CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-350

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 28, 2009
From	Hylton V. Joffe, M.D., M.M.Sc.
Subject	Cross-Discipline Team Leader Review
NDA #	22-350
Applicant	Bristol-Myers Squibb
Date of Submission	June 30, 2008
PDUFA Goal Date	July 30, 2009
Proprietary Name / Established (USAN) names	Onglyza (saxagliptin)
Dosage forms / Strength	2.5 mg and 5 mg tablets
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommended:	*Approval, pending agreement on labeling*

Cross Discipline Team Leader Review

1. Introduction

Incretin hormones, such as glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP), are released from the gastrointestinal tract during meals and stimulate insulin release from the pancreatic beta-cell in a glucose-dependent manner. GLP-1 and GIP have short half-lives (<2 minutes) due to rapid degradation by dipeptidyl peptidase (DPP)-4. Saxagliptin (proposed tradename Onglyza) is an oral DPP-4 inhibitor that has been developed by Bristol-Myers Squibb as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. The original user fee goal date for this application was April 30, 2009. An unexpected teratogenicity finding in a rat embryofetal development study designed to support the saxagliptin/metformin fixed-dose combination tablet (see below) prompted submission of the non-clinical study report to FDA within 3 months of the user fee goal date. The Division classified this submission as a major amendment and extended the user fee goal date by 3 months to July 30, 2009.

This memorandum discusses the saxagliptin new drug application (NDA) with a focus on key findings from the various review disciplines and the phase 2/3 development program.

2. Background

DPP-4 inhibitors tend to have modest efficacy but these medications appear to be generally well-tolerated with neutral effects on body weight and a low risk for hypoglycemia. Currently, Januvia (sitagliptin phosphate) is the only FDA-approved DPP-4 inhibitor. Labeled safety concerns with Januvia include postmarketing reports of hypersensitivity reactions, including Stevens-Johnson Syndrome, and minor increases in serum creatinine in patients with moderate or severe renal impairment. Postmarketing reports of pancreatitis in association with Byetta and Januvia are under FDA review. Other toxicities associated with at least one DPP-4 inhibitor include necrotic skin lesions in monkeys, sometimes near clinical exposures (e.g. vildagliptin, dutogliptin) and possible hepatotoxicity (vildagliptin).

In July 2008, the Division convened a public, 2-day advisory committee meeting to discuss cardiovascular assessment for drugs and biologics developed for the treatment of type 2 diabetes. After considering the recommendations of the advisory committee panel and other data, the Division published a December 2008 Guidance for Industry entitled *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*. This guidance document requests that sponsors of new pharmacologic therapies for type 2 diabetes show that these treatments do not result in an unacceptable increase in cardiovascular risk. Of note, the saxagliptin NDA and two other NDAs for the treatment of type 2 diabetes were submitted to FDA prior to the July 2008 advisory committee meeting and prior to the December 2008 guidance. Nonetheless, FDA has requested that the sponsors for these three products provide adequate evidence of cardiovascular safety in accordance with the

guidance to support approvability. Therefore, cardiovascular safety was a major focus of the clinical and statistical reviews for saxagliptin.

3. CMC

The chemistry/manufacturing/controls (CMC) portion of the NDA was submitted as part of the Office of New Drug Quality Assessment (ONDQA) Quality-by-Design Pilot Program to explore science and risk-based approaches to assuring product quality. The drug substance for Onglyza is saxagliptin ( )available in dosage strengths of 2.5 mg and 5 mg. The saxagliptin molecule contains chiral centers but there is no chiral conversion *in vivo*. The drug product does not contain novel excipients and is manufactured using a

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(Based on stability data, the CMC reviewers are granting the two dosage strength presentations a 36-month stability period with labeling that states "Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]."

CMC has determined that the application qualifies for a categorical exclusion from an environmental assessment report because the expected introduction concentration of the active moiety at the point of entry into the aquatic environment is less than 1 part per billion.

The Office of Compliance issued an acceptable recommendation on the manufacturing facilities of the drug product.

CMC deficiencies identified during the review have been adequately resolved. All Drug Master Files are acceptable or the pertinent information has been adequately provided. The CMC reviewers have determined that the drug product is acceptable and recommend approval of the NDA. Please see reviews by Drs. Sharmista Chatterjee, John Hill, Prafull Shiromani, and Christine Moore for further details.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewers have concluded that there are reasonable safety margins between animal toxicities and clinical exposures with the proposed maximum daily dose of 5 mg, and recommend approval pending agreement on labeling. As explained below, the reviewers are also recommending two required non-clinical postmarketing studies to further explore an unexpected teratogenicity finding in a rat embryofetal development study that co-administered saxagliptin and metformin. The sponsor has already initiated these studies but the pharmacology/toxicology reviewers have determined that the protocols are inadequate (e.g., too high a dose of metformin is being tested). The Division is in the process of communicating the protocol inadequacies to the sponsor and has informed the sponsor that new studies will be needed. Please see reviews by Drs. Fred Alavi, Todd Bourcier, and Paul Brown for further details.

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In this embryofetal study, two fetuses from one litter of rats that had been exposed to co-administered saxagliptin (at doses 114-fold above clinical exposures) and metformin (at doses 4-fold above clinical exposures with the 2,000 mg daily dose) developed malformations (one case of craniorachischisis, a rare neural tube defect involving incomplete closure of the skull and spinal cord, and one case of cleft palate). The sponsor attributed this finding to metformin alone (via potential alterations to vitamin B_{12} and folate) but the embryofetal study did not have a metformin alone treatment arm to support this assertion. Furthermore, Dr. Bourcier notes that this study had two combination dose groups that had equal exposures to metformin, yet teratogenicity occurred only in the group with the higher dose of saxagliptin. In addition, Dr. Bouricer notes that the original embryofetal studies conducted for metformin did not report craniorachischisis.

Based on this finding, the pharmacology/toxicology reviewers are recommending that the Division require two non-clinical postmarketing studies under the FDA Amendments Act (FDAAA), one in rats and another in rabbits, that further explores this signal using study designs that include separate treatments arms for metformin alone, saxagliptin alone, and the combination of saxagliptin+metformin.

Results from this study have relevance to the saxagliptin NDA because saxagliptin will be frequently co-administered with metformin, if approved. Therefore, the pharmacology/ toxicology reviewers are recommending a statement in the label describing this finding and will reassess the labeling once results from these two more definitive studies are available. Of note, the reviewers (with input from the Associate Director and Director of Pharmacology/Toxicology and the Reproductive Toxicology Subcommittee at FDA) are recommending Pregnancy Category B for saxagliptin, because saxagliptin alone was not teratogenic in rats and rabbits at very high exposure multiples.

Saxagliptin is metabolized by CYP3A4 to active metabolite BMS-510849 in all test species. This active metabolite is two-fold less potent than saxagliptin but more selective at inhibiting DPP-4 versus off-target DPP-8 and DPP-9. In patients with diabetes, exposures to this metabolite are 4-7-fold higher than exposures to saxagliptin whereas in animals, exposures to this metabolite are no greater than exposures to saxagliptin. Nonetheless, Dr. Alavi has determined that this metabolite and several minor metabolites formed in humans have been adequately assessed for toxicity in the non-clinical studies.

Brain lesions occurred in male rats administered very high doses (>350-fold safety margin) of saxagliptin. Per Dr. Bourcier, the sponsor has convincingly demonstrated that these lesions are caused by release of cyanide from saxagliptin via CYP2C11, an androgen-regulated metabolizing enzyme that is abundant in male rats but not present in humans. Per Dr. Alavi, saxagliptin administration to female rats and to both genders of other species used in non-clinical studies did not lead to measurable quantities of cyanide. In addition, whole blood cyanide concentrations were below the limit of quantification in all healthy volunteers receiving up to 40 mg of saxagliptin daily for 14 consecutive days in Study 181031. Dr. Alavi

has determined that there is little or no risk that these findings in male rats are applicable to humans.

Some DPP-4 inhibitors cause cutaneous lesions in monkeys, possibly due to cross-reactivity with DPP-8 and DPP-9. Sitagliptin, the only FDA-approved DPP-4 inhibitor, does not cause these lesions but saxagliptin does. However, per Dr. Alavi the risk of skin lesions to humans treated with saxagliptin is minimal because there are large safety margins for this toxicity (exposures 20-fold above the clinical dose cause only minimal non-necrotizing cutaneous lesions; exposures approximately 60-fold above the clinical dose cause severe necrotizing lesions). Saxagliptin also induced minimal erosive lesions of the paws in dogs after 12 months exposure at doses ≥35-fold above clinical exposure.

Dr. Bourcier notes that splenic lymphoid proliferation and multi-organ lymphoid/monocytic infiltration occurred in all animal species but characterizes these findings as minimal and reversible. Reductions in lymphocyte counts occurred in rats, dogs, and monkeys given high doses of saxagliptin. However, Dr. Bourcier states that the animal data do not provide much insight into the reduction in lymphocytes reported in humans (see the safety section of this memorandum) because the animal finding was not consistent across studies and did not follow dose- or time-dependency. Dr. Bourcier concludes that there is minimal to no risk of severe immunotoxicity but cannot exclude subtle changes in immunity.

Exposure in human milk is expected because saxagliptin is detected in rat milk.

In the 2-year rat and mouse carcinogenicity studies, there were no drug-related increases in neoplastic lesions despite high exposures to study drug (up to 1,000- to 2,200-fold margins for saxagliptin and up to 68- to 300-fold margins for active metabolite BMS-510849).

There is no evidence of cardiovascular toxicity based on non-clinical testing in healthy animals.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology reviewers recommend approval pending agreement on labeling. Please see the joint review co-authored by Drs. Jayabharathi Vaidyanathan, Immo Zdrojewski, and Justin Earp for details.

As mentioned above, saxagliptin has one major metabolite (BMS-510849) that is also an inhibitor of DPP-4. This metabolite is two-fold less potent than saxagliptin but has greater selectivity than saxagliptin for DPP-4 over DPP-8 (948-fold vs. 391-fold) and DPP-9 (163-fold vs. 75-fold) at 37°C.

Saxagliptin and BMS-510849 have negligible protein binding. The median Tmax for saxagliptin is between 1.5-2.0 hours and the elimination half-life is 2.3-3.3 hours. BMS-510849 has a median Tmax of 3.0 hours and a mean apparent terminal half-life of 3.6 hours. Saxagliptin has similar pharmacokinetics in patients with type 2 diabetes and healthy subjects. However, in patients with type 2 diabetes mean exposures to BMS-510849 are 4-7-fold higher

than exposures to saxagliptin, whereas healthy subjects have mean exposures to BMS-510849 that are 2-3 fold higher than exposures to saxagliptin.

The amount of DPP-4 inhibition at 24 hours is 37% with the 2.5 mg saxagliptin dose and 65% with the 5 mg saxagliptin dose.

Saxagliptin can be dosed regardless of food. No dosage adjustment is needed based on age, race, or gender. Table 1 summarizes the percent changes in mean exposures to saxagliptin and BMS-510849 in patients with various degrees of renal impairment.

Table 1. Percent changes in mean exposures to saxagliptin and metabolite BMS-510849 in patients with renal impairment

Degree of renal impairment	Saxagliptin		BMS-510849	
	AUC_{0-T}	Cmax	AUC_{0-T}	Cmax
Mild	+15%	+39%	+67%	+40%
Moderate	+40%	+7%	+191% (2.9-fold)	+47%
Severe	+110%	+38%	+347% (4.5-fold)	+46%
Hemodialysis	-23%	-15%	+306% (4.1-fold)	+36%

AUC = area under the time-concentration curve

Based on these data, the clinical pharmacology reviewers agree with the sponsor's proposed dosage adjustment to 2.5 mg for moderate, severe and end-stage renal impairment and agree that no dosage adjustment is needed for mild renal impairment. Dr. Bourcier notes that the moderate increase in drug exposure in patients with renal impairment who inadvertently receive the unadjusted 5 mg clinical dose is unlikely to reproduce toxicities noted in animals.

Saxagliptin is predominantly metabolized in the liver by CYP3A4/5 and is a P-glycoprotein substrate. In the hepatic impairment pharmacokinetic study, subjects with severe hepatic impairment had a geometric mean decrease in saxagliptin Cmax of 6% and a geometric mean increase in overall saxagliptin exposure (area under the time-concentration curve or AUC) of approximately 75% compared to subjects with normal hepatic impairment. Based on these data, the clinical pharmacology reviewers agree with the sponsor that no dosage adjustment is needed in patients with hepatic impairment.

Drug interaction studies were conducted with ketoconazole, diltiazem, rifampin, Maalox Max, famotidine, omeprazole, glyburide, pioglitazone, metformin, digoxin and simvastatin. The sponsor did not conduct a drug interaction study with warfarin. The oral contraceptive drug interaction study has not yet been completed.

CYP3A4/5 induction with rifampin reduced saxagliptin AUC by 80% and increased BMS-510849 Cmax by 40% with a five-fold increase in the metabolite-to-parent AUC ratio. CYP3A4/5 induction also reduced the saxagliptin half-life from 3.0 hours to 1.7 hours. Dr. Vaidyanathan states that the clinical significance of these changes is unknown but is not recommending dosage adjustment because there is only a 25% decrease in exposure to the total active moiety (molar parent exposure + one-half molar metabolite exposure).

The sponsor conducted two drug interaction studies with ketoconazole, which is a strong CYP3A4/5 inhibitor. In the first ketoconazole study (CV181005), subjects received saxagliptin 100 mg on Days 1 and 9 and ketoconazole on Days 3-11. Ketoconazole resulted in a 2.5-fold geometric mean increase in saxagliptin AUC. All subjects had normal lymphocyte counts at baseline. On Day 10, fourteen of the 15 subjects had a reduction from baseline in lymphocyte counts (range -14% to -80%). Seven of these subjects had Day 10 lymphocyte counts below the lower limit of the reference range that returned to within the reference range on Day 12. Five of these seven subjects with lymphopenia developed fever and chills in the evening on Day 9 and all seven patients had reductions from baseline in platelet counts on Day 10 (range -7% to -24%), although the platelet counts remained within the reference range.

In the second ketoconazole study (CV181022), subjects were randomized to Sequence 1 (saxagliptin 5 mg on Days 1 and 9), Sequence 2 (saxagliptin 20 mg on Days 1 and 9), or Sequence 3 (saxagliptin 20 mg on Days 1 and 9 and ketoconazole on Days 3-11). Ketoconazole resulted in a 3.8-fold geometric mean increase in saxagliptin AUC. There were no reports of pyrexia or chills in the subjects randomized to Sequence 3 but these subjects had a 31% mean reduction in absolute lymphocyte counts compared to a mean reduction of 22% for Sequence 1 and a mean reduction of 19% for Sequence 2.

It is unknown to what extent ketoconazole will increase exposures for a 5 mg saxagliptin dose. However, based on the 3.8-fold geometric mean increase in saxagliptin AUC with ketoconazole in Study CV181022, the clinical pharmacology reviewers are recommending a dose reduction to 2.5 mg for patients co-administered strong CYP3A4/5 inhibitors.

The sponsor also conducted a drug interaction study with diltiazem, which is a moderate CYP3A4/5 inhibitor. Subjects received saxagliptin 10 mg on Days 1 and 9 and diltiazem on Days 2-10. None of the subjects reported fever or chills. Three of the 14 subjects had lymphocyte counts at study end that were lower than the lymphocyte counts at screening or baseline, but these 3 subjects had lymphocyte counts well within the reference range. Diltiazem resulted in a 2.1-fold geometric mean increase in saxagliptin AUC. Based on these results, the clinical pharmacology reviewers are not recommending saxagliptin dosage adjustment for patients on moderate CYP3A4/5 inhibitors.

The clinical pharmacology reviewers have concluded that none of the other tested drug interactions are likely to be clinically relevant.

Saxagliptin has no significant prolongation effect on the QT interval. In the Thorough QT Study, 40 healthy subjects were randomized in a double-blind, crossover fashion to each of the following four treatments: saxagliptin 10 mg, saxagliptin 40 mg (8-fold higher than the proposed 5 mg maximum recommended dose), placebo, and moxifloxacin 400 mg (positive control). Moxifloxacin was given as a single dose whereas the other treatments were given once daily for 4 days. Per the QT Interdisciplinary Review Team, the upper limits of the two-sided 90% confidence intervals for the mean QT difference between saxagliptin and placebo were below 10 msec, the threshold for regulatory concern as described in the International Conference on Harmonisation (ICH) E14 guideline. Please see Dr. Christine Garnett's review under the saxagliptin investigational new drug application (IND) for further details.

A new tablet color and embossing are the only differences between the phase 3 formulations and the to-be-marketed formulations. At the pre-NDA meeting, the Division agreed that there is no need for a pivotal bioequivalence study based on these minor differences.

The clinical pharmacometrics group modeled the relationship between saxagliptin exposure and absolute lymphocyte count using phase 3 monotherapy study CV181011 and population pharmacokinetic data. The reviewers concluded that the decrease in absolute lymphocyte count is linear to the increase of the total active moiety exposures within the tested daily saxagliptin dose range of 2.5-10 mg. The mean reduction in lymphocyte count with 5 mg and 10 mg was 4% at 24 weeks. Please see the safety section of this memorandum for further details.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

This section will focus on the efficacy results from the controlled, phase 2/3 clinical trials, which consists of one 12-week phase 2 dose-ranging study and six 24-week phase 3 clinical trials. Please see Dr. Naomi Lowy's clinical review for further details.

The NDA includes a 12-week trial (CV181041) evaluating saxagliptin 5 mg vs. placebo on measures of beta-cell function in treatment-naïve patients with type 2 diabetes. This trial did not have primary or secondary traditional efficacy endpoints (e.g. HbA1c) and only 36 patients were randomized. Therefore, this trial will not be discussed in this memorandum even though the sponsor classified it as a phase 3 study.

The phase 2 dose-ranging study (CV181008) compared the efficacy and safety of saxagliptin 2.5 mg, 5 mg, 10 mg, 20 mg, and 40 mg once daily to placebo in patients with inadequate glycemic control on diet and exercise. The protocol was amended 6 months into the trial to allow for randomization of additional patients to a 100 mg dose group of saxagliptin vs. a second placebo group for 6 weeks.

The phase 2/3 clinical trials included in the original NDA were randomized, multinational, double-blind, and either placebo- or active-controlled. The phase 3 trials had a 1-4-week placebo run-in period prior to randomization. Saxagliptin was to be taken prior to the morning meal except for one of the treatment arms in monotherapy study CV181038 (see below), which also evaluated the effect of dosing saxagliptin prior to the evening meal.

The 24-week phase 3 clinical trials evaluated saxagliptin in the following settings:

CV181011 and CV181038: Monotherapy trials in treatment-naïve patients

- Patients were to have ≤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.

- Study -011 compared saxagliptin 2.5 mg, 5 mg, and 10 mg vs. placebo. This study also included an open-label, non-randomized cohort with screening HbA1c >10% to 12% who were treated with saxagliptin 10 mg daily. This uncontrolled cohort will not be extensively reviewed in this memorandum.
- Study -038 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 compared 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.

CV181013: Add-on to thiazolidinedione

- Patients were to be taking rosiglitazone ≥4 mg/day or pioglitazone ≥30 mg/day monotherapy for ≥12 weeks prior to screening.
- This trial compared add-on saxagliptin 2.5 mg and 5 mg vs. add-on placebo.

CV181014: Add-on to metformin

- Patients were to be taking stable metformin monotherapy (1,500-2,550 mg) for ≥8 weeks prior to screening.
- This trial compared add-on saxagliptin 2.5 mg, 5 mg, and 10 mg vs. add-on placebo.

CV181040: Add-on to sulfonylurea

- Patients were to be taking a submaximal dose (less than the maximum approved dose) of sulfonylurea monotherapy for ≥2 months prior to screening.
- After the 4-week run-in period, patients discontinued their current sulfonylurea therapy and started open-label glyburide 7.5 mg daily.
- This trial compared add-on saxagliptin 2.5 mg and 5 mg vs. add-on placebo + uptitrated glyburide. The add-on placebo + uptitrated glyburide treatment arm received placebo plus 2.5 mg of blinded glyburide as add-on to the 7.5 mg background dose of open-label glyburide. In this treatment arm, the blinded glyburide dose was uptitrated to a maximum dose of 7.5 mg (total daily glyburide dose of 15 mg) at Weeks 2 and 4 based on prespecified criteria for fasting plasma or whole blood glucose.

CV181039: Initial combination with metformin

- Patients were to have ≤3 consecutive days and <7 non-consecutive days of anti-diabetic therapy within the 8 weeks prior to screening, and <1 month total of prior anti-diabetic therapy.
- This trial compared saxagliptin 10 mg + metformin, saxagliptin 10 mg + placebo, metformin + placebo, and saxagliptin 5 mg + metformin.
- 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.
- This trial did not include a saxagliptin 5 mg + placebo treatment arm, limiting the ability to assess the contribution of saxagliptin 5 mg to the saxagliptin 5 mg + metformin arm.

These clinical trials had similar inclusion and exclusion criteria. Entry criteria included age between 18-77 years and type 2 diabetes with baseline HbA1c 7-10% (7.5-10% for the add-on to sulfonylurea trial; 7-10.5% for the add-on to thiazolidinedione trial; 8-12% for the initial combination with metformin trial). Exclusion criteria included elevated serum creatinine (≥1.5 mg/dL for men and ≥1.4 mg/dL for women in the monotherapy trials and in the trials that used metformin as background or randomized therapy; ≥2.0 mg/dL for the add-on to sulfonylurea and add-on to thiazolidinedione trials) and history of significant cardiovascular history, such as myocardial infarction, coronary intervention, or cerebrovascular accident within the 6 months prior to study entry. These trials also excluded patients with a history of New York Heart Association Class III or IV heart failure or known left ventricular ejection fraction ≤40%.

The primary efficacy timepoint was 24 weeks for all phase 3 trials. The sponsor labeled the 24-week period of each trial as the "short-term" phase. Each phase 3 trial had a "long-term" phase of at least 12 months duration that followed the short-term phase. Patients continued receiving double-blind study medication during the long-term phase. Patients were eligible to enter the long-term phase upon completion of the 24-week short-term phase or upon early discontinuation from the short-term phase because of the need for glycemic rescue therapy.

Three of the phase 3 trials had treatment regimens in the long-term phase that differed from the treatments in the corresponding short-term phase:

- In monotherapy studies -011 and -038, the placebo arm in the short-term phase was re-assigned to placebo + blinded metformin 500 mg daily in the long-term phase
- In monotherapy study -038, all saxagliptin groups could be titrated to 10 mg according to prespecified HbA1c criteria in the long-term phase
- In the add-on to sulfonylurea trial, glyburide in the placebo + uptitrated glyburide arm could be titrated to 20 mg (vs. titration to 15 mg in the short-term phase)

All short-term treatment periods were completed at the time of NDA submission whereas interim data were presented for the long-term treatment periods. Ms. Joy Mele, the biostatistics reviewer, focused the efficacy evaluation on the data from the short-term phase only. I agree with this approach because the efficacy data from the long-term phase are confounded by glycemic rescue therapy, are based on only a subset of randomized patients (79-90%) entering the long-term phase, and are limited by smaller sample sizes at the time of the long-term efficacy assessments (24-72% of patients discontinued from the combined short-term and long-term phases as of the 120-day safety update).

As shown in Tables 5.4 and 5.5 in Dr. Lowy's review, glycemic rescue criteria were similar, but not identical, across the phase 3 trials. For the 24-week short-term phase, progressively more stringent cutpoints for fasting plasma or whole blood glucose were used to prompt initiation of glycemic rescue therapy. In the long-term phase, progressively more stringent cutpoints for HbA1c were used to prompt initiation of glycemic rescue therapy, permitting HbA1c measurements as high as 8.0% early during the long-term phase but only allowing HbA1c as high as 7.0% towards the latter part of the long-term phase. The open-label rescue therapy was metformin for all phase 3 trials (initiated at 500 mg and titratable to 2,000 or 2,500 mg) except for the add-on to metformin trial and the initial combination with metformin trial, which used pioglitazone as rescue (initiated at 15 mg and titratable to 30 or 45 mg).

The objective of all phase 3 trials was to show superiority of saxagliptin over control on the primary efficacy endpoint of change from baseline to Week 24 in HbA1c. Other efficacy endpoints included change from baseline in fasting plasma glucose (FPG), HbA1c responder analyses, change from baseline in AUC from 0-180 minutes for post-prandial glucose response to an oral glucose tolerance test, and the proportion of patients requiring glycemic rescue, failing to achieve pre-specified glycemic targets, or discontinuing for lack of efficacy. The AUC endpoint for post-prandial glucose is not readily interpretable to clinicians. The remaining endpoints are typical for trials designed to support approvability of anti-diabetic medications.

As discussed by Ms. Mele the primary statistical population for each trial consisted of all randomized patients with a baseline and at least one post-baseline assessment of the parameter of interest. The last-observation-carried-forward (LOCF) method was used for patients with missing data and for patients who initiated glycemic rescue therapy. The primary efficacy analysis was conducted using analysis of covariance (ANCOVA) with baseline HbA1c as a covariate.

As noted by Dr. Lowy, the Russian government suspended the export of biological samples for several weeks, requiring the sponsor to use an emergency central laboratory in Moscow for all Russian sites involved in the conduct of monotherapy study -038 and the initial combination with metformin trial. This government suspension affected samples for HbA1c and glucose, which were to be immediately frozen, shipped on dry ice to the Moscow laboratory, and stored at -70 degrees Celcius until the embargo was lifted, at which point the samples were shipped on dry ice to the central laboratory. Based on stability testing performed by the sponsor and other data published in peer-reviewed literature, the sponsor concluded that the freezing, storage, and thawing of these samples would not impact the reliability of the measured HbA1c and glucose. Approximately 30% of patients in monotherapy study -038 and 22% of patients in the initial combination with metformin trial had at least one frozen HbA1c sample. However, using the frozen samples in the calculation of the primary efficacy endpoint yielded virtually identical results to a sensitivity analysis that treated frozen samples as missing. Therefore, the frozen samples are included in the efficacy analyses summarized in this memorandum.

Demographics: Dr. Lowy and Ms. Mele discuss the patient demographics in detail. Briefly, the mean age across the six phase 3 trials was approximately 55 years. Most patients (82-89%) were <65 years old. Men and women were generally equally represented, although monotherapy study -038 and the add-on to sulfonylurea trials had a slight (55%) female predominance. Most patients were Caucasian (55%-85%) with blacks comprising 2-7% of the randomized patients. Asian representation was reasonable in four of the phase 3 trials (monotherapy -038, add-on to thiazolidinedione, add-on to sulfonylurea, initial combination with metformin), ranging from 16-35% of randomized patients but Asians accounted for only 3-5% in the remaining two trials. As expected, mean duration of diagnosed diabetes was shortest in the three trials enrolling treatment-naïve patients (2-3 years) and longest for the three add-on combination therapy trials (5-7 years). Mean body mass index ranged from 29.0-

31.7 kg/m^2. Mean baseline HbA1c was 7.9-8.4% across all trials except for the initial combination with metformin trial, which had a mean baseline HbA1c of 9.5%.

Efficacy Results:

HbA1c: Table 2, adapted from Dr. Mele's statistical review and the sponsor's integrated summary of efficacy, shows the primary efficacy results using the intent-to-treat population with the LOCF method. In the 12-week phase 2 trial, the mean reduction in HbA1c was approximately 0.5% with saxagliptin doses ranging from 2.5 mg to 40 mg relative to placebo. There was no convincing evidence of additional lowering of HbA1c with 10 mg beyond that achieved with 5 mg in the four phase 2/3 trials that included both treatment arms. The ability of 5 mg to provide additional HbA1c lowering beyond that achieved with the 2.5 mg dose is questionable, except in the add-on to thiazolidinedione trial (adjusted mean reduction in HbA1c of -0.4% with 2.5 mg and -0.6% with 5 mg) and, perhaps, the add-on to sulfonylurea trial (adjusted mean reduction in HbA1c of -0.6% with 2.5 mg and -0.7% with 5 mg). Ms. Mele has concluded that none of the phase 3 trials show a dose response, but states that the sponsor has adequately shown saxagliptin to be effective at lowering HbA1c with consistent results using sensitivity analyses.

In the add-on to sulfonylurea trial, the placebo + uptitrated glyburide treatment arm had a 0.1% mean increase in HbA1c from baseline even though 94% of patients were blindly uptitrated to a total daily glyburide dose of 15 mg during the first few weeks of the trial. Therefore, an increase in the baseline glyburide dose from 7.5 mg to 15 mg in most patients did not result in an overall reduction from baseline in HbA1c. Of note, patients were eligible to participate in this trial if there was inadequate glycemic control on submaximal doses of sulfonylurea monotherapy. Although the sponsor did not provide the doses of prior sulfonylurea use, the most likely explanation for the lack of additional HbA1c lowering with uptitration of glyburide is that patients were already sulfonylurea-failures at study start.

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 and approximately 0.8% greater than the reduction with saxagliptin alone. The mean reduction from baseline in HbA1c with metformin alone was approximately 0.3% greater than the mean reduction with saxagliptin alone.

Using the data in Study -038, Ms. 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.

Ms. Mele notes that patients in Study -038 who were titrated from 2.5 mg to 5 mg had an additional 0.2% mean reduction in HbA1c (p=0.07) suggesting that 5 mg may provide additional efficacy for some patients who do not adequately respond to the 2.5 mg dose.

Table 2. HbA1c (%) results for the phase 2 and 3 clinical trials (intent-to-treat population)

Study	N	Baseline mean ± SE[1]	Change from baseline Adj. mean ± SE[2]	Difference in adjusted mean change 95% CI	p-value
Study CV181008 (dose-ranging) – 12-weeks for cohort 1; 6 weeks for cohort 2					
Saxa 2.5 mg (cohort 1)	55	7.6±0.8	-0.7±0.1	-0.5 (-0.8, -0.1)	<0.01
Saxa 5 mg (cohort 1)	47	8.1±1.1	-0.9±0.1	-0.6 (-1.0, -0.3)	<0.001
Saxa 10 mg (cohort 1)	63	7.8±1.0	-0.8±0.1	-0.5 (-0.9, -0.2)	<0.001
Saxa 20 mg (cohort 1)	54	7.9±1.0	-0.7±0.1	-0.5 (-0.8, -0.1)	<0.01
Saxa 40 mg (cohort 1)	52	7.8±1.0	-0.8±0.1	-0.5 (-0.9, -0.2)	<0.01
Placebo (cohort 1)	67	7.9±1.0	-0.3±0.1		
Saxa 100 mg (cohort 2)	44	7.8±1.0	-1.1±0.1	-0.7 (-1.0,-0.5)	Not provided
Placebo (cohort 2)	41	7.6±1.1	-0.4±0.1		
Study CV181011 (monotherapy)					
Saxa 2.5 mg	100	7.9±0.9	-0.4±1.0	-0.6 (-0.9, -0.3)	<0.0001
Saxa 5 mg	103	8.0±1.1	-0.5±1.0	-0.6 (-0.9, -0.4)	<0.0001
Saxa 10 mg	95	7.8±0.9	-0.5±0.8	-0.7 (-1.0, -0.4)	<0.0001
Placebo	92	7.9±0.9	0.2±1.2		
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
axa 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 CV181013 (add-on to thiazolidinedione)					
Saxa 2.5 mg	192	8.2±0.1	-0.7±0.1	-0.4 (-0.6, -0.2)	<0.001
Saxa 5 mg	183	8.4±0.1	-0.9±0.1	-0.6 (-0.8, -0.4)	<0.001
Placebo	180	8.2±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		
Study CV181040 (add-on to sulfonylurea)					
Saxa 2.5 mg	246	8.4±0.1	-0.5±0.1	-0.6 (-0.8, -0.5)	<0.001
Saxa 5 mg	250	8.5±0.1	-0.7±0.1	-0.7 (-0.9, -0.6)	<0.001
Placebo + glyburide	264	8.4±0.1	+0.1±0.1		
Study CV181039 (initial combination with metformin)					
Saxa 5 mg + met	306	9.4±0.1	-2.5±0.1	-	-
Saxa 10 mg + met	315	9.5±0.1	-2.5±0.1	-	-
Saxa 10 mg	317	9.6±0.1	-1.7±0.1	-	-
Met	313	9.4±0.1	-2.0±0.1	-	-

[1]±SD for -008 and -011; [2]±SD for -011; SE=standard error; CI=confidence interval

Fasting plasma glucose: Saxagliptin 5 mg was marginally more efficacious than 2.5 mg on fasting plasma glucose in the add-on to metformin trial (adjusted mean difference ~7 mg/dL) (Table 3). Differences between 2.5 mg and 5 mg on fasting plasma glucose are more questionable in the add-on to thiazolidinedione trial (adjusted mean difference ~3 mg/dL) and in the add-on to sulfonylurea trial (adjusted mean difference ~2 mg/dL). The 2.5 mg and 5 mg doses have comparable efficacy on fasting plasma glucose in the two monotherapy trials.

Table 3. Fasting plasma glucose (mg/dL) in the phase 3 clinical trials (intent-to-treat population)

Study	N	Baseline mean ± SE	Change from baseline Adj. mean ± SE	Difference in adjusted mean change ± SE	p-value
Study CV181011 (monotherapy)					
Saxa 2.5 mg	101	178±4	-15±4	-21 (-32, -10)	<0.001
Saxa 5 mg	105	171±4	-9±4	-15 (-26, -4)	<0.01
Saxa 10 mg	97	177±4	-17±4	-23 (-34, -12)	<0.0001
Placebo	92	172±5	6±4		
Study CV181038 (monotherapy)					
Saxa 2.5 mg (AM)	70	157±4	-11±5	-15 (-27, -2)	0.02
Saxa 2.5 mg→5 mg (AM)	71	171±6	-13±5	-16 (-28, -3)	0.01
Saxa 5 mg (AM)	71	162±4	-11±5	-14 (-26, -2)	0.03
Saxa 5 mg (PM)	71	160±5	-8±4	-11 (-23, 1)	0.08
Placebo	71	159±5	3±4		
Study CV181013 (add-on to thiazolidinedione)					
Saxa 2.5 mg	193	163±4	-14±3	-12 (-20, -3)	0.005
Saxa 5 mg	185	160±3	-17±3	-15 (-23, -6)	<0.001
Placebo	181	162±3	-3±3		
Study CV181014 (add-on to metformin)					
Saxa 2.5 mg	188	174±3	-14±2	-16 (-23, -9)	<0.0001
Saxa 5 mg	187	179±3	-22±2	-23 (-30, -16)	<0.0001
Saxa 10 mg	181	176±4	-21±3	-22 (-29, -15)	<0.0001
Placebo	176	175±3	1±3		
Study CV181040 (add-on to sulfonylurea)					
Saxa 2.5 mg	247	170±3	-7±2	-8 (-14, -1)	0.02
Saxa 5 mg	252	175±3	-10±2	-10 (-17, -4)	0.002
Placebo + glyburide	265	174±3	1±2		
Study CV181039 (initial combination with metformin)					
Saxa 5 mg + met	315	199±3	-60±2	-	-
Saxa 10 mg + met	317	204±3	-62±2	-	-
Saxa 10 mg	327	201±3	-31±2	-	-
Met	320	199±3	-47±2	-	-

SE=standard error; CI=confidence interval

HbA1c responder analyses and glycemic rescue: Table 4 summarizes the proportion of patients achieving HbA1c <7% and the proportion of patients requiring glycemic rescue in the phase 3 trials.

Differences between 2.5 mg and 5 mg on the proportion of patients achieving HbA1c <7% were greatest for monotherapy study -038 (~9 percentage points higher with 5 mg) and in the add-on to metformin trial (~7 percentage points higher with 5 mg). However, differences were more questionable in the other monotherapy trial (~3 percentage points higher with 5 mg) and there were no differences in the add-on to thiazolidinedione and the add-on to sulfonylurea trials.

In monotherapy study -011, approximately 20% of patients on saxagliptin 5 mg required glycemic rescue compared to 14% of patients on saxagliptin 2.5 mg. However, for the other four trials that included 2.5 mg and 5 mg treatment arms, there were no differences in glycemic rescue rates for these two doses. Ms. Mele notes that there is no dose response regarding rescue.

Placebo-treated patients had higher glycemic rescue rates compared to saxagliptin-treated patients in monotherapy study -011, in the add-on to metformin trial, and in the add-on to sulfonylurea trial, but the saxagliptin and placebo treatment groups had comparable glycemic rescue rates in monotherapy study -038 and the add-on to thiazolidinedione trial. Ms. Mele notes that glycemic rescue rates or discontinuation rates were approximately twice as high in the sites within the United States (U.S.) compared to foreign sites. For example, in monotherapy study -011, approximately 28% of patients from U.S. sites were rescued compared to 12% of patients from non-U.S. sites. Ms. Mele notes that this difference in glycemic rescue rates is likely attributable to differences in baseline characteristics (e.g., higher baseline FPG values in the United States) and not to inadequate application of the glycemic rescue criteria at the foreign sites. Ms. Mele included a term in the HbA1c ANCOVA model for U.S. vs. non-U.S. sites but this modification did not alter the sponsor's conclusions, which were based on a model without such a term.

The glycemic rescue rate with saxagliptin alone in the initial combination with metformin trial (baseline HbA1c ~9.5%) is comparable to the glycemic rescue rate with saxagliptin in the add-on to sulfonylurea trial (baseline HbA1c ~8.4%) and approximately 1.5 to 2-fold higher than the glycemic rescue rate with saxagliptin in the other phase 3 trials (baseline HbA1c 7.9-8.3%).

Subgroup analyses for HbA1c: Ms. Mele conducted subgroup analyses for the proposed 5 mg dose of saxagliptin vs. placebo using monotherapy study -011, the add-on to metformin trial, and the initial combination with metformin trial. Ms. Mele notes a statistically significant interaction between HbA1c and gender in Study -011 ($p=0.01$) with a larger effect seen in men, but did not observe this subgroup effect in the two other studies. Consistent effects on HbA1c were seen by age subgroup (<65 vs. ≥65 years old) with interaction p-values all greater than 0.80 and by body mass index with interaction p-values all greater than 0.20. There was a significant interaction in Study -011 ($p=0.07$) and Study -039 ($p=0.008$) between HbA1c and race (Caucasian vs. Asian vs. all others). In these two studies, there appears to be a larger treatment effect in Asians, prompting Ms. Mele to question whether saxagliptin could have a different safety profile in Asians.

Table 4. Proportion of patients achieving glycemic targets or requiring glycemic rescue		
	Proportion of patients achieving HbA1c <7%	**Proportion of patients requiring glycemic rescue**
Study CV181011 (monotherapy)		
Saxa 2.5 mg	(35%)	(14%)
Saxa 5 mg	(38%)	(20%)
Saxa 10 mg	(41%)	(14%)
Placebo	(24%)	(26%)
Study CV181038 (monotherapy)		
Saxa 2.5 mg (AM)	(36%)	(11%)
Saxa 2.5 mg→5 mg (AM)	(44%)	(13%)
Saxa 5 mg (AM)	(45%)	(14%)
Saxa 5 mg (PM)	(39%)	(11%)
Placebo	(35%)	(15%)
Study CV181013 (add-on to thiazolidinedione)		
Saxa 2.5 mg	(42%)	(9%)
Saxa 5 mg	(42%)	(7%)
Placebo	(26%)	(8%)
Study CV181014 (add-on to metformin)		
Saxa 2.5 mg	(37%)	(13%)
Saxa 5 mg	(44%)	(12%)
Saxa 10 mg	(44%)	(14%)
Placebo	(17%)	(25%)
Study CV181040 (add-on to sulfonylurea)		
Saxa 2.5 mg	(22%)	(17%)
Saxa 5 mg	(23%)	(16%)
Placebo	(9%)	(29%)
Study CV181039 (initial combination with metformin)		
Saxa 5 mg + met	(60%)	(7%)
Saxa 10 mg + met	(60%)	(6%)
Saxa 10 mg	(32%)	(21%)
Met	(41%)	(8%)

b(4)

8. Safety

The safety dataset consists of all randomized patients who received at least one dose of study medication. The study reports for the individual phase 2/3 trials used different versions of MedDRA (7-10.1). The integrated summary of safety submitted with the NDA used MedDRA version 10.1 and the 120-day safety update used MedDRA version 11.0. A hands-on review comparing MedDRA preferred terms affected by the switch to versions 10.1 and 11.0 did not raise any concerns about miscoding.

Table 5 summarizes patient exposures in the saxagliptin development program at the time of NDA submission and in the 120-day safety update. These sample sizes meet or exceed the exposures recommended in the February 2008 draft guidance for industry *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention.*

Table 5. Patient exposures to saxagliptin

	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg	All Saxa	Control
At NDA filing					
≥24 weeks	773	1038	831	2642	942
≥52 weeks	417	399	264	1080	360
≥100 weeks	108	108	141	357	80
At 120-day safety update					
≥24 weeks	773	1059	842	2683	956
≥52 weeks	622	772	543	1937	689
≥100 weeks	150	155	182	487	112
Patient-years (phase 2/3 trials[1])	1149	1462	1194	3833	1293
Patient-years (phase 3 trials[2])	1136	1439	1105	3680	1263

[1]Includes 12 patient-years (PY) for saxa 20 mg, 12 PY for saxa 40 mg, and 5 PY for saxa 100 mg
[2]Includes the monotherapy trials, add-on combination trials, and the initial combination with metformin trial

Based on the Cockcroft-Gault formula, approximately 550 patients with renal impairment (estimated creatinine clearance ≤80 mL/min) – mostly of mild severity - were randomized into the short-term periods of the six core phase 3 trials. A dedicated renal safety trial in patients with moderate, severe, and end-stage renal disease is ongoing.

Patient disposition: Table 6 summarizes patient disposition for the short-term periods of the phase 3 trials (the long-term periods are ongoing). Approximately 75% of saxagliptin-treated patients and 67% of placebo-treated patients completed the short-term periods of the pooled phase 3 monotherapy and add-on combination therapy trials. The higher discontinuation rate with placebo was driven by a higher proportion of placebo-treated patients with lack of efficacy. Withdrawal due to adverse events was approximately two-fold higher with saxagliptin 5 mg and 10 mg compared to saxagliptin 2.5 mg and placebo.

Completion rates in the initial combination with metformin trial were highest for the combination treatment arms (approximately 80%), intermediate with metformin monotherapy (74%), and lowest with saxagliptin 10 mg monotherapy (67%). The higher discontinuation rates in the monotherapy treatment arms in this trial were predominantly driven by a higher proportion of these patients with lack of efficacy. Discontinuations due to adverse events in this trial were numerically lower in the saxagliptin-containing regimens (2.2-2.4%) compared to the metformin alone treatment arm (3.4%).

Approximately 85% of patients who were randomized in the short-term periods continued into the long-term periods.

setting of a car accident, a wrist fracture occurred in the setting of a fall, and the setting for a lower limb fracture was not described. Excluding the three reports of fracture associated with car accidents and one fracture that had occurred prior to the first dose of saxagliptin (this fracture was captured due to the subsequent removal of a prosthetic device used to treat the fracture), the incidence of remaining fractures reported as a serious adverse event was 0.2% in the saxagliptin group and 0.1% in the placebo group. Fractures are discussed further in the common adverse event section of this memorandum.

In the pooled dataset, there were 12 saxagliptin-treated patients (0.6%) with a serious adverse event of cholecystitis (coded as cholecystitis or cholecystitis acute) compared to 1 report in a placebo-treated patient (0.1%). In the initial combination with metformin trial, there was 1 additional report of cholecystitis, occurring in the metformin only treatment arm. When all these data are pooled, the incidence of cholecystitis as a serious event was 0.4% in the saxagliptin group and 0.2% in the comparator group. Data are even more reassuring when the overall incidence of serious and non-serious cholecystitis is computed: 0.4% with saxagliptin and 0.5% with comparator.

Table 7. Serious adverse events occurring in the short-term and long-term periods of the pooled phase 3 monotherapy and add-on combination therapy trials (up to cutoff date for 120-day safety update)*

System Organ Class Preferred term	Saxa 2.5 mg N=882 n (%)	Saxa 5 mg N=882 n (%)	Saxa 10 mg N=279 n (%)	All Saxa N=2043 n (%)	Placebo N=799 n (%)
Patients with ≥1 serious adverse event	77 (8.7)	78 (8.8)	29 (10.4)	184 (9.0)	69 (8
Cardiac Disorders	12 (1.4)	14 (1.6)	6 (2.2)	32 (1.6)	19 (2
Atrial fibrillation	1 (0.1)	3 (0.3)	0	4 (0.2)	0
Injury, Poisoning & Procedural Comps	10 (1.1)	12 (1.4)	1 (0.4)	23 (1.1)	2 (0.3)
Overdose	2 (0.2)	3 (0.3)	0	5 (0.2)	0
Infections and Infestations	18 (2.0)	10 (1.1)	5 (1.8)	33 (1.6)	10 (1.3)
Gastroenteritis	3 (0.3)	1 (0.1)	0	4 (0.2)	0
Nervous System Disorders	5 (0.6)	10 (1.1)	2 (0.7)	17 (0.8)	7 (0.9)
Cerebrovascular accident	2 (0.2)	2 (0.2)	2 (0.7)	6 (0.3)	1 (0.1)
Hepatobiliary Disorders	5 (0.6)	6 (0.7)	3 (1.1)	14 (0.7)	4 (0.5)
Cholecystitis acute/cholecystitis	5 (0.6)	5 (0.6)	2 (0.7)	12 (0.6)	1 (0.1)

*Table shows preferred terms reported in >2 patients in the all saxagliptin group, and occurring >0.1% more frequently in the all saxagliptin group compared to the placebo group

Withdrawals due to adverse events: Because withdrawals due to adverse events were also relatively infrequent, combined short-term and long-term data from the phase 3 monotherapy and add-on combination therapy trials were pooled to increase the likelihood of detecting important differences between treatment groups. Table 8 summarizes these data up to the cutoff date for the 120-day safety update.

Only alanine aminotransferase, blood creatinine increased, and lymphopenia were reported as adverse events leading to discontinuation in more than 2 saxagliptin-treated patients and >0.1% more frequently with saxagliptin compared to placebo. However, the incidence of each

of these events leading to discontinuation was low (0.3-0.5% in the saxagliptin group) and reported only 0.2% more frequently with saxagliptin than with placebo.

All 7 (0.3%) saxagliptin-treated patients who discontinued due to alanine aminotransferase (ALT) increased or liver function test abnormal had elevated pre-treatment ALT (up to 3x ULN). Peak ALT ranged from approximately 4x to 6x ULN. Time to peak ALT ranged from approximately Week 4 to Week 19. ALT improved in six patients after discontinuation of saxagliptin but did not necessarily reach baseline values. Several patients had fatty liver on ultrasound but no other etiology for the transaminitis was noted. None of the patients were reported to have elevated bilirubin. Please see the laboratory section of this memorandum for further discussion of liver test abnormalities.

Eleven (0.5%) saxagliptin-treated patients in the pooled dataset were discontinued due to blood creatinine increased. The narratives for 5 of these 11 patients state that the patients were no longer eligible to receive metformin, either as background therapy or as rescue therapy. Four of these 5 patients had an increase in serum creatinine of ≤0.3 mg/dL and the fifth patient had an increase of 0.4 mg/dL (although one day after study drug discontinuation, the serum creatinine for this fifth patient was only 0.1 mg/dL above the baseline value). Four of the remaining six patients were also receiving metformin but the narratives do not explicitly state that the use of metformin was the basis for discontinuing study medication. For these six other patients, four had an increase in serum creatinine of ≤0.5 mg/dL, one had an increase of 0.6 mg/dL, and the remaining patient had an increase of 0.9 mg/dL. Only one of the 11 patients had a known potential contributing factor for the increased serum creatinine (increasing captopril dose for treating hypertension) but information on all cases is limited. Additional information on renal safety will be forthcoming from the ongoing clinical trial involving patients with moderate and severe renal impairment. Please see the laboratory section of this memorandum for further discussion of the serum creatinine data.

Select narratives for other patients who prematurely discontinued are summarized below:

- The patient with pulmonary tuberculosis was diagnosed on Day 284. His lymphocyte counts were well within the reference range throughout the study.

- The patient with extremity necrosis had a history of left lower extremity amputation. She developed an infected right lower extremity ulcer on Day 421 and was found to have arterial obstruction in the leg. The patient underwent revascularization with a bypass graft that failed, requiring suprapatellar amputation.

- There were 2 saxagliptin-treated patients who discontinued due to thrombocytopenia. The first patient had a platelet count higher than the baseline value on the day study medication was discontinued. The second patient had persistent thrombocytopenia months after study medication was discontinued.

- There were 2 saxagliptin-treated patients discontinued due to reductions in neutrophil counts. One patient is coded as having neutropenia but the neutrophil nadir was 1,140 c/mcL, which does not meet the definition of neutropenia (absolute neutrophil count <500

c/mcL). The second patient was coded as having hematology test abnormal, but more specifically, had a reduction in neutrophils. The patient had a low neutrophil count at baseline that nadired at 810 c/mcL on Day 161. The patient's last dose of study medication was on Day 160. The neutrophil count subsequently improved but was still below the lower limit of the reference range approximately 3 months after the last dose of study medication.

- Adverse events related to pancreatitis and lymphopenia are discussed in later sections of this memorandum.

Table 8. Discontinuations due to adverse events in the short-term and long-term periods of the pooled phase 3 monotherapy and add-on combination trials (up to cutoff date for 120-day safety update)*

System Organ Class Preferred term	Saxa 2.5 mg N=882 n (%)	Saxa 5 mg N=882 n (%)	Saxa 10 mg N=279 n (%)	All Saxa N=2043 n (%)	Placebo N=799 n (%)
Patients discontinuing due to adverse event	50 (5.7)	59 (6.7)	19 (6.8)	128 (6.3)	37 (4.6)
Investigations	13 (1.5)	15 (1.7)	4 (1.4)	32 (1.6)	8 (1.0)
ALT increased/liver function test abnormal	3 (0.3)	3 (0.3)	0	7 (0.3)	1 (0.1)
Blood creatinine increased	7 (0.8)	2 (0.2)	2 (0.7)	11 (0.5)	2 (0.3)
Blood and Lymphatic System Disorders	3 (0.3)	8 (0.9)	3 (1.1)	14 (0.7)	1 (0.1)
Lymphopenia/lymphocyte count decreased	2 (0.2)	4 (0.5)	1 (0.4)	8 (0.4)	1 (0.1)
Potentially important events leading to withdrawal and occurring less frequently than above					
Thrombocytopenia	0	1 (0.1)	1 (0.4)	2 (<0.1)	0
Pancreatitis acute/pancreatitis	0	1 (0.1)	1 (0.4)	2 (<0.1)	0
Hematology test abnormal	0	1 (0.1)	0	1 (<0.1)	0
Neutropenia	0	1 (0.1)	0	1 (<0.1)	0
Pulmonary tuberculosis	1 (0.1)	0	0	1 (<0.1)	0
Extremity necrosis	0	1 (0.1)	0	1 (<0.1)	0

*Upper portion of table shows events occurring in >2 patients in the all saxagliptin group and occurring >0.1% more frequently in the all saxagliptin group compared to the placebo group

In the initial combination with metformin trial, 36 saxagliptin-treated patients (3.7%) and 13 metformin-treated patients (4.0%) discontinued due to adverse events. Potential events of interest include blood creatinine increased (5 cases or 0.5% with saxagliptin vs. 0 cases with metformin) and preferred terms related to liver test abnormalities (alanine aminotransferase increased, hepatic enzyme increased, hepatic function abnormal or transaminitis) reported in 7 (0.7%) saxagliptin-treated patients and 3 (0.9%) metformin-treated patients.

With regard to the 5 saxagliptin-treated patients who were discontinued for blood creatinine increased, four had an increase in serum creatinine of only 0.2 mg/dL and the remaining patient had a serum creatinine that normalized 1 day after the last dose of study medication.

The most striking narrative regarding discontinuations due to liver test abnormalities involves a patient who was randomized to the saxagliptin 10 mg monotherapy arm. Baseline liver tests were normal. Liver tests were also normal on Day 260 but on Day 269, ALT increased to 474

U/L (13x ULN), alkaline phosphatase increased to 293 U/L (2.9x ULN), and total bilirubin peaked at 2 mg/dL (upper limit of normal, 1.2). The patient was reportedly asymptomatic. The patient reported an adverse event of urinary tract infection on Day 269. Concomitant medications included felodipine (started on Day -35) and pioglitazone rescue therapy (started on Day 269). Study medication was interrupted on Day 273 and the patient was discontinued from the study on Day 288. Liver tests normalized after study drug discontinuation. This patient does not meet Hy's Law based on total bilirubin (value is <2x ULN) and alkaline phosphatase (value is >2x ULN).

Common adverse events: Table 9 summarizes the common adverse events (incidence ≥3% in the all saxagliptin group) and occurring more frequently (≥0.5%) with saxagliptin compared to placebo during the short-term periods of the phase 3 trials. This analysis focuses on individual 24-week phase 3 trials (except for pooling of the two phase 3 monotherapy trials) and excludes data after rescue therapy to limit confounding. Headache, upper respiratory tract infection and arthralgia are the only adverse events showing some consistency, meeting the above criteria in three or four of the five phase 3 settings shown in Table 9. However, there is no evidence of a consistent dose response relationship for these three adverse events.

In the combined short-term and long-term periods of the pooled phase 3 trials including the initial combination with metformin trial but excluding the small mechanism-of-action trial (120-day safety update database), the overall incidence of depression-related events was 1.5 per 100 patient-years for saxagliptin and 1.4 per 100 patient-years for comparator. In this database, the incidence of anxiety was 1.3 per 100 patient-years for saxagliptin and 1.0 per 100 patient-years for comparator.

In the add-on to thiazolidinedione trial, peripheral edema occurred more frequently with saxagliptin 5 mg (8.1%) compared to saxagliptin 2.5 mg (3.1%) and placebo (4.3%). This trial did not include a saxagliptin 10 mg treatment arm, which would have permitted a better assessment for dose-response. All peripheral edema events in this trial were categorized by investigators as mild or moderate and none of these events resulted in patient discontinuation from the trial. An imbalance in peripheral edema was not present in the other phase 3 trials.

The combined short-term and long-term periods of the phase 3 trials up to the cutoff date for the 120-day safety update contains 3 treatment-emergent reports of prostate cancer, all occurring with saxagliptin. This incidence is consistent with the randomization scheme and numbers are too low for meaningful conclusions. The overall incidence of events coded to the Neoplasms SOC was 0.8% with saxagliptin and 0.6% with comparator.

Table 9. Common adverse events (incidence ≥3% in the all saxagliptin group) and occurring more frequently (≥0.5%) with saxagliptin than with comparator in the short-term period (prior to rescue)

Preferred term	Saxa 2.5 mg n (%)	Saxa 5 mg n (%)	Saxa 10 mg n (%)	All Saxa n (%)	Placebo n (%)
Pooled monotherapy trials	**N=247**	**N=252**	**N=98**	**N=597**	**N=169**
≥1 event	159 (64.4)	165 (65.5)	75 (76.5)	399 (66.8)	101 (59.8)
Urinary tract infection	12 (4.9)	12 (4.8)	4 (4.1)	28 (4.7)	6 (3.6)
Sinusitis	11 (4.5)	8 (3.2)	6 (6.1)	25 (4.2)	3 (1.8)
Arthralgia	5 (2.0)	9 (3.6)	5 (5.1)	19 (3.2)	3 (1.8)
Pain in extremity	10 (4.0)	8 (3.2)	3 (3.1)	21 (3.5)	5 (3.0)
Diarrhea	11 (4.5)	5 (2.0)	6 (6.1)	22 (3.7)	4 (2.4)
Add-on to sulfonylurea trial	**N=248**	**N=253**	**-**	**N=501**	**N=267**
≥1 event	177 (71.4)	178 (70.4)	-	355 (70.9)	198 (74.2)
Back pain	12 (4.8)	15 (5.9)	-	27 (5.4)	12 (4.5)
Headache	19 (7.7)	19 (7.5)	-	38 (7.6)	15 (5.6)
Hypertension	9 (3.6)	16 (6.3)	-	25 (5.0)	6 (2.2)
Add-on to metformin	**N=192**	**N=191**	**N=181**	**N=564**	**N=179**
≥1 event	150 (78.1)	133 (69.6)	130 (71.8)	413 (73.2)	116 (64.8)
Nasopharyngitis	18 (9.4)	13 (6.8)	18 (9.9)	49 (8.7)	14 (7.8)
Headache	18 (9.4)	11 (5.8)	16 (8.8)	45 (8.0)	13 (7.3
Upper respiratory tract infection	13 (6.8)	9 (4.7)	15 (8.3)	37 (6.6)	9 (5.(
Urinary tract infection	10 (5.2)	10 (5.2)	9 (5.0)	29 (5.1)	8 (4.5)
Arthralgia	8 (4.2)	8 (4.2)	9 (5.0)	25 (4.4)	5 (2.8)
Vomiting	9 (4.7)	6 (3.1)	4 (2.2)	19 (3.4)	5 (2.8)
Add-on to thiazolidinedione	**N=195**	**N=186**	**-**	**N=381**	**N=184**
≥1 event	120 (61.5)	138 (74.2)	-	258 (67.7)	122 (66.3)
Upper respiratory tract infection	15 (7.7)	17 (9.1)	-	32 (8.4)	13 (7.1)
Sinusitis	7 (3.6)	5 (2.7)	-	12 (3.1)	1 (0.5)
Arthralgia	11 (5.6)	5 (2.7)	-	16 (4.2)	5 (2.7)
Musculoskeletal pain	5 (2.6)	7 (3.8)	-	12 (3.1)	3 (1.6)
Myalgia	8 (4.1)	4 (2.2)	-	12 (3.1)	4 (2.2)
Headache	9 (4.6)	10 (5.4)	-	19 (5.0)	7 (3.8)
Edema peripheral	6 (3.1)	15 (8.1)	-	21 (5.5)	8 (4.3)
Initial therapy with metformin	**Saxa 5 mg+met N=320**	**Saxa 10 mg+met N=323**	**Saxa 10 mg N=335**	**All Saxa N=978**	**Met N=328**
≥1 event	174 (54.4)	182 (56.3)	178 (53.1)	534 (54.6)	190 (57.9)
Nasopharyngitis	22 (6.9)	8 (2.5)	14 (4.2)	44 (4.5)	13 (4.0)
Upper respiratory tract infection	11 (3.4)	12 (3.7)	11 (3.3)	34 (3.5)	6 (1.8)
Headache	24 (7.5)	32 (9.9)	21 (6.3)	77 (7.9)	17 (5.2)
Back pain	12 (3.8)	13 (4.0)	7 (2.1)	32 (3.3)	8 (2.4)
Hypertension	15 (4.7)	17 (5.3)	15 (4.5)	47 (4.8)	11 (3.

In the combined short-term and long-term periods of the pooled phase 3 trials including the initial combination with metformin trial but excluding the small mechanism-of-action trial (120-day safety update database), the incidence of fracture is 1.1% in the saxagliptin group and 0.6% in the comparator group without evidence of a relationship to saxagliptin dose (Table 10). When corrected for patient exposure, the incidence of fracture is 1.0 per 100 patient-years for saxagliptin and 0.6 per 100 patient-years for comparator. There were 30 fractures among women (26 [0.9%] on saxagliptin vs. 4 [0.4%] on comparator) and 15 fractures among men (8 [0.3%] on saxagliptin vs. 3 [0.3%] on comparator). Nineteen (0.6%) saxagliptin patients (eight on 2.5 mg, six on 5 mg, and five on 10 mg) and 4 (0.4%) comparator patients had fractures within the first 6 months of treatment. There were an additional 8 (0.3%) saxagliptin patients and 3 (0.3%) comparator patients with fracture occurring between 6 months and 1 year of treatment and another 7 (0.2%) saxagliptin patients and no comparator patients with fracture after 1 year of treatment. Data on the non-serious fractures are limited. Three saxagliptin-treated patients and 1 comparator patient were documented to have fracture in the setting of major trauma. Another saxagliptin-treated patient had a fracture prior to the first dose of saxagliptin (this fracture was captured due to the subsequent removal of a prosthetic device used to treat the fracture). Excluding these patients, the incidence of fracture is 0.8 per 100 patient-years for saxagliptin and 0.5 per 100 patient-years for comparator. Because the fracture imbalance persists, this finding should be included in the package insert and fractures should be an adverse event of interest in the cardiovascular outcomes trial. Of note, bone changes in animal studies (bone marrow myeloid depletion and hypoplasia) were minor, not dose-dependent, and occurred at exposure multiples >35 times the clinical dose.

Table 10. Treatment-emergent bone fractures – phase 3 short-term and long-term periods combined, including rescue (monotherapy, add-on combination trials, and initial combination with metformin trial) (120-day safety update database)

	Saxa 2.5 mg N=882 n (%)	Saxa 5 mg N=1202 n (%)	Saxa 10 mg N=937 n (%)	All Saxa N=3021 n (%)	Comparator N=1127 n (%)
Patients with at least 1 fracture event	**13 (1.5)**	**11 (0.9)**	**10 (1.1)**	**34 (1.1)**	**7 (0.6)**
Patients with a typical osteoporotic fracture	**6 (0.7)**	**4 (0.3)**	**2 (0.2)**	**12 (0.4)**	**1 (0.1)**
Rib fracture	3 (0.3)	2 (0.1)	1 (0.1)	6 (0.2)	0
Spinal compression fracture	0	1 (0.1)	0	1 (<0.1)	0
Hip fracture	1 (0.1)	1 (0.1)	0	2 (0.1)	0
Radius fracture	2 (0.2)	0	1 (0.1)	3 (0.1)	1 (0.1)
Patients with other fractures	**7 (0.8)**	**7 (0.6)**	**8 (0.9)**	**22 (0.7)**	**6 (0.5)**
Facial fracture (excluding nose)	0	1 (0.1)	0	1 (<0.1)	0
Lower limb fracture (excluding hip)	4 (0.5)	4 (0.3)[2]	5 (0.5)	13 (0.4)	4 (0.4)
Upper limb fracture (excluding radius)	4 (0.5)[1]	2 (0.1)	3 (0.3)	9 (0.3)	3 (0.3)[3]

[1]One patient had two events of upper limb fracture
[2]A report of stress fracture of the tibia occurring in a saxagliptin 5 mg-treated patient is not included
[3]One patient had two events of hand fracture

Adverse events of interest:

Major adverse cardiovascular events: As discussed in Section 2, the Division has requested that sponsors of new pharmaceuticals for type 2 diabetes show that these treatments do not result in an unacceptable increase in cardiovascular risk. The 2008 guidance on this topic asks sponsors to do the following during the planning stage of their drug development programs for therapies for type 2 diabetes:

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

The guidance states that to support approvability from a cardiovascular standpoint, the sponsor should compare the incidence of major cardiovascular events with the investigational agent to the incidence of major cardiovascular events occurring with the control group and show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8 with a reassuring point estimate. If this upper bound is between 1.3 and 1.8 and the overall risk-benefit analysis supports approval then a postmarketing cardiovascular trial generally will be needed to definitively show that this upper bound is less than 1.3. If the premarketing data show that this upper bound is less than 1.3 and the overall risk-benefit analysis supports approval then a postmarketing cardiovascular trial generally may not be necessary.

Although the saxagliptin development program was completed well in advance of this guidance, the Division has requested that all pending NDAs will be held to the 1.3 and 1.8 goalposts described above. This decision affected two other NDAs (alogliptin and liraglutide) submitted to FDA prior to the publication of the guidance. To standardize the approach for assessing cardiovascular safety for all three products, the Division requested that the sponsors of these applications perform similar post-hoc analyses of cardiovascular events, as summarized below and discussed in detail in Dr. Lowy's clinical review. Of note, none of the programs had pre-specified definitions or prospective adjudication of major cardiovascular events and, because of the retrospective nature of these analyses, some events have insufficient information to definitively determine whether a cardiovascular event of interest had occurred.

The Division requested two cardiovascular endpoints. The first endpoint, termed "Broad SMQ MACE" was defined as a composite endpoint of cardiovascular death and all preferred terms in the Standardised MedDRA Queries (SMQs) for "Myocardial Infarction" and "Central Nervous System Haemorrhages and Cerebrovascular Accidents." Although some of the preferred terms in the "Broad SMQ MACE" could be consistent with cardiovascular events of interest, there may be an alternate explanation in some patients. For example, "blood creatine phosphokinase increased" is a preferred term in the Myocardial Infarction SMQ, but could be related to exercise, muscle trauma, medications, or a variety of other causes. Therefore, this

analysis will detect all patients with reported preferred terms that could be consistent with, but not necessarily diagnostic of, the condition of interest.

A second endpoint, called "Custom MACE", was also analyzed. The "Custom MACE" endpoint is a subset of "SMQ MACE" and was created as follows. Without considering which events had occurred, the 3 clinical reviewers for saxagliptin, alogliptin, and liraglutide independently reviewed the list of all preferred terms included in the "Broad SMQ MACE" endpoint with the following question in mind: "If I had a patient who actually had a myocardial infarction or a stroke, is this a Preferred Term that I might actually have chosen for such an event?" The goal was to select only those preferred terms that seemed more likely to represent events of myocardial infarction or stroke as reported by investigators.

The lists generated by the 3 clinical reviewers were compared and consensus was reached regarding inclusion or exclusion for all preferred terms. A listing of the preferred terms included in the "Broad SMQ MACE" and "Custom MACE" endpoints are shown in the January 2009 information request in the Division Files System (DFS).

The MACE analysis was conducted using eight phase 2/3 clinical trials (the phase 2 dose-ranging trial, the mechanism-of-action trial, the two phase 3 monotherapy trials, and the three add-on combination trials). The MACE analysis on the short-term period excludes data after glycemic rescue, whereas the MACE analysis on the combined short-term and long-term periods (using the 120-day safety update database) includes data after initiation of glycemic rescue therapy.

As noted by Dr. Lowy, reports of "blood creatine phosphokinase increased" represented a large proportion of the Broad SMQ MACE events (e.g., 50 of the 58 events for saxagliptin and 14 of the 25 events for comparator in the short-term period of the phase 2/3 trials). This finding is likely explained by routine measurement of creatine phosphokinase in all patients at select clinic visits. As discussed above, elevated creatine phosphokinase is non-specific; therefore, the proportion of such events that truly represent myocardial infarction is unknown (because of limited data collection) but probably low.

The saxagliptin cardiovascular results were discussed at an April 1, 2009, advisory committee meeting (see Section 9 of this memorandum for details). Table 11, adapted from Ms. Mele's review summarizes the MACE findings for both the Broad and Custom endpoints.
Event rates for Custom MACE were low (0.1-1.3%). The point estimates for the odds ratios for the MACE analyses all favor saxagliptin (<1.0) and the upper bounds of the corresponding 95% confidence intervals do not exceed 1.5 for Broad MACE and do not exceed 1.0 for Custom MACE. Therefore, all of Ms. Mele's analyses satisfy the 1.8 criterion in the diabetes cardiovascular guidance. Based on these findings, I agree with the majority of the advisory panel that these findings provide adequate evidence of cardiovascular safety to support approval. The sponsor has proposed including a statement in the label that saxagliptin . Such a statement should not be b(4)
permitted at the present time because of the limitations of the data (e.g., post-hoc, non-adjudicated nature of the analyses, low event rates, low-risk patient population) and the potential for inappropriate promotion.

For the Custom MACE analyses (but not for Broad MACE), the upper bound of the 95% confidence interval for the odds ratio satisfies the 1.3 criterion. The diabetes cardiovascular guidance states that postmarketing cardiovascular trials may not be needed if the 1.3 criterion is satisfied. However, I agree with all 12 advisory panel members that a definitive postmarketing cardiovascular safety trial should still be required even though saxagliptin technically meets 1.3 for Custom MACE. The low event rates (11 total events in the short-term period and 40 total events in the combined short-term and long-term periods), the low-risk patient population, the post-hoc cardiovascular assessment, and the lack of adjudication raise uncertainty about whether the sponsor has satisfied this higher level of assurance regarding cardiovascular safety.

Table 11. MACE analyses using the eight phase 2/3 trials

	Saxagliptin N=3356	**Comparator N=1251**	**Odds Ratio* (95% confidence interval)**
Broad MACE			
Short-term period	58 (1.8%)	25 (2.0%)	0.90 (0.6, 1.5)
Combined short-term and long-term period	100 (3.1%)	41 (3.2%)	0.96 (0.7, 1.4)
Custom MACE			
Short-term period	4 (0.1%)	7 (0.6%)	0.21 (0.04, 0.8)
Combined short-term and long-term period	23 (0.7%)	17 (1.3%)	0.52 (0.3, 1.0)
*Common odds ratio stratified on study			

Hypoglycemia: Table 12 summarizes the hypoglycemia data for the short-term periods of the phase 3 trials (excluding rescue) using two approaches:

- "Hypoglycemia adverse events" are based on tabulated adverse events coded to preferred terms of hypoglycemia, blood glucose decreased, and blood glucose abnormal. This approach is somewhat subjective because different investigators may have different thresholds for reporting blood glucose as decreased. In addition, the preferred term blood glucose abnormal is non-specific because it could also represent an elevated blood glucose measurement.

- "Confirmed hypoglycemia" was recorded on a hypoglycemia case report form and was defined as a fingerstick glucose ≤50 mg/dL in the setting of symptoms consistent with hypoglycemia (e.g., diaphoresis, shaky, hunger, confusion). This approach likely underestimates the true incidence of hypoglycemia because patients sometimes treat symptoms of hypoglycemia without first measuring the blood glucose.

Both approaches show that saxagliptin has a low risk of hypoglycemia. The incidence of confirmed hypoglycemia with saxagliptin is comparable to placebo in the monotherapy, add-on to metformin, and add-on to thiazolidinedione settings. There appears to be an increase in the incidence of hypoglycemia (whether assessed by adverse events or confirmed hypoglycemia) when saxagliptin is added to sulfonylurea, although the incidence of confirmed hypoglycemia with the 5 mg dose is comparable to the incidence of confirmed hypoglycemia

with placebo. The 10 mg dose of saxagliptin does not appear to increase the risk of hypoglycemia as compared to placebo when added to metformin. In addition, saxagliptin 10 mg monotherapy does not increase the risk of confirmed hypoglycemia beyond that seen with metformin monotherapy in patients who are treatment naïve.

In the phase 2 dose-ranging study, confirmed hypoglycemia occurred in two patients receiving saxagliptin 100 mg daily and in no patients receiving ≤40 mg daily.

One hypoglycemic event during the short-term period led to discontinuation (fingerstick glucose 27 mg/dL on Day 77 in a patient receiving saxagliptin 5 mg add-on to glyburide; this patient had two episodes of hypoglycemia with fingerstick glucoses in the 50 mg/dL range during the run-in period).

None of the hypoglycemic events in the short-term periods required medical assistance.

Table 12. Hypoglycemia data – short-term period excluding rescue

	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg	All Saxa	Placebo
Hypoglycemia adverse events					
Pooled monotherapy	10/247 (4.0%)	14/252 (5.6%)	8/92 (8.2%)	32/597 (5.4%)	7/169 (4.1%)
Add-on to metformin	15/192 (7.8%)	10/191 (5.2%)	7/181 (3.9%)	32/564 (5.7%)	9/179 (5.0%)
Add-on to sulfonylurea	33/248 (13.3%)	37/253 (14.6%)	-	70/501 (14.0%)	27/267 (10.1%)
Add-on to thiazolidinedione	8/195 (4.1%)	5/186 (2.7%)	-	13/381 (3.4%)	7/184 (3.8%)
Confirmed hypoglycemia					
Pooled monotherapy	0	0	0	0	0
Add-on to metformin	1/192 (0.5%)	1/191 (0.5%)	1/181 (0.6%)	3/565 (0.5%)	1/179 (0.6%)
Add-on to sulfonylurea	6/248 (2.4%)	2/253 (0.8%)	-	8/501 (1.6%)	2/267 (0.7%)
Add-on to thiazolidinedione	1/195 (0.5%)	0/186 (0%)	-	1/381 (0.3%)	0/184 (0%)
Initial therapy with metformin	**Saxa 5 mg+met**	**Saxa 10 mg+met**	**Saxa 10 mg**	**All Saxa**	**Met**
Hypoglycemia adverse events	11/320 (3.4%)	16/323 (5.0%)	5/335 (1.5%)	32/978 (3.3%)	13/328 (4.0%)
Confirmed hypoglycemia	0	2/323 (0.6%)	0	2/978 (0.2%)	1/328 (0.3%)

Hypersensitivity reactions: The sponsor identified potential cases of hypersensitivity in the combined short-term and long-term periods of the phase 3 trials using a collection of 65 preferred terms (MedDRA Version 11.0) related to anaphylactic reaction, angioedema, hypersensitivity, edema, and urticaria.

In the pooled phase 3 monotherapy and add-on combination therapy trials (120-day safety update database), the incidence of hypersensitivity reactions based on the 65 MedDRA preferred terms was higher with saxagliptin (2.4%) compared to placebo (0.6%), driven predominantly by preferred terms for hypersensitivity (0.9% vs. 0%) and urticaria (0.8% vs. 0.3%) (Table 13). In contrast, the incidence of hypersensitivity reactions in the initial combination with metformin trial was comparable in the saxagliptin-containing regimens (0.9%) and the metformin alone group (0.9%).

None of the identified events were reported to meet the regulatory definition of serious.

There were no reports of Stevens-Johnson syndrome.

One saxagliptin-treated patient reported angioedema on Day 27, but had a history of chronic idiopathic urticaria and angioneurotic edema occurring approximately 6 times each year during the preceding 6-7 years. Concomitant medications did not include an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB).

Across the phase 2/3 program, four patients (2 saxagliptin; 2 placebo) had hypersensitivity events that were characterized by the investigator to be of severe intensity. The 2 events in the saxagliptin group (urticaria on Day 159 and allergy attributed to oxaprozin on Day 21) did not result in patient discontinuation.

Across the phase 2/3 program, only 4 patients (3 saxagliptin; 1 placebo) had hypersensitivity events leading to study medication discontinuation, as summarized below:

- CV181008-126-98: This patient receiving 40 mg of saxagliptin reported facial edema, periorbital edema, headache, abdominal pain, and black stool on Day 93. Study medication was discontinued with resolution of the facial edema and periorbital edema (both classified as mild) after 16 days. Concomitant medications did not include an ACE inhibitor or ARB. There was a placebo-treated patient in the phase 3 program who discontinued on Day 119 due to circumoral edema and urticaria.

- CV181040-100-1169: This saxagliptin 2.5 mg-treated patient had several reports of urticaria during the treatment period. On Day 219, the patient reported urticaria on the chest, abdomen, and upper back. Study medication was discontinued on Day 226 and the event resolved 38 days later.

- CV181040-49-1894: This saxagliptin 5 mg-treated patient developed generalized urticaria on Day 29, confirmed by a dermatologist. The event was associated with facial and periorbital edema. The patient was treated with an anti-histamine and hydroxyzine. Saxagliptin was discontinued on Day 28 and the event resolved on Day 42. Concomitant medications did not include an ACE inhibitor or ARB.

The sponsor provided narratives for the events that coded to "hypersensitivity". All of these events were coded as mild or moderate in intensity and none resulted in discontinued of study medication. Most of these events were related to environmental allergies, such as allergic rhinitis.

Table 13. Hypersensitivity reactions in the short-term and long-term pooled phase 3 monotherapy and add-on combination therapy trials up to the cutoff date for the 120-day safety update

System Organ Class Preferred term	Saxa 2.5 mg N=882 n (%)	Saxa 5 mg N=882 n (%)	Saxa 10 mg N=279 n (%)	All Saxa N=2043 n (%)	Placebo N=799 n (%)
Total patients with an event	20 (2.3)	21 (2.4)	9 (3.2)	50 (2.4)	5 (0.6)
Hypersensitivity	5 (0.6)	10 (1.1)	3 (1.1)	18 (0.9)	0
Urticaria	8 (0.9)	5 (0.6)	3 (1.1)	16 (0.8)	2 (0.3)
Eye swelling	0	2 (0.2)	1 (0.4)	3 (0.1)	0
Eyelid edema	1 (0.1)	2 (0.2)	0	3 (0.1)	1 (0.1)
Swelling face	1 (0.1)	2 (0.2)	0	3 (0.1)	0
Allergic edema	0	1 (0.1)	0	1 (<0.1)	0
Face edema	3 (0.3)	1 (0.1)	1 (0.4)	5 (0.2)	1 (0.1)
Palatal edema	0	1 (0.1)	0	1 (<0.1)	0
Scrotal swelling	0	1 (0.1)	0	1 (<0.1)	0
Angioedema	1 (0.1)	0	0	1 (<0.1)	0
Circumoral edema	0	0	0	0	1 (0.1)
Drug hypersensitivity	0	0	1 (0.4)	1 (<0.1)	2 (0.3)
Gingival edema	1 (0.1)	0	0	1 (<0.1)	0
Lip swelling	1 (0.1)	0	0	1 (<0.1)	0
dial therapy with metformin	**Saxa 5 mg+met N=320**	**Saxa 10 mg+met N=323**	**Saxa 10 mg N=335**	**All Saxa N=978**	**Met N=328**
Total subjects with an event	3 (0.9)	2 (0.6)	4 (1.2)	9 (0.9)	3 (0.9)
Urticaria	1 (0.3)	1 (0.1)	1 (0.3)	3 (0.3)	1 (0.3)
Hypersensitivity	1 (0.3)	0	1 (0.3)	2 (0.2)	0
Swelling face/face edema	0	1 (0.3)	2 (0.6)	3 (0.3)	1 (0.3)
Drug hypersensitivity	0	0	1 (0.3)	1 (0.1)	0
Eyelid edema/orbital edema	1 (0.3)	0	0	1 (0.1)	1 (0.3)

Skin and localized edema: Some DPP-4 inhibitors cause dose- and treatment duration-dependent necrotic skin lesions at distal sites (e.g., digits, ears, nose, feet, scrotum, and tail) in monkeys, sometimes at or near clinical exposures. Localized edema appears to precede the development of the skin lesions in some cases. Saxagliptin causes minimal non-necrotizing skin lesions in monkeys at exposures 20-fold above the clinical dose and causes severe necrotizing lesions with exposures approximately 60-fold above the clinical dose. There is negligible risk for skin lesions in humans because clinical exposures to saxagliptin are not expected to increase to this extent based on the available data from clinical pharmacology studies. Nonetheless, the sponsor prespecified a list of 32 MedDRA preferred terms (Version 11.0) that could be consistent with the monkey findings (e.g., ulceration, necrosis, and erosion). Table 14 summarizes the combined short-term and long-term findings for these events and for localized edema reported in the pooled phase 3 monotherapy and add-on combination therapy trials and in the initial combination with metformin trial (120-day safety

update database). The incidence of such events was low (0.2-0.4%) and consistent with the randomization scheme. The overall incidence of skin ulceration was comparable in the saxagliptin (0.3%) and comparator (0.2%) groups.

As discussed by Dr. Lowy, the overall incidence of rash events was increased with saxagliptin (3.3% with 2.5 mg, 3.8% with 5 mg, and 6.8% with 10 mg) compared to placebo (2.2%) in the combined short-term and long-term periods of the pooled monotherapy and add-on combination therapy trials in the NDA database. This difference was predominantly driven by the preferred terms for rash (1.9-5.0% with saxagliptin vs. 1.3% with placebo) and rash papular (0-1.4% with saxagliptin vs. 0.1% with placebo).

The incidence of localized edema events was low and comparable in the saxagliptin and comparator groups (Table 14). None of the edema events occurring in unusual body locations (e.g., hands, face) were classified as serious or resulted in study medication discontinuation. In the dose-ranging study, the incidence of edema was low and comparable among patients treated with saxagliptin >10 mg per day and patients treated with placebo (1 event of pedal edema with saxagliptin 20 mg, 1 event of periorbital edema with saxagliptin 40 mg, no events with saxagliptin 100 mg, and 1 event of finger edema with placebo).

Infections: DPP-4 has many substrates other than GIP and GLP-1, including chemokines involved in immune development and function. In addition, DPP-4 is expressed on a subset of CD4+ and CD8+ T-cells and natural killer cells. Table 15 summarizes the incidence of select infections in the phase 3 program up to the cut-off date of the 120-day safety update. In the pooled phase 3 monotherapy and add-on combination therapy trials, the higher incidence of overall infections in the saxagliptin 10 mg dose is driven predominantly by nasopharyngitis (14% vs. 8-10% with the other saxagliptin doses and 10% with placebo), influenza (13% vs. 7% with the other saxagliptin doses and 8% with placebo) and sinusitis (9% vs. 3-4% with the other saxagliptin doses and 3% with placebo). As shown in Table 15, saxagliptin does not appear to increase the incidence of unusual infections.

Table 14. Predefined skin and localized edema events (short-term and long-term phase 3 trials)					
System Organ Class Preferred term	**Saxa 2.5 mg N=882 n (%)**	**Saxa 5 mg N=882 N (%)**	**Saxa 10 mg N=279 n (%)**	**All Saxa N=2043 n (%)**	**Placebo N=799 n (%)**
Pooled phase 3 monotherapy and add-on combination therapy trials					
Select skin and subcutaneous disorders					
Total patients with an event	3 (0.3)	5 (0.6)	0	8 (0.4)	3 (0.4)
Skin ulcer	1 (0.1)	3 (0.3)	0	4 (0.2)	2 (0.3)
Infected skin ulcer	1 (0.1)	1 (0.1)	0	2 (<0.1)	0
Skin erosion	0	1 (0.1)	0	1 (<0.1)	0
Lip ulceration	1 (0.1)	0	0	1 (<0.1)	0
Nasal ulcer	0	0	0	0	1 (0.1)
Localized edema					
Total patients with an event	13 (1.5)	26 (2.9)	4 (1.4)	43 (2.1)	15 (1.9)
Excluding foot edema	4 (0.5)	7 (0.8)	2 (0.7)	13 (0.6)	2 (0.3)
Edema hands/hand swelling	3 (0.3)	2 (0.2)	1 (0.4)	6 (0.3)	1 (0.1)
Eye swelling	0	1 (0.1)	1 (0.4)	2 (0.1)	0
Eyelid edema/periorbital swelling	1 (0.1)	3 (0.3)	0	4 (0.2)	1 (0.1)
Scrotum swelling	0	1 (0.1)	0	1 (<0.1)	0
l therapy with metformin	**Saxa 5 mg+met N=320**	**Saxa 10 mg+met N=323**	**Saxa 10 mg N=335**	**All Saxa N=978**	**Met N=328**
Select skin and subcutaneous disorders					
Total subjects with an event	1 (0.3)	0	1 (0.3)	2 (0.2)	1 (0.3)
Infected skin ulcer	0	0	1 (0.3)	1 (0.1)	0
Skin ulcer	1 (0.3)	0	0	1 (0.1)	0
Lip ulceration	0	0	0	0	1 (0.3)
Localized edema					
Total patients with an event	3 (0.9)	2 (0.6)	1 (0.3)	6 (0.6)	1 (0.3)
Excluding foot edema	2 (0.6)	0	0	2 (0.2)	1 (0.3)
Edema fingers	1 (0.3)	0	0	1 (0.1)	0
Edema palpebral/orbital edema	1 (0.3)	0	0	1 (0.1)	1 (0.3)

Table 15. Select infections reported as adverse events (short-term and long-term phase 3 trials)					
System Organ Class Preferred term	**Saxa 2.5 mg N=882 n (%)**	**Saxa 5 mg N=882 n (%)**	**Saxa 10 mg N=279 n (%)**	**All Saxa N=2043 n (%)**	**Placebo N=799 n (%)**
Total patients with an event	447 (51)	440 (50)	156 (56)	1043 (51)	388 (49)
Occurring in >2% of saxagliptin 5 mg-treated patients (and more frequently with all saxa than placebo)					
Upper respiratory tract infection	97 (11.0)	103 (11.7)	34 (12.2)	234 (11.5)	80 (10.0)
Urinary tract infection	87 (9.9)	94 (10.7)	26 (9.3)	207 (10.1)	70 (8.8)
Bronchitis	42 (4.8)	42 (4.8)	14 (5.0)	98 (4.8)	34 (4.3)
Sinusitis	39 (4.4)	32 (3.6)	24 (8.6)	95 (4.7)	24 (3.0)
Gastroenteritis	33 (3.7)	29 (3.3)	7 (2.5)	69 (3.4)	16 (2.0)
Unusual infections/infestations occurring in at least 1 saxagliptin-treated patient					
Amebiasis	1 (0.1)	5 (0.6)	0	6 (0.3)	2 (0.3)
Ascariasis	2 (0.2)	5 (0.6)	1 (0.4)	8 (0.4)	2 (0.3)
Trichuriasis	1 (0.1)	3 (0.3)	0	4 (0.2)	1 (0.1)
Giardiasis	1 (0.1)	2 (0.2)	0	3 (0.1)	0
Amebic dysentery	2 (0.2)	1 (0.1)	0	3 (0.1)	2 (0.3)
Chikungunya virus infection	0	1 (0.1)	0	1 (<0.1)	0
Parasitic gastroenteritis	5 (0.6)	1 (0.1)	0	6 (0.3)	8 (1.0)
Toxocariasis	0	1 (0.1)	0	1 (<0.1)	0
Gastroenteritis salmonella	1 (0.1)	0	0	1 (<0.1)	0
Helminthic infection	1 (0.1)	0	1 (0.4)	2 (<0.1)	1 (0.1)
Pulmonary tuberculosis	1 (0.1)	0	0	1 (<0.1)	0
Typhoid fever	1 (0.1)	0	0	1 (<0.1)	0
Initial therapy with metformin	**Saxa 5 mg+met N=320**	**Saxa 10 mg+met N=323**	**Saxa 10 mg N=335**	**All Saxa N=978**	**Met N=328**
Total subjects with an event	93 (29)	97 (30)	123 (37)	313 (32)	104 (32)
Occurring in >2% of saxagliptin 5 mg+metformin-treated patients (and more frequently than metformin)					
Nasopharyngitis	28 (8.8)	18 (5.6)	24 (7.2)	70 (7.2)	17 (5.2)
Upper respiratory tract infection	14 (4.4)	17 (5.3)	14 (4.2)	45 (4.6)	9 (2.7)
Bronchitis	13 (4.1)	10 (3.1)	11 (3.3)	34 (3.5)	3 (0.9)
Gastroenteritis	8 (2.5)	8 (2.5)	6 (1.8)	22 (2.2)	3 (0.9)
Unusual infections/infestations occurring in at least 1 saxagliptin-treated patient					
Acariasis	0	0	2 (0.6)	2 (0.2)	0
Parasitic gastroenteritis	2 (0.6)	0	0	2 (0.2)	2 (0.6)
Amebiasis	0	0	1 (0.3)	1 (0.1)	0
Ascariasis	1 (0.3)	0	0	1 (0.1)	0
Dengue fever	0	0	1 (0.3)	1 (0.1)	0
Giardiasis	0	0	1 (0.3)	1 (0.1)	0
Helminthic infection	0	1 (0.3)	0	1 (0.1)	1 (0.3)
Tetanus	1 (0.3)	0	0	1 (0.1)	0
Typhoid fever	0	0	1 (0.3)	1 (0.1)	0

Other immune disruption: Perturbations of the immune system could potentially precipitate autoimmune disease or some cancers. The incidence of such events in the phase 3 program (120-day safety update) is very low and consistent with the randomization scheme (Table 16).

In the phase 3 program, there are 9 (0.3%) reports (all non-serious) of lymphadenopathy with saxagliptin vs. 0 cases with comparator. All events were reported to occur in the cervical or submandibular region. None of these 9 reports were associated with lymphopenia or malignancy and none led to discontinuation of study medication. Four of the 9 reports were coincident with infection (three with upper respiratory tract infection and one with gingivitis). The etiology of the remaining 5 cases is uncertain. These 5 cases were detected on physical exam and no further imaging or diagnostic evaluations were reported. Four of the 5 cases resolved while on study medication (within 15-75 days).

Table 16. Autoimmune disease, blood neoplasms, and lymph node adverse events (short-term and long-term phase 3 trials up to the cutoff date for the 120-day safety update)

System Organ Class Preferred term	Saxa 2.5 mg N=882 n (%)	Saxa 5 mg N=882 n (%)	Saxa 10 mg N=279 n (%)	All Saxa N=2043 n (%)	Placebo N=799 n (%)
Autoimmune disease					
Inflammatory bowel disease	0	1 (0.1)	0	1 (<0.1)	0
Temporal arteritis	0	1 (0.1)	0	1 (<0.1)	0
Rheumatoid arthritis	1 (0.1)	1 (0.1)	0	2 (<0.1)	2 (0.3)
Polymyalgia rheumatica	1 (0.1)	0	0	1 (<0.1)	0
Blood neoplasms					
Myelodysplastic syndrome	0	1 (0.1)	0	1 (<0.1)	0
Non-Hodgkin's lymphoma	1 (0.1)	0	0	1 (<0.1)	0
Lymph node adverse events					
Lymphadenopathy	6 (0.7)	1 (0.1)	1 (0.4)	8 (0.4)	0
Lymphadenitis	0	0	0	0	1 (0.1)
Initial therapy with metformin*	**Saxa 5 mg+met N=320**	**Saxa 10 mg+met N=323**	**Saxa 10 mg N=335**	**All Saxa N=978**	**Met N=328**
Blood neoplasms					
Lymphoproliferative disorder	1 (0.3)	0	0	1 (0.1)	0
Lymph node adverse events					
Lymphadenopathy	1 (0.3)	0	0	1 (0.1)	0

*there were no adverse event reports of autoimmune disease in the initial combination with metformin trial

Pancreatitis: As of the cutoff date for the 120-day safety update, there were 6/3356 (0.2%) saxagliptin-treated patients and 2/1251 (0.2%) comparator-treated patients (both receiving metformin) in the phase 2/3 program with events that coded to the MedDRA preferred terms for pancreatitis, acute pancreatitis, or chronic pancreatitis. There were no adverse events coded to preferred terms for abnormal serum amylase or lipase.

There were no fatal outcomes or reports of hemorrhagic or necrotizing pancreatitis.

The diagnosis of an acute episode of pancreatitis is uncertain for the two comparator patients (both of whom had a history of chronic pancreatitis), because there are no serum amylase or lipase concentrations available at the time of the event.

Narratives for the six reports of pancreatitis among the saxagliptin-treated patients are summarized below. The first two reports occurred on Days 9 and 23. The remaining events occurred on Days 199-693. Five of the 6 reports had at least one known risk factor for pancreatitis (alcohol use, cholelithiasis, history of hypertriglyceridemia, or history of pancreatitis). There is limited information for the 4 reports that did not meet the regulatory definition for serious. Serum amylase or lipase measurements are not available at the time of diagnosis for 2 of the 6 cases. A third patient had a serum amylase of only 1.1-fold above the upper limit of the reference range without measurement of serum lipase. Despite the uncertainty regarding some cases, the incidence of pancreatitis as assessed by investigator-reported terms that coded to pancreatitis, acute pancreatitis, or chronic pancreatitis is comparable in the saxagliptin and comparator-treated patients without evidence of a relationship to saxagliptin dose.

- One saxagliptin 10 mg+metformin treated patient with a history of chronic pancreatitis was reported to have acute pancreatitis on Day 9. Ultrasound on Day 16 reportedly showed hepatomegaly, an enlarged pancreas, and cholelithiasis. The investigator identified cholelithiasis as a possible cause of the pancreatitis. There are no serum amylase or lipase measurements available at the time of presentation. Study medication was discontinued.

- One saxagliptin 5 mg+metformin treated patient was reported to have pancreatitis, duodenitis, and gastritis on Day 23. Serum amylase was 1.1-fold above the upper limit of the reference range. Serum lipase was not measured. No precipitating factors were identified. No action was taken with study medication.

- One saxagliptin 2.5 mg treated patient having 1-2 drinks per week was reported to have signs of chronic pancreatitis and hepatomegaly on ultrasound during a bout of abdominal pain with increased serum transaminases. Serum amylase and lipase were not measured. No action was taken with study medication.

- One saxagliptin 5 mg treated patient was diagnosed with cholelithiasis following an episode of abdominal pain, nausea, and vomiting. Seven days later, the patient presented to the emergency room with increased abdominal pain, nausea, and diarrhea. She had an elevated serum lipase (456 U/L), without evidence of pancreatitis on CT scan, and underwent laparoscopic cholecystectomy. The narrative does not mention whether there was evidence of active or recent common bile duct obstruction. No action was taken with study medication.

- One saxagliptin 5 mg treated patient consuming 2 alcoholic beverages daily was hospitalized on Day 236 with pancreatitis with serum lipase of 302 U/L (ULN 60 U/L). An unspecified abdominal radiographic study on Day 263 reportedly showed signs of chronic pancreatitis. Study medication was discontinued.

Table 6. Patient disposition – short-term periods for the phase 3 trials				
Disposition	**Saxa 2.5 mg**	**Saxa 5 mg**	**Saxa 10 mg**	**Placebo**
Pooled monotherapy trials and add-on combination trials				
Randomized and treated	882	882	279	799
Completed the short-term period	679 (77%)	658 (75%)	209 (75%)	534 (67%)
Discontinued from the short-term period				
Lack of efficacy	116 (13%)	109 (12%)	41 (15%)	166 (21%)
Withdrew consent	36 (4.1%)	47 (5.3%)	9 (3.2%)	53 (6.6%)
Adverse event	13 (1.5%)	27 (3.1%)	9 (3.2%)	13 (1.6%)
Lost to follow-up	17 (1.9%)	21 (2.4%)	7 (2.5%)	15 (1.9%)
Other	21 (2.4%)	20 (2.3%)	4 (1.4%)	18 (2.3%)
Continued into the long-term period	773 (88%)	752 (85%)	245 (88%)	671 (84%)
Initial combination with metformin trial	**Saxa 5 mg+met**	**Saxa 10 mg+met**	**Saxa 10 mg**	**Met**
Randomized and treated	320	323	335	328
Completed the short-term period	262 (82%)	261 (81%)	225 (67%)	243 (74%)
Discontinued from the short-term period				
Lack of efficacy	20 (6.3%)	19 (5.9%)	64 (19.1%)	30 (9.1%)
Withdrew consent	10 (3.1%)	17 (5.3%)	12 (3.6%)	13 (4.0%)
Adverse event	7 (2.2%)	7 (2.2%)	8 (2.4%)	11 (3.4%)
Lost to follow-up	11 (3.4%)	10 (3.1%)	15 (4.5%)	15 (4.6%
Other	10 (3.1%)	9 (2.8%)	3 (0.9%)	9 (2.7%)
Continued into the long-term period	276 (86%)	275 (85%)	286 (85%)	266 (81%)

Deaths: Including the 120-day safety update, there have been a total of 23 deaths in the combined short-term and long-term periods in the phase 2/3 trials. Ten deaths (0.3%) occurred among saxagliptin-treated patients and 13 deaths (1.0%) occurred among comparator-treated patients. As expected for this patient population, most of these deaths (7/10 for saxagliptin; 11/13 for comparator) were due to cardiovascular causes, such as myocardial infarction (1 case with saxagliptin vs. 2 cases with comparator), stroke (1 case with saxagliptin vs. 3 cases with comparator), sudden death or cardiac arrest (4 cases with saxagliptin vs. 3 cases with comparator), and heart failure (2 cases with comparator). Non-cardiovascular causes of death included 1 case each of pneumonia, car accident, and tetanus among the saxagliptin-treated patients and 1 case each of pneumonia and sepsis among the comparator-treated patients. The saxagliptin-treated patient who died of tetanus sustained a puncture wound and was non-complaint with the tetanus toxoid injection. No deaths have been reported in patients dosed with more than 10 mg of saxagliptin, although patient exposures to these higher doses are limited. In summary, there is no concerning signal for death with saxagliptin, although event rates are low.

Serious adverse events: Dr. Lowy reviewed the narratives and serious adverse events (prior to rescue and regardless of rescue) in the short-term periods and in the combined short-term and

long-term periods for each of the individual phase 3 trials. Please see her review for further details.

Because serious adverse events were relatively infrequent, data from the short-term and long-term periods for the two phase 3 monotherapy trials and the three add-on combination trials were pooled to increase the likelihood of detecting important differences between treatment groups. Table 7 summarizes these data up to the cutoff date for the 120-day safety update. Because there are approximately 2.5 times more saxagliptin-treated patients (n=2,043) compared to placebo-treated patients (n=799), only those preferred terms reported by more than 2 saxagliptin-treated patients and occurring >0.1% more frequently than placebo are shown. Note that this table does not include the four serious adverse events occurring during the double-blind treatment period of the 12-week dose-ranging study (one report each of pneumonia, gastroenteritis, and appendicitis among the saxagliptin-treated patients and one report of ventral umbilical hernia in a placebo-treated patient). This table also does not include data from the initial combination with metformin trial. There were no preferred terms in this combination trial reported in more than 2 saxagliptin-treated patients and occurring more frequently with saxagliptin compared to metformin alone.

Serious adverse events in the pooled phase 3 monotherapy trials and add-on combination therapy trials were reported in 184 (9.0%) saxagliptin-treated patients and 69 (8.6%) placebo-treated patients. Most of the individual preferred terms in Table 7 occurred infrequently, typically reported in 0-5 saxagliptin-treated patients in any given treatment group and none of the preferred terms appeared to have a relationship to saxagliptin dose. Preferred terms in Table 7 typically occurred <0.3% more frequently with saxagliptin than with placebo. In the Injury, Poisoning, and Procedural Complications System Organ Class (SOC), the incidence of serious adverse events was 1.1% in the saxagliptin group and 0.3% in the placebo group. This difference was not driven by any particular preferred term, although in this SOC, the saxagliptin group had 5 (0.2%) serious reports of overdose (vs. 0 reports with placebo) and 7 (0.3%) serious reports of fracture (vs. 1 report with placebo in the add-on to thiazolidinedione trial). In the initial combination with metformin trial, there were 2 additional reports of overdose (both in saxagliptin-containing regimens) and 3 additional reports of fracture (all three in saxagliptin-containing regimens).

The 7 reports of overdose were all related to transient inadvertent intake of more than the prescribed number of study medication tablets and were not related to suicidal ideation. These patients reported no adverse events during the period of incorrect dosing and continued in the trials after the dosing error had been corrected. There were no saxagliptin-treated patients with preferred terms that coded to the Standardised MedDRA Query of "Suicide/self-injury".

With regard to serious adverse events of fracture, the saxagliptin group in the pooled dataset had two reports of hip fracture, two reports of ankle fracture and one report each of spine fracture, knee fracture, and arm fracture. None of these fractures occurred in the add-on to thiazolidinedione trial. One fracture (hip) occurred in a patient with prostate cancer (there is no mention whether this was a pathological fracture), two fractures (ankle, arm) occurred in the setting of car accidents, and three fractures (ankle, spine, hip) were associated with mechanical falls. In the initial combination with metformin trial, an upper limb fracture occurred in the

- One saxagliptin 10 mg+metformin treated patient with a history of hypertriglyceridemia (extent of triglyceride elevation not described) was reported to have pancreatitis. Serum lipase was 623 U/L (ULN 60 U/L) with normal serum transaminases. Study medication was discontinued.

Laboratory data: This memorandum will focus on lymphocyte counts, platelet counts, liver test abnormalities and tests of renal function using the 120-day safety update database. I concur with Dr. Lowy that there is no clinically meaningful effect of saxagliptin on the other laboratory parameters. Please see Dr. Lowy's review for further details.

Lymphocyte counts: Table 17 shows the mean and median percent change from baseline in lymphocyte count for the pooled monotherapy and add-on combination therapy trials (120-day safety update database). Smaller sample sizes beyond Month 12 limit conclusions at the later timepoints (Months 24 and 30 only include data from monotherapy study -011 and the add-on to metformin trial).

Based on mean percent change from baseline, the saxagliptin 2.5 mg group and the placebo group had comparable effects on absolute lymphocyte counts, although the median data suggest that the 2.5 mg dose results in an incremental 1-3% absolute percent reduction in lymphocyte count over placebo.

Based on both the mean and median data, saxagliptin 5 mg results in an incremental 3-4% absolute percent reduction in lymphocyte count over placebo at Months 6, 12, and 18, although no consistent difference is seen between these treatment groups at Months 24 and 30.

Based on both the mean and median data, saxagliptin 10 mg results in an incremental 5-10% absolute percent reduction in lymphocyte count over placebo at all timepoints.

Table 17. Percent change from baseline in lymphocyte count for the combined short-term and long-term periods of the pooled monotherapy and add-on combination trials; 120-day safety update database)

	6 months	12 months	18 months	24 months	30 months
Saxa 2.5 mg	**N=742**	**N=660**	**N=423**	**N=140**	**N=83**
Mean % change	+2.0%	-0.2%	-0.2%	-5.6%	-2.8%
Median % change	-1.8%	-3.5%	-4.7%	-5.9%	-6.7%
Saxa 5 mg	**N=721**	**N=655**	**N=416**	**N=151**	**N=95**
Mean % change	-1.6%	-2.6%	-4.3%	+0.2%	-4.9%
Median % change	-4.6%	-5.0%	-5.1%	-7.6%	-5.4%
Saxa 10 mg	**N=235**	**N=216**	**N=193**	**N=161**	**N=91**
Mean % change	-3.1%	-9.5%	-9.9%	-10.7%	-9.8%
Median % change	-6.3%	-12.2%	-12.2%	-12.0%	-12.6%
Placebo	**N=640**	**N=566**	**N=337**	**N=106**	**N=59**
Mean % change	+2.6%	+2.0%	-0.3%	-5.9%	-6.1%
Median % change	-1.1%	-0.8%	-2.0%	-5.2%	-4.5%

Table 18 summarizes the proportion of patients with ≥10%, ≥20%, and ≥30% reduction in lymphocyte count over time for the treatment groups in the pooled monotherapy and add-on combination therapy trials (120-day safety update database). Smaller sample sizes beyond Month 18 limit conclusions at the later timepoints (Months 24 and 30 only include data from monotherapy study -011 and the add-on to metformin trial).

The saxagliptin 2.5 mg group and placebo group generally had a similar proportion of patients with ≥10%, ≥20%, and ≥30% reduction in lymphocyte count over time, although there may be some differences not favoring the 2.5 mg group at some timepoints (e.g., Month 12 in the ≥10% and ≥20% categories).

At the 6, 12, and 18 month timepoints, a consistently greater proportion of patients in the saxagliptin 5 mg group met the ≥10%, ≥20%, and ≥30% criteria than did patients in the placebo group (40% vs. 28-36% in the ≥10% category, 21-23% vs. 13-18% in the ≥20% category, and 8-10% vs. 5-7% in the ≥30% category). No consistent difference is seen between these treatment groups at Months 24 and 30.

An even greater proportion of patients in the saxagliptin 10 mg group met the ≥10%, ≥20%, and ≥30% criteria than did patients in the placebo group with the largest differences at Month 12 (56% vs. 28% in the ≥10% category, 31% vs. 13% in the ≥20% category, and 15% vs. 5% in the ≥30% category). No consistent difference is seen between these treatment groups at Months 6, 24 and 30 for the ≥30% category.

Table 18. Patients with various percent reductions in lymphocyte count (short-term and long-term poo monotherapy and add-on combination trials up to cutoff date for 120-day safety update)

Percent Reduction from Baseline	Saxa 2.5 mg N=882	Saxa 5 mg N=882	Saxa 10 mg N=279	All Saxa N=2043	Placebo N=799
≥10%					
6 months	236/742 (32%)	287/721 (40%)	96/235 (41%)	619/1698 (37%)	193/640 (30%)
12 months	232/660 (35%)	269/655 (41%)	121/216 (56%)	622/1531 (41%)	161/566 (28%)
18 months	158/423 (37%)	171/416 (41%)	103/193 (53%)	432/1032 (42%)	122/337 (36%)
24 months	60/140 (43%)	64/151 (42%)	90/161 (56%)	214/452 (47%)	42/106 (40%)
30 months	35/83 (42%)	38/95 (40%)	47/91 (52%)	120/269 (45%)	25/59 (42%)
≥20%					
6 months	105/742 (14%)	153/721 (21%)	50/235 (21%)	308/1698 (18%)	93/640 (15%)
12 months	123/660 (19%)	150/655 (23%)	67/216 (31%)	340/1531 (22%)	71/566 (13%)
18 months	76/423 (18%)	96/416 (23%)	65/193 (34%)	237/1032 (23%)	60/337 (18%)
24 months	35/140 (25%)	39/151 (26%)	55/161 (34%)	129/452 (29%)	26/106 (25%)
30 months	23/83 (28%)	26/95 (27%)	27/91 (30%)	76/269 (28%)	16/59 (27%)
≥30%					
6 months	38/742 (5.1%)	62/721 (8.6%)	13/235 (5.5%)	113/1698 (6.7%)	44/640 (6.9%)
12 months	43/660 (6.5%)	53/655 (8.1%)	33/216 (15.3%)	129/1531 (8.4%)	29/566 (5.1%)
18 months	37/423 (8.7%)	42/416 (10%)	32/193 (17%)	111/1032 (11%)	25/337 (7.4%)
24 months	20/140 (14%)	18/151 (12%)	20/161 (12%)	58/452 (13%)	12/106 (1
30 months	9/83 (11%)	10/95 (11%)	12/91 (13%)	31/269 (12%)	8/59 (14

The reference range for absolute lymphocyte counts is 1,000-4,000 cells/mcL (c/mcL). The sponsor incorporated the following algorithm for lymphocyte counts in the phase 3 trials after noting an effect of saxagliptin on lymphocyte counts in the phase 1 and 2 trials.

Run-in periods:

- Patients with a lymphocyte count <1,000 c/mcL were to be discontinued.

Short-term and long-term phases:

- Patients with a lymphocyte count ≤500 c/mcL were to be discontinued
- Patients with a lymphocyte count >500 but ≤750 c/mcL were to have study medication withheld with repeat testing within 72 hours and permanent discontinuation if the repeat lymphocyte count was ≤500 c/mcL. If the repeat lymphocyte count was >500 but <1000 c/mcL, the patient was to undergo weekly testing until the lymphocyte count was ≥1000 c/mcL, at which point study medication could be restarted.

The sponsor defined a markedly low lymphocyte count as ≤750 c/mcL. In the combined short-term and long-term periods of the phase 2/3 trials (120-day safety update database), the incidence of markedly low lymphocyte counts was similar in the saxagliptin 2.5 mg group (0.9%) and the control group (0.7%), but more frequent in the saxagliptin 5 mg (1.6%) and 10 mg groups (1.6%). The 2.5 mg group includes patients who were uptitrated to 5 mg or 10 mg in monotherapy study -038 and the 5 mg group includes patients who were uptitrated to 10 mg in monotherapy study -038.

The sponsor defined an "isolated" decline in lymphocyte count as a one-time markedly low lymphocyte count (≤750 c/mcL) that subsequently recovered to above the lower limit of the reference range and did not decline below the lower limit of the reference range at any time during the remainder of the trial. In the phase 2/3 program (120-day safety update database), the proportion of patients with an isolated decline in lymphocyte count was comparable in the control group (0.6%) and saxagliptin group (0.6%). Study medication was interrupted for several days in 12 patients (2 placebo, 10 saxagliptin) because of the lymphocyte decline but lymphocyte counts remained above the lower limit of the reference range with rechallenge. None of the patients with an isolated decline in lymphocyte count had an unusual treatment-emergent infection. Four saxagliptin-treated patients reported infections around the time of the lymphocyte count nadir – 2 reports of urinary tract infection, 1 report of influenza, and 1 report of upper respiratory tract infection.

The sponsor defined a "non-isolated" decline in lymphocyte count as a lymphocyte count ≤750 c/mcL that did not meet the above definition for an "isolated" decline. In the phase 2/3 program (120-day safety update database), there were 2 (0.2%) control patients and 29 (0.8%) saxagliptin patients (5 or 0.5% on 2.5 mg, 12 or 0.9% on 5 mg, 9 or 0.8% on 10 mg, 2 or 3.7% on 20 mg, and 1 or 1.9% on 40 mg) with a non-isolated decline in lymphocyte count. Nine of these 31 patients (1 control patient and 8 saxagliptin patients) had baseline lymphocyte counts below the lower limit of the reference range.

Fourteen of the 31 patients with a non-isolated decline in lymphocyte count had an interruption of study medication dosing (1 or 0.1% receiving comparator, 3 or 0.3% receiving

2.5 mg, 6 or 0.5% receiving 5 mg, and 4 or 0.4% receiving 10 mg). Four of these 14 patients reported infections (2 patients with nasopharyngitis, 1 patient with urinary tract infection and upper respiratory tract infection, and 1 patient with viral gastroenteritis and upper respiratory tract infection) that appeared to be temporally associated with the reduced lymphocyte counts. Only one saxagliptin-treated patient (5 mg) had study medication interrupted again upon rechallenge. This patient had a baseline lymphocyte count of 1,080 c/mcL and had interruption in study medication on Days 59-67, 73-83, 199-204, 211-213, 225-239, 246-253, and 274-275.

Ten of the patients with a non-isolated decline in lymphocyte count were discontinued (1 or 0.1% receiving comparator, 2 or 0.2% receiving 2.5 mg, 4 or 0.3% receiving 5 mg, and 3 or 0.3% receiving 10 mg). Five of these 9 saxagliptin-treated patients were discontinued after positive rechallenge, 2 were discontinued because the lymphocyte count declined below 500 c/mcL and 2 were discontinued even though rechallenge would have been acceptable per the algorithm. Three of the patients who were discontinued reported infections (1 patient with gastroenteritis, 1 patient with pharyngitis and respiratory tract infection, and 1 patient with prostatitis, oral herpes, orchitis and urinary tract infection) that appeared to be temporally associated with the reduced lymphocyte counts.

In the combined short-term and long-term periods (120-day safety update database) of the phase 3 trials (excluding the small mechanism-of-action trial), there were 9 saxagliptin-treated patients who were discontinued due to an adverse event of lymphopenia or lymphocyte count decreased. All these patients are included in the tallies above except for one patient who was discontinued for a lymphocyte count of 920 c/mcL on Day 98 (this patient did not have any temporally associated infections and did not qualify for discontinuation based on the lymphocyte algorithm; repeat lymphocyte count off saxagliptin was normal).

In the phase 2 dose-ranging study, the mean absolute lymphocyte count was 1,820-2,020 c/mcL across treatment groups. For the 0-40 mg cohort, the mean change from baseline to Week 12 in absolute lymphocyte counts was 0 c/mcL for placebo and saxagliptin 2.5 mg, -30 c/mcL for 5 mg, -70 c/mcL for 10 mg, -260 c/mcL for 20 mg, and -380 c/mcL for 40 mg. For the 0, 100 mg cohort, the mean change from baseline to Week 6 in absolute lymphocyte counts was -10 c/mcL for placebo and -280 c/mcL for saxagliptin 100 mg. These effects were reversible upon discontinuation of study medication. The number of patients with ≥30% reduction in lymphocyte counts from baseline was 2 (4%) with placebo, 1 (2%) with saxagliptin 2.5 mg, 2 (6%) with 5 mg, 0 with 10 mg, 4 (10%) with 20 mg, and 11 (26%) with 40 mg. In the 0, 100 mg cohort, the number of patients with ≥30% reduction in lymphocyte counts from baseline was 1 (3%) with placebo and 7 (17%) with saxagliptin 100 mg.

Ms. Mele raised the possibility that Asians may be at higher risk for adverse events with saxagliptin (see the efficacy section of this memorandum). In the short-term periods of the phase 3 trials (excluding the mechanism-of-action trial), 493 Asians were randomized to saxagliptin and 195 Asians were randomized to comparator. Among these 688 patients, only 2 had lymphocyte counts ≤750 c/mcL, one treated with placebo in the add-on to sulfonylurea trial and the other treated with saxagliptin 10 mg. Therefore, Asians do not appear to be at increased risk for markedly low lymphocyte counts compared to non-Asians.

Platelet counts: In the pooled monotherapy and add-on combination therapy trials (120-day safety update database), saxagliptin had minor effects on platelet count as assessed by percent changes from baseline at Months 6 and 12 (-2.5% to -3.5% median reduction in the saxagliptin group without evidence of a dose-response relationship compared to -1.5% median reduction with placebo). In this dataset, saxagliptin and placebo had comparable percent changes from baseline in platelet counts beyond Month 12, although smaller samples sizes at the later timepoints limit conclusions.

In the pooled monotherapy and add-on combination therapy trials (120-day safety update database), a slightly higher proportion of saxagliptin-treated patients developed ≥10% reduction in platelet counts compared to placebo-treated patients without evidence of a dose-response relationship (26% vs. 23% at Month 6; 28% vs. 23% at Month 12; 28% vs. 23% at Month 18; 19% vs. 14% at Month 24). However, the saxagliptin and placebo groups had a comparable proportion of patients with ≥20% and ≥30% reductions in platelet counts at these timepoints.

The incidence of markedly low and markedly high platelet counts in the phase 2/3 program (120-day safety update database) was comparable in the saxagliptin and control treatment groups (0.1% vs. 0.1% for platelets $<50x10^9$x/L and 0.2% vs. 0.3% for platelets >1.5x ULN).

Liver tests: As shown in Table 19, the saxagliptin and comparator groups in the phase 2/3 program (120-day safety update database) had a similar incidence of ALT >3x ULN (1.3% vs. 1.4%, respectively) and >5x ULN (0.3% vs. 0.2%, respectively). However, all 4 cases of ALT >10x ULN occurred in the saxagliptin group. Narratives for 3 cases are summarized below. The remaining case is summarized under the section discussing withdrawals due to adverse events.

- One patient on saxagliptin 100 mg had normal ALT at baseline but elevated ALT of 75 U/L on Day 29 and 343 U/L (10x ULN) on Day 43 (the end of the 6-week treatment period). Pravastatin (which the patient had been taking for approximately 3 years) was discontinued on Day 51. The ALT declined during the 4-week follow-up period (when the patient was no longer receiving saxagliptin) to 74 U/L on Day 53 and 44 U/L (1.3x ULN) on Day 74. This patient does not meet the definition for Hy's Law because total bilirubin remained within the reference range.

- One patient treated with saxagliptin 2.5 mg was diagnosed with acute hepatitis C.

- One patient treated with saxagliptin 2.5 mg+metformin had normal ALT at baseline and was diagnosed with hepatitis A on Day 511. ALT was 815 U/L (19x ULN) on Day 526 but normalized by Day 541 while continuing study medication.

Two saxagliptin-treated patients (0.1%) and one comparator patient (0.1%) developed Hy's Law as defined as ALT or AST >3x ULN and total bilirubin >2x ULN. However, all three patients do not meet the true criteria for Hy's Law because they have an alternate explanation for the liver test abnormalities (acute hepatitis C and acute cholecystitis in the two saxagliptin-treated patients and pancreatic neoplasm in the comparator-treated patient).

In renal safety study CV181062, a 60-year old man with end-stage renal disease on saxagliptin 2.5 mg developed asymptomatic, but marked ALT elevation to 2,375 U/L (~60x ULN) on Day 19 with elevated alkaline phosphatase (1.6x ULN) and total bilirubin at the upper limit of normal. Study medication was permanently discontinued on Day 24. Two days later ALT was 537 U/L. The narrative states that hepatitis B and C testing were negative, but it is unclear whether testing occurred as part of the screening process or at the time of the abnormal liver tests. No other diagnostic tests were performed. Saxagliptin pharmacokinetic data are not available for this patient. Concomitant medications included quinapril and ginkgo biloba (both initiated 3 months prior to the liver event) and ticlopidine (initiated 1.5 years prior to the liver event). ALT normalized three weeks after the elevated ALT was detected despite continued treatment with these concomitant medications, making it unlikely that any of these concomitant medications caused the liver test abnormalities. The investigator attributed the liver test elevation to an undiagnosed virus or problem with the hemodialysis machine. The investigator discussed the case with the chief of the hemodialysis unit and stated that there was "a similar problem" involving other patients who were not receiving any experimental therapies. The sponsor has initiated follow-up with the investigator in an attempt to obtain additional relevant information. Based on the current data, this case does not meet Hy's Law (serum bilirubin not >2x ULN).

The sponsor was asked to clarify whether there have been any Hy's Law cases or additional cases of ALT>10x ULN in saxagliptin trials after the database lock for the 120-day safety update. The sponsor unblinded patients meeting these criteria and reported that there have been 3 new liver cases among saxagliptin-treated patients as of July 13, 2009. Narratives for these 3 patients are summarized below and do not support a signal for severe drug-induced liver injury with saxagliptin:

- One saxagliptin-treated patient developed ALT of 981 U/L (27x ULN) with normal serum bilirubin 4 days after undergoing left leg amputation due to gangrene. Of note, saxagliptin had been permanently discontinued (due to myocardial infarction) 22 days prior to the markedly elevated ALT. Liver tests within 1 week prior to saxagliptin discontinuation were normal.

- One saxagliptin-treated patient with normal liver tests at baseline developed ALT of 209 U/L on Day 455 (6x ULN) with normal serum bilirubin. This finding prompted an unscheduled clinic visit on Day 470. At this follow-up visit, serum transaminases were normal although total bilirubin was 2.5 mg/dL (ULN is 1.2 mg/dL). On Day 473, abdominal ultrasound showed "calculous cholecystitis non-activ" (sic). Of note, study medication was continued throughout. Subsequent liver tests were normal and the patient completed the trial on Day 533.

- One saxagliptin-treated patient with mildly elevated ALT of 56 U/L at baseline (1.2x ULN) had persistently elevated ALT throughout the trial, peaking at 509 U/L approximately 1-year into the trial. ALT declined to 345 U/L two weeks later, at which point study medication was discontinued due to inadequate glycemic control. Of note, serum bilirubin was normal at all timepoints and the ALT was 295 U/L three weeks after

discontinuation from the trial. According to the investigator, the patient confirmed that he had daily intake of alcohol during a 2-week vacation that ended 1 day prior to the clinic visit when ALT peaked at 509 U/L. At this visit, AST was greater than ALT.

Including data up until July 13, 2009, there are 7 saxagliptin-treated patients and 3 comparator-treated patients with ALT >10x ULN. Data are blinded for ongoing trials that account for six of these 10 patients (3 on saxagliptin and 3 on comparator); therefore overall incidence rates cannot be calculated. However, the two ongoing clinical trials contributing these additional 6 liver events randomized patients 1:1 to saxagliptin or comparator. Therefore, the overall events of 7 vs. 3 for ALT >10x ULN is consistent with the overall randomization scheme (three-fold higher patient-year exposure for saxagliptin relative to comparator in the 120-day safety update database and 1:1 randomization for the two ongoing clinical trials) and a description of these liver events with saxagliptin does not need to be labeled at the present time.

Renal function: Saxagliptin had no effects on serum creatinine. In the combined short-term and long-term periods of the pooled phase 3 program (120-day safety update database; excluding the small mechanism-of-action trial), the median change from baseline in serum creatinine in the saxagliptin 2.5 mg, 5 mg, and 10 mg treatment groups was 0.0 mg/dL at Weeks 24, 50, 76, 102, and 128). In this dataset, 7.2% of saxagliptin-treated patients and 7.5% of comparator-treated patients developed serum creatinine >1.5x the baseline serum creatinine value.

Other: Table 20 summarizes the incidence of other marked laboratory abnormalities in the phase 2/3 program up to the cut-off date for the 120-day safety update. Marked lymphocyte counts are discussed above. The incidence of other markedly abnormal laboratory tests was low and comparable in the overall saxagliptin and comparator treatment groups.

Table 19. Liver test abnormalities in the combined short-term and long-term periods of the phase 2/3 trials (up to the cut-off date for the 120-day safety update)

Parameter	Saxagliptin							Control N=1232 n (%)
	2.5 mg N=926 n (%)	5 mg N=1254-1255 n (%)	10 mg N=1046 n (%)	20 mg N=54 n (%)	40 mg N=51 n (%)	100 mg N=44 n (%)	All Saxa N=3375-3376 n (%)	
ALT >3x ULN	16 (1.7)	20 (1.6)	7 (0.7)	0	0	1 (2.3)	44 (1.3)	17 (1.4)
ALT >5x ULN	4 (0.4)	3 (0.2)	2 (0.2)	0	0	1 (2.3)	10 (0.3)	2 (0.2)
ALT >10x ULN	2 (0.2)	0	1 (0.1)	0	0	1 (2.3)	4 (0.1)	0
Total bilirubin >2x ULN	2 (0.2)	3 (0.2)	2 (0.2)	0	0	0	7 (0.2)	1 (0.1)
Alkaline phosphatase >1.5x ULN	42 (4.5)	46 (3.7)	42 (4.0)	0	0	0	130 (3.9)	64 (5.2)
ALT or AST >3x ULN and total bilirubin >2x ULN	2 (0.2)	0	0	0	0	0	2 (0.1)	1 (0.1)

ULN = upper limit of normal
N represents the number of patients with laboratory data, which varies for some parameters in the 5 mg group

Table 20. Select marked laboratory abnormalities in the combined short-term and long-term periods of the phase 2/3 trials (up to the cut-off date for the 120-day safety update)

Parameter	Saxagliptin							Control N=1228-1232 n (%)
	2.5 mg N=922-926 n (%)	5 mg N=1252-1255 n (%)	10 mg N=1040-1046 n (%)	20 mg N=54 n (%)	40 mg N=51 n (%)	100 mg N=44 n (%)	All Saxa N=3363-3375 n (%)	
Hematocrit <0.75x pre-treatment	6 (0.6)	17 (1.4)	9 (0.9)	0	0	0	32 (0.9)	8 (0.7)
Platelets <50x10^9 c/L	0	2 (0.2)	1 (0.1)	0	1 (2.0)	0	4 (0.1)	1 (0.1)
Platelets >1.5x ULN	1 (0.1)	0	6 (0.6)	0	0	0	7 (0.2)	4 (0.3)
Leukocytes <2x10^3 c/mcL	1 (0.1)	0	1 (0.1)	0	0	0	2 (0.1)	1 (0.1)
Eosinophils >0.9x10^3 c/mcL	49 (5.3)	67 (5.3)	40 (3.8)	0	0	0	156 (4.6)	68 (5.5)
Lymphocytes ≤0.75x10^3 c/mcL	8 (0.9)	20 (1.6)	17 (1.6)	2 (3.7)	1 (2.0)	0	48 (1.4)	9 (0.7)
Serum creatinine >2.5 mg/dL	3 (0.3)	1 (0.1)	2 (0.2)	0	0	0	6 (0.2)	1 (0.1)
Creatine kinase >5x ULN	10 (1.1)	19 (1.5)	11 (1.1)	1 (1.9)	1 (2.0)	1 (2.3)	43 (1.3)	14 (1.1)

ULN = upper limit of normal
N represents the number of patients with laboratory data, which varies for some parameters in the 2.5, 5, and 10 mg groups

Vital signs: Dr. Lowy reviewed the blood pressure and heart rate data for the short-term periods from the individual phase 3 trials. Saxagliptin does not have any clinically meaningful effect on these vital signs.

Table 21 summarizes the mean changes from baseline in body weight for monotherapy study -011, the add-on combination therapy trials, and the initial combination with metformin trial. Data are presented for the short-term periods prior to glycemic rescue to limit confounding. All treatment groups, including placebo, had small changes from baseline in body weight (<2 kg), with increases from baseline across all treatment groups in the add-on to sulfonylurea and add-on to thiazolidinedione trials and decreases across all treatment groups in the other trials.

Table 21. Mean change (±SE) in body weight (kg) from baseline to Week 24 in the phase 3 trials (prior to rescue with last-observation carried forward)

	Saxa 2.5 mg n (%)	Saxa 5 mg n (%)	Saxa 10 mg n (%)	Placebo n (%)
Monotherapy trial -011	**N=247**	**N=252**	**N=98**	**N=169**
N	101	105	97	93
Baseline	92.0±1.8	90.8±1.8	89.4±1.8	86.3±1.7
Change from baseline	-1.2±0.3	-0.1±0.4	-0.1±0.2	-1.4±0.3
Add-on to sulfonylurea trial	**N=248**	**N=253**	-	**N=267**
N	247	253	-	265
Baseline	75.1±0.9	76.2±1.1	-	75.6±1.1
Change from baseline	0.7±0.1	0.8±0.1	-	0.3±0.1
Add-on to metformin	**N=192**	**N=191**	**N=181**	**N=179**
N	188	191	181	177
Baseline	86.1±1.3	87.3±1.2	87.8±1.4	87.5±1.3
Change from baseline	-1.4±0.2	-0.9±0.2	-0.5±0.3	-0.9±0.2
Add-on to thiazolidinedione	**N=195**	**N=186**	-	**N=184**
N	193	185	-	182
Baseline	82.3±1.6	80.5±1.4	-	80.9±1.6
Change from baseline	1.3±0.2	1.4±0.2	-	0.9±0.2
Initial therapy with metformin	**Saxa 5 mg+met N=320**	**Saxa 10 mg+met N=323**	**Saxa 10 mg N=335**	**Met N=328**
n	318	320	329	322
Baseline	82.2±0.9	82.4±0.9	83.1±0.9	82.9±1.0
Change from baseline	-1.8±0.2	-1.4±0.2	-1.1±0.2	-1.6±0.2

Electrocardiograms: Standard 12-lead electrocardiograms were obtained in the short-term periods of the phase 3 trials at screening, Week 12, and Week 24. These data are limited because the electrocardiograms were reviewed by investigators and were not read centrally by a cardiologist. In addition, the sponsor analyzed the data by showing shift tables from a normal reading at baseline to an abnormal reading post-baseline (per investigator assessment) without including dedicated analyses for the individual electrocardiogram parameters. However,

saxagliptin does not have a clinically meaningful effect on the QT interval based on results from the Thorough QT Study and there are no signals of cardiovascular toxicity based on the animal data or clinical adverse events. The sponsor will be conducting a definitive cardiovascular safety trial and the electrocardiograms from the completed phase 3 program can be centrally read in the future, if needed, based on any unexpected findings.

Findings with higher saxagliptin doses: Doses of saxagliptin considerably higher than the doses proposed for marketing have been tested to a limited extent in some phase 1/2 trials. Relevant findings from the two drug interaction studies with ketoconazole (CV181005 and CV181022) are described in the clinical pharmacology section of this memorandum. Relevant safety findings from other trials are summarized here:

- CV181032: In this Thorough QT Study, approximately 40 healthy subjects received two saxagliptin doses (10 mg and 40 mg) administered for 4 days. None of the saxagliptin-treated subjects developed the influenza-like symptoms described in the ketoconazole trials and none had markedly low absolute lymphocyte counts (<750 c/mcL).

- CV181031: The primary objective of this study was to evaluate the effect of single and multiple doses of saxagliptin on lymphocyte count. A total of 48 healthy subjects were randomized to one of four treatment sequences: (1) saxagliptin 40 mg on Days 2 and 10-23, (2) saxagliptin 10 mg on Days 2-15 and 23, (3) saxagliptin 40 mg on Days 2-15 and 23, or (4) placebo on Days 1-23. Two patients in the saxagliptin 10 mg treatment sequence reported headaches but there were no reports in this trial of an influenza-like syndrome. No patients had markedly low absolute lymphocyte counts (<0750 c/mcL). No patients had ALT>3x ULN, although three saxagliptin 40 mg-treated patients met the sponsor's criteria for markedly high ALT (>1.25x ULN or >1.25x pre-treatment values for patients with baseline ALT>ULN). Six patients had markedly low hemoglobin (<0.85x pre-treatment value), 5/36 (14%) receiving saxagliptin (2 in each of the saxagliptin 40 mg regimens and 1 in the 10 mg regimen) and 1/12 (8%) receiving placebo. The sponsor conducted flow cytometry on the cohort receiving saxagliptin 40 mg on Days 2-15 and 23, comparing patients with larger decreases in lymphocyte counts 24 hours after the Day 23 dose (n=5; mean decrease 40%) to patients with smaller decreases (n=7; mean decrease 9%). The sponsor concluded that saxagliptin did not affect any particular lymphocyte population and that saxagliptin did not likely alter lymphocyte proliferation rate or necrosis/apoptosis. Of note, none of these patients developed lymphocyte counts below the lower limit of the reference range, which may limit conclusions.

- CV 181017: In this drug interaction study with metformin, subjects were randomized to receive, in random order, single doses of saxagliptin 100 mg alone, metformin 1000 mg alone, and saxagliptin+metformin. One subject developed an influenza-like syndrome, but had normal lymphocyte counts. A second subject was diagnosed with an upper respiratory infection associated with a transient reduction in lymphocyte count to 500 c/mcL. A third subject presented with chills and photophobia associated with a transient reduction in lymphocyte count to 600 c/mcL. All three events occurred after exposure to the second dose of saxagliptin.

- CV181010: In this multiple ascending dose study, healthy volunteers were randomized to saxagliptin (40, 100, 150, 200, 300, and 400 mg) or placebo once daily for 14 days. One subject receiving 200 mg developed rash on Day 9 and was discontinued. One subject receiving 200 mg developed fever on Day 6 that resolved on Day 7. No subjects had a markedly low absolute lymphocyte count (<750 c/mcL). Markedly low hemoglobin and/or hematocrit (<0.85x pre-treatment value) occurred in 6 subjects, all receiving saxagliptin (1 receiving 100 mg, 1 receiving 200 mg, 2 receiving 300 mg, and 2 receiving 400 mg). Markedly low platelet counts (<128 $x10^9$ c/L) occurred in two subjects, one receiving 300 mg (baseline 173→115 x 10^9 c/L on Day 16) and one receiving 400 mg (baseline 181→115 $x10^9$ c/L on Day 16). Platelet counts for both individuals normalized at post-treatment follow-up visits. No subject had ALT >3x ULN although 3 subjects (1 receiving 40 mg, 1 receiving 300 mg, and 1 receiving 400 mg) met the protocol pre-specified criteria for a markedly abnormal ALT (>1.25x ULN or >1.25x pre-treatment value if the pretreatment value was >ULN) ranging from 1.3-2.5x ULN and all normalizing in post-treatment follow-up visits.

- CV181008: Relevant findings from this dose-ranging phase 2 trial have been described in the efficacy and safety sections of this memorandum.

- CV181001: In this first-in-human trial, there were 9 panels of 8 healthy volunteers who were each randomized 6:2 to a single ascending dose of saxagliptin or placebo. Saxagliptin doses >10 mg included 20 mg, 30 mg, and 50 mg. After a 7-day washout, saxagliptin-treated subjects received a single dose of saxagliptin with food. One subject (saxagliptin 75 mg) had fever, chills, and headache during the food portion of the trial. No subjects had a markedly low absolute lymphocyte count (<750 c/mcL).

- CV181002: In this multiple ascending dose study, patients with type 2 diabetes were randomized to saxagliptin or placebo once daily for 14 days. Saxagliptin doses >10 mg included 15, 30, and 50 mg. None of the patients in this trial reported the influenza-like syndrome or had a markedly low absolute lymphocyte count (<750 c/mcL). No patient had ALT >3x ULN.

9. Advisory Committee Meeting

On April 1, 2009, an advisory committee meeting was held to discuss whether there is adequate evidence of cardiovascular safety with saxagliptin to support approvability, as recommended in the diabetes cardiovascular guidance. The panel consisted of members from the Endocrinologic and Metabolic Drugs advisory committee populated with two cardiologists and a member of the Drug Safety and Risk Management advisory committee. After extensive discussion about the saxagliptin development program, including the low event rates and the post-hoc cardiovascular assessment, the panel was asked to vote on the following questions:

"Based on the preceding discussion, has the applicant provided appropriate evidence of cardiovascular safety to conclude that saxagliptin rules out an unacceptable excess cardiovascular risk relative to comparators, including evidence that the upper bound of the

two-sided 95% confidence interval for the risk ratios/odds ratios is less than 1.8?" Ten panel members voted yes and two panel members voted no. The two cardiologists were split in their vote. The cardiologist voting no stated that his vote was chosen to reflect that labeling should restrict use to a population at low risk for cardiovascular events because few high-risk patients were studied in the saxagliptin program and it is unknown whether cardiovascular safety will apply to that patient population also. The other no vote also stated that the number of events is too low to provide an adequate assessment of cardiovascular safety. The cardiologist voting yes stated that the 1.8 criterion had been met and additional assurance about cardiovascular safety will be obtained post-approval. This cardiologist agreed with the limitations such as lack of adjudication but was reassured by the odds ratios for MACE events, with all point estimates <1.0 and the upper bounds of the corresponding 95% confidence intervals far enough to the left of 1.8. This cardiologist also acknowledged the lack of data in patients at high cardiovascular risk and recommended a statement in labeling that cardiovascular safety in high-risk patients has not been evaluated.

The second voting question stated "For the Custom MACE endpoint, the upper bound of the two-sided 95% confidence interval for the risk ratios/odds ratio was less than 1.3. These data involved a total of 11 cardiovascular events in the 24-week double-blind short-term study periods and a total of 40 cardiovascular events in the combined short-term and long-term study periods of median 62-week exposure. Are these data adequate to conclude that post-marketing cardiovascular safety trials are unnecessary?" All 12 voting panel members voted no. Although the Custom MACE endpoint satisfied the 1.3 criterion, there was concern that the low event rates and other limitations described above do not provide sufficient assurance on this more stringent level of confidence on cardiovascular safety.

10. Pediatrics

The sponsor has requested a deferral for children ≥10 years old and a waiver for children <10 years old. The Division and the Pediatric Review Committee (PeRC) agree with this proposal, which is consistent with our approach to other oral treatments for type 2 diabetes (there are too few children less then 10 years of age with type 2 diabetes; therefore, studies in this population are highly impractical).

The sponsor's proposed pediatric plan consists of a single randomized, double-blind, placebo-controlled trial that will evaluate the efficacy, safety, tolerability, and pharmacokinetics of saxagliptin monotherapy in at least 136 pediatric patients with type 2 diabetes and inadequate glycemic control on diet and exercise. The sponsor proposes a 16-week, randomized, double-blind phase followed by a 36-week extension phase of continued double-blind treatment (group randomized to saxagliptin) or a cross-over to double-blind metformin treatment (group randomized to placebo). The sponsor is also proposing an open-label, non-randomized saxagliptin add-on study arm for up to 70 patients not qualifying for participation in the main study due to existing metformin use. Prior to initiation of the main study, there will be a pre-randomization pharmacokinetic sub-study conducted in 12-24 children who will then be randomized into the main trial.

A 1-year, controlled treatment period is appropriate but the Division and PeRC have interest in obtaining controlled pediatric data for patients who are treatment naïve and for patients who are on existing metformin therapy. Revisions to the proposed pediatric trial will be discussed with the sponsor in more detail post-approval. The sponsor has proposed the following timelines for the pediatric trial, which are acceptable:

Submission of the finalized protocol: June 30, 2010
Completion of the pediatric trial: March 31, 2015
Submission of the complete study report: June 15, 2015

The sponsor justified this 5-year timeframe based on the prior experience with the Glucovance pediatric study (20 months to enroll and complete the 26-week trial, which had more liberal HbA1c criteria than the currently proposed saxagliptin trial) and the increased competition for the limited pool of pediatric patients with type 2 diabetes.

11. Other Relevant Regulatory Issues

Tradename: The Division of Medication Error Prevention and Analysis (DMEPA) has found the proposed tradename "Onglyza" to be acceptable. Please see the reviews of Dr. Anne Crandall and Ms. Melina Griffis for details. Ms. Griffis' review was completed on July 2, 2009, within 90 days of the anticipated action date of July 30, 2009.

DMEPA also identified potential vulnerability to confusion in the blister pack and tray labeling that could lead to medication errors. The sponsor submitted revised labeling that DMEPA has found to be satisfactory. Please see Dr. Melina Griffis' review for details. The only remaining recommendation from DMEPA is that the font size of the 5 mg strength designation on the physician sample pack be increased. This recommendation has been communicated to the sponsor and a response is pending at the time of this review.

Financial disclosures: Dr. Lowy reviewed the financial disclosure statements for investigators and sub-investigators involved in the saxagliptin clinical trials. The sponsor is missing disclosure information for one principal investigator, but this person only enrolled 2 patients in a single phase 3 trial. Two investigators disclosed potential financial conflicts of interest but only randomized a total of 7 patients across the phase 3 trials.

The sponsor is missing financial disclosure information for one or more sub-investigators at a total of 11 clinical sites. These sites randomized a total of 26 patients in the clinical trials.

I concur with Dr. Lowy that the above-described findings are not expected to meaningfully impact the conclusions of the trials because few patients were involved. In addition, the double-blind study designs and objective primary efficacy endpoint limit bias.

Division of Scientific Investigations: The Division of Scientific Investigations (DSI) inspected four clinical sites (enrolled/randomized a total of 57 patients in phase 3 trials), HbA1c data for a total of 62 patients at two clinical laboratories [redacted] b(4)

and some of the sponsor's records. Regulatory violations were noted at the sponsor (e.g., shipping of investigational drug to a location where the clinical trial was no longer taking place) and were noted at three of the four clinical sites (e.g., a few adverse events were recorded in source documents but not reported to the sponsor, inadequate records concerning reasons for patient discontinuation from trials, delayed reporting of a serious adverse event to the sponsor). However, DSI has concluded that the studies appear to have been conducted adequately and that the data generated by the clinical sites can be used to support the proposed indication. Please see Dr. Susan Leibenhaut's memorandum for further details.

After submission of the NDA, the sponsor terminated clinical trial agreements with [redacted] (a site management organization) because of allegations from one of the investigators claiming misconduct on the part of this organization (e.g., incorrect billing of the sponsor for activities that never occurred, forging of signatures). This company was involved with 3 sites that randomized a total of 41 patients into the phase 3 trials. Any irregularities involving this small number of patients would not be expected to alter the NDA's efficacy or safety conclusions. b(4)

12. Labeling

Labeling discussions are ongoing at the time of this review. Key issues are summarized below. Please see the final label for further details.

- Some of the clinical trials included a 10 mg treatment arm. I concur with the sponsor that the 5 mg dose should be the highest approved dose (see below). Although the 10 mg dose will be mentioned in the trial descriptions, the label should contain an explicit statement that the 10 mg dose is not recommended and explain why. The label should not contain efficacy data for the 10 mg dose.
- The 2.5 mg and 5 mg doses had comparable efficacy in the dose-ranging phase 2 trial and in several phase 3 trials. Therefore, the recommended dose should be 2.5-5 mg daily.
- The label should mention the need for dosage adjustment in patients with moderate or severe renal impairment or end-stage renal disease and in patients taking strong CYP3A4/5 inhibitors.
- The sponsor has proposed including a statement in the label that saxagliptin is [redacted]. Such a statement should not be permitted at the present time because of limitations of the cardiovascular data (e.g., post-hoc, non-adjudicated nature of the analyses, low event rates, low-risk patient population) and the potential for inappropriate promotion. b(4)
- The label should include a description of the lymphocyte findings and advice to measure lymphocytes when clinically indicated.
- The label should contain limited, if any, efficacy data from the long-term periods because of limitations associated with those data (see the efficacy section of this memorandum).
- The sponsor is proposing to present postprandial glucose data from the clinical trials using AUC. The postprandial glucose data should be presented in a form that is more readily interpretable to clinicians (e.g., 2-hour postprandial glucose).
- The imbalance in fractures not favoring saxagliptin should be included in the label because an imbalance persists after fractures due to high impact trauma (e.g., car accidents) are excluded.

- If saxagliptin cannot be reasonably excluded as a cause for the marked ALT elevation in the end-stage renal disease patient, that finding should be described in the label.
- Inappropriate promotional statements have been revised with input from the Division of Drug Marketing, Advertizing and Communications (DDMAC) (see the review of Dr. Samuel Skariah for further details).
- The formatting has been reviewed by the Study Endpoints and Label Development (SEALD) group to ensure consistency with the Physician's Labeling Rule (see the review of Ms. Jeanne Delasko for further details).
- The patient package insert (PPI) has been reviewed by the Division of Risk Management (DRISK) to ensure patient-friendly language is used (see the review of Ms. Jessica Diaz for further details).

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval, pending agreement on labeling.

- Risk Benefit Assessment

Saxagliptin results in a modest, but clinically meaningful improvement in glycemic control in patients with type 2 diabetes with generally neutral effects on body weight and minimal risk for hypoglycemia.

In the phase 3 clinical trials, the 5 mg dose is marginally more effective than the 2.5 mg dose in some, but not all, settings. However, based on the available data, it is probable that 5 mg may be more efficacious than 2.5 mg in some patients. For this reason, the recommended dose should be 2.5 mg or 5 mg daily for the general patient population with type 2 diabetes. Based on increased pharmacokinetic exposures, only the 2.5 mg dose is recommended for patients with moderate or severe renal impairment or end-stage renal disease and for patients on strong CYP3A4/5 inhibitors. Although a 10 mg treatment arm was included in some of the phase 3 trials, this dose did not offer incremental glycemic benefit beyond that achieved with the 5 mg dose. In addition, the 10 mg dose was associated with greater reductions in the absolute lymphocyte count compared to the 5 mg dose (see below). Therefore, the maximum recommended approved dose should be 5 mg daily.

There is an imbalance in fracture adverse events not favoring saxagliptin. The fracture imbalance persists after excluding events related to major trauma. Therefore, the fracture imbalance should be included in the package insert and fractures should be an adverse event of interest in the required postmarketing cardiovascular outcomes trial (see below).

With regard to liver, a comparable proportion of saxagliptin and comparator patients discontinued due to adverse events of liver test abnormalities in the phase 3 program. In addition, there is no imbalance in the proportion of saxagliptin and comparator-treated patients with ALT>3x or >5x ULN. In the phase 2/3 database, there are 4 cases of ALT >10x ULN among saxagliptin-treated patients and no cases with comparator. Two of these 4 cases are

attributable to viral hepatitis. The other 2 cases are unexplained, but neither meet the criteria for Hy's Law and one of these cases occurred in a patient receiving 100 mg daily. The 2 vs. 0 cases of unexplained ALT >10x ULN is consistent with the three-fold higher patient-year exposure for saxagliptin relative to comparator.

There are no cases of true Hy's Law (ALT >3x ULN, total bilirubin >2x ULN, alkaline phosphatase <2x ULN, and no alternate explanation for the liver test abnormalities) among saxagliptin-treated patients, including data analyzed after the 120-day safety update submission up to July 2009. Therefore, based on the currently available data there is no evidence of severe drug-induced liver injury with saxagliptin.

At the proposed doses for marketing (2.5 mg and 5 mg), saxagliptin causes minor, but dose-dependent reductions in lymphocyte counts without evidence in the clinical trials of an increased incidence of overall infections or opportunistic infections, autoimmune disease, or hematological cancers. Of the 3 tested doses in the phase 3 program, the 10 mg dose (which will not be marketed) results in the largest mean reductions in lymphocyte counts (reductions as high as 5-10% compared to placebo). The incidence of overall infections with the 10 mg dose is increased in the pooled placebo-controlled phase 3 trials (56% vs. 49% with placebo) driven predominantly by differences in the incidence of several common infections (nasopharyngitis, influenza, and sinusitis). The 10 mg dose is not associated with an increased incidence of unusual infections or other evidence of immune disruption.

In the phase 2/3 database, the incidence of markedly low lymphocyte counts (defined by the sponsor as ≤750 c/mcL; the lower limit of the reference range is 1,000 c/mcL) was similar in the saxagliptin 2.5 mg group (0.9%) and the control group (0.7%), but more frequent in the saxagliptin 5 mg (1.6%) and 10 mg groups (1.6%). Of note, the sponsor incorporated an algorithm in all phase 3 trials for interrupting or permanently discontinuing study medication based on lymphocyte count values. A small proportion of patients with a non-isolated decline in lymphocyte count had an interruption of study medication dosing (1 or 0.1% receiving comparator, 3 or 0.3% receiving 2.5 mg, 6 or 0.5% receiving 5 mg, and 4 or 0.4% receiving 10 mg) or permanent discontinuation of study medication (1 or 0.1% receiving comparator, 2 or 0.2% receiving 2.5 mg, 4 or 0.3% receiving 5 mg, and 3 or 0.3% receiving 10 mg). It is unknown whether the few patients who had an interruption or discontinuation of the saxagliptin dose based on the lymphocyte algorithm would have had any untoward effect if the algorithm was not instituted and possibly prolonged reductions in lymphocyte counts persisted. The package insert should advise healthcare providers to measure the lymphocyte count when clinically indicated (e.g., unusual or prolonged infection). This approach is similar to measuring white blood cell counts, when clinically indicated, to assess for agranulocytosis (incidence approximately 0.2%) with antithyroid drugs.

In clinical practice, a small proportion of saxagliptin-treated patients may have prolonged periods of reduced lymphocyte counts. These patients are not necessarily in well-supervised environments like clinical trials where the lymphocyte count is carefully followed and study medication is discontinued based on a clinical trial algorithm. To provide additional reassurance that these patients will not have any untoward long-term effects, the lymphocyte algorithm should not be incorporated into the required postmarketing cardiovascular trial (see

below). In this trial, blinded lymphocyte counts should be measured but not shared with investigators. Instead, the investigators should independently assess lymphocyte counts when clinically indicated and use their own discretion as to when to interrupt or discontinue study medication.

Saxagliptin has minor effects on platelet counts that do not appear to be clinically relevant.

- Recommendation for Postmarketing Risk Management Activities

The Periodic Adverse Drug Experiences Reports (PADERs) should include summary sections on adverse events of interest, including liver events, lymphopenia, and unusual infections (e.g., opportunistic organisms). Hepatotoxicity events and unusual infections should undergo expedited reporting during the initial years following approval.

- Recommendation for other Postmarketing Study Commitments

As discussed in this memorandum, the sponsor should be required to conduct a postmarketing cardiovascular outcomes trial to rule out an unacceptable increase in cardiovascular risk (i.e., to show that the upper bound of the 95% confidence interval for the risk ratio comparing MACE events with saxagliptin to MACE events with comparator is <1.3). The adverse events of interest for all drugs in the DPP-4 inhibitor class (e.g., hypersensitivity reactions, hepatotoxicity, pancreatitis, infections, skin reactions, and renal safety) should be included as adverse events of interest in the cardiovascular trial. The cardiovascular trial should also include 2 other adverse events of interest – fractures and lymphocyte counts.

The sponsor will also be required to conduct a pediatric study under the Pediatric Research Equity Act (PREA) as discussed in Section 10 of this memorandum.

The sponsor is planning to conduct several postmarketing epidemiological studies comparing saxagliptin and other anti-diabetic medications with regard to cardiovascular events, severe hypersensitivity and cutaneous reactions, hospitalizations for infections, risk factors for lymphopenia, and events of acute renal failure and hepatic failure. The required large, controlled cardiovascular safety trial will also evaluate these events of interest. However, epidemiological studies may also be particularly useful for evaluating hypersensitivity reactions and severe hepatic events because such events (if associated with saxagliptin) are likely to be rare. For this reason, in addition to the required postmarketing cardiovascular trial, the Division should require postmarketing epidemiological studies only for severe hypersensitivity and cutaneous reactions and severe hepatic events.

Lastly, I recommend that, in addition to the standard reporting requirements for an approved NDA, the sponsor submit as 15-day expedited reports, all postmarketing cases of (1) liver test abnormalities accompanied by jaundice or hyperbilirubinemia, (2) opportunistic infections and (3) pancreatitis associated with the use of saxagliptin, regardless of whether these reports are classified as serious or unexpected.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22350	ORIG 1	BRISTOL MYERS SQUIBB CO	SAXAGLIPTIN

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/s/

HYLTON V JOFFE
07/28/2009

MARY H PARKS
07/28/2009