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APPLICATION NUMBER:
200678Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	October 28, 2010
From	Hylton V. Joffe, M.D., M.M.Sc.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	200678
Applicant	Bristol-Myers Squibb
Date of Submission	December 29, 2009
PDUFA Goal Date	October 29, 2010
Proprietary Name / Established (USAN) names	Kombiglyze XR (saxagliptin/metformin XR fixed-dose combination product)
Dosage forms / Strength	2.5/1000 mg, 5/500 mg, 5/1000 mg
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate
Recommended:	<i>Approval</i>

Cross Discipline Team Leader Review Template

1. Introduction

This memorandum reviews a new drug application (NDA) for the saxagliptin-metformin extended-release (metformin XR) fixed dose-combination (FDC) tablet. This NDA was submitted by Bristol-Myers Squibb (BMS), which has an alliance with AstraZeneca for commercializing saxagliptin-related products. This is a 505(b)(1) application because BMS has the right of reference for both the saxagliptin (NDA 22350) and metformin XR (Glucophage XR NDA 21202) components of the FDC product.

The sponsor has conducted a typical development program for the FDC. Specifically, there is a series of clinical pharmacology studies that attempt to bridge the FDC to co-administration of the individual components. In addition, the sponsor is relying on efficacy data from two phase 3 trials conducted as part of the saxagliptin NDA (a saxagliptin add-on to metformin trial in patients with inadequate glycemic control on metformin alone and a saxagliptin plus metformin co-administration trial in patients naïve to anti-diabetic medication). The sponsor is relying on safety data from these two trials as well as safety data from recently completed and ongoing trials that involve co-administration of saxagliptin and metformin. Note that the FDC product contains metformin XR and is proposed for once daily dosing with the evening meal. In contrast, most of the supporting clinical data are derived from once daily saxagliptin co-administered with twice-daily metformin immediate-release (metformin IR). Other components of the development program include a chemistry/manufacturing/controls package to support the FDC formulation as well as a standard bridging non-clinical toxicology program. This memorandum will focus on the adequacy of all these findings to support approvability of the FDC product.

2. Background

Saxagliptin is a dipeptidyl-peptidase 4 (DPP-4) inhibitor approved in July 2009 as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The recommended dose of saxagliptin is 2.5 mg or 5 mg once daily regardless of meals. The maximum recommended dose is 2.5 mg once daily for patients with moderate or severe renal impairment and for patients on strong CYP3A4/5 inhibitors. Adverse events of interest for saxagliptin and/or other DPP-4 inhibitors include pancreatitis, hypersensitivity reactions (e.g., angioedema, anaphylaxis), skin lesions (some DPP-4 inhibitors cause necrotic skin lesions in monkeys – saxagliptin does so but with large safety margins), infections (chemokines are substrates of DPP-4 and DPP-4 is also expressed on a subset of T-cells and natural killer cells; saxagliptin can cause mild lymphopenia at approved doses), and liver safety (at least one DPP-4 inhibitor – vildagliptin - has a signal for hepatotoxicity in the premarketing program).

Metformin, a biguanide, is recommended by the American Diabetes Association as first-line therapy for the treatment of type 2 diabetes. Metformin is generally well tolerated but can cause gastrointestinal symptoms such as nausea and diarrhea. These side effects are minimized by taking metformin with meals and by slowly uptitrating the dose. Gastrointestinal side effects may also be reduced by using metformin XR, which has a 20% lower C_{max} but comparable overall exposure (area under the time-concentration curve or AUC) to metformin IR. Metformin XR is usually dosed once daily with the evening meal whereas metformin IR is usually dosed twice daily with breakfast and dinner. Glucophage XR, which is the metformin XR produced by BMS, is available as 500 mg and 750 mg tablets. The usual starting dose is 500 mg once daily with the evening meal with weekly uptitration by 500 mg to a maximum of 2000 mg once daily or a maximum of 1000 mg twice daily. The most serious adverse reaction of metformin therapy is lactic acidosis, which is rare, but is the basis for a contraindication in patients with renal impairment (metformin is substantially renally cleared).

The sponsor has proposed 3 dosage strengths for the FDC:

- Saxagliptin 5 mg / metformin XR 500 mg
- Saxagliptin 5 mg / metformin XR 1000 mg
- Saxagliptin 2.5 mg / metformin XR 1000 mg

(b) (4)

3. CMC

The Chemistry reviewers recommend approval without the need for postmarketing commitments. Please see Dr. Elsbeth Chikhale's review for details.

The drug product consists of a (b) (4)

The commercial drug product will be manufactured at the BMS Mount Vernon facility. A Quality by Design approach was used for (b) (4)

The saxagliptin drug substance and manufacturing site is identical to that used for the saxagliptin NDA. The metformin drug substance information is provided in Drug Master Files (b) (4) and found by the CMC reviewers to be acceptable for use in this FDC NDA. The metformin XR (b) (4) is manufactured as per the current commercial process for Glucophage XR 500 mg. There is no currently marketed Glucophage XR 1000 mg tablet but there is a marketed Glucophage XR 750 mg tablet. The metformin XR 1000 mg (b) (4) for the FDC product is manufactured (b) (4)

CMC found all excipients to be acceptable.

Based on the stability data, Dr. Chikhale recommends a shelf-life of 15 months for the blisters and 21 months for the bottles when stored at 20-25 degrees Celsius, (b) (4)

Dr. Chikhale agrees with the sponsor's claim that the application qualifies for a categorical exclusion from an environmental assessment report.

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology reviewers recommend approval of the NDA. Please see the reviews by Drs. Lauren Murphree Mihalcik and Todd Bourcier reviews for details.

Most of the nonclinical pharmacology and toxicology data for the FDC are derived from data established for saxagliptin and metformin XR as individual components. The sponsor conducted a bridging 3-month general toxicology study in dogs assessing saxagliptin and metformin separately and in combination. The doses used in this study achieved saxagliptin, BMS-510849 (the major saxagliptin metabolite) and metformin exposures (AUC) that were 70

times, 16 times, and 1.5 times the maximum recommended human dose, respectively. Dr. Mihalcik and Bourcier did not identify unique toxicities when the drugs were co-administered and noted that the toxicity of each drug alone was reasonably similar to the toxicology profile that supported approval of the individual drugs.

During the review cycle for NDA 22350, the sponsor submitted results from an embryofetal study in rats showing neural tube defects in 2 fetuses (from 1 litter) with coadministered saxagliptin and metformin. The study lacked separate treatment arms for saxagliptin and metformin precluding the ability to determine whether the observed neural tube defects were related to combination therapy with saxagliptin and metformin or to one of the individual therapies. Therefore, under the saxagliptin NDA we required the sponsor to conduct postmarketing embryofetal studies in rats and rabbits with the drugs alone and in combination. According to Dr. Mihalcik, these completed studies did not identify a drug-related neural tube defect despite using in the repeat rat study higher doses of metformin (10 times the maximum recommended human dose based on AUC) than that used in the original rat study. In addition, the incidence of neural tube defects observed in the original rat study was shown to be consistent with updated historical control data from the study site. Therefore, the nonclinical pharmacology/toxicology reviewers have concluded that the saxagliptin/metformin combination is not teratogenic in animals. The pregnancy labeling for the FDC will reflect the most current embryofetal animal data. The sponsor has requested that the embryofetal animal data also be updated in the saxagliptin label and has included the revised language as part of an efficacy supplement that is currently in-house under review. Once the agreed-upon labeling is approved under the saxagliptin NDA, the sponsor's postmarketing required embryofetal studies will be considered fulfilled and administratively closed out.

Other findings of note from the embryofetal studies include additive decreases in weight gain observed in the drug-treated groups and a slight increase in wavy ribs in the combination drug group. The wavy ribs were not considered an adverse effect because this finding is commonly observed in the offspring of dams with reduced body weight gain and typically resolves postnatally in the rat. In the rabbit study, there was a neural tube defect in a single fetus but this incidence was within the historical control range. In this study, there was a significant increase of offspring with small or absent gallbladder in the saxagliptin-alone group (but not in the combination group). This is similar to the finding in the saxagliptin alone study but human risk is considered low because of high multiples of drug exposure (200 times the maximum recommended dose based on AUC). In the rabbit study, the metformin dose was approximately equivalent to the maximum recommended human dose based on AUC and the saxagliptin dose was at least 200 times the maximum recommended human dose. In this 13-day study, 12 of the 30 rabbits given both saxagliptin and metformin died compared to 1 death in the metformin-only group and no deaths in the saxagliptin-only group. Some of the animals that died had sporadic low bicarbonate concentrations suggesting that lactic acidosis may have contributed to some of the deaths although the combination-treated rabbits did not have higher plasma concentrations of metformin. This higher incidence of death is unexplained but in further discussions with Drs. Mihalcik and Bourcier, they confirmed that clinical relevance is unlikely given that the finding is species-specific (not seen in rats, dogs, or humans) with high saxagliptin doses used in combination with metformin and the fact that there are reassuring clinical data from phase 3 trials that co-administered saxagliptin and metformin.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology reviewers have found the clinical pharmacology data to be unacceptable because the batch sizes of the formulation used in the two pivotal bioequivalence studies did not meet the biobatch size criteria of (b) (4) of the proposed commercial production batch of (b) (4) units, whichever is greater. Specifically, the batch sizes were (b) (4) to (b) (4) tablets when they should have been (b) (4) tablets because the commercial batch size is (b) (4) tablets. The clinical pharmacology reviewers communicated this finding to the biopharmaceutics team in the Office of New Drug Quality Assessment (ONDQA), which is responsible for the review of the biobatch criteria. Dr. Patrick Marroum provided a rationale for why the smaller batch sizes is justified in this instance and concluded that the sponsor does not need to repeat these pivotal clinical pharmacology studies. See the clinical pharmacology review by Dr. Ritesh Jain and the biopharmaceutics memorandum by Dr. Marroum for details.

The clinical pharmacology program for the FDC product consists of two pivotal and five supporting clinical pharmacology studies. The phase 3 trials used metformin IR tablets and one supportive 4-week trial used the approved metformin XR 500 mg tablets manufactured in Evansville, Indiana. The proposed to-be-marketed FDC tablets will be manufactured in Mt. Vernon, Indiana. During the Pre-NDA meeting, the clinical pharmacology reviewers determined that there was no direct bridge between the FDC tablets (manufactured in Mt. Vernon) and the approved metformin XR 500 mg formulation (manufactured in Evansville). The sponsor chose to address these concerns by conducting two new pivotal bioequivalence studies, CV181111 and CV181112, which are summarized below. Because these two studies provide direct bridging for the FDC, the clinical pharmacology reviewers did not review the five supporting studies, which attempted to indirectly bridge the FDC to the approved metformin XR formulation.

Pivotal study CV181111 was an open-label, randomized, crossover study in healthy volunteers that compared the bioequivalence of the FDC 5/500 mg tablet to co-administered saxagliptin 5 mg and metformin XR 500 mg using a low-fat meal.

Pivotal study CV181112 was an open-label, randomized, crossover study in healthy volunteers that compared the bioequivalence of the FDC 5/1000 mg tablet to co-administered saxagliptin 5 mg and two tablets of metformin XR 500 mg (there is no approved metformin XR 1000 mg tablet) using a low-fat meal. The clinical pharmacology reviewers requested a Division of Scientific Investigations (DSI) inspection of the clinical and analytical portions of this trial. DSI did not identify major issues and concluded that the results from this study can be accepted for review.

As shown in Figures 1 and 2, adapted from Dr. Jain's review, the sponsor met the standard bioequivalence criteria for both pivotal bioequivalence studies because the 90% confidence intervals for the ratios of geometric least-square means for area under the time-concentration curve (AUC) and C_{max} were contained within 0.80-1.25.

Study CV181111 compared the pharmacokinetics of saxagliptin and metformin when the FDC 5/500 mg tablet was given under fed vs. fasted conditions. Based on these data, Dr. Jain has concluded that there is no significant food effect for the FDC (clinically, it is recommended that all metformin-containing products be taken with meals to reduce gastrointestinal side effects). Note that food-effect is usually tested with a high-fat meal. The sponsor chose to use a low-fat meal in this study claiming that these medications should be used as an adjunct to diet. However, there are many patients using anti-diabetic medications who are likely not compliant with diet. Nonetheless, the clinical pharmacology reviewers are not recommending that the sponsor repeat the study with a high-fat meal. Their rationale is that it is unlikely that FDC exposures with a high-fat meal will exceed those seen when saxagliptin alone and metformin XR alone were tested with a high-fat meal under their individual NDAs.

Figure 1. Study CV181111: Ratios of geometric means for the FDC 5/500 mg tablet relative to the individual components together with 90% confidence intervals (from Dr. Jain’s review).

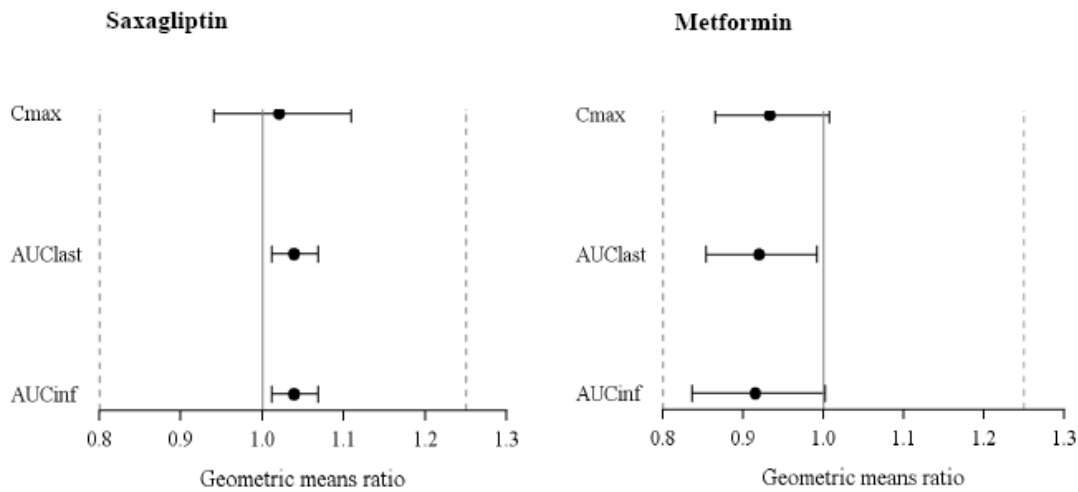
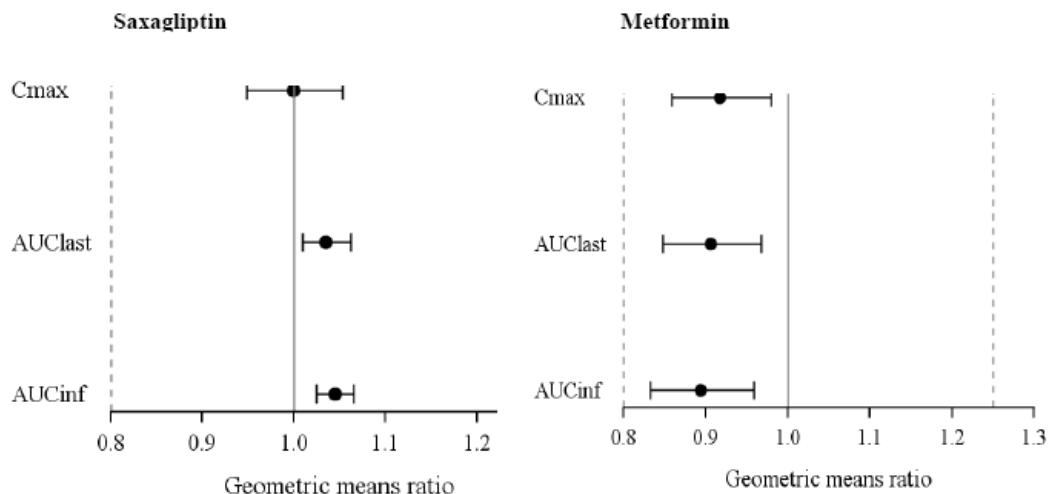


Figure 2. Study CV181112: Ratios of geometric means for the FDC 5/1000 mg tablet relative to the individual components (metformin XR given as two 500 mg tablets) together with 90% confidence intervals (from Dr. Jain’s review).



Study CV181112 also evaluated the steady-state pharmacokinetics of saxagliptin and metformin after the FDC was administered for 4 days under fed conditions. There was no evidence of accumulation for metformin, saxagliptin and major saxagliptin metabolite BMS 510849. The single-dose and steady-state findings with the FDC were consistent with those described for saxagliptin and Glucophage XR.

The sponsor conducted a drug-drug interaction study between saxagliptin and metformin under the saxagliptin NDA. In this study, saxagliptin did not have any effect on the pharmacokinetics of metformin. Metformin decreased the Cmax for saxagliptin by ~20% but did not alter overall saxagliptin exposure (AUC). Therefore, the effect of metformin on saxagliptin pharmacokinetics was considered to be not clinically meaningful.

Dr. Houda Mahayni in the Biopharmaceutics group reviewed the sponsor's request for a biowaiver from studying the FDC 2.5/1000 mg tablet in a bioequivalence trial. She concurs that a biowaiver for this dose of the FDC tablet is acceptable. Dr. Mahayni also reviewed data from *in vitro* dissolution studies with the FDC 5/500 mg and 5/1000 mg tablets to assess whether ethanol (5-25% concentrations) could lead to dose-dumping or accelerated release of metformin and found no evidence for concern. Please see Dr. Mahayni's review for details.

6. Clinical Microbiology

The clinical microbiology reviewers recommend approval. Please see the review by Dr. Jessica Cole for additional details. The drug product is a (b) (4) tablet. The (b) (4) and microbial testing specifications were deemed to be acceptable.

7. Clinical/Statistical- Efficacy

To support the FDC, the sponsor is predominantly relying on efficacy findings from the short-term (24-week) treatment periods of the following multi-national, randomized, controlled, double-blind trials that have already been reviewed for the saxagliptin NDA. Note that none of these three trials tested the FDC or tested saxagliptin in combination with metformin XR. In

addition, saxagliptin was to be administered with the morning meal in these trials except for one of the treatment arms in Study CV181038, which administered saxagliptin with dinner.

Study CV181014: Add-on to metformin trial

- This trial randomized patients with type 2 diabetes and inadequate glycemic control on stable metformin monotherapy (1,500-2,550 mg for ≥ 8 weeks prior to screening) to add-on therapy with saxagliptin 2.5 mg, 5 mg, or 10 mg vs. add-on placebo.

Study CV181039: Initial combination with metformin trial

- This trial randomized patients with type 2 diabetes to saxagliptin 5 mg + metformin, saxagliptin 10 mg + metformin, saxagliptin 10 mg + placebo, and metformin + placebo.
- Patients were to have had minimal exposure to prior anti-diabetic therapy (≤ 3 consecutive days and < 7 non-consecutive days of anti-diabetic therapy within the 8 weeks prior to screening, and < 6 months total of prior anti-diabetic therapy).
- The 3 treatment arms randomized to metformin started 500 mg of the immediate-release formulation that was blindly uptitrated through Week 5 to a maximum of 2,000 mg/day in divided doses based on prespecified criteria for fasting plasma or whole blood glucose.

Study CV181038: Monotherapy trial in treatment-naïve patients

- This monotherapy trial compared saxagliptin 2.5 mg AM (dosed prior to the morning meal), 5 mg AM, 5 mg PM (dosed prior to the evening meal), and 2.5 mg AM with possible titration to 5 mg AM (based on prespecified fasting plasma or whole blood glucose values at Weeks 4, 8, 12, and 24) vs. placebo.
- The primary objective was to compare the AM treatment arms to placebo. A secondary objective compared the PM treatment arm to placebo. The protocol did not prespecify a comparison between the AM and PM dosing regimens. However, FDA statisticians conducted a *post hoc* analysis for AM vs. PM dosing as part of the original saxagliptin NDA review.
- Note that Study CV181038 does not evaluate saxagliptin and metformin co-administration. Instead, the sponsor is submitting these data to support evening dosing of saxagliptin given that the proposed dosing for the FDC is with the evening meal (because of the metformin XR component).

This memorandum will show only the primary efficacy data (HbA1c) for these three trials and summarize the evidence of efficacy to support the FDC product. Please refer to the clinical and statistical reviews of the original saxagliptin NDA for further details.

Tables 1 and 2 show the primary efficacy results (change from baseline in HbA1c at Week 24) for the above 3 trials using the intent-to-treat population with the last-observation-carried-forward method.

Using the data in Study -038, Ms. Joy Mele calculated the reduction in HbA1c with dosing saxagliptin 5 mg prior to breakfast compared to the reduction in HbA1c with dosing 5 mg prior to dinner. The treatment difference was -0.1% (favoring the breakfast dosing) with a 95% confidence interval of -0.3 to +0.2, showing essentially no difference between the two

treatment regimens. Therefore, these data provide support for evening dosing of saxagliptin in the FDC product.

In the add-on to metformin trial, saxagliptin 2.5 mg and 5 mg resulted in a statistically significant mean reduction in HbA1c of 0.7-0.8% relative to placebo ($p < 0.001$). As shown in the original saxagliptin NDA reviews, this efficacy compares favorably to the efficacy achieved in the monotherapy and other combination therapy treatment settings. As discussed in the original saxagliptin NDA reviews, there is no convincing evidence of additional lowering of HbA1c with 10 mg of saxagliptin beyond that achieved with 5 mg in the add-on to metformin trial or in any of the other phase 3 trials. The 5 mg dose of saxagliptin was marginally more effective than the 2.5 mg dose in some, but not all, phase 3 trials. Based on the available data, both the 2.5 and 5 mg doses were approved because it was concluded that 5 mg may be more efficacious than 2.5 mg in some patients and both doses had favorable benefit-risk profiles.

In the initial combination with metformin trial, the mean reduction in HbA1c when saxagliptin 5 mg or 10 mg was initiated with metformin, was approximately 0.5% greater than the reduction in HbA1c with metformin alone ($p < 0.0001$) and approximately 0.8% greater than the reduction with saxagliptin 10 mg alone ($p < 0.0001$). The mean reduction from baseline in HbA1c with metformin alone was approximately 0.3% greater than the mean reduction with saxagliptin 10 mg alone ($p < 0.0001$). Note that this trial did not include a saxagliptin 5 mg + placebo treatment arm, which limits the ability to directly assess the contribution of saxagliptin 5 mg to the saxagliptin 5 mg + metformin arm.

The sponsor has also submitted supportive efficacy data from a newly completed trial, Study CV181066. This randomized, double-blind, placebo-controlled trial enrolled patients with type 2 diabetes and inadequate glycemic control on a stable (≥ 8 weeks) dose of metformin ≥ 1500 mg per day. At the beginning of the 4-week run-in period, those patients on metformin IR were switched to the nearest equivalent dose of metformin XR while those already on metformin XR continued their same dose. At the end of the run-in period, patients were randomized to saxagliptin 5 mg or placebo as add-on therapy to metformin XR. Because the FDC product contains metformin XR and not metformin IR, the sponsor chose to submit data from this trial to support the FDC NDA. Note that the data from this trial are not pivotal because the trial had only a 4-week treatment period, used a non-traditional primary efficacy endpoint of 24-hour mean-weighted blood glucose, and randomized only 46 patients to the saxagliptin arm and only 47 patients to the placebo arm. (b) (4)




Table 1. HbA1c (%) results for the monotherapy and add-on to metformin trials used to support the fixed-dose combination product (intent-to-treat population with last-observation-carried-forward)					
Study	N	Baseline mean ± SE	Change from baseline Adj. mean ± SE	Difference in adjusted mean change (95% CI)	p-value
Study CV181038 (monotherapy)					
Saxa 2.5 mg (AM)	67	8.0±0.1	-0.7±0.1	-0.5 (-0.7, -0.2)	<0.01
Saxa 2.5 mg→5 mg (AM)	69	8.0±0.1	-0.6±0.1	-0.4 (-0.7, -0.1)	0.01
Saxa 5 mg (AM)	69	7.9±0.1	-0.7±0.1	-0.4 (-0.7, -0.1)	<0.01
Saxa 5 mg (PM)	70	7.9±0.1	-0.6±0.1	-0.4 (-0.6, -0.1)	0.02
Placebo	68	7.8±0.1	-0.3±0.1		
Study CV181014 (add-on to metformin)					
Saxa 2.5 mg	186	8.1±0.1	-0.6±0.1	-0.7 (-0.9, -0.5)	<0.001
Saxa 5 mg	186	8.1±0.1	-0.7±0.1	-0.8 (-1.0, -0.6)	<0.001
Saxa 10 mg	180	8.0±0.1	-0.6±0.1	-0.7 (-0.9, -0.5)	<0.001
Placebo	175	8.1±0.1	+0.1±0.1		
SE=standard error; CI=confidence interval					

Table 2. HbA1c (%) results for the initial combination with metformin trial (Study CV181039) used to support the fixed-dose combination product (intent-to-treat population with last-observation-carried-forward)					
Study	N	Baseline mean ± SE	Change from baseline LS mean ± SE	Vs. Metformin LS mean (95% CI); p-value	Vs. Saxagliptin 10 mg LS mean (95% CI); p-value
Saxa 5 mg + met	306	9.4±0.1	-2.5±0.1	-0.5 (-0.7, -0.3); <0.0001	-0.8 (-1.0, -0.6); <0.0001
Saxa 10 mg + met	315	9.5±0.1	-2.5±0.1	-0.5 (-0.7, -0.3); <0.0001	-0.8 (-1.0, -0.6); <0.0001
Saxa 10 mg	317	9.6±0.1	-1.7±0.1	+0.3 (0.2, 0.5); <0.0001	-
Metformin	313	9.4±0.1	-2.0±0.1	-	-

SE=standard error; CI=confidence interval

8. Safety

The sponsor has not conducted clinical trials with the FDC. Most of the safety data are derived from clinical trials in which saxagliptin is either given as add-on therapy in patients with inadequate glycemic control on metformin IR or co-administered with metformin IR as initial therapy in treatment-naïve patients. This section of the memorandum will summarize key findings from these supportive trials. Please refer to Dr. Arlet Nedeltcheva's clinical review for additional details.

Study CV181066: This is a 4-week, randomized, double-blind, placebo-controlled trial in patients with inadequate glycemic control on metformin. A total of 93 patients were randomized to saxagliptin or placebo, both dosed with dinner together with metformin XR. The sponsor submitted this completed trial to support evening dosing of the FDC. There were no saxagliptin-treated patients who died, reported serious adverse events (SAEs), withdrew due to adverse events, reported hypoglycemia (defined as a fingerstick glucose ≤ 50 mg/dL in the presence of symptoms), had lymphopenia, or had serum alanine aminotransferase (ALT) $>3x$ ULN. Diarrhea was reported in two patients (4.3%) in both treatment groups. This trial's small sample sizes and short treatment duration limit conclusions.

Study CV181038: This randomized, double-blind, placebo-controlled monotherapy trial in treatment-naïve patients had 5 treatment arms – placebo, saxagliptin 5 mg in the evening, saxagliptin 2.5 mg in the morning, saxagliptin 5 mg in the morning, and saxagliptin 2.5 mg in the morning with possible titration to 5 mg. At the beginning of the long-term period (which remained blinded), placebo-treated patients started blinded metformin 500 mg. In the saxagliptin arms there was blinded uptitration to 10 mg during the long-term period based on pre-specified glycemic rescue criteria with ~80% of patients in the 5 mg QAM arm and 74% of patients in the 5 mg QPM arm undergoing uptitration. Note that sample sizes are relatively small, which limits conclusions. Approximately 75 patients were randomized per treatment arm into the short-term period with ~60-65 patients per treatment arm entering the long-term period and ~40-50 patients per treatment arm completing the long-term extension.

The complete study report for the short-term (24-week) treatment period and an interim report for the long-term treatment period were submitted and reviewed for the saxagliptin NDA. The 120-day safety update for the FDC contains the data from the completed long-term period. Here I will focus on new safety data for the long-term period available since the interim analysis conducted for the saxagliptin NDA.

Deaths: Since the interim analysis, there has been one death in a saxagliptin-treated patient attributed to metastatic pancreatic cancer. Dr. Nedeltcheva notes that this patient had received saxagliptin for only 13 days at the time of diagnosis, which essentially excludes any relationship to treatment.

Serious adverse events: In the completed short-term plus long-term period, there were 26 reported SAEs (8.9%) in the combined saxagliptin group (n=291) and 5 reported SAEs (6.8%) in the control group (n=74). Review of the new SAEs occurring since the saxagliptin NDA

interim analysis does not raise new safety concerns for saxagliptin regardless of dosing in the morning or afternoon. One saxagliptin-treated patient developed serum ALT of 403 U/L (8.4x ULN) with total bilirubin of 2.4 mg/dL on Day 345, thereby meeting the biochemical definition for Hy's Law. However, he had a probable alternate etiology for these abnormalities because he was hospitalized for acute calculous cholecystitis on Day 351 and underwent uncomplicated cholecystectomy on Day 357. Study medication was temporarily discontinued on Day 351 and restarted on Day 361. His liver tests were normal on Day 435.

Discontinuations due to adverse events: In the completed short-term plus long-term period, twelve saxagliptin-treated patients (4.1%) and 3 control patients (4.1%) discontinued due to adverse events. There were only two saxagliptin-treated patients who discontinued after the interim analysis for the saxagliptin NDA – one patient with onychomycosis and one patient with elevated serum ALT. The patient with increased ALT had a baseline serum ALT of 59 U/L that increased to 67 U/L on Day 89 and 150 U/L on Day 208. Study medication was discontinued on Day 369 when the ALT was 144 U/L. Total bilirubin was consistently normal; therefore, the patient did not meet criteria for Hy's Law. An abdominal ultrasound on Day 257 showed fatty liver.

Hypoglycemia: In the completed short-term plus long-term period, confirmed fingerstick blood glucose ≤ 50 mg/dL in the presence of symptoms occurred in two saxagliptin-treated patients - one receiving 5 mg in the morning (1.4%) and the other receiving 5 mg in the evening (1.4%). Both events were mild and self-treated. There was also one event in a control-treated patient (1.4%).

Liver: There were three patients in the combined short-term plus long-term period with serum ALT $>5x$ ULN – one patient in the saxagliptin 5 mg QAM arm (1.4%), one patient in the 2.5/5 mg QAM arm, and one patient in the control group (1.4%). One of these saxagliptin-treated patients is discussed under the Serious Adverse Events section. The other saxagliptin-treated patient had a normal serum ALT at baseline and on Day 362 but developed an ALT of 209 U/L (5.6x ULN) - with normal total bilirubin - on Day 455. On Day 470, the ALT had normalized but the total bilirubin was now elevated at 2.5 mg/dL. The investigator reported an event of “calculous cholecystitis non active” on Day 473. All liver tests had normalized on Day 490 despite continuing study medication.

Pancreatitis: In the combined short-term plus long-term period there were no reports of pancreatitis.

Lymphopenia: Since the interim analysis for the saxagliptin NDA, there were no new reports of lymphopenia. During the short-term plus long-term period combined, the saxagliptin 5 mg QAM arm and the saxagliptin 5 mg QPM arm had similar reductions in lymphocyte counts. For example, mean lymphocyte count reductions from baseline to Week 76 were -0.13×10^3 c/mcL with saxagliptin 5 mg QAM and -0.12×10^3 c/mcL with saxagliptin 5 mg QPM compared to $+0.03 \times 10^3$ c/mcL with comparator. Similarly, in the combined short-term plus long-term period combined, 7/43 (16%) patients in the saxagliptin 5 mg QAM arm and 8/42 (19%) patients in the saxagliptin 5 mg QPM arm had $\geq 30\%$ reduction in lymphocyte counts from baseline compared to 2/41 (5%) control patients.

Study CV181039: This blinded trial randomized patients with minimal exposure to prior anti-diabetic therapy to saxagliptin 5 mg + metformin (n=320), saxagliptin 10 mg + metformin (n=323), saxagliptin 10 mg + placebo (n=335), and metformin + placebo (n=328). The treatment arms randomized to metformin started 500 mg of the immediate-release formulation that was blindly uptitrated through Week 5 to a maximum of 2,000 mg/day. The complete study report for the short-term (24-week) treatment period and an interim report for the long-term treatment period were submitted and reviewed for the saxagliptin NDA. The 120-day safety update for the FDC contains the data from the completed short-term plus long-term period. Approximately 72% of patients randomized to the saxagliptin + metformin arms completed the long-term period compared to 67% of patients randomized to metformin and 62% of patients randomized to saxagliptin 10 mg. Differences between treatment groups with regard to completion rates was predominantly driven by lack of efficacy (5.6% in the combination groups, 10.4% with saxagliptin alone, 8.8% with metformin alone) and not by adverse events (3.1-4.4% in the combination groups, 4.2% with saxagliptin alone, and 4.3% with metformin alone).

Deaths: There has been only one new death since the saxagliptin NDA interim analysis. This patient was in the saxagliptin 10 mg arm, developed two transient ischemic attacks after approximately 500 days of treatment and after brain angiography had loss of consciousness that progressed to death. Stroke is the most likely cause of death.

Serious adverse events: In the combined short-term plus long-term period, the percentage of patients with at least one SAE was 5.0% for saxagliptin 5 mg + metformin, 6.8% for saxagliptin 10 mg + metformin, 4.8% for saxagliptin 10 mg alone, and 4.6% for metformin alone. Preferred terms for most of the reported SAEs occurred in isolated patients. The minor differences in incidence of SAEs for the saxagliptin groups (particularly saxagliptin 10 mg + metformin) compared to the metformin group are not driven by any particular preferred term. SAEs of note include one report of pancreatitis in the saxagliptin 10 mg + metformin group (there was also one case in the metformin alone group) and one report of lymphopenia in the saxagliptin 10 mg + metformin group. Both of these SAEs had occurred prior to the interim analysis and were reviewed under the saxagliptin NDA.

Discontinuations due to adverse events: In the combined short-term plus long-term period, discontinuations due to adverse events occurred at a comparable incidence in the combined saxagliptin groups (3.1%-4.4%) compared to the metformin alone group (4.3%). Since the interim analysis, only one additional patient discontinued due to an adverse event (blood creatinine increased in a saxagliptin 10 mg-treated patient). This patient had a baseline serum creatinine of 1.2 mg/dL that increased to 1.5 mg/dL on Day 211 then to 1.6 mg/dL on Day 224, prompting discontinuation of study medication on Day 226. Follow-up serum creatinine on Day 229 was 1.2 mg/L. The objective laboratory data for this trial (means, marked abnormalities) did not identify differences between treatment groups. A second patient was reported to have discontinued due to an adverse event of biliary duct cancer but this event was reported 34 days after the patient had already discontinued from the trial.

Hypoglycemia: In the combined short-term plus long-term period, there were no patients with confirmed hypoglycemia (blood glucose ≤ 50 mg/dL in the presence of symptoms) in the saxagliptin 5 mg + metformin and saxagliptin 10 mg alone groups compared to three patients in the saxagliptin 10 mg + metformin (0.9%) group and two patients in the metformin alone group (0.6%). None of the events were classified as an SAE and none required third-party assistance. Since the interim analysis, only one of the hypoglycemia events is new. This patient was in the saxagliptin 10 mg + metformin arm and had a total of three episodes of hypoglycemia occurring on Days 522, 528, and 532 with the lowest reading of 38 mg/dL. The patient attributed these episodes to “dietary indiscretion”.

Hypersensitivity reactions: There have been no new reports of hypersensitivity reactions since the interim analysis for the saxagliptin NDA.

Liver: In the combined short-term plus long-term period, there were 4 patients in the saxagliptin 5 mg + metformin group (1.3%) who developed serum ALT $>3x$ ULN compared to one patient in the saxagliptin 10 mg + metformin group (0.3%), two patients in the saxagliptin 10 mg alone group (0.6%) and seven patients in the metformin alone group (2.1%). Of these patients with ALT $>3x$ ULN, there was one patient in each of the three saxagliptin groups who developed ALT $>5x$ ULN compared with no patients in the metformin group. One of these patients (saxagliptin 5 mg + metformin) had ALT $>5x$ ULN on Day 449 that resolved despite continued treatment with study medication. The complete study report for the short-term plus long-term period does not contain narratives for the other two patients with ALT $>5x$ ULN; however, none of the saxagliptin-treated patients met the biochemical criteria for Hy’s Law. As is seen with many of the study reports submitted to support the FDC, narratives for adverse events of interest are missing or have sparse information. The sponsor will be informed that the quality of narratives needs to be improved for future clinical trials.

Pancreatitis: There have been no new reports of pancreatitis since the interim analysis for the saxagliptin NDA.

Lymphopenia: Since the interim analysis, there have been three new saxagliptin-treated patients and one new metformin-treated patient with lymphocyte counts meeting the markedly low criteria ($\leq 0.75 \times 10^3$ c/mcL). Two of these saxagliptin-treated patients had isolated reductions in the lymphocyte count that returned to within the reference range while continuing study medication. The third saxagliptin-treated subject (5 mg + metformin) had a lymphocyte count of 0.54×10^3 c/mcL on the last study visit. These findings do not change our overall assessment of the effects of saxagliptin on lymphocyte counts.

Study CV181014: This randomized, double-blind trial compared saxagliptin 2.5 mg, 5 mg, or 10 mg vs. placebo, all as add-on to metformin in patients with inadequate glycemic control on metformin alone. A total of 743 patients were randomized into the 24-week short-term period, of which 703 entered the 42-month long-term period. The short-term and interim long-term data from this trial were reviewed for the saxagliptin NDA. The 120-day safety update for the FDC summarizes new interim data from the still ongoing long-term period. Because this trial is ongoing and a complete study report is not yet available, the analyses of safety data presented by the sponsor are somewhat limited.

Deaths: No new deaths were reported since the interim saxagliptin analysis.

Serious adverse events: In the combined short-term and long-term treatment period, the percentage of patients with at least one SAE was similar in the saxagliptin groups (12% for 2.5 mg; 14% for 5 mg; 12% for 10 mg), and numerically greater than that in the placebo group (8.4%). This difference was not driven by any particular preferred term, with most preferred terms occurring in isolated saxagliptin and/or placebo-treated patients. New notable SAEs in the saxagliptin group since the interim analysis include one report each of meningitis tuberculous (10 mg arm; see the integrated analysis of tuberculosis cases at the end of the Safety section) and drug hypersensitivity (2.5 mg arm). The SAE of hypersensitivity represented urticaria and hyperpnea in a hospitalized patient who had recurrent infection after hernia repair surgery. The hypersensitivity reaction was temporally related to vancomycin, which was discontinued with resolution of the symptoms.

Discontinuations due to adverse events: There were only five new discontinuations due to adverse events in the saxagliptin groups since the interim analysis – one event of breast cancer (diagnosed on Day 1190), one event of multifocal, bilateral pneumonia on Day 958 (this patient simultaneously presented with heart failure), one event of tuberculous meningitis (see below), and three events related to renal impairment (blood creatinine increased or renal failure acute). Of note, a comparable percentage of patients in each saxagliptin group (0.5-0.6%) and in the placebo group (0.6%) developed a markedly abnormal serum creatinine (defined as >2.5 mg/dL). Further conclusions in this ongoing trial are limited by lack of mean and median changes from baseline and lack of shift analyses for serum creatinine. However, an integrated analysis of renal safety in the pooled short-term and long-term periods of the phase 3 program reviewed for the saxagliptin NDA revealed no effects of saxagliptin on serum creatinine. In addition, there is no signal for renal toxicity based on the objective laboratory data in the other completed phase 3 trials included in this FDC submission. More extensive data on renal safety will come from the ongoing, large, long-term cardiovascular outcomes trial that will include patients with baseline renal impairment.

Hypoglycemia: Since the interim analysis, there have been no cases of severe hypoglycemia requiring third party assistance. One saxagliptin-treated patient had confirmed hypoglycemia (fingerstick blood glucose \leq 50 mg/dL) that occurred on Days 568 and 968 and were attributed to physical activity.

Hypersensitivity reactions: Besides the hypersensitivity reaction described under the Serious Adverse Events section, there were three other new events of hypersensitivity since the interim analysis. All events occurred among saxagliptin-treated patients. One of these events was urticaria (already labeled for saxagliptin). The two other events were related to environmental allergies. None of these events led to discontinuation of saxagliptin.

Liver: There have been no cases of Hy's Law in this trial.

Pancreatitis: There have been no reports of pancreatitis in this trial.

Lymphopenia: Since the interim analysis, one new saxagliptin-treated patient (10 mg) had an adverse event of lymphopenia that occurred on Day 1261. However, the lymphocyte count had normalized again on Day 1282 while the patient continued study medication. Since the interim analysis, two new saxagliptin-treated patients met the prespecified criteria for markedly low lymphocyte counts ($\leq 0.75 \times 10^3$ c/mL). However, in both patients, the markedly low lymphocyte count was an isolated finding with normalization of the lymphocyte count on subsequent testing despite continued saxagliptin therapy.

Study CV181054: This is a 2-year, randomized, double-blind, active-controlled, non-inferiority trial comparing saxagliptin 5 mg (n=293) to glipizide (n=293), both as add-on therapy in patients with inadequate glycemic control on metformin alone. The completed 1-year data from this trial were submitted as an efficacy supplement to the saxagliptin NDA in April. These same data, together with blinded ongoing Year 2 data are included in the 120-day safety update to support the FDC.

The sponsor reports that saxagliptin is non-inferior to glipizide based on the prespecified non-inferiority margin for HbA1c of 0.35% in both the intent-to-treat population with last-observation-carried-forward and in the per protocol population. The efficacy analyses are undergoing extensive review for the saxagliptin efficacy supplement. I will focus only on safety here.

The glipizide dose was titrated during the first 18 weeks of the trial based on fasting plasma glucose. Approximately 80% of the glipizide-treated patients reached a final dose of 10 mg daily with 50% of the glipizide-treated patients reaching a final dose of 20 mg daily.

Deaths: There were four deaths during the 52 weeks of treatment, two with saxagliptin and two with glipizide. The deaths in the saxagliptin group were (1) skull fracture with brain contusion (confirmed by autopsy) in a 63-year old man resulting from a fall due to alcohol and (2) sudden death attributed to congestive heart failure. The deaths in the glipizide group were (1) sudden death in a patient with a history of myocardial infarction (no autopsy performed) and (2) ischemic stroke complicated by intracerebral hemorrhage.

Serious adverse events: At least one SAE was reported by 9.1% of saxagliptin-treated patients and 7.4% of glipizide-treated patients. Virtually all of the SAEs were reported in isolated patients. SAEs of interest in the saxagliptin group include one case each of pulmonary tuberculosis (see the integrated analysis of tuberculosis at the end of the Safety section), hypersensitivity, and acute renal failure. The hypersensitivity SAE occurred approximately 11 months after initiating saxagliptin and was characterized as facial edema, heavy breathing, throat discomfort, dizziness, and “eye constriction” occurring after drinking a glass of soy milk. The patient was treated for one day with an antihistamine and glucocorticoid and the event was considered resolved the same day. The patient was on concomitant ACE inhibitor therapy but this medication had been started >2 years prior to enrollment into the trial. A relationship to saxagliptin is unlikely because the event resolved even though the patient continued saxagliptin. The SAE of acute renal failure was attributed to dehydration from vomiting due to a viral infection. The event resolved after administering intravenous fluids.

Discontinuations due to adverse events: A comparable percentage of patients in both treatment groups (73-74%) completed 52 weeks of treatment and a comparable percentage dropped out due to adverse events (4.2% with saxagliptin and 4.4% with glipizide). Adverse events of interest leading to dropout include hypoglycemia in six glipizide-treated patients (and in no saxagliptin-treated patients) and rash (only reported in 1 saxagliptin-treated patient). The rash occurred bilaterally on the calves approximately one week after starting study medication. Treatment was discontinued and the event was resolved 2 weeks later. The distribution of the rash isolated to the calves does not seem likely to represent a hypersensitivity reaction to drug.

Hypoglycemia: Hypoglycemia was classified as major, minor, or suggestive events based on criteria from the European Medicines Agency. Major hypoglycemia had to meet all of the following criteria: at least one symptom, required third-party assistance, had an associated plasma glucose <63 mg/dL, and had prompt recovery (start and stop dates on the same day). Hypoglycemia was classified as minor if the patient did not require third-party assistance and the plasma glucose was <63 mg/dL regardless of whether there were symptoms. Hypoglycemia was classified as suggestive if there was at least one symptom and the plasma glucose was ≥ 63 mg/dL or unavailable.

I do not think the “major” and “suggestive” definitions for hypoglycemia are ideal. For example, a patient would not be classified as having major hypoglycemia if there was no associated glucose measurement even if the event resulted in loss of consciousness that resolved with glucagon administration. For “suggestive” hypoglycemia, the definition permits a plasma glucose ≥ 63 mg/dL but does not set an upper limit on an acceptable plasma glucose. For example, a patient with a blood glucose of 140 mg/dL does not have hypoglycemia even if there are concomitant symptoms suggestive of hypoglycemia.

Based on the above definitions, there were two glipizide-treated patients (0.5%) who had three major hypoglycemic events and no saxagliptin-treated patients who had major hypoglycemia. There were 4 saxagliptin-treated patients (0.9%) who had 5 minor hypoglycemic events and 113 glipizide-treated patients (26%) who had 346 minor hypoglycemic events. More detailed analyses of the hypoglycemia events with better definitions will be requested from the sponsor during our review of the in-house efficacy supplement.

Hypersensitivity reactions: The sponsor identified only one saxagliptin-treated patient with a possible hypersensitivity reaction. This patient is described in the Serious Adverse Event section above. However, there is one saxagliptin-treated patient who had a non-serious adverse event of bronchospasm. There is insufficient information to determine whether this event represented a true hypersensitivity reaction.

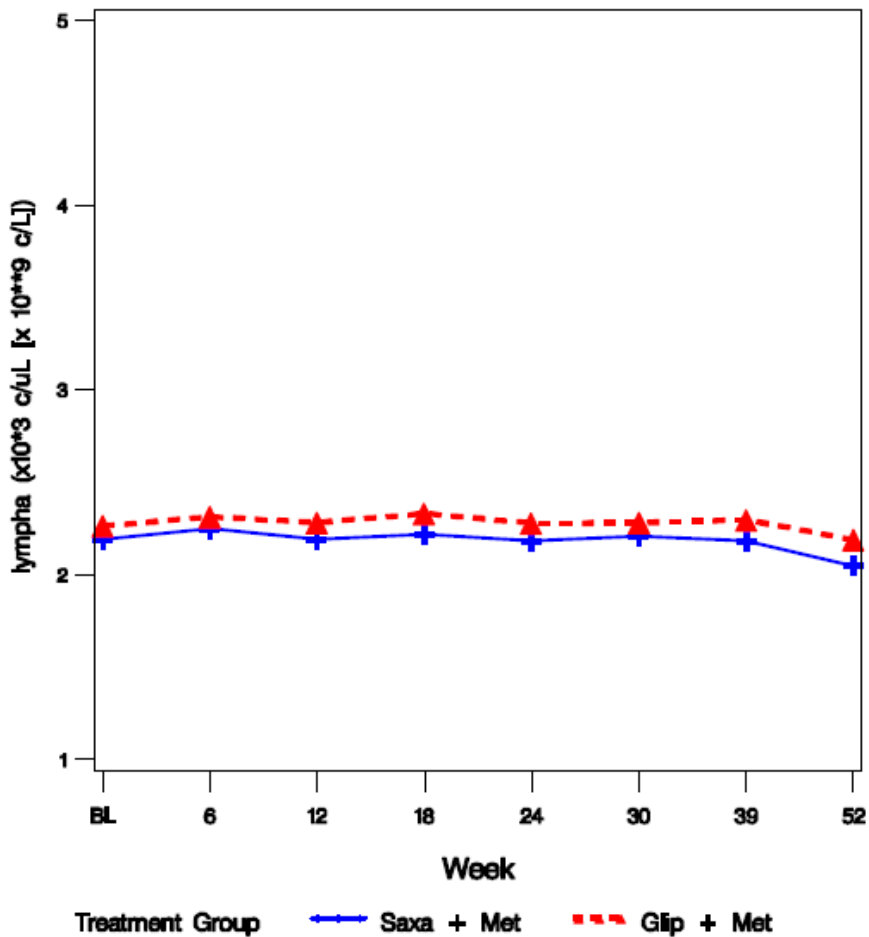
Liver: There were numerically fewer saxagliptin-treated patients compared to glipizide-treated patients who developed serum ALT >3x ULN (n=3 or 0.7% vs. n=6 or 1.4%), serum ALT >5x ULN (n=2 or 0.5% vs. n=3 or 0.7%), and serum ALT >10x ULN (n=1 or 0.2% vs. n=2 or 0.5%). No patients had serum bilirubin >2x ULN. With regard to the 3 saxagliptin-treated patients who developed serum ALT >3x ULN, one had the abnormal measurement (301 U/L or 8.1x ULN) on Day 85 and had normal ALT measurements for the remaining visits through the 52 weeks of treatment. Another had a baseline ALT of 69 U/L (1.4 ULN) that remained

stable through Day 127. The ALT was 239 U/L (5.0x ULN) on Day 260, 195 U/L (4.1x ULN) on Day 275, and 509 U/L (10.6x ULN) at Week 52. The last patient had baseline ALT of 64 U/L (1.7x ULN) that increased to 128 U/L (3.5x ULN) on Day 171, declined to 95 U/L (2.6x ULN) on Day 274, and was 158 U/L (4.3x ULN) at Week 52. There are no additional details for these patients (e.g., results of work-up for other causes of transaminitis), but it is reassuring that none met the criteria for Hy's Law. The sponsor will be asked to provide better narratives for all Adverse Events of Interest in future saxagliptin trials.

Pancreatitis: No saxagliptin-treated patients reported pancreatitis during the 52 weeks of treatment.

Lymphopenia: Mean lymphocyte counts were slightly lower in the saxagliptin group compared to the glipizide group over the course of the trial, although values were relatively stable and the curves were parallel (Figure 3). In contrast, there was a numerically greater proportion of glipizide-treated patients (2.1%) than saxagliptin-treated patients (1.2%) who developed at least one lymphocyte count $\leq 0.75 \times 10^9$ cells/L during the course of the trial.

Figure 3. Mean absolute lymphocyte counts during the first 52 weeks of Study CV18054



Study CV181056: The sponsor submitted the complete study report for this trial in the FDC 120-day safety update. No results from this trial have been previously reviewed. This was an 18-week, randomized, double-blind, active-controlled trial comparing the efficacy and safety of saxagliptin 5 mg (n=400) to sitagliptin 100 mg (n=395), both as add-on therapy in patients with inadequate glycemic control on metformin. Because this trial was submitted in the 120-day safety update and the sponsor is not proposing labeling, I will focus on the safety data. It is interesting, however, to note that saxagliptin was non-inferior to sitagliptin in the per protocol analysis (the sponsor's primary analysis) based on a prespecified non-inferiority margin of 0.3%. In this analysis, the baseline HbA1c in both treatment groups was 7.7%, the adjusted mean change from baseline in HbA1c was -0.5% with saxagliptin and -0.6% with sitagliptin, and the mean treatment difference (saxagliptin minus sitagliptin) for change in HbA1c from baseline to Week 18 was +0.1% (95% confidence interval -0.01%, 0.20%). However, saxagliptin was both statistically inferior and non-inferior to sitagliptin in the intent-to-treat population with last-observation-carried-forward. In this analysis, the adjusted mean change from baseline in HbA1c was -0.4% with saxagliptin and -0.6% with sitagliptin and the mean treatment difference (saxagliptin minus sitagliptin) for change in HbA1c from baseline to Week 18 was +0.2% (95% confidence interval 0.06%, 0.28%).

Deaths: No deaths were reported in this trial.

Serious adverse events: Seven patients in the saxagliptin arm (1.7%) and five patients in the sitagliptin arm (1.3%) reported at least one SAE. Events of interest include a motor vehicle accident in a saxagliptin-treated patient (no mention of blood glucose data around the time of the event) and two patients with hypoglycemia (0.5%) associated with loss of consciousness reported as SAEs in sitagliptin-treated patients. One of the hypoglycemia events was precipitated by exercise and occurred during Week 16 while the patient was driving home, resulting in a crash into a tree. Her consciousness spontaneously returned (likely due to having eaten some food when the hypoglycemic symptoms first appeared). She was able to continue to self-treat when she awoke and subsequently continued in the study without a change in study medication. The other hypoglycemia event occurred while the patient was performing house work. After losing consciousness she was taken to the hospital by a family member where she regained consciousness and had a glucose of 36 mg/dL. This narrative is unclear as to how a family member transported an unconscious person to the hospital and whether the patient spontaneously regained consciousness or only regained consciousness after glucose or glucagon administration. Study medication was interrupted for 2 days and then restarted. The remaining SAEs occurred in isolated patients across a wide range of preferred terms and do not raise any new safety concerns for saxagliptin or sitagliptin.

Discontinuations due to adverse events: Approximately 91% of saxagliptin-treated patients and 94% of sitagliptin-treated patients completed the trial. Discontinuations due to adverse events occurred in 9 (2.2%) saxagliptin-treated patients and 9 (2.3%) sitagliptin-treated patients. Adverse events leading to discontinuation generally occurred in isolated patients across a wide range of preferred terms and do not raise any new safety concerns for saxagliptin or sitagliptin.

Hypoglycemia: Review of the hypoglycemia data reveals that no patients required medical assistance to treat the hypoglycemia (although one of the hypoglycemia SAEs – see above – suggests there may have been a sitagliptin-treated patient who required medical assistance to treat the hypoglycemia). Another sitagliptin-treated patient was classified as having major hypoglycemia although the line listing shows that the patient's blood glucose of 58 mg/dL was easily managed by the patient with help from family or a friend suggesting that this may not necessarily be a true case of severe hypoglycemia.

Using the same definition for minor hypoglycemia as described above for Study CV181054, four saxagliptin-treated patients (1.0%) had a total of seven minor hypoglycemia events compared to a single minor hypoglycemic event among the sitagliptin-treated patients (0.3%). These data support the currently held view that the rate of hypoglycemia is low when DPP-4 inhibitors are used in combination with metformin. Event rates are too low to confirm a quantitative difference between saxagliptin and sitagliptin with regard to hypoglycemia.

Hypersensitivity reactions: There was one report of angioedema in a sitagliptin-treated patient that was not classified as an SAE and that did not lead to dropout. I was unable to verify whether this was a true case of angioedema because no narrative was provided. Note, however, that angioedema is already labeled for sitagliptin.

Liver: No patients discontinued due to liver test abnormalities. There were two (0.5%) saxagliptin-treated patients and no sitagliptin-treated patients with serum ALT >3x ULN. One of these patients had a baseline ALT of 130 U/L (2.7x ULN) that increased to 210 U/L (4.4x ULN) at study end. The second patient had a baseline ALT of 83 U/L (2.2x ULN) that increased to 119 U/L (3.2x ULN) on Day 53, when she was discontinued from the trial due to hyperglycemia. As mentioned previously, the narratives do not contain complete information to assess relationship to study medication. It is reassuring that there were no cases of Hy's Law.

Pancreatitis: There were no reports of pancreatitis in this trial.

Lymphopenia: Plots of mean lymphocyte counts with saxagliptin and with sitagliptin were virtually superimposable over the course of the trial. However, a numerically greater proportion of saxagliptin-treated patients compared to sitagliptin-treated patients had a $\geq 10\%$ reduction (36% vs. 31%), $\geq 20\%$ reduction (15% vs. 11%), and $\geq 30\%$ reduction (5.3% vs. 4.4%) in absolute lymphocyte counts from baseline to Week 18. One saxagliptin-treated patient (0.3%) and two (0.5%) sitagliptin-treated patients had a reduction in lymphocyte counts from within the range of >0.75 to $\leq 5.00 \times 10^3$ c/mL at baseline to the markedly low range ($\leq 0.75 \times 10^3$ c/mL) at Week 18 (or last-observation-carried-forward).

Study CV 181064: The sponsor submitted the complete study report for this trial in the FDC 120-day safety update. No results from this trial have been previously reviewed. This was a 24-week, randomized, double-blind, placebo-controlled trial comparing saxagliptin 5 mg (n=283) to placebo (n=287), both as add-on therapy in patients with inadequate glycemic control on metformin. This trial was conducted exclusively in China, South Korea and India to support efficacy and safety in the Asian population. The mean baseline HbA1c was 7.9% in

both treatment groups. According to the sponsor's analysis using the intent-to-treat population with last-observation-carried-forward, there was a mean reduction in HbA1c of 0.8% with saxagliptin and 0.4% with placebo, resulting in a treatment difference of -0.4% (95% confidence interval -0.6%, -0.3%; $p < 0.0001$).

Deaths: No deaths were reported in this trial.

Serious adverse events: Eight saxagliptin-treated patients (2.8%) and three placebo-treated patients (1.0%) reported at least one SAE. This numerical imbalance was driven by infections, which occurred in four (1.4%) saxagliptin-treated patients and one (0.3%) placebo-treated patient. However, even for infection SAEs, the events were distributed across different preferred terms (one case each of appendicitis, hepatitis B, anal abscess, and confirmed pulmonary tuberculosis - please see the integrated analysis of tuberculosis cases at the end of the safety section for more details).

Discontinuations due to adverse events: Approximately 90% of saxagliptin-treated patients and 86% of placebo-treated patients completed the trial with six (2.1%) saxagliptin-treated patients and three (1.0%) placebo-treated patients dropping out due to adverse events. Events of note leading to dropout include one case each of lymphopenia, abdominal discomfort, and hepatic function abnormal. The patient who dropped out due to abnormal liver tests had a baseline ALT of 42 U/L (reference range 6-37 U/L) that increased to 67 U/L (1.8x ULN) at Week 8 leading to study drug discontinuation. This patient also reported eyelid edema occurring approximately one month after starting saxagliptin. The eyelid symptoms resolved within three days while the patient was still on saxagliptin. The patient who dropped out due to lymphopenia had a reduced lymphocyte count at baseline that was lower than all lymphocyte counts during treatment. The patient who dropped out due to abdominal discomfort developed this symptom approximately 2 weeks into the trial and was not hospitalized but there is insufficient information to assess whether the symptoms may have reflected mild pancreatitis.

Hypoglycemia: Using the same definitions for major and minor hypoglycemia as described above for Study CV181054, there were no cases of major hypoglycemia and three cases of minor hypoglycemia, two (0.7%) with saxagliptin and one (0.3%) with placebo. These data again support the currently held view that the rate of hypoglycemia is low when DPP-4 inhibitors are used in combination with metformin.

Hypersensitivity reactions: The sponsor identified the following potential cases of hypersensitivity reactions: One patient with eyelid edema (this symptom lasted 3 days and resolved despite continued treatment with saxagliptin – see Discontinuations due to Adverse Events above), one patient with facial edema that lasted one day and resolved while continuing saxagliptin, and one patient with periorbital edema starting on Day 40 and lasting 5 days, resolving while saxagliptin was continued. It is unlikely that these events represent true hypersensitivity reactions because symptoms resolved despite continued treatment with saxagliptin.

Liver: There were no cases of Hy's Law. One patient discontinued due to abnormal liver tests but the ALT increased from 1.1x ULN at baseline to only 1.8x ULN. There were two

saxagliptin-treated patients (0.7%) who developed ALT >3x ULN (one of whom developed ALT >5x ULN) compared to no placebo-treated patients. The patient with ALT >5x ULN had a pre-randomization ALT of 43 U/L (1.2x ULN) that normalized at baseline and Week 4 then increased to the 50-60 U/L (1.7x ULN) range at Weeks 8-20, and reached 239 U/L (6.5x ULN) at Week 24. Total bilirubin was normal throughout the study but had increased to 1.4x ULN at Week 24. The event was reported resolved 2 weeks after study completion. Relevant concomitant medications included a statin (started months prior to study start) and cefixime (started 4 days prior to the Week 24 visit to treat an upper respiratory tract infection). Cefixime is labeled for reports of liver test abnormalities. The patient with ALT >3x ULN had only a transient increase in ALT that resolved despite continued treatment with saxagliptin. This patient had a baseline ALT of 40 U/L, an ALT of 139 U/L (3.8x ULN) ~18 weeks into the study, and ALT values of 42-44 U/L at Weeks 20 and 24.

Pancreatitis: There were no reports of pancreatitis in this trial.

Lymphopenia: Plots of mean lymphocyte counts with saxagliptin and with placebo were virtually superimposable over the course of the trial. There were three saxagliptin-treated patients (1.1%) and two placebo-treated patients (0.7%) with at least one lymphocyte count $\leq 0.75 \times 10^3$ c/mL during the course of the trial. None of the saxagliptin-treated patients met the $\leq 0.75 \times 10^3$ c/mL criterion at study endpoint. There was a higher incidence of reported infections in the saxagliptin group (21%) compared to the placebo group (15%) with this difference driven predominantly by upper respiratory tract infection (6.7% vs. 4.5%) and by urinary tract infection (4.6% vs. 2.8%).

Other trials: The 120-day safety update for the FDC also contains safety data from five ongoing, randomized, controlled trials of 4-52 weeks duration (CV181080, CV181085, CV181086, CV181089, and CV181090), all of which are testing saxagliptin in combination with metformin and most of which have only recently been initiated. The number of enrolled patients in each of these trials is generally low (n=43, n=46, n=63, n=130, n=152) and these trials remain blinded. Review of the limited blinded data reveals no deaths and only five SAEs - stroke, seizure (with inadequate information to attribute to hypoglycemia), prostate cancer, chronic obstructive pulmonary disease, and cataract. These limited data do not raise any new safety concerns with combination saxagliptin and metformin therapy.

Integrated Analysis of Tuberculosis and Opportunistic Infections:

During review of this NDA, we noted a total of three cases of tuberculosis across the clinical trials submitted to support the FDC. There was one case each in Study 181014, 181054, and 181064. All three cases occurred in saxagliptin-treated patients. Based on this finding, the sponsor was asked to query their entire controlled clinical trial database and postmarketing reports for other tuberculosis cases and for opportunistic infections. The sponsor used a list of ~45 preferred terms containing the phrase “tuberculosis”, “tuberculoma”, or “tuberculous” to search for potential cases of tuberculosis. This list is a subset of a larger list of preferred terms that the sponsor used to search for opportunistic infections. This larger list was based on opportunistic infections included in the 1993 Centers for Disease Control (CDC) list of AIDS-defining diagnoses. In the unblinded, controlled, clinical trial database for saxagliptin to date,

there have been 6 (0.12%) reports of tuberculosis among the 4959 saxagliptin-treated patients (1.1 per 1000 patient-years) compared to no reports of tuberculosis among the 2868 comparator-treated patients. There is a suggestion of a relationship to saxagliptin dose, as there was one patient on saxagliptin 2.5 mg (0.71 per 1000 patient-years), three patients on saxagliptin 5 mg (1.19 per 1000 patient-years), and two patients on saxagliptin 10 mg (1.40 per 1000 patient-years).

None of the six cases occurred in the United States or in Western Europe. One case occurred in Canada in a patient who had ~1-month visit to Indonesia ~3 months prior to diagnosis. Two (one from China and the other from the Philippines) of these six cases were confirmed with laboratory testing (e.g., acid-fast staining of sputum). The remaining cases had limited information or had presumptive diagnoses of tuberculosis. For example, the patient in Canada had a neck mass that decreased in size with therapy for presumptive tuberculosis even though excisional biopsy was negative for tuberculosis on cultures and polymerase chain reaction (PCR). A patient in Brazil was diagnosed presumptively with tuberculosis meningitis after lumbar puncture for headache showed increased protein and monocyte predominance. Staining for acid-fast bacilli was negative but PCR was not performed. A patient in Russia was diagnosed with presumptive tuberculosis after failing therapy for bacterial pneumonia. Sputum analysis and bronchoscopy were negative for tuberculosis.

The duration of treatment with saxagliptin until report of tuberculosis ranged from 144 to 929 days. Post-treatment lymphocyte counts were consistently within the reference range for four cases. The patient from China with confirmed tuberculosis had lymphopenia prior to initiation of saxagliptin that remained stable throughout saxagliptin treatment. The patient from Russia with presumptive tuberculosis had isolated lymphopenia at one study visit approximately four months prior to the report of tuberculosis.

There has been another case of confirmed pulmonary tuberculosis recently reported in a patient from Peru diagnosed on Day 126 in an ongoing study but treatment assignment remains blinded. There have been no spontaneous postmarketing reports of tuberculosis associated with saxagliptin use. Based on these data, there are too few cases to date to determine whether tuberculosis is related to saxagliptin use.

Referencing World Health Organization data from 2003, the sponsor notes that all seven cases of tuberculosis occurred in patients who lived or visited countries with higher endemic rates of tuberculosis (45-168 cases per 100,000 population) compared to the United States (5 cases per 100,000 population).

There has been one case of a potential opportunistic infection in the unblinded, controlled clinical trial database to date in a saxagliptin-treated patient who developed fatal salmonella sepsis after approximately 600 days of saxagliptin therapy. The patient's wife had concurrent symptoms of enteritis. There have been no spontaneous postmarketing reports of opportunistic infections associated with saxagliptin use.

9. Advisory Committee Meeting

The FDC contains two products that are already FDA-approved for the treatment of type 2 diabetes. Review of this NDA did not identify new safety or efficacy concerns that rose to the level of needing input from an external advisory panel. Therefore, an advisory committee meeting was not held for this NDA.

10. Pediatrics

The efficacy and safety of metformin IR have been established in pediatric patients with type 2 diabetes and metformin is the preferred pharmacological therapy in this patient population. In April 2006, BMS was granted a full waiver for studying Glucophage XR in the pediatric population (the approved label states that the efficacy and safety of Glucophage XR has not been established in the pediatric population). The rationale for the waiver included (1) the fact that metformin IR has been shown to be safe and effective in pediatric patients, (2) that pharmacokinetics for metformin IR are similar in the pediatric and adult populations, and (3) that Glucophage XR is not widely used by adults and by extension would not be used in a substantial number of pediatric patients.

For the FDC NDA, [REDACTED] (b) (4)

[REDACTED] the sponsor will conduct a new pediatric trial under the FDC NDA. This trial will enroll patients aged 10- (b) (4) years old with type 2 diabetes and inadequate glycemic control [REDACTED] (b) (4)

[REDACTED] (b) (4) Therefore, this trial will provide supportive efficacy and safety information for co-administered saxagliptin and metformin (both the IR and MR formulations).

In addition, the sponsor will be conducting a [REDACTED] (b) (4) clinical pharmacology study in [REDACTED] (b) (4) pediatric patients with type 2 diabetes comparing the pharmacokinetics of [REDACTED] (b) (4) the FDC to co-administered saxagliptin [REDACTED] (b) (4) and metformin IR [REDACTED] (b) (4)

Metformin XR tablets are large. Glucophage XR 500 mg is 19 mm x 9.3 mm x 6.7 mm. The FDC containing saxagliptin 5 mg/metformin XR 500 mg is 19.6 mm x 9.7 mm x 7.2 mm, which is only marginally larger than Glucophage XR. The metformin XR 1000 mg [REDACTED] (b) (4) tablet for the FDC is 22.5 mm x 10.4 mm x 7.6 mm, which is also similar to the overall dimensions of the FDC containing saxagliptin 5 mg/metformin XR 1000 mg (23.2 mm x 10.9 mm x 8.1

mm). The sponsor will assess swallowability of the FDC in the small clinical pharmacology study and will assess swallowability of metformin XR in the add-on to metformin trial (the findings from metformin XR should be reasonably applicable to the FDC given that the FDC and metformin XR alone do not have appreciable differences in tablet size).

Proposed timelines for the pediatric clinical pharmacology study:

- Protocol submission: October 31, 2011
- Study report submission: December 31, 2013

Propose timelines for the pediatric add-on to metformin clinical trial:

- Protocol submission: June 30, 2011
- Study completion: April 30, 2015
- Study report submission: December 31, 2015

Note that the clinical pharmacology study will still be ongoing when the phase 3 add-on to metformin trial is started. This is consistent with the approach used for the saxagliptin monotherapy pediatric program where clinical pharmacology data are being obtained within the phase 3 monotherapy trial.

The sponsor's proposal was discussed with the Pediatric Review Committee (PeRC) on October 6, 2010. PeRC concurred with the sponsor's overall approach including the deferral and partial waiver. (b) (4)

11. Other Relevant Regulatory Issues

Tradename: The sponsor's three previously proposed tradenames have been found unacceptable by the Division of Medication Error Prevention and Analysis (DMEPA) and/or the Division of Drug Marketing, Advertising, and Communications (DDMAC). DMEPA concluded that (b) (4) DDMAC concluded that (b) (4).

The third proposed tradename, (b) (4) was also found unacceptable. The fourth proposed tradename, Kombiglyze XR, was found to be acceptable.

Financial conflicts of interest: Dr. Nedeltcheva reviewed the financial disclosure form for the relevant clinical trials and did not identify any potential financial conflicts of interest.


Division of Scientific Investigations (DSI): For the saxagliptin NDA, DSI inspected four clinical sites, HbA1c data at two clinical laboratories and some of the sponsor's records. The main efficacy and safety data for the FDC NDA were reviewed as part of the saxagliptin NDA. Therefore, no new DSI inspections of clinical sites or the sponsor were deemed necessary for this NDA.

The Clinical Pharmacology reviewers asked DSI to inspect the clinical and analytical portions of pivotal bioequivalence study CV181112 (FDC 5/1000 mg tablet vs. saxagliptin 5 mg and two metformin XR 500 mg tablets). DSI did not identify any major issues and concluded that results from Study CV181112 can be accepted for review. See the review of Dr. Gopa Biswas for details.

12. Labeling

The label should incorporate relevant findings from both the saxagliptin package insert and from the Glucophage/Glucophage XR package insert.

Major comments that we asked the sponsor to incorporate into the label include:

- The need for clear instructions regarding how to dose the FDC in various settings (e.g., patients who are metformin naïve, patients needing metformin in combination with only 2.5 mg of saxagliptin)
- Data showing how the morning dosing of saxagliptin (used in most phase 3 trials) compares to evening dosing (used with the FDC)
- Clear statements that the supportive efficacy and safety findings are derived from phase 3 trials that used saxagliptin in combination with metformin IR and not metformin XR and that none of the phase 3 trials tested the FDC directly
- To delete from the Pharmacodynamics section of the label (b) (4)

- The findings from the integrated analysis of tuberculosis cases across the saxagliptin clinical trial database

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval

- Risk Benefit Assessment

The sponsor has conducted a typical development program for an anti-diabetic FDC tablet including an adequate CMC package, a bridging toxicology study, pivotal bioequivalence studies showing that the FDC is bioequivalent to co-administered components, and supportive phase 3 clinical trials with the co-administered components. Four issues are worth mentioning below:

First, the FDC is to be administered with dinner and contains metformin XR whereas all the >4-week clinical trials involving co-administration of saxagliptin and metformin administered saxagliptin in the morning and used twice-daily metformin IR. However, a 6-month

monotherapy trial included treatment arms with morning and evening dosing of saxagliptin and showed a comparable placebo-corrected reduction in HbA1c with evening and morning dosing. This provides adequate support for dosing saxagliptin in the evening as part of the FDC. With regard to metformin, it is reasonable to extrapolate the findings with metformin IR to metformin XR. Although C_{max} is ~20% lower with metformin XR, the AUC is comparable to metformin IR. Therefore, any safety concerns that could be related to C_{max} should be no greater with metformin XR than with metformin IR. In addition, the efficacy and safety of metformin XR have previously been established.

Second, we consider two indications for anti-diabetic FDC products. The more broad indication states that the FDC can be used in patients whenever treatment with both components is considered appropriate. A more limited indication states that the FDC is indicated to improve glycemic control in patients who are already on at least one component of the FDC. To obtain the broader indication, the sponsor must conduct a factorial trial to show that initiating both components of the FDC (or the FDC itself) in patients who are treatment naïve does not lead to unacceptable rates of untoward effects (e.g., hypoglycemia). The sponsor conducted a factorial trial for saxagliptin but this study did not include a saxagliptin 5 mg alone arm (which is the maximum recommended approved saxagliptin dose). This trial had a saxagliptin 10 mg alone arm, metformin alone arm, saxagliptin 10 mg + metformin arm, and saxagliptin 5 mg + metformin arm. However, review of the data for saxagliptin 10 mg + metformin vs. saxagliptin 10 mg vs. metformin as well as review of data for the saxagliptin 5 mg + metformin arm vs. metformin alone did not identify safety concerns that would preclude use of saxagliptin 5 mg + metformin as initial therapy in treatment-naïve patients. Therefore, it is reasonable to grant the sponsor the broader indication for this FDC.

Third, the clinical pharmacology reviewers noted that the pivotal bioequivalence studies did not meet the recommended biobatch criteria. However, biopharmaceutics, which is the team responsible for evaluating the biobatch criteria concluded that the used batch size was acceptable in this instance and that the sponsor does not need to repeat the pivotal bioequivalence studies with a larger batch size.

Lastly, there is a small imbalance in reports of tuberculosis across the controlled, unblinded saxagliptin trial database (six cases with saxagliptin vs. 0 cases with comparator). This imbalance persists even after accounting for the ~2:1 randomization and patient-year exposures. The small numbers of events limits the ability to establish causality at this time. Nonetheless, this imbalance should be added to the FDC label and the saxagliptin label - we will ask the sponsor to submit a Changes Being Effected (CBE) supplement to the saxagliptin NDA based on the agreed-upon language for the FDC. Infections are an Adverse Event of interest in the large, long-term cardiovascular outcomes trial and we will continue to monitor for tuberculosis events and opportunistic infections through spontaneous postmarketing reports, Periodic Adverse Drug Experience Reports (PADERS), and review of other completed saxagliptin trials.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

No new safety concerns were identified that prompt the need for Risk Evaluation and Mitigation Strategies (REMS). Januvia, the only other approved DPP-4 inhibitor has a Medication Guide-only REMS for pancreatitis. None of the findings in this review, including pancreatitis, rise to the level of needing a REMS for saxagliptin but we will continue active surveillance.

- Recommendation for other Postmarketing Requirements and Commitments

The postmarketing required embryofetal studies will be classified as fulfilled and closed out administratively when the findings from these studies are incorporated into the saxagliptin label (currently in-house as part of a pending efficacy supplement).

There are several PMRs that are ongoing for saxagliptin including epidemiology studies evaluating hypersensitivity reactions and liver injury as well as a large, long-term, ongoing cardiovascular outcomes trial designed to meet the recommendations of the 2008 diabetes cardiovascular guidance. Secondary objectives of this cardiovascular trial include an assessment of the long-term effects of saxagliptin on lymphocyte counts, infections, hypersensitivity reactions, liver, bone fracture, pancreatitis, skin reactions, and renal safety.

- Recommended Comments to Applicant

Narratives for adverse events of interest reviewed in trials to support the FDC were generally poor. For example, there is no description of risk factors or work-up for alternate etiologies for patients presenting with liver test abnormalities or elevated serum creatinine. The sponsor will be asked to improve the quality of the narratives for Adverse Events of Interest for future trials.

The sponsor will be asked to submit a CBE supplement to the saxagliptin NDA based on the agreed-upon tuberculosis language incorporated into the FDC label.

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/s/

HYLTON V JOFFE
10/28/2010

MARY H PARKS
11/04/2010