic patients

Study 1218.23
A double-blind phase III study to evaluate the efficacy of linagliptin 5 mg and 10 mg versus placebo for 12 weeks and versus voglibose 0.6 mg for 26 weeks in patients with type 2 diabetes mellitus and insufficient glycemic control, followed by an extension study to 52 weeks to evaluate long-term safety

Study 20, (glimepiride active control study) discussed in the *Combination Therapy* section due to the add on metformin design and placement in the label, was presented with data to 52 weeks. Please refer to this section for discussion of this trial. Study 1218.40 (referred to from this point as study 40), is the long term extension of the

pivotal studies, 15, 16, 17 and 18. The 42 week data was submitted by the applicant and will be discussed in this section of the review.

Of note, voglibose is an alpha-glucosidase inhibitor marketed and approved in Japan.

General Overview and Study Design—Long Term Treatment

Study 40—Long Term Extension Study

The patients enrolled in the Pivotal Studies were included in this trial. They continued their treatment from the preceding trial (study 15—pioglitazone, study 17—metformin, study 18—metformin plus SU). The exception was that patients that had been receiving placebo were switched to linagliptin 5 mg. Therefore, there was no continuing treatment in study 15 (which had been linagliptin versus placebo only) other than linagliptin. This trial was open label.

Study 23—Active Control with Voglibose

This trial consisted of three phases including a four-week observation phase, a 26-week double-blind treatment phase (of which the first stage was 12 weeks and the second stage was 14 weeks), and in addition, a 26-week extension treatment phase.

During the observation phase, any previous OAD was washed out and during the latter two weeks and placebo was administered (run-in). During the first stage of the 26 week double-blind treatment phase, the efficacy of linagliptin 5 mg and 10 mg are compared to placebo. At 12 weeks, the placebo patients were switched to either 5 mg or 10 mg of linagliptin. Fourteen weeks later at the end of the second stage, the efficacy of linagliptin 5 mg or 10 mg was compared to voglibose 0.6 mg (0.2 mg three times daily).

The extension treatment phase was 26 weeks. The long-term safety of linagliptin 5 mg and 10 mg was evaluated in the total 52 week treatment period. Patients that had received voglibose for 26 weeks were switched to linagliptin 5 mg or 10 mg for the 26 week extension. The study design is shown in Figure 12.

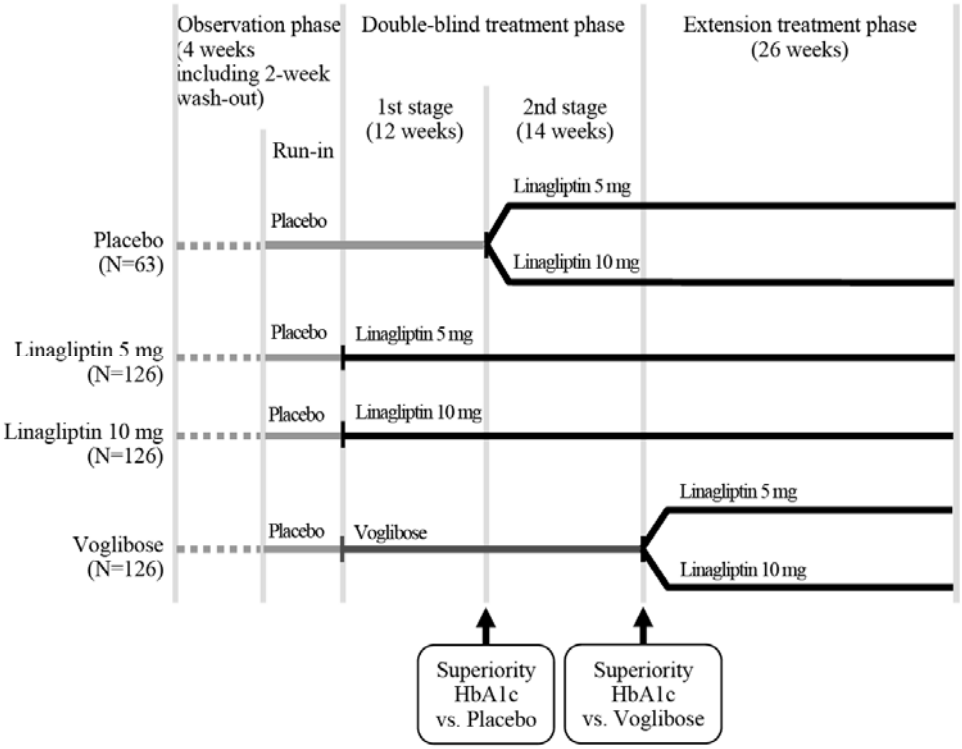

Figure 12 Study Design—Study 23
Source (b) (4) Table 9.1: 1, page 60

Reviewer's Comments
The only trial here that will be presented in detail for long term efficacy data is study 20 as the long term extensions of both study 23 and study 40 are not controlled. Furthermore, voglibose is not marketed in the U.S.
As discussed, study 20 is presented in the *Combination Therapy* section.

Objectives—Long Term Treatment

Study 40—Long Term Extension Study

This was a study designed by the applicant to show efficacy, safety and tolerability of 5 mg linagliptin administered for 78 weeks. This review will present the 42 week data submitted by the applicant.

Study 23—Active Control with Voglibose

The objective of this trial was to investigate the efficacy, safety, and tolerability of linagliptin (5 mg or 10 mg once daily) compared with placebo given for 12 weeks and

voglibose for 26 weeks as monotherapy in patients with T2DM with insufficient glycemic control. Long-term safety was evaluated with the extension treatment to 52 weeks.

Endpoints—Long Term Treatment

Study 40—Long Term Extension Study

Primary endpoints listed by the applicant were safety endpoints. These will be discussed in the *Review of Safety*. The applicable endpoint here for efficacy is HbA1c change over time, including at 42 weeks. This will be presented in the Secondary Endpoints discussion below.

Reviewer's Comments
This extension study was not designed to examine long term efficacy as a primary endpoint. Therefore, the long term efficacy data reviewed and presented is not of the same value as that from study 20, which was controlled and designed with HbA1c as the primary endpoint. This is more of an exploratory presentation.

Study 23—Active Control with Voglibose

At 12 weeks of treatment, the primary endpoint was the change in HbA1c from baseline in 5 mg or 10 mg of linagliptin treatment compared to placebo. Also considered a primary endpoint was superiority of linagliptin to voglibose at 26 weeks of treatment. The change in HbA1c from baseline was the primary variable to compare the efficacy of linagliptin (5 mg or 10 mg) with that of the active control, voglibose 0.6 mg (0.2 mg three times daily). The HbA1c response at 52 weeks is listed as a secondary endpoint.

Reviewer's Comments
The design of this study has limited usefulness for the purposes of this review. Therefore, this study will only be discussed in relevant parts of this review. The 12 week data for linagliptin will be only briefly discussed as studies with longer treatment duration (18 and 24 weeks) as well as treatment responses over time are both discussed extensively in this review. The 52 week HbA1c data (a secondary endpoint) will be described briefly in an exploratory manner.

Randomization—Long Term Treatment

Study 40—Long Term Extension Study

Not applicable. This was determined at the time of entry into the Pivotal Studies. All patients in this study were on linagliptin per the study design.

Study 23—Active Control with Voglibose

Randomization was stratified by HbA1c, gender and number of previous OADs.

Eligibility Criteria—Long Term Treatment

Study 40—Long Term Extension Study

This was based on successful completion of one of four of the pivotal studies. They were eligible for entry in spite of rescue medication treatment as long as they had completed the entire double-blinded study treatment. Patients that withdrew during the treatment period in the pivotal studies, were not eligible.

Study 23—Active Control with Voglibose

Generally, T2DM Japanese patients treated with none, one or two oral OAD(s) other than glitazones were eligible. HbA1c requirements were 7.0% to 10.0% for patients not treated with OADs at Visit 1. The criteria were 7.0% to 9.0% for patients treated with one or two OADs**.**

6.1.2 Demographics

Pivotal Studies

A total of 4508 patients were enrolled into one of the four pivotal studies. In the FAS, 58.8% of the screened patients were randomized to receive either linagliptin (42.4% of those screened) or placebo (16.4% of those screened), according to treatment allocation ratios (linagliptin:placebo) of 2:1 in studies 15 and 16 and of 3:1 in studies 17 and 18.

As summarized in Table 5, about half of the patients (51.2%) were male. The mean age was about 57 years, and the mean BMI was 29 kg/m^2. Overall, 59.9% of patients were white, 39.5% were Asian, and 0.6% were black. There was a preponderance of white patients and Asians were the second most prevalent group. White patients were studied predominantly in European countries. The percentage of male patients was highest in study 15 (61.1%) and lowest in study 18 (47.2%). Overall, there were similar numbers of males and females in the studies.

Table 5 Demographics in the Four Pivotal 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 (b) (4) Table 3.1.2.1, page 51

The total number of Hispanic patients in the pivotal studies was 407. In the placebo arms there were 104 Hispanic patients, which is 14% of the study population. 304 Hispanic patients were treated with linagliptin (16.2%) and a total of 15.6% of the study population, FAS, was Hispanic.

Reviewer's Comments

The number of Hispanic patients is appropriate for U.S. T2DM population representation. Yet, very few patients in the pivotal studies were African American, which is not a proportion representative of the U.S. T2DM population. Most of the study sites were European and Asian which could be contributing to this issue. However, upon review of study sites, there appear to be sufficient U.S. sites for the studies, so this cannot fully explain the issue. This raises concern for efficacy in this racial group. However, the PK data from the study in African American patients is reassuring, please see *Section 4.4 PK Studies* for more details. Safety in this population will be addressed in the *Review of Safety*. Demographics and analysis of patients by renal function/impairment are described in *Section 6.1.7 Subpopulations.*

The patients in the pivotal trials had a mean HbA1c value of 8.2% and a mean baseline FPG value of 168.0 mg/dL. Overall, 14.6% of patients had been diagnosed with diabetes within one year, 30.6% had received this diagnosis one to five years ago, and 54.8% had been diagnosed more than five years ago. The four individual studies differed in their HbA1c inclusion criteria (see *Methods*). Yet, mean baseline HbA1c values are similar for all the studies.

While studies 17 (add on to metformin) and 18 (add on to metformin and SU) did not recruit drug-naïve patients, 49.7% of patients in study 15 and 56.3% of patients in study 16 had not taken any prior antidiabetic medication. All studies except study 18 recruited patients who had been pre-treated with one OAD. This is reflected in the proportion of patients who had been diagnosed with diabetes for more than five years being highest in study 18 (73.3%).

The baseline characteristics of patients in the pivotal studies were similar in the linagliptin and placebo groups. However, when the data from the four studies are combined, the percentage of patients without prior use of OADs was 16.5% for linagliptin and 21.7% for placebo. In addition, 52.7% of patients were on two or more OADs in the linagliptin study group and this was the case for 46.6% of placebo of patients.

Table 6 Baseline Disease Characteristics in the Pivotal Trials—FAS

Study/ treatment group	Number of patients	Baseline HbA_{1c}, mean (SD) [%]	Baseline FPG, mean (SD) [mg/dL]	Time since diagnosis of diabetes, N (%)	Number of antidiabetic drugs at enrolment, N (%)		
				>5 years	None	One	Two or more
1218.15/							
Placebo	128	8.6 (0.9)	190.3 (43.8)	54 (42.2)	65 (50.8)	40 (31.3)	23 (18.0)
Linagliptin	252	8.6 (0.8)	189.8 (42.7)	107 (42.5)	124 (49.2)	80 (31.7)	48 (19.0)
1218.16/							
Placebo	163	8.0 (0.9)	168.7 (39.3)	41 (25.2)	93 (57.1)	70 (42.9)	0 (0.0)
Linagliptin	333	8.0 (0.9)	164.7 (41.9)	84 (25.2)	186 (55.9)	147 (44.1)	0 (0.0)
1218.17/							
Placebo	175	8.0 (0.9)	166.4 (41.9)	93 (53.1)	0 (0.0)	121 (69.1)	54 (30.9)
Linagliptin	513	8.1 (0.9)	169.6 (43.5)	285 (55.6)	0 (0.0)	351 (68.4)	162 (31.6)
1218.18/							
Placebo	262	8.1 (0.8)	162.6 (37.1)	193 (73.7)	0 (0.0)	0 (0.0)	262 (100.0)
Linagliptin	778	8.1 (0.8)	159.3 (36.5)	569 (73.1)	0 (0.0)	0 (0.0)	778 (100.0)
EFF-1 pool/							
Placebo	728	8.2 (0.9)	169.9 (41.1)	381 (52.3)	158 (21.7)	231 (31.7)	339 (46.6)
Linagliptin	1876	8.2 (0.8)	167.3 (41.5)	1045 (55.7)	310 (16.5)	578 (30.8)	988 (52.7)

Source (b) (4) Table 3.1.2.2: 1, page 58

Reviewer's Comments
Baseline HbA1c in study 15 is notably higher than others in the group. This study had a washout of all therapies and pioglitazone was started as a new therapy. The inclusion criterion was 0.5% higher HbA1c than the three other studies; this is not surprising, in view of the study design: all subjects in the trial were to receive new active treatment (pioglitazone alone or pioglitazone and linagliptin).

Monotherapy

Study 50—Nonpivotal Placebo-only Arm Study

More than 60% of the population treated were female (61.2%) and the majority of patients were white (69.2%), with Asians comprising 27.8% of treated patients. There were few patients in other racial categories. The distribution of both race and ethnic origin was similar between treatment groups.

In the treated set, the mean age at enrollment was 56.5 years, and was comparable between treatment groups. Age and mean BMI were similar between groups. There were more patients with BMI <25 in the placebo group (14.5%) than in the linagliptin

group (27.8%). Overall, fewer than 10% of patients met the criteria for classification as moderate or severe/end stage renal impairment using either eGFR (MDRD classification) or Cockcroft-Gault classification. See Table 7.

Table 7 Demographics—Study 50, Treated Set

	Placebo	Linagliptin	Total
Number of patients, N(%)	76 (100.0)	151 (100.0)	227 (100.0)
Gender, N(%)			
Male	33 (43.4)	55 (36.4)	88 (38.8)
Female	43 (56.6)	96 (63.6)	139 (61.2)
Race, N (%)			
American Indian or Alaska Native	1 (1.3)	0 (0.0)	1 (0.4)
Asian	21 (27.6)	42 (27.8)	63 (27.8)
Black or African American	3 (3.9)	2 (1.3)	5 (2.2)
Native Hawaiian or other Pacific Islander	0 (0.0)	1 (0.7)	1 (0.4)
White	51 (67.1)	106 (70.2)	157 (69.2)
Ethnicity – hispanic / latino , N(%)			
Not hispanic / latino	62 (81.6)	120 (79.5)	182 (80.2)
Hispanic / latino	14 (18.4)	31 (20.5)	45 (19.8)
Age [years]			
Mean (SD)	56.7 (9.7)	56.4 (10.6)	56.5 (10.3)
Age groups [years], N(%)			
<65	54 (71.1)	115 (76.2)	169 (74.4)
65 to 74	20 (26.3)	31 (20.5)	51 (22.5)
≥75	2 (2.6)	5 (3.3)	7 (3.1)
Baseline weight [kg]			
Mean (SD)	80.9 (19.1)	77.0 (18.8)	78.3 (18.9)
Baseline weight, categorical [kg], N(%)			
≤70	23 (30.3)	53 (35.1)	76 (33.5)
>70 to ≤80	14 (18.4)	36 (23.8)	50 (22.0)
>80 to ≤90	18 (23.7)	25 (16.6)	43 (18.9)
>90	21 (27.6)	37 (24.5)	58 (25.6)
Baseline BMI [kg/m^2]			
Mean (SD)	30.19 (4.97)	29.09 (5.62)	29.46 (5.42)
Baseline BMI, categorical [kg/m^2], N(%)			
<25	11 (14.5)	42 (27.8)	53 (23.3)
25-<30	28 (36.8)	48 (31.8)	76 (33.5)
≥30	37 (48.7)	61 (40.4)	98 (43.2)
Baseline eGFR [mL/min]			
≥90	46 (60.5)	81 (53.6)	127 (55.9)
60 to <90	24 (31.6)	54 (35.8)	78 (34.4)
30 to <60	6 (7.9)	15 (9.9)	21 (9.3)
<30	0 (0.0)	1 (0.7)	1 (0.4)
Baseline eCCR [mL/min]			
>80	61 (80.3)	108 (71.5)	169 (74.4)
50 to 80	10 (13.2)	27 (17.9)	37 (16.3)
30 to <50	5 (6.6)	14 (9.3)	19 (8.4)
<30	0 (0.0)	2 (1.3)	2 (0.9)

eCcr: estimated creatinine clearance
Source (b) (4) Study 50, Table 11.2:11, page 74

Reviewer's Comments
There are sufficient patients of Hispanic ethnicity (19.8%). Again, few patients are of African American origin. I reviewed sites for this study; there were more than 50 patients from U.S. sites; therefore, I would have expected more patients of this racial category. This issue is addressed in the PK study review section as well as in the *Review of Safety*.
While baseline BMI was similar between the two groups, the patients in the linagliptin arm are at some treatment advantage in that there are more patients (27.8% versus 14.5%) patients with lower BMI (<25 kg/m^2). In general, these patients would exhibit better glycemic control. Given the randomization ratio (Linagliptin: Placebo—2: 1, and the smaller size of this trial), I am not concerned, however, that the overall results will be affected by this BMI imbalance. BMI as a subgroup will be discussed further in the 6.1.7.2 *Subgroups* section.

There are seven more patients in the treated set than the FAS. This was due to lack of baseline or on treatment HbA1c value. The overall mean baseline HbA1c was 8.1%, which was similar between both treatment groups. The percentage of patients in each of the four HbA1c categories was comparable between groups. A total of 16 patients (7.3%) had a baseline HbA1c below 7.0%. Note that this is below the limit used for the relevant inclusion criterion at Visit 2; this is because the values immediately prior to randomization were used for this summary. The overall mean FPG at baseline was 182.4 mg/dL, which was similar between the treatment groups. The percentage of patients in each of the four FPG categories was comparable between groups. See Table 8.

Table 8 Baseline Disease Characteristics —Study 50, FAS

	Placebo	Linagliptin	Total
Number of patients	73	147	220
Baseline HbA_{1c} [%]			
Mean (SD)	8.06 (0.89)	8.11 (0.95)	8.09 (0.93)
Baseline HbA_{1c}, categorical, N(%)			
<7.0%	5 (6.8)	11 (7.5)	16 (7.3)
7.0% to <8.0%	31 (42.5)	60 (40.8)	91 (41.4)
8.0% to <9.0%	26 (35.6)	52 (35.4)	78 (35.5)
≥9.0%	11 (15.1)	24 (16.3)	35 (15.9)
Baseline FPG [mg/dL]			
Mean (SD)	180.5 (44.7)	183.3 (46.4)	182.4 (45.8)
Number of prior anti-diabetes drugs, N(%)			
0	38 (52.1)	81 (55.1)	119 (54.1)
1	34 (46.6)	63 (42.9)	97 (44.1)
≥2	1 (1.4)	3 (2.0)	4 (1.8)

Source (b) (4) Study 50, Table 11.2: 4, page 77

Reviewer's Comments
Patients from both arms were similar in baseline disease characteristics.

Combination Therapy

Study 20—Active Control Study

In study 20, the study population contained slightly more male patients (60.2%), but this difference was consistent between the two treatment groups. The majority of patients were white (84.6%) and the mean age was 59.7 years. Patients in the glimepiride group tended to have more underlying conditions than patients in the linagliptin group. For example, a higher incidence of underlying cardiac disorders (16.6% linagliptin; 19.5% glimepiride) was seen in the glimepiride group. The majority of patients had either normal renal function eGFR based on MDRD staging ≥90 mL/min; 47.9%) or mild renal impairment (eGFR 60 to <90 mL/min; 45.0%). There were no patients with severe renal impairment (eGFR <30 mL/min), however, metformin is contraindicated in patients with moderate and severe renal disease. Demographics are summarized in Table 9.

Table 9 Baseline Demographics—Study 20, Treated Set

	Linagliptin	Glimepiride	Total
Number of patients, N (%)	778 (100.0)	781 (100.0)	1559 (100.0)
Gender, N (%)			
Male	462 (59.4)	477 (61.1)	939 (60.2)
Female	316 (40.6)	304 (38.9)	620 (39.8)
Race, N (%)			
White	660 (84.8)	659 (84.4)	1319 (84.6)
Asian	96 (12.3)	102 (13.1)	198 (12.7)
Black or African American	20 (2.6)	18 (2.3)	38 (2.4)
American Indian or Alaska Native	1 (0.1)	1 (0.1)	2 (0.1)
Native Hawaiian or other Pacific Islander	1 (0.1)	1 (0.1)	2 (0.1)
Ethnicity, N (%)			
Not Hispanic/Latino	756 (97.2)	761 (97.4)	1517 (97.3)
Hispanic/Latino	21 (2.7)	19 (2.4)	40 (2.6)
Missing	1 (0.1)	1 (0.1)	2 (0.1)
Age [years]			
Mean (SD)	59.7 (9.4)	59.7 (9.4)	59.7 (9.4)
Categorical age groups [years], N (%)			
<65	527 (67.7)	526 (67.3)	1053 (67.5)
65 to 74	216 (27.8)	224 (28.7)	440 (28.2)
≥75	35 (4.5)	31 (4.0)	66 (4.2)
Baseline weight [kg]			
Mean (SD)	86.10 (17.41)	86.73 (16.66)	86.42 (17.04)
Baseline weight, categorical [kg], N (%)			
≤70	151 (19.4)	132 (16.9)	283 (18.2)
>70 to ≤80	148 (19.0)	148 (19.0)	296 (19.0)
>80 to ≤90	174 (22.4)	186 (23.8)	360 (23.1)
>90	305 (39.2)	315 (40.3)	620 (39.8)
Baseline BMI [kg/m^2]			
Mean (SD)	30.21 (4.74)	30.31 (4.56)	30.26 (4.65)
Baseline BMI, categorical [kg/m^2], N (%)			
<25	106 (13.6)	93 (11.9)	199 (12.8)
25 to <30	290 (37.3)	281 (36.0)	571 (36.6)
≥30	382 (49.1)	407 (52.1)	789 (50.6)
Baseline eGFR according to MDRD [mL/min], N (%)			
≥90 (normal renal function)	385 (49.5)	361 (46.2)	746 (47.9)
60 to 89 (mild renal impairment)	341 (43.8)	361 (46.2)	702 (45.0)
30 to 59 (moderate renal impairment)	35 (4.5)	38 (4.9)	73 (4.7)
Missing	17 (2.2)	21 (2.7)	38 (2.4)

Source (b) (4) Table 11.2: 1, page 74

Reviewer's Comments

In this study, there are few patients of either black race or Hispanic ethnicity. This is not representative of the U.S. T2DM population. There are adequate patients of Hispanic background in the pivotal studies, which is reassuring, and the issue of African American race has also been addressed. Otherwise, patients are similar in baseline demographics for both arms of the study.

Disease characteristics for study 20 at baseline are summarized in Table 10. Baseline mean HbA1c percent values were identical in both treatment groups: 7.7% in the linagliptin group and 7.7% in the glimepiride group. The baseline mean FPG values were also comparable between the treatment groups with 164.3 mg/dL in the linagliptin group and 166.7 mg/dL in the glimepiride group.

Table 10 Baseline Disease characteristics —Study 20, FAS

	Linagliptin	Glimepiride	Total
Number of patients, N (%)	766 (100.0)	761 (100.0)	1527 (100.0)
Baseline HbA_{1c} [%]			
Mean (SD)	7.69 (0.88)	7.70 (0.87)	7.69 (0.87)
Baseline HbA_{1c}, categorical, N (%)			
<7.0%	174 (22.7)	162 (21.3)	336 (22.0)
7.0% to <8.0%	319 (41.6)	348 (45.7)	667 (43.7)
8.0% to <9.0%	203 (26.5)	176 (23.1)	379 (24.8)
≥9.0%	70 (9.1)	75 (9.9)	145 (9.5)
Baseline FPG [mg/dL]			
Mean (SD)	164.25 (42.99)	166.70 (42.52)	165.47 (42.76)
Number of prior antidiabetic drugs in addition to metformin, N (%)			
0	536 (70.0)	540 (71.0)	1076 (70.5)
1	229 (29.9)	220 (28.9)	449 (29.4)
2	1 (0.1)	1 (0.1)	2 (0.1)
Daily dose of metformin at randomisation[1], N (%)			
<1500 mg	58 (7.6)	45 (5.9)	103 (6.7)
>1500 mg	708 (92.4)	716 (94.1)	1424 (93.3)

[1] Based on FAS (LOCF) population

Source (b) (4) Table 11.2: 2, page 77

Reviewer's Comments

Patient groups from both arms are similar in disease characteristics.

Study 35—Add on to SU Study

In study 35, about half of the population was male (52.7%). There were more males in the placebo group (61.9%) than in the linagliptin group (47.8%). The patient population mostly consisted of Asian (48.6%), white (43.7%) and black patients (6.9%). 17.1% of the patients were of Hispanic / Latino origin. The mean age was similar in both groups. In the placebo group, there were more patients (58.3%) with normal renal function, fewer patients (32.1%) with mild renal impairment, and more patients (8.3%) with a baseline eGFR of 30 to <60 mL/min (moderate renal impairment) than in the linagliptin group (51.6, 41.6 and 4.3%, respectively). There was one patient in each group with severe renal impairment (eGFR <30 mL/min) at baseline. See Table 11.

Table 11 Baseline Demographics—Study 35, Treated Set

	Placebo	Linagliptin	Total
Number of patients, N (%)	84(100.0)	161(100.0)	245(100.0)
Gender, N (%)			
Male	52 (61.9)	77 (47.8)	129 (52.7)
Female	32 (38.1)	84 (52.2)	116 (47.3)
Race, N (%)			
American Indian/Alaska Native	1 (1.2)	1 (0.6)	2 (0.8)
Asian	43 (51.2)	76 (47.2)	119 (48.6)
Black/African American	6 (7.1)	11 (6.8)	17 (6.9)
White	34 (40.5)	73 (45.3)	107 (43.7)
Ethnicity, N (%)			
Not Hispanic/Latino	70 (83.3)	133 (82.6)	203 (82.9)
Hispanic/Latino	14 (16.7)	28 (17.4)	42 (17.1)
Age [years]			
Mean (SD)	56.2 (10.2)	57.2 (9.8)	56.9 (9.9)
Age groups [years], N (%)			
<65	70 (83.3)	120 (74.5)	190 (77.6)
65 to 74	11 (13.1)	38 (23.6)	49 (20.0)
≥75	3 (3.6)	3 (1.9)	6 (2.4)
Baseline weight [kg]			
Mean (SD)	76.08 (17.02)	74.5 (16.97)	75.04 (16.97)
Baseline weight, categorical [kg], N (%)			
≤70	38 (45.2)	74 (46.0)	112 (45.7)
>70 to 80	15 (17.9)	34 (21.1)	49 (20.0)
>80 to 90	12 (14.3)	22 (13.7)	34 (13.9)
>90	19 (22.6)	31 (19.3)	50 (20.4)
Baseline BMI [kg/m^2]			
Mean (SD)	28.21 (5.12)	28.4 (5.02)	28.33 (5.04)
Baseline BMI, categorical [kg/m^2], N (%)			
<25	23 (27.4)	46 (28.6)	69 (28.2)
25 to <30	33 (39.3)	60 (37.3)	93 (38.0)
≥30	28 (33.3)	55 (34.2)	83 (33.9)
Baseline eGFR (MDRD staging) [mL/min], N (%)			
≥90	49 (58.3)	83 (51.6)	132 (53.9)
60 to <90	27 (32.1)	67 (41.6)	94 (38.4)
30 to <60	7 (8.3)	7 (4.3)	14 (5.7)
<30	1 (1.2)	1 (0.6)	2 (0.8)

Source (b) (4), Table 11.2: 1, page 72

Reviewer's Comments

Study 35 was a smaller study than most others in this review, with only 245 patients in total. The proportion of different races represented the US diabetic

population better than in the other studies; around 7% of patients were of African-American background. This is still fewer than in the U.S. T2DM population, however. There is an imbalance in age group for this study, with more patients in the placebo arm being less than 65 years of age (83.3%) than the linagliptin arm (74.5%). Given the smaller size of this trial, this imbalance is not concerning as the age is more equally distributed in the overall dataset.

Baseline mean HbA1c percent values were the same between both treatment groups: 8.6%. A large proportion of patients had a baseline HbA1c between 8% to <9% with 42.7% in the placebo group and 44.3% in the linagliptin group. The baseline mean FPG values were also comparable between the treatment groups with 174.9 mg/dL in the placebo group and 182 mg/dL in the linagliptin group. In the placebo group, there were slightly less patients with a baseline FPG of 140 to <200 mg/dL (48.8%) or ≥ 200 mg/dL (28%) than in the linagliptin group (51.9% and 31%, respectively). Details are in Table 12.

Table 12 Baseline Disease Characteristics —Study 35, FAS

	Placebo	Linagliptin	Total
Baseline HbA_{1c} [%]			
Number of patients, N (%)	82 (100.0)	158 (100)	240 (100)
Mean (SD)	8.6 (0.72)	8.61 (0.85)	8.61 (0.81)
Baseline HbA_{1c} ,categorical, N (%)			
<7.0	0 (0.0)	2 (1.3)	2 (0.8)
7.0 to <8.0	18 (22.0)	30 (19.0)	48 (20.0)
8.0 to <9.0	35 (42.7)	70 (44.3)	105 (43.8)
≥9.0	29 (35.4)	56 (35.4)	85 (35.4)
Number of prior antidiabetic drugs, N (%)			
Number of patients, N (%)	82 (100.0)	158 (100)	240 (100)
1	55 (67.1)	102 (64.6)	157 (65.4)
2	27 (32.9)	56 (35.4)	83 (34.6)
Baseline FPG [mg/dL]			
Number of patients, N (%)	82 (100.0)	158 (100)	240 (100)
Mean (SD)	174.9 (49)	182 (51.8)	179.6 (50.9)

Source (b) (4), Table 11.2: 2, page 75

Reviewer's Comments
Baseline disease characteristics were similar between both groups.

Trials with Long Term Treatment

Study 40—Long Term Extension Study

Demographic data was similar between patients in the Pivotal Studies and those that continued into the open label extension study. Over two thousand patient from the

pivotal studies continued into this long term study. As seen in the *Pivotal Studies* discussion (although this discussion compares the linagliptin arms to the placebo arms—here the placebo arm patients have become the "New lina" group), the demographic background of the patients was similar. See Table 13.

Table 13 Demographic Parameters—Study 40, Treated Set

	Old lina		New lina		Total	
Number of patients [n (%)]	1532	(100.0)	589	(100.0)	2121	(100.0)
Age [years]						
Mean (SD)	57.8	(9.8)	56.7	(10.0)	57.5	(9.9)
Sex [n (%)]						
Male	790	(51.6)	310	(52.6)	1100	(51.9)
Female	742	(48.4)	279	(47.4)	1021	(48.1)
Race [n (%)]						
American Indian/Alaska Native	7	(0.5)	5	(0.8)	12	(0.6)
Asian	646	(42.2)	245	(41.6)	891	(42.0)
Black/African American	8	(0.5)	3	(0.5)	11	(0.5)
Hawaiian/Pacific Islander	4	(0.3)	1	(0.2)	5	(0.2)
White	867	(56.6)	335	(56.9)	1202	(56.7)
Baseline weight [kg]						
Mean (SD)	78.7	(16.9)	80.1	(16.9)	79.1	(16.9)
Baseline weight, categorical [kg], [n (%)]						
≤70 kg	525	(34.3)	193	(32.8)	718	(33.9)
>70 to 80 kg	360	(23.5)	132	(22.4)	492	(23.2)
>80 to 90 kg	275	(18.0)	107	(18.2)	382	(18.0)
>90 kg	372	(24.3)	157	(26.7)	529	(24.9)
Baseline BMI [kg/m^2]						
Mean (SD)	28.9	(4.8)	29.2	(4.9)	29.0	(4.9)
Baseline BMI, categorical [kg/m^2], [n (%)]						
<25 kg/m^2	359	(23.4)	137	(23.3)	496	(23.4)
25 to <30 kg/m^2	606	(39.6)	222	(37.7)	828	(39.0)
≥30 kg/m^2	567	(37.0)	230	(39.0)	797	(37.6)
Baseline waist circumference [cm]						
Mean (SD)	98.4	(13.2)	99.7	(13.1)	98.7	(13.2)
Baseline eGFR [mL/min], [n (%)]						
≥90	852	(55.6)	347	(58.9)	1199	(56.5)
60 to <90	606	(39.6)	222	(37.7)	828	(39.0)
30 to <60	73	(4.8)	20	(3.4)	93	(4.4)
<30	1	(0.1)	0		1	(0.0)[1]
Baseline eCcr [mL/min], [n (%)]						
≥80	1160	(75.7)	477	(81.0)	1637	(77.2)
50 to <80	339	(22.1)	101	(17.1)	440	(20.7)
30 to <50	32	(2.1)	10	(1.7)	42	(2.0)
<30	1	(0.1)	1	(0.2)	2	(0.1)

[1] 0.0% due to rounding of numbers

Source (b) (4) Table 11.2: 1, page 59

The frequency of patients using concomitant therapies between the old and new linagliptin groups was similar (54.6% in the old group versus 55.2% in the new group).

Baseline efficacy variables revealed expected differences as the old group had not received linagliptin in the previous pivotal studies. In the case of study 16, there had been no medical T2DM therapy at all. Please see Table 14.

Table 14 Baseline Disease Characteristics —Study 40, Treated Set

	Old lina		New lina		Total	
Number of patients [n (%)]	1532	(100.0)	589	(100.0)	2121	(100.0)
Baseline HbA_{1c} [%]						
Mean (SD)	7.38	(0.90)	7.87	(1.04)	7.51	(0.97)
Baseline HbA_{1c}, categorical [n (%)]						
<7.0%	532	(34.7)	108	(18.3)	640	(30.2)
7.0% to <8.0%	640	(41.8)	230	(39.0)	870	(41.0)
8.0% to <9.0%	272	(17.8)	164	(27.8)	436	(20.6)
≥ 9.0%	88	(5.7)	87	(14.8)	175	(8.3)
Baseline FPG [mg/dL]						
Number of patients	1530	(100.0)	588	(100.0)	2118	(100.0)
Mean (SD)	151.60	(35.27)	164.19	(37.33)	155.10	(36.29)
Baseline FPG, categorical [n (%)]						
<126 mg/dL	340	(22.2)	77	(13.1)	417	(19.7)
126 to <140 mg/dL	264	(17.3)	78	(13.3)	342	(16.1)
140 to <200 mg/dL	788	(51.5)	331	(56.3)	1119	(52.8)
≥ 200 mg/dL	138	(9.0)	102	(17.3)	240	(11.3)
Time since diagnosis of T2DM, categorical [n (%)]						
Up to 1 year	226	(14.8)	110	(18.7)	336	(15.8)
>1 to 5 years	476	(31.1)	196	(33.3)	672	(31.7)
>5 years	830	(54.2)	283	(48.0)	1113	(52.5)

Baseline taken from Visit 1 of 1218.40, or last available value

Source (b) (4) Table 11.2: 2, page 61

Reviewer's Comments

The HbA1c and FPG at baseline of the extension study (end of the controlled period) are consistent with what would be expected given the primary endpoint analysis of the pivotal studies, which will be discussed. This reflects the lack of linagliptin treatment in the New linagliptin group.

6.1.3 Subject Disposition

Pivotal Studies

A total of 1857 patients (41.2% of those screened) were not randomized, mainly because of violations of inclusion or exclusion criteria. Study 18 had the lowest percentage of screened patients who were later not randomized (33.8%), possibly because none of the patients in this trial was required to undergo a washout of previous OADs.

Table 15 Disposition of Patients—Pivotal Trials, Screened Set

Study	Enrolled, N (%)	Performed washout, N (%)	Randomised, N (%)		Not randomised, N (%)				
			Placebo	Linagliptin	Total	AEs	In/ex crit.	Admin.	Other
1218.15	707 (100.0)	397 (54.7)	130 (18.4)	259 (36.6)	318 (45.0)	1 (0.1)	271 (38.3)	29 (4.1)	17 (2.4)
1218.16	935 (100.0)	402 (43.0)	167 (17.9)	336 (35.9)	432 (46.2)	10 (1.1)	357 (38.2)	42 (4.5)	23 (2.5)
1218.17	1268 (100.0)	405 (31.9)	177 (14.0)	524 (41.3)	567 (44.7)	13 (1.0)	456 (36.0)	64 (5.0)	34 (2.7)
1218.18	1598 (100.0)	0 (0.0)	265 (16.6)	793 (49.6)	540 (33.8)	4 (0.3)	478 (29.9)	43 (2.7)	15 (0.9)
EFF-1 pool	4508 (100.0)	1194 (26.5)	739 (16.4)	1912 (42.4)	1857 (41.2)	28 (0.6)	1562 (34.6)	178 (3.9)	89 (2.0)

In/ex crit = in- or exclusion criteria not met; Admin. = administrative reasons (lost to follow-up or consent withdrawn)

Source (b) (4), Table 3.1.1.1: 1, page 35

Of the patients in the pivotal studies FAS population, most completed the 24-week treatment periods of the trials as planned (94.0%). Overall, the frequency of premature discontinuation was slightly lower for the patients treated with linagliptin (5.2%) than for those receiving placebo (8.2%). The applicant reports that this difference was mainly due to the higher percentage of patients in the placebo group who withdrew their consent, did not comply with the study protocol, refused study medication or were lost to follow-up.

Premature discontinuations were similarly frequent in the linagliptin groups of all four trials (range: 3.6% to 5.7%), but there were differences for the placebo groups. The incidence of premature discontinuations in the placebo group of study 15 (13.3%) was higher than in the placebo groups of the other 3 studies (6.7% to 7.6%). The applicant could not discern an explanation for this.

Table 16 Discontinuations in the Pivotal Trials—FAS

Study/ treatment group	Treated, [a] N (%)	Not prematurely discontinued, N (%)	Prematurely discontinued, N (%)				
			Total	AEs	Lack of efficacy [b]	Admin.	Other
1218.15/							
Placebo	128 (100.0)	111 (86.7)	17 (13.3)	5 (3.9)	1 (0.8)	8 (6.3)	3 (2.3)
Linagliptin	252 (100.0)	243 (96.4)	9 (3.6)	3 (1.2)	1 (0.4)	4 (1.6)	1 (0.4)
1218.16/							
Placebo	163 (100.0)	152 (93.3)	11 (6.7)	3 (1.8)	2 (1.2)	2 (1.2)	4 (2.5)
Linagliptin	333 (100.0)	318 (95.5)	15 (4.5)	4 (1.2)	0 (0.0)	7 (2.1)	4 (1.2)
1218.17/							
Placebo	175 (100.0)	163 (93.1)	12 (6.9)	3 (1.7)	0 (0.0)	7 (4.0)	2 (1.1)
Linagliptin	513 (100.0)	484 (94.3)	29 (5.7)	5 (1.0)	1 (0.2)	16 (3.1)	7 (1.4)
1218.18/							
Placebo	262 (100.0)	242 (92.4)	20 (7.6)	4 (1.5)	4 (1.5)	12 (4.6)	0 (0.0)
Linagliptin	778 (100.0)	734 (94.3)	44 (5.7)	16 (2.1)	2 (0.3)	26 (3.3)	0 (0.0)
EFF-1 pool/							
Placebo	728 (100.0)	668 (91.8)	60 (8.2)	15 (2.1)	7 (1.0)	29 (4.0)	9 (1.2)
Linagliptin	1876 (100.0)	1779 (94.8)	97 (5.2)	28 (1.5)	4 (0.2)	53 (2.8)	12 (0.6)

Admin. = administrative reasons (non-compliance to study protocol, lost to follow-up, or refusal to continue study medication)

a This table is based on the FAS. Therefore, the number of treated patients includes only those with a baseline HbA_{1c} and at least one on-treatment HbA_{1c} value.

b Includes patients who discontinued due to hyperglycaemia

Source (b) (4) Table 3.1.1.1: 2, page 36

Reviewer's Comments

I would have expected to see the highest rate of discontinuation in the placebo group of study 16 (not in study 15) as this is monotherapy study. Aside from this, the disposition was similar across all studies.

Monotherapy

Study 50—Nonpivotal Placebo-only Study

Of the 571 patients enrolled, 166 had been pre-treated with prior anti-diabetes medication and entered a 6-week washout period with a placebo run-in during the last two weeks. There were 124 patients who were not pre-treated with an anti-diabetes medication and these directly entered the two week placebo run-in period. A total of 290 patients entered the placebo run-in period. 227 patients were randomized to receive either linagliptin (151 patients) or placebo (76 patients); 334 of the enrolled patients (60.2%) were not randomized. The main reasons for non-randomization were inclusion or exclusion criteria not met (53.1% of the enrolled patients). See Table 17.

Table 17 Disposition of Patients—Study 50, Screened Set

	Total N (%)
Enrolled	571 (100.0)
Started washout period	166 (29.1)
Started placebo run-in period	290 (50.8)
Randomised	227 (39.8)
Not randomised	344 (60.2)
Adverse event	2 (0.4)
Inclusion / exclusion criteria not met	303 (53.1)
T2DM treatment naïve or previously treated with 1 anti-diabetes medication	6 (1.1)
medication (unchanged for 10 weeks)	
HbA_{1c} out of range at Visit 1a	225 (39.4)
HbA_{1c} out of range at Visit 2	226 (39.6)
Age out of range at Visit 1a	1 (0.2)
BMI out of range at Visit 1a	5 (0.9)
Ineligible for metformin therapy	8 (1.4)
Treatment with rosiglitazone or pioglitazone within 3 months	3 (0.5)
Impaired hepatic function at Visit 1a	4 (0.7)
Severe renal impairment at Visit 1a	6 (1.1)
Not willing to comply with protocol requirements	5 (0.9)
Patients considered unreliable	3 (0.5)
Lost to follow-up	9 (1.6)
Consent withdrawn	13 (2.3)
Other reason	17 (3.0)

Source (b) (4) Table 10.1: 2, page 68

Of the randomized patients, 93.0% were metformin intolerant due to a gastrointestinal side effect. See Table 18.

Table 18 Metformin Intolerance by Stratum—Study 50

Reason for Metformin Intolerance	**Placebo N (%)**	**Linagliptin N (%)**	**Total N (%)**
Total	76 (100)	151 (100)	227 (100)
Gastrointestinal AE	71 (93.4)	140 (92.7)	211 (93.0)
Raised creatinine	5 (6.6)	11 (7.3)	16 (7.0)

Of the 227 randomized patients, 201 patients were still participating at the end of the 18 week treatment period in Part One of the study, whereas 26 patients (11.5 %) prematurely discontinued trial medication. The most frequent reasons for premature discontinuation were due to refusal to continue medication (6.6% placebo and 3.3%

linagliptin), and lost to follow up (2.6% in both groups). One patient (1.3%) in the placebo group discontinued due to lack of efficacy and two (1.3%) in the linagliptin group. The patient receiving placebo reported hyperglycemia. Two patients recorded increased glucose levels (>240mg/dL) over a period of more than one month, but these were not recorded as hyperglycemic events. See Table 19.

Table 19 Disposition of Randomized Patients—Study 50

	Placebo N (%)	Linagliptin N (%)	Total N (%)
Enrolled			571
Randomised	76	151	227
Treated[1]	76 (100.0)	151 (100.0)	227 (100.0)
Ongoing at the end of treatment part 1	64 (84.2)	137 (90.7)	201 (88.5)
Prematurely discontinued trial medication	12 (15.8)	14 (9.3)	26 (11.5)
Adverse event	0 (0.0)	1 (0.7)	1 (0.4)
Study disease worsening	0 (0.0)	0 (0.0)	0 (0.0)
Other disease worsening	0 (0.0)	1 (0.7)	1 (0.4)
Other AE	0 (0.0)	0 (0.0)	0 (0.0)
Lack of efficacy [2]	1 (1.3)	2 (1.3)	3 (1.3)
Non-compliance to protocol	2 (2.6)	1 (0.7)	3 (1.3)
Lost to follow-up	2 (2.6)	4 (2.6)	6 (2.6)
Refused to continue trial medication	5 (6.6)	5 (3.3)	10 (4.4)
Other reason	2 (2.6)	1 (0.7)	3 (1.3)

[1] In all tables 'treated' refers to treatment with randomised study drug
[2] Includes patients who discontinued due to hyperglycaemia

Source (b) (4), Table 10.1: 4 page 70

Reviewer's Comments
it is reassuring that there were more discontinuations in the placebo treated subjects than those treated with linagliptin.

Combination Therapy

Study 20—Active Control Study

In study 20, a total of 2300 patients were screened by 209 trial sites in 16 countries. Of these, 1560 patients were enrolled and randomized in a 1:1 ratio to receive treatment with either linagliptin (779 patients) or glimepiride (781 patients) as add on to metformin. One patient in the linagliptin group was not treated, resulting in 778 patients treated in this group.

There were over 700 patients not randomized to study treatment. The most frequent reason was listed as failure to meet inclusion criteria (503 patients). Of these the HbA1c criteria was the most common criterion that was not met..

A total of 1559 patients (linagliptin 778 patients; glimepiride 781 patients) were treated with study medication. Of those, 1274 patients (81.7%) were still in the study at the time of the interim cut-off date. A total of 285 patients (18.3%) prematurely discontinued trial medication before the cut-off date. The percentage of patients prematurely discontinuing from the study was similar between the two groups (18.0% linagliptin and 18.6% glimepiride). Table 20 gives an overview of the most frequent reasons for premature discontinuation. The most frequent reason for premature discontinuation were due to AEs, with more patients withdrawing in the glimepiride group (9.9%) compared to the linagliptin group (5.8%). Discontinuations due to lack of efficacy (hyperglycemia in all cases) were slightly higher in the linagliptin group (3.7%) compared to the glimepiride group (1.2%).

Table 20 Disposition of Randomized Patients—Study 20

	Linagliptin N (%)	Glimepiride N (%)	Total N (%)
Enrolled			2300
Randomised	779	781	1560
Treated[1]	778 (100.0)	781 (100.0)	1559 (100.0)
Not prematurely discontinued trial medication	638 (82.0)	636 (81.4)	1274 (81.7)
Prematurely discontinued trial medication	140 (18.0)	145 (18.6)	285 (18.3)
Adverse events	45 (5.8)	77 (9.9)	122 (7.8)
Study disease worsening	6 (0.8)	5 (0.6)	11 (0.7)
Other disease worsening	4 (0.5)	5 (0.6)	9 (0.6)
Other AE	35 (4.5)	67 (8.6)	102 (6.5)
Lack of efficacy[2]	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)

1 'Treated' refers to treatment with randomised study drug
2 Includes patients who discontinued due to hyperglycaemia

Source (b) (4), Table 10.1: 3, page 70

Reviewer's Comments

Out of the randomized patients, the number of overall discontinuations is similar between both arms. There were more discontinuations due to AEs in the Glimepiride group, however the linagliptin group had more discontinuations due to lack of efficacy. This observation indicates a difference that arises repeatedly in discussions of this study.

The mean dose for glimepiride during the treatment period was 3 mg. The majority of patients were on 4 mg during the treatment period (47.5%). There were no up-titrations during the treatment period (as the protocol designated); however, there were several patients that had their dose decreased. See Table 21 for details. This table was submitted as an amendment to NDA in response to inquiry for this information.

Table 21 Assigned Glimepiride Dose at Scheduled Visits and Dose Adjustments—Study 20, FAS

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Visit	Patients on treatment N (%)	Mean	SD	Median	Mode	1 mg N	1 mg (%)	2 mg N	2 mg (%)	3 mg N	3 mg (%)	4 mg N	4 mg (%)
Treatment start (Visit 3)	761 (100.0)	1.0	0.0	1.0	1	761	(100.0)	0	(0.0)	0	(0.0)	0	(0.0)
Dose decrease at Visit 3: N						0		0		0		0	
Dose increase at Visit 3: N						0		0		0		0	
Week 0 to 3 #													
Dose decrease from Visit 3 to 4: N						0		0		0		0	
Dose increase from Visit 3 to 4: N						0		0		0		0	
Week 4 (Visit 4)	750 (100.0)	1.7	0.5	2.0	2	228	(30.4)	522	(69.6)	0	(0.0)	0	(0.0)
Dose decrease at Visit 4: N						0		0		0		0	
Dose increase at Visit 4: N						0		522		0		0	
Week 4 to 7 #													
Dose decrease from Visit 4 to 5: N						2		0		0		0	
Dose increase from Visit 4 to 5: N						0		1		0		0	
Week 8 (Visit 5)	734 (100.0)	2.4	0.8	3.0	3	138	(18.8)	183	(24.9)	413	(56.3)	0	(0.0)
Dose decrease at Visit 5: N						7		0		0		0	
Dose increase at Visit 5: N						0		91		413		0	
Week 8 to 11 #													
Dose decrease from Visit 5 to 6: N						1		3		0		0	
Dose increase from Visit 5 to 6: N						0		0		1		0	
Week 12 (Visit 6)	716 (100.0)	3.1	1.1	4.0	4	109	(15.2)	109	(15.2)	135	(18.9)	363	(50.7)
Dose decrease at Visit 6: N						4		2		0		0	
Dose increase at Visit 6: N						0		26		96		363	
Week 12 to 15 #													
Dose decrease from Visit 6 to 7: N						0		2		1		0	
Dose increase from Visit 6 to 7: N						0		0		0		0	

Time intervals between scheduled visits exclude actual days of visit.
* Last available dose up to Week 52 (inclusive) compared to dose assigned at Visit 6
Mean, SD, median and mode refer to assigned dose at the start of the interval (i.e. at the scheduled visit).
Dose change after Visit 9 for Patient 22327 not counted due to premature discontinuation after Visit 9
Continued

Source NDA Amendment 12/17, Table 1.1

Reviewer's Comments

This active control study for non-inferiority compares linagliptin to glimepiride at a dose that is not the maximally approved dose for the patients on this arm. First, the dose was forced to a maximum of 4 mg, and not 8 mg, which is the maximum dose approved. Then, the mean dose was actually 3 mg; much less than the maximum approved. When reviewing the results of this study, I considered these issues and what impact they have on the results.

Study 35—Add on to SU Study

Of the 471 patients enrolled, 245 were randomized to receive either placebo or linagliptin and all of the randomized patients were treated (84 patients with placebo and 161 patients with linagliptin); 226 of the enrolled patients were not randomized. The main reason was inclusion or exclusion criteria not met (42.5% of the enrolled patients. Most of the criteria not met were HbA1c criteria. Table 22 details the disposition.

Table 22 Disposition of Patients—Study 35, Screened Set

	Total N (%)
Enrolled	471 (100.0)
Started Wash-out Period	114
Started Placebo Run-in Period	280
Not randomised	226
Randomised	245
Adverse event	3 (0.6)
Inclusion / exclusion criteria not met	200 (42.5)
Anti-diabetic therapy has to be unchanged for 10 weeks prior to informed consent…	2 (0.4)
Sulphonylurea dose of at least ½ the maximum dose (or less if as maximum tolerated dose of at least 12 weeks)	10 (2.1)
HbA_{1c} at Visit 1 (Screening) out of range	163 (34.6)
HbA_{1c} out of range at Visit 2	159 (33.8)
Age out of range at Screening	2 (0.4)
BMI <=40 kg/m^2 at Screening	3 (0.6)
Impaired hepatic function at Screening	4 (0.8)
Renal failure or renal impairment at Screening	1 (0.2)
Lost to follow-up	3 (0.6)
Consent withdrawn	11 (2.3)
Other reason	9 (1.9)

Source (b) (4), Table 10.1: 2, page 67

Of the 245 patients treated with randomized study medication, 228 patients (93.1%) completed the 18-week treatment period (91.7% placebo and 93.8% linagliptin), and 17 patients (6.9%) prematurely discontinued trial medication (8.3% placebo and 6.2% linagliptin). Table 23 presents the most frequent reasons for premature discontinuation. These were mostly due to adverse events (total 3.6% placebo and total 3.1% linagliptin) and refusal to continue medication (1.2% placebo and 1.2% linagliptin).

Table 23 Disposition of Randomized Patients—Study 35

	Placebo N (%)	Linagliptin N (%)	Total N (%)
Enrolled			471
Randomised	84	161	245
Treated[1]	84 100.0)	161 (100.0)	245 (100.0)
Not prematurely discontinued trial medication	77 (91.7)	151 (93.8)	228 (93.1)
Prematurely discontinued trial medication	7 (8.3)	10 (6.2)	17 (6.9)
Adverse event	3 (3.6)	5 (3.1)	8 (3.3)
Study disease worsening	1 (1.2)	0 (0.0)	1 (0.4)
Other disease worsening	0 (0.0)	0 (0.0)	0 (0.0)
Other AE	2 (2.4)	5 (3.1)	7 (2.9)
Lack of efficacy	0 (0.0)	0 (0.0)	0 (0.0)
Non-compliance to protocol	0 (0.0)	1 (0.6)	1 (0.4)
Lost to follow-up	2 (2.4)	0 (0.0)	2 (0.8)
Refused to continue trial medication	1 (1.2)	2 (1.2)	3 (1.2)
Other reason	1 (1.2)	2 (1.2)	3 (1.2)

Source (b) (4), Table 10.1: 4, page 69

Reviewer's Comments
Both treatment groups in this study received medication for T2DM. Thus, the continuation rate being above 90% for both groups is expected. The rates of discontinuations and the rate for each cause of discontinuation are low.

Trials with Long Term Treatment

Study 40—Long Term Extension Study

Only three patients were screened and not treated for this trial because they withdrew informed consent. A total of 163 patients prematurely discontinued the trial medication up to the interim analysis cut off presented here. Treatment groups are designated as Old linagliptin (patients that were on linagliptin in the pivotal studies) and New linagliptin (patients started on linagliptin for this extension) in Table 24.

Table 24 Disposition of Patients—Study 40, Screened Set

	Old lina		New lina		Total	
	n	(%)	n	(%)	n	(%)
Screened					2124	
Treated	1532	(100.0)	589	(100.0)	2121	(100.0)
Not prematurely discontinued trial medication	1408	(91.9)	550	(93.4)	1958	(92.3)
Prematurely discontinued trial medication	124	(8.1)	39	(6.6)	163	(7.7)
Adverse Events (AE)	40	(2.6)	12	(2.0)	52	(2.5)
Study disease worsening	5	(0.3)	4	(0.7)	9	(0.4)
Other disease worsening	6	(0.4)	0		6	(0.3)
Other	29	(1.9)	8	(1.4)	37	(1.7)
Lack of efficacy[1]	9	(0.6)	6	(1.0)	15	(0.7)
Non compliant with protocol	5	(0.3)	4	(0.7)	9	(0.4)
Lost to follow up	4	(0.3)	2	(0.3)	6	(0.3)
Refused continued medication	32	(2.1)	9	(1.5)	41	(1.9)
Other	34	(2.2)	6	(1.0)	40	(1.9)

[1] Including patients who discontinued due to hyperglycaemia

Source (b) (4) Table 10.1: 3, page 56

Reviewer's Comments
The discontinuation rates for both groups are similar which is expected as patients in both groups are receiving the same treatments.

6.1.4 Analysis of Primary Endpoint(s)

Pivotal Trials

The primary endpoint in all four trials was the change in HbA1c from baseline to the last on-treatment visit. Baseline HbA1c was defined as the last available HbA1c value before the start of randomized study medication, excluding values determined before the start of a washout period. HbA1c measurements were regarded as "on-treatment" if they were taken after the first dose of study medication up to period of seven days after the last dose of study medication.

As described earlier, the primary analysis method was analysis of covariance (ANCOVA) For the analysis of the changes from baseline in HbA1c to the last on-treatment visit, a last observation carried forward (LOCF) approach was used to replace missing data. Values measured after a patient had taken rescue medication during the randomized treatment period were set to missing, and these missing values were imputed using the LOCF method.

In all four pivotal studies, linagliptin 5 mg provided statistically significant reductions in HbA1c after 24 weeks of treatment compared with placebo (Table 25). The treatment

effect of linagliptin was consistent across the pivotal placebo-controlled studies, irrespective of antidiabetic background therapy. The pooled analysis of the four studies confirmed the results for the individual trials.

Study 15 compared linagliptin in initial combination with pioglitazone against pioglitazone alone. Mean baseline HbA1c was very similar in both treatment groups (both essentially 8.6%). In contrast to the other three studies in the pivotal studies group, patients in both treatment groups of study 15 received new active treatments at baseline; patients in the linagliptin group received 5 mg linagliptin plus 30 mg pioglitazone once daily, and patients in the control arm received placebo plus 30 mg pioglitazone once daily. As a result, patients in both treatment groups showed a decrease from baseline in HbA1c after 24 weeks of treatment; the adjusted mean change in HbA1c from baseline was -0.6 in the pioglitazone alone group and -1.1% in the linagliptin + pioglitazone group. The reduction in HbA1c was significantly greater in the linagliptin + pioglitazone group than in the pioglitazone alone group (treatment difference -0.5%; 95% CI -0.71, -0.30; p <0.0001).

Reviewer's Comment
This study is not equivalent to the add on studies presented by the applicant. Here, both therapies are new to the patient, linagliptin or pioglitazone. The improvement in HbA1c is seen in both groups which is expected as both groups were washed out and began new therapies. The linagliptin + pioglitazone group had greater benefit than with pioglitazone alone. The applicant uses this study to support the combination therapy claim on their proposed label.

Study 16 tested linagliptin versus placebo without antidiabetic background therapy. From a mean baseline HbA1c of 8.0% in both treatment groups, mean HbA1c after 24 weeks of treatment increased in the placebo group and decreased in the linagliptin group (adjusted mean change from baseline: 0.3% vs. -0.4%). The adjusted mean difference in the HbA1c change from baseline was -0.7 (95% CI -0.8, -0.5; p <0.0001).

Study 17 tested linagliptin versus placebo as add-on to ongoing metformin therapy. Mean baseline HbA1c was 8.0% in the placebo group and 8.1% in the linagliptin group. Similar to study 16, a mean increase from baseline in HbA1c was seen in the placebo group after 24 weeks of treatment, as opposed to a mean decrease in the linagliptin group. The adjusted mean change from baseline in HbA1c was 0.2% for placebo and -0.5% for linagliptin. Linagliptin as add-on to metformin was superior to placebo plus metformin in regard to the HbA1c change from baseline after 24 weeks, with a clinically relevant adjusted mean difference of -0.6% (95% CI -0.8, -0.5; p <0.0001).

Study 18 compared linagliptin with placebo added to ongoing combination therapy with metformin and an SU. Mean baseline HbA1c was nearly identical in both treatment groups (placebo: 8.1%; linagliptin: 8.2%). Superiority of linagliptin over placebo with regard to the adjusted mean change in HbA1c after 24 weeks of treatment was shown

in this study as well. Adjusted mean changes from baseline in HbA1c were -0.1% in the placebo group and -0.7% in the linagliptin group, leading to a difference in adjusted means of -0.6% (95% CI -0.73, -0.50; p <0.0001).

Pooling of the data from the four pivotal studies led to a mean baseline HbA1c of 8.2% for both treatment groups. The adjusted mean change from baseline in HbA1c after 24 weeks of treatment was 0.0% for placebo and -0.6% for linagliptin. Thus, for the four pivotal placebo-controlled studies combined, an adjusted mean difference between linagliptin and placebo of -0.6% (95% CI -0.7, -0.5; p <0.0001) was found.

Table 25 Main Efficacy Endpoint: Differences Between Adjusted means for HbA1c (%) Change from Baseline at Week 24 for Pivotal Studies—FAS

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 (b) (4), Table 3.2.1.1: 1, page 84

Reviewer's Comments

The adjusted change in the linagliptin treated group is greater than 0.5% in each trial, under varying conditions: no other therapy, pioglitazone, metformin and metformin plus SU. As expected, the most robust adjusted response is seen in

study 16, where there is more decline in glycemic control in the placebo only group. The add on placebo groups, the metformin (study 17) and metformin plus an SU (study 18) showed minimal improvement. In addition, notable benefit in both groups was seen in study 15 where treatment was new to both groups, HbA1c at baseline was higher than the other studies (baseline HbA1c for both groups was 8.6 versus closer to 8.0 with the other three studies; a reflection of the higher HbA1c inclusion criteria) and there was lack of restriction of OAD prior to screening.

Overall, the efficacy response is significant and similar to that seen with other DPP4 inhibitors currently marketed, although such comparisons are limited in their validity due to differences in trial designs and populations. More importantly, the response is consistent among all the linagliptin trials. These efficacy data will be considered with other aspects of this review (efficacy from sensitivity analyses, other studies and most importantly the *Review of Safety*) to determine the overall risk/benefit of treatment.

The FAS—completers observed cases (OC) group was defined as the group of patients in the FAS who completed a required minimum treatment duration, did not prematurely discontinue the trial **and that did not have any missing values replaced**. The analysis of linagliptin effects in the OC groups had similar results to the analysis of the full FAS for the individual trials. See Table 26.

Table 26 Main Efficacy Endpoint: Differences Between Adjusted means for HbA1c (%) Change from Baseline at Week 24 for Pivotal Studies, FAS—OC

			Change from Baseline in HbA1c		Difference from placebo	
Study/Treatment Group	**Number of Patients**	**Baseline HbA1c mean (SE)**	**Mean (SD)**	**Adjusted Mean (SE)**	**95% CI**	**p-value**
15						
Placebo	106	8.5 (0.09)	-1.1 (0.12)	-0.9 (0.10)		
Linagliptin	236	8.6 (0.05)	-1.5 (0.07)	-1.2 (0.07)	-0.56, -0.14	0.0011
16						
Placebo	148	7.8 (0.07)	0.04 (0.1)	0.06 (0.07)		
Linagliptin	312	7.9 (0.05)	-0.6 (0.05)	-0.6 (0.05)	-0.73, -0.39	<0.0001
17						
Placebo	156	7.9 (0.07)	-0.01 (0.08)	-0.02 (0.07)		
Linagliptin	468	8.0 (0.04)	-0.6 (0.04)	-0.7 (0.04)	-0.72, -0.42	<0.0001
18						
Placebo	236	8.0 (0.06)	-0.2 (0.06)	-0.2 (0.05)		
Linagliptin	725	8.1 (0.03)	-0.7 (0.03)	-0.8 (0.03)	-0.66, -0.42	<0.0001

Reviewer's Comments
The benefit of pioglitazone in study 15 is even more robust with this analysis. The least amount of benefit with this group of patients (minus rescue patients) is seen in study 16 which has placebo only as the comparator (no background medication). This is in contrast to the lowest effect seen in study 15 in the FAS-LOCF group.
Overall, the benefit of linagliptin is seen in both analyses and is consistent.

HbA1c Changes Over Time

For the FAS set of patients, the changes in HbA1c can be seen over time in all four pivotal studies. The mean change from baseline in HbA1c over time was analyzed by using the same model as used for the primary analysis.

In study 15, significant difference between treatment groups was observed over time ($p<0.0001$). The difference between treatments in terms of adjusted mean change from baseline in HbA1c increased over time reaching up to week 18 (-0.5% placebo+pioglitazone; -1.1% linagliptin+pioglitazone) with a difference between treatments of -0.5% that remained constant to week 24. As seen in Figure 13, the response to treatment is noticed immediately.

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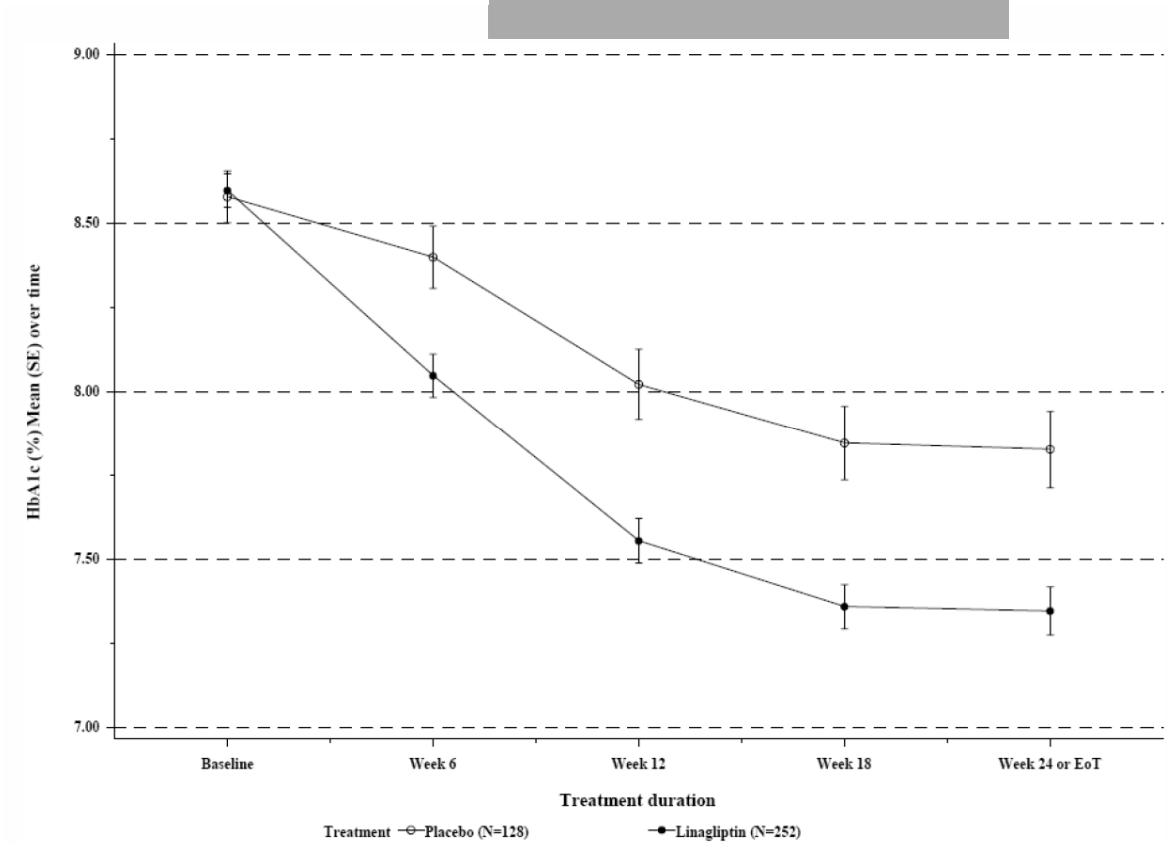

Figure 13 Mean HbA1c (%) and SE Over Time—Study 15, FAS
Source (b) (4) Figure 11.4.1.1.2: 1, page 79

In study 16, from baseline to week 24, across each visit, statistically significant ($p<0.0001$) differences between the adjusted means of HbA1c (linagliptin - placebo) were observed, see Figure 14. The placebo-adjusted mean treatment differences ranged from -0.5% at Week 6 to -0.7% at Week 24

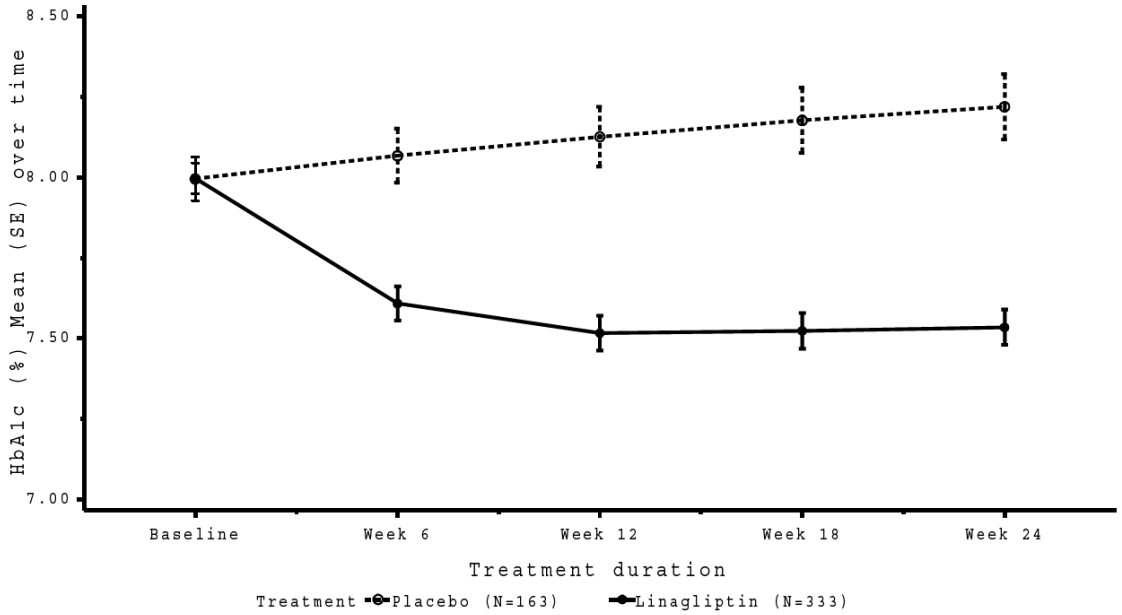

Figure 14 Mean HbA1c (%) and SE Over Time—Study 16, FAS
Source (b) (4) Figure 11.4.1.1.2: 1, page 79

In study 17 the difference between treatments in terms of adjusted mean change from baseline in HbA1c decreased from -0.4% at week 6 to -0.7% at week 18 and continued nearly unchanged up to week 24 (-0.6%). All of these differences are statistically significant with p-values below 0.0001, see Figure 15.

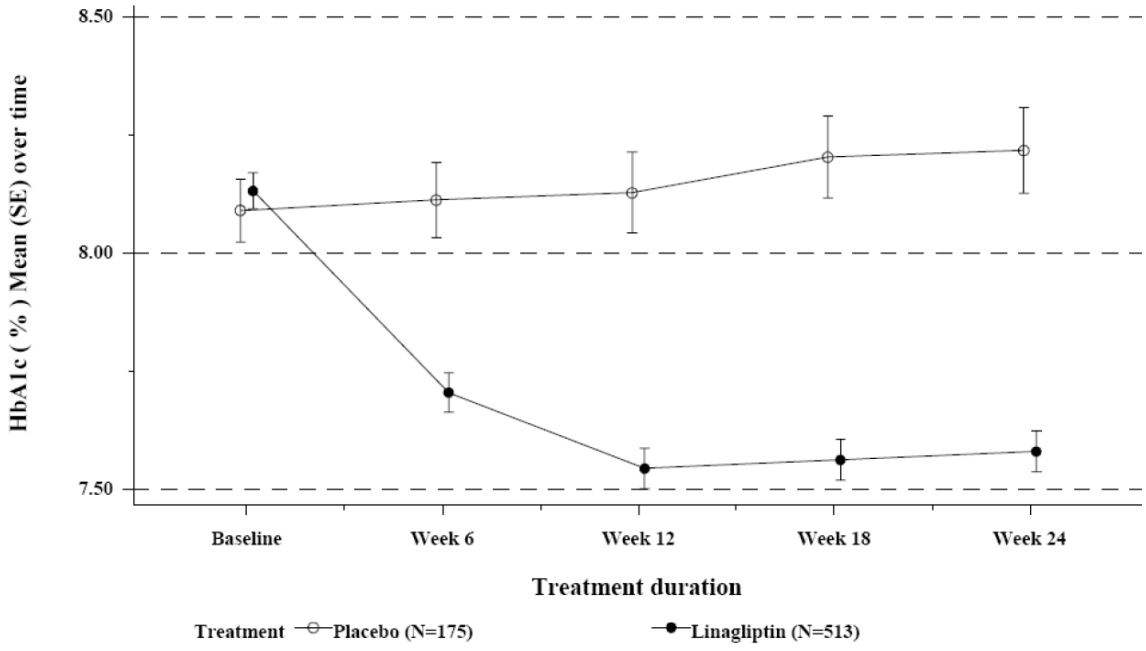

Figure 15 Mean HbA1c (%) and SE Over Time—Study 17, FAS
Source (b) (4) Figure 11.4.1.1.2: 1, page 80

In study 18, there was a statistically significant difference (linagliptin-placebo) between the adjusted means of HbA1c (SE) at all observed time points; p<0.0001. In the linagliptin treatment group, the maximum adjusted mean reduction in HbA1c (SE) was observed at Week 12 (-0.84%). For both groups, after week 12, there was an increase in HbA1c, which was greater in the linagliptin group, see Figure 16.

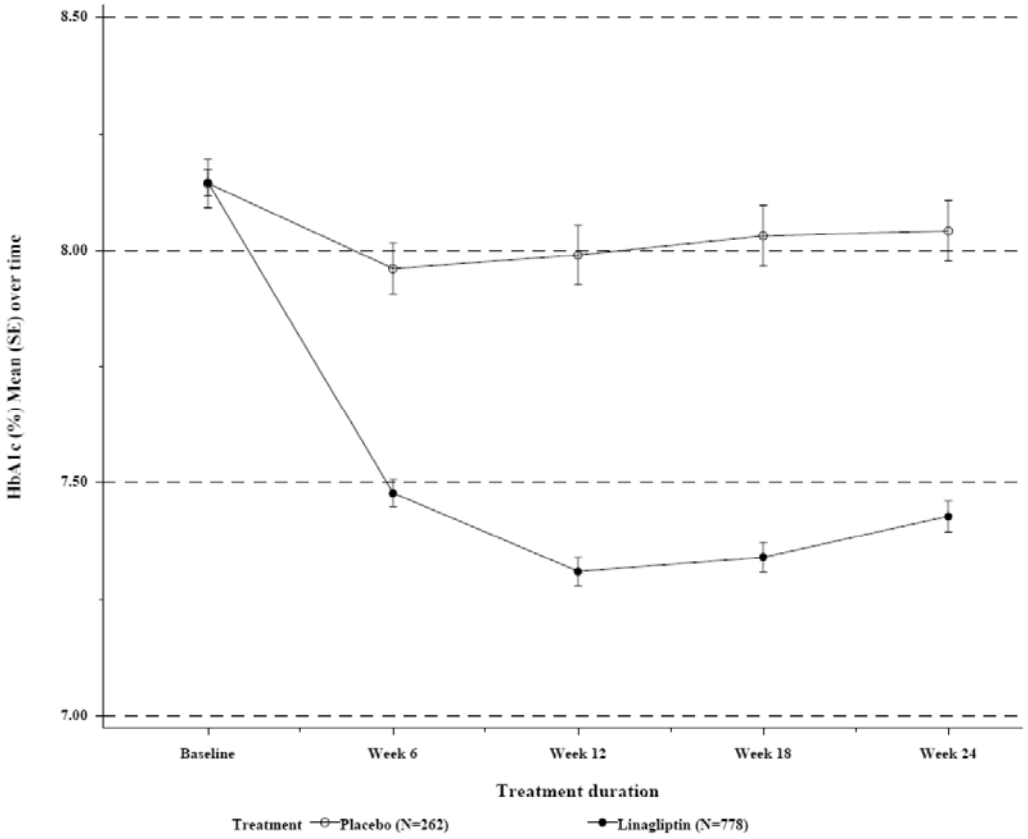

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Figure 16 Mean HbA1c (%) and SE Over Time—Study 18, FAS
Source (b) (4), Figure 11.4.1.1.2: 1, page 80

Reviewer's Comments
These applicant-designed figures displayed above amplify the region of interest and emphasizes the effect of linagliptin.
Overall, for the pivotal studies, most effect is seen by week 12 and maintained to week 24.
The slight increase in study 18 of HbA1c in the FAS group is most likely not due to imputation of missing values of rescue patients. Only 5.4% (42 patients) of the linagliptin treatment group received rescue medication. Furthermore, the OC

results display better HbA1c results at 24 weeks than the FAS analyses. The reason for this upward trend in HbA1c is not clear.

Monotherapy

Study 50—Nonpivotal Placebo-only Arm Study

In study 50, the mean difference (linagliptin minus placebo) in change from baseline in HbA1c after 18 weeks, adjusted for the stratification factors and baseline HbA1c as a covariate, was -0.6% with 95% confidence interval (-0.9, -0.3). This difference was statistically significant (p<0.0001), indicating superiority of linagliptin over placebo in the reduction of HbA1c. See Table 27.
Results for Study 16 (the other monotherapy study) are discussed in Section 6.1.4.1 *Pivotal Studies*.

Table 27 Adjusted Means for Change in HbA1c (%) from Baseline to Week 18—Study 50, FAS

	Placebo	Linagliptin
Number of patients	73	147
Baseline		
Mean (SE)	8.06 (0.10)	8.11 (0.08)
Change from baseline		
Mean (SE)	0.25 (0.12)	-0.33 (0.08)
Adjusted[1] mean (SE)	0.14 (0.16)	-0.44 (0.14)
Comparison vs. placebo (difference linagliptin – placebo)		
Adjusted[1] mean (SE)		-0.57 (0.14)
95% Confidence interval		(-0.86, -0.29)
p-value		<0.0001

1 Model includes continuous baseline HbA1c, number of prior anti-diabetes drugs, reason for metformin intolerance and treatment
SE = Standard error
Source (b) (4), Table 11.4.1.1.1: 1, page 79

Reviewer's Comments
As expected, patients on placebo only treatment had worsened glycemic control. The adjusted mean comparing to placebo treatment 0.6%. This response is similar to that seen in the pivotal studies.

A repeated measures analysis in the OC group was performed to assess the impact of missing data and the consistency of treatment effects. As explained, missing data were not imputed with this group. Superiority of linagliptin was demonstrated over placebo at all measured time points (Weeks 6, 12 and 18) in this analysis. In particular, at Week 18, the adjusted mean difference (linagliptin minus placebo) in change from baseline in HbA1c was -0.6% with 95% confidence interval (-0.91, -0.27) and p=0.0003, which is consistent with the results of the primary analysis. See Table 28.

Table 28 Adjusted means for HbA1c (%) Change from Baseline Over Time, Sensitivity Analysis—OC, Study 50

	Placebo Mean (SE)	Linagliptin Mean (SE)	Difference (Linagliptin - Placebo) Mean (CI)	p-value
HBA1C				
Baseline (unadjusted means)	8.06 (0.10)	8.11 (0.08)		
Week 6	0.22 (0.14)	-0.24 (0.12)	-0.47 (-0.709,-0.222)	0.0002
Week 12	0.32 (0.15)	-0.36 (0.12)	-0.68 (-0.965,-0.399)	<0.0001
Week 18	0.19 (0.16)	-0.40 (0.13)	-0.59 (-0.911,-0.274)	0.0003

Source (b) (4) Table 15.2.1.2.1: 5, page 191

Reviewer's Comments
The progressive improvement in HbA1c is evident with the OC analysis. In addition, the 18 week result is reassuringly consistent with the FAS analysis.

HbA1c results over time in the FAS analysis were consistent with the OC analysis. Linagliptin reduced HbA1c from baseline more than placebo did on average at each of Weeks 6, 12 and 18. See Figure 17.

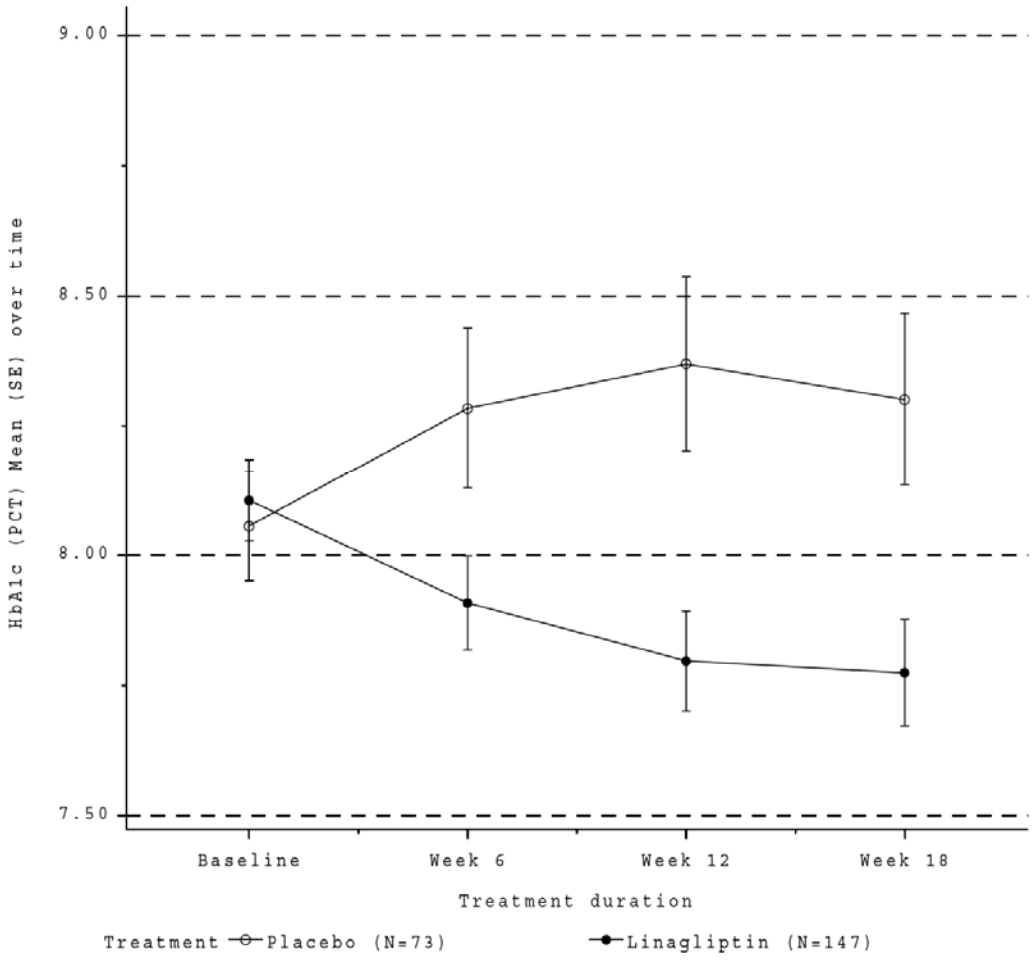

Figure 17 Mean HbA1c (%) and SE Over Time—Study 50, FAS
Source (b) (4) Figure 11.4.1.1.2: 1, page 81

Reviewer's Comments
The trend in improvement in HbA1c noted at 6 weeks and continuing to 18 weeks is consistent with the pivotal studies. This improvement continues to 18 weeks. As expected, the group on placebo only has overall worsening of glycemic control.

Combination Therapy

Study 20—Active Control Trial

The primary endpoint for this interim analysis of study 20 was the change from baseline in HbA1c after 52 weeks of treatment. Baseline HbA1c was defined as the last available

HbA1c measurement prior to the start of randomized study treatment (excluding values taken before a washout period, when applicable).

The non-inferiority margin for linagliptin versus glimepiride was set at 0.35% (two-sided 97.5% CI). The mean treatment difference in HbA1c from baseline to 52 weeks with linagliptin compared to glimepiride was 0.22% (97.5% CI: 0.13, 0.31), showing non-inferiority of linagliptin compared to glimepiride (1-sided p-value for non-inferiority=0.0007 <1-sided alpha=0.0125), based on a non-inferiority margin of 0.35%.

Table 29 Adjusted Means for Change in HbA1c (%) from Baseline to Week 52—Study 20, FAS—LOCF

	Linagliptin	Glimepiride
Number of patients	766	761
Number of patients with baseline and on-treatment results	766	761
Baseline		
Mean (SE)	7.69 (0.03)	7.70 (0.03)
Change from baseline		
Mean (SE)	-0.43 (0.03)	-0.65 (0.03)
Adjusted[1] mean (SE)	-0.38 (0.03)	-0.60 (0.03)
Treatment difference comparison (linagliptin – glimepiride)		
Adjusted[1] mean (SE)		0.22 (0.04)
97.5% Confidence interval		(0.13, 0.31)
1-sided p-value (non-inferiority)		0.0007
2-sided p-value (superiority)		<0.0001

[1] Model includes continuous baseline HbA_{1c}, number of prior antidiabetic drugs, and treatment
SE=Standard error

Source (b) (4), Table 11.4.1.1.1: 1, page 81

Reviewer's Comments

The applicant met their objective and was able to display noninferiority with this study. Clearly, glimepiride provides better glycemic control than linagliptin based on the adjusted mean. The rate of patients discontinuing from either arm of the study was similar. The major problem with the interpretation of the findings come from the study design. The maximum dose of glimepiride given in this study was 4 mg, with most patients on 3 mg. Therefore, linagliptin is noninferior to glimepiride, at least to the doses of glimepiride tested in the study, which were not the maximal daily approved dose of 8 mg. Clinical application of this study is limited. The label discussion of this study will be edited to clarify this. The mean glimepiride dose of 3 mg should also be stated in the label.

The mean change from baseline in HbA1c over time is shown in Figure 18 and was analyzed using the same model as the primary analysis. Both treatment groups show a decrease from baseline to week 16 in HbA1c. The decreases in the glimepiride group

are greater, which is consistent with Table 29. After week 16 the values start to increase in the glimepiride group and are more stable in the linagliptin group. The difference between the groups was statistically significant at all time points ($p<0.0001$) for all weeks except week four, in favor of glimepiride.

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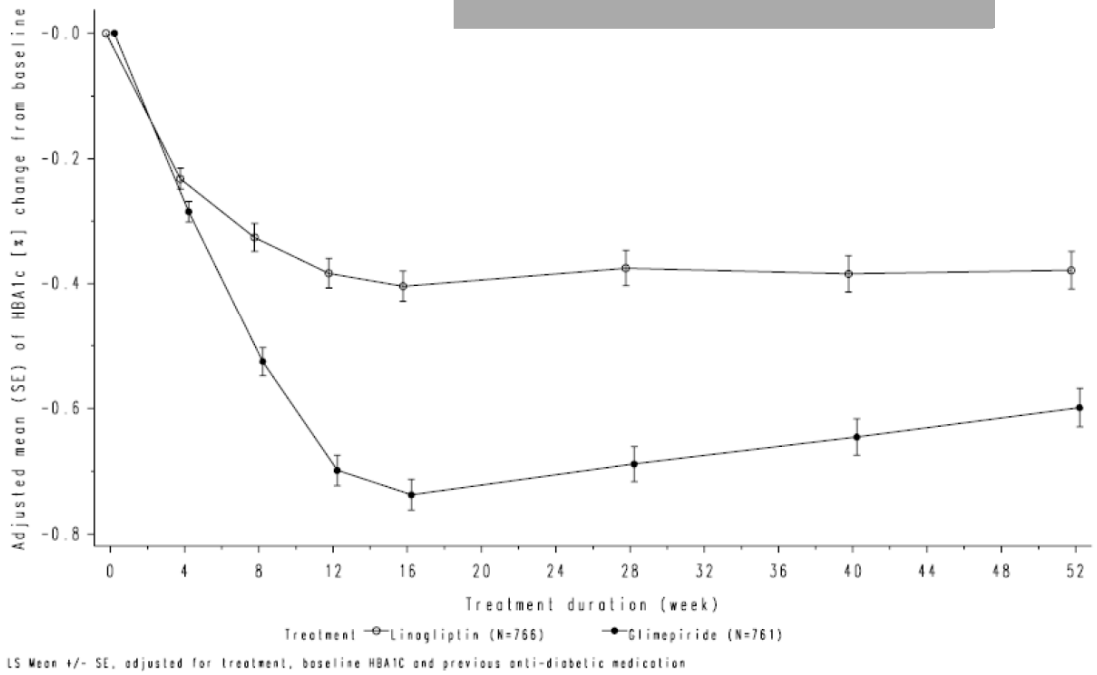


Figure 18 Adjusted Mean HbA1c (SE) Over Time, Study 20—FAS
Source (b) (4) Figure 11.4.1.1.2: 1

Reviewer's Comments
The improvement in HbA1c when compared to glimepiride is noninferior by statistical analysis. However, from Table 29 and Figure 18, the HbA1c values, while they do begin to increase around week 16 in the active control arm, are better on glimepiride. Linagliptin was non-inferior by the predetermined margin, but the mean dose of glimepiride was only 3 mg. Furthermore, the non-inferiority result contrasts the data revealing better glycemic control with glimepiride therapy. Most importantly, this study was reviewed in the context of other efficacy and safety data to determine the overall benefit of linagliptin.

The results over time, and also at week 52 were explored through the OC sensitivity analysis. While linagliptin results in improvement of the HbA1c as discussed above, the difference between the improvements caused by glimepiride, at every checked time point, are significantly better than those caused by linagliptin.

Table 30 Adjusted Means for HbA1c (%) Change from Baseline Over Time in Repeated Analysis—Study 20, OC

	Linagliptin			Glimepiride			Difference Linagliptin - Glimepiride				
	N	Adj* mean	SE	N	Adj* mean	SE	Adj* mean	SE	95% CI LL	95% CI UL	p-value
Baseline (unadjusted means)	766	7.69	0.03	761	7.70	0.03					
Change from baseline at Week 4	754	-0.23	0.02	749	-0.28	0.02	0.05	0.02	0.01	0.10	0.0223
Change from baseline at Week 8	730	-0.34	0.02	715	-0.55	0.02	0.21	0.03	0.15	0.27	<0.0001
Change from baseline at Week 12	707	-0.41	0.02	696	-0.74	0.02	0.33	0.03	0.27	0.40	<0.0001
Change from baseline at Week 16	705	-0.42	0.02	691	-0.78	0.02	0.35	0.03	0.29	0.42	<0.0001
Change from baseline at Week 28	675	-0.40	0.03	672	-0.73	0.03	0.33	0.04	0.25	0.40	<0.0001
Change from baseline at Week 40	620	-0.43	0.03	632	-0.70	0.03	0.27	0.04	0.19	0.35	<0.0001
Change from baseline at Week 52	556	-0.44	0.03	559	-0.64	0.03	0.20	0.04	0.12	0.29	<0.0001

Source (b) (4), Table 15.2.1.2.1: 9, page 285

Reviewer's Comments

The OC sensitivity analysis is consistent with the FAS analysis. Overall, glimepiride provides glycemic control that is superior to that of linagliptin. However, the degree of glycemic control is not the only factor affecting the choice of an antidiabetic product. As I will discuss in the safety review of this study, glimepiride is associated with more hypoglycemia and weight gain, compared to linagliptin, and all these factors are important considerations to inform the prescriber.

Study 35—Add on to SU Study

There were 82 patients treated with placebo and 158 patients treated with linagliptin in the FAS. The mean treatment difference, adjusted for prior use of OAD and baseline HbA1c, at the end of 18 weeks of treatment with linagliptin or placebo, was -0.5% (95% CI -0.7, -0.2) in HbA1c change from baseline to 18 weeks (p<0.0001).

Table 31 Adjusted Means for Change in HbA1c (%) from Baseline to Week 18—Study 35, FAS

	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

Source (b) (4), Table 11.4.1.1.1: 1, page 78

Reviewer's Comments
The adjusted mean change in HbA1c at 18 weeks of treatment is consistent with that seen in the other efficacy trials.

The between groups difference in adjusted mean change in HbA1c is the same in the analyses of both the OC and FAS datasets. See Table 32.

Table 32 Adjusted means for HbA1c (%) change from baseline at Week 18—Study 35, OC

	Placebo	Linagliptin
Number of patients in analysis set	77	150
Number of patients analysed	65	139
Baseline		
Mean (SE)	8.59 (0.09)	8.58 (0.07)
Week 18		
Mean (SE)	8.41 (0.12)	7.93 (0.09)
Change from baseline		
Mean (SE)	-0.18 (0.09)	-0.65 (0.08)
Adjusted* mean (SE)	-0.14 (0.11)	-0.61 (0.07)
Comparison vs. Placebo (diff. Linagliptin - Placebo)		
Adjusted* mean (SE)		-0.47 (0.13)
95% Confidence interval		(-0.72, -0.22)
p-value		0.0002

Source (b) (4) Table 15.2.1.2.1: 2, page 219

From baseline to Week 18, across each visit differences between the adjusted means of HbA1c (linagliptin - placebo) was observed as seen in Figure 19.

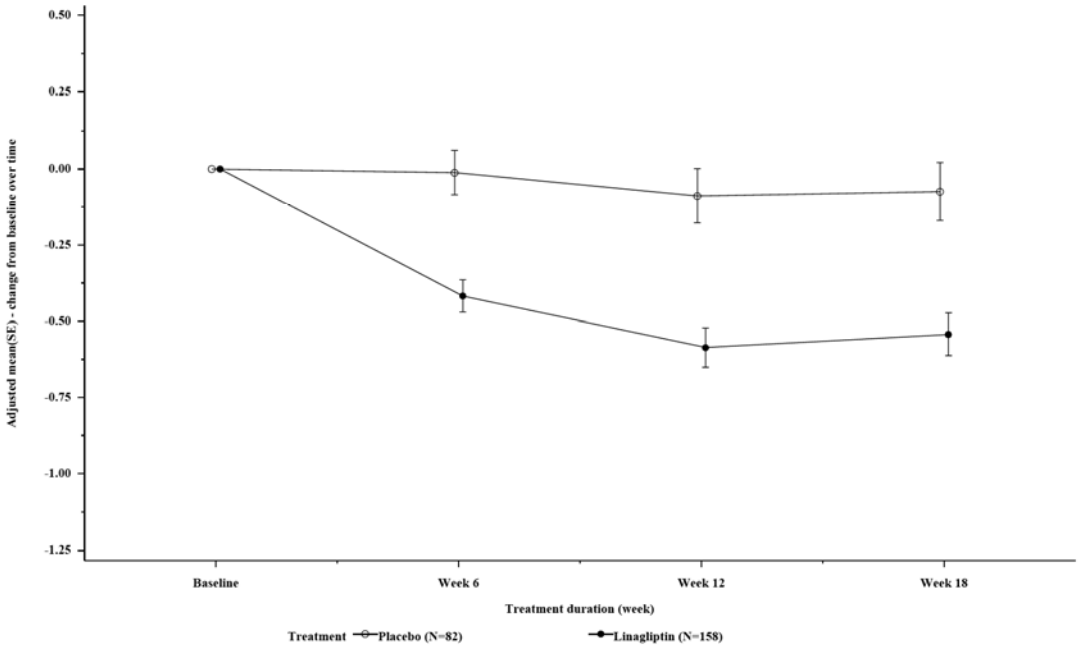


Figure 19 Adjusted HbA1c Mean Change from Baseline Over Time—Study 35, FAS
Source (b) (4) Figure 15.2.1.2.2: 1, page 188

Reviewer's Comments
The improvement seen by week 6 is consistent with that of the other efficacy trials. The slight increase seen between weeks 12 and 18 could be an effect of the smaller population size of this trial. The plateau effect does begin to appear around week 12 in the larger scale trials.

Trials with Long Term Treatment

Study 40—Long Term Extension Study

The HbA1c results in this study were secondary endpoints. As discussed, the old linagliptin group is defined as patients in the four pivotal trials that had been linagliptin during the 24 week treatment time. The new linagliptin group consists of patients switched to linagliptin from placebo at week 24. In the old linagliptin group, the mean reduction in HbA1c levels achieved during the 24 weeks of treatment in the previous trials was maintained through 66 weeks of treatment, although a large proportion of patients dropped out towards the end of the extension period. In the new linagliptin group, a decrease in HbA1c levels until Week 30 was observed as expected. Please see Table 33.

Table 33 Descriptive Statistics of HbA1c (%) Over Time by Exposure to Linagliptin—Study 40, Treated Set

	Old lina (N=1532)						New lina (N=589)					
	N	Mean	SD	Min	Median	Max	N	Mean	SD	Min	Median	Max
Baseline	1532	7.38	0.90	5.1	7.30	12.3	589	7.87	1.04	5.3	7.80	11.7
Week 6	1444	7.35	0.91	5.1	7.20	12.9	548	7.40	0.89	4.9	7.30	10.6
Week 18	1459	7.35	0.88	4.9	7.20	11.7	567	7.18	0.83	4.8	7.10	10.4
Week 30	1419	7.32	0.86	5.1	7.20	12.7	548	7.18	0.84	4.9	7.10	10.5
Week 42	1032	7.38	0.81	5.3	7.30	11.1	408	7.26	0.84	5.3	7.20	11.3
Week 54	342	7.44	0.86	5.4	7.30	11.4	127	7.32	0.91	5.3	7.30	10.5
Week 66	26	7.32	0.65	6.2	7.40	8.6	7	7.56	0.94	6.4	7.30	8.9
Change from baseline to week 6	1444	-0.02	0.48	-3.5	0.00	3.0	548	-0.47	0.51	-2.7	-0.40	1.1
Change from baseline to week 18	1459	-0.01	0.70	-4.8	0.00	3.0	567	-0.68	0.78	-4.3	-0.60	2.1
Change from baseline to week 30	1419	-0.04	0.81	-4.4	0.00	5.1	548	-0.66	0.87	-4.7	-0.60	2.3
Change from baseline to week 42	1032	0.02	0.80	-4.2	0.10	3.5	408	-0.61	0.91	-4.1	-0.50	2.3
Change from baseline to week 54	342	0.16	0.86	-4.1	0.20	4.4	127	-0.36	0.92	-2.8	-0.40	2.5
Change from baseline to week 66	26	0.28	0.60	-1.0	0.30	1.5	7	-0.21	0.72	-0.9	-0.40	1.2

Source (b) (4) Table 15.2.2.1.1: 1, page 191

The mean change from baseline in HbA1c in the patients who participated the pivotal studies and then continued in the extension study 40 is displayed in Figure 20. The results are shown by the treatment groups the patients were assigned to in the initial studies. “Placebo/lina” represents patients randomized to placebo in the initial studies and switched to linagliptin in the extension study. The group designated “Lina 5 mg” is the patients who were already on linagliptin in the initial studies. The applicant shows results for a duration up to 78 weeks, because the number of patients with efficacy data after 90 weeks of treatment was small (n = 26). For this analysis, the applicant displays the OC data, with no missing data imputed.

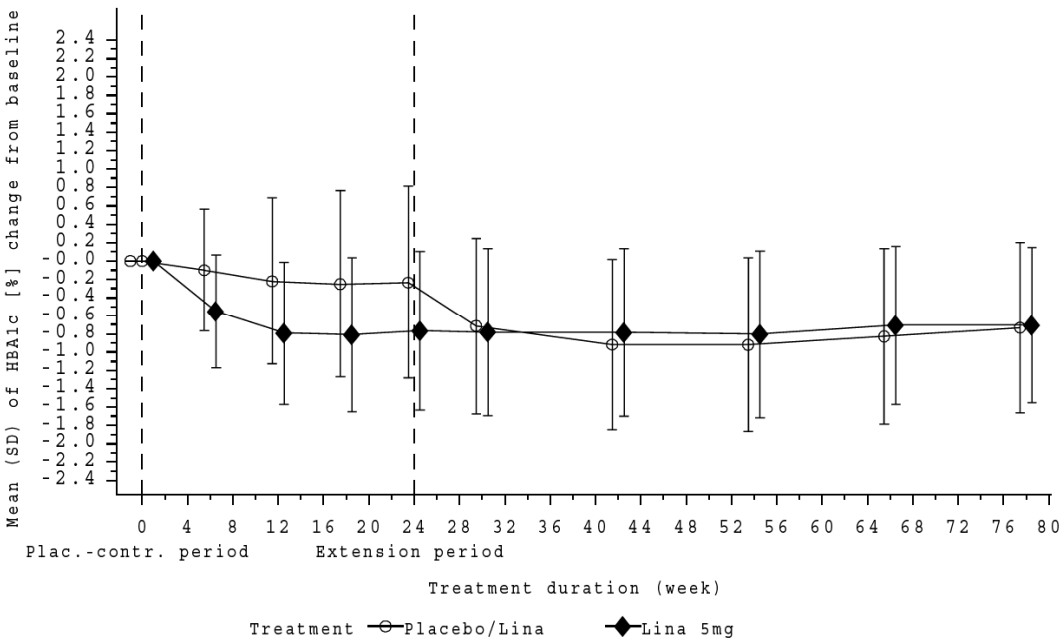


Figure 20 Mean Change From Baseline in HbA1c over time in the Pivotal Studies and the Extension Study 40
Source (b) (4), Figure 5.1: 3, page 133

Reviewer's Comments
This extension study was designed primarily to assess safety; efficacy data are only exploratory. Overall, it is reassuring that the linagliptin effect on glycemic control remains stable. Study 18 (pivotal study, add on to metformin and SU), in contrast to other pivotal studies, displayed an upward trend in glycemic control and thus maintained long term efficacy is important to consider.

Study 23—Active Control with Voglibose

The analysis after the first 12 weeks of the study treatment compared linagliptin to placebo. As seen in Table 34, the adjusted mean change from baseline in HbA1c at Week 12 in the relevant 5 mg group was -0.2% for linagliptin 5 mg and 0.6% for placebo.

Table 34 Adjusted Mean for the Change in HbA1c (%) from Baseline at Week 12—FAS, Study 23

	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	

Source (b) (4) Table 11.4.1.1.1.1: 1, page 157

Adjusted mean changes from baseline in HbA1c at Week 26 were -0.1% for linagliptin 5 mg, -0.2% for linagliptin 10 mg, and 0.2% for voglibose. These results are displayed in Table 35.

Table 35 Adjusted Mean for Change in HbA1c (%) from Baseline at Week 26—Study 23, FAS

	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 (b) (4) Table 11.4.1.1.1.2: 1, page 158

Mean baseline value and adjusted mean change from baseline in HbA1c at Week 52 were 8.07% and 0.07% for linagliptin 5 mg. See Table 36.

Table 36 Adjusted Mean for Change in HbA1C (%) Week 52 for Patients Who Started with Linagliptin—Study 23, FAS

	Linagliptin 5 mg
Number of patients	159
Number of patients with baseline and on-treatment results	159
Baseline	
Mean (SE)	8.07 (0.05)
Change from baseline	
Mean (SE)	-0.16 (0.07)
Adjusted[1)] mean (SE)	0.07 (0.08)

Adapted from (b) (4) Table 11.4.1.2.1.4: 2, page 176

Reviewer's Comments

As we have data from longer than 12 weeks for linagliptin, voglibose is not marketed in the U.S. and there is no placebo compared adjusted mean for the 52 week data, the results have limited usefulness.

6.1.5 Analysis of Secondary Endpoints(s)

Pivotal Trials

Fasting Plasma Glucose (FPG)

Results of linagliptin effects on fasting plasma glucose are proposed for labeling. The change from baseline in FPG after 24 weeks of treatment was a secondary endpoint in all of the pivotal studies. It was analyzed in a statistically similar way as described in Section 5.2 Review Strategy for the HbA1c change from baseline. The analysis of FPG was performed in an exploratory fashion, without adjusting for multiple testing.

The analysis of the FPG change from baseline in the four pivotal studies showed that treatment with linagliptin alone or in combination with one or two OADs led to a lowering of FPG from baseline after 24 weeks of treatment. However, this effect varied across the studies. The adjusted mean difference between linagliptin and placebo in the FPG change from baseline was smaller in studies 15 (add on to pioglitazone; both pioglitazone and linagliptin as initial therapy) and 18 (add on to metformin and SU) (-14. mg/dL and -13. mg/dL respectively) than in studies 16 (placebo only) and 17 (add on to metformin) (-23 mg/dL and -21 mg/dL respectively). This is seen in Table 37.

Table 37 Change from Baseline in FPG (mg/dL) After 24 Weeks in the Pivotal Studies—FAS

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 (b) (4) Table 3.2.1.2: 1, page 87

Reviewer's Comments

As noted, studies 15 and 18 had lower mean responses in FPG. For study 15, although the FPG adjusted mean is lower than the other studies, this can be explained by examining the breakdown of both arms; the linagliptin (plus pioglitazone) group and placebo (pioglitazone only) group. Patients were completely washed out in this study as there was no ongoing therapy. Therefore, the patients that began two therapies (linagliptin plus pioglitazone) had a more dramatic response than those that began just the pioglitazone alone.

In study 18, there were two ongoing therapies, therefore the baseline FPG was already better than those in the other studies. The subsequent improvement is not as robust.

The only study that examined linagliptin treatment in monotherapy in this group is study 16 (linagliptin versus placebo). A more robust response, as seen here, might be expected if linagliptin is to provide glycemic benefit.

Patients with HbA1c <7% on Treatment

For patients treated with linagliptin, the proportion of patients with HbA1c <7.0% after 24 weeks of treatment ranged from 28.2% in study 16 (linagliptin versus placebo only) to 42.9% in study 15 (pioglitazone or pioglitazone plus linagliptin with no prior medication due to washout). Placebo patients had lower percentages of people achieving this level of glycemic control.

The results from the logistic regression showed that the odds of achieving an on-treatment HbA1c <7.0% after 24 weeks of treatment were significantly higher for patients treated with linagliptin than those receiving placebo, in all pivotal studies. These data are all presented in Table 38.

Table 38 Patients with HbA1c below 7% after 24 Weeks in the Pivotal Studies, FAS

	Patients with HbA_{1c} <7.0%, N (%)			Logistic regression	
Study/ treatment group	No	Yes	Total	Odds ratio linagliptin:placebo	p-value
1218.15/				2.09 [a]	0.0055 [a]
Placebo	89 (69.5)	39 (30.5)	128 (100.0)		
Linagliptin	144 (57.1)	108 (42.9)	252 (100.0)		
1218.16/				2.48 [a]	0.0007 [a]
Placebo	138 (84.7)	25 (15.3)	163 (100.0)		
Linagliptin	239 (71.8)	94 (28.2)	333 (100.0)		
1218.17/				4.29 [a]	<0.0001 [a]
Placebo	155 (88.6)	20 (11.4)	175 (100.0)		
Linagliptin	368 (71.7)	145 (28.3)	513 (100.0)		
1218.18/				5.60 [b]	<0.0001 [b]
Placebo	238 (90.8)	24 (9.2)	262 (100.0)		
Linagliptin	535 (68.8)	243 (31.2)	778 (100.0)		
EFF-1 pool/				3.49 [c]	<0.0001 [c]
Placebo	620 (85.2)	108 (14.8)	728 (100.0)		
Linagliptin	1286 (68.6)	590 (31.4)	1876 (100.0)		

a Model includes baseline HbA_{1c}, washout, and treatment
b Model includes baseline HbA_{1c} and treatment
c Model includes baseline HbA_{1c}, washout, treatment, and study

Source (b) (4) Table 3.2.1.3: 1, page 88

Reviewer's Comments

Studies 15 and 18 have the highest proportion of linagliptin-treated patients with HbA1c below 7% at the end of the treatment period. Study 15 was designed to evaluate the effect of one or two new drugs in treatment-naïve subjects, which could explain the more robust glycemic control in this case. Study 18 had two ongoing therapies with an added one (linagliptin). This more robust glycemic

control could be due to the three therapies in this grouping; there were no other arms in the pivotal studies that had three medications simultaneously.

Use of Rescue Therapy

As an additional measure for the efficacy of treatment with linagliptin, the applicant analyzed how many patients in the pivotal studies required rescue medication. Rescue medication was defined as rescue therapy as pre-specified in the trial protocols as well as any addition of an OAD to the treatment regimens and dose increases of background OADs after randomization.

For study 15 and 16:
Rescue was initiated in case a patient has a confirmed glucose level >240 mg/dl (>13.3 mmol/L) after an overnight fast.

Metformin will be given as rescue therapy to the end of the trial. In case rescue medication has to be initiated, this should be undertaken in accordance with the metformin label.

If glucose levels remain >240 mg/dl despite introduction of metformin, the patient was discontinued from the trial.

For study 17:
Rescue had the same rules but glimepiride was used.

For study 18:
Rescue had the same rules but pioglitazone was used.

Fewer patients treated with linagliptin required rescue therapy compared with patients receiving placebo. As seen in Table 39, of the patients treated with linagliptin, only between 5.4% (18) and 10.2% (16) needed rescue medication, compared with 13.0% (18) to 20.9% (16) of in the placebo groups. Overall, only 7.2% of all patients treated with linagliptin needed rescue therapy, but 16.3% of those receiving placebo needed rescue.

Table 39 Number of Patients with Use of Rescue Medication in the Pivotal Trials, FAS

	Placebo			Lina 5mg		
	Rescue Medication			Rescue Medication		
Trial Number	No N[%]	Yes N[%]	Total N[%]	No N[%]	Yes N[%]	Tota N[%]
1218.15	110 (85.9)	18 (14.1)	128 (100.0)	232 (92.1)	20 (7.9)	252
1218.16	129 (79.1)	34 (20.9)	163 (100.0)	299 (89.8)	34 (10.2)	333
1218.17	142 (81.1)	33 (18.9)	175 (100.0)	473 (92.2)	40 (7.8)	513
1218.18	228 (87.0)	34 (13.0)	262 (100.0)	736 (94.6)	42 (5.4)	778
Pooled	609 (83.7)	119 (16.3)	728 (100.0)	1740 (92.8)	136 (7.2)	1876

Source ISE, Table 4.1.7.1, page 1121

The logistic regression showed that the odds of requiring rescue therapy were significantly lower for patients treated with linagliptin than for those receiving placebo in all four studies. The odds ratios for linagliptin:placebo ranged from 0.28 in study 17 to 0.46 in study 15. This indicates that the odds of requiring rescue medication were about two to four times lower for patients treated with linagliptin than for those receiving placebo in the context of the specific trials as designed (i.e., HbA1c range at baseline, study duration, glycemic improvement in the placebo depending on factors independent of linagliptin's effects).

Two Hour Post Prandial Glucose (2hPPG)

Only pivotal studies 16 (linagliptin in monotherapy) and 17 (linagliptin as add-on to metformin plus SU) had two hour PPG values measured following standardized mixed meals tests (MTT). In these trials, MTT were performed on a subgroup of patients at baseline and then at 24 weeks of treatment. The change from baseline in plasma glucose values two hours after intake of a standardized meal was analyzed. The MTT set of patients had a valid MTT performed and recorded at baseline.

Linagliptin was superior to placebo in reducing 2hPPG levels after 24 weeks of treatment in both studies. Based on the pooled results from these two studies, the treatment difference in the adjusted mean 2hPPG change was -61 mg/dL ($p < 0.0001$). The treatment difference in study 17 (-66 mg/dL) was higher than in study 16 (-57 mg/dL), which was possibly due to higher mean baseline 2hPPG levels in study 17 (linagliptin: 270 mg/dL; placebo: 274 mg/dL) than in study 16 (linagliptin: 258 mg/dL; placebo: 244 mg/dL). See Table 40.

Table 40 Change from Baseline in 2hPPG (mg/dL) in Studies 16 & 17, MTT set

Study/ treatment group	Number of patients	Baseline 2hPPG, mean (SD)	Change from baseline in 2hPPG		Difference from placebo		
			Mean (SD)	Adjusted mean (SE) [a]	Adjusted mean (SE) [a]	95% CI	p-value
1218.16/							
Placebo	24	243.75 (83.34)	27.42 (52.74)	19.11 (11.42)			
Linagliptin	67	258.00 (79.72)	-35.48 (59.13)	-37.40 (6.82)	-56.51 (13.27)	(-82.69, -30.34)	<0.0001
1218.17/							
Placebo	21	274.48 (68.36)	23.24 (76.63)	28.10 (12.43)			
Linagliptin	78	269.89 (66.57)	-39.55 (69.20)	-37.51 (6.81)	-65.61 (13.71)	(-92.67, -38.56)	<0.0001
EFF-9 pool/							
Placebo	45	258.09 (77.43)	25.47 (64.25)	23.61 (8.44)			
Linagliptin	145	264.40 (72.92)	-37.67 (64.55)	-37.46 (4.82)	-61.06 (9.54)	(-79.88, -42.25)	<0.0001

a Model includes baseline HbA_{1c}, baseline 2hPPG, washout, treatment, study, and treatment-by-study interaction

Source (b) (4) Table 3.2.7.1: 1, page 109

Reviewer's Comments
These 2hPPG results are very similar for both studies and show the improvement caused by linagliptin treatment.
Since linagliptin has an incretin based mechanism of action, I do expect to see that the post prandial glucose effects that are larger than that seen in the fasting glucose results. This was observed as expected.

Monotherapy

Study 50 (nonpivotal placebo-only arm) is discussed here, as study 16 (the other monotherapy study) is covered under Pivotal Studies discussions.

Fasting Plasma Glucose (FPG)

The adjusted mean difference (linagliptin minus placebo) in change from baseline in FPG after 18 weeks was -20 mg/dL with 95% confidence interval (-31, -10). This difference was statistically significant (p=0.0002). Of note, there were 17 patients in the FAS (7 placebo, 9 linagliptin) who were not included in the analysis because they did not have both a baseline and a post-baseline FPG value.

Table 41 Adjusted Means for the Change in FPG (mg/dL) from Baseline at Week 18—FAS, Study 50

	Placebo	Linagliptin
Number of patients in analysis set	73	147
Number of patients analysed	66	138
Baseline		
Mean (SE)	175.6 (4.5)	178.4 (3.6)
Change from baseline		
Mean (SE)	7.2 (4.4)	-14.3 (3.6)
Adjusted[1] mean (SE)	7.2 (6.0)	-13.3 (5.2)
Comparison vs. placebo (difference linagliptin – placebo)		
Adjusted[1] mean (SE)		-20.5 (5.4)
95% Confidence interval		(-31.1, -9.9)
p-value		0.0002

1 Model includes continuous baseline HbA_{1c}, continuous baseline FPG, number of prior anti-diabetes drugs, reason for metformin intolerance and treatment

Source (b) (4) Table 11.4.1.2.1: 1, page 85

Reviewer's Comments
This result is similar to that seen in the pivotal studies.

Patients with HbA1c <7% on Treatment

In patients with baseline HbA1c ≥7.0%, 11.8% of patients in the placebo group and 23.5% of the patients in the linagliptin group achieved HbA1c <7.0% at Week 18 (Table 42). The odds for patients with a baseline HbA1c of ≥7.0% to have a response of HbA1c reduced to <7.0% at 18 weeks was over 2.5 times higher for patients treated with linagliptin compared with placebo (odds ratio = 2.576; 95% confidence interval (1.057, 6.279)).

Table 42 Number of Patients with HbA1c <7% at Week 18—Study 50, FAS

	Placebo (N=73)			Linagliptin (N=147)		
	HbA1c<7.0%			HbA1c<7.0%		
	No	Yes	Total	No	Yes	Total
Baseline HbA1c [N (%)]						
N(non-missing)	62 (84.9)	11 (15.1)	73 (100.0)	106 (72.1)	41 (27.9)	147 (100.0)
<7%	2 (40.0)	3 (60.0)	5 (100.0)	2 (18.2)	9 (81.8)	11 (100.0)
>=7%	60 (88.2)	8 (11.8)	68 (100.0)	104 (76.5)	32 (23.5)	136 (100.0)

Source, adapted from (b) (4), Table 15.2.2.2: 2, page 232

Reviewer's Comments
The result of 23.5% of linagliptin patients achieving HbA1c less than 7% is similar to that seen in the pivotal studies and is especially close to the value seen in study 16 (28.2%) for all patients achieving HbA1c of less than 7%. Study 16 is also a monotherapy trial.

Use of Rescue Therapy

Use of rescue therapy was initiated in this trial if during the first 12 weeks of randomized treatment, a patient had a confirmed glucose level >240 mg/dL (>13.3 mmol/L) after an overnight fast, or a glucose level of >400 mg/dL (>22.2 mmol/L) (>324 mg/dL (>18 mmol/L) in Ukraine. During the remaining weeks of randomized treatment, rescue medication was initiated only if a patient had a confirmed glucose level of >200 mg/dL (11.1 mmol/L) after an overnight fast, or of >400 mg/dL (>22.2 mmol/L) (>324 mg/dL (>18 mmol/L) in Ukraine.

The percentage of patients requiring rescue therapy during Part One of the trial was higher in the placebo group (17.8%) compared with the linagliptin group (11.6%), see Table 43. From the logistic regression analysis (adjusted for stratification factors and baseline HbA1c), the odds of requiring rescue therapy was less than half for patients treated with linagliptin compared with those treated with placebo (odds ratio = 0.444; 95% confidence interval (0.181, 1.090)).

Table 43 Number of Patients with Rescue Therapy, Study 50, FAS

	Placebo	Linagliptin
Number of patients	73 (100.0)	147 (100.0)
Rescue medication [N (%)]		
N	73 (100.0)	147 (100.0)
Yes	13 (17.8)	17 (11.6)
No	60 (82.2)	130 (88.4)

Source adapted from (b) (4) Table 15.2.3.1: 2, page 245

Reviewer's Comments
These results are consistent with those seen in the pivotal studies.

Combination Therapy

There are two studies used to support this indication in addition to those from the pivotal studies. One is study 20 (active control study against glimepiride) and study 35 (18 week study add on to SU study). With the exception of the FPG, only study 20 (active control study) will be discussed here. For FPG data, which is referenced in the proposed labeling, both studies are discussed. For other secondary endpoints, the data from the 52 week, a much larger scale study, will be discussed.

Use of Rescue Therapy

Study 20—Active Control Study

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 significant treatment difference in the adjusted mean FPG change of 7.62 mg/dL (p <0.0001; Table 44) was observed.

Table 44 Change from Baseline in FPG (mg/dL) after 52 Weeks—Study 20, FAS

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 (b) (4) Table 3.2.2.3: 1, page 94

Reviewer's Comments
This result is consistent with the primary endpoint analysis that glimepiride provides better glycemic control. As discussed with previous analyses, this will be considered as part of the risk/benefit analysis for linagliptin. Linagliptin was found noninferior based on the agreed margin for HbA1c.

Study 35—Add on to SU Study

Study 35 compared linagliptin with placebo added to ongoing therapy with an SU. All patients in this study had been pre-treated with an SU; those who had received an additional OAD at enrollment washed out the additional OAD before randomization. The adjusted mean FPG reduction from baseline after 18 weeks was greater for linagliptin than for placebo (-6.42 mg/dL), however this was not statistically significant (p = 0.2406; Table 45).

Table 45 Change from Baseline in FPG (mg/dL)—Study 35, FAS

Grouping/ Study/ treatment group	Number of patients [a]	Baseline FPG, mean (SD)	Change from baseline in FPG		Difference from placebo		
			Mean (SD)	Adjusted mean (SE) [b]	Adjusted mean (SE) [b]	95% CI	p-value

EFF-7/1218.35/				**Endpoint assessed after 18 weeks**			
Placebo	78	171.00 (46.88)	1.21 (43.79)	-1.79 (4.54)			
Linagliptin	155	180.10 (49.82)	-10.05 (46.75)	-8.21 (3.28)	-6.42 (5.46)	(-17.18, 4.34)	0.2406

Source (b) (4) adapted from Table 3.2.6.2: 1, page 107

Reviewer's Comments
The applicant notes that this study does have a smaller sample size than the other larger efficacy trials. This could account for the lack of statistical significance.

Patients with HbA1c <7% on Treatment

Among patients with baseline HbA1c ≥7.0%, 29.6% of the patients in the linagliptin group and 38.9% of the patients in the glimepiride group achieved HbA1c <7.0% (Table 46). This was calculated using a noncompleters considered failure (NCF) approach. This means that missing data due to premature discontinuation was considered a failure.

Table 46 Number of Patients with HbA1c <7% at Week 52—Study 20, NCF FAS

	Linagliptin			Glimepiride		
	n[1]	(%)	N[2]	n[1]	(%)	N[2]
Response criterion						
HbA_{1c}<7.0%	303	(39.6)	766	340	(44.7)	761
Among patients with baseline HbA_{1c} ≥7.0%	175	(29.6)	592	233	(38.9)	599

Source (b) (4), Adapted from Table 11.4.1.2.3: 1, page 91

Use of Rescue Therapy

For study 20, pioglitazone was the rescue medication. Rescue medication could be initiated only during the randomized period if a patient had a confirmed glucose level >240 mg/dL (>13.3 mmol/L) after an overnight fast. It could also be initiated if HbA1c >8.5% during the treatment phase from week 28 to week 104.

The proportion of patients requiring rescue therapy was higher in the linagliptin group compared to the glimepiride group (16.3% in the linagliptin group and 12.1% in the glimepiride group) (Table 47).

Table 47 Number of Patients with Rescue Therapy—Study 20, FAS

	Linagliptin			Glimepiride		
	Rescue Medication			Rescue Medication		
	No	Yes	Total	No	Yes	Total
Total						
N (%)	641 (83.7)	125 (16.3)	766 (100.0)	669 (87.9)	92 (12.1)	761 (100.0)

Source (b) (4) Table 15.2.3.1: 2, page 401

Reviewer's Comments
From the primary endpoint efficacy discussion and other endpoint discussions of study 20, it is expected that more patients in the linagliptin group would need rescue than in the glimepiride group, as glycemic control is worse on linagliptin.

Two Hour PPG

The change in 2hPPG was analyzed for the **MTT52 set** (the group in the study for which MMT results are available). Missing values were imputed (LOCF approach). The adjusted mean change from baseline in 2hPPG at Week 52 was similar between the two treatment groups, (p=0.7502).

Table 48 Adjustment Means for the Change from Baseline in 2hPPG at Week 52—Study 20, MTT52 set

	Linagliptin	Glimepiride
Number of patients in analysis set	252	249
Number of patients with baseline and on-treatment results	146	143
Baseline		
Mean (SE)	258.36 (6.02)	268.35 (6.04)
Change from baseline		
Mean (SE)	-32.92 (5.39)	-36.16 (5.82)
Adjusted[1] mean (SE)	-31.98 (5.19)	-29.85 (5.21)
Treatment difference comparison (linagliptin – glimepiride)		
Adjusted[1] mean (SE)		-2.13 (6.70)
95% Confidence interval		(-15.31, 11.04)
p-value		0.7502

[1] Model includes continuous baseline HbA_{1c}, continuous baseline 2hPPG, number of prior antidiabetic drugs, and treatment

Source Table 11.4.1.2.4: 2, page 92

Reviewer's Comments
Most endpoints examined in this study show better treatment effect with glimepiride.

6.1.6 Other Endpoints

Weight

Weight was a secondary endpoint in study 20 (active control study with glimepiride). Specifically, the applicant looked at change from baseline in body weight after 52 weeks of treatment.

After 52 weeks of treatment, a decrease in mean body weight was noted for the patients treated with linagliptin (adjusted mean change -1.13 kg), as opposed to a mean weight gain in the patients receiving glimepiride (1.36 kg). Linagliptin was shown to be superior to glimepiride with change in body weight after 52 weeks of treatment, with a treatment difference of -2.49 kg (p <0.0001; Table 49).

Table 49 Change from baseline in body weight [kg] after 52 weeks in the active controlled trial—Study 20, FAS

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 (b) (4), Table 3.2.2.2: 1, page 93

Reviewer's Comments
The applicant proposes to discuss this weight change difference in the label under the efficacy table for study 20 in section 14. This is similar to their discussion of weight change for the other studies presented. In this context, I find this acceptable. However, weight related findings should not be included in the tables for this or other studies. This is consistent with labels for other members of this class.

6.1.7 Subpopulations

The largest pooling of patients for discussion of subgroup analyses are the Pivotal Studies and study 20, the active control study with glimepiride. These are presented here. First, however, is discussion of the study in patients with renal impairment.

Study 43—Study in Renal Impairment

A phase III, randomized, double-blind, placebo-controlled, parallel group, safety and efficacy study of linagliptin (5 mg), compared to placebo as add on to pre-existing antidiabetic therapy (insulin or any combination with insulin; sulfonylurea or glinides as monotherapy; pioglitazone or any other antidiabetics, excluding only DPP-4 inhibitors other than linagliptin) over 52 weeks in type 2 diabetic patients with severe chronic renal impairment

Objective

The objective of this trial was to determine the safety and efficacy of 5 mg linagliptin administered once daily over 52 weeks compared to placebo in patients with T2DM and severe renal impairment (estimated GFR<30 ml/min).

Study Design

After screening, patients entered a two week open-label placebo run-in period. Patients who successfully completed this phase and who still met the inclusion/exclusion criteria were randomized to the 52 week treatment period and received either 5 mg of linagliptin or placebo in addition to their pre-existing insulin and/or sufonylurea therapy. All patients continued their current antidiabetic therapies during the study. The background therapy doses remained unchanged during the first 12 weeks of the treatment period in order to assess the glucose lowering efficacy of linagliptin in this patient population. Dose reduction was allowed for hypoglycemia. The study is ongoing and patients may continue on study medication for up to 52 weeks. During the following 40-week period, the insulin and/or other antidiabetic background therapy dose can be adjusted according to glucose parameters.

Only the first 12 weeks of data were submitted with the NDA and are reported here.

Primary endpoint:

The change from baseline in HbA1c (HbA1c after 12 weeks of treatment).

Main Inclusion Criteria

- Male and female patients with T2DM treated with sulfonylurea and/or subcutaneous insulin and a GFR<30 ml/min (calculated using the MDRD equation) and who were not on any form of chronic dialysis. Insulin and/or sulfonylurea doses were stable for at least 8 weeks. The antidiabetic background therapy could include insulin or any combination of insulin, sulphonylurea or glinides as monotherapy and pioglitazone or any other antidiabetics excluding DPP-4 inhibitors other than linagliptin.
- HbA1c at Visit 1 (Screening): HbA1c >7.0 to ≤10.0%
- Age ≥18 and ≤80 years at Visit 1
- BMI (Body Mass Index) ≤45 kg/m^2 at Visit 1

Main Exclusion Criteria

- Myocardial infarction, stroke or TIA within 6 months prior to informed consent
- Renal impairment requiring any form of chronic dialysis.
- Impaired hepatic tests, defined by serum levels of either ALT (SGPT), AST (SGOT), or alkaline phosphatase above 3 x ULN as determined at Visit 1
- Pre-menopausal women who are nursing or pregnant or are of child-bearing potential and are not practicing an acceptable method of birth control
- Current treatment with systemic steroids at time of informed consent or change in dosage of thyroid hormones within 6 weeks prior to informed consent.
- Renal transplant recipient
- Unstable or acute congestive heart failure

The proportion of patients with a baseline HbA1c <7.0% was 1.6% (1 patient) in the placebo group and larger at 7.6% (5 patients) in the linagliptin group. The distribution of patients on one drug versus two or more drugs was slightly different as well, with more patients on linagliptin being on more than two antidiabetic therapies. See Table 50.

Table 50 Baseline Disease Characteristics – Study 43, FAS

	Placebo	Linagliptin	Total
Baseline HbA_{1c} [%]			
Number of patients, N (%)	62 (100.0)	66 (100)	128 (100)
Mean (SD)	8.2 (0.9)	8.2 (1.1)	8.2 (1.0)
Baseline HbA_{1c} ,categorical, N (%)			
<7.0	1 (1.6)	5 (7.6)	6 (4.7)
7.0 to <8.0	23 (37.1)	29 (43.9)	52 (40.6)
8.0 to <9.0	25 (40.3)	21 (31.8)	46 (35.9)
≥9.0	13 (21.0)	11 (16.7)	24 (18.8)
Number of background antidiabetic drugs, N (%)			
1	51 (82.3)	46 (69.7)	97 (75.8)
2 or more	11 (17.7)	20 (30.3)	31 (24.2)
Baseline FPG [mg/dL]			
Mean (SD)	160.1 (65.4)	149.5 (79.5)	154.6 (72.9)

Source (b) (4), Table 11.2: 3, page 87

The demographic data of the treated set of patients are summarized in Table 51. There were 5 people in the eGFR 30-<60 ml/min grouping taking linagliptin versus 14 patients in the placebo group. See Table 51 for all baseline demographics.

Table 51 Demographic data—Study 43, Treated Set

	Placebo	Linagliptin	Total
Number of patients	65 (100.0)	68 (100.0)	133 (100.0)
Gender [N (%)]			
Male	35 (53.8)	45 (66.2)	80 (60.2)
Race, N (%)			
Asian	11 (16.9)	8 (11.8)	19 (14.3)
Black/African Amer.	7 (10.8)	6 (8.8)	13 (9.8)
Hawaiian/Pacif. Isle	2 (3.1)	1 (1.5)	3 (2.3)
White	45 (69.2)	53 (77.9)	98 (73.7)
Ethnicity, N (%)			
Not Hispanic/Latino	61 (93.8)	64 (94.1)	125 (94.0)
Hispanic/Latino	4 (6.2)	4 (5.9)	8 (6.0)
Age [years]			
Mean (SD)	64.9 (9.6)	64.0 (10.9)	64.4 (10.3)
Age groups [years], N (%)			
<65	30 (46.2)	29 (42.6)	59 (44.4)
65 to 74	25 (38.5)	31 (45.6)	56 (42.1)
≥75	10 (15.4)	8 (11.8)	18 (13.5)
Baseline weight [kg]			
Mean (SD)	85.7 (17.6)	89.9 (19.0)	87.8 (18.3)
Baseline weight, categorical [kg], N (%)			
≤70	15 (23.1)	9 (13.2)	24 (18.0)
>70 to 80	9 (13.8)	13 (19.1)	22 (16.5)
>80 to 90	17 (26.2)	15 (22.1)	32 (24.1)
>90	24 (36.9)	31 (45.6)	55 (41.4)
Baseline BMI [kg/m^2]			
Mean (SD)	31.70 (5.87)	32.32 (5.87)	32.02(5.86)
Baseline BMI, categorical [kg/m^2], N (%)			
<25	8 (12.3)	7 (10.3)	15 (11.3)
25 to <30	19 (29.2)	11 (16.2)	30 (22.6)
≥30	38 (58.5)	50 (73.5)	88 (66.2)
Baseline eGFR (MDRD) [mL/min], N (%)			
≥90	0	0	0
60 to <90	0	0	0
30 to <60	14 (21.5)	5 (7.4)	19 (14.3)
<30	51 (78.5)	63 (92.6)	114 (85.7)

Source (b) (4), Table 11.2: 2, page 85

Reviewer's Comments

The slight imbalances seen in the baseline disease characteristics as well as baseline demographics are likely due to the small number of patients in the study.

The most frequent reasons for premature discontinuation were due to adverse events (9 patients in the placebo group and 4 in the linagliptin group), and refusal to continue medication (4 patients on linagliptin and 0 on placebo).

Table 52 Disposition of Randomized Patients—Study 43

	Placebo N (%)	Linagliptin N (%)	Total N (%)
Enrolled			307
Randomised	65	68	133
Treated[1]	65 (100.0)	68 (100.0)	133 (100.0)
Still on study drug	50 (76.9)	59 (86.8)	109 (82.0)
Not prematurely discontinued trial medication	1 (1.5)	0	1 (0.8)
Prematurely discontinued trial medication	14 (21.5)	9 (13.2)	23 (17.3)
Adverse event	9 (13.8)	4 (5.9)	13 (9.8)
Study disease worsening	0	0	0
Other disease worsening	3 (4.6)	1 (1.5)	4 (3.0)
Other AE	6 (9.2)	3 (4.4)	9 (6.8)
Lack of efficacy [2]	1 (1.5)	0	1 (0.8)
Non-compliance to protocol	0	0	0
Lost to follow-up	2 (3.1)	1 (1.5)	3 (2.3)
Refused to continue trial medication	0	4 (5.9)	4 (3.0)
Other reason	2 (3.1)	0	2 (1.5)

1 In all tables 'treated' refers to treatment with randomised study drug
2 Includes patients who discontinued due to hyperglycaemia

Source (b) (4) Table 10.1: 4, page 78

The primary efficacy analysis was the change from baseline in HbA1c at 12 weeks of treatment analyzed using ANCOVA. The mean treatment difference in HbA1c at the end of 12 weeks of treatment with linagliptin or placebo, was -0.59% (95% CI -0.88, -0.29) in HbA1c change from baseline to 12 weeks.

Table 53 Adjusted Means for Change in HbA1c (%) from Baseline at Week 12—Study 43, FAS

	Placebo	Linagliptin
Number of patients	62	66
Number of patients analysed	62	66
Baseline		
Mean (SE)	8.25 (0.11)	8.19 (0.14)
Change from baseline		
Mean (SE)	0.02 (0.10)	-0.55 (0.12)
Adjusted[1] mean (SE)	-0.18 (0.15)	-0.76 (0.14)
Comparison vs. placebo (difference linagliptin - placebo)		
Adjusted[1] mean (SE)		-0.59 (0.15)
95% Confidence interval		(-0.88, -0.29)
p-value		0.0001

[1] Model includes treatment, continuous HbA1c and creat. clear at baseline and background anti-diab drugs
SE = Standard error
Source (b) (4) Table 11.4.1.1.1: 1, page 91

Reviewer's Comments
The efficacy of linagliptin in the renal impaired population to 12 weeks is in line with the results in typical T2DM patients reported in this review.

Demographics and Baseline Characteristics in Pivotal Studies Subgroups

Renal Impairment

For the subgroup analysis of renal impairment in the pivotal studies, renal impairment analysis was based on the estimated glomerular filtration rate (eGFR), as calculated using the Modification of Diet in Renal Disease (MDRD) formula. The applicant originally planned to investigate four categories (none, mild, moderate, and severe). Limitations to the studies prevented this. Studies 17 and 18 were conducted with metformin as background medication and therefore excluded patients with a serum creatinine level above 1.5 mg/dL. For study 15, patients on hemodialysis were not eligible due to use of a TZD in this study. There were no patients with severe renal impairment in the pivotal studies according to the MDRD classification and the subgroup analysis was confined to the categories: none, mild and moderate.

In general, patients with lower renal function were on average older; the overall mean age increased from 54.0 years in patients with normal renal function to 65.8 years in those with moderate renal impairment. In the moderate impairment group, there is an imbalance in the number of males, with more being in the linagliptin group. See Table 54. There is also an imbalance in the number of white patients in this group; 67.5% in the linagliptin group versus 55.2% in the placebo group.

Table 54 Key Demographics in the Pivotal Studies by Renal Impairment (MDRD)—FAS

Renal impairment [a]/ treatment group	Number of patients	Age, mean (SD) [years]	Male gender, N (%)	Race, N (%)			BMI, mean (SD) [c] [kg/m^2]
				White	Black [b]	Asian	
None (eGFR ≥90 mL/min)/							
Placebo	406	53.6 (10.0)	220 (54.2)	226 (55.7)	4 (1.0)	176 (43.3)	29.07 (4.91)
Linagliptin	1006	54.1 (9.6)	499 (49.6)	558 (55.5)	9 (0.9)	439 (43.6)	28.84 (4.90)
Mild (eGFR 60 to <90 mL/min)/							
Placebo	272	59.9 (9.1)	140 (51.5)	180 (66.2)	0 (0.0)	92 (33.8)	29.30 (4.72)
Linagliptin	715	61.3 (8.7)	374 (52.3)	459 (64.2)	2 (0.3)	254 (35.5)	29.10 (4.86)
Moderate (eGFR 30 to <60 mL/min)/							
Placebo	29	65.4 (6.3)	12 (41.4)	16 (55.2)	0 (0.0)	13 (44.8)	28.56 (4.98)
Linagliptin	80	66.0 (7.8)	39 (48.8)	54 (67.5)	0 (0.0)	26 (32.5)	28.56 (4.30)

a based on eGFR (calculated using the MDRD formula)
b or African American
c baseline value

Source (b) (4) Table 3.1.2.3: 7, page 69

The number of patients that had not been on prior treatment with OADs was higher in the patients with mild renal impairment (23.1%) than in the other two renal impairment categories. The number of patients with a diagnosis of diabetes of more than five years was higher in those with moderate renal impairment (70.6%) than in those with mild impairment (54.9%) and in those with normal renal function (53.9%). Details are seen in Table 55.

Table 55 Key Baseline Characteristics in the Pivotal Studies by Renal Impairment (MDRD)—FAS

Renal impairment/[a] treatment group	Number of patients	Baseline HbA_{1c}, mean (SD) [%]	Baseline FPG, mean (SD) [mg/dL]	Time since diagnosis of diabetes, N (%)	Number of antidiabetic drugs at enrolment, N (%)		
				>5 years	None	One	Two or more
None (eGFR ≥90 mL/min) /							
Placebo	406	8.2 (0.9)	171.4 (41.1)	209 (51.5)	74 (18.2)	124 (30.5)	208 (51.2)
Linagliptin	1006	8.2 (0.9)	167.8 (41.7)	552 (54.9)	137 (13.6)	304 (30.2)	565 (56.2)
Mild (eGFR 60 to <90 mL/min) /							
Placebo	272	8.1 (0.9)	167.1 (40.3)	147 (54.0)	78 (28.7)	88 (32.4)	106 (39.0)
Linagliptin	715	8.1 (0.8)	166.4 (41.1)	395 (55.2)	150 (21.0)	228 (31.9)	337 (47.1)
Moderate (eGFR 30 to <60 mL/min) /							
Placebo	29	8.2 (0.9)	172.1 (43.4)	19 (65.5)	2 (6.9)	9 (31.0)	18 (62.1)
Linagliptin	80	8.3 (1.0)	172.6 (44.6)	58 (72.5)	10 (12.5)	24 (30.0)	46 (57.5)

a Based on eGFR (calculated using the MDRD formula)

Source (b) (4) Table 3.1.2.4: 7, page 76

Reviewer's Comments

The trends seen with the demographics are expected given the nature of the disease. For example, older patients have lower renal function, patients with worse renal function have T2DM diagnosed for longer and are on more previous medications. The racial imbalance is expected, based on my previous efficacy discussion of the pivotal studies, but remains concerning. The applicant has two ongoing studies in patients with renal impairment. One is discussed above, study 43. The other is study 1218.64, a safety and efficacy trial in T2DM patients with moderate to severe renal impairment. There is a 40 week active control (glimepiride) phase of this trial. There are 240 patients enrolled, half of the patients are on each arm. Full reports from these studies will offer more insight into this population.

The frequency of premature discontinuations was similar for patients with normal renal function and those with mild renal impairment (placebo: 7.1% vs. 8.8%; linagliptin: 5.4% vs. 4.3%). Premature discontinuations were seen more often in the patients with moderate renal impairment. Although this difference was seen in both groups, it was more notable for patients in the placebo group than for those in the linagliptin group. Of the patients with moderate renal impairment, 17.2% of those receiving placebo, but only 8.8% of those treated with linagliptin discontinued treatment prematurely.

Age

The applicant defined four age categories, see Table 56. The key demographics are generally balanced across the age groups. Of note, in the racial categories, the number of Asian patients decreased by age group and the number of white patients increased. Gender and BMI were fairly well balanced.

Table 56 Key Demographics in the Pivotal Studies by Age—FAS

Age group/ treatment group	Number of patients	Male gender, N (%)	Race, N (%)			BMI, mean (SD) [b] [kg/m^2]
			White	Black [a]	Asian	
≤50 years/						
Placebo	194	113 (58.2)	83 (42.8)	0 (0.0)	111 (57.2)	29.52 (5.10)
Linagliptin	442	245 (55.4)	185 (41.9)	3 (0.7)	254 (57.5)	29.03 (4.86)
51 to 64 years/						
Placebo	363	188 (51.8)	240 (66.1)	2 (0.6)	121 (33.3)	29.36 (4.82)
Linagliptin	970	455 (46.9)	607 (62.6)	4 (0.4)	359 (37.0)	28.99 (4.85)
65 to 74 years/						
Placebo	152	77 (50.7)	99 (65.1)	2 (1.3)	51 (33.6)	28.08 (4.34)
Linagliptin	398	209 (52.5)	278 (69.8)	4 (1.0)	116 (29.1)	28.82 (5.00)
≥75 years/						
Placebo	19	10 (52.6)	16 (84.2)	0 (0.0)	3 (15.8)	29.29 (5.33)
Linagliptin	66	37 (56.1)	51 (77.3)	1 (1.5)	14 (21.2)	28.27 (4.00)

a or African American
b baseline value

Source (b) (4) Table 3.1.2.3: 1, page 64

Baseline efficacy characteristics for HbA1c and baseline FPG were generally balanced among the age groups. The time since diagnosis as >5 years increased by age group, with the highest percentages in the oldest group. This was also true for the number of OADs at enrollment. See Table 57.

Table 57 Key Baseline Characteristics in the Pivotal Studies by Age—FAS

Age group/ treatment group	Number of patients	Baseline HbA_{1c}, mean (SD) [%]	Baseline FPG, mean (SD) [mg/dL]	Time since diagnosis of diabetes, N (%)	Number of antidiabetic drugs at enrolment, N (%)		
				>5 years	None	One	Two or more
≤50 years/							
Placebo	194	8.2 (0.9)	168.2 (40.6)	62 (32.0)	48 (24.7)	71 (36.6)	75 (38.7)
Linagliptin	442	8.2 (0.9)	167.1 (42.1)	169 (38.2)	87 (19.7)	146 (33.0)	209 (47.3)
51 to 64 years/							
Placebo	363	8.2 (0.9)	171.2 (40.2)	193 (53.2)	82 (22.6)	116 (32.0)	165 (45.5)
Linagliptin	970	8.2 (0.8)	167.8 (40.7)	557 (57.4)	153 (15.8)	300 (30.9)	517 (53.3)
65 to 74 years/							
Placebo	152	8.1 (0.9)	169.2 (44.9)	110 (72.4)	26 (17.1)	41 (27.0)	85 (55.9)
Linagliptin	398	8.1 (0.8)	166.1 (41.6)	263 (66.1)	66 (16.6)	115 (28.9)	217 (54.5)
≥75 years/							
Placebo	19	8.1 (0.8)	167.5 (34.5)	16 (84.2)	2 (10.5)	3 (15.8)	14 (73.7)
Linagliptin	66	8.0 (0.8)	168.5 (50.0)	56 (84.8)	4 (6.1)	17 (25.8)	45 (68.2)

Source (b) (4) Table 3.1.2.4: 1, page 71

Reviewer's Comments
The proportion of Asian patients being fewer in the older age groups is not clear. This may have had to do with recruitment strategies at these sites.
The other trends seen as the age group increased, such as longer time since diagnosis, and more OADs are to be expected given the progressive nature of the disease. The increased glycemic control offered by these additional OADs is evident in the balanced HbA1c and FPG across age groups.

Gender

Genders were balanced among the pivotal studies. Age, race and BMI were all similar, see Table 58.

Table 58 Key Demographics in the Pivotal Studies by Gender—FAS

Gender/ treatment group	Number of patients	Age, mean (SD) [years]	Race, N (%)			BMI, mean (SD) [b] [kg/m^2]
			White	Black [a]	Asian	
Male/						
Placebo	388	56.3 (10.3)	231 (59.5)	2 (0.5)	155 (39.9)	28.56 (4.62)
Linagliptin	946	57.3 (10.4)	559 (59.1)	2 (0.2)	385 (40.7)	28.56 (4.48)
Female/						
Placebo	340	56.9 (10.1)	207 (60.9)	2 (0.6)	131 (38.5)	29.79 (5.01)
Linagliptin	930	57.5 (9.5)	562 (60.4)	10 (1.1)	358 (38.5)	29.33 (5.18)

a or African American
b baseline value

Source (b) (4) Table 3.1.2.3: 2, page 65

Baseline characteristics were also well balanced between the genders. See Table 59.

Table 59 Key Baseline Characteristics in the Pivotal Studies by Gender—FAS

Gender/ treatment group	Number of patients	Baseline HbA_{1c}, mean (SD) [%]	Baseline FPG, mean (SD) [mg/dL]	Time since diagnosis of diabetes, N (%)	Number of antidiabetic drugs at enrolment, N (%)		
				>5 years	None	One	Two or more
Male/							
Placebo	388	8.1 (0.9)	171.1 (43.1)	210 (54.1)	84 (21.6)	134 (34.5)	170 (43.8)
Linagliptin	946	8.1 (0.8)	168.9 (41.0)	523 (55.3)	156 (16.5)	318 (33.6)	472 (49.9)
Female/							
Placebo	340	8.2 (0.9)	168.6 (38.9)	171 (50.3)	74 (21.8)	97 (28.5)	169 (49.7)
Linagliptin	930	8.2 (0.9)	165.6 (42.0)	522 (56.1)	154 (16.6)	260 (28.0)	516 (55.5)

Source (b) (4) Table 3.1.2.4: 2, page 72

Ethnicity

There were two ethnicity categories, Hispanic/Latino and Nonhispanic/Latino. Overall, 407 patients in the pivotal studies were of Hispanic/Latino ethnicity; 2185 patients were not Hispanic/Latino. Here the demographic Hispanic/Latino data is presented to see differences in the placebo versus linagliptin groups. This group was overall balanced between linagliptin and placebo in regard to the key demographic parameters. The exception to this was the number of patients in the racial categories, white and Asian; 92.9% of the patients who were of Hispanic/Latino ethnicity were white. In contrast, only 6.6% of these patients were Asian (Table 60).

Table 60 Key Demographics in the Pivotal Studies, Hispanic/Latino Ethnicity Group—FAS

Ethnicity: Hispanic/Latino	Placebo	Lina 5mg	Total
Number of patients	103 (100.0)	304 (100.0)	407 (100.0)
Gender, [N (%)]			
Male	54 (52.4)	144 (47.4)	198 (48.6)
Female	49 (47.6)	160 (52.6)	209 (51.4)
Race, [N (%)]			
White	92 (89.3)	286 (94.1)	378 (92.9)
Black	0 (0.0)	2 (0.7)	2 (0.5)
Asian	11 (10.7)	16 (5.3)	27 (6.6)
Geographical region [N (%)]			
Asia	7 (6.8)	10 (3.3)	17 (4.2)
Europe	8 (7.8)	13 (4.3)	21 (5.2)
N. America (incl. New Zealand,Australia)	6 (5.8)	29 (9.5)	35 (8.6)
South America (incl. Mexico)	82 (79.6)	252 (82.9)	334 (82.1)
Age [years]			
N	103	304	407
Mean	57.3	57.9	57.8
SD	9.3	9.5	9.4
Min	33	30	30
Median	59.0	59.0	59.0
Max	76	79	79
Age groups [years], [N (%)]			
<=50 years	24 (23.3)	61 (20.1)	85 (20.9)
51 -<65 years	54 (52.4)	167 (54.9)	221 (54.3)
65 -<75 years	22 (21.4)	68 (22.4)	90 (22.1)
>=75 years	3 (2.9)	8 (2.6)	11 (2.7)
Baseline weight [kg]			
N	103	304	407
Mean	80.73	80.20	80.33
SD	15.99	15.77	15.80
Min	53.0	49.4	49.4
Median	80.00	79.30	79.80
Max	130.2	138.5	138.5

Source ISE, Table 3.1.2.4, page 275

Mean HbA1c and FPG values at baseline were comparable between the placebo and linagliptin groups at baseline as seen in Table 61.

Table 61 Baseline Characteristics in the Pivotal Studies in the Hispanic/Latino Ethnicity Group—FAS

Ethnicity: Hispanic/Latino	Placebo	Lina 5mg	Total
Number of patients	103 (100.0)	304 (100.0)	407 (100.0)
Baseline HbA1c [%]			
N	103	304	407
Mean	8.1	8.1	8.1
SD	0.9	0.8	0.8
Min	7	7	7
Median	8.1	8.1	8.1
Max	10	11	11
Baseline HbA1c categorical [%], [N (%)]			
<7.0%	7 (6.8)	13 (4.3)	20 (4.9)
7.0% to <8.0%	43 (41.7)	120 (39.5)	163 (40.0)
8.0% to <9.0%	34 (33.0)	125 (41.1)	159 (39.1)
>=9.0%	19 (18.4)	46 (15.1)	65 (16.0)
Baseline fasting plasma glucose [mg/dL]			
N	92	279	371
Mean	167.2	165.4	165.9
SD	43.8	44.1	44.0
Min	85	65	65
Median	162.0	160.0	162.0
Max	353	418	418
Baseline fasting plasma glucose categorical [mg/dL], [N (%)]			
<126 mg/dL	15 (14.6)	43 (14.1)	58 (14.3)
126 to <140 mg/dL	12 (11.7)	34 (11.2)	46 (11.3)
140 to <200 mg/dL	44 (42.7)	145 (47.7)	189 (46.4)
>= 200 mg/dL	21 (20.4)	57 (18.8)	78 (19.2)
Missing	11 (10.7)	25 (8.2)	36 (8.8)
Duration of diabetes, [N (%)]			
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Up to 1 year	9 (8.7)	19 (6.3)	28 (6.9)
>1 to 5 years	31 (30.1)	88 (28.9)	119 (29.2)
>5 years	63 (61.2)	197 (64.8)	260 (63.9)
Number of antidiabetic drugs at enrollment [N (%)]			
0	5 (4.9)	6 (2.0)	11 (2.7)
1	21 (20.4)	69 (22.7)	90 (22.1)
>=2	77 (74.8)	229 (75.3)	306 (75.2)

Source ISE, Table 3.2.2.4, page 445

Race

Key demographic data of white and Asian patients were comparable between linagliptin and placebo groups. When demographics were compared between these two races, lower values for mean age and mean BMI were observed for Asian patients than for white patients. There were few black patients in the pivotal studies. See Table 62.

Table 62 Key Demographics in the Pivotal Studies by Race—FAS

Race/ treatment group	Number of patients	Age, mean (SD) [years]	Male gender, N (%)	BMI, mean (SD) [a] [kg/m^2]
White/				
Placebo	438	58.2 (9.6)	231 (52.7)	31.09 (4.48)
Linagliptin	1121	59.3 (9.4)	559 (49.9)	30.84 (4.36)
Black or African American/				
Placebo	4	62.5 (7.3)	2 (50.0)	30.74 (1.22)
Linagliptin	12	60.2 (14.0)	2 (16.7)	31.43 (5.20)
Asian/				
Placebo	286	54.0 (10.5)	155 (54.2)	26.11 (3.72)
Linagliptin	743	54.5 (10.0)	385 (51.8)	26.03 (4.04)

a baseline value

Source (b) (4) Table 3.1.2.3: 3, page 66

Mean HbA1c was very similar for white and Asian patients. The mean baseline FPG was higher in the white group. Of the few black patients, higher HbA1c at baseline was seen, along with higher FPG and all had prior OADs, see Table 63.

Table 63 Key Baseline Characteristics in the Pivotal Studies by Race—FAS

Race/ treatment group	Number of patients	Baseline HbA_{1c}, mean (SD) [%]	Baseline FPG, mean (SD) [mg/dL]	Time since diagnosis of diabetes, N (%)	Number of antidiabetic drugs at enrolment, N (%)		
				>5 years	None	One	Two or more
White/							
Placebo	438	8.2 (0.9)	177.1 (42.4)	235 (53.7)	92 (21.0)	162 (37.0)	184 (42.0)
Linagliptin	1121	8.1 (0.8)	174.0 (42.9)	635 (56.6)	175 (15.6)	413 (36.8)	533 (47.5)
Black or African American/							
Placebo	4	7.8 (0.5)	157.5 (21.2)	2 (50.0)	0 (0.0)	2 (50.0)	2 (50.0)
Linagliptin	12	8.6 (1.0)	167.3 (54.8)	7 (58.3)	0 (0.0)	2 (16.7)	10 (83.3)
Asian/							
Placebo	286	8.2 (0.9)	159.5 (37.1)	144 (50.3)	66 (23.1)	67 (23.4)	153 (53.5)
Linagliptin	743	8.2 (0.9)	157.5 (37.1)	403 (54.2)	135 (18.2)	163 (21.9)	445 (59.9)

Source Table 3.1.2.4: 3, page 73

Body Mass Index (BMI)

The total mean baseline HbA1c was identical for both BMI categories; however, the mean baseline FPG value in patients with baseline BMI of 30 kg/m^2 or above (174.5

mg/dL) was higher than in patients with baseline BMI below 30 kg/m^2 (164.0 mg/dL). See Table 64.

Table 64 Key Baseline Characteristics in the Pivotal Studies by BMI—FAS

Baseline BMI/ treatment group	Number of patients	Baseline HbA_{1c}, mean (SD) [%]	Baseline FPG, mean (SD) [mg/dL]	Time since diagnosis of diabetes, N (%)	Number of antidiabetic drugs at enrolment, N (%)		
				>5 years	None	One	Two or more
<30 kg/m^2/							
Placebo	443	8.1 (0.9)	165.5 (40.3)	250 (56.4)	95 (21.4)	123 (27.8)	225 (50.8)
Linagliptin	1165	8.2 (0.8)	163.4 (40.3)	699 (60.0)	183 (15.7)	322 (27.6)	660 (56.7)
≥30 kg/m^2/							
Placebo	285	8.2 (0.9)	176.8 (41.5)	131 (46.0)	63 (22.1)	108 (37.9)	114 (40.0)
Linagliptin	711	8.2 (0.9)	173.7 (42.7)	346 (48.7)	127 (17.9)	256 (36.0)	328 (46.1)

Source (b) (4) Table 3.3.5: 1, page 115

Disposition of Patients in the Subgroups in the Pivotal Studies

The disposition of randomized patients in the different subgroups was in line with the findings for the overall population pivotal studies analysis. In the majority of subgroups, a slightly higher frequency of premature discontinuations was observed in the patients receiving placebo than in those treated with linagliptin. The disposition is summarized in Table 65.

Table 65 Disposition of the Patients in the Pivotal Studies by Subgroup—FAS

	Placebo		Linagliptin	
	Treated, N (%)	Prematurely discontinued, N (%)	Treated, N (%)	Prematurely discontinued, N (%)
Age				
≤50 years	194 (100.0)	17 (8.8)	442 (100.0)	28 (6.3)
51 to 64 years	363 (100.0)	22 (6.1)	970 (100.0)	48 (4.9)
65 to 74 years	152 (100.0)	18 (11.8)	398 (100.0)	16 (4.0)
≥75 years	19 (100.0)	3 (15.8)	66 (100.0)	5 (7.6)
Gender				
Male	388 (100.0)	36 (9.3)	946 (100.0)	46 (4.9)
Female	340 (100.0)	24 (7.1)	930 (100.0)	51 (5.5)
Race				
White	438 (100.0)	42 (9.6)	1121 (100.0)	58 (5.2)
Black or African American	4 (100.0)	0 (0.0)	12 (100.0)	0 (0.0)
Asian	286 (100.0)	18 (6.3)	743 (100.0)	39 (5.2)
Ethnicity [a]				
Hispanic/Latino	103 (100.0)	6 (5.8)	304 (100.0)	19 (6.3)
Not Hispanic/Latino	619 (100.0)	54 (8.7)	1566 (100.0)	78 (5.0)
Baseline BMI				
<30 kg/m^2	443 (100.0)	36 (8.1)	1165 (100.0)	58 (5.0)
≥30 kg/m^2	285 (100.0)	24 (8.4)	711 (100.0)	39 (5.5)
Baseline HbA_{1c}				
<7.0%	43 (100.0)	5 (11.6)	91 (100.0)	2 (2.2)
7.0% to <8.0%	292 (100.0)	13 (4.5)	749 (100.0)	29 (3.9)
8.0% to <9.0%	251 (100.0)	23 (9.2)	671 (100.0)	41 (6.1)
≥ 9.0%	142 (100.0)	19 (13.4)	365 (100.0)	25 (6.8)
Time since diagnosis of diabetes				
≤1 year	120 (100.0)	5 (4.2)	261 (100.0)	12 (4.6)
>1 to ≤5 years	227 (100.0)	17 (7.5)	570 (100.0)	28 (4.9)
>5 years	381 (100.0)	38 (10.0)	1045 (100.0)	57 (5.5)
Renal impairment [b]				
None (eGFR ≥90 mL/min)	406 (100.0)	29 (7.1)	1006 (100.0)	54 (5.4)
Mild (eGFR 60 to <90 mL/min)	272 (100.0)	24 (8.8)	715 (100.0)	31 (4.3)
Moderate (eGFR 30 to <60 mL/min)	29 (100.0)	5 (17.2)	80 (100.0)	7 (8.8)

a For 12 patients in EFF-1, ethnicity information is not available.
b Based on eGFR, as calculated using the MDRD formula. There was no patient in EFF-1 with severe renal impairment (eGFR < 30 mL/min). For 96 patients in EFF-1, the renal impairment status at baseline is unknown.

Source (b) (4) Table 3.1.1.2: 1, page 46

Reviewer's Comments
These disposition trends are expected. In the group of patients with low baseline HbA1c in the placebo group, the discontinuation rate is almost as high as the group with HbA1c greater than 9%. This could be due to loss of glycemic control as the patients were taking placebo.

Efficacy Results in Pivotal Study Subgroups

The HbA1c results from the subgroups reveal superiority over placebo by the point estimate which the upper limit of the 95% confidence interval never crosses 0. There is only one small subgroup (eGFR <60) with the upper limit of the 95% confidence interval access 0. In general, the subgroups that do not have a large number of patients (n) have larger confidence intervals. Still, all the subgroups show a similar efficacy with reduction of HbA1c.

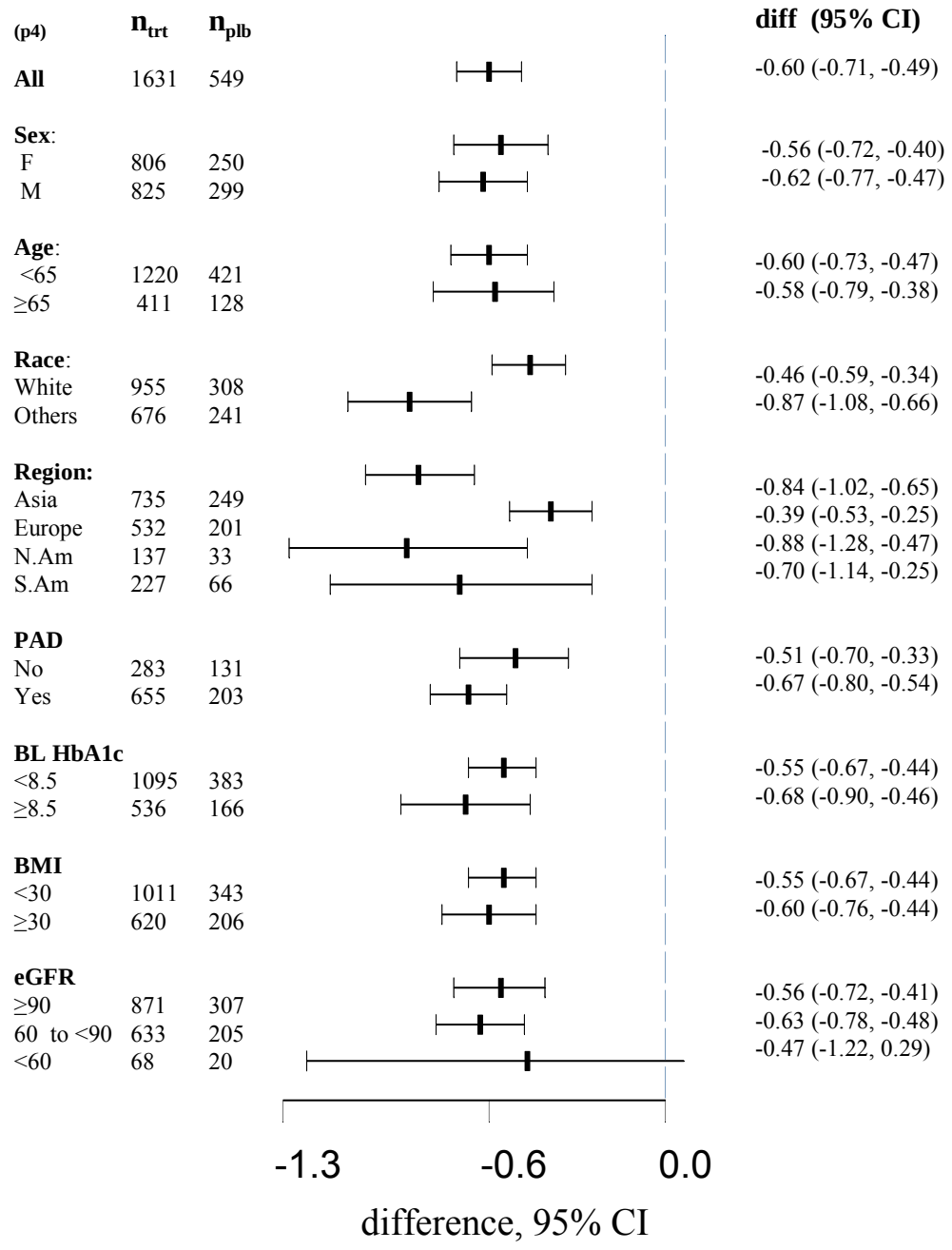


Figure 21 Forest Plot of HbA1c results for Pivotal Studies Subgroups

Reviewer's Comments
In the label, in section 14, under the monotherapy discussion, the applicant makes a claim that HbA1c changes are not affected by gender, age, race, prior antihyperglycemic therapy, baseline BMI, or a standard index of insulin resistance (HOMA-IR). Here I have discussed the major subgroups of gender, age, race and baseline BMI. All groupings show a balanced benefit in treatment with linagliptin.

Study 20 Subgroups

The unadjusted means for the change from baseline in HbA1c after 52 weeks by subgroups are presented in Table 66. The treatment-subgroup interaction was not significant for most of the subgroups (i.e. p>0.1 for the treatment-subgroup interaction); indicating that there is no treatment difference between these subgroups.

However, of note, significant treatment by subgroup interaction was seen for baseline HbA1c by categories (treatment difference=0.26, p=0.0543; Table 67) in favor of glimepiride. There was also a difference found in gender (treatment difference=0.20, p=0.0237; Table 68), in favor of glimepiride. Males overall benefitted more from glimepiride than females.

Table 66 Unadjusted Mean Change from Baseline in HbA1c (%) by Subgroups—Study 20, FAS

	Linagliptin (N=766)			Glimepiride (N=761)		
	N	Mean	(SD)	N	Mean	(SD)
Baseline HbA_{1c} (%)						
<7.5%	361	-0.26	0.58	345	-0.40	0.72
7.5% to <8.0%	132	-0.32	0.72	165	-0.58	0.74
8.0% to <9.0%	203	-0.60	0.96	176	-0.89	0.85
≥9.0%	70	-0.96	1.23	75	-1.40	1.26
Number of prior antidiabetic drugs						
1	536	-0.47	0.79	540	-0.67	0.88
2	229	-0.32	0.88	220	-0.61	0.87
Region						
Europe	585	-0.45	0.83	577	-0.70	0.80
Asia	86	-0.45	0.74	80	-0.59	1.02
North America (incl. New Zealand and Australia)	68	-0.16	0.82	75	-0.25	1.21
Africa	27	-0.62	0.74	29	-0.83	0.76
Age group [years]						
<65	519	-0.41	0.83	511	-0.64	0.94
65 to 74	213	-0.43	0.79	219	-0.66	0.73
≥75	34	-0.71	0.88	31	-0.73	0.64
Gender						
Male	454	-0.42	0.84	465	-0.70	0.91
Female	312	-0.44	0.79	296	-0.58	0.81
Race						
Asian	96	-0.47	0.74	99	-0.65	0.99
Black or African American	19	-0.30	0.94	17	-0.22	1.72
White	649	-0.43	0.83	644	-0.67	0.82
Ethnicity						
Hispanic/Latino	20	-0.04	0.55	19	-0.02	1.25
Not hispanic/Latino	745	-0.44	0.83	741	-0.67	0.86
BMI [kg/m^2]						
<30	389	-0.47	0.79	365	-0.65	0.93
≥30	377	-0.38	0.85	396	-0.65	0.83
Time since diagnosis of diabetes						
Up to 1 year	51	-0.50	0.85	58	-0.66	0.83
>1 to 5 years	317	-0.38	0.80	293	-0.58	0.88
>5 years	398	-0.45	0.84	410	-0.70	0.88
Metabolic syndrome at screening						
No	253	-0.39	0.87	223	-0.74	0.88
Yes	512	-0.44	0.80	538	-0.62	0.87

Source (b) (4) Table 11.4.1.1.2: 1, page 84

Table 67 Adjusted Mean HbA1c (%) Change from Baseline at Week 52 by Baseline HbA1c (4 categories)—Study 20, FAS

Baseline HbA1C (categorical)		N	Linagliptin	N	Glimepiride
<7.5%	Adjusted mean change from baseline (SE)	361	-0.20 (0.04)	345	-0.33 (0.05)
	Difference to Glimepiride (SE)		0.14 (0.06)		
	p-value		0.0251		
7.5% to <8.0%	Adjusted mean change from baseline (SE)	132	-0.28 (0.07)	165	-0.54 (0.06)
	Difference to Glimepiride (SE)		0.26 (0.09)		
	p-value		0.0057		
8.0% to <9.0%	Adjusted mean change from baseline (SE)	203	-0.58 (0.06)	176	-0.86 (0.06)
	Difference to Glimepiride (SE)		0.28 (0.08)		
	p-value		0.0006		
>=9.0%	Adjusted mean change from baseline (SE)	70	-0.95 (0.10)	75	-1.40 (0.09)
	Difference to Glimepiride (SE)		0.45 (0.13)		
	p-value		0.0008		
Total	Adjusted mean change from baseline (SE)	766	-0.50 (0.04)	761	-0.78 (0.03)
	Difference to Glimepiride (SE)		0.28 (0.05)		
	95% CI		(0.19, 0.38)		
	p-value		<.0001		

Source (b) (4) Table 15.2.1.2.3.1: 2, page 296

Table 68 Adjusted Mean HbA1c (%) Change from Baseline at Week 52 by Gender at Baseline—Study 20, FAS

Gender		N	Linagliptin	N	Glimepiride
Male	Adjusted mean change from baseline (SE)	454	-0.37 (0.04)	465	-0.66 (0.04)
	Difference to Glimepiride (SE)		0.29 (0.05)		
	p-value		<.0001		
Female	Adjusted mean change from baseline (SE)	312	-0.41 (0.05)	296	-0.51 (0.05)
	Difference to Glimepiride (SE)		0.11 (0.06)		
	p-value		0.1024		
Total	Adjusted mean change from baseline (SE)	766	-0.39 (0.03)	761	-0.59 (0.03)
	Difference to Glimepiride (SE)		0.20 (0.04)		
	95% CI		(0.12, 0.28)		
	p-value		<.0001		

Source (b) (4) Table 15.2.1.2.3.6: 1, page 320

Reviewer's Comments

The lack of treatment difference between the most of the subgroups is reassuring. Overall, the treatment differences seen in the HbA1c categories are expected given that data from this study has repeatedly displayed glimepiride lowers HbA1c more than linagliptin. The differences seen in gender, with males benefiting dramatically more than females is not concerning as this is with regards to glimepiride treatment. Furthermore, the pivotal studies did not show a difference in treatment by gender with linagliptin.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

This is not applicable as there is only one proposed dose for linagliptin—5 mg.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Please see discussions of Combination Therapy and Long Term Therapy in the main efficacy discussion. Study 20 is the main source of data for long term efficacy as it was a controlled study with 52 weeks of linagliptin treatment time.

6.1.10 Additional Efficacy Issues/Analyses

Linagliptin at the proposed 5 mg dose has been found to be effective in lowering HbA1c from baseline when compared to placebo in my analysis. The adjusted range in this group is 0.5 – 0.7 % reduction. When compared to glimepiride it meets the noninferiority margin. For all analyses, please see above.

7 Review of Safety

Safety Summary

7.1 Methods

Overall data from all clinical studies, including single dose and pharmacokinetic (PK) studies, were reviewed for safety. Deaths and SAEs were reviewed from the entire linagliptin-treated database and all deaths that occurred during the treatment phase of any trial are presented here. There were two deaths in screened only patients that are not included in this safety review.

Four safety groupings are discussed in this *Review of Safety*. One is SAF-1; this includes all patients with T2DM from all studies with at least one dose of linagliptin. Two other groups are discussed for Adverse Events (AEs). One is SAF-2; this group includes patients in all studies with T2DM that were placebo controlled. Patients that had linagliptin 5 mg and placebo patients were compared. The other group is study 20 (the applicant termed this SAF-4), the active control with glimepiride study. These two groups were also discussed for laboratory findings.

For more details on the SAF-2 and study 20 group, see Table 69.

Table 69 SAF-2 and Study 20 Study Grouping—Doses and Patients

								Patient numbers N (%)		
Safety grouping	Objective	Trial characteristics	Studies	Phase	Treatment duration	Doses	Patients / Healthy subjects	Total (random.)	Linagliptin (treated)	Linagliptin 5 mg (treated)
SAF-2	Safety in patients with T2DM on linagliptin 5 mg	Placebo-controlled trials with lingliptin 5 mg in patients with T2DM	1218.2	I	12 days	1, 2.5, 5, 10 mg	P	48 (100.0)	35 (72.9)	8 (16.7)
			1218.3	I	28 days	2.5, 5, 10 mg	P	77 (100.0)	59 (76.6)	15 (19.5)
			1218.5[o]	II	12 weeks	0.5, 2.5, 5 mg	P	302 (100.0)	170 (56.3)	55 (18.2)
			1218.6[p]	II	12 weeks	1, 5, 10 mg	P	333 (100.0)	197 (59.2)	66 (19.8)
			1218.15	III	24 weeks	5 mg	P	389 (100.0)	259 (66.6)	259 (66.6)
			1218.16	III	24 weeks	5 mg	P	503 (100.0)	336 (66.8)	336 (66.8)
			1218.17	III	24 weeks	5 mg	P	701 (100.0)	523 (74.6)	523 (74.6)
			1218.18	III	24 weeks	5 mg	P	1058 (100.0)	792 (74.9)	792 (74.9)
			1218.23[q]	III	52 weeks[b]	5, 10 mg	P (Japan)	561 (100.0)	319 (56.9)	159 (28.3)
			1218.35	III	18 weeks	5 mg	P	245 (100.0)	161 (65.7)	161 (65.7)
			1218.37	II	4 weeks	5 mg	P	121 (100.0)	40 (33.1)	40 (33.1)
			1218.50	III	18 weeks[e]	5 mg	P	227 (100.0)	151 (66.5)	151 (66.5)
Total patient numbers in SAF-2, N (%)								4565 (100.0)	3042 (66.6)	2565 (56.2)

								Patient numbers N (%)		
Safety grouping	Objective	Trial characteristics	Studies	Phase	Treatment duration	Doses	Patients / Healthy subjects	Total (random.)	Linagliptin (treated)	Linagliptin 5 mg (treated)
SAF-4	Long-term safety in actively controlled trial	Controlled trial with long-term exposure in patients with T2DM	1218.20	III	≥52 weeks[a]	5 mg	P	1560 (100.0)	778 (49.9)	778 (49.9)
Total patient numbers in SAF-4, N (%)								1560 (100.0)	778 (49.9)	778 (49.9)

Adapted from (b) (4), Table 1.1.3: 1, page 28

SAF-3, the four pivotal studies group (15, 16, 17 and 18—see Table 70) was used for the discussion of some laboratory parameters (measurements of central tendency) and vital signs. This was the only group that was analyzed by the applicant for vital sign findings, and an explanation for this was not given. However, this is a large group of patients with a standard treatment time (all pivotal studies had a 24 week treatment period), so this group is useful for this type of analysis. I requested this group for my discussion of measurements of central tendency due to this standardized treatment time.

Table 70 SAF-3 Study Grouping—Doses and Patients

Safety grouping	Objective	Trial characteristics	Studies	Phase	Treatment duration	Doses	Patients / Healthy subjects	Patient numbers N (%) Total (random.)	Linagliptin (treated)	Linagliptin 5 mg (treated)
SAF-3	Corresponding safety set for efficacy analyses (EFF-1)	Pivotal placebo-controlled trials with lingliptin 5 mg in patients with T2DM	1218.15	III	24 weeks	5 mg	P	389 (100.0)	259 (66.6)	259 (66.6)
			1218.16	III	24 weeks	5 mg	P	503 (100.0)	336 (66.8)	336 (66.8)
			1218.17	III	24 weeks	5 mg	P	701 (100.0)	523 (74.6)	523 (74.6)
			1218.18	III	24 weeks	5 mg	P	1058 (100.0)	792 (74.9)	792 (74.9)
Total patient numbers in SAF-3, N (%)								2651 (100.0)	1910 (72.0)	1910 (72.0)

Adapted from (b) (4) Table 1.1.3: 1, page 28

The Treated Sets (TS) are discussed for the safety groupings. The TS consisted of all patients who received at least one dose of study medication. When my own database searches were done, I used the entire database provided, which includes all randomized patients. However, for my SAF-2 searches, study 37 was not included as I did not have the database at the time. This is a small four week Phase II study with only about 40 patients receiving linagliptin.

For long term safety results, study 20 is presented and contains data from 52 weeks of linagliptin treatment. Studies 23 (active control with voglibose, with uncontrolled linagliptin-only extension phase) and 40 (the extension study for the pivotal studies) are discussed briefly as well. However, the extension phases are uncontrolled and these data have limited value.

Data from the Four Month Safety Update (4MSU) were included in the discussion on deaths and serious adverse events (SAEs). Discussion about non-serious and other adverse events is based on the initial NDA submission. 4MSU data were reviewed in entirety and will be commented on when relevant.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

This is discussed above.

7.1.2 Categorization of Adverse Events

There are four categories of AEs discussed for two safety groupings (SAF-2 and study 20). One is serious adverse events (SAEs) and another is AEs that led to discontinuation. The third category is under section 7.3.5 *Submission Specific Primary Safety Concerns* section. This section includes discussion of hypoglycemia and also of AEs of special interest that were requested of the applicant. AEs of special interest are hypersensitivity reactions, renal events, hepatic events, severe cutaneous adverse

reactions, and pancreatitis. Finally, common AEs were discussed. For the SAF-2 group, these are AEs that occurred in at least 1% of patients. For study 20, these are AEs that occurred in more than 5% of patients.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The pools used for this safety discussion are discussed above.

7.2 Adequacy of Safety Assessments

The applicant has used MedDRA dictionary Version 12.1 for preferred terms (PT) and for classification of AEs into system organ classes in the NDA. Version 13 was used for the 4MSU. I compared the verbatim terms to the preferred term for selected AE reports, particularly in cases of AEs leading to dropouts, and these events were appropriately classified.

The exposure information is discussed below. I believe exposure to linagliptin 5 mg is adequate to allow assessment of safety in T2DM patients. In addition, safety assessments conducted in the trials have been adequate to characterize the safety of linagliptin.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

At total of 454 healthy subjects were randomized to clinical trials in this program and treated with linagliptin (any dose).

In all trials in patients with T2DM, 6198 patients were randomized. Out of these, 4687 patients were treated with linagliptin (any dose) and 4040 patients received linagliptin 5 mg. Trial 1218.26, pharmacokinetic study with healthy subjects or patients that had renal impairment or T2DM, had a total of 21 T2DM patients treated with linagliptin 5 mg. This brings the number of patients with T2DM to a total of 4061. Of the patients with T2DM treated with linagliptin 5 mg, 3430 patients were exposed for 6 months or longer, 2390 patients for 12 months or longer, and 536 patients for 18 months or longer. Table 71 displays exposure in detail.

Table 71 Total Exposure to Linagliptin 5 mg in all T2DM Patients

Exposure categories	T2DM Patients (N)
≥1 day	4061
≥2 weeks	4000
≥4 weeks	3981
≥12 weeks	3811
≥24 weeks	3430
≥52 weeks	2390
≥78 weeks	536
Duration of treatment exposure [days]	
Mean (±SD)	364.7 (165.5)
Median (minimum, maximum)	400 (1, 685)
Overall patient years	4034.2

For the two main safety groupings discussed here, the exposure was as follows:

Table 72 Exposure to Linagliptin in SAF-2 and Study 20

Study Grouping	Study Duration	Linagliptin Treatment in patient-years	Comparator Treatment in patient-years
SAF-2	12 days – 24 weeks	1041.4	433.8 (placebo)
Study 20	52 weeks	887.5	872 (glimepiride)

SAF-2
In this group, 1183 patients received placebo and 2566 patients linagliptin 5 mg. The planned study duration in this grouping ranged from 12 days (BI trial 1218.2) to 24 weeks (four pivotal trials). Of note, trial 23 (active control with voglibose) had a planned duration of 52 weeks, however only 12 week data of the placebo-controlled period are presented. For trial 50 (monotherapy study) only the 18 week data are presented. The mean treatment duration was 133.9 days for patients treated with placebo and 148.2 days for patients treated with linagliptin 5 mg. The overall duration of treatment was 1041.4 patient-years in the linagliptin group.

Study 20—Active Control with Glimepiride
In this study, 778 patients received linagliptin 5 mg and 781 patients received glimepiride. The study duration was 52 weeks for the interim analysis (with 104 weeks planned for total study duration). The mean treatment duration was 416.7 days for patients treated with linagliptin 5 mg and 408.0 days for patients treated with glimepiride. The overall treatment duration was 887.5 patient-years for the linagliptin 5 mg group.

7.2.2 Explorations for Dose Response

The applicant has chosen only one dose for the treatment of T2DM. Exposure to the 5 mg dose was detailed above in 7.2.1 *Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations*.

7.2.3 Special Animal and/or In Vitro Testing

Please refer to Dr. David Carlson's review for full details.

7.2.4 Routine Clinical Testing

Routine laboratory and vital sign checks were performed during the course of the trials reviewed here. I did not identify any missing key safety measures during the clinical program.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please see *4.4 Clinical Pharmacology* section of this review and also refer to Dr. Lokesh Jain's review for full details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

7.3 Major Safety Results

7.3.1 Deaths

In the initial NDA submission there were overall 12 deaths: seven patients died under treatment with linagliptin and three patients died under treatment with glimepiride; two patients died during the post- linagliptin treatment period. The 4MSU was submitted during the course of this review. This included safety data from study 40, the 78 week extension study to all the pivotal trials (15, 16, 17 and 18). By the 4MSU, there were 13 additional deaths. Seven were during treatment with linagliptin and four deaths occurred on either comparator or placebo treatment. There was also one death each in the post treatment period following linagliptin, and glimepiride treatment.

The applicant's estimates of death rate incidences per 1000 patient exposure years when examining all patients treated with linagliptin at the NDA submission time are displayed in Table 73. In linagliptin 5 mg, the incidence rate per 1000 years at risk is 2.8. This is in between that reported for active comparator (2.1) and combined comparator (3.3). The incidence rate in placebo treated patients is more than two times higher (5.8).

Table 73 Estimates of Death Incidences per 1000 Patient Years Exposure, All Patients Treated with Linagliptin

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 trials in patients with T2DM[1]	Linagliptin ≤2.5 mg	261	44.1	0	49.1	0.0
	Linagliptin 5 mg	4338	2800.4	8	2826.8	2.8
	Linagliptin 10 mg	310	105.2	0	107.5	0.0
	Placebo	1798	683.4	4	695.5	5.8
	Active comparator	1178	1389.5	3	1399.0	2.1
	Combined comparator	2912	2072.9	7	2094.6	3.3
Uncontrolled extension trials[2]	Linagliptin 5 mg	2379	2857.6	6	2870.5	2.1
	Linagliptin 10 mg	265	127.9	0	133.0	0.0

[1] BI trials 1218.2, 1218.3, 1218.5, 1218.6, 1218.12, 1218.15, 1218.16, 1218.17, 1218.18, 1218.20, 1218.23, 1218.35, 1218.37, 1218.43, 1218.46, 1218.50, 1218.52
[2] BI trials 1218.23, 1218.40

Source FDA Information Request February 14, 2011

The cause of death by system organ class and PT, including study and duration of treatment is listed in Table 74.

Table 74 Patients with AEs Leading to Death by Treatment, Primary System Organ Class and Preferred Term, Treated Set

System organ class/ Preferred term	Actual TRT at onset of AE	Trial number	Patient	Age/ Gender	Start day@	Stop day@	Dura-tion	Action taken	The-rapy	Outcome
Infections and infestations/										
Endocarditis	Lina 5mg	1218_0018	85375	55/F	389*	391*	2*	Disc	Yes	Fatal
Pneumonia	L5+Pio30	1218_0015	53629	61/M	266*	302*	36*	Disc	Yes	Fatal
Neoplasms benign, malignant and unspecified (incl cysts and polyps)/										
Bronchial carcinoma	Lina 5mg	1218_0020	20714	76/M	411*	501*	90*	Disc	No	Fatal
Cardiac disorders/										
Acute myocardial infarction	Lina 5mg	1218_0043	64302	48/F	61*	62*	1*	Disc	No	Fatal
Cardiac failure acute	Lina 5mg	1218_0043	64302	48/F	61*	62*	1*	Disc	No	Fatal
Cardiac failure congestive	Lina 5mg	1218_0043	64302	48/F	61*	62*	1*	Disc	No	Fatal
Cardiac tamponade	Post-treat	1218_0016	65103	60/M	611*	612*	1*	Disc	No	Fatal
Cardio-respiratory arrest	Lina 5mg	1218_0020	29071	56/M	272*	273*	1*	Disc	No	Fatal
	Lina 5mg	1218_0035	50630	64/F	94*	95*	1*	None	No	Fatal
	L5+Pio30	1218_0015	53014	52/F	42*	43*	1*	Disc	No	Fatal
Myocardial infarction	Post-treat	1218_0050	55591	68/M	85*	110*	25*	Disc	Yes	Fatal
Vascular disorders/										
Aortic aneurysm	Lina 5mg	1218_0020	28314	72/M	575*	576*	1*	Disc	No	Fatal
Respiratory, thoracic and mediastinal disorders/										
Pulmonary embolism	Lina 5mg	1218_0016	62263	63/M	309*	310*	1*	Disc	No	Fatal
General disorders and administration site conditions/										
Polyp	Lina 5mg	1218_0018	85375	55/F	389*	391*	2*	Disc	Yes	Fatal
Sudden cardiac death	Post-treat	1218_0020	20995	54/F	41*	42*	1*	Disc	No	Fatal
	Lina 5mg	1218_0018	82262	53/M	466*	467*	1*	Disc	No	Fatal
Ulcer	Lina 5mg	1218_0018	85375	55/F	389*	391*	2*	Disc	Yes	Fatal

AE records may be intermittent, i.e. not always continuing from start to stop day.
@ Related to start of treatment, § = censored, * = partial date or missing date/time imputed,
# = Lost to follow up, & = Follow up sufficient
MedDRA version used for reporting: 13.0
Study grouping: MSU1

Adapted from 4 MSU, Table 8.1.2.1.1, page 2765

Brief Narratives of Deaths

From the Integrated Summary of Safety in the Original NDA Submission

Patient 50630, Trial 35
This was a 64 year old white female patient who began linagliptin on 26 August 2009. On (b) (6), the patient experienced cardio-respiratory arrest which led to death. Concomitant medical diseases included hypertension, ex-smoker, and mixed dyslipidemia. The patient was noted by the investigator to have no personal or family

history of cardiac disease. The patient reportedly never had history of cardiac ischemia nor evidence of cardio-pulmonary symptoms.

Patient 55591, Trial 50
This 68 year old Asian male patient was began linagliptin on 15 May 2009. On (b) (6) the patient was diagnosed with a non fatal MI and study medication was discontinued on the same day. The patient had a history of cardiovascular disease since 2005, hypertension, renal insufficiency, and also a previous MI. The patient was discharged (b) (6), apparently stable with resolution of symptoms. However, on 09 Sep 2009 the site was informed by the patient's daughter that the patient had died at home on (b) (6); this was three weeks after stopping linagliptin. He was not brought to the hospital.

Patient 29071, Trial 20
This patient was a 56 year old Asian male and received his first dose of linagliptin on 02 July 2008. On (b) (6), the patient experienced a fatal event of cardio-respiratory arrest at home. The patient had no relevant past medical history or relevant concurrent conditions.

Patient 20995, Trial 20
This was a 54 year old White female patient who received her first dose of linagliptin on 18 June 2008. On (b) (6) the patient was found dead. The event was recorded as a sudden cardiac death, with the cause of death thought to be arrhythmia. An autopsy was not performed. The patient's medical history included arrhythmia (since 2004), hypertension (since 2005), diabetes mellitus (since 2006) and gonarthrosis (since 2005).

From the 4MSU

Patient 28314, Trial 20
A 74 year old white man with a history of hypertension experienced a fatal aortic aneurysm on (b) (6). The patient had been on Ramipril for several months and metformin for several years. He had been on linagliptin 5 mg for over a year, beginning 20 November 2008 and was on treatment at the time of the event.

Patient 20166, Trial 20—post treatment
This patient is a 64 year old white man with a history of small cell bronchial carcinoma, diagnosed in April 2010. He had both bone and liver metastases at diagnosis and had been on linagliptin for two years. Both linagliptin and metformin (which he had been on since 2007) were discontinued at the time of diagnosis. In (b) (6) he experienced a fatal hemorrhage, location of this hemorrhage was not given.

Patient 95083, Trial 40

This patient was a 63 year old white male with a history of depression and asthma. He was treated with multiple medications including metformin and Diaprel (a sulfonylurea not marketed in the US) for T2DM and Ventolin spray for asthma. After being on linagliptin since 4 June 2009, the patient developed pneumonia about 10 months later. Several antibiotic therapies were initiated but the patient subsequently died of pneumonia and respiratory insufficiency on (b) (6).

Patient 93343, Trial 40
62 year old white male with a history of dyslipidemia, aortic valve stenosis and hypertension died of cardiac tamponade after more than one year of treatment with linagliptin. He had been on concomitant therapy including Crestor, lisinopril and acetylsalicylic acid cardio for aortic valve stenosis.

Patient 94336, Trial 40
This was a 54 year old Asian male with no concomitant medical history or medications, except that the patient was on pioglitazone per protocol.
The patient experienced a sudden cardiac fatal event; he had been on linagliptin for several months (23 April 2009 through date of death (b) (6)).

Patient 38807, Trial 43
This was a 59 year old woman in the study with patients that have severe chronic renal impairment. The duration of treatment at the time of event was unknown; however the patient was enrolled in the trial on 29 October 2009 and died on (b) (6). The death is reported as cardiac death.

Patient 4724, Trial 36
This was a 48 year old female patient with a history of depression that worsened while on treatment. The patient had several comorbidities including anemia and development of a foot ulcer while on treatment. The cause of the patient's death is unexplained. She had a friend assist with her insulin dose that morning due to fatigue; this was common for her. She was later found deceased by family members. Duration of treatment was 23 June 2010 through (b) (6).

Patient 48735, Trial 52
This 61 year old female patient died from what is described as a cardiac incident after a car crash. It is not known if the patient had hypoglycemia at the time of the accident, but she was the driver at the time. She was not reportedly on insulin, her medications included hydrocholorthiazide, enalapril and simvastatin. Treatment duration was 15 April 2009 through date of accident (b) (6).

Reviewer's Comments
The causes of deaths are varied and there is no evidence at this time of a fatal drug effect at the dose and duration of treatment investigated. The incidence

rates reported for linagliptin (per 1000 years at risk) are lower than that for placebo treated patients and combined comparator.

7.3.2 Nonfatal Serious Adverse Events

SAF-2 All Placebo Controlled Trials

The number of patients with serious adverse events (SAEs) up to the time of the 4MSU was low and the frequencies were comparable between treatments: 62 patients (3.8%) placebo and 94 patients (3.1%) linagliptin 5 mg. The frequency of SAEs on the PT level ≤0.2% in each treatment group with no clear trends towards particular System Organ Classes (SOCs) or PTs in either treatment group.

The only SOC that occurred in the linagliptin group at a rate greater than 0.1% compared to placebo was Vascular Disorders. This SOC had a 0.4% rate in the linagliptin group compared to placebo at 0.1%. On the PT level in the Vascular Disorders SOC, there were no events that occurred at more than 0.1% frequency. Most events in this SOC in the linagliptin group came from hypertensive crisis (4 patients—0.1%--versus 0 patients on placebo) at the preferred term level

Table 75 displays SAEs by SOC by treatment group

Table 75 Frequency [N (%)] of Patients with SAEs by Treatment, SOC—SAF-2, TS

System organ class	Placebo N (%)	Lina 5mg N (%)
Number of patients	1611 (100.0)	3062 (100.0)
Total with serious adverse events	62 (3.8)	94 (3.1)
Blood and lymphatic system disorders	1 (0.1)	3 (0.1)
Cardiac disorders	14 (0.9)	24 (0.8)
Ear and labyrinth disorders	0 (0.0)	1 (0.0)
Endocrine disorders	0 (0.0)	1 (0.0)
Eye disorders	2 (0.1)	3 (0.1)
Gastrointestinal disorders	8 (0.5)	5 (0.2)
General disorders and administration site conditions	3 (0.2)	3 (0.1)
Hepatobiliary disorders	1 (0.1)	4 (0.1)
Immune system disorders	1 (0.1)	0 (0.0)
Infections and infestations	12 (0.7)	16 (0.5)
Injury, poisoning and procedural complications	6 (0.4)	13 (0.4)
Investigations	3 (0.2)	0 (0.0)
Metabolism and nutrition disorders	4 (0.2)	7 (0.2)
Musculoskeletal and connective tissue disorders	6 (0.4)	7 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.2)	4 (0.1)
Nervous system disorders	5 (0.3)	5 (0.2)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	0 (0.0)
Renal and urinary disorders	8 (0.5)	12 (0.4)
Reproductive system and breast disorders	1 (0.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	5 (0.3)	8 (0.3)
Skin and subcutaneous tissue disorders	0 (0.0)	2 (0.1)
Surgical and medical procedures	0 (0.0)	1 (0.0)
Vascular disorders	2 (0.1)	13 (0.4)

Adapted from 4MSU Information Request, Table 5.2.6.1, page 230

SAF-2 consisted of studies with differing treatment periods. The overall person-years of exposure for linagliptin was 1041.1 and for placebo it was 434. The rate of SOC Vascular disorders using these treatment times was 0.01 for linagliptin and 0.004 for placebo. However, when looking at the PT, the rate of hypertensive crisis was extremely low in the linagliptin treated group (0.004).

Reviewer's Comments

For most SAEs, the rate between the linagliptin and placebo groups is very similar. At the PT level, the rates for these SAEs when looking at patient-years of

treatment are extremely low (very few patients) and comparisons are difficult. The events that were noted with more frequency in the linagliptin group are most likely attributable to the larger population in this group. This is overall reassuring. The rates of SAEs in study 16 and study 50 which are both placebo ONLY controlled trials also have very low rates of SAEs, and this is consistent in both study 16 and 50.

Study 20—Active Control Study with Glimepiride

SAEs for this group were reviewed including the 4MSU data. The number of patients with SAEs was higher in the glimepiride group (156 patients, 20%) than in the linagliptin group (122 patients, 15.7%). The frequency of SAEs for each PT level was below 1% in each treatment group. There was only one SOC that had a higher rate of SAEs in the linagliptin group than glimepiride group ≥0.5%. This was Respiratory, thoracic and mediastinal disorders. At the PT level, most events in the linagliptin group in this SOC had chronic obstructive pulmonary disease (COPD) (0.4% in 3 patients, versus 0 patients in the glimepiride group).

Table 76 Frequency [N (%)] of Patients with SAEs by Treatment, SOC—Study 20, TS

System Organ Class	Linagliptin 5 mg N (%)	Glimepiride N (%)
Number of Patients	778	781
Total with SAE	122 (15.7)	156 (20.0)
Blood and Lymphatic System Disorders	3 (0.4)	3 (0.4)
Cardiac Disorders	22 (2.8)	32 (4.1)
Congenital, familial and Genetic Disorders	1 (0.1)	2 (0.3)
Ear and Labyrinth Disorders	1 (0.1)	3 (0.4)
Eye Disorders	3 (0.4)	2 (0.3)
Gastrointestinal Disorders	6 (0.8)	11 (1.4)
General Disorders, Administration Site Conditions	4 (0.5)	5 (0.6)
Immune System Disorders	3 (0.4)	0 (0)
Infections and Infestations	18 (2.3)	24 (3.1)
Injury, Poisoning and Procedural Complications	13 (1.7)	10 (1.3)
Investigations ALT Increase	1 (0.1)	1 (0.1)
Investigations AST Increase	1 (0.1)	0 (0)
Investigations Alkaline Phosphatase Increase	1 (0.1)	0 (0)
Investigations Hepatic Enzyme Increase	1 (0.1)	0 (0)
Investigations GGT Increase	0 (0)	1 (0.1)
Investigations Liver Function Test Abnormal	1 (0.1)	0 (0)
Metabolism and Nutrition	2 (0.3)	5 (0.6)
Musculoskeletal and Connective Tissue Disorders	15 (1.9)	17 (2.2)
Neoplasms, Benign, Malignant and Unspecified, Including Cysts and Polyps	17 (2.2)	16 (1.9)
Nervous System Disorders	9 (1.2)	25 (3.2)
Psychiatric Disorders	4 (0.5)	4 (0.5)
Renal and Urinary Disorders	7 (0.9)	12 (1.5)
Reproductive System and Breast Disorders	7 (0.9)	7 (0.9)

Respiratory, Thoracic and Mediastinal Disorders	8 (1.0)	4 (0.5)
Skin and Subcutaneous Tissue Disorders	2 (0.3)	3 (0.4)
Surgical and Medical Procedures	2 (0.3)	0 (0)
Vascular Disorders	7 (0.9)	7 (0.9)

Adapted from 4MSU, Table 5.2.4.6.1.1, page 1666

Exposure to linagliptin in this study at the 52 week cut off was 887 person-years of treatment. Glimepiride had 872 person-years of treatment. Analysis using this method for SAEs by SOC or PT for this study does not raise any additional concerns.

Reviewer's Comments
The rates of SAEs when compared to glimepiride are not concerning.

7.3.3 Dropouts and/or Discontinuations

SAF-2 All Placebo Controlled Trials

This analysis was performed with data submitted in the original NDA. The number of patients with adverse events leading to discontinuation were higher in the placebo group (43 patients, 3.6%) compared to the linagliptin 5 mg group (58 patients, 2.3%). The frequencies of AEs leading to discontinuation were smaller than 1% (in any treatment group on PT level). In sponsor investigations, blood glucose increase occurred more often in the placebo group. A summary of all AEs leading to discontinuation by treatment and system organ class (SOC) can be seen in Table 77. The review of the 4MSU did not reveal significant changes in these trends.

Table 77 Frequency [N (%)] of Patients with AEs Leading to Discontinuation by Treatment, SOC—SAF-2 TS

System Organ Class	Placebo N (%)	Linagliptin 5mg N (%)
Number of Patients	1183	2566
Total with AE leading to Treatment Discontinuation	43 (3.6)	58 (2.3)
Cardiac Disorders	1 (0.1)	5 (0.2)
Ear and Labyrinth Disorders	1 (0.1)	1 (0)
Endocrine Disorders	0 (0)	1(0)
Eye Disorders	1 (0.1)	0 (0)
Gastrointestinal Disorders	3 (0.3)	9 (0.4)
General Disorders, Administration Site Conditions	4 (0.3)	5 (0.2)
Hepatobiliary Disorders	0 (0)	2 (0.1)
Infections and Infestations	0 (0)	2 (0.1)
Injury, Poisoning and Procedural Complications	1 (0.1)	2 (0.1)
Investigations ALT increase	1 (0.1)	1 (0)
Investigations AST Increase	0 (0)	1 (0)
Investigations Amylase Increase	0 (0)	1 (0)
Investigations CPK Increase	0 (0)	1 (0)

Investigations Blood Glucose Increase	5 (0.4)	3 (0.1)
Investigations Hepatic Enzyme Increase	0 (0)	1 (0)
Investigations Weight Increase	1 (0.1)	0 (0)
Metabolism and Nutrition	17 (1.4)	13 (0.5)
Musculoskeletal and Connective Tissue Disorders	0 (0)	6 (0.2)
Neoplasms, Benign, Malignant and Unspecified, Including Cysts and Polyps	2 (0.2)	1 (0)
Nervous System Disorders	3 (0.3)	1 (0)
Psychiatric Disorders	1 (0.1)	2 (0.1)
Renal and Urinary Disorders	3 (0.3)	1 (0)
Reproductive System and Breast Disorders	1 (0.1)	0 (0)
Respiratory, Thoracic and Mediastinal Disorders	0 (0)	2 (0.1)
Skin and Subcutaneous Tissue Disorders	1 (0.1)	5 (0.2)
Vascular Disorders	0 (0)	2 (0.1)

Adapted from ISS, Table 5.2.2.4.1.1, page 3435

Study 20—Active Control Study with Glimepiride

Fewer patients were reported with AEs leading to discontinuation in the linagliptin 5 mg group (45 patients, 5.8%) compared to the glimepiride group (77 patients, 9.9%). The most frequent AE leading to discontinuation was hypoglycemia (under the Metabolism and nutrition disorders SOC), which occurred at a higher frequency in the glimepiride group (2.3%) compared to the linagliptin group (0.3%). Hypoglycemia is a known side-effect of glimepiride treatment. Other AEs leading to discontinuation occurred with a frequency of less than 1% (on PT level). There were no AEs leading to discontinuation that occurred with notable higher frequency in the linagliptin group. See Table 78 for the AEs by SOC grouping.

Table 78 Frequency [N (%)] of Patients with AEs Leading to Discontinuation by Treatment, SOC—Study 20, TS

System Organ Class	Linagliptin 5 mg N (%)	Glimepiride N (%)
Number of Patients	778	781
Total with AE leading to Treatment Discontinuation	45 (5.8)	77 (9.9)
Blood and Lymphatic System Disorders	0 (0)	1 (0.1)
Cardiac Disorders	5 (0.6)	4 (0.5)
Ear and Labyrinth Disorders	0 (0)	2 (0.3)
Eye Disorders	1 (0.1)	1 (0.1)
Gastrointestinal Disorders	6 (0.8)	14 (1.8)
General Disorders, Administration Site Conditions	4 (0.5)	8 (1.0)
Immune System Disorders	0 (0)	1 (0.1)
Infections and Infestations	1 (0.1)	6 (0.8)
Injury, Poisoning and Procedural Complications	3 (0.4)	0 (0)
Investigations ALT Increase	1 (0.1)	3 (0.4)
Investigations AST Increase	0 (0)	1 (0.1)
Investigations Alkaline Phosphatase Increase	1 (0.1)	0 (0)
Investigations Hepatic Enzyme Increase	0 (0)	1 (0.1)

Investigations Liver Function Test Abnormal	1 (0.1)	0 (0)
Investigations Weight Decrease	1 (0.1)	0 (0)
Investigations Weight Increase	0 (0)	1 (0.1)
Metabolism and Nutrition	9 (1.2)	20 (2.6)
Musculoskeletal and Connective Tissue Disorders	3 (0.4)	3 (0.4)
Neoplasms, Benign, Malignant and Unspecified, Including Cysts and Polyps	4 (0.5)	3 (0.4)
Nervous System Disorders	2 (0.3)	11 (1.4)
Psychiatric Disorders	1 (0.1)	3 (0.4)
Renal and Urinary Disorders	2 (0.3)	2 (0.3)
Reproductive System and Breast Disorders	0 (0)	1 (0.1)
Respiratory, Thoracic and Mediastinal Disorders	5 (0.6)	0 (0)
Skin and Subcutaneous Tissue Disorders	5 (0.6)	7 (0.9)
Social Circumstances	1 (0.1)	0 (0)
Vascular Disorders	0 (0)	2 (0.1)

Adapted from ISS, Table 5.2.4.4.1.1, page 5006

Reviewer's Comments
In both major safety groups, discontinuations due to AEs are higher in the patients treated with either placebo or glimepiride.

7.3.4 Significant Adverse Events

SAF-2 All Placebo Controlled Trials

Please see the next section, *7.3.5 Submission Specific Primary Safety Concerns*.

7.3.5 Submission Specific Primary Safety Concerns

Submission specific safety concerns include hypoglycemia, as this is a common effect of OADs. For this particular class of drug, DPP-4 inhibitor, the concurrent administration of a sulfonylurea is known to increase this risk. In addition, the applicant was asked to investigate a group of AEs of special interest. This was due to possible class effect or class concerns for DPP-4 inhibitors. These AEs were: hypersensitivity reactions, renal events, hepatic events, severe cutaneous adverse reactions, and pancreatitis. Trends seen in all presented AE sections were compared to those presented in the 4MSU. No major deviations from those presented in the NDA were noted.

SAF-2 Placebo Controlled Trials

Hypoglycemia

More patients in the linagliptin 5 mg group (196 patients, 7.6%) were reported with hypoglycemia compared to the placebo group (49 patients, 4.1%). Special search

category (SSC) hypoglycemia is composed of higher level term hypoglycemic conditions, not elsewhere classified and PT blood glucose decreased. See Table 79.

Table 79 Frequency [N (%)] of Patients with Hypoglycemic AEs by Preferred Terms—SAF-2, TS

System organ class/ Preferred term	Placebo N (%)	Lina 5mg N (%)
Number of patients	1183 (100.0)	2566 (100.0)
Total with hypoglycaemic adverse events of SSC 'hypoglycaemia'	49 (4.1)	196 (7.6)
Metabolism and nutrition disorders	49 (4.1)	195 (7.6)
Hypoglycaemia	49 (4.1)	195 (7.6)
Investigations	0 (0.0)	1 (0.0)
Blood glucose decreased	0 (0.0)	1 (0.0)

Adapted from ISS, Table 5.3.2.1, page 5846

As discussed earlier, SAF-2 includes studies with background metformin and SU medications, which are known to increase the risk of hypoglycemia when given in combination with other antidiabetic medications. For this reason, individual studies were reviewed for hypoglycemia. The applicant presents Investigator Defined Hypoglycemia which is protocol defined categories of hypoglycemia and other preferred terms related to symptoms of hypoglycemia. When each individual study is reviewed, the majority of hypoglycemic events are seen in study 18, which was on background of metformin + SU. The majority of hypoglycemic events in both treatment groups came from studies where SU was given as background medication (studies 18 and 35). This breakdown can be seen Table 80.

Table 80 Frequency of Patients with Investigator Defined Hypoglycemia by Phase III Studies in SAF-2, TS

	Placebo N (%)	Linagliptin 5 mg N (%)
Number of patients (Phase III studies only)	977 (100.0)	2381 (100.0)
Number of patients with investigator defined hypoglycaemia [N (% of patients treated)]	52 (5.3)	206 (8.7)
Number of patients with investigator defined hypoglycaemia by Phase III studies [N (% in study) patients in study]		
1218.15	0 (0.0) 130	3 (1.2) 259
1218.16	1 (0.6) 167	1 (0.3) 336
1218.17	5 (2.8) 177	3 (0.6) 523
1218.18	42 (16.0) 263	188 (23.7) 792
1218.23	0 (0.0) 80	0 (0.0) 159
1218.35	4 (4.8) 84	9 (5.6) 161
1218.50	0 (0.0) 76	2 (1.3) 151
Studies without sulphonylurea[a]	6 (1.0) 630	9 (0.6) 1428
Studies with sulphonylurea[b]	46 (13.3) 347	197 (20.7) 953

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

Source (b) (4) Table 2.2.5.1: 2, page 111

Reviewer's Comments

A possible explanation for the dramatically higher rate of hypoglycemia seen in study 18 is that linagliptin in combination with an SU can cause more hypoglycemia. The rate of hypoglycemia is only higher in the linagliptin treated group in the studies with an SU. This information is included in the proposed label and also in other DPP-4 inhibitor labels.

AEs of Special Interest

Overall, the numbers of patients with adverse events of special interest by narrow standardized medDRA queries (SMQs) were comparable between linagliptin-treated patients to patients treated with placebo (both linagliptin and placebo were frequently add on to other therapies as discussed). Hypersensitivity reactions were reported by 6 patients (0.5%) in the placebo group and 18 patients (0.7%) in the linagliptin 5 mg group. The rate of other AEs of special interest were otherwise similar between the two groups. See Table 81 for the frequency of patients with these AEs of special interest.

Table 81 Frequency of Patients with AEs of Special Interest Based on Narrow SMQs—SAF-2, TS

	Placebo N (%)	Linagliptin 5 mg N (%)
Patient years of exposure	433.8	1041.4
Number of patients	1183 (100.0)	2566 (100.0)
Patients with hypersensitivity reactions[a]	6 (0.5)	18 (0.7)
Circulatory collapse	0 (0.0)	2 (0.1)
Eye swelling	1 (0.1)	1 (0.0)
Eyelid oedema	1 (0.1)	0 (0.0)
Face oedema	1 (0.1)	2 (0.1)
Gingival swelling	0 (0.0)	1 (0.0)
Lip swelling	0 (0.0)	2 (0.1)
Swelling face	1 (0.1)	2 (0.1)
Urticaria	1 (0.1)	6 (0.2)
Asthma	1 (0.1)	1 (0.0)
Bronchial hyperreactivity	1 (0.1)	1 (0.0)
Bronchospasm	0 (0.0)	1 (0.0)
Patients with renal events[b]	2 (0.2)	3 (0.1)
Renal failure	1 (0.1)	0 (0.0)
Renal failure acute	0 (0.0)	1 (0.0)
Renal impairment	1 (0.1)	2 (0.1)
Patients with hepatic events[c]	14 (1.2)	25 (1.0)
Hyperbilirubinaemia	0 (0.0)	2 (0.1)
Hepatic steatosis	3 (0.3)	8 (0.3)
Chronic hepatitis	0 (0.0)	1 (0.0)
Alanine aminotransferase increased	5 (0.4)	7 (0.3)
Aspartate aminotransferase increased	4 (0.3)	8 (0.3)
Blood bilirubin increased	0 (0.0)	1 (0.0)
Gamma-glutamyltransferase increased	4 (0.3)	3 (0.1)
Hepatic enzyme increased	1 (0.1)	2 (0.1)
Hepatic function abnormal	1 (0.1)	1 (0.0)
Hyperbilirubinaemia	0 (0.0)	2 (0.1)
Liver function test abnormal	1 (0.1)	0 (0.0)
Patients with severe cutaneous adverse reactions[d]	0 (0.0)	1 (0.0)
Dermatitis exfoliative	0 (0.0)	1 (0.0)
Patients with pancreatitis[e]	0 (0.0)	1 (0.0)
Pancreatitis	0 (0.0)	1 (0.0)

[a] Based on SMQs 'anaphylactic reaction', 'angioedema', and 'asthma-bronchospasm'.
[b] Based on SMQ 'acute renal failure'.
[c] Based on SMQs 'liver-related investigations, signs and symptoms', 'choleastasis and jaundice of hepatic origin', 'hepatitis, non-infectious', and 'hepatic failure, fibrosis, cirrhosis and other liver damage-related conditions'.
[d] Based on SMQ 'severe cutaneous adverse reaction'.
[e] Based on SMQ 'acute pancreatitis'.

Source (b) (4) Table 2.2.5.2: 1, page 113

These results were confirmed with my own database searches. However, the applicant's search for pancreatitis and skin disorders was very narrow. When searching for broader PTs in the SAF-2 database for any events that could represent pancreatitis, the findings are seen in Table 82. While the rate is higher in the linagliptin treated patients (0.5%--13 patients versus 2 patients in placebo group—0.1%), the numbers are overall very small for any pancreatic related event (neoplasms and cysts were not

included in this search). Skin disorders were also searched with broader terms, with insignificant results.

Table 82 Incidence of Pancreatic-Related Adverse Events—SAF-2 (minus study 37), Randomized Patients

Preferred Term	Linagliptin 5mg	Placebo
Number of Patients	2529	1145
Patients with Event	13 (0.5)	2 (0.2)
Blood amylase increased	7 (0.3)	2 (0.2)
Hyperamylasemia	2 (0.1)	0 (0)
Hyperlipasemia	0 (0)	0 (0)
Lipase increased	0 (0)	0 (0)
Pancreatic disorder	0 (0)	0 (0)
Pancreatitis	2 (0.1)	0 (0)
Pancreatitis acute	0 (0)	0 (0)
Pancreatitis chronic	2 (0.1)	0 (0)

Information from FDA Inquiry:
The search done for pancreatitis in the NDA was performed using the broad Search MEDdra Query “acute pancreatitis.” The result is reported in Table 82 above for SAF-2. For the entire treated set (which the applicant denotes SAF-1), the reported number of pancreatitis cases was 4. According to the applicant, this was deemed unspecific and a search using PT “pancreatitis chronic” was added to the acute PT for a more special search category. In this search, 11 total cases of pancreatitis were found, 3 of these were post treatment, thus the applicant reports 8 in the current proposed label. These cases are briefly described in Table 83. Two of these cases were exacerbations of chronic pancreatitis.

Table 83 Cases of Pancreatitis in All Patients 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

Reviewer's Comments

In addition to the higher rate of pancreatic events in the linagliptin group , there is also higher incidence of pancreatic/amylase related events in patients treated with linagliptin. At this time, the inclusion of 8 total patients with pancreatitis in the label is acceptable. Given the randomization ratio and the description of events, I do not recommend other additions regarding pancreatitis to the label at this time. There is further discussion of a related laboratory, amylase, in the 7.4.2 *Laboratory Findings.*

Study 20—Active Control Study with Glimepiride

Hypoglycemia

More patients in the glimepiride group were reported with hypoglycemia than in the linagliptin group (30.5% versus 5.3%).

Table 84 Frequency [N (%)] of Patients with Hypoglycemic AEs by Preferred Terms, Study 20--TS

System organ class/ Preferred term	Lina 5mg N (%)	Glim N (%)	Posttrt N (%)
Number of patients	778 (100.0)	781 (100.0)	283 (100.0)
Total with hypoglycaemic adverse events of SSC 'hypoglycaemia'	41 (5.3)	238 (30.5)	1 (0.4)
Metabolism and nutrition disorders	41 (5.3)	237 (30.3)	1 (0.4)
Hypoglycaemia	41 (5.3)	237 (30.3)	1 (0.4)
Investigations	0 (0.0)	3 (0.4)	0 (0.0)
Blood glucose decreased	0 (0.0)	3 (0.4)	0 (0.0)

Source ISS Table 5.3.4.1, page 5869

In the linagliptin group, the majority of patients had time to onset of their first event occurring after 28 days after the start of treatment (73.8% of the patients with an investigator defined hypoglycemia). In the glimepiride group, the majority of patients had time to onset of their first event occurring after 28 days after the start of treatment (70.6% of the patients with an investigator defined hypoglycemia).

AEs of Special Interest

There were no patients with severe cutaneous adverse reactions or pancreatitis in study 20. Hypersensitivity reactions were reported by 10 patients (1.3%) in the linagliptin 5 mg group and by 15 patients (1.8%) in the glimepiride group. The other AEs of special interest had higher rates in the glimepiride group, but all events were few.

Table 85 Frequency of Patients with AEs of Special Interest Based on Narrow SMQs—Study 20, TS

	Linagliptin 5 mg N (%)	Glimepiride N (%)
Patient years of exposure	887.5	872.4
Number of patients	778 (100.0)	781 (100.0)
Patients with hypersensitivity reactions[a]	10 (1.3)	15 (1.8)
Anaphylactic reaction	1 (0.1)	0 (0.0)
Eyelid oedema	0 (0.0)	1 (0.1)
Lip swelling	0 (0.0)	1 (0.1)
Pharyngeal oedema	1 (0.1)	0 (0.0)
Swelling face	0 (0.0)	2 (0.3)
Urticaria	4 (0.5)	3 (0.4)
Asthma	4 (0.5)	6 (0.8)
Bronchial hyperreactivity	0 (0.0)	1 (0.1)
Patients with renal events[b]	0 (0.0)	6 (0.8)
Renal failure	0 (0.0)	1 (0.1)
Renal failure acute	0 (0.0)	2 (0.3)
Renal impairment	0 (0.0)	3 (0.4)
Patients with hepatic events[c]	21 (2.7)	26 (3.3)
Hyperbilirubinaemia	0 (0.0)	1 (0.1)
Jaundice	1 (0.1)	0 (0.0)
IIepatic fibrosis	1 (0.1)	0 (0.0)
Hepatic steatosis	5 (0.6)	4 (0.5)
Liver disorder	0 (0.0)	1 (0.1)
Varices oesophageal	0 (0.0)	1 (0.1)
Hepatitis	0 (0.0)	1 (0.1)
Alanine aminotransferase increased	9 (1.2)	9 (1.2)
Aspartate aminotransferase increased	4 (0.5)	2 (0.3)
Blood bilirubin increased	2 (0.3)	1 (0.1)
γ-glutamyltransferase increased	3 (0.4)	7 (0.9)
Hepatic enzyme abnormal	1 (0.1)	0 (0.0)
Hepatic enzyme increased	1 (0.1)	1 (0.1)
Hepatomegaly	0 (0.0)	1 (0.1)
Hyperbilirubinaemia	0 (0.0)	1 (0.1)
Liver function test abnormal	1 (0.1)	1 (0.1)
Patients with severe cutaneous adverse reactions[d]	0 (0.0)	0 (0.0)
Patients with pancreatitis[e]	0 (0.0)	0 (0.0)

[a] Based on SMQs 'anaphylactic reaction', 'angioedema', and 'asthma-bronchospasm'.
[b] Based on SMQ 'acute renal failure'.
[c] Based on SMQs 'liver-related investigations, signs and symptoms', 'choleastasis and jaundice of hepatic origin', 'hepatitis, non-infectious', and 'hepatic failure, fibrosis, cirrhosis and other liver damage-related conditions'.
[d] Based on SMQ 'severe cutaneous adverse reaction'.
[e] Based on SMQ 'acute pancreatitis'.

Source (b) (4) Table 2.4.5.2: 1, page 152

Again, my own review of the AE database from study 20 did not reveal major divergences from that presented in the applicant's report. AEs searched with narrow terms (skin disorders and pancreatic related events) were searched with broader terms and no deviations were found. Of note, the PT "contact dermatitis" was found in five patients in the linagliptin treated group, but 0 of the glimepiride group. However, what was coded as allergic dermatitis and dermatitis alone were coded in 11 glimepiride patients and 9 linagliptin patients.

Reviewer's Comments
The searches performed by both the applicant and myself for hypoglycemia and AEs of special interest does not reveal any particular concerns at this time. As mentioned, the higher rate of hypoglycemia in combination with an SU should be reported.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common adverse event data presented below were compared to those submitted with the 4MSU and were very similar.

SAF-2 All Placebo Controlled Trials

The proportion of patients with adverse events that occurred at least in 1% of patients on the preferred term level, were comparable between treatments (53.8% placebo, 55.0% linagliptin 5 mg) per the applicant's report, see Table 86.

Table 86 Frequency of Patients with AEs in more than 1% of Patients by Treatment, Sorted by SOC—SAF-2, TS

	Placebo N (%)	Linagliptin 5 mg N (%)
Patient years of exposure	433.8	1041.4
Number of patients	1183 (100.0)	2566 (100.0)
Patients with any AE	636 (53.8)	1412 (55.0)
Gastrointestinal disorders	127 (10.7)	269 (10.5)
Abdominal pain upper	15 (1.3)	18 (0.7)
Constipation	21 (1.8)	40 (1.6)
Diarrhoea	27 (2.3)	53 (2.1)
Nausea	14 (1.2)	28 (1.1)
General disorders and administration site conditions	61 (5.2)	124 (4.8)
Asthenia	9 (0.8)	28 (1.1)
Fatigue	17 (1.4)	13 (0.5)
Infections and infestations	244 (20.6)	491(19.1)
Nasopharyngitis	65 (5.5)	150 (5.8)
Upper respiratory tract infection	53 (4.5)	84 (3.3)
Urinary tract infection	28 (2.4)	56 (2.2)
Investigations	49 (4.1)	102 (4.0)
Blood glucose increased	16 (1.4)	16 (0.6)
Metabolism and nutrition disorders	208 (17.6)	408 (15.9)
Dyslipidaemia	13 (1.1)	31 (1.2)
Hyperglycaemia	125 (10.6)	128 (5.0)
Hypoglycaemia	49 (4.1)	195 (7.6)
Musculoskeletal and connective tissue disorders	102 (8.6)	264 (10.3)
Arthralgia	21 (1.8)	47 (1.8)
Back pain	30 (2.5)	50 (1.9)
Pain in extremity	11 (0.9)	34 (1.3)
Nervous system disorders	81 (6.8)	183 (7.1)
Dizziness	21 (1.8)	51 (2.0)
Headache	41 (3.5)	76 (3.0)
Respiratory, thoracic and mediastinal disorders	26 (2.2)	102 (4.0)
Cough	10 (0.8)	47 (1.8)
Vascular disorders	28 (2.4)	92 (3.6)
Hypertension	22 (1.9)	58 (2.3)

Source (b) (4), Table 2.2.1: 2, page 102

I explored the musculoskeletal conditions (MSK conditions in Table 87 below) with my own database search. This was due to the increase rate seen here (10.3% seen in linagliptin group versus 8.6% seen in the placebo group). In addition, Dr. Lokesh Jain uncovered a possible dose response finding with back pain and arthralgia, see Figure 22. The largest difference is seen with asthenia (2.3% in linagliptin group versus 0.8% in placebo group). The total rate is similar, a difference is observed with asthenia, however. Asthenia is under the General disorders and administration site conditions in the applicant's table above. Their reported rate is slightly lower than what I report.

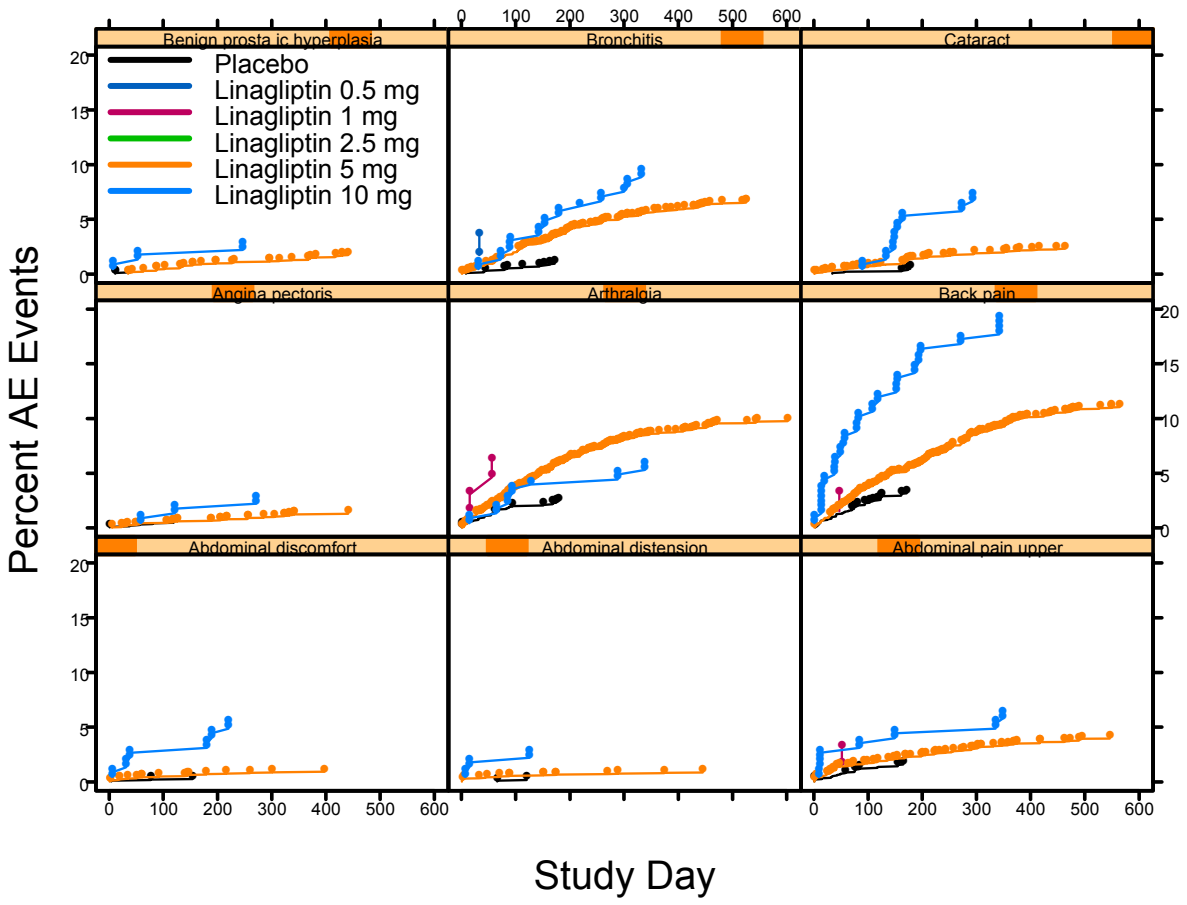


Figure 22 Incidence of Selected AE Across Time and Dose—Phase 2 and Phase 3 Trials
Source Dr. Lokesh Jain's Review, Figure 12

Table 87 Incidence of Musculoskeletal Conditions—SAF-2 (minus study 37)

Preferred Term	Linagliptin 5mg	Placebo
Number of Patients	2529	1145
Total Patients with MSK Condition	118 (0.5)	37 (0.3)
Arthralgia	17 (0.7)	5 (0.4)
Asthenia	32 (1.3)	10 (0.9)
Back pain	36(1.4)	21 (1.7)
Muscular weakness	2 (0.1)	0 (0)
Musculoskeletal pain	2 (0.1)	0 (0)
Myalgia	0 (0)	1 (0.1)
Pain in extremity	2 (0.1)	0 (0)

Reviewers' Comments
There are no common AEs that occur in at least 5% of patients that occur at a rate higher of at least 1% in the linagliptin group. There are no particular concerns detected based on the applicant's presentation. My own review of musculoskeletal conditions did not display any clear trends with the exception of asthenia.
When comparing rates to placebo only controlled studies (studies 16 and 35 with no background medications), rates were similar.

An additional analysis was performed based on SAF-2 to identify adverse events that could be associated with linagliptin in the settings of various background medications. The analysis was limited to the overall comparison of placebo and linagliptin. Table 88 presents the following:

• AEs with an incidence ≥2% with linagliptin and 2-fold higher incidence than in the placebo group or when the incidence in the placebo group was zero, and/or

•AEs likely related based on medical plausibility—known effects of drugs and/or

•AEs that had a consistent pattern over antidiabetic background treatments, i.e. the incidence in the linagliptin groups was consistently higher than in the placebo groups in every antidiabetic background medication

Table 88 AEs Possibly Associated with Linagliptin Based on SAF-2 by Background Medication—SAF-2, TS

Identified Risk SOC Category	No background	Metformin	SU	Metformin+ SU	TZD
	Placebo - Lina	Placebo - Lina	Placebo - Lina	Placebo - Lina	Placebo - Lina
	Reason for inclusion by criterion				
Infections and infestations					
Nasopharyngitis	-	-	a	-	-
N (%)	-	-	1 (1.2) - 7 (4.3)	-	-
Immune system disorders					
Hypersensitivity [1]	b	b	b	b	b
N (%)	2 (0.4) - 3 (0.4)	1 (0.4) - 2 (0.3)	1 (1.2) - 3 (1.9)	2 (0.8) - 9 (1.1)	0 - 1 (0.4)
Metabolism and nutrition disorders					
Hypoglycemia [2]	-	-	-	b	-
N (%)				39 (14.8) - 181 (22.9)	
Hypertriglyceridaemia [3]	-	-	a	-	-
N (%)			0 (0.0) - 4 (2.4)		
Hyperlipidemia	-	-	-	-	a
N (%)					1 (0.8) - 7 (2.7)
Nervous system disorders					
Dizziness [4]	-	a	-	-	-
N (%)		1 (0.4) - 14 (2.4)			
Respiratory, thoracic and mediastinal disorders					
Cough [5]	c	c	c	a, c	c
N (%)	4 (0.9) - 12 (1.6)	3 (1.2) - 13 (2.2)	0 (0.0) - 2 (1.2)	3 (1.1) - 19 (2.4)	0 - 1 (0.4)
Gastrointestinal disorders					
Pancreatitis [6]	b	b	b	b	b
N (%)	0 - 0	0 - 1 (0.2)	0 - 0	0 - 1 (0.1)	0 - 0
Musculoskeletal and connective tissue disorders					
Myalgia [7]	-	a	-	-	-
N (%)		2 (0.8) - 15 (2.5)			
Investigations					
Weight increased	-	-	-	-	a
N (%)					1 (0.8) - 6 (2.3)

(a) AEs with an incidence ≥2% with linagliptin and 2 fold higher incidence than in the placebo group or when the incidence in the placebo group wars zero, and/or
(b) AEs that were likely related based on medical plausability, and/or
(c) AEs that had a consistent pattern over antidiabetic background treatments, i.e. the incidence in the linagliptin groups was consistently higher than in the placebo groups in every antidiabetic background medication.
(-) The hyphen indicates no identified risk

1 'Hypersensitivity' included the SMQs for 'anaphylactic reaction', 'angioedema', and 'asthmabronchospasm'.
2 'Hypoglycemia' included the HLT 'hypoglycaemic conditions NEC' plus the MedDRA PT 'low blood glucose'.
3 'Hypertriglyceridaemia included the PTs 'blood triglycerides increased' and 'hypertriglyceridaemia'.
4 'Dizziness' included the PTs dizziness, dizziness postural, dizziness exertional, vertigo.
5 'Cough' included the PTs cough, productive cough.
6 'Pancreatitis' was calculated based on the SMQ 'acute pancreatitis' and the PT 'chronic pancreatitis'.
7 'Myalgia' included the PTs myalgia, muscle tightness, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness.

Source (b) (4), Table 5.3.3.1: 1, page 235

(b) (4)

Reviewer's Comments
This table is similar to others in OAD medication labels at the current time. It displays useful findings from the studies by add on medication. I recommend this remain in the label.

Study 20—Active Control with Glimepiride

The data presented here are from 52 weeks in contrast to the 26 week data presented with the other grouping, SAF-2. At the preferred term level, those that occurred in 5% or more patients were most useful to display as those occurring in 1% cutoff were numerous and notable imbalances were not seen, see Table 90. There were no events at this rate in the post treatment groups, so this was not presented. Overall, consistent with other AE discussion for this study, fewer patients were reported with AEs in the linagliptin 5 mg group than in the glimepiride group. Hypoglycemia occurred at a much higher rate in the glimepiride group which was discussed earlier. Patients in this study had background metformin medication, this may contribute to the higher rate of gastrointestinal disorders seen here compared to SAF-2. There was one SOC that had more events in the linagliptin group; this was musculoskeletal and connective tissue disorders (25.2% linagliptin, 22.3% glimepiride).

Table 90 Frequency of Patients with AEs in more than 5% of Patients by Treatment, Sorted by SOC—Study 20, TS

System Organ Class -Preferred Term	Linagliptin 5mg N (%)	Glimepiride N (%)
Number of Patients	778	781
Patients with Any AE	611 (78.5)	662 (84.8)
Gastrointestinal Disorders	168 (21.6)	177 (22.7)
--Diarrhea	36 (5.0)	52 (6.7)
Infections and Infestations	305 (39.2)	321 (41.1)
--Bronchitis	35 (4.5)	40 (5.1)
--Nasopharyngitis	100 (12.9)	102 (13.1)
--Upper Respiratory Tract Infection	43 (5.5)	46 (5.9)
Metabolism and Nutrition	107 (13.8)	280 (35.9)
--Hypoglycemia	41 (5.3)	237 (30.3)
Musculoskeletal and Connective Tissue Disorders	196 (25.2)	174 (22.3)
--Arthralgia	44 (5.7)	27 (3.5)
--Back Pain	50 (6.4)	41 (5.2)
Nervous System Disorders	114 (14.7)	143 (18.3)
--Headache	44 (5.7)	33 (4.2)
Vascular Disorders	71 (9.1)	82 (10.5)
--Hypertension	34 (4.4)	41 (5.2)

Adapted from ISS, Table 5.2.4.1.1.1, page 4273

The higher rate of arthralgia reported in the linagliptin group was confirmed by my own analyses. No other notable imbalances in musculoskeletal conditions were seen.

Reviewer's Comments

The only common AE occurring in more than 5% of patients treated with linagliptin at a rate at least 1% higher than glimepiride are arthralgias, back pain and headache. This was not seen in SAF-2, but this important finding from this 52 week data should be mentioned in the label in the AE section. There should be a table with these findings in the label under Adverse Events.

7.4.2 Laboratory Findings

Standard laboratory parameters (hematology, clinical chemistry, and urinalysis) were evaluated for the treated sets presented and discussed here. The following safety laboratory parameters were measured (or assessed):

• Hematology: hematocrit, hemoglobin, erythrocyte count, total and automated differential leukocyte counts (neutrophils, eosinophils, basophils, lymphocytes, monocytes) in absolute counts, platelet count

• Clinical chemistry: amylase, aspartate aminotransferase (AST/SGOT), alanine aminotransferase (ALT/SGPT), gamma-glutamyl transferase (GGT), Alkaline Phosphatase, lactate dehydrogenase (LDH), total bilirubin, total protein, potassium, sodium, creatinine, urea, calcium, inorganic phosphorous, uric acid, albumin, creatine kinase (CK), CK-MB (if CK was elevated), total cholesterol, HDL cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides
• Urinalysis: albumin, creatinine (spot urine – quantitative measurement), protein, ketones, leukocytes, glucose; urine sediment was only done if there was a positive finding in the urinalysis

Samples were collected at almost all visits and then analyzed by central laboratories.

SAF-3 Central Tendency Laboratory Values

Only the pivotal studies, (15, 16, 17 and 18) had a common treatment time (24 weeks) and were placebo controlled. For this reason, I will display the changes from baseline to week 24 for this dataset. There were no noteworthy trends observed in the linagliptin treated patients when compared to placebo. These data were used, in part, to guide my review of lab data in other safety datasets.

Table 91 Mean and Median Changes from Baseline to Week 24 by Treatment—TS, SAF-3

	Placebo		Linagliptin 5 mg	
	N	Mean change from baseline to Week 24 (±SD) Median (minimum, maximum)	N	Mean change from baseline to Week 24 (±SD) Median (minimum, maximum)
Haematology				
Haematocrit	643	-0.8 (4.6) 0.0 (-15.0, 15.0)	1726	-0.3 (4.6) 0.0 (-31.5, 37.5)
Haemoglobin	643	-0.1 (1.0) 0.0 (-5.2, 2.8)	1726	-0.1 (1.2) -0.1 (-9.8, 12.2)
Erythrocytes	643	0.0 (0.4) 0.0 (-1.5, 1.3)	1726	0.0 (0.4) 0.0 (-2.3, 4.2)
Leukocytes	643	0.0 (1.5) -0.1 (-5.6, 8.7)	1726	0.2 (1.5) 0.2 (-6.1, 10.6)
Thrombocytes	639	-5 (30) -4 (-137, 170)	1707	-6 (30) -7 (-171, 184)
Neutrophils	640	0 (8) 0 (-26, 44)	1717	1 (8) 1 (-34, 61)
Eosinophils	640	0 (2) 0 (-11, 22)	1717	0 (3) 0 (-16, 30)
Basophils	640	0 (0) 0 (-2, 3)	1717	0 (0) 0 (-3, 3)
Lymphocytes	640	0 (4) 0 (-16, 15)	1717	0 (3) 0 (-29, 17)
Monocytes	640	0 (2) 0 (-10, 13)	1717	1 (2) 0 (-10, 10)
Clinical chemistry				
Sodium	650	1 (4) 0 (-12, 54)	1729	1 (4) 0 (-13, 29)
Potassium	650	0.0 (0.5) 0.0 (-1.9, 1.9)	1724	0.0 (0.5) 0.0 (-6.6, 2.5)
Calcium	652	-0.02 (0.13) -0.03 (-0.77, 0.87)	1734	-0.02 (0.14) -0.03 (-1.70, 1.36)
Phosphate	650	0.00 (0.16) 0.00 (-0.66, 0.51)	1722	0.01 (0.16) 0.00 (-0.56, 0.75)
AST	640	-1 (19) -2 (-130, 106)	1693	-1 (18) 0 (-159, 263)
ALT	640	-2 (21) -1 (-136, 115)	1693	-2 (19) -2 (-168, 190)
Alkaline phosphatase	652	-3 (33) -3 (-167, 286)	1733	-10 (35) -9 (-244, 663)
GGT	652	-3 (43) 0 (-450, 309)	1733	-2 (45) 0 (-894, 392)

LDH	634	3 (33) 3 (-184, 138)	1659	2 (32) 1 (-234, 320)
Creatine kinase	652	-3 (151) 0 (-1351, 2013)	1722	11 (178) 5 (-1420, 5112)
CK-MB enzymatic	35	-1 (6) 0 (-31, 5)	77	-1 (4) 0 (-25, 7)
Amylase	652	3 (23) 2 (-177, 140)	1731	6 (23) 5 (-170, 240)
Clinical chemistry				
Glucose	650	-6 (49) -5 (-217, 160)	1740	-18 (46) -16 (-215, 279)
Cholesterol, total	652	4 (16) 3 (-95, 123)	1736	2 (13) 2 (-79, 61)
HDL	648	2 (10) 1 (-54, 72)	1721	1 (11) 1 (-186, 178)
LDL	645	7 (24) 6 (-85, 109)	1710	5 (24) 5 (-147, 180)
Urea	652	0.1 (0.6) 0.0 (-2.2, 3.3)	1737	0.1 (0.6) 0.1 (-3.8, 4.6)
Creatinine	652	0.0 (0.1) 0.0 (-0.5, 0.7)	1735	0.0 (0.1) 0.0 (-0.9, 0.7)
Bilirubin, total	650	0.0 (0.2) 0.0 (-0.7, 1.9)	1718	0.0 (0.2) 0.0 (-1.0, 0.8)
Triglycerides	650	-5 (189) -1 (-2209, 2092)	1722	-12 (123) -8 (-1387, 1249)
Uric acid	652	-0.2 (1.4) -0.2 (-7.1, 5.1)	1737	0.1 (1.4) 0.1 (-9.4, 9.8)
Protein, total	652	0.0 (0.5) 0.0 (-1.1, 3.1)	1734	0.0 (0.4) 0.0 (-1.6, 2.8)
Albumin	652	0.0 (0.4) 0.0 (-1.3, 2.9)	1737	0.0 (0.4) 0.0 (-1.6, 2.8)
Urine analysis				
Urine microalbumin creatinine ratio	535	19.8 (315.2) 1.7 (-3732, 3487.2)	1356	2.3 (180.7) 0.0 (-2426, 2483.1)
UACR				
Normal	388	9.77 (40.78) 1.8 (-18.6, 517.1)	965	10.58 (92.98) 0.9 (-24.8, 2560.9)
Elevated	125	40.03 (242.11) -7.1 (-234.3, 2263.9)	333	5.55 (102.18) -13.3 (-240.4, 695.7)
High	22	-68.11 (1174.75) 2.2 (-3848.9, 2568.9)	58	-155.40 (652.06) -167.1 (-2501.7, 2371.8)

N = Number of patients with at least one on-treatment measurement, UACR = urine albumin to creatinine ratio
UACR subgroups (at baseline): normal ≤30µg/mg, elevated >30 to ≤300µg/mg, high >300 µg/mg

Source Response to FDA Inquiry Feb 14, 2011

SAF-2 Placebo Controlled Trials

Laboratory values were evaluated for trends, significant increases or decreases. The only laboratory values that had 0.5% increase in frequency of abnormal lab values were hematocrit decrease (1.6% in placebo group, 2.3% in linagliptin group), amylase increase (2.2% in placebo, 2.8% in linagliptin) and uric acid increase (1.3% in placebo and 2.7% in linagliptin).

Transitions from normal to high values were observed in the linagliptin group at a rate higher than 0.5% in creatine kinase, amylase, LDL, uric acid, protein, and natriuretic peptide type B (however, this was measured in only one study—15). These shifts are seen in Table 92.

Table 92 Normal to High Values ≥0.5% Higher in Linagliptin Group Versus Placebo—SAF-2

Laboratory	Linagliptin (%)	Placebo (%)
Creatine Kinase	5.7	4.5
Amylase	5.7	4.7
LDL	6.3	5.4
Uric Acid	5.5	3.4
Protein	5.2	3.9
Natriuretic Peptide B	7.7	4.2

Due to potential class effect concerns, and the consistently higher levels of amylase observed in patients treated with linagliptin, a search for amylase levels that were above 150 U/L and also above 300 U/L in the SAF-2 database was done (see *Adverse Events of Special Interest* and discussion of trends above, see also discussion of laboratory trends in study 20 below). Of note, high was above 100 U/L for all studies except the active control with voglibose study in Japan—study 23, where it was 125 U/L. This search yielded slightly higher incidence in the linagliptin group as seen in Table 93.

Table 93 Incidence of Elevated Amylase in SAF-2 (minus study 37)

	Linagliptin 5 mg	Placebo/Other Treatments
Number of Patients	2529	1145
Patients with Amylase >150 U/L—n (%)	138 (5.5)	55 (4.2)
Patients with Amylase >300 U/L—n (%)	9 (0.3)	4 (0.3)

The frequency of outliers with higher levels of amylase seen in linagliptin treated patients can be visualized in Figure 23.

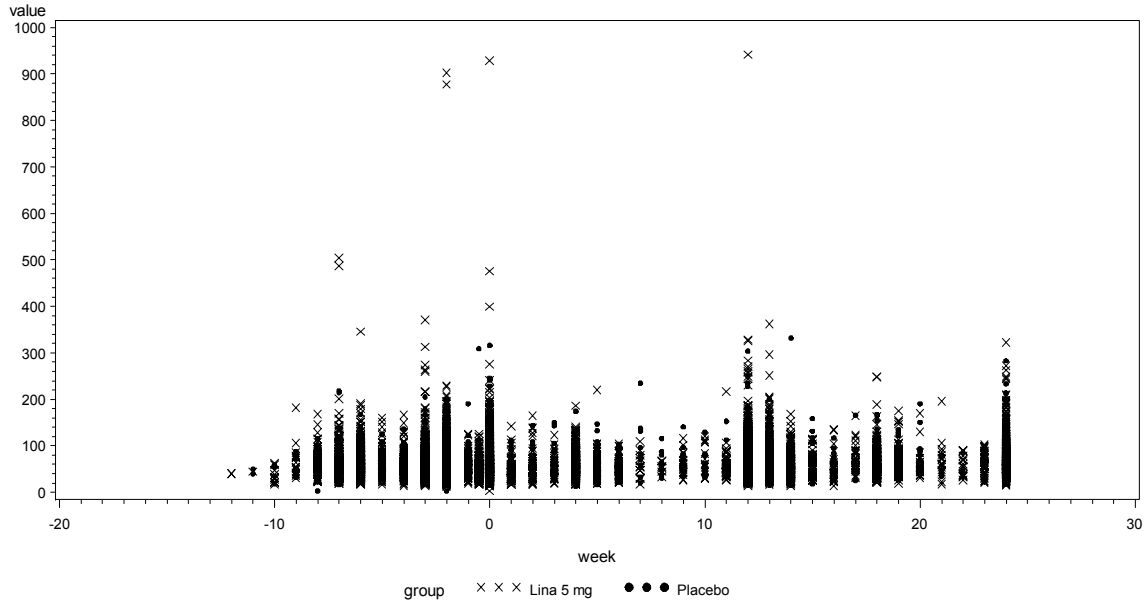


Figure 23 Amylase Over Time in SAF-2
Source Dr. Wei Liu

The trend in uric acid appears to be due to outliers does not seem to come from an overall increase in uric acid for the treated patients. See Figure 24.

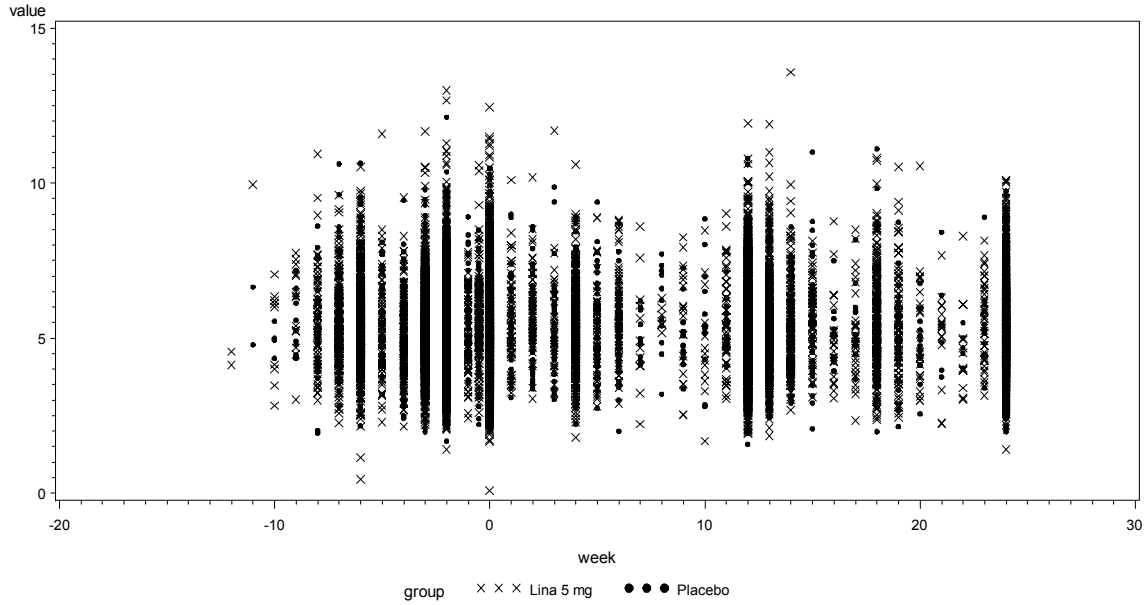


Figure 24 Uric Acid Over Time—SAF-2

Source Dr. Wei Liu

Similar to uric acid, the trend seen in creatine kinase (CK) also is due to what Figure 25 displays as an outlier effect, rather than an overall increase in CK levels over time. Of note, CK is the only laboratory value, other than amylase that shows a similar trend in the study 20 group which will be discussed below.

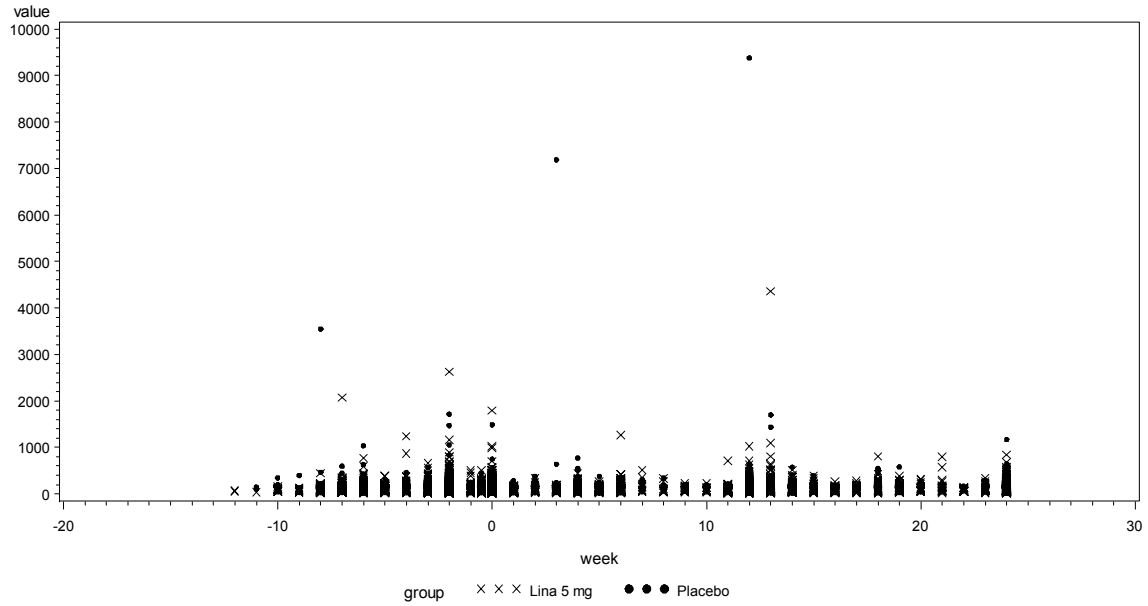


Figure 25 CK Over Time—SAF-2
Source Dr. Wei Liu

Study 15 (a study grouped in SAF-2), the add on to pioglitazone study, had some laboratory findings that the applicant presents in the proposed label. A shift from low or normal values to high values for high density lipoprotein (HDL) was seen in 4.1% of patients treated with linagliptin and pioglitazone versus 2.6% treated with pioglitazone and placebo. This trend was also seen for triglycerides (TG), 12.9% (linagliptin group) versus 11.1% (placebo); and for low density lipoprotein (LDL), 14.2% (linagliptin group) versus 8.7% (placebo group).

Another study (35) with laboratory findings presented in the label from SAF-2 is the 18-week add on to SU study. (b) (4)

(b) (4)

Discussion of Liver-related Laboratories

No patient fulfilled the criteria for Hy's law in any of the safety groupings. Based upon the conservative approach to list patients that were reported with one or two of the laboratory parameters for Hy's law and had a missing value for the remaining parameter(s) at the same time point, one case that was termed as a potential Hy's Law case in this grouping was identified. Please see Table 94 for this patient's liver enzyme tests (LFTs). This patient was in study 16. The LFTs on 12 Aug 2008 have >3 fold upper limit of normal (ULN) for AST and ALT. Bilirubin at that time was normal. The following time point has >3 fold ULN for ALT. AST is not as high at this time and the value for bilirubin is missing. Analysis of all liver laboratory values for this patient does not indicate liver injury

Table 94 Potential Hy's Law Case—SAF-2

Date	Time	ALT/GPT, SGPT [U/L]	ULN	AST/GOT, SGOT [U/L]	ULN	Bilirubin, total [mg/dL]	ULN	Alkaline phosphatase [U/L]	ULN
25APR2008	10:00	98.0	45.0	57.0	39.0			76.0	123.0
30APR2008	8:20	104.0	45.0	61.0	39.0	0.5	1.28	70.0	123.0
07MAY2008	8:35	127.0	45.0	76.0	39.0	0.6	1.28	70.0	123.0
19MAY2008	9:05	131.0	45.0	74.0	39.0	0.5	1.28	70.0	123.0
12AUG2008	8:10	164.0	45.0	136.0	39.0	0.8	1.28	68.0	123.0
18AUG2008*	8:10	165.0	45.0	92.0	39.0				
28AUG2008	9:00	147.0	45.0	72.0	39.0	0.7	1.28	74.0	123.0
04SEP2008	8:10	115.0	45.0	61.0	39.0	0.6	1.28	60.0	123.0
14MAY2008	9:40	22.0	45.0	22.0	39.0				

Adapted from ISS, Table 6.4.1.1, page 6331

The applicant describes a grading system for LFTs. The second grade category and incidence rates are seen in Table 94. There was only one patient in SAF-2 treated with linagliptin that had an ALT (5-10X ULN). There was also one patient in this group that had a total bilirubin >2x ULN. There were no patients with AST 5-10x ULN. In the placebo group, there was one patient in the described AST category, 0 in the ALT category and 3 patients in the bilirubin category.

Table 95 Frequency of Patients with Grade 2 LFTs—SAF-2

Grade 2 LFT Limits	Linagliptin N=2360 N (%)	Placebo N=1078 N (%)
ALT 5-10x ULN	1 (0)	0 (0)
AST 5-10x ULN	0 (0)	1 (0.1)
Bilirubin >2x ULN	1 (0)	3 (0.4)

N are treated patients with at least one LFT grading on treatment

Study 20—Active Control with Glimepiride

Laboratory values were evaluated for trends, significant increases or decreases. There were no transitions from normal baseline values to high last values on treatment observed for any laboratory values occurring at a higher rate in the linagliptin group. In addition, no relevant transitions to low were detected (i.e. hematocrit).

The only laboratory values that had at least a 0.5% increase in frequency of abnormal lab values in linagliptin compared to glimepiride were hemoglobin (5.3% in glimepiride, 6.3% in linagliptin), increase in AST (0.7% in glimepiride group, 1.3% in linagliptin group), increase in creatine kinase (1.2% glimepiride group, 1.7% linagliptin group), amylase (4.3% glimepiride, 5% linagliptin).

Table 96 Laboratory Abnormality Incidences—Study 20, TS

	Linagliptin			Glimepiride		
	N	Decrease n (%)	Increase n (%)	N	Decrease n (%)	Increase n (%)
Haematology						
Haematocrit	761	28 (3.7)	0	749	27 (3.6)	0
Haemoglobin	761	48 (6.3)	0	749	40 (5.3)	0
Erythrocytes	761	10 (1.3)	0	749	12 (1.6)	0
Leucocytes	761	6 (0.8)	0	749	2 (0.3)	3 (0.4)
Eosinophils	760	0	36 (4.7)	748	0	47 (6.3)
Platelets	758	1 (0.1)	0	748	1 (0.1)	0
Clinical chemistry						
Amylase	760	0	38 (5.0)	749	0	32 (4.3)
AST	759	0	10 (1.3)	747	0	5 (0.7)
ALT	759	0	9 (1.2)	747	0	13 (1.7)
GGT	760	0	22 (2.9)	749	0	23 (3.1)
Alkaline phosphatase	760	0	2 (0.3)	749	0	2 (0.3)
LDH	758	0	0	746	0	2 (0.3)
Total bilirubin	760	0	0	748	0	1 (0.1)
Albumin	760	1 (0.1)	0	749	3 (0.4)	0
Creatine kinase	760	0	13 (1.7)	748	0	9 (1.2)
Potassium	760	0	45 (5.9)	749	3 (0.4)	52 (6.9)
Sodium	760	7 (0.9)	0	749	4 (0.5)	0
Creatinine	760	0	13 (1.7)	749	0	18 (2.4)
Calcium	760	4 (0.5)	0	749	2 (0.3)	1 (0.1)
Phosphate	760	6 (0.8)	6 (0.8)	749	10 (1.3)	8 (1.1)
Uric acid	760	0	52 (6.8)	749	0	59 (7.9)
Triglycerides	741	0	69 (9.3)	730	0	74 (10.1)
Glucose	767	2 (0.3)	0	762	2 (0.3)	0
Urine microalbumin creatinine ratio	741	0	25 (3.4)	727	0	21 (2.9)

N = Number of patients with at least one on-treatment measurement
n = Number of patients with possibly clinically significant decrease or increase

Source (b) (4) Table 12.4: 1, page 119

The incidence of amylase levels greater than 150 U/L and 300 U/L was explored in this database as well. There were more abnormal amylase values seen in this database, see Table 96 above. The results are depicted below in Table 97.

Table 97 Incidence of Elevated Amylase—Study 20

	Linagliptin 5 mg	**Glimepiride**
Number of Patients	778	781
Patients with Amylase >150 U/L—n (%)	56 (7.2)	37 (4.7)
Patients with Amylase >300 U/L—n (%)	3 (0.4)	7 (0.9)

Again, the outliers in the linagliptin group responsible for this overall higher incidence of amylase can be visualized in Figure 26.

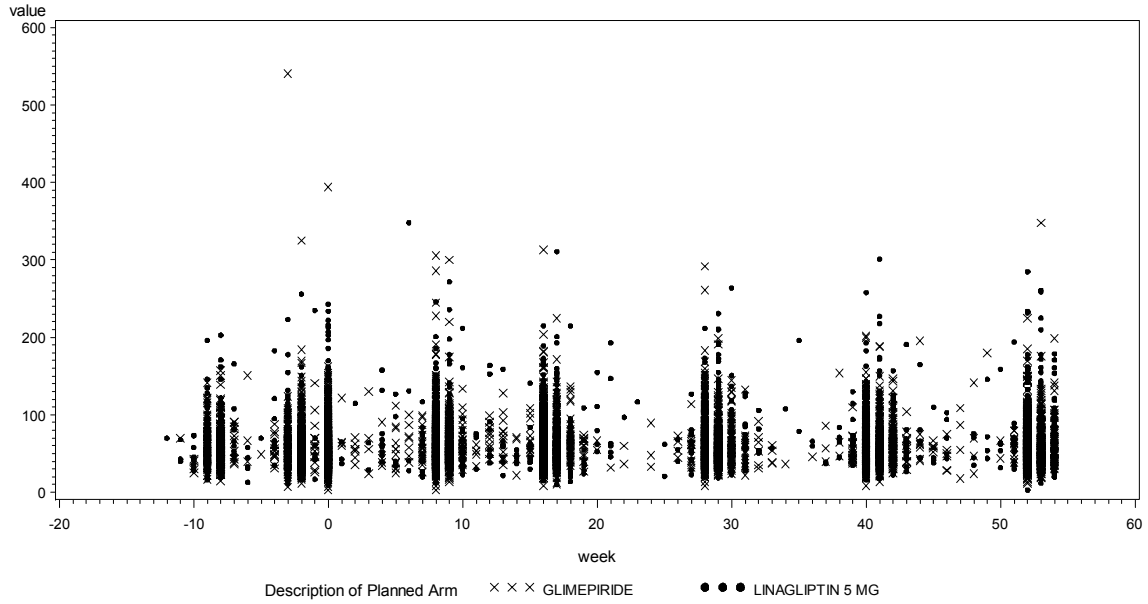


Figure 26 Amylase Over Time, Study 20
Source Dr. Wei Liu

CK shows a similar trend in this safety group as with SAF-2. Figure 27 displays these results over time. They are a result of outliers and this is overall more similar between linagliptin and glimepiride than was seen in Figure 25 with SAF-2.

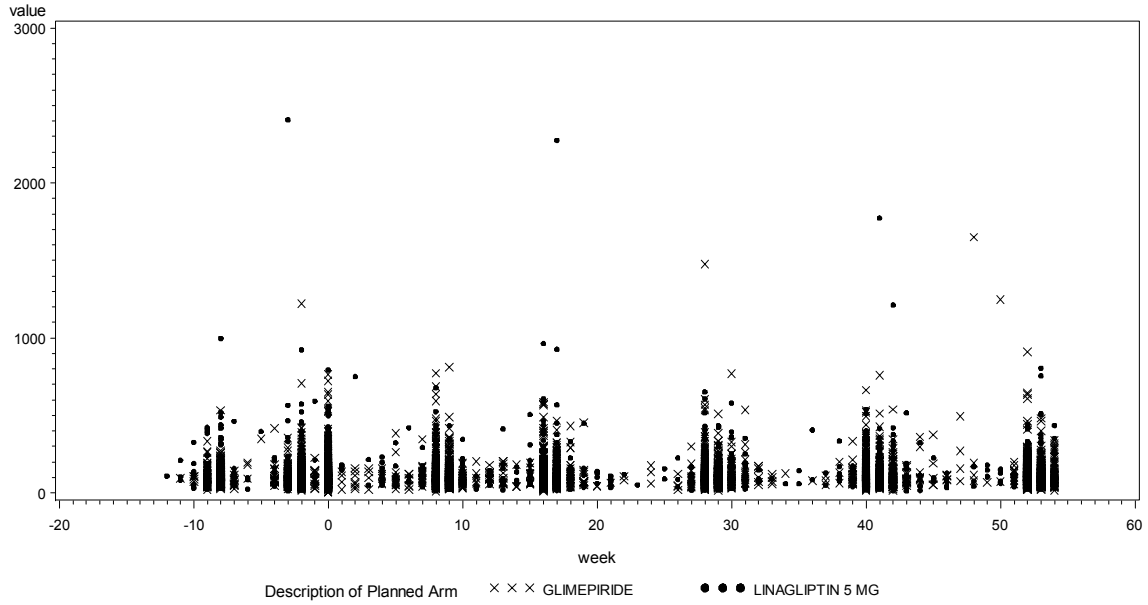


Figure 27 CK Over Time—Study 20

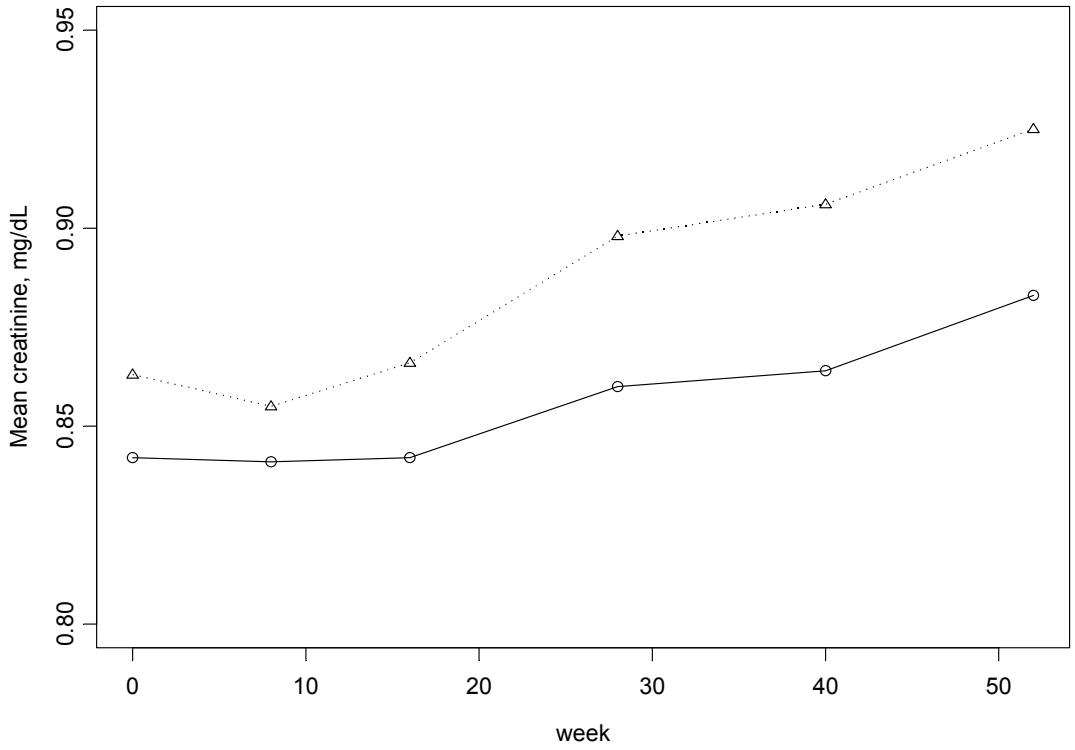
Source Dr. Wei Liu

Reviewer's Comments
Amylase levels are consistently higher in linagliptin treated patients, in both datasets. However, with clinically significant elevations (300 U/L—high enough to fulfill a criterion for pancreatitis), the rates become very similar and no cases were observed in study 20 at all. Based on this and my discussion of pancreatitis in *Adverse Events of Special Interest,* I recommend adding pancreatitis to the *Adverse Reactions* section of the label *Highlights*; the applicant already included information in the *Adverse Reactions* section of the label. We will continue to monitor in Periodic Safety Update Reports, requests for AE of special interest (to include pancreatitis) of the applicant, and the 18 month post marketing review for potential pancreatitis signals. In addition, pancreatitis cases will be followed in the dedicated cardiovascular study as an AE of special interest.

With the exception of amylase and creatine kinase, there were no laboratory values that displayed similar normal to high or relevant normal to low values in both the SAF-2 or study 20 groupings. At this time, I do not feel that a post marketing requirement/commitment are needed for these slight trends. Trends seen in the SAF-2 group will be added to the label *Adverse Reaction* section.

Creatinine

Table 96 above shows that the overall values of creatinine increased in 1.7% of patients treated with linagliptin and 2.4% of patients treated with glimepiride. Renal safety is of concern in other drugs of this class, so this was investigated in more detail. Study 20 presented the longest controlled data to examine these results.
On further investigation, the mean value of creatinine in the linagliptin group at baseline was 0.8 mg/dL (SD 0.2) and by last value on treatment it was 0.9 mg/dL (SD 0.2). The mean and SD values were the same for baseline and last value for the glimepiride patients.
The trend in creatinine can be seen in Figure 28. The increasing mean values are increasing over time and more so in the glimepiride group, as expected.



o=Linagliptin
△=Glimepiride
Source Dr. Wei Liu
Figure 28 Mean Serum Creatinine Over Time—Study 20, TS

Discussion of Liver-related Laboratories

No patient fulfilled the criteria for Hy's law in this study. Based upon the conservative approach to list patients that were reported with one or two of the laboratory parameters listed above and had a missing value for the remaining parameter(s) at the same time point, one potential Hy's Law case in this grouping on linagliptin treatment was identified. Review of LFTs for this patient reveals only ALT at any point was >3x ULN. There was only one bilirubin missing and the other values were all within normal limits.

For Grade 2 LFT elevations as was similarly described for SAF-2, there were more reported in the linagliptin treated group.

Table 98 Frequency of Patients with Grade 2 LFTs—Study 20

Grade 2 LFT Limits	Linagliptin N=760 N (%)	Glimepiride N=749 N (%)
ALT 5-10x ULN	3 (0.4)	0 (0)
AST 5-10x ULN	1 (0.1)	1 (0.1)
Bilirubin >2x ULN	1 (0.1)	1 (0.1)

N are treated patients with at least one LFT grading on treatment

Reviewer's Comments
While the rates are slightly higher in study 20 for grade 2 LFT elevations, the overall low incidence of elevated LFTs and lack of Hy's law cases in both safety groupings cause minimal concern for drug induced liver injury at this time.

7.4.3 Vital Signs

SAF-3 Pivotal Studies, studies 15, 16, 17 and 18

For vital signs, the data from the pivotal studies was reported. Vital signs were measured at all visits except the screening visit (and the follow up visit, if performed as a telephone visit). Systolic and diastolic blood pressure (SBP and DBP) as well as pulse rate (assessed electronically or by palpitation for one minute) were measured after five minutes of rest in the seated position and blood pressure measurements were to be made using the same blood pressure recording instrument on the same arm.

Systolic and diastolic blood pressure values were comparable between treatment groups at baseline. In the linagliptin group, overall a decrease in systolic and diastolic BP over time from baseline to end of treatment was observed, with the maximum difference from baseline reached at Week 6 in systolic BP (-0.62 mmHg) and Week 24 in diastolic BP (-0.36 mmHg). See Table 99.

At 24 weeks of treatment, there were no patients that had systolic values ≥ 200 mmHg, ≤ 80 mmHg, or diastolic values ≤ 40 mmHg in either the linagliptin or placebo treated groups. There was one patient in the linagliptin group that had a diastolic value ≥ 115 mmHg.

Table 99 Mean Changes in Systolic and Diastolic Blood Pressure from Baseline over Time for the SAF-3 (pivotal trials) - TS

	Placebo		Linagliptin 5 mg	
	N	Mean (±SD)	N	Mean (±SD)
Systolic blood pressure [mmHg]				
Baseline	737	129.72 (14.84)	1910	130.04 (15.33)
Week 6	717	128.83 (15.55)	1863	129.49 (15.52)
Week 12	698	129.72 (16.38)	1832	129.93 (15.14)
Week 18	681	129.63 (14.81)	1811	130.14 (15.25)
Week 24	715	130.28 (15.64)	1867	129.73 (14.97)
Change from baseline to Week 6	717	-0.94 (13.13)	1863	-0.62 (12.75)
Change from baseline to Week 12	698	0.14 (13.79)	1832	-0.28 (13.83)
Change from baseline to Week 18	681	0.12 (13.45)	1811	-0.11 (14.23)
Change from baseline to Week 24	715	0.36 (14.10)	1867	-0.42 (14.02)
Diastolic blood pressure [mmHg]				
Baseline	737	78.61 (9.04)	1910	78.47 (8.64)
Week 6	717	78.40 (9.26)	1863	78.53 (8.95)
Week 12	698	78.23 (9.03)	1832	78.23 (8.83)
Week 18	681	78.87 (8.73)	1811	78.46 (8.51)
Week 24	715	78.29 (8.74)	1867	78.11 (8.69)
Change from baseline to Week 6	717	-0.19 (8.37)	1863	0.03 (8.01)
Change from baseline to Week 12	698	-0.27 (8.45)	1832	-0.31 (8.63)
Change from baseline to Week 18	681	0.42 (9.00)	1811	-0.07 (8.87)
Change from baseline to Week 24	715	-0.31 (8.73)	1867	-0.36 (8.87)

Source (b) (4), Table 4.1: 1, page 201

Pulse rate was comparable between both treatment groups at baseline. Overall, in both treatment groups, a very small pulse rate increased over time from baseline to end of treatment. There were no patients with pulse rate < 40 beats per minute (bpm) or > 150 bpm at 24 weeks of treatment in the linagliptin or placebo treated groups.

Study 20—Active Control Study with Glimepiride

Baseline systolic and diastolic blood pressure values were comparable between the linagliptin 5 mg and glimepiride treatment groups. There were no marked trends observed for the mean changes from baseline by patient per visit for systolic or diastolic blood pressure; however, in the linagliptin 5 mg group most of the observations tended to show small reductions with respect to baseline for both SBP and DBP. Table 100 summarizes the mean changes.

At 52 weeks of treatment, there were no patients that had systolic values ≥ 200 mmHg, ≤ 80 mmHg, diastolic values ≤ 40 mmHg or ≥ 115 mmHg in either group.

Table 100 Mean Changes in Systolic and Diastolic Blood Pressure from Baseline Over Time for Study 20 - TS

	Linagliptin 5 mg			Glimepiride		
	N	Mean (±SD)		N	Mean (±SD)	
Systolic blood pressure [mmHg]						
Baseline	778	134.83	(16.02)	780	135.21	(15.37)
Change from baseline to Week 4	763	−0.41	(14.02)	749	−0.50	(13.13)
Change from baseline to Week 8	749	−1.00	(14.71)	731	0.34	(13.38)
Change from baseline to Week 12	734	−0.99	(14.45)	715	−0.44	(14.05)
Change from baseline to Week 16	725	−0.86	(13.84)	707	−0.07	(14.41)
Change from baseline to Week 28	703	0.08	(15.04)	688	0.17	(13.93)
Change from baseline to Week 40	677	−0.64	(15.64)	665	−0.14	(14.65)
Change from baseline to Week 52	626	−0.38	(15.30)	619	−1.53	(14.40)
Change from baseline to Week 65	323	−0.20	(15.22)	310	−0.41	(14.58)
Change from baseline to Week 78	73	−0.68	(14.65)	70	0.37	(16.54)
Change from baseline to Week 104/EoT	112	−0.20	(15.48)	104	0.15	(13.87)
Diastolic blood pressure [mmHg]						
Baseline	778	80.05	(8.64)	780	79.98	(8.64)
Change from baseline to Week 4	763	0.26	(8.96)	749	0.58	(8.37)
Change from baseline to Week 8	749	−0.01	(8.92)	731	0.68	(8.04)
Change from baseline to Week 12	734	−0.17	(8.76)	715	0.37	(8.32)
Change from baseline to Week 16	725	−0.19	(8.49)	707	0.00	(8.27)
Change from baseline to Week 28	703	−0.39	(8.94)	688	−0.14	(8.70)
Change from baseline to Week 40	677	−0.53	(8.96)	665	−0.07	(8.78)
Change from baseline to Week 52	626	−0.56	(9.22)	619	−0.71	(8.70)
Change from baseline to Week 65	323	0.06	(9.57)	310	0.86	(9.02)
Change from baseline to Week 78	73	1.33	(8.67)	70	1.21	(9.55)
Change from baseline to Week 104/EoT	112	−1.80	(8.90)	104	0.64	(8.62)

Source (b) (4), Table 4.1: 3, page 205

Pulse rate was comparable between both treatment groups at baseline. There were no observable trends over time in the changes from baseline in either treatment group. There were no patients with pulse rate < 40 beats per minute (bpm) or > 150 bpm at 52 weeks of treatment in either group.

Reviewer's Comments
Vital sign changes seen over time with both safety groupings are likely not clinically relevant.

7.4.4 Electrocardiograms (ECGs)

12-lead ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) were recorded at screening and selected visits during treatment. The ECGs were evaluated by the investigator or other designated site personnel. Additional ECGs could be collected by the investigator for safety reasons such as hypotension. Clinically relevant abnormal findings in 12-lead ECG measurements and in the physical examination were to be reported as adverse events and are included in the sections discussing AEs.
In SAF-2 with the high level term (HLT) "ECG investigations" one patient was reported with an ECG finding for placebo and one patient for linagliptin 5 mg. Under the HLT

"cardiac arrhythmias" there were 6 patients (0.5%) in the placebo group compared to 28 patients (1.1%) in the linagliptin group. The difference was mainly due to the HLT "supraventricular arrhythmias" (0.2% versus 0.5%).

In study 20 (actively controlled trial with glimepiride), under the HLT "ECG investigations", two patients (0.3%) were reported with ECG findings in both treatment groups. Under "cardiac arrhythmias" there were 20 patients (2.6%) in the linagliptin group compared to 22 patients (2.8%) in the glimepiride group.

7.4.5 Special Safety Studies/Clinical Trials

Renal Safety

There are two groups discussed here. One is the SAF-2 grouping; the largest grouping with renally impaired patients, the other from the interim analysis of study 43, a study in patients with severe renal function impairment. Creatinine and values over time were discussed in *7.4.2 Laboratory Findings* section.

SAF-2

This group included 2104 patients without renal impairment (MDRD calculated GFR ≥90 mL/min), 1380 patients with mild renal impairment (60 to <90 mL/min) and 162 patients with moderate renal impairment (30 to <60 mL/min). There were only 3 patients with severe renal impairment (<30 mL/min). The AE incidence is similar in the renal impairment categories "none" (53.0% placebo and 53.8% linagliptin) and "mild" (55.0% placebo and 55.1% linagliptin 5 mg). In patients with moderate renal impairment, higher incidences of adverse events were observed in the linagliptin group (50.0% placebo and 65.2% linagliptin). In most of the system organ classes, the higher incidences in the linagliptin 5 mg group in patients with moderate renal impairment were due to single patient events.

Table 101 SOCs with Higher Frequency (≥2.5% in Moderate Renal Impairment) in Linagliptin Treated Patients—SAF-2, TS

	Moderate renal impairment		Mild renal impairment		No renal impairment	
	Placebo	Linagliptin 5 mg	Placebo	Linagliptin 5 mg	Placebo	Linagliptin 5 mg
Number of patients	50 (100.0)	112 (100.0)	436 (100.0)	944 (100.0)	675 (100.0)	1429 (100.0)
Number of patient with adverse events	25 (50.0)	73 (65.2)	240 (55.0)	520 (55.1)	358 (53.0)	769 (53.8)
Blood and lymphatic system disorders	0 (0.0)	3 (2.7)	4 (0.9)	11 (1.2)	7 (1.0)	14 (1.0)
Anaemia	0 (0.0)	1 (0.9)	3 (0.7)	6 (0.6)	3 (0.4)	7 (0.5)
Eosinophilia	0 (0.0)	1 (0.9)	1 (0.2)	2 (0.2)	0 (0.0)	3 (0.2)
Leukopenia	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neutropenia	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Ear and labyrinth disorders	0 (0.0)	3 (2.7)	3 (0.7)	4 (0.4)	6 (0.9)	4 (0.3)
Tinnitus	0 (0.0)	1 (0.9)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Vertigo	0 (0.0)	2 (1.8)	1 (0.2)	3 (0.3)	1 (0.1)	3 (0.2)
Investigations	0 (0.0)	7 (6.3)	22 (5.0)	44 (4.7)	0 (0.0)	1 (0.1)
Blood amylase increased	0 (0.0)	1 (0.9)	2 (0.5)	5 (0.5)	0 (0.0)	1 (0.1)
Blood creatine phosphokinase increased	0 (0.0)	1 (0.9)	1 (0.2)	6 (0.6)	3 (0.4)	8 (0.6)
Blood creatinine increased	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood pressure increased	0 (0.0)	1 (0.9)	1 (0.2)	5 (0.5)	0 (0.0)	3 (0.2)
Body temperature increased	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Urine albumin/ creatinine ratio increased	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	7 (14.0)	21 (18.8)	83 (19.0)	149 (15.8)	113 (16.7)	220 (15.4)
Dyslipidaemia	1 (2.0)	2 (1.8)	6 (1.4)	10 (1.1)	6 (0.9)	19 (1.3)
Gout	0 (0.0)	1 (0.9)	1 (0.2)	3 (0.3)	1 (0.1)	0 (0.0)
Hyperglycaemia	3 (6.0)	8 (7.1)	48 (11.0)	46 (4.9)	72 (10.7)	70 (4.9)
Hyperuricaemia	1 (2.0)	3 (2.7)	2 (0.5)	4 (0.4)	1 (0.1)	6 (0.47)
Hypoglycaemia	3 (6.0)	11 (9.8)	21 (4.8)	73 (7.7)	23 (3.4)	101 (7.1)
Vitamin B complex deficiency	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Renal and urinary disorders	1 (2.0)	6 (5.4)	10 (2.3)	27 (2.9)	21 (3.1)	27 (1.9)
Diabetic nephropathy	0 (0.0)	1 (0.9)	1 (0.2)	3 (0.3)	0 (0.0)	3 (0.2)
Dysuria	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Pyuria	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)
Renal failure acute	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal impairment	0 (0.0)	2 (1.8)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	1 (2.0)	6 (5.4)	14 (3.2)	32 (3.4)	15 (2.2)	60 (4.2)
Acne	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	15 (2.2)	60 (4.2)
Eczema	0 (0.0)	2 (1.8)	0 (0.0)	3 (0.3)	1 (0.1)	4 (0.3)
Erythema	0 (0.0)	1 (0.9)	0 (0.0)	2 (0.2)	1 (0.1)	0 (0.0)
Pruritus	1 (2.0)	2 (1.8)	3 (0.7)	6 (0.6)	2 (0.3)	11 (0.8)
Rash	0 (0.0)	1 (0.9)	1 (0.2)	2 (0.2)	1 (0.1)	6 (0.4)

Degree of renal impairment is based on MDRD staging; none ≥90 mL/min; mild 60 to <90 mL/min; moderate 30 to <60 mL/min, and severe <30 mL/min.
Note that only the PTs of the respective SOCs in the moderate renal impairment group are given.

Source (b) (4) Table 5.1.2.1: 2, page 220-221

Changes in Renal Function—SAF-2

The majority of patients remained within normal renal function or mild renal impairment throughout the trials. In both treatment groups, the numbers of patients with moderate renal impairment (eGFR 30 to <60 mL/min) was low at baseline (placebo 3.8%; linagliptin 5 mg 4.1%). Severe or end-stage renal impairment (eGFR <30 mL/min) was reported for 1 patient (0.1%) in the placebo group at baseline; this did not change. In the linagliptin 5 mg group, 2 patients (0.1%) presented with severe or end-stage renal impairment at baseline and shifted to moderate renal impairment by the end of the trial (last value on treatment). However, in addition, by the end of the trials, 2 patients (0.1%) shifted to severe or end-stage renal impairment in the linagliptin group (both having moderate renal impairment at baseline). There were several missing values for this data, see Table 102.

Table 102 Frequency of Patients [N(%)] with Shifts in Renal Impairment—SAF−2, TS

Parameter=Creatinine clearance (Cockcroft-Gault)

Treatment / Baseline RR	Last value on treatment: Normal renal function	Mild renal impairment	Moderate renal impairment	Severe or end-stage renal impairment	Missing	Total
Placebo (N=1183)						
Normal renal function	619 (52.3)	42 (3.6)	1 (0.1)	0	37 (3.1)	699 (59.1)
Mild renal impairment	39 (3.3)	107 (9.0)	6 (0.5)	0	11 (0.9)	163 (13.8)
Moderate renal impairment	0	4 (0.3)	18 (1.5)	1 (0.1)	1 (0.1)	24 (2.0)
Severe or end-stage renal impairment	0	0	0	2 (0.2)	0	2 (0.2)
Missing	5 (0.4)	3 (0.3)	1 (0.1)	0	286 (24.2)	295 (24.9)
Total	663 (56.0)	156 (13.2)	26 (2.2)	3 (0.3)	335 (28.3)	1183 (100.0)
Lina 5mg (N=2566)						
Normal renal function	1499 (58.4)	108 (4.2)	1 (0.0)	0	72 (2.8)	1680 (65.5)
Mild renal impairment	61 (2.4)	351 (13.7)	21 (0.8)	0	14 (0.5)	447 (17.4)
Moderate renal impairment	0	18 (0.7)	33 (1.3)	3 (0.1)	3 (0.1)	57 (2.2)
Severe or end-stage renal impairment	0	0	0	1 (0.0)	1 (0.0)	2 (0.1)
Missing	27 (1.1)	6 (0.2)	1 (0.0)	0	346 (13.5)	380 (14.8)
Total	1587 (61.8)	483 (18.8)	56 (2.2)	4 (0.2)	436 (17.0)	2566 (100.0)

Source ISS, Table 6.6.2.1, page 6404

Study 43—Study in Renal Impairment

Study 43 is entitled:
A phase III, randomized, double-blind, placebo-controlled, parallel group, safety and efficacy study of BI 1356 (5 mg), compared to placebo as add on to pre-existing antidiabetic therapy (insulin or any combination with insulin; sulfonylurea or glinides as monotherapy; pioglitazone or any other antidiabetics, excluding only DPP-4 inhibitors other than linagliptin over 52 weeks in type 2 diabetic patients with severe chronic renal impairment

SAEs

There were 17 patients (26.2%) in the placebo group and 16 patients (23.5%) in the linagliptin group who were reported with SAEs during the treatment period, as of the cut-off date for the NDA interim report (12 weeks of treatment). The treatment period was defined as the time of administration of the first dose of study medication until 7 days after the discontinuation of study medication. The only SAE by preferred term that occurred in the linagliptin treated group at a rate more than 2% greater than placebo was acute myocardial infarction (4.4%--3 patients), pneumonia (4.4%-3 patients) and hypoglycemia (2.9%--2 patients). See Table 103. The rate in the placebo treated patients for all these events was 0%.

Table 103 Frequency of Patients SAE by Treatment, SOC and PT—Study 43, TS

System organ class/ Preferred term	Placebo N (%)	Linagliptin N (%)
Number of patients	65 (100.0)	68 (100.0)
Total with serious adverse events	17 (26.2)	16 (23.5)
Blood and lymphatic system disorders	0 (0.0)	2 (2.9)
Haemorrhagic anaemia	0 (0.0)	1 (1.5)
Nephrogenic anaemia	0 (0.0)	1 (1.5)
Cardiac disorders	5 (7.7)	5 (7.4)
Acute myocardial infarction	0 (0.0)	3 (4.4)
Angina pectoris	0 (0.0)	1 (1.5)
Angina unstable	1 (1.5)	0 (0.0)
Arrhythmia	1 (1.5)	0 (0.0)
Atrial fibrillation	0 (0.0)	1 (1.5)
Cardiac arrest	0 (0.0)	1 (1.5)
Cardiac failure acute	0 (0.0)	1 (1.5)
Cardiac failure congestive	1 (1.5)	1 (1.5)
Cardio-respiratory arrest	1 (1.5)	0 (0.0)
Coronary artery stenosis	0 (0.0)	1 (1.5)
Left ventricular failure	0 (0.0)	1 (1.5)
Mitral valve incompetence	0 (0.0)	1 (1.5)
Myocardial infarction	2 (3.1)	1 (1.5)
Ventricular hypokinesia	0 (0.0)	1 (1.5)
Ventricular tachycardia	0 (0.0)	1 (1.5)
Ear and labyrinth disorders	0 (0.0)	1 (1.5)
Vertigo positional	0 (0.0)	1 (1.5)
Gastrointestinal disorders	4 (6.2)	0 (0.0)
Abdominal pain	1 (1.5)	0 (0.0)
Abdominal pain upper	1 (1.5)	0 (0.0)
Gastritis	1 (1.5)	0 (0.0)
Vomiting	1 (1.5)	0 (0.0)
General disorders and administration site conditions	3 (4.6)	2 (2.9)
Cardiac death	1 (1.5)	0 (0.0)
Chest pain	1 (1.5)	2 (2.9)
Pyrexia	1 (1.5)	0 (0.0)
Infections and infestations	0 (0.0)	5 (7.4)
Cellulitis	0 (0.0)	1 (1.5)
Pneumonia	0 (0.0)	3 (4.4)
Sepsis	0 (0.0)	1 (1.5)
Urinary tract infection	0 (0.0)	1 (1.5)
Injury, poisoning and procedural complications	0 (0.0)	1 (1.5)
Humerus fracture	0 (0.0)	1 (1.5)
Investigations	1 (1.5)	0 (0.0)
Occult blood positive	1 (1.5)	0 (0.0)
Metabolism and nutrition disorders	1 (1.5)	3 (4.4)
Dehydration	0 (0.0)	1 (1.5)
Hyperkalaemia	1 (1.5)	0 (0.0)
Hypoglycaemia	0 (0.0)	2 (2.9)

Musculoskeletal and connective tissue disorders	1 (1.5)	1 (1.5)
Myositis	0 (0.0)	1 (1.5)
Rhabdomyolysis	0 (0.0)	1 (1.5)
Trigger finger	1 (1.5)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	1 (1.5)
Parathyroid tumour benign	0 (0.0)	1 (1.5)
Nervous system disorders	2 (3.1)	1 (1.5)
Carotid artery stenosis	1 (1.5)	0 (0.0)
Cerebrovascular accident	0 (0.0)	1 (1.5)
Syncope	1 (1.5)	0 (0.0)
Renal and urinary disorders	3 (4.6)	5 (7.4)
Renal failure	1 (1.5)	0 (0.0)
Renal failure acute	2 (3.1)	3 (4.4)
Renal impairment	0 (0.0)	2 (2.9)
Respiratory, thoracic and mediastinal disorders	4 (6.2)	4 (5.9)
Acute pulmonary oedema	0 (0.0)	1 (1.5)
Dyspnoea	2 (3.1)	0 (0.0)
Dyspnoea paroxysmal nocturnal	0 (0.0)	1 (1.5)
Haemoptysis	0 (0.0)	1 (1.5)
Pulmonary congestion	2 (3.1)	1 (1.5)
Pulmonary hilar enlargement	0 (0.0)	1 (1.5)
Pulmonary oedema	1 (1.5)	0 (0.0)
Respiratory failure	0 (0.0)	1 (1.5)
Vascular disorders	1 (1.5)	2 (2.9)
Hypertensive crisis	0 (0.0)	1 (1.5)
Ischaemia	0 (0.0)	1 (1.5)
Peripheral ischaemia	1 (1.5)	0 (0.0)

Source (b) (4) Table 12.3.2: 1, page 119-120

Reviewer's Comments

The number of patients in both treatment groups is similar. Therefore, the imbalance seen with the numbers of patients with acute myocardial infarction and pneumonia are noteworthy. However, the study size is very small as this is a special population and this is only an interim analysis. Furthermore, these trends are not seen outside of this particular study. The full study, once submitted, will be reviewed for these and other trends.

AEs That Led to Premature Discontinuation

There were 5 patients (7.4%) in the linagliptin treatment group and 9 patients (13.8%) in the placebo group who reported with AEs leading to discontinuation of study medication, as of the cut-off date for this interim report (Table 104). There were no SOCs or preferred term AEs that were higher in the linagliptin group by 2% or more that led to discontinuation.

Table 104 Frequency of patients with AEs Leading to Treatment Discontinuation by Treatment, SOC and PT—Study 43, TS

System organ class/ Preferred term	Placebo N (%)	Linagliptin N (%)
Number of patients	65 (100.0)	68 (100.0)
Total with adverse events leading to treatment discontinuation	9 (13.8)	5 (7.4)
Infections and infestations	0 (0.0)	1 (1.5)
Sepsis	0 (0.0)	1 (1.5)
Blood and lymphatic system disorders	1 (1.5)	0 (0.0)
Leukopenia	1 (1.5)	0 (0.0)
Nervous system disorders	2 (3.1)	1 (1.5)
Cerebrovascular accident	0 (0.0)	1 (1.5)
Dizziness	1 (1.5)	0 (0.0)
Syncope	1 (1.5)	0 (0.0)
Cardiac disorders	3 (4.6)	2 (2.9)
Myocardial infarction	2 (3.1)	0 (0.0)
Acute myocardial infarction	0 (0.0)	2 (2.9)
Arrhythmia	1 (1.5)	0 (0.0)
Cardiac failure acute	0 (0.0)	1 (1.5)
Cardiac failure congestive	0 (0.0)	1 (1.5)
Cardio-respiratory arrest	1 (1.5)	0 (0.0)
Vascular disorders	1 (1.5)	0 (0.0)
Aortic stenosis	1 (1.5)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (1.5)	1 (1.5)
Muscle spasms	1 (1.5)	0 (0.0)
Myositis	0 (0.0)	1 (1.5)
Rhabdomyolysis	0 (0.0)	1 (1.5)
Renal and urinary disorders	1 (1.5)	0 (0.0)
Renal failure	1 (1.5)	0 (0.0)

Source (b) (4) Table 12.2.2: 3, page 113

Most Common AEs

The preferred term AEs in order of highest to lowest frequency is displayed in Table 105. By preferred term, the events that were reported in a higher rate in linagliptin patients (by more than 2%) were hypoglycemia (51.5% in linagliptin group versus 27.7% in placebo group), hyperkalemia (25% in linagliptin group versus 10.8% in placebo group), diarrhea (10.3% in linagliptin group, 7.7% in the placebo group) and pneumonia (4.4% in the linagliptin group versus 1.5% in the placebo group).

Table 105 Frequency of Patients with AEs Occurring More Than 2.0% in Either Treatment Group on the Preferred Term Level—Study 43, TS

Preferred Term	Placebo N (%)	Linagliptin N (%)
Number of patients	65 (100.0)	68 (100.0)
Total with adverse events	53 (81.5)	59 (86.8)
Hypoglycaemia	18 (27.7)	35 (51.5)
Hyperkalaemia	7 (10.8)	17 (25.0)
Hyperglycaemia	9 (13.8)	5 (7.4)
Diarrhoea	5 (7.7)	7 (10.3)
Upper respiratory tract infection	6 (9.2)	2 (2.9)
Blood creatine phosphokinase increased	5 (7.7)	6 (8.8)
Renal impairment	2 (3.1)	6 (8.8)
Urinary tract infection	4 (6.2)	6 (8.8)
Constipation	2 (3.1)	5 (7.4)
Oedema peripheral	4 (6.2)	4 (5.9)
Arthralgia	0 (0.0)	4 (5.9)
Nasopharyngitis	2 (3.1)	4 (5.9)
Nausea	0 (0.0)	4 (5.9)
Anaemia	3 (4.6)	3 (4.4)
Blood potassium increased	3 (4.6)	0 (0.0)
Cough	3 (4.6)	1 (1.5)
Dizziness	3 (4.6)	0 (0.0)
Dyspnoea	3 (4.6)	1 (1.5)
Headache	3 (4.6)	1 (1.5)
Lethargy	3 (4.6)	2 (2.9)
Renal failure acute	3 (4.6)	3 (4.4)
Acute myocardial infarction	0 (0.0)	3 (4.4)
Chest pain	1 (1.5)	3 (4.4)
Gout	1 (1.5)	3 (4.4)
Haemoglobin decreased	0 (0.0)	3 (4.4)
Pain in extremity	2 (3.1)	3 (4.4)
Pneumonia	1 (1.5)	3 (4.4)
Abdominal pain	2 (3.1)	1 (1.5)
Back pain	2 (3.1)	2 (2.9)
Blood creatinine increased	2 (3.1)	1 (1.5)
Cardiac failure congestive	2 (3.1)	1 (1.5)
Fall	2 (3.1)	0 (0.0)
Head injury	2 (3.1)	0 (0.0)
Hypertension	2 (3.1)	2 (2.9)
Limb injury	2 (3.1)	0 (0.0)
Muscular weakness	2 (3.1)	0 (0.0)
Musculoskeletal pain	2 (3.1)	1 (1.5)
Myocardial infarction	2 (3.1)	1 (1.5)
Oropharyngeal pain	2 (3.1)	1 (1.5)
Pulmonary congestion	2 (3.1)	1 (1.5)
Renal failure	2 (3.1)	0 (0.0)
Seasonal allergy	2 (3.1)	1 (1.5)
Toothache	2 (3.1)	0 (0.0)
Viral infection	2 (3.1)	1 (1.5)
Vomiting	2 (3.1)	1 (1.5)

Cardiac murmur	0 (0.0)	2 (2.9)
Cellulitis	0 (0.0)	2 (2.9)
Gastroenteritis	0 (0.0)	2 (2.9)
Gastrooesophageal reflux disease	0 (0.0)	2 (2.9)
Joint sprain	1 (1.5)	2 (2.9)
Joint swelling	0 (0.0)	2 (2.9)
Sinusitis	1 (1.5)	2 (2.9)
Vision blurred	0 (0.0)	2 (2.9)

Source (b) (4) Table 12.2.2: 1, page 109

Since there were more patients in the linagliptin treatment group than placebo who were reported with hyperkalemia, the laboratory data for potassium values measured were of special interest. The applicant reports no overall mean changes over time in potassium values measured for either treatment group and no apparent differences in the treatment groups in mean potassium values at baseline (5.1 mmol/L in placebo 5.2 mmol/L in linagliptin group) or the last value on treatment (5.1 mmol/L for both). In addition, there were 19 patients (28.4%) in the linagliptin group and 19 patients (30.6%) in the placebo group with what the applicant terms as possibly clinically significant (see *7.4.2 Laboratory Findings*, to see definition) increases in potassium.

Reviewer's Comments
The rate of AEs in this trial, although only 12 week data is presented, is very high compared to that presented with the SAF-2 grouping (55% in the linagliptin treated group). As mentioned, this population has higher morbidity with renal disease, so this higher rate is expected. The AEs of particular concern include hypoglycemia and hyperkalemia, as the rate differences were notable when compared to other safety groupings; hyperkalemia was not seen in other groupings. One possible explanation for the rate of hypoglycemia seen in the linagliptin treated patients is the background medications allowed in this study (all OADs and insulin, except other DPP-4 inhibitors). As discussed earlier, the combination of SU and linagliptin is associated with more hypoglycemia.
At this time, the data is from 12 weeks only. These events must be followed in the full study report once submitted. Of particular concern will be hyperkalemia.

Hepatic Impairment

The number of patients with hepatic impairment was very small in the linagliptin clinical program (total n = 34) compared to patients without hepatic impairment (total n = 3713). Overall the numbers of patients with an adverse event were higher in patients with hepatic impairment (80.0% placebo and 66.7% linagliptin) compared to those patients without hepatic impairment (53.6% placebo and 54.9% linagliptin). No trends were observed.

7.4.6 Immunogenicity

Linagliptin is not a protein and not expected to cause immunogenic response.

7.6 Other Safety Explorations

Rescue Medication

SAF-2 All Placebo Controlled Trials

The applicant defined rescue medication in this analysis as rescue therapy pre-specified in the trial protocols as well as addition of an OAD to the treatment regimens, or dose increases of antidiabetic background medication after randomization.

Out of the patients using rescue medication, 52.4% of patients in the placebo group and 45.5% of patients in the linagliptin 5 mg group were reported with adverse events. The pattern adverse events did not change when rescue medication was used. Both placebo and linagliptin groups had more patients that had rescue when hyperglycemia was observed. See Table 106.

Table 106 Frequency of Patients with AEs by Use of Rescue Medication in More than 1% by Treatment Group on the Preferred Term Level, Sorted by System Organ Class—SAF-2, TS

	Placebo N (%)	Linagliptin 5 mg N (%)	Placebo + rescue medication N (%)	Linagliptin 5 mg + rescue medication N (%)
Number of patients	977 (100.0)	2381 (100.0)	145 (100.0)	165 (100.0)
Patients with AEs with respect to use of rescue medication	507 (51.9)	1299 (54.6)	76 (52.4)	75 (45.5)
Eye disorders	19 (1.9)	62 (2.6)	3 (2.1)	3 (1.8)
Cataract	3 (0.3)	10 (0.4)	2 (1.4)	1 (0.6)
Gastrointestinal disorders	99 (10.1)	245 (10.3)	13 (9.0)	5 (3.0)
Abdominal pain	6 (0.6)	11 (0.5)	3 (2.1)	1 (0.6)
Abdominal pain upper	12 (1.2)	16 (0.7)	2 (1.4)	0 (0.0)
Constipation	15 (1.5)	37 (1.6)	3 (2.1)	0 (0.0)
Diarrhoea	18 (1.8)	49 (2.1)	2 (1.4)	0 (0.0)
Dyspepsia	7 (0.7)	24 (1.0)	2 (1.4)	0 (0.0)
General disorders and administration site conditions	41 (4.2)	108 (4.5)	10 (6.9)	6 (3.6)
Fatigue	12 (1.2)	10 (0.4)	2 (1.4)	0 (0.0)
Oedema peripheral	6 (0.6)	13 (0.5)	4 (2.8)	1 (0.6)
Pyrexia	5 (0.5)	17 (0.7)	2 (1.4)	0 (0.0)
Infections and infestations	200 (20.5)	460 (19.3)	18 (12.4)	12 (7.3)
Gastroenteritis	6 (0.6)	15 (0.6)	3 (2.1)	1 (0.6)
Influenza	14 (1.4)	33 (1.4)	0 (0.0)	1 (0.6)
Nasopharyngitis	50 (5.1)	140 (5.9)	2 (1.4)	2 (1.2)
Pharyngitis	7 (0.7)	19 (0.8)	2 (1.4)	1 (0.6)
Upper respiratory tract infection	47 (4.8)	81 (3.4)	3 (2.1)	2 (1.2)
Urinary tract infection	23 (2.4)	54 (2.3)	3 (2.1)	1 (0.6)
Wound infection	0 (0.0)	3 (0.1)	2 (1.4)	0 (0.0)
Investigations	31 (3.2)	85 (3.6)	6 (4.1)	8 (4.8)
Blood glucose increased	6 (0.6)	9 (0.4)	4 (2.8)	5 (3.0)
Metabolism and nutrition disorders	160 (16.4)	378 (15.9)	46 (31.7)	38 (23.0)
Diabetes mellitus inadequate control	1 (0.1)	4 (0.2)	2 (1.4)	2 (1.2)
Dyslipidaemia	12 (1.2)	30 (1.3)	1 (0.7)	2 (1.2)
Hyperglycaemia	86 (8.8)	103 (4.3)	37 (25.5)	32 (19.4)
Hyperlipidaemia	4 (0.4)	13 (0.5)	0 (0.0)	3 (1.8)
Hypoglycaemia	44 (4.5)	193 (8.1)	6 (4.1)	4 (2.4)

Source (b) (4), Table 2.2.1.4: 1, page 106

Study 20—Active Control Study with Glimepiride

Out of the patients using rescue medication, 53.6% in the linagliptin 5 mg group and 60.2% in the glimepiride group were reported with adverse events. The pattern of adverse events did not change when rescue medication was used. Again, in both

treatment groups, more patients with hyperglycemia were observed when rescue medication was used. See Table 107.

Table 107 Frequency of Patients with AEs by Use of Rescue Medication in More than 1% by Treatment Group on the Preferred Term Level, Sorted by SOC—SAF-2, TS

	Linagliptin 5 mg N (%)	Glimepiride 5 mg N (%)	Linagliptin 5 mg + rescue medication N (%)	Glimepiride + rescue medication N (%)
Number of patients	777 (100.0)	781 (100.0)	125 (100.0)	93 (100.0)
Patients with AEs with respect to use of rescue medication	591 (76.1)	649 (83.1)	67 (53.6)	56 (60.2)
Blood and lymphatic system disorders	27 (3.5)	20 (2.6)	1 (0.8)	2 (2.2)
Anaemia	18 (2.3)	10 (1.3)	1 (0.8)	1 (1.1)
Ear and labyrinth disorders	24 (3.1)	35 (4.5)	2 (1.6)	1 (1.1)
Vertigo	12 (1.5)	19 (2.4)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	159 (20.5)	169 (21.6)	10 (8.0)	14 (15.1)
Abdominal pain	8 (1.0)	17 (2.2)	2 (1.6)	0 (0.0)
Constipation	24 (3.1)	12 (1.5)	1 (0.8)	0 (0.0)
Diarrhoea	37 (4.8)	50 (6.4)	2 (1.6)	5 (5.4)
Dyspepsia	17 (2.2)	11 (1.4)	1 (0.8)	2 (2.2)
Nausea	26 (3.3)	28 (3.6)	1 (0.8)	2 (2.2)
General disorders and administration site conditions	80 (10.3)	88 (11.3)	6 (4.8)	6 (6.5)
Fatigue	13 (1.7)	21 (2.7)	2 (1.6)	0 (0.0)
Infections and infestations	284 (36.6)	312 (39.9)	31 (24.8)	20 (21.5)
Bronchitis	32 (4.1)	38 (4.9)	3 (2.4)	2 (2.2)
Gastroenteritis	17 (2.2)	28 (3.6)	3 (2.4)	2 (2.2)
Influenza	19 (2.4)	21 (2.7)	3 (2.4)	0 (0.0)
Nasopharyngitis	99 (12.7)	99 (12.7)	2 (1.6)	4 (4.3)
Sinusitis	20 (2.6)	14 (1.8)	2 (1.6)	2 (2.2)
Upper respiratory tract	43 (5.5)	45 (5.8)	2 (1.6)	2 (2.2)
Urinary tract infection	34 (4.4)	31 (4.0)	3 (2.4)	1 (1.1)
Metabolism and nutrition disorders	95 (12.2)	269 (34.4)	15 (12.0)	15 (16.1)
Hyperglycaemia	21 (2.7)	13 (1.7)	11 (8.8)	5 (5.4)
Hypoglycaemia	39 (5.0)	229 (29.3)	4 (3.2)	8 (8.6)
Musculoskeletal and connective tissue disorders	190 (24.5)	168 (21.5)	9 (7.2)	7 (7.5)
Arthralgia	44 (5.7)	25 (3.2)	0 (0.0)	2 (2.2)
Back pain	47 (6.0)	40 (5.1)	3 (2.4)	1 (1.1)
Osteoarthritis	24 (3.1)	18 (2.3)	1 (0.8)	1 (1.1)
Pain in extremity	24 (3.1)	14 (1.8)	3 (2.4)	1 (1.1)

Source (b) (4) Table 2.4.1.4: 1, page 143

Other Long Term Safety Data—Uncontrolled Extensions

There are two other studies that were reviewed for long term safety data. They are listed below and are discussed in more detail in the Summary of Efficacy. Study 40 is the uncontrolled long term extension trial for the four pivotal studies, 15, 16, 17 and 18. All patients in the extension are on linagliptin. Similarly, in study 23, the long term extension consists of patients only on linagliptin. In addition, the active comparator in this study is not marketed in the U.S. The study was held in Japan where voglibose is approved.

Study 40
A 78 week open-label extension trials assessing the safety and efficacy of linagliptin (5 mg) as monotherapy or in combination with other antidiabetic medications in type 2 diabetic patients

Study 23
A double-blind phase III study to evaluate the efficacy of linagliptin 5 mg and 10 mg versus placebo for 12 weeks and versus voglibose 0.6 mg for 26 weeks in patients with type 2 diabetes mellitus and insufficient glycemic control, followed by an extension study to 52 weeks to evaluate long-term safety

These studies were reviewed for long term safety data. This data was compared to rates of SAEs, common AEs, discontinuations due to AEs, and AEs of special interest, including hypoglycemia.

Study 40, to date (this is interim data as this an ongoing study), has a rate of any AEs (66.1%) that is in between that seen in linagliptin treated patients in SAF-2 (55%) and study 20 (78.5%). The rate of SAEs (6.3%) is also between the other two groupings (SAF-2 with 2.4% and study 20 with 12%). In addition, the rate of AE leading to discontinuation is similar to the SAF-2 (2.3%). See Table 108 for rates in the extension study, study 40.

Table 108 Summary of Adverse Events by Treated Group—Study 40, TS

	Old lina		New lina		Total	
Number of patients [n (%)]	1532	(100.0)	589	(100.0)	2121	(100.0)
Patients with any AEs	1015	(66.3)	388	(65.9)	1403	(66.1)
Patients with severe AEs	45	(2.9)	11	(1.9)	56	(2.6)
Patients with investigator defined drug-related AEs	165	(10.8)	59	(10.0)	224	(10.6)
Patients with pre-specified significant AEs[1]	26	(1.7)	10	(1.7)	36	(1.7)
Patients with other significant AEs[2]	21	(1.4)	8	(1.4)	29	(1.4)
Patients with AEs leading to discontinuation of study drug	35	(2.3)	10	(1.7)	45	(2.1)
Patients with SAEs	100	(6.5)	33	(5.6)	133	(6.3)
Fatal	2	(0.1)	1	(0.2)	3	(0.1)
Immediately life-threatening	3	(0.2)	2	(0.3)	5	(0.2)
Requiring hospitalisation	89	(5.8)	30	(5.1)	119	(5.6)
Prolonging hospitalisation	2	(0.1)	1	(0.2)	3	(0.1)
Other	12	(0.8)	2	(0.3)	14	(0.7)

[1] i.e. hypersensitivity reactions, renal AEs, increased liver enzymes (based on investigator reporting)
[2] Defined according to ICH E3 as non-serious AEs that led to treatment discontinuation or dose reduction

Source (b) (4) Table 12.2.1: 1, page 74

The 52 week data from study 23 has very similar rates for SAEs as study 40 described above. The total number of AEs, however, is higher but similar to those seen in study 20, the active controlled glimepiride study arm treated with linagliptin (78.5%). The rate of AEs leading to discontinuation is also similar to study 20 (5.8%).

Table 109 Adverse Events Summary for 52 weeks—Study 20, TS

	Linagliptin 5 mg		Linagliptin 10 mg	
	N	(%)	N	(%)
Number of patients	266	(100.0)	274	(100.0)
Patients with any AE	204	(76.7)	224	(81.8)
Patients with severe AEs	3	(1.1)	3	(1.1)
Patients with investigator defined drug-related AEs	27	(10.2)	29	(10.6)
Patients with significant AEs (protocol-specified events)[1)]	2	(0.8)	3	(1.1)
Patients with other significant AEs (according to ICH E3)	11	(4.1)	12	(4.4)
Patients with AEs leading to discontinuation of trial drug	16	(6.0)	16	(5.8)
Patients with serious AEs	20	(7.5)	14	(5.1)
Fatal	0	(0.0)	0	(0.0)
Immediate life-threatening	0	(0.0)	0	(0.0)
Disability/incapability	1	(0.4)	1	(0.4)
Required hospitalisation	19	(7.1)	14	(5.1)
Prolonged hospitalisation	0	(0.0)	0	(0.0)
Congenital anomaly	0	(0.0)	0	(0.0)
Other	5	(1.9)	2	(0.7)

Abbreviations: AE=adverse event; SAE=serious adverse event

Source (b) (4) Table 12.2.1.3: 1, page 232

Reviewer's Comments

Both the extensions from study 40 and study 23 are uncontrolled and the use of this data is limited. However, the similar rates of various AE groups seen here and also in the SAF-2 and study 20 groupings are reassuring. The rates in study 23 being more similar to those seen in study 20 are expected since both studies have completed data to 52 weeks. Furthermore, although the applicant does not plan to market the 10 mg dose, the AE rates seen in both doses in study 23 are very similar.

7.5.1 Dose Dependency for Adverse Events

The applicant plans to market one dose of linagliptin (5 mg), if approved. There is little data available on other doses to explore dose dependency for AEs.

7.5.2 Time Dependency for Adverse Events

I have explored some exposure data for AEs in the individual AE sections. In addition, in the AE sections, I have presented data from study 20, which is the longest controlled data we have for linagliptin.

7.5.3 Drug-Demographic Interactions

SAF-2
Table 110 displays the AE incidence rate difference between linagliptin treated and placebo treated patients among the various demographics.

Table 110 Incidence of AEs by Demographic—SAF-2, TS

	Placebo n (%) N	Linagliptin 5 mg n (%) N
Age [years]		
≤50	144 (50.0) 288	319 (53.9) 592
51 to <65	326 (56.0) 582	699 (53.7) 1301
65 to <75	149 (52.1) 286	339 (57.4) 591
≥75	17 (63.0) 27	55 (67.1) 82
Gender		
Male	353 (52.8) 668	689 (52.0) 1324
Female	283 (55.0) 515	723 (58.2) 1242
Race		
White	374 (51.8) 722	809 (53.9) 1502
Black	12 (57.1) 21	16 (59.3) 27
Asian	250 (56.8) 440	587 (56.6) 1037
Ethnicity[a]		
Not Hispanic/Latino	540 (53.4) 1012	1153 (53.4) 2160
Hispanic/Latino	81 (59.1) 137	247 (65.7) 376
Geographical region		
Europe	237 (49.1) 483	419 (46.8) 895
North America	79 (57.7) 137	170 (66.1) 257
South America	58 (57.4) 101	202 (66.9) 302
Asia	262 (56.7) 462	621 (55.8) 1112
Body mass index [kg/m^2]		
<30	391 (54.5) 717	882 (55.0) 1605
≥30	245 (52.6) 466	530 (55.2) 961
Concomitant p-gp inhibitors		
Yes	34 (72.3) 47	65 (77.4) 84
No	602 (53.0) 1136	1347 (54.3) 2482
Concomitant CYP3A4 inhibitors		
Yes	55 (78.6) 70	89 (82.4) 108
No	581 (52.2) 1113	1323 (53.8) 2458
Concomitant ACE inhibitors		
Yes	172 (52.1) 330	400 (56.7) 705
No	464 (54.4) 853	1012 (54.4) 1861
Concomitant oral antidiabetic drugs		
None	243 (53.1) 458	376 (49.2) 765
Metformin	131 (52.8) 248	309 (52.4) 590
SU	36 (42.9) 84	68 (42.2) 161
Metformin + SU	157 (59.7) 263	523 (66.1) 791
Pioglitazone	69 (53.1) 130	136 (52.5) 259
Renal impairment[b]		
None	358 (53.0) 675	769 (53.8) 1429
Mild	240 (55.0) 436	520 (55.1) 944
Moderate	25 (50.0) 50	73 (65.2) 112
Severe	1 (100.0) 1	1 (50.0) 2
Hepatic impairment[c]		
Yes	8 (80.0) 10	16 (66.7) 24
No	628 (53.6) 1172	1395 (54.9) 2541

N = number of patients per subgroup category, n = number of patients with adverse events per subgroup category
[a] Note that ethnicity data were not collected in France.
[b] Based on eGFR as calculated by the MDRD formula; none ≥90 mL/min; mild 60 to <90 mL/min; moderate 30 to <60 mL/min, and severe <30 mL/min. In addition, eCcr was estimated using the Cockcroft Gault formula, results are provided in the SCS Appendix 2 in [U10-1607, Module 5.3.5.3]; none ≥80 mL/min, mild ≥50 to <80 mL/min, moderate ≥30 to <50 mL/min, and severe <30 mL/min.
[c] Increase is defined as 2x upper limit of normal (ULN) of aspartate transaminase or 2x ULN of alanine transaminase.

Source Response to FDA Inquiry February 14, 2011

Gender and race are covered in more detail below.

Gender SAF-2
For most system organ classes there were only minimal differences between male and female patients, fewer were greater than 1% greater in females than in males that were also seen in a higher rate in the linagliptin treated patients. One of these groups was Musculoskeletal and connective tissue disorders, which occurred in 12.9% or 160 female patients on linagliptin (10.3%--53 patients/females on placebo) versus 7.9% or 104 males on linagliptin (7.3%/43males on placebo). However, on a PT level, there were no trends or PTs that occurred at higher rates in women that were treated with linagliptin that were concerning. Another SOC with a similar profile was Vascular Disorders. Here, the only PT of note was hypertension seen in more females on linagliptin than males (2.4%/30 patients versus 2.1%/28 patients). In the placebo group, hypertension rates were lower (1.9%/10 females and 1.8%/12 males).

Race SAF-2
Although rates in the three ethnic groups showed higher incidence of AE in blacks and Asians (56.6 and 59.3% respectively), there were few SOCs or PTs with any significant trends. Also, the number of AEs in black patients was very few, and there were no noteworthy PTs observed.

On the PT level, there were no black or white patients on linagliptin that experienced the PT acute cholecystitis. However, there were 3 patients (0.4%) of Asian patients on linagliptin versus 0 placebo patients that did.

Study 20
Table 111 displays the AE incidence rate by demographics for SAF-2.

Table 111 Incidence of AEs by Demographic—Study 20, TS

	Linagliptin 5 mg n (%) N	Glimepiride n (%) N
Age [years]		
≤50	105 (80.2) 131	114 (87.0) 131
51 to <65	312 (78.8) 396	330 (83.5) 395
65 to <75	166 (76.9) 216	194 (86.6) 224
≥75	28 (80.0) 35	24 (77.4) 31
Gender		
Male	354 (76.6) 462	397 (83.2) 477
Female	257 (81.3) 316	265 (87.2) 304
Race		
White	512 (77.6) 660	553 (83.9) 659
Black	18 (90.0) 20	17 (94.4) 18
Asian	81 (82.7) 98	92 (88.5) 104
Ethnicity[a]		
Not Hispanic/Latino	594 (78.6) 756	646 (84.9) 761
Hispanic/Latino	17 (81.0) 21	15 (78.9) 19
Renal impairment[b]		
None	308 (80.0) 385	302 (83.7) 361
Mild	264 (77.4) 341	307 (85.0) 361
Moderate	28 (80.0) 35	36 (94.7) 38
Severe	0 (0.0) 0	0 (0.0) 0

N = number of patients per subgroup category, n = number of patients with adverse events per subgroup category
[a] Note that ethnicity data were not collected in France.
[b] Based on eGFR as calculated by the MDRD formula; none ≥90 mL/min; mild 60 to <90 mL/min; moderate 30 to <60 mL/min, and severe <30 mL/min. In addition, eCcr was estimated using the Cockcroft Gault formula, results are provided in the SCS Appendix 2 in [U10-1607, Module 5.3.5.3]; none ≥80 mL/min, mild ≥50 to <80 mL/min, moderate ≥30 to <50 mL/min, and severe <30 mL/min.

Source Response to FDA Inquiry February 14, 2011

Both gender and race are discussed in further detail below.

Gender—Study 20
More female patients taking glimepiride (27.0%) were reported with SOC gastrointestinal disorders than female patients taking linagliptin 5 mg (22.2%) or male patients (21.2% linagliptin 5 mg and 19.9% glimepiride). However, on the PT level there were no notable differences.

Race—Study 20
There were no major SOC differences. The only notable differences at the PT level were pyrexia reported in 9 patients on linagliptin (9.2%) and in 3 patients on glimepiride (2.9%) versus 2 white patients on linagliptin (0.3%). In addition, musculoskeletal pain reported in 4 Asian patients on linagliptin (4.1%) versus 2 patients on glimepiride (2.9%) and 13 white patients on linagliptin (2%).

Reviewer's Comments
By PT, there were no concerning differences for AE incidence in the different demographic groups. This concurs with lack of clinically significant PK/PD differences found among groups.

7.5.4 Drug-Disease Interactions

Analysis of patients with renal impairment has been discussed throughout this review.

7.5.5 Drug-Drug Interactions

Please see section *4.4.3. Pharmacokinetics* for details on studies of drug-drug interactions. For more details, please refer to Dr. Lokesh Jain's review.

7.4 Additional Safety Evaluations

Cardiovascular Safety

Please refer to Dr. Xiao Ding's review for a full report on cardiovascular safety.

The applicant was required to assess, in a meta-analysis, the cardiovascular (CV) risk associated with treatment of linagliptin in patients with T2DM. Per agency guidance, the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio for cardiovascular risk must be less than 1.8.

An independent Clinical Event Committee adjudicated all major CV events prospectively. The primary endpoint for this was Major Cardiovascular Events (MACE) which was limited to CV death, non-fatal stroke, non-fatal myocardial infarction (MI). In addition, the applicant was allowed to include hospitalization for unstable angina pectoris (UAP).

Eight trials involving 5239 subjects were used for the meta-analysis. These are listed in Table 112. For details on study design and demographics of these individual studies please see the Review of Efficacy, as all are detailed in that section.

Table 112 Studies Included in the CV Meta-analysis

Trial / Status	Description	Duration	Treatments	Treated patients
1218.15 / completed	Efficacy and safety vs. placebo as add-on to pioglitazone	24 weeks	Linagliptin 5 mg Placebo	259 130
1218.16 / completed	Efficacy and safety vs. placebo as monotherapy	24 weeks	Linagliptin 5 mg Placebo	336 167
1218.17 / completed	Efficacy and safety vs. placebo as add-on to metformin	24 weeks	Linagliptin 5 mg Placebo	523 177
1218.18 / completed	Efficacy and safety vs. placebo as add-on to metformin + SU	24 weeks	Linagliptin 5 mg Placebo	792 263
1218.20 / interim analysis	Efficacy and safety vs. glimepiride as add-on to metformin	52 weeks interim results	Linagliptin 5 mg Glimepiride 1-4 mg	778 781
1218.23 / completed	Efficacy and safety vs. placebo and voglibose as monotherapy (In Japanese subjects)	26 weeks of controlled treatment	Linagliptin 5 mg Linagliptin 10 mg Voglibose 0.6 mg Placebo	159 160 162 80
1218.35 / completed	Efficacy and safety vs. placebo as add-on to SU	18 weeks	Linagliptin 5 mg Placebo	161 84
1218.50 / interim analysis	Efficacy and safety vs. placebo where metformin therapy is inappropriate Placebo patients are switched to glimepiride after primary endpoint at 18 weeks	18 weeks interim results	Linagliptin 5 mg Placebo / Glimepiride 1-4 mg	151 76

Source CV Meta-analysis, Table 3, page 23

Drug exposure in the linagliptin group was median 175 days, ranging from 1 to 617. Corresponding median exposure in the placebo and active comparator group were 169 and 409 days, ranging from 1 to 367 and 1 to 619, respectively. Accumulated years of exposure were 2060 for linagliptin and 1372 for total comparators (422 placebo, 872 glimepiride and 78 voglibose).

Characteristics of the study cohort are detailed in Table 113. The predominant race in the cohort was white. There were more white patients in the active comparator (glimepiride and voglibose) group. There were also much fewer Hispanic patients in this group than in the Linagliptin and placebo groups. In total, 78.3% of the cohort was above 50 years of age (28.2% ≥ 65 years, 3.6 % [n=189] ≥ 75 years) whereas 37.8% and 38.8% had a BMI of 25.0-30 kg/m^2 or ≥ 30 kg/m^2, respectively.

Table 113 Demographics of CV Study Cohort

	Linagliptin	Placebo	Active Comparator	Total Comparator
N treated (% female)	3319 (46.3%)	977 (45.3%)	943 (37.2%)	1920 (41.4%)
Age (years)	58±10	57±10	60±10	58±10
≤ 50 years	21.6%	25.8%	17.8%	21.9%
50 – 65 years	50.4%	49.6%	49.4%	49.5%
≥ 65 years	28.0%	24.6%	32.8%	28.6%
BMI (kg/m^2)	28.8±5.0	28.7±5.0	29.5±4.8	29.1±4.9
25 – 30	38.0%	38.5%	36.5%	37.5%
≥ 30	37.8%	36.1%	45.4%	40.7%
Race and ethnicity				
White	59.7%	54.0%	69.9%	61.8%
Black	1.4%	1.3%	1.9%	1.6%
Asian	38.9%	44.6%	28.2%	36.6%
Not hispanic/Latino	88.0%	85.8%	97.9%	91.7%
Hispanic/Latino	11.8%	13.6%	2.0%	7.9%
Missing	0.2%	0.6%	0.1%	0.4%

Source CV Meta-analysis, Table 4, page 24

In total, 52.4% of the cohort had diabetes duration > 5 years (Table 114) and the majority (82.7%) had previously received one or more OAD(s) (45.5% monotherapy [metformin most common regimen] and 37.0% dual therapy [metformin + SU most common regimen]).

Table 114 Baseline T2DM Characteristics for CV Study Cohort

	Linagliptin	Placebo	Active Comparator	Total Comparator
n	3319	977	943	1920
Diabetes related complications				
Diabetic retinopathy	8.4%	8.6%	6.4%	7.5%
Diabetic neuropathy	13.4%	14.5%	12.7%	13.6%
HbA1c (%)	8.1±0.9	8.2±0.9	7.8±0.9	8.0±0.9
< 7.0%	8.8%	4.9%	18.2%	11.5%
7.0-9.0%	74.4%	75.1%	70.9%	73.1%
> 9.0%	16.7%	20.0%	10.8%	15.5%
Fasting plasma glucose (mg/dL)	168±42	171±42	166±41	169±41
Diabetes duration				
≤ 1 years	12.1%	16.0%	8.4%	12.2%
1 – 5 years	34.8%	34.4%	38.8%	36.6%
> 5 years	53.1%	49.6%	52.8%	51.2%
Previous glucose lowering therapy				
No OADs	17.3%	24.9%	9.5%	17.3%
1 OAD	42.8%	36.0%	64.4%	49.9%
Metformin	78.6%	60.5%	93.7%	81.5%
SU	18.1%	36.4%	3.1%	15.3%
TZD	0.4%	0.3%	0%	0.1%
Others	2.9%	2.8%	3.2%	3.0%
2 OADs	39.7%	38.8%	26.0%	32.5%
Metformin+ SU	91.6%	92.3%	85.3%	89.6%
Others	8.4%	7.7%	14.7%	10.4%
3 or more OADs	0.2%	0.3%	0.1%	0.2%

Source CV Meta-analysis, Table 5, page 25

CV risk factors and complications are displayed in Table 115. In general, the patients in the active comparator grouping (either on glimepiride or voglibose) had patients with a higher percentage of risk factors, including metabolic syndrome, hypertension, antihypertensive medications, lipid lowering medications and aspirin therapy. On the other hand, the number of patients with smoking history was higher in the linagliptin group than the active comparator group. The placebo and linagliptin groups were very similar in distribution of risk factors. Renal impairment was similar across all groups.

Table 115 CV Risk at Baseline in the CV Study Cohort Displayed by Treatment

	Linagliptin	Placebo	Active Comparator	Total Comparator
n	3319	977	943	1920
Metabolic syndrome	60.3%	55.9%	67.8%	61.7%
Previous CAD	10.4%	10.1%	11.9%	11.0%
Previous CVD	2.9%	3.6%	4.1%	3.9%
Previous POAD	2.3%	2.7%	3.3%	3.0%
Hypertension	63.8%	60.2%	72.1%	66.0%
Never smoked	62.7%	64.8%	54.8%	59.9%
Ex-smoker	22.9%	19.1%	29.5%	24.2%
Current smoker	14.4%	16.1%	15.7%	15.9%
Renal function as determined by estimated GFR using Cockroft-Gault/MDRD formula				
Normal	74.9%/55.4%	76.7%/58.3%	78.0%/52.3%	77.3%/55.4%
Mildly impaired	19.9%/37.3%	18.3%/34.9%	18.7%/41.4%	18.5%/38.1%
Moderately impaired	2.2%/4.3%	2.7%/4.5%	4.1%/4.1%	1.9%/4.3%
Severely impaired	0.1%/0.1%	0.2%/0.1%	0%/0%	0.1%/0.1%
Missing	2.9%/2.9%	2.1%/2.1%	2.2%/2.2%	2.2%/2.2%
ASA	29.5%	28.8%	32.2%	30.5%
Any anti-HT drug	60.0%	56.4%	69.8%	63.0%
Beta-blockers	32.7%	31.8%	34.3%	33.2%
ACE inhib	44.8%	45.6%	34.3%	43.5%
ARBs	22.0%	21.8%	21.0%	21.9%
Diuretics	22.9%	23.3%	41.3%	22.0%
Others	46.9%	64.0%	77.7%	49.6%
Any lipid lowering therapy	39.5%	36.5%	47.9%	42.1%
Statins	86.6%	84.3%	92.5%	88.9%
Fibrates	14.9%	19.7%	7.3%	12.7%
Others	8.3%	7.3%	8.5%	8.2%
Any ASA, anti-HT or lipid lowering therapy	72.8%	69.7%	81.5%	75.5%
Estimated 10 year risk for coronary heart disease based on Framingham score				
Framingham risk	9.8±8.2%	9.1±8.1%	11.6±8.6%	10.3±8.4%
Framingham risk > 15%	27.8%	24.7%	37.8%	31.1%

Abbreviations: CAD – coronary artery disease, CVD – cerebrovascular disease, POAD – peripheral artery disease, ASA - Acetyl salicylic acid, HT – hypertensive, ACE – angiotensinogen converting enzyme, ARB – angiotensin II receptor blocker

Source CV Meta-analysis, Table 6, page 26

Reviewer's Comments

The imbalances noted in the ethnic and racial demographics between the Linagliptin/placebo groupings and the active comparator group may be attributed the sites at which these studies were predominantly done. Study 23, active control with voglibose was a Japanese study. Study 20, active control with glimepiride, had only 9.5% of patients from the United States. Overall, the small number of black patients studied has been addressed in this review. There are notable differences in risk factors for CV disease between the groupings. This imbalance could affect the results of this CV meta-analysis if even to a small degree, as the study that is driving the result that follows is the active control study, study 20. This is one of two studies in the Active Comparator grouping.

An inquiry for the demographic breakdown for the various studies was requested of the applicant. Upon review, the imbalance was not noted between the randomized groups in study 20, or any other study. The imbalance, instead, appears to come from a higher rate of CV risk seen overall in study 20 versus other studies. Please see Table 116 which displays Framingham risk for the studies in the meta-analysis.

Table 116 CV Meta-analysis Framingham Risk by Study

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

Source Dr. Xiao Ding

CV Events

In total 11 primary events occurred in the linagliptin group and 3 in the placebo and 20 in the glimepiride groups. These are displayed in Table 117.

Table 117 Summary of MACE Event by Study and Treatment

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
Com=comparator
Source Dr. Ding's Review

CV Results

Linagliptin was not associated with increased CV risk. In their own analysis, the applicant states that the primary endpoint for linagliptin was significantly lower versus total comparators whether it was expressed as Cox regression hazard ratio (HR) 0.34 (95% CI 0.16;0.70/98% CI 0.14; 0.80), Poisson regression risk ratio (RR) 0.34 (95% CI 0.15;0.74/98% CI 0.13; 0.84), exact test for stratified 2x2 tables odds ratio (OR) 0.34 (95% CI 0.15; 0.75/98% CI 0.13; 0.85) or stratified Cochran-Mantel-Haenszel (CMH), with treatment arm continuity correction, RR 0.39 (95% CI 0.19; 0.80/98% CI 0.16; 0.91).

These results were confirmed by Dr .Ding. The CMH analysis performed yielded a relative risk ratio of 0.34 (95% CI 0.13; 0.74). See Figure 29.

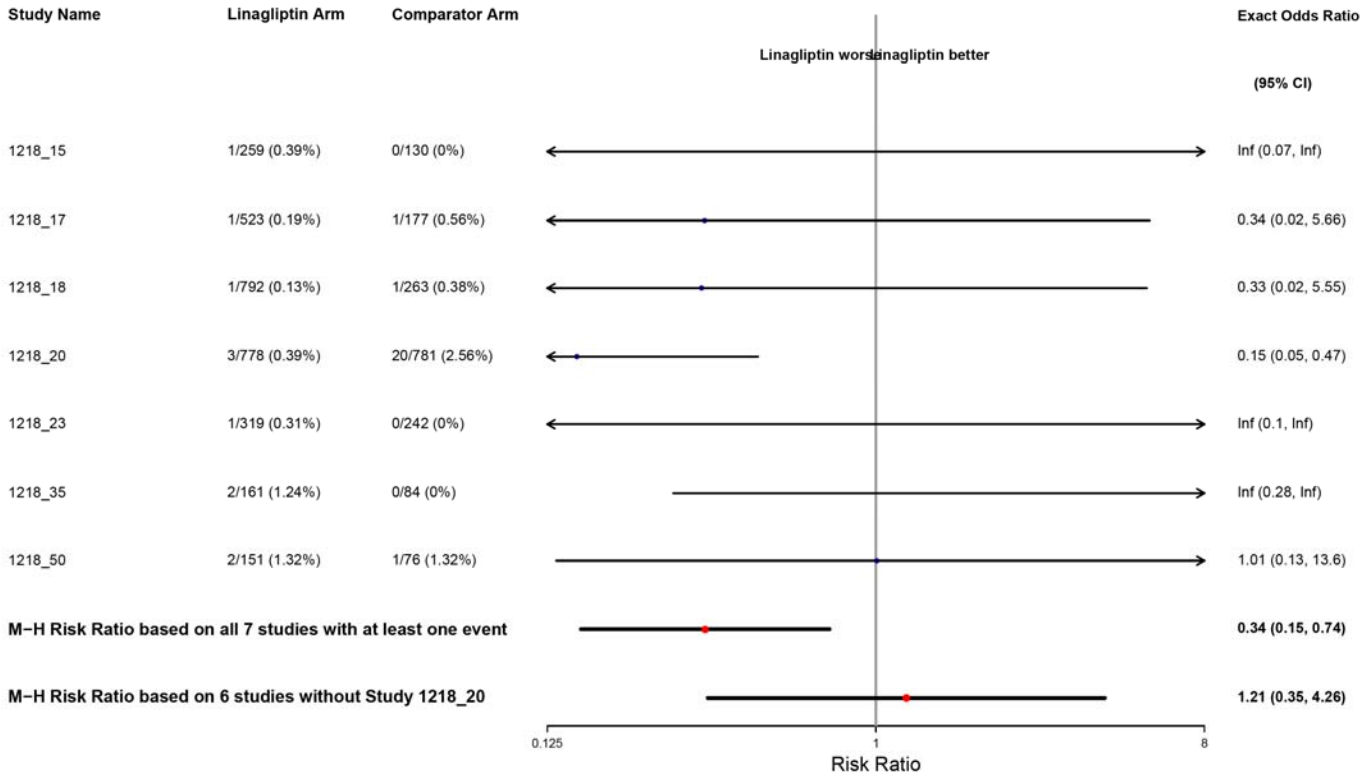


Figure 29 Forest Plot of Relative Risk by Study Based on CMH Analysis

Reviewer's Comments
The results of this analysis are based on very few events. While the results are reassuring, the events are few and from predominantly study 20 only. The dedicated CV trial will be useful in yielding more detailed results to assess cardiovascular risk.

7.6.1 Human Carcinogenicity

Linagliptin did not appear carcinogenic in the nonclinical program. I saw no imbalance of neoplasms during my review of safety data. Furthermore, there were no unusual neoplasms reported.

7.6.2 Human Reproduction and Pregnancy Data

Pregnant and nursing mothers were excluded from the studies in the linagliptin clinical development program. However, during the clinical program, 4 patients became pregnant while receiving linagliptin 5 mg, 1 patient became pregnant that was receiving linagliptin 5 mg + metformin 1000 mg. Brief narratives are given here:

Patient 90981 (study 40), a 34 year old female, started study medication (linagliptin 5 mg) on 10 Jan 2009. She took linagliptin (b) (6) prior to the pregnancy. On (b) (6), the patient delivered a premature newborn with congenital anomalies. The male infant weighted 1.6 kg at birth and had Apgar scores of 5 and 8. The congenital anomalies were patent ductus arteriosus and single umbilicary artery. Group B streptococcal was cultured from vaginal swabs done after delivery.

Patient 20689 (study 20), a 39 year old female, started study medication (linagliptin 5 mg) on 09 May 2008. On (b) (6) the patient was found to be pregnant and study medication and metformin were discontinued on the same day. On (b) (6), a male baby with a high birth weight of 4700 g was born; a high birth weight.

Patient no. 94874 (study 40), a 38 year old female, started study medication (linagliptin 5 mg) on 09 Jan 2009. The study medication was discontinued on 23 Oct 2009. The estimated date of delivery is (b) (6). No further information was available.

Patient 55642 (study 50), a 33 year old female, study medication (linagliptin 5 mg) was started 14 Jul 2009. On (b) (6) the patient was found to be pregnant; the trial medication was discontinued on 22 Aug 2009. On (b) (6) the patient had a still birth. The event was considered as serious.

Patient 49633 (study 46), a 39 year old female, started study medication (linagliptin 5 mg and metformin 1000 mg) on 30 Jun 2009. On (b) (6), the patient had an induced abortion which she recovered from by (b) (6).

Reviewer's Comments
While a still birth and an infant with congenital anomalies are reported here, conclusions regarding safety in pregnancy cannot be made with such few patients. Mothers with diabetes are more prone to have infants with birth defects and also to have larger infants. Control of diabetes plays a major role in the likelihood of such events.

7.6.3 Pediatrics and Assessment of Effects on Growth

Studies in pediatric patients have not been performed.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No potential for abuse was detected or expected with linagliptin. In addition, no withdrawal or rebound effects were noted in any patients.

7.7 Additional Submissions / Safety Issues

There are not additional issues to report at this time.

8 Postmarket Experience

There has been no post market experience with linagliptin.

9 Appendices

9.1 Literature Review/References

1. Centers for Disease Control and Prevention. 2011 National Diabetes Fact Sheet. Dowloaded at http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf.

9.2 Labeling Recommendations

Label recommendations are being made directly to the proposed label. Many of my recommendations are noted in this review.

9.3 Advisory Committee Meeting

Not applicable.

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

/s/

SOMYA VERMA
03/11/2011

ILAN IRONY
03/13/2011
I concur with Dr. Dunn's review and recommendations. Please refer to my CDTL memo.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 201280 **Applicant: Boehringer Ingelheim** **Stamp Date: July 2, 2010**

Drug Name: Linagliptin **NDA/BLA Type: New NDA**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			All tables, no text
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			All tables, no text
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			In the Clinical Overview
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: 1218.5 Study Title: A randomized, double-blind, placebo-controlled, five parallel group study investigating the efficacy and safety of BI 1356 BS (0.5 mg, 2.5 mg and 5 mg administered orally once daily) over 12 weeks in drug naïve and treated patients with Type 2 diabetes with insufficient glycemic control (study includes an open-label metformin treatment arm) Sample Size: 302 Arms: 0.5 mg, 2.5 mg, 5 mg Location in submission: Section 5.3.5	x			

	Content Parameter	Yes	No	NA	Comment
	Study Number: 1218.6 Study Title: A randomized, double-blind, placebo-controlled, five parallel groups study investigating the efficacy and safety of BI 1356 (1 mg, 5 mg and 10 mg administered orally once daily) over 12 weeks as add-on therapy in patients with type 2 diabetes and insufficient glycemic control despite metformin therapy, including an open-label glimepiride treatment arm Sample Size: 669 Arms: 1 mg, 5 mg, 10 mg Location in submission: Section 5.3.5				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 A randomized, double-blind, placebo controlled, parallel group, 24-week study to assess the efficacy and safety of linagliptin (5 mg) in combination with 30 mg pioglitazone (both administered orally once daily), compared to 30 mg pioglitazone plus placebo in drug naive or previously treated type 2 diabetic patients with insufficient glycemic control Indication: Improved Glycemic Control in Type II Diabetes Mellitus Pivotal Study #2 A randomized, double-blind, placebo-controlled parallel group efficacy and safety study of linagliptin (5 mg administered orally once daily) over 24 weeks, in drug naïve or previously treated (6 weeks washout) type 2 diabetic patients with insufficient glycemic control Indication: Improved Glycemic Control in Type II Diabetes Mellitus Pivotal Study #3 A randomized, double-blind, placebo-controlled parallel group efficacy and safety study of linagliptin (5 mg administered orally once daily) over 24 weeks in type 2 diabetic patients with insufficient glycemic control despite metformin therapy Indication: Improved Glycemic Control in Type II Diabetes Mellitus Pivotal Study #4 A randomized, double-blind, placebo-controlled parallel group efficacy and safety study of linagliptin (5 mg) administered orally once daily over 24 weeks in type 2 diabetic patients with insufficient glycemic control despite a therapy of metformin in combination with a sulfonylurea	x			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Indication: Improved Glycemic Control in Type II Diabetes Mellitus				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		x		A small proportion of the study sites were located in the US.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	x			Consult review Jan 29, 2010. No further follow up needed.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	x			T2D pts treated with linagliptin 5 mg, 3430 patients were exposed for 6 months or longer, 2390 patients for 12 months or longer and 536 patients for 18 months or longer--pg 41 Clinical Overview.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			hypersensitivity reactions, renal events, hepatic events, severe cutaneous adverse reactions, pancreatitis

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			Section 5.3.5.3 of the eCTD application
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			CV meta-analysis, QT and AE of special interest analysis
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Waiver for ≤ 9 years Deferral 10-(b)(4) years
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	x			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		x		
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	No composites in the pivotal studies
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- Both the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) in the linagliptin NDA are in tabular form only. Please send a revised version that contains textual explanations for the tables presented.

- Your NDA is based on data derived largely from international sites. Please submit your rationale for assuming the applicability of foreign data to U.S. population/practice of medicine.

- As some of your studies are ongoing, please clarify your plan to submit updated analyses of cardiovascular safety based on accrued cardiovascular events for contributing to the overall linagliptin cardiovascular meta-analysis. This plan should be submitted prior to the four month safety update.

Somya Verma Dunn	August 11, 2010
Reviewing Medical Officer	Date
Ilan Irony	August 11, 2010
Clinical Team Leader	Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201280	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	Linagliptin (BI 1356) Tablets.

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

/s/

SOMYA VERMA
08/11/2010

ILAN IRONY
08/15/2010
I concur with Dr. Dunn's decision on filing, and on the comments to be conveyed to the applicant.