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APPLICATION NUMBER:

200678Orig1s000

MEDICAL REVIEW(S)

MEMO TO THE FILE

NDA	200678
Sponsor	Bristol-Myers Squibb
Drug Product	Kombiglyze XR (saxagliptin/metformin extended release) fixed dose combination tablets
Date of Submission	December 29, 2009
PDUFA goal date	October 29, 2010

Kombiglyze XR is a fixed-dose combination (FDC) tablet of saxagliptin and metformin HCl extended-release (met XR). The drug product is a tablet (b) (4) The proposed dosage strengths are:

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

The development of a FDC applies the policy outlined in 21 CFR 300.50 in which "two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug". In the development of FDC products for the treatment of anti-diabetic agents, the applicant would need to provide clinical trial data demonstrating that each of the individual components makes a contribution to the claimed effects of the FDC, and that the combination is acceptably safe. Of late, it has not been unusual for many companies to develop FDC of two approved anti-diabetic agents. In this setting, if clinical efficacy and safety data are available from a trial showing the individual components co-administered provide greater efficacy (and are safe) than the individual components alone, it may be sufficient for the FDC development program to only demonstrate bioequivalence between the FDC and individual components co-administered. This BE study would serve as the bridge between the FDC tablet and the clinical efficacy and safety trial of the individual components.

This NDA is a 505(b)(1) application as the applicant is the NDA holder for all drugs relied upon in support of efficacy and safety of the FDC. These NDAs include:

- NDA 22-350 Onglyza (saxagliptin) approved at doses of 2.5 mg and 5.0 mg
- NDA 20-357 Glucophage (metformin HCl) approved at doses of 500 mg, 850 mg, and 1000 mg
- NDA 21-202 Glucophage XR (metformin HCl) approved at doses of 500 mg and 750 mg

Although it would seem that this NDA is straightforward since Bristol-Myers Squibb has full right of reference to all of the referenced NDA, some of the data submitted did not involve a direct bridge between the FDC and the referenced product relied upon for labeling. Instead, an indirect bridge was

relied upon in which an intermediate drug product served as the link between the FDC and the drug product studied in the clinical efficacy and safety trial.

This memo will only summarize the bridging clinical data and what has led FDA to conclude an FDC product may be approved, even if relying on indirect bridging data. Please see Dr. Joffe's CDTL memo and the Clinical Pharmacology review for complete details of the clinical program.

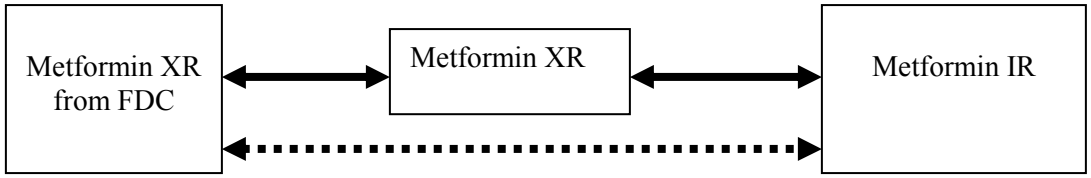
All clinical efficacy and safety data for saxagliptin plus metformin HCl summarized in this label are from NDA 22-350 and involves the immediate-release formulation of metformin HCl. There is no direct bridge between Kombiglyze XR and these two individual components nor have there been any clinical trials conducted with Kombiglyze XR. Instead the following pivotal BE studies were conducted:

Pivotal BE Study	**Test**	**Comparators**
CV181111	FDC of saxagliptin 5 mg and 500 mg metformin XR manufactured in Mt Vernon, IN	Marketed Saxagliptin 5 mg and metformin XR 500 mg co-administered
CV181112	FDC of saxagliptin 5 mg and 1000 mg metformin XR manufactured in Mt Vernon, IN	Marketed saxagliptin 5 mg and metformin XR 500 mg x 2 co-administered

As noted in the review by Dr. Jain and Choe, the FDC of saxagliptin 5mg/metXR 500 mg and saxagliptin 5 mg/metXR 1000 mg were bioequivalent to their individual components co-administered. A biowaiver was granted for the lower dosage strength of saxagliptin 2.5 mg/metXR 1000 mg. These two studies allow us to conclude that when the FDC is administered, a similar PK profile can be expected to when saxagliptin and metformin XR are co-administered. However, these two studies do not provide a direct bridge to clinical efficacy and safety data (b) (4).

As noted in the reviews of Drs. Joffe and Peneva, the efficacy and safety data for saxagliptin plus metformin, in treatment-naïve and as add-on therapy, are from trials using metformin immediate-release formulation. To bridge these data to the Kombiglyze XR, the applicant had to rely on the Glucophage and Glucophage XR NDAs in which these two different formulations of metformin were evaluated. In her addendum to the original Clinical Pharmacology review, Drs. Jain and Choe summarize the different PK characteristics between these two metformin formulations. Although the Cmax for Glucophage XR is lower than Glucophage by approximately 20%, the extent of absorption (AUC) is comparable between these two drug products with the ratio of the geometric means and accompanying 90% CI being 1.00 (0.93, 1.07). The differences in PK profiles were not considered clinically relevant as a 24-week clinical trial comparing efficacy between patients continued on metformin immediate-release versus being switched to metformin extended-release did not appear to have marked differences in efficacy. Despite this, the label for Glucophage/Glucophage XR does recommend monitoring of glycemic control when switching from the immediate-release to the extended-release formulation.

The following diagram depicts the direct and indirect bridging of data to support a conclusion that Kombiglyze XR should result in similar efficacy as saxagliptin plus metformin IR.



It not uncommon that multiple bridging studies are conducted to link clinical data, even within a single development program as drug products undergo different formulation changes or scale up in manufacturing. However, there has been a noticeable increase in applications for FDCs for the treatment of diabetes and while the rationale for their development is reasonable (majority of diabetics are on multiple anti-diabetic therapies), these products are convenience products with no evidence of improved patient compliance resulting in better diabetes management. Consequently, labeling for a FDC product should accurately summarize the source from which clinical efficacy and safety data are derived. In the case of Kombiglyze XR, the following text has been added to Section 14, Clinical Studies:

There have been no clinical efficacy or safety studies conducted with KOMBIGLYZE XR to characterize its effect on hemoglobin A1c (A1C) reduction. Bioequivalence of KOMBIGLYZE XR with coadministered saxagliptin and metformin hydrochloride extended-release tablets has been demonstrated; however, relative bioavailability studies between KOMBIGLYZE XR and coadministered saxagliptin and metformin hydrochloride immediate-release tablets have not been conducted. The metformin hydrochloride extended-release tablets and metformin hydrochloride immediate-release tablets have a similar extent of absorption (as measured by AUC) while peak plasma levels of extended-release tablets are approximately 20% lower than those of immediate-release tablets at the same dose.

The Dosage and Administration section of labeling also recommends appropriate monitoring of glycemic control after any change in diabetes therapy, specifically when switching of metformin formulations.

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/s/

MARY H PARKS
11/04/2010

CLINICAL REVIEW

Application Type	505(b)(1)
Application Number(s)	NDA 200678
Priority or Standard	Standard
Submit Date(s)	
Received Date(s)	12/29/09
PDUFA Goal Date	10/29/10
Division / Office	DMEP
Reviewer Name(s)	Arlet V. Nedeltcheva
Review Completion Date	08/20/2010
Established Name	(Saxagliptin + Metformin XR) FDC
(Proposed) Trade Name	(b) (4)
Therapeutic Class	DPP4 inhibitor and a biguanide
Applicant	BMS
Formulation(s)	**5 mg saxagliptin/500 mg metformin XR, 2.5 mg saxagliptin/1000 mg metformin XR, 5 mg saxagliptin/1000 mg metformin XR**
Dosing Regimen	***once daily in the evening***
Indication(s)	**As an adjunct to diet and exercise to improve glycemic control in T2DM when treatment with both saxagliptin and metformin is appropriate.**
Intended Population(s)	***Type 2 Diabetes mellitus***

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

From a clinical perspective, the application is recommended for approval.

1.2 Risk Benefit Assessment

The saxagliptin/metformin XR FDC contains two approved medications with known risks in a single tablet. The benefit of the FDC is the convenience of the patients taking less pills, which may decrease noncompliance to drug treatment.

1.3 Recommendations for Post-market Risk Evaluation and Mitigation Strategies

There are no Risk Evaluation and Mitigation Strategies (REMS) in place for saxagliptin or metformin and no new safety issues were identified with co-administration. Therefore, there is no need for a REMS for this FDC.

1.4 Recommendations for Post-market Requirements and Commitments

There are several required postmarketing studies for saxagliptin. For additional information refer to the NDA 22350 Approval letter, date July 31, 2009. No distinct required postmarketing studies are needed for the FDC.

2 Introduction and Regulatory Background

Saxagliptin is an inhibitor of dipeptidyl peptidase-4 (DPP4) that was developed for treatment of hyperglycemia in patients with type 2 diabetes mellitus. Dipeptidyl peptidase 4 inactivates the incretin hormone glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Those incretin hormones are released from the gastrointestinal tract during meals and stimulate insulin release from the pancreatic beta-cell in a glucose-dependent manner.

DPP4 inhibitors increase the levels of intact glucagon-like peptide-1 (GLP-1). The intact GLP-1 regulates blood glucose via stimulation of glucose-dependent insulin secretion, delaying of gastric emptying, inhibiting of glucagon secretion, and as a result of all these actions, improves the pre-prandial and postprandial glycemic profile.

Metformin is a biguanide, that decreases elevated blood glucose with predominant effect on fasting hyperglycemia, reduces hepatic glucose output, improves peripheral glucose uptake and utilization, leads to improved insulin sensitivity.
The combination therapy with DPP4 inhibitor and metformin lowers the glucose via different mechanisms of action.

Metformin XR is proposed to be used as the metformin component in the fixed-dose saxagliptin/metformin product. This gives an advantage of a saxagliptin/metformin XR fixed-dose combination product of being dosed once-daily in the evening , which may improve patient compliance over a twice daily dosing product if metformin immediate-release (IR) was used.

2.1 Product Information

Saxagliptin/metformin XR FDC tablets have been developed at dose strengths of 5 mg saxagliptin/ 500 mg metformin XR, 2.5 mg saxagliptin/ 1000 mg metformin XR, and 5 mg saxagliptin/ 1000 mg metformin XR.

In the saxagliptin/metformin XR FDC tablets, (b) (4)

Drug class: DPP4 inhibitor (dipeptidyl peptidase-4 inhibitor) and a biguanide

Established name: saxagliptin and metformin XR FDC

Proposed trade name: (b) (4)

Target patient population and indication: Treatment of type 2 diabetes mellitus

Formulation: Film coated tablets for oral administration

Dosage forms and strengths for saxagliptin/metformin HCl extended-release available:

- *saxagliptin/metformin HCl XR 5mg/500 mg tablets are light brown, capsule-shaped, film-coated tablets with "5/500" printed on one side and "4221" printed on the reverse side in blue ink*
- *saxagliptin/metformin HCl XR 5 mg/1000 mg tablets are pink, capsule-shaped, film-coated tablets with "5/1000" printed on one side and "4223" printed on the reverse side, in blue ink*
- *saxagliptin/metformin HCl XR 2.5 mg /1000 mg tablets are yellow, capsule-shaped, film-coated tablets with "2.5/1000" printed on one side and "4222" printed on the reverse side, in blue ink*

Proposed dosing: *The dosage of antihyperglycemic therapy should be individualized based on the effectiveness and tolerability in each patient with type 2 diabetes mellitus. When the saxagliptin/metformin XR FDC is considered appropriate treatment by the physician, the recommended starting dose of saxagliptin is 2.5 mg or 5 mg once daily and the recommended starting dose of metformin XR is 500 mg once daily, which can be gradually titrated to 2000 mg once daily to reduce the gastrointestinal side effects associated with metformin. The maximum*

dose is saxagliptin 5 mg /metformin XR 2000 mg taken as two 2.5 mg/1000 mg tablets once daily with the evening meal.

Proposed indication: *saxagliptin/ metformin XR FDC is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate.*

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 The available treatments for Type 2 Diabetes

Drug class	***Drug***	***Mechanism of action***	***HbA1c (%) decrease****	***Advantage***	***Disadvantage***
Biguanides	***Metformin***	Decrease hepatic glucose production Increase insulin sensitivity	1.5	Weight neutral Inexpensive	GI side effects Lactic acidosis Contraindicated in renal failure
Sufonylureas	***Glimepiride Glyburide Glipizide***	Insulin secretagogue	1.5	Inexpensive	Hypoglycemia Weight gain
Thiazolidinediones	***Rosiglitazone Pioglitazone***	Increases insulin sensitivity	0.5-1.4	Lower risk of hypoglycemia	Fluid retention Weight gain Expensive
Insulin	***Lispro NPH insulin Glargine***	Stimulates glucose uptake in muscle and adipose tissue	1.5-2.5	No dose limit Inexpensive Improve lipid profile	Injections Frequent monitoring Hypoglycemia Weight gain
Alpha-glucosidase inhibitors	***Acarbose Miglitol***	Slow GI absorption of carbohydrates	0.5-0.8	Weight neutral	Frequent GI side effects TID dosing Expensive
Meglitides	***Repaglinide Nateglinide***	Insulin secretagogue	1-1.5	Short duration	TID dosing Expensive
Amylin analogues	***Pramlintide***	Slow gastric emptying Suppresses glucagon	0.5-1.0	Weight loss	TID dosing GI side effects Expensive Limited

		secretion Promotes satiety Decreases appetite			experience
GLP-1 analogues	***Exenatide***	Stimulated glucose- dependent insulin release Slows gastric emptying Inhibits glucagon secretion Reduces food intake	0.5-1.0	Weight loss Lower risk of hypoglycemia except when used with insulin secretagogues	GI side effects Expensive Limited clinical experience Pancreatitis
DPP-IV inhibitors	***Sitagliptin*** ***Saxagliptin***	Inhibits the enzyme DPP-IV prolonging the action of endogenous GLP-1 and GIP	0.5-0.8	Weight neutral Lower risk of hypoglycemia except when used with insulin secretagogues	Limited clinical experience Hyper-sensitivity
Bile acid sequestrant	***Colesevelam***	Unknown	0.4-0.8	Favorable lipid effects	Frequent GI side effects
Dopamine agonist	***Bromocriptine***	Unknown	0.4-0.6	Weight neutral Minimal hypoglycemia	-

HbA1c (%) decrease * is not placebo-corrected. Part of HbA1c reduction depends on the patient's baseline level of HbA1c.
Note: GI-gastrointestinal; GLP-1 – glucagon-like peptide-1; DPP-IV –dipeptidyl peptidase-4; GIP- glucose-dependent insulinotropic polypeptide.

2.3 Availability of Proposed Active Ingredient in the United States

The saxagliptin/metformin XR FDC film coated tablets contain the active ingredients saxagliptin (BMS-477118) and metformin hydrochloride. The NDA for saxagliptin (Onglyza NDA 22350)

was approved by FDA on July 31, 2009. Metformin hydrochloride is a well-characterized drug. The extended release dosage forms of metformin hydrochloride (metformin XR) are currently approved in the United States for the treatment of type 2 diabetes mellitus. Bristol-Myers Squibb branded Glucophage XR, 500 mg and 750 mg tablets.

2.4 Important Safety Issues With Consideration to Related Drugs

Metformin XR is contraindicated in patients with renal disease or renal dysfunction (serum creatinine > 1.5 mg/dl for males and > 1.4 mg/dl for females or abnormal creatinine clearance), in patients with hypersensitivity to metformin hydrochloride, and in patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis.
Saxagliptin does not have contraindications, although there is need to lower saxagliptin doses in patients with moderate or severe renal impairment. This is not relevant to the FDC because the FDC will not be appropriate for patients with renal disease because of the metformin component. There is also need to lower saxagliptin doses in patients on strong CYP3A4 inhibitors. Hypersensitivity reactions and pancreatitis were observed with Januvia (another DPP-4 inhibitor).

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

The pre-submission regulatory activity consist of pre-NDA meeting on October 15, 2009, in which the content of the Safety Update were agreed to by the FDA and correspondence between the sponsor and the FDA, which included sponsor's proposal only the safety report forms for deaths and discontinuations due to SAEs to be submitted to FDA with which FDA agreed. After the Pre NDA meeting but prior to submission, there was a teleconference with the sponsor to discuss clinical pharmacology issues (see the clinical pharmacology review for details). During the review cycle, the Division initiated a teleconference with the sponsor to discuss the proposed pediatric plan.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was well organized. NDA 200678 was in the Electronic Common Technical Document (eCTD) format.

3.2 Compliance with Good Clinical Practices

The submission contains a statement of the applicant's compliance with Good Clinical Practice, statement that the clinical trials were conducted under the supervision of an IRB and with adequate informed consent procedures.

3.3 Financial Disclosures

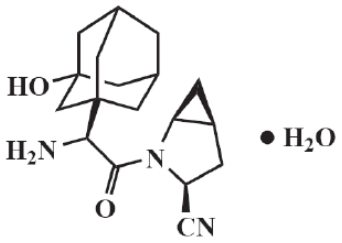
All investigators certified that no financial interests existed during the conduct of the clinical trial. The sponsor certified that they did not enter any financial arrangements where the value of the compensation of the investigator could be affected by the outcome of the study.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

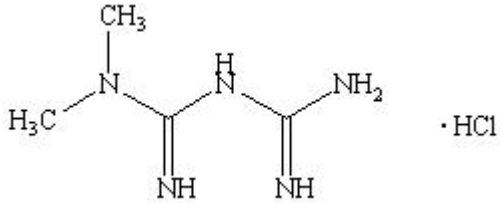
Saxagliptin:
The chemical name of saxagliptin is (1S,3S,5S)-2-[(2S)-2-Amino-2-(3-hydroxytricyclo [3.3.1.13,7]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate. The molecular formula is : $C_{18}H_{25}N_30_2.H_2O$. Saxagliptin monohydrate is a white to light yellow or light brown crystalline powder.

Figure 1 The structural formula of saxagliptin



Metformin Hydrochloride (N,N -dimethylimidodicarbonimidic diamide hydrochloride) is a biguanide. Metformin hydrochloride is a white crystalline (b) (4) with a molecular formula of C4H11N5•HCl.

Figure 2 The structural formula of metformin



metformin hydrochloride

See the CMC review for a discussion of the characteristics of the FDC tablet.

4.2 Clinical Microbiology

Not applicable- saxagliptin is not an antimicrobial.

4.3 Preclinical Pharmacology/Toxicology

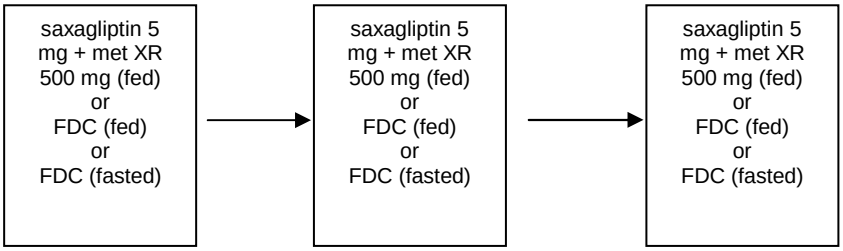
The sponsor conducted a 3-month bridging toxicology study in rats that showed possible teratogenecity when saxagliptin and metformin were co-administered. The sponsor was required to conduct two additional studies PMR-1493-2, that was an Embryo-fetal development study of saxagliptin and metformin in combination in rats, that included saxagliptin monotherapy and metformin monotherapy treatment arms and PMR 1493-3, that was an Embryo-fetal development study with saxagliptin and metformin in combination in rabbits, that included saxagliptin monotherapy and metformin monotherapy treatment arms. The embryo fetal toxicity was not observed in the results of the PMR-1493-2 and PMR 1493-3 study; therefore, the findings in the initial bridging study were considered to be a play of chance. See the pharmacology/toxicology review for details.
TNJS06-074A study was quantitative determination of BMS-477118 and its metabolite, BMS-510849, in human plasma by LC/MS/MS using enhanced chromatography.

LCMSB 153.5 and LCMS 153.5 were quantitation of metformin in human plasma studies.

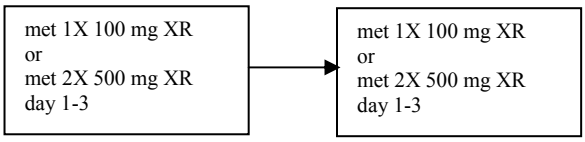
4.4 Clinical Pharmacology

The sponsor conducted several clinical pharmacology studies to bridge the FDC formulation to coadministered components.

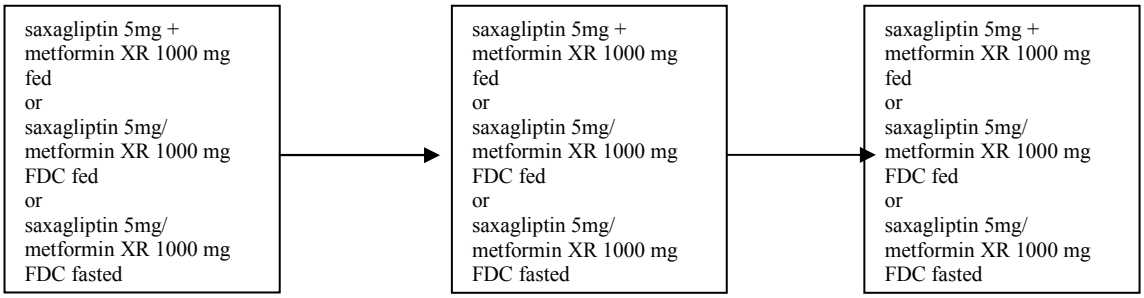
Study CV181060 was a bioequivalence study of the fixed dose combination of 5 mg saxagliptin and 500 mg metformin XR relative to 5 mg of saxagliptin and 500 mg metformin XR coadministered to healthy subjects in fed or fasted condition.



Study CV181074 was a bioequivalence study of a metformin XR 1X1000 mg tablet relative to metformin XR 2X 500 mg tablets in healthy subjects in a fed condition. Wash out period was 4-7 days.



Study CV181076 was a bioequivalence study of the fixed dose combination of 5 mg saxagliptin and 1000 mg metformin XR tablet relative to a 5 mg saxagliptin tablet and a 1000 mg metformin XR tablet co-administered to healthy subjects in a fed or fasted condition. There was 7 days wash out period between treatment periods.



Study CV138098 was a bioequivalence study of a metformin XR 500 mg tablet manufactured in Mt. Vernon, IN, USA relative to a metformin XR 500 mg tablet manufactured in Evansville, IN, USA in healthy subjects in the fasted state and fed state.

Sequence	Period 1	Period 2	Period 3	Period 4
ADBC	A	D	B	C
BACD	B	A	C	D
CBDA	C	B	D	A
DCAB	D	C	A	B

A: metformin XR 500 mg (Evansville) fasted
B: metformin XR 500 mg (Mt Vernon) fasted
C: metformin XR 500 mg (Evansville) fed
D: metformin XR 500 mg (Mt Vernon) fed
Note that only metformin was tested in this study.

Study 138100 was a bioequivalence study of a metformin XR 1000 mg tablet manufactured in Mt Vernon, IN, USA relative to a metformin XR 1000 mg tablet manufactured in Evansville, IN, USA in healthy subjects in the Fasted state and fed state.

Sequence	Period 1	Period 2	Period 3	Period 4
ADBC	A	D	B	C
BACD	B	A	C	D

CBDA	C	B	D	A
DCAB	D	C	A	B

A: metformin XR 1000 mg (Evansville) fasted
B: metformin XR 1000 mg (Mt Vernon) fasted
C: metformin XR 1000 mg (Evansville) fed
D: metformin XR 1000 mg (Mt Vernon) fed
Additional information for the bioequivalence studies is included in Section 7.4. Supportive safety results. For discussion of the results and conclusions from the bioequivalence studies please refer to the clinical pharmacology review.

Mechanism of Action
Saxagliptin:
Saxagliptin is DPP4 inhibitor that decreases the inactivation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) which are released into bloodstream from the small intestine in response to meals. These hormones cause insulin release from pancreatic beta cells in a glucose-dependent manner and are inactivated by the dipeptidyl peptidase-4 (DPP4) enzyme. GLP-1 additionally lowers glucagon secretion from pancreatic alpha cells, diminishing hepatic glucose production. In patients with type 2 diabetes, concentrations of GLP-1 are diminished , nevertheless the insulin response to GLP-1 is preserved. Saxagliptin diminishes the inactivation of incretin hormones, increases their blood concentration and reduces the fasting and postprandial glucose concentration in a glucose-dependent manner.

Metformin, a biguanide, reduces blood glucose levels by inhibiting hepatic glucose production. When taken in combination, saxagliptin and metformin XR provide additive benefits and lead to improved glycemic control in patients with type 2 diabetes mellitus.

5 Sources of Clinical Data

The review uses clinical data derived from studies conducted by Sponsor to support NDA 200678 and studies that were reviewed from FDA as part of saxagliptin NDA 22350, approved July 31, 2009. The NDA 200678 was submitted in electronic Common Technical Document format, with the following path:
\\CDSESUB1\EVSPROD\NDA200678\200678.enx
The data supporting NDA22350 was also submitted in electronic Common Technical Document format, with the following path:
\\CDSESUB1\EVSPROD\NDA022350
The sponsor has submitted five clinical studies that present the bioequivalence data for the saxagliptin/metformin XR FDC and 10 studies (4 completed short term and long term, 1 completed short term, and 5 ongoing) that provide clinical safety and efficacy data to support the saxagliptin/metformin FDC application.

5.1 Tables of Studies/Clinical Trials

Table 2 Listing of saxagliptin clinical studies that support the FDC NDA

Study Number	Type of study	Study Design and type of Control	Target Population/Number of subjects (dosed/ completed)	Objectives of the Study	Dosage Regimen	Treatment duration at time of FDC NDA submission
CV181074	Bioequivalence	Open-label, randomized, crossover	Healthy 18/16	Bioequivalence and safety	Fed dose strength equivalence: 2x500 mg metformin XR vs. 1X 1000 mg Metformin XR	2 single doses
CV181060	Bioequivalence	Open-label, randomized, crossover	Healthy 24/23	Bioequivalence and safety	Fed bioequivalence and food effect: 5 mg saxagliptin/500 mg metformin XR FDC	3 single doses
CV181076	Bioequivalence	Open-label, randomized, crossover	Healthy 24/23	Bioequivalence and safety	Fed bioequivalence and food effect: 5 mg saxagliptin/1000 mg metformin XR FDC	3 single doses
CV138098	Bioequivalence	Open-label, randomized, crossover	Healthy 28/25	Bioequivalence and safety	Fasted and fed bioequivalence: Manufacturing site change for 500 mg metformin XR tablet core	4 single doses
CV138100	Bioequivalence	Open-label, randomized, crossover	Healthy 28/25	Bioequivalence and safety	Fasted and fed bioequivalence: Manufacturing site changes for 1000 mg metformin XR tablets core	4 single doses
CV181014 ongoing	Safety and efficacy	Randomized, double-blind, parallel-group, placebo-controlled	T2DM, metformin failure ≥1500 ≤2550 mg 743/543	Safety and efficacy	Open-label metformin +saxagliptin 2.5, 5, 10 mg or open-label metformin +placebo	ST 24 weeks LT 42 months
CV181039 completed	Safety and efficacy	Randomized, double-blind, parallel-group, active-controlled	T2DM, drug naive, HbA1C >8% and <12.0% 1306/991	Safety and efficacy	saxagliptin 5 or 10 mg+ metformin 500(titrate); or saxagliptin 10 mg; or metformin 500 mg(titrate); PO; QD	ST 24 weeks, LT ≤12 months
CV181056 completed	Safety and efficacy	Randomized, double-blind, parallel-group, active-controlled	T2DM, HbA1C >6.5% and ≤ 10% 801/739	Safety and efficacy	saxagliptin 5 mg+ open label metformin 1500 to 3000 mg; or sitagliptin (DPP4i) 100 mg+ open label metformin 1500 to 3000 mg; PO; QD	18 weeks
CV181038 completed	Safety and efficacy	Randomized, double-blind, parallel-group, placebo-controlled	T2DM, drug naive, HbA1C ≥ 7% and ≤ 10% 365/272	Safety and efficacy	saxagliptin 2.5 mg QAM, 2.5 mg titrate to 5 mg QAM, 5 mg QAM, 5 mg QPM, or placebo, QD	ST 24 week, LT ≤ 12 months
CV181066 completed	Safety and efficacy	Randomized, double-blind,	T2DM, metformin	Safety and efficacy	Open-label metformin XR≥1500 mg+ saxagliptin	4 weeks

		parallel-group, placebo-controlled	failure ≥ 1500 mg/d for at least 8 weeks, HbA1C ≥ 7 ≤10%, 93/91		5 mg or open-label metformin XR ≥ 1500 mg + placebo, PO, QPM	
CV181054 ongoing	Safety and efficacy	Randomized, double-blind, parallel-group, active-controlled	T2DM, HbA1C > 6.5% and ≤ 10%, 858/ ongoing	Safety and efficacy	saxagliptin 5 mg+ open-label metformin 1500 to 3000 mg; or glipizide (SU) 5 to 20 mg + open-label metformin 1500 to 3000 mg, PO, QD	52 weeks, LT 52 weeks
CV181064	Safety and efficacy	Randomized, double-blind, parallel-group, placebo-controlled	T2DM, metformin failure ≥ 1500 mg/d at least for 8 weeks, HbA1C ≥ 7%≤10%, 530/ ongoing	Safety and efficacy	Open-label metformin ≥ 1500 mg + saxagliptin 5 mg QAM or open-label metformin ≥ 1500 mg + placebo, PO, QD	24 weeks
CV181080	Safety and efficacy	Randomized, double-blind, parallel-group, placebo-controlled	T2DM,metformin failure ≥ 1500 mg IR, HbA1C≥ 7 %≤10%, ongoing	Safety and efficacy	Open-label metformin IR 500, 850, or 1000 mg +saxagliptin 2.5 mg or open-label metformin IR 500, 850,or 1000 mg +placebo	12 weeks
CV181085	Safety and efficacy	Randomized, double-blind, parallel-group, active-controlled	T2DM, HbA1C≥ 7.5% ≤11.5%, metformin IR or XR ≥850 mg and ≤1500 mg for at least 8 weeks	Safety and efficacy	saxagliptin 5 mg +metformin XR 1500 mg or metformin XR 1500 mg up-titrated to metformin XR 2000 mg, PO, QPM	4 weeks
CV181086	Safety and efficacy	Randomized, double-blind, parallel-group, active-controlled	T2DM, HbA1C≥ 7.5% ≤11.5%, metformin IR or XR ≥850 mg and ≤1500 mg for at least 8 weeks	Safety and efficacy	saxagliptin 5 mg +metformin XR 1500 mg or metformin XR 1500 mg up-titrated to metformin XR 2000 mg, PO, QPM	18 weeks

Abbreviations: LT-=long term; QD-once daily; QAM= once in the morning; QPM=once in the evening; ST=short term; SU= sulfonylurea; T2DM= type 2 diabetes mellitus; DPP4i= dipeptidyl peptidase4 inhibitor

5.2 Review Strategy

Sources of clinical data in this review are the NDA 200678 submission, pertinent data from the NDA 22350 submission, and the 120-day safety update to NDA 200678.

In the efficacy evaluation the main efficacy data was obtained from CV181014 (placebo-controlled, saxagliptin add-on to metformin study), CV181039 (initial treatment with combination saxagliptin and metformin with active control metformin alone and saxagliptin alone) and CV181038 study (comparison of AM and PM dosing of saxagliptin). Completed data from the short term periods (24 weeks) and interim data from the long-term periods of those studies (CV181014, CV181039, and CV181038) were reviewed as part of NDA 22350 for saxagliptin (Onglyza), which was approved by FDA on July 31, 2009. Study CV181066 has not been reviewed previously and is a placebo-controlled, saxagliptin add-on to metformin XR study, which is short in duration (4 weeks) and contains a small number of subjects (around 100 subjects total). It was designed to be the second study contributing relevant information to the PM dosing of the saxagliptin/metformin XR FDC, but because of its small size and sort duration, it was reviewed as a supportive study.
All trials were used in the integrated safety analysis with a focus on new data that were not previously reviewed under NDA 22350.

5.3 Discussion of Individual Studies/Clinical Trials

The following studies of saxagliptin in subjects with type 2 diabetes are used by the sponsor to support the FDC program:
Three studies (CV181014 ST, which was 24 weeks long, CV181039, ST of 24 weeks and LT 12 months, and CV181056, which was 18 weeks long) were completed and support safety and efficacy of saxagliptin/metformin XR FDC. Studies CV181014 and CV181056 are double-blind studies with metformin IR with add-on either saxagliptin or placebo (CV181014), or add-on saxagliptin or active comparator sitagliptin (CV181056). In CV181039 study co-administration of saxagliptin and metformin IR is compared in a randomized, double-blind fashion to treatment with saxagliptin alone or metformin IR alone.
There are two completed double-blind, randomized studies that are submitted from the sponsor to support the use of saxagliptin in the PM. One is a monotherapy study comparing saxagliptin to placebo (CV1810138, where metformin was used as a rescue therapy) and the other is in combination with metformin XR, compared to co-administration of metformin and placebo, QPM (CV181066).

Five randomized, double-blind studies (CV181054, CV181064, CV181080, CV181085, and CV181086) that support saxagliptin/metformin XR FDC therapy are ongoing. CV1810154 is a study with metformin IR with add on saxagliptin or active comparator Glipizide (SU). Studies CV181064 and CV181080 compare safety and efficacy of open-label metformin treatment with add on saxagliptin 5 mg QAM and 2.5 mg, respectively, compared to add on placebo. Studies CV181085 and CV181086 compare the safety and efficacy of co-administration of saxagliptin and metformin XR to up-titration of metformin XR, QPM.

The individual studies are discussed below in more detail.

Individual clinical trials:
Efficacy and safety experience with saxagliptin administered in PM (monotherapy or combination with metformin)

Study CV181038 was titled *"A multi-center, randomized, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of saxagliptin (BMS-477118) as monotherapy with titration in subjects with type 2 diabetes who have inadequate glycemic control with diet and exercise".*

Primary objective of the study was to compare, after 24 weeks (ST) and 12 Months (LT) of double-blind treatment, the change from baseline in glycosylated hemoglobin (HbA1C) level achieved with saxagliptin 2.5 mg QAM, 5 mg QAM and 2.5 mg titrated to 5 mg QAM (2.5/5 mg QAM) versus placebo in drug-naive subjects with type 2 diabetes who have inadequate glycemic control defined as A1C ≥ 7 % and ≤ 10 % on diet and exercise.

Study CV181038 was submitted as a part of NDA 22350 and the ST period and interim data from LT period (cut-off dates January 30, 2008 and June 20, 2008, respectively) have been previously reviewed. Please see the clinical and statistical reviews from the saxagliptin NDA 22350 for further details. The saxagliptin/metformin XR FDC NDA 200678 is mostly based on bioequivalence data. The CV181038 study does not include patients on metformin and, therefore, does not support co-administration of saxagliptin and metformin. The study was submitted to support recommended administration of saxagliptin/metformin XR once daily with the evening meal with showing similar efficacy of 5 mg saxagliptin QAM and 5 mg saxagliptin QPM administration.
This review will show the primary efficacy results for the ST period and focus on the comparison of QAM vs. QPM dosing. Note that the protocol did not prespecify a comparison of efficacy between the AM and PM dosing regimens but FDA statisticians analyzed these data as part of the original saxagliptin NDA. The key findings are summarized below.

The second study submitted by the sponsor to support the PM use of saxagliptin and that is also supporting the use of saxagliptin with metformin XR is ***CV181066,*** titled " *A 4-week , multicenter, randomized, double-blind, placebo-controlled Phase 3 trial to evaluate the efficacy and safety of saxagliptin in comparison to placebo as add-on treatment to metformin XR in subjects with type 2 diabetes who have inadequate glycemic control (screening HbA1C ≥ 7 % and ≤ 10 %) with diet and exercise and a stable dose of metformin XR ≥ 1500 mg/day.*

Primary objective in the study is to compare the change from baseline to week 4 in 24-hour mean weighted glucose (MWG) achieved with 5 mg versus placebo as add on treatment to a stable dose of metformin XR ≥ 1500 mg/day.

Study CV181066 was submitted as part of NDA 200678. It was short in duration, with small number subjects (around 100 total) and will contribute relevant information to PM dosing of saxagliptin/metformin XR FDC. Because of its size and duration it will be treated as a supportive

study. The CV181066 study was a randomized, double-blind, placebo-controlled study. The study included men and women age 18 to 77 years with type 2 diabetes requiring treatment of 1500 to 2550 mg metformin IR or 2000 mg of metformin XR as monotherapy for at least 8 weeks prior screening. Other inclusion criteria were HbA1C ≥ 7 % and ≤ 10 % obtained at the screening visit, fasting C-peptide concentration ≥ 1 ng/mL and body mass index ≤ 40 kg/m^2 at screening. The study had adequate requirements for contraception use for women of childbearing potential (WOCBP) and requirement for serum or urine pregnancy test with negative result within 72 hours prior to the start of investigational product administration. The patients with poorly controlled diabetes, with history of ketoacidosis, hyperosmolar nonketotic coma or on insulin therapy were excluded. WOCBP who were pregnant or were breastfeeding were excluded. Patients with a history of myocardial infarction, coronary angioplasty, bypass graft, valvular disease, unstable angina, transient ischemic attack, cerebrovascular accident within six months prior the study, congestive heart failure (New York Heart Association stage III and IV), known left ventricular ejection fraction ≤ 40 %, or progressing renal disease were excluded. The laboratory test findings that were part of the exclusion criteria were AST and/or ALT > 2XULN and/or serum bilirubin > 2 mg/dL, positive anti-HAV (IgM), HbsAg, anti-HCV, serum creatinine ≥ 1.5 mg/dL for males and ≥ 1.4 mg/dL for females, creatine kinase ≥ 3XULN, hemoglobin ≤ 12 g/dL for men and ≤ 11g/dL for women, or abnormal values of TSH and T4. Treatment with systemic cytochrome P450 3A4 inducers was prohibited.
Primary objective was to compare the change in 24 hour mean weighted glucose (MWG) from baseline to week 4 after treatment with saxagliptin 5 mg or placebo as add on to a stable dose of metformin XR ≥ 1500 mg/day. The 24 hour mean weighted glucose (in mg /dL) was assessed at baseline visit and at week 4. The mean weighted glucose was estimated by calculating the AUC for the full 24 hours and dividing by 24. The first glucose measurement over the 24-hour period was obtained 30 minutes before the evening meal. The glucose measurements (it was not specified if samples were obtained with glucometer or blood sampled from the vein) were collected 30 minutes before and 0 minutes before each meal and at 30, 60, 120, and 180 minutes after each meal (there was additional measurement 240 minutes after the evening meal), midnight, 3 am, and last sample was 24 hours after the measurement done 30 minutes before the evening meal on the first day of admission.
Safety and tolerability assessment was based on analyzing AEs, laboratory test results, ECG, and vital signs. Laboratory test included hematology (hemoglobin, hematocrit, RBC, WBC count with differential, and platelet counts), serum chemistry (ALT, AST, alkaline phosphatase, creatine kinase, total bilirubin, BUN, serum creatinine, calculated creatinine clearance, sodium, potassium, chloride, total protein, and albumin), and urinalysis (dipstick evaluation for pH, protein, leukocyte esterase, and blood).

Study CV181039 was titled *" A multicenter, randomized, double-blind, active-controlled, Phase 3 trial to evaluate the efficacy and safety of saxagliptin in combination with metformin IR as initial therapy compared to saxagliptin monotherapy and to metformin IR monotherapy in subjects with type 2 diabetes who have inadequate glycemic control".*
Primary objective was to assess the change from baseline in HbA1C after 24 weeks and 12 months of treatment in the 4 treatment arms saxagliptin 5 mg + metformin IR , saxagliptin 10 mg + metformin IR, saxagliptin 10 mg + placebo, and metformin + placebo. Secondary

objectives were to assess the change from baseline in fasting plasma glucose, postprandial glucose AUC after 24 weeks and 12 months of treatment in these 4 treatment arms and to assess safety and tolerability of the above mentioned treatments after 24 weeks and after long term extension of 12 months.

Study CV181056 was titled "An 18-week, randomized, parallel-group, double-blind, active-controlled phase III b study to evaluate the efficacy and safety of saxagliptin in combination with metformin in comparison with sitagliptin in combination with metformin in adult patients with type 2 diabetes who have inadequate glycemic control on metformin therapy alone".

Primary objective of the study was to assess if after 18 weeks of treatment the change from baseline in HbA1C achieved with saxagliptin 5 mg per day added to metformin is non-inferior to sitagliptin 100 mg per day added to metformin in patients with type 2 diabetes who have inadequate glycemic control on 1500 mg or higher doses of metformin therapy alone. The secondary objectives were to compare the effects of saxagliptin 5 mg versus sitagliptin 100 mg as add-on therapy to metformin after 18 weeks treatment by evaluating the change from baseline in fasting plasma glucose, change from baseline in postprandial glucose and to evaluate safety and tolerability of these treatments.
The study was an 18-week randomized, parallel-group, double-blind, active-controlled study. Men and women with type 2 diabetes , age ≥ 18 years, who were on treatment with metformin on stable dose above 1500 mg for at least 8 weeks were included in the trial. There were appropriate requirement for adequate method of contraception for women of childbearing potential (WOCBP). To participate in the study patients were selected to be with HbA1C ≥ 6.5 % and ≤ 10 %. Exclusion criteria for the study were pregnancy, breastfeeding, history of diabetic ketoacidosis or hyperosmolar non-ketonic coma, previous treatment with any DPP4 inhibitor, treatment with thiazolidinedione within 12 weeks before study, treatment with systemic glucocorticoids, treatment with cytochrome P450 3A4 inducers (carbamazepine, dexamethazone, phenobarbital, phenytoin, rifampin), treatment with antiviral drugs (delavirdine, indinavir, nelfinavir, ritonavir, saquinavir). Patients were excluded from the trial if they had congestive heart failure (New York Heart Association class III and IV) and/or left ventricular ejection fraction of ≤ 40 %. History of myocardial infarction, coronary angioplasty or bypass graft, valvular disease or repair, unstable angina pectoris, transient ischemic attack, or cerebrovascular accident within 6 months of starting study excluded patients from the study. Subjects with hemoglobinopathies (sickle cell anemia, thalassemias, sideroblastic anemia) were not allowed to participate in the trial.
The primary endpoint was change in HBA1C from baseline to week 18. Safety evaluation was performed by analyzing adverse events, clinical laboratory test results, ECG, vital signs, abnormal findings on physical examination.
Saxagliptin plus metformin would be considered non inferior to sitagliptin plus metformin if the upper limit of the 2-sided 95 % CI of the difference in the change in HbA1C from baseline to week 18 between saxagliptin plus metformin and sitagliptin plus metformin is less than 0.3 %.
Note that the study results were submitted as part of the 120-day safety update and the sponsor is not requesting that the efficacy data be included in the label. Therefore, my review of this trial will focus only on the safety findings.

Study CV181064, titled "A 24-week international, multi-center, randomized, parallel-group, double-blind, placebo-controlled, phase III study to evaluate the efficacy and safety of saxagliptin in combination with metformin in adult patients with type 2 diabetes who have inadequate glycemic control on metformin therapy in addition to diet and exercise". This study

was conducted in 21 sites in China, 7 sites India and 12 sites in South Korea. Primary efficacy objective of the study was to compare the absolute change from baseline to week 24 in HbA1C achieved with saxagliptin 5 mg plus metformin administration versus placebo plus metformin in patients with type 2 diabetes. The three secondary objectives were to compare the change from baseline in fasting plasma glucose, the change from baseline in the area under the curve from 0 to 180 minutes for postprandial glucose during a mixed tolerance test, and the proportion of patients achieveving a therapeutic glycemic response defined as HbA1C < 7 %. This study had a 24 week, double-blind, randomized, parallel-group design. The study had an enrollment period, a 2 week placebo lead-in period, and a 24 week randomized treatment period. In the lead-in period the subjects were given placebo in a single-blind fashion and OL metformin was started and the dose was gradually increase to 2500 mg and remained stable for the duration of the study.
Men and women with type 2 diabetes, aged above 18 years and HbA1C between 7.2 % and 10 % were included in the study. Adequate method of contraception was required for the women of childbearing potential to prevent pregnancy during the study and 4 weeks after the study. Men were required to take precautions not to father a baby while participating in the study and 4 weeks thereafter.
Exclusion criteria for participation in the study were pregnancy and breastfeeding, insulin treatment in the 1 year prior to the study, previous treatment with any DPP4-inhibitor, systemic treatment with glucocorticoids, cytochrome P450 3A4 inducers (carbamazepine, dexamethazone, phenobarbital, phenytoin, rifampin), antiviral medications (delavirdine, indinavir, nelfinavir, ritonavir, saquinavir). History of congestive heat failure (New York heart association III and IV), left ventricular ejection fraction of ≤ 40 %, history within the past 6 months of myocardial infarction, coronary angioplasty or bypass graft, valvular disease or repair, unstable angina pectoris, transient ischemic attack or cerebrovascular accident excluded patients from participation in the trial. Patients with history of poorly controlled diabetes were excluded. Patients with serum creatinine above 1.5 mg/dL for men and 1.4 mg/dL for women were excluded. Patients with abnormal liver tests defined as AST >1.5X ULN and/or ALT > 1.5X ULN and/or total bilirubin > 1.5X ULN were not included in the study. Creatinine kinase > 3X ULN was another exclusion criteria.

Ongoing studies
Study CV181054 is titled "A 52-week randomized, parallel-group, double-blind, active-controlled, phase III study with 52-weeek extension period to evaluate the safety and efficacy of saxagliptin in combination with metformin compared with glipizide (sulphonylurea) in combination with metformin in adult patients with type 2 diabetes who have inadequate glycemic control on metformin therapy alone". Efficacy data was not submitted at the time of NDA 200678 submission. At the time of 120 days safety update, the sponsor submitted the clinical study report of the 52 week study. Efficacy data with patients datasets were submitted for NDA 22350 Efficacy supplement, which is under review. Primary efficacy objective of the study was to assess if, after a 52-week oral administration of double-blind treatment, the change from baseline in HbA1C achieved with saxagliptin added to metformin is non- inferior to glipizide (SU) added to metformin in patients with type 2 diabetes who have inadequate glycemic control on 1500 mg or higher dose of metformin alone. Secondary objectives were to compare effects of saxagliptin versus glipizide as add-on therapy to metformin after 52 weeks by evaluation of

proportion of patients reporting at least one episode of hypoglycemic event at week 52, change from baseline in body weight at week 52, change from baseline in fasting plasma glucose. Tertiary objective was to assess the long term safety, tolerability of saxagliptin versus glipizide as add-on therapy to metformin after 52 (ST) and 104 weeks (ST+LT) treatment.
The dose of saxagliptin used was 5 mg and the dose used for glipizide was 5 – 20 mg. The dose regimen for glipizide was following the dosing recommended in the glipizide label. The study was randomized, double-blind, active-comparator study. Saxagliptin plus metformin would be considered non-inferior to glipizide plus metformin if the upper limit of the 2-sided 95 % CI of the difference in change in HBA1C from baseline to week 52 between saxagliptin plus metformin and glipizide plus metformin was less than 0.35 %.
Men and women aged above 18 years with type 2 diabetes and HBA1C between 6.5 % and 10 % were included in the study. Adequate methods of contraception were used to prevent pregnancy in women of childbearing potential.
Exclusion criteria were type 1 diabetes, diabetic ketoacidosis, hyperosmolar non-ketotic coma, pregnancy and breastfeeding, insulin treatment in the year before the study, treatment with any DPP4 inhibitor, treatment with thiazolidindione within 12 weeks prior to the study, treatment with systemic glucocorticoids, treatment with cytochrome P450 3A4 inducers (carbamazepine, dexamethazone, phenobarbital, rifampin) and antiviral treatment with delavirdine, indinavir, nelfinavir, ritomavir, and saquinavir. Patients with congestive heart failure (New York Heart association class III and IV), or left ventricular ejection fraction < 40 %, myocardial infarction, coronary angioplasty or bypass graft, valvular disease or repair, unstable angina pectoris, transient ischemic attack, or cardiovascular accident were excluded. Primary efficacy endpoint was change from baseline in HbA1c to week 52 for the two treatment arms performed on the per protocol population. Safety and tolerability were observed based on adverse events, ECG, clinically important abnormalities in laboratory test results, vital signs and physical examination.

Study CV181014 was titled "A multicenter, randomized, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of saxagliptin in combination with metformin in subjects with type 2 diabetes who have inadequate glycemic control on metformin alone". The primary objective was to compare the change from baseline to week 24 and after 42 months in HBA1C achieved with saxagliptin (2.5 mg, 5 mg, or 10 mg) plus metformin or placebo plus metformin. Another objective was to evaluate safety and tolerability of saxagliptin (2.5 mg, 5 mg, or 10 mg) + metformin, compared to placebo after 24 week (ST) and after 42 weeks (LT) extension. The data from ST and some data from LT was reviewed under NDA 22350.

Study CV181080 is a phase 3, randomized, parallel-group, double-blind, placebo-controlled study in subjects with type 2 diabetes who have inadequate glycemic control on metformin alone. The duration of the study is 12 weeks. The study is ongoing. It compares the effect of saxagliptin 2.5 mg BID + OL metformin IR BID and placebo + OL metformin IR BID. Only safety data (with cut-off date January 22, 2010) from the study was submitted with 120 day SU to NDA 200678.
Recently initiated
Studies *CV181085, CV181086, CV181089, and CV181090* were recently initiated with small number of patients and will not be reviewed under this NDA.

The saxagliptin/metformin XR FDC is also partly based on bioequivalence studies. See the clinical pharmacology review for details.

6 Review of Efficacy

6.1 Indication

This NDA 200678 was submitted in support of the use of saxagliptin/metformin HCl extended-release in Type 2 diabetes as an adjunct to diet and exercise to improve glycemic control when treatment with both saxagliptin and metformin is appropriate.

6.1.1 Methods

The main efficacy data were obtained from CV181014 (placebo-controlled, saxagliptin add-on to metformin study), CV181039 (initial treatment with combination saxagliptin and metformin with active control metformin and saxagliptin alone) and CV181038 study (comparison of AM and PM dosing of saxagliptin). Data from the short term periods (24 week) of those studies (CV181014 , CV181039, and CV181038) were reviewed as a part of NDA 22350 for saxagliptin (Onglyza).
Main efficacy data is obtained from studies which use metformin IR, only study CV181066 was conducted using Metformin XR, nevertheless it is acceptable to rely on these studies to support the FDC product, which contains metformin XR, because the extent of metformin absorption (as measured by AUC) from metformin XR at a 2000 mg once-daily dose is similar to the same total daily dose administered as metformin IR tablets 1000 mg twice daily, within-subject variability in Cmax and AUC of metformin from metformin XR is comparable to that of metformin IR, and results from a randomized trial suggested that patients receiving metformin IR may be safely switched to metformin XR once daily at the same total daily dose up to 2000 mg once daily (Please refer to Glucophage XR package insert).

Study Number	Study Design and type of Control	Target Population/Number of subjects (dosed/ completed)	Dosage Regimen
CV181014	Randomized, double-blind, parallel-group, placebo-controlled	T2DM, metformin failure ≥1500 ≤2550 mg 743/543	Open-label metformin +saxagliptin 2.5, 5, 10 mg or open-label metformin +placebo
CV181039	Randomized, double-blind, parallel-group, active-controlled	T2DM, drug naive, HbA1C >8% and <12.0% 1306/991	saxagliptin 5 or 10 mg+ metformin 500(titrate); or saxagliptin 10 mg; or metformin 500 mg(titrate); PO; QD
CV181038	Randomized, double-blind, parallel-group, placebo-controlled	T2DM, drug naive, HbA1C ≥ 7% and ≤ 10% 365/272	saxagliptin 2.5 mg QAM, 2.5 mg titrate to 5 mg QAM, 5 mg QAM, 5 mg QPM, or placebo, QD

6.1.2 Demographics

The studies differed by dosing and were not pooled for the efficacy or safety analyses. Therefore, the demographics of the studies are reviewed separately for each study.
The subjects age, weight, and BMI were characteristic of type 2 diabetes population. The studies are not perfectly balanced by gender and racial distribution.

Study CV181038 (saxagliptin 5 mg QAM, saxagliptin 2.5 titrated to 5 mg QAM, saxagliptin 5 mg QAM, saxagliptin 5 mg QPM, compared to placebo, comparing AM and PM effects of saxagliptin in ST period 24 weeks and LT period 12 months) – demographics:
Mean age of the subjects studied in all treatment groups was 55 years old with approximately 17 % of the subjects being over 65 years old. Mean weight and body mass index (BMI) were 85 kg and 31 kg/m^2, respectively, with 54 % of the subjects being obese with BMI above 30 kg/m^2. More males were studied in 5 mg saxagliptin QAM arm (51 %), compared to 5 mg saxagliptin QPM (46 %) and placebo arm (47 %). Racial distribution differed slightly from general US population with 70 % white in the study (80 % in US population), blacks 7 % (13 % of US population), and Asian 23 % (4.5 % of US population). The study groups had similar mean duration of type 2 diabetes of 1.7 years, 2 years, 1.7 years for saxagliptin 5 mg QAM, saxagliptin 5 mg QPM , and placebo, respectively with slightly longer duration of the disease in the saxagliptin 5 mg QPM group. The patients in the treatment groups had similar mean baseline value of HbA1C of 8% for saxagliptin 5 mg QAM, 7.9% for saxagliptin 5 mg QPM and 7.8 % for placebo group.

Table 3 Study CV181038 demographics (Randomized Analysis set)

	saxagliptin 5 mg QAM	saxagliptin 5 mg QPM	placebo
n	74	72	74
Age (years)	55±10	55±10	56±10
Weight (kg)	87±20	83±19	85±14
BMI (kg/m^2)	31±5	30±5	31±4
Gender Male (%)	51 %	46 %	47%

Race			
White	66%	67%	72%
African American	7%	11%	5%
Asian	27%	22%	23%
Other	0%	0%	0%
Duration of diabetes (years)	1.7±3	2±5	1.7±3
Baseline HbA1C	8±1	7.9±1	7.9±1

The data is represented as mean and SD.

Study CV181054 (saxagliptin 5 mg + OL metformin 1500 to 3000 mg, compared to glipizide (SU) 5 to 20 mg +OL metformin 1500- 3000 mg, comparing effects of saxagliptin and active control in patients with inadequate glycemic control on metformin, 52 week study with 52 week long term period)-demographics:
The study was ongoing as of the data cut-off for the 120 day safety update for NDA 200678. All patients have completed the first 52 week (ST+LT) period. Clinical study report was submitted for the ST period to NDA 22350 and was reviewed for that NDA). The glipizide plus metformin treatment arm had more males randomized (54%) compared to saxagliptin plus metformin arm (50%). By racial distribution the two treatment arms had similar percentage of white patients (82 % saxagliptin plus metformin and 84 % saxagliptin plus metformin), but only one African American subject was studied in Saxagliptin plus metformin arm and the percentage of Asian patients studied (approximately 16 %) was higher than is the US population (4.5%). The mean body mass index was 31 kg/m^2 for the two treatment arms. The mean duration of type 2 diabetes and mean baseline HbA1C level were 6.1 years and 7.4% in saxagliptin plus metformin arm and 5.4 years and 7.7 % in the glipizide plus metformin treatment arm, respectively.

Table 4 Study CV181054 demographics (Randomized analysis set)

	saxagliptin 5 mg + OL metformin 1500 to 3000 mg	glipizide (SU) 5 to 20 mg +OL metformin 1500- 3000 mg
n	428	430
Age (years)	58±10	58±10
Weight (kg)	89±19	89±20
BMI (kg/m^2)	32±6	31±6
Gender Male (%)	50%	54%
Race		
White	82%	84%
African American	0.2%	0%
Asian	17%	15%
Other	0.8%	1%
Duration of diabetes (years)	6.1±4	5.4±5
Baseline HbA1C	7.4±1	7.7±1

Study CV181056 was previously submitted to the Onglyza IND 63634 to evaluate the effects of saxagliptin 5 mg and OL metformin 1500 to 3000 mg, compared to active-control sitagliptin (DPP4i) 100 mg and open OL metformin 1500 mg to 3000 mg, QD for 18 weeks.

The study groups were matched by age and weight. There was a bigger percentage of female subjects in the saxagliptin plus metformin group (53 %), compared to sitagliptin plus metformin (49 %). The racial distribution was balanced between the arms , but the percentage of white subjects and African American subjects was smaller than it is in the US population (66 % white, 9 % AA, respectively compared to US population – 80 % white and 13 % AA). Almost all subjects were obese. Mean duration of diabetes in the two treatment arms was 6.3 years and mean baseline HbA1C was 7.7 %.

Table 5 CV181056 demographics (Randomized analysis set)

	saxagliptin 5 mg and OL metformin 1500 to 3000 mg	sitagliptin (DPP4i) 100 mg and open OL metformin 1500 mg to 3000 mg
n	403	398
Age (years)	59±10	58±11
Weight (kg)	86±18	85±18
Height (cm)		
BMI (kg/m^2)	>39	>45
Gender Male (%)	47%	51%
Race		
White	68%	65%
African American	7%	8%
Asian	8%	10%
Other	17%	17%
Duration of diabetes (years)	6.3±5	6.3±5
Baseline HbA1C	7.7±1	7.7±1

Study CV181014 (OL metformin + saxagliptin 2.5 mg, 5, 10 mg compared to OL Metformin + placebo, 24 weeks ST period with 18 months) and CV181039 (saxagliptin 5 mg or 10 mg + metformin 500-titrated, compared to saxagliptin 10 mg or Metformin 500 mg titrated, 24 week ST period and 12 months LT period) were reviewed as part of the Onglyza NDA 22350. Please refer for details to the review of Dr. Naomi Lowy.

Study CV181066 (4 week trial, assessing efficacy of saxagliptin 5 mg versus placebo as add on treatment with metformin XR > 1500 mg/day)- demographics:
This is a small study with a total of 93 subjects supporting the concomitant use of metformin XR and saxagliptin. The patients in the two treatment arms were matched by age, weight, and BMI. There was a gender and race difference between the subjects of the two treatment arms. In the placebo plus metformin arm there were more white patients (92%) that would be expected in the US population. In the saxagliptin 5 mg plus metformin group the mean duration of diabetes was shorter (6 years) compared to the placebo plus metformin arm (approximately 6.9 years). Baseline HbA1c was 8.1 % for the two treatment groups.

Table 6 CV181066 demographics

	saxagliptin 5 mg plus metformin XR >1500 mg	placebo plus metformin XR >1500 mg
n	46	46
Age (years)	55±9	56±9
Weight (kg)	88±17	89±17
Height (cm)		
BMI (kg/m^2)	31±4	32±4
Gender Male (%)	57%	56%
Race		
White	85%	92%
African American	7%	4%
Asian	4	2%
Other	4%	2%
Duration of diabetes (years)	6.1±5	6.9±6
Baseline HbA1C	8.1±1	8.1±1

Study CV 181064 (OL metformin > 1500 mg + saxagliptin 5 mg QAM compared to OL metformin > 1500 mg + placebo, 24 weeks). The study was conducted in Asian patients (21 sites in China, 7 sites in India, and 12 sites in South Korea) and for that reason will be reviewed only as a supportive study, as it is not representative for most patients with type 2 diabetes in the US population. The study arms were matched by age (54 years), BMI (26 kg/m^2), mean duration of diabetes and mean baseline HbA1C.

Table 7 CV181064 demographics

	OL metformin > 1500 mg + saxagliptin 5 mg QAM	OL metformin > 1500 mg + placebo
n	283	287
Age (years)	54±10	54±10
Weight (kg)	69±12	69±12
Height (cm)		
BMI (kg/m^2)	26	26
Gender Male (%)	48%	48%
Race		
White	0%	0%
African American	0%	0%
Asian	100%	100%
Other	0%	0%
Duration of diabetes (years)	5.1±5	5.1±4
Baseline HbA1C	7.9±1	7.9±1

Reviewer's comment: The racial distribution is slightly different from U.S. demographics but typical of what is seen in diabetes clinical trials. Foreign clinical sites enrolled less African American subjects. Some of the studies were not perfectly balanced by gender, but because the differences are small I do not expect this to have an impact on the study results.

Support for the saxagliptin/metformin XR FDC is also based on ***bioequivalence data.***
Study CV181060 (Bioequivalence study of the FDC of 5 mg saxagliptin and 500 mg metformin XR relative to 5 mg of saxagliptin and 500 mg metformin XR coadministered to healthy subjects in a fed condition).
Study CV181074 (Bioequivalence study of a metformin XR 1X 1000 mg tablet relative to metformin XR 2X500 mg tablets in healthy subjects in fed condition).
Study 181076 (Bioequivalence study of the FDC of 5 mg saxagliptin and 1000 mg metformin XR tablet relative to 5 mg of saxagliptin tablet and 1000 mg metformin XR tablet co-administered to healthy subjects in fed condition).
Study CV181098 (Bioequivalence study of a metformin XR 500 mg tablet manufactured in Mt Vernon, IN, USA relative to a metformin XR 500 mg tablet manufactured in Evansville, IN, USA in healthy subjects in the fasted state and fed state).

Study CV138098 (Bioequivalence study of metformin XR 500 mg tablets manufactured in Mt Vernon, IN, USA relative to a metformin XR 500 mg tablet manufactured in Evansville, IN, USA in healthy subjects in the fasted state and fed state).
Study 138100 (Bioequivalence study of metformin XR 1000 mg tablets manufactured in Mt.Vernon, IN, USA relative to a metformin XR 1000 mg tablet manufactured in Evansville, IN, USA in healthy subjects in the fasted state and fed state). This was open label, randomized, 4-period, 4-treatment, 4-way crossover study in fasted and fed healthy subjects.

For detailed review of all bioequivalence studies refer to the Clinical Pharmacology review.

6.1.3 Subject Disposition

Table 8 Summary table based on ST + LT (LT is complete for all studies below except for Study 181054) - Major reason for discontinuation (n, %) in some of the studies reviewed for this NDA. Further details are provided for each study separately below.

CV181038	5 mg saxagliptin QPM	Placebo
Withdrew consent	9 (13)	5 (7)
CV181039	5 mg saxagliptin + met	met
Lack of efficacy	18 (6)	29 (9)
CV181056	5 mg saxagliptin + met	100 mg sitagliptin (DPP4i) + met
Subject no longer meets study criteria	14 (4)	7 (2)
CV 181054	5 mg saxagliptin + met	5 – 20 mg glipizide (SU) + met
Major reason for not completion-no longer met study criteria	70 (16)	66 (15)
CV181064	5 mg saxagliptin + met	Placebo + met
Subjects withdrew consent	13 (5)	23 (8)

Completed studies

Study CV181038

In the combined ST+LT treatment period (total of 24 weeks/12 months), a similar percentage of patients completed the study when treatment was with saxagliptin 5 mg QPM (64%) and when the treatment was placebo (65%), although the completion rate was slightly higher for the 5 mg

QAM arm (70%). The percentage of patients completed the ST+LT study with out being rescued was lower in saxagliptin 5 mg QPM arm (38 %), compared to placebo arm (42%) but higher than the saxagliptin 5 mg QAM arm (30 %). These very low completion rates for the ST+LT period limit interpretability re: long-term efficacy beyond the ST period. The most common reason for discontinuation from the study was "subject withdrew consent" , which was 13 % , 11 %, and 7% for saxagliptin 5 mg QPM, QAM, and placebo arm, respectively. There was no additional information provided for the main reason for the participants who withdrew consent.

Table 9 Disposition of the subjects in ST + LT treatment period and primary reason for discontinuation from study

	saxagliptin 5 mg QPM	saxagliptin 5 mg QAM	Placebo
Subjects randomized	72	74	74
Completed the study, n (%)	46 (64)	52 (70)	48 (65)
Completed the study without rescue	27 (38)	35 (47)	31 (42)
Discontinuing from the study	26 (36)	22 (30)	26 (35)
Major reason-withdrew consent	9 (13)	8 (11)	5 (7)
Lost to follow-up	8 (11)	6 (8)	6 (8)
Lack of efficacy	4 (6)	3 (4)	6 (8)
Adverse events	1 (1)	2 (3)	3 (4)

Study CV181039

In the combined ST+LT period, the main reason for discontinuation in this study was lack of efficacy, which was 6 % for saxagliptin 5 mg + metformin arm and 9 % for metformin arm. More subjects completed the study without being rescued in saxagliptin 5 mg + metformin arm (56 %), compared to metformin arm (44 %).

Table 10 Disposition of Subjects in ST + LT treatment period and primary reason for discontinuation from Study CV181039.

	saxagliptin 5 mg + met	met
Subjects randomized	320	328
Completed the study, n (%)	229 (72)	219 (67)
Completed the study without rescue	179 (56)	144 (44)
Discontinuing from the study	91 (28)	109 (33)
Major reason- Lack of efficacy	18 (6)	29 (9)
Withdrew consent	20(6)	25 (8)
Lost to follow	22 (7)	22 (7)
Adverse events	14 (4)	14 (4)

Study CV181056

Main reason for discontinuation of the study was "subject no longer meets study criteria", which was 4 % for saxagliptin 5 mg + metformin arm and 2 % for sitagliptin 100 mg + metformin arm.

Table 11 Disposition of the subjects CV 1810156

	saxagliptin 5 mg + met	sitagliptin (DPP4i) 100 mg + met
Subjects randomized	403	398
Completed the study, n (%)	365 (91)	374 (94)
Discontinuing from the study	38 (9)	24 (6)
Major reason – Subjects no longer meets study criteria	14 (4)	7 (2)
Adverse events	8 (2)	7 (2)
Incorrect enrollment	7 (2)	1 (0.3)
Withdrew consent	5 (1)	4 (1)
Lost to follow-up	0	3 (1)

"Subject no longer meets study criteria" group of patients can be further evaluated as

	saxagliptin 5 mg + met N=403 n (%)	sitagliptin (DPP4i) 100 mg + met N=398 n (%)
FPG > 270 at week 4	1 (0.2)	1 (0.3)
FPG > 240 at week 8	4 (1)	0
FPG > 220 at week 12	8 (2)	3 (0.8)
serum creatinine (men > 1.5 and women > 1.4 mg/dL	0	2 (0.5)
use prohibited medications	1 (0.2)	0
use systemic glucocorticoids	0	1 (0.3)

Study CV181066

The study was of small size and duration and is reviewed as supporting data for the use of metformin XR in the FDC.

Table 12 Disposition of subjects CV181066 randomized and treated

	saxagliptin 5 mg + met XR	placebo + met XR
Subjects randomized	46	47
Completed the study, n (%)	45 (98)	46 (98)
Discontinuing from the study	1 (2)	1 (2)
Major reason for discontinuation-withdrew consent	1 (2)	0
Adverse events	0	1 (2)

Study CV181064

The study was conducted in 21 sites in China, 7 sites in India, and 12 sites in South Korea.

Table 13 Disposition of Subjects from study CV 181064

	saxagliptin + met n (%)	Placebo + met n (%)
Subjects randomized and treated	283	287
Subjects completed 24 weeks of treatment	254 (90)	247 (86)

Subjects not completed the period	29 (10)	40 (14)
Subject withdrew consent	13 (5)	23 (8)
Adverse events	5 (2)	4(1)
Subject no longer met study criteria	4 (1)	11 (4)

The reason why patients withdrew consent was not stated. Fewer subjects discontinued the study in saxagliptin 5 mg + metformin arm (10%), compared to placebo + metformin (14%).
The subjects who discontinued due to AEs had AEs that belonged to different SOCs and are not raising a particular safety risk. For additional information please refer to section 7.3.3. AEs leading to discontinuation.
The subjects "no longer met study criteria" can be subdivided in the following groups:

	saxagliptin + met N=283 n (%)	Placebo + met N=287 n (%)
FPG> 270 mg/dL at week 2 and week 4	0	1 (0.3)
FPG > 240 mg/dL at week 6 and week 8	0	4 (1)
FPG > 220 mg/dL at week 12, 16, and 20	2 (1)	6 (2)
Pregnancy	1 (0.4)	0
Treatment with chronic systemic glucocorticoids	1 (0.4)	0

The most common unmet criteria was FPL > 220 mg/dL at week 12, 16, and 20.

Ongoing studies

Study CV181054

The study is ongoing. Safety data from the completed year 1 of the study and selected safety data from ongoing year 2 was submitted with the 120 day safety report.

Table 14 Disposition of the subjects in Year 1 of Study CV181054 (randomized and treated)

	saxagliptin 5 mg + met	glipizide (SU) 5-20 mg + met
Subjects randomized	428	430
Completed 52 week period, n (%)	312 (73)	321 (75)
Subjects not completing 52 week period	116 (27)	109 (25)
Major reason for not completing-no longer met study criteria(↑FPG, ↑HbA1C, ↑ creatinine, or hypoglycemia)	70 (16)	66 (15)
subject withdrew consent	19 (4)	18 (4)
Adverse events	10 (2)	7 (2)
Subjects continuing in the study	312 (73)	315 (73)

Study CV181014
All available information was submitted in the final ST and interim LT report and reviewed under the Onglyza NDA. The 42 month LT period of this study is currently ongoing.
Recently initiated
Studies CV181085, CV181086 were recently initiated with small number of patients and will not be reviewed under this NDA.
As of January 31, 2010 the study CV181080 was ongoing and blinded.

6.1.4 Analysis of Primary Endpoint(s)

Completed studies

Study CV181038: This study provided evidence for the efficacy of PM dosing of saxagliptin. The efficacy analysis includes only results prior to rescue. Efficacy data after rescue are considered missing and are imputed using the last-observation (prior to rescue) carried forward.

The data analyzed below is covering ST + LT period. The very low completion rate do not allow reliable conclusions from the data from ST + LT period. Therefore my conclusions on efficacy are based on the analysis of ST period data only which will be discussed separately below. Treatment with saxagliptin 5 mg QPM and QAM resulted in similar placebo-corrected change from baseline to week 76 in HbA1c of – 0.3 % and – 0.4%, respectively. All saxagliptin treatment arms showed better effect than placebo on the change in HbA1C.

Table 15 Change from baseline to week 76 in HbA1C study CV181038 (LOCF) during ST + LT period

week 76 (ST+LT)	***saxagliptin 5 mg QPM n= 72***	***saxagliptin 5 mg QAM n= 74***	***placebo n= 74***
n	70	69	68
n of observed values at week 76	26 (37%)	34 (49%)	31 (46%)
Baseline mean (SE)	7.9 (0.1)	7.9 (0.1)	7.8 (0.1)
Week 76 mean (SE)	7.6 (0.1)	7.6 (0.1)	7.7 (0.1)
Mean change from baseline (SE)	- 0.3 (0.1)	- 0.4 (0.1)	- 0.1 (0.1)
Placebo-corrected change from baseline mean (SE) 95% two-sided CI	- 0.3 (0.1) (-0.6, -0.1)	- 0.4 (0.1) (-0.6, -0.2)	- 0.2(0.1) (- 0.4, 0.1)

The analysis of the data from ST + LT treatment period showed similar hypoglycemic effect of 5 mg saxagliptin QPM and 5 mg saxagliptin QAM.

The data from ST (24 week) treatment period is presented below using LOCF. Because of the higher completion rate for ST period I consider these data more reliable than the ST+LT data.

	N	Baseline mean ± SE	Change from baseline Adj. mean ± SE	Difference in adjusted mean change 95 % CI	p-value
saxagliptin 2.5 mg AM	67	8.0±0.1	-0.7±0.1	-0.5 (-0.7,-0.2)	<0.01
saxagliptin 2.5 mg→5 mg AM	69	8.0±0.1	-0.6±0.1	-0.4 (-0.7,-0.1)	0.01
saxagliptin 5 mg AM	69	7.9±0.1	-0.7±0.1	-0.4 (-0.7,0.1)	<0.01
saxagliptin 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		

The reduction in HbA1C with dosing of saxagliptin 5 mg AM compared to reduction in HbA1C with dosing PM was calculated by Ms. Mele. The treatment difference was -0.1% (favoring the AM dosing) with 95 % CI of -0.3 to +0.2, showing no difference between the AM and PM treatment regimens. Saxagliptin 5mg PM showed favorable hypoglycemic effect compared to placebo.

Study CV181038 - Secondary endpoints

Because of the lower completion rate in LT period as was mentioned previously the analysis of the secondary endpoint will focus on the data from ST (24 weeks) treatment

Table 16 Fasting Plasma glucose Change from baseline to week 24 (LOCF) during ST treatment period of study 181038

	N	Baseline mean ± SE	Change from baseline Adj. mean ± SE	Difference in adjusted mean change 95 % CI	p-value
saxagliptin 2.5 mg AM	70	157±4	-11±5	-15 (-27, -2)	0.02
saxagliptin 2.5 mg→5 mg AM	71	171±6	-13±5	-16 (-28, -3)	0.01
saxagliptin 5 mg AM	71	162±4	-11±5	-14 (-26, -2)	0.03
saxagliptin 5 mg PM	71	160±5	-8±4	-11 (-23, 1)	0.08
placebo	71	159±5	3±4		

Saxagliptin 5 mg AM had numerically a slightly greater placebo-corrected reduction in fasting plasma glucose (adjusted mean change -14 mg/dL) than did saxagliptin 5 mg PM (adjusted mean change -11 mg/dL). Saxagliptin 5 mg PM showed favorable hypoglycemic effect compared to placebo.

Study CV181039

Efficacy analysis include only results prior to glycemic rescue. In the study there were four treatment arms: saxagliptin 5 mg + metformin, saxagliptin 10 mg + metformin, saxagliptin 10 mg, and metformin. We will focus on analysis of the results from 5 mg + metformin and metformin arms, because we consider that they are relevant to the FDC, which has as components saxagliptin 5 mg or 2.5 mg.

The co-administration of saxagliptin and metformin showed clinically significant change in HbA1C after 76 weeks of treatment. The saxagliptin 5 mg + metformin treatment effect captured by point estimate was – 0.6 % change in HbA1C relative to metformin alone.

Table 17 Change in HbA1C from baseline to week 76 (LOCF) during ST+LT treatment period study of study CV181039

	saxagliptin 5 mg + met N=320	met N= 328
n	306	313
n of observed values at week 76	177 (58%)	147 (45%)
Baseline mean (SE)	9.4 (0.1)	9.4 (0.1)
76 week visit mean (SE)	7.1 (0.1)	7.8 (0.1)
Mean change from baseline (SE)	- 2.2 (0.1)	- 1.7 (0.1)
Difference vs met Mean (SE) 95% two-sided CI	- 0.6 (0.1) (- 0.8, - 0.4)	

Taking in consideration that more that 50 % of the subjects in the LT period did not complete the study, I will focus on the results of the ST (24 weeks) period to draw conclusions for the efficacy.

Table 18HbA1C (%) results for ST period of study CV181039 using LOCF

	N	Baseline mean ± SE	Change from baseline Adj. mean ± SE
saxagliptin 5 mg + metformin	306	9.4±0.1	-2.5±0.1
saxagliptin 10 mg + metformin	315	9.5±0.1	-2.5±0.1
saxagliptin 10 mg	317	9.6±0.1	-1.7±0.1
metformin	313	9.4±0.1	-2.0±0.1

The co-administration of saxagliptin 5 mg and metformin leads to numerically greater decrease in HbA1C than metformin alone after 24 weeks treatment.

Secondary endpoint- change in fasting plasma glucose

The treatment with saxagliptin combined with metformin led after 76 weeks to 28 % decrease in fasting plasma glucose, compared to 15 % decrease in fasting plasma glucose by comparator metformin. The treatment effect relative to metformin captured by the point estimate was – 16

mg/dl decrease in fasting plasma glucose. The data obtained in the study was comparable with a treatment effect in the general population as great as – 23 mg/dl change in fasting plasma glucose and as small as – 8 mg/dl decrease in fasting plasma glucose.

Table 19 Fasting plasma glucose Change from baseline to week 76 (LOCF) during ST + LT treatment period of study CV181039

mg/dl	saxagliptin 5 mg + met N=320	met N= 328
n	317	320
n of observed values at week 76	151 (48%)	125 (39%)
Baseline mean (SE)	204 (3)	199 (3)
76 week visit mean (SE)	148 (3)	161 (3)
Mean change from baseline (SE)	- 56 (3)	- 38 (3)
Adjusted change from baseline mean (SE) 95% two-sided CI	- 54 (3) (- 59, - 49)	- 39 (3) (- 44, - 34)
Difference vs met Mean (SE) 95% two-sided CI	- 16 (4) (- 23, - 8)	

Because of the low completion rate from LT period I will focus my analysis on ST treatment period, which is presented below.

Table 20 Change from baseline to week 24 (ST) in fasting plasma glucose (mg/dL) using LOCF

	N	Baseline mean ± SE	Change from baseline Adj. mean ± SE
saxagliptin 5 mg + metformin	315	199±3	-60±2
saxagliptin 10 mg + metformin	317	204±3	-62±2
saxagliptin 10 mg	327	201±3	-31±2
metformin	320	199±3	-47±2

The 24-week treatment with saxagliptin 5 mg co-administered with metformin resulted in 30 % decrease in fasting plasma glucose, which was numerically greater compared to 23 % decrease when metformin alone was administered.

Study CV181056

The sponsor prespecified a non-inferiority margin of 0.3%. As shown in the table below, saxagliptin was non-inferior to sitagliptin because the upper bound (0.28) of the 2-sided 95% confidence interval for the treatment difference was < than the non-inferiority margin of 0.3 specified by the sponsor. However, because the lower bound of that confidence interval is above 0, saxagliptin is also statistically inferior to sitagliptin.

The sponsor has not requested adding this study to the label. Therefore, the efficacy findings have not been reviewed by FDA biostatisticians and my focus will be on the safety data from this study to support FDC.

The drug treatment effect compared to sitagliptin captured by the point estimate is 0.2 %. The baseline values of the two treatment arms for HbA1C were the same and the sitagliptin + metformin arm showed greater adjusted mean decrease in HbA1C from baseline (- 0.6%) than saxagliptin + metformin treatment arm (– 0.4%).

Table 21 HbA1C change from baseline at week 18 (LOCF) of the study CV181056

units = %	**Saxagliptin 5 mg + met N= 400**	**sitagliptin + met N= 395**
n	399	392
Baseline mean (SE)	7.7 (0.04)	7.7 (0.04)
18 week visit mean (SE)	7.3 (0.1)	7.1 (0.1)
Mean change from baseline (SE)	- 0.4 (0.04)	- 0.6 (0.04)
Adjusted change from baseline mean (SE) 95% two-sided CI	- 0.4 (0.04) (- 0.5, -0.3)	- 0.6 (0.04) (- 0.7, -0.5)
Difference vs sitagliptin + met Mean (SE) 95% two-sided CI	0.2 (0.1) (0.1, 0.28)	

Secondary endpoint – Fasting plasma glucose

Saxagliptin + metformin treatment decreased fasting plasma glucose by 6 %, compared to sitagliptin + metformin treatment that decreased fasting plasma glucose by 10 %. The drug treatment effect was captured by a point estimate of 5.4 showing that saxagliptin + metformin had smaller change from baseline in fasting plasma glucose (- 11 mg/dl), compared to the sitagliptin + metformin (- 16 mg/dl).

Table 22 Change from baseline fasting plasma glucose from baseline to week 18 (LOCF) of the study CV181056

units = mg/dl	saxagliptin 5 mg + met N = 400	sitagliptin + met N= 395
Baseline mean (SE)	160 (2)	160 (2)
18 week visit mean (SE)	149 (2)	144 (2)
Mean change from baseline (SE)	- 11 (2)	- 16 (2)
Adjusted change from baseline	- 11 (1)	- 16 (2)

mean (SE) **95% two-sided CI**	(- 14, - 8)	- 19, - 13
Difference vs sitagliptin + met **Mean (SE)** **95% two-sided CI**	5.4 (2) (1, 9)	

Study CV181066

The study supported the use of metformin XR in the FDC. The study was of short duration (4 weeks) and involved a small number of subjects.

The primary efficacy endpoint was change in 24 hour mean weighted glucose from baseline to week 4. There was a statistical significant difference in the mean change from baseline to week 4 in the saxagliptin + metformin group compared with placebo + metformin group. The difference in the adjusted mean change from baseline versus placebo + metformin was – 17 mg/dL (95% CI= - 25, -9;p = 0.0001 for saxagliptin 5 mg + metformin group.

Table 23 24 hour mean weighted glucose (MWG-mg/dL) - change from baseline at week 4 (LOCF)

	saxagliptin 5 mg + met N=46	Placebo + met N=47
n	41	44
Baseline mean (SE)	178 (5)	181 (6)
week 4 mean (SE)	164 (5)	184 (7)
Mean change from baseline (SE)	- 14 (3)	3 (3)
Adj. change from baseline mean (SE) 95 % two-sided CI	- 14 (3) (-20, -8)	3 (3) (-3, 9)
Difference vs placebo + met* mean (SE)** 95% two-sided CI p-value	- 17 (4) (-25, -9) 0.0001	

* Difference in adj. change from baseline vs. placebo + met

** Adj. mean change for saxagliptin – adj. mean change for placebo + met

Secondary endpoint

The secondary endpoint in the trial was the change from baseline in 4-hour mean weighted postprandial plasma glucose after evening meal.

Statistically significant reduction in 4-hour mean weighted PPG after evening meal was observed in saxagliptin 5 mg + metformin group compared with the placebo + metformin group.

Table 24 4-hour mean weighted postprandial plasma glucose- changes from baseline at week 4 (LOCF)

	saxagliptin 5 mg + met N=46	placebo + met N=47
n	40	44
Baseline mean (SE)	212 (7)	211 (7)
Week 4 mean (SE)	181 (7)	211 (8)
Mean change from baseline (SE)	- 31 (5)	- 0.4 (5)
Adj. change from baseline mean (SE)	- 31 (5)	- 0.4 (5)

95% two-sided	(-41, - 20)	(- 10, 9)
Difference vs placebo + met mean (SE) 95 % two-sided CI p-value	- 30 (7) (-44, - 16) < 0.0001	

Ongoing studies
The data from clinical study report for the ST treatment period and interim LT report for Study CV181014 was reviewed under the Onglyza NDA. The 42 month extension period of this study is ongoing. The data from 120 day safety update will be reviewed for safety only.

Study CV181054
The primary endpoint of this trial was change in HbA1C (%) from baseline to week 52 (ST). The change from baseline to week 52 in HBA1C showed that saxagliptin 5 mg added to metformin is non-inferior to glipizide added to metformin in reducing HbA1C based on the upper confidence limit of the between treatment difference < 0.35 %. The between group difference in adjusted mean change from baseline for HbA1C was 0.09 (95% CI -0.02, 0.20). The glipizide was initiated at 5 mg per day morning dose, titrated in 3 weeks to 20 mg per day (10 mg in the morning and 10 mg in the evening).

Table 25 Change in HbA1C (%) from baseline to week 52 (LOCF)

	saxagliptin 5 mg + met N=426	glipizide + met N=426
n	423	423
Baseline mean (SE)	8 (0.04)	8 (0.04)
week 52 mean (SE)	7 (0.1)	7 (0.1)
Mean change from baseline mean (SE)	- 0.6 (0.03)	- 0.7 (0.04)
Adj. change from baseline mean (SE) 95% 2-sided CI	- 0.6 (0.04) (- 0.6, - 0.5)	- 0.7 (0.04) (- 0.7, - 0.6)
Difference vs glipizide + met mean (SE) 95% 2-sided CI	0.09 (0.1) - 0.02 (0.2)	

One of the secondary endpoints is the change in 120-minute postprandial glucose from baseline to week 52. Postprandial glucose was sampled 120 min after OGTT, using venous blood sample. The data is based on a small sample size (18 subjects in saxagliptin + metformin arm and 17 subjects in glipizide + metformin arm) to draw conclusions.
The difference in adjusted mean change between the saxagliptin + metformin and glipizide + metformin groups was – 21 mg/dL (95% CI – 69, 28 mg/dL).

Table 26 Change in 120-minute postprandial glucose from baseline to week 52 (LOCF)

	saxagliptin 5 mg + met N=426	glipizide + met N=426
n	18	17
Baseline mean (SE)	285 (12)	280 (16)
week 52 mean (SE)	236 (18)	252 (21)
Mean change from baseline mean (SE)	- 50 (16)	- 28 (17)
Adj. change from baseline mean (SE) 95% 2-sided CI	- 49 (16) (- 83, - 15)	- 28 (17) (-63, 6)
Difference vs glipizide + met mean (SE)	- 21 (24)	

95% 2-sided CI	(-69, 28)	

Recently initiated
Studies CV181085, CV181086 were recently initiated with small number of patients and will not be reviewed under this NDA.

6.1.5 Analysis of Secondary Endpoints(s)

Please refer for analysis of secondary endpoints to section 6.1.4. The analysis of secondary endpoints follows the analysis of primary endpoints of each study.

6.1.6 Subpopulations

Subpopulation analysis of the data of the studies was done under NDA 22350. The subgroup analysis did not reveal a differential effect of saxagliptin in subgroups.
Analysis of Clinical Information Relevant to Dosing Recommendations
The data relevant to the dosing recommendations was reviewed under the Onglyza NDA 22350.

7 Review of Safety

Safety Summary
The data sources used in the safety analysis were adequate because the data came from several well-conducted randomized, controlled and double-blind trials.
The risks of the saxagliptin/metformin XR FDC are expected to be the same as the risks of each of the components. Lactic acidosis, hypersensitivity to metformin component, hypoglycemia, skin disorders, localized edema, infections, fractures, pancreatitis, cardiovascular risk, lymphopenia, thrombocytopenia, and liver toxicity were carefully evaluated. The clinical trials reviewed did not identify new or unexpected safety concerns.

7.1 Methods

The data source for the safety analysis was the set of studies submitted by the sponsor (CV181014, CV181038, CV181066, CV181054, CV181056, CV181064, CV181039). Of those studies CV181038, CV181056, CV181064, CV181039 are completed. The data from short term (24 weeks) and interim LT treatment period of studies CV1810138, CV181039, and CV181014 was reviewed under Onglyza NDA 22350. The studies CV181038 (LT period), CV181039 (LT period), CV181056, and CV181064 are completed and data was submitted with 120 safety update. Study CV181014 (LT period of 42 months) is ongoing, although unblinded safety information from ST period and interim LT report was reviewed under NDA 22350. The studies CV181054 and CV181080 were ongoing as of the cut-off date to the 120 day safety update for NDA 200678. The long term data from CV181054 is still blinded. For the studies which are ongoing only blinded safety data was reviewed with cut-off dates January 28, 2010 for study CV181054 and January 25, 2010 for study CV181014, Studies CV181085, CV181086,

CV181089, and CV181090 are in early stages at the clinical cutoff date January 30, 2010 with small number of subjects enrolled (63, 43, 46, and 130, respectively), therefore data from those studies were not submitted under this NDA.
Safety and tolerability were assessed by review of the deaths, all adverse events, laboratory measurements, and vital signs.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Studies CV181038, CV 181039, CV 181056, CV181054, CV181014, CV 181066, CV181064, and study CV181080 will be evaluated for safety.

7.1.2 Categorization of Adverse Events

The sponsor has used MedDRA version 11.1 for preferred terms and for classification of AEs into system organ classes (SOC).

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

Because of differences in study design of the trials supporting the saxagliptin/metformin XR FDC no pooling of data was performed and the findings from the studies are represented separately for each trial.

7.2 Adequacy of Safety Assessments

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

The data was reviewed under the Onglyza NDA 22350.

7.2.2 Explorations for Dose Response

The sponsor has studied the safety and efficacy of 2.5, 5, and 10 mg saxagliptin as a part on NDA 22350. (b) (4)
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7.3 Major Safety Results

7.3.1 Deaths

In regard to deaths saxagliptin safety profile is comparable to placebo and comparable to active comparator (metformin, sitagliptin, glipizide).

Table 27 Summary table of the deaths in the studies reviewed for this NDA

CV181038 completed (ST+LT)	5 mg saxagliptin QPM	5 mg saxagliptin QAM	Placebo
Deaths, n (%)	0	0	0
CV181039 completed (ST+LT)	5 mg saxagliptin + met	10 mg saxagliptin + met, saxagliptin 10 mg	met
Deaths, n (%)	1 (0.3)	4 (0.6)	5 (1.5)
CV181056 completed (18 weeks)	5 mg saxagliptin + met	100 mg sitagliptin (DPP4i) + met	N/A
Deaths, n (%)	0	0	
CV 181054 completed ST investigators blinded for LT	5 mg saxagliptin + met	5 – 20 mg glipizide (SU) + met	N/A
Deaths, n (%)	2 (0.5)	2 (0.5)	
CV181014 completed ST investigators blinded for LT	5 mg saxagliptin + met	Placebo + met	2.5 mg saxagliptin + met
Deaths, n (%)	0	2 (1.1)	1 (0.5)

Completed studies

Study CV181038

During the ST+LT period there were no deaths in the saxagliptin 5 mg QPM and 5 mg QAM arms or in the placebo arm. There were two deaths in patients in the 2.5/5 mg saxagliptin arm (which were pneumococcal sepsis in a splenectomized patient- CV181038-85-572, who died on day 54 of treatment and pancreatic carcinoma - CV181038-31-838 died on day 502, 484 days after discontinuation of the study drug. Treatment drug was administered for 13 days), when the patient was diagnosed with pancreatic carcinoma.

Study CV181039

Study CV181039 is the only study evaluating initial treatment with saxagliptin and metformin. There were numerically fewer deaths in all saxagliptin arms compared to the metformin arm.
The case of tetanus (CV181039-155-2139) in the saxagliptin 5 mg+ metformin arm was reported in the interim long-term period Clinical Study report, narrative for the case was not submitted in this submission. The 4 deaths in the two other arms on saxagliptin were at doses of 10 mg, which is 2X higher than the dose that will be used in the FDC product. There were 5 deaths in

the metformin treatment arm (sudden death, acute MI, cardiac failure, cerebrovascular accident, pancreatic neoplasm/ sepsis).

Table 28 Deaths: Study CV181039 (treated patients)

	saxagliptin 5 mg + met N=320	saxagliptin 10 mg + met and saxagliptin 10 mg N=323 + 335 =658	met N=328
Deaths, (%)	1 (0.3)	4 (0.6)	5 (1.5)
Tetanus	1 (0.3)		
Cardiac arrest		1 (0.3)	
Sudden death		1 (0.3)	1 (0.3)
Arteriosclerosis coronary artery		1 (0.3)	
Ischemic stroke		1 (0.3)	
Acute MI			1 (0.3)
Cardiac failure			1 (0.3)
Cerebrovascular accident			1 (0.3)
Pancreatic neoplasm *			1 (0.3)
Sepsis *			1 (0.3)

* - reported in one patient

Three of the deaths in the metformin arm were reported during the NDA 22350 review (CV181039-60-1617, cardiac failure; CV181039-140-1597, acute MI; CV181039-141-1059, cerebrovascular accident). The death in the patient treated with 5 mg saxagliptin (CV181039-155-2139, tetanus) and two deaths on saxagliptin 10 mg together with one death (CV181039-193-688 pancreatic neoplasm/sepsis) in metformin treatment arm occurred during the long term treatment period and were reported in the interim clinical study report to NDA 22350. There were two deaths in the 10 mg saxagliptin plus metformin arm (cardiac arrest, ischemic stroke) and one death on metformin (which was sudden death) that occurred after the interim clinical study report to NDA 22350 and are considered new data for this NDA. The narratives for these 3 new deaths are summarized below.

Subject CV181039-237-1549*, a 71 year old male, on 10 mg saxagliptin plus 500 mg metformin with type 2 diabetes and history of MI, coronary artery bypass graft on cilostazol, simvastatin, Diltiazem, and isosorbide mononitrate as concomitant medications. On Day 377 patient was transported to hospital for chest pain, where he died from cardiac arrest. The last dose of study medication was administered on day 377.*

Subject CV181039-237-2639*, a 64 year old male, treated with 10 mg saxagliptin and metformin? with history of T2DM, hypertension, current tobacco use had ischemic stroke on Day 221 and transient ischemic attack on Day 507. Patient was hospitalized and on day 511 of the study developed left Hemiparesis with basilar artery involvement shown on MRI. On day 512 100% occlusion of the basilar artery was diagnosed with angiography. After the angiography procedure the patient lost consciousness and required mechanical ventilation. The subject died on Day 524 of the study.*

Subject CV181039-222-1033*, a 58 year old male with history of T2DM and hypertension was on metformin treatment and died of pulmonary edema (diagnosis from the death certificate) on Day 383.*

Study CV181056
There were no deaths reported in this 18-week study which was comparing the effects of 5 mg saxagliptin plus open label metformin to sitagliptin (DPP4i) 100 mg plus metformin.

Safety CV181066
This study was of short duration of 4 weeks and was conducted mainly to support the use of metformin XR in saxagliptin/metformin XR FDC. There were no deaths reported during the study.

Ongoing studies
Study CV181054
The data from the completed 52 weeks (ST) of the study was submitted with the 120 day safety report of NDA 200678. The data for ST period was analyzed by an independent statistician so that the blinded data for the LT period could remain firewalled. There was an equal percentage of deaths in the 5 mg saxagliptin treatment arm (0.5) and the comparator- glipizide arm (0.5). The cause of death in the two groups was due to CV or neurological causes.

Table 29 Deaths in study CV181054 (treated subjects)

	Saxagliptin 5 mg + OL metformin N=428	Glipizide (SU) 5-20 mg + OL Metformin N=430
Total deaths	2 (0.5)	2 (0.5)
Head injurie	1 (0.2)	0
Cardiac failure	1 (0.2)	0
MI	0	1 (0.2)
Ischemic stroke	0	1 (0.2)

Subject D1680C00001-1205-120528, a 63 year old male, with history of type 2 diabetes, hypertension, stenosis of left carotid artery, who was on saxagliptin 5 mg plus metformin 2000 mg treatment since (b) (6). On (b) (6) the patient fell at home due to alcohol. The patient was not hypoglycemic at the time of the fall. CT was performed after his hospitalization and he was diagnosed with subdural hematoma and left temporoparietal fracture. The patient died (b) (6) days later.

Subject D1680C00001-1213-1212005, a 60 year old male with T2DM and hypertension treated with 5 mg saxagliptin and metformin 2000 mg. The concomitant medications were Atorvastatin, Ramipril. The patient had a sudden death on Day 256. Autopsy showed pulmonary edema and cardiac decompensation.

Subject D1680C00001-1205-1205036, a 78 year old female with history of T2DM, hypertension, peripheral vascular disease, previous MI was on 5 mg glipizide and 1500 mg metformin. The

patient died at home during the night and the cause of death was stated to be Myocardial infarction.
Subject D1680C00001, a 68 year old male with history of type 2 diabetes, hypertension, and congestive heart failure. Sixteen days after the initiation of treatment with glipizide 5 mg and metformin 2000 mg he was hospitalized for ischemic stroke and 7 days later had an intracerebral hemorrhage and died on day 28 since starting study medication.

Study CV181014
Unblinded safety data of saxagliptin 2.5, 5, 10 mg plus metformin was reviewed (final ST and interim LT period) as part of Onglyza NDA 22350. The 42 month LT period of the study is still ongoing. There are no new deaths since the 120 Day safety update for Onglyza NDA. No deaths have been reported for the saxagliptin 5 mg plus metformin arm compared to 2 deaths in the placebo plus metformin arm (1.1%).

Recently initiated
Studies CV181085, CV181086, CV181089, and CV181090 were recently initiated. As of the cut-off date (January 30, 2010) there was small number of patients enrolled (63, 43, 46 and 130, respectively).

7.3.2 Nonfatal Serious Adverse Events

As monotherapy, saxagliptin 5 mg QPM had a comparable profile to placebo in regard to SAEs. Further details on SAEs are provided by individual study below.

Table 30 Summary table of the SAEs in the studies reviewed for this NDA

CV181038 (ST+LT)	5 mg saxagliptin QPM	Placebo	5 mg saxagliptin QAM
SAEs, n (%)	4 (5.6)	5 (6.8)	8 (10.8)
CV181039 (ST+LT)	5 mg saxagliptin + met	met	-
SAEs, n (%)	16 (5)	15 (4.6)	
CV181056 (18 weeks)	5 mg saxagliptin + met	100 mg sitagliptin (DPP4i) + met	-
SAEs, n (%)	7 (1.7)	5 (1.3)	
CV 181054 (ST+interim LT)	5 mg saxagliptin + met	5 – 20 mg glipizide (SU) + met	-
SAEs, n (%)	39 (9.1)	32 (7.4)	
CV181014 (ST+interim LT)	5 mg saxagliptin + met	Placebo + met	-
SAEs, n (%)	8 (4.1)	1 (0.6)	

Completed studies
Study CV181038
This study was submitted to support the safety of the 5 mg saxagliptin QPM dosing. In the analysis all subjects that were randomized and treated are included. The detailed analysis of the SAEs from ST + interim LT periods of the trial were reviewed under NDA 22350. Here I will focus on SAEs in saxagliptin 5 mg QPM, saxagliptin 5 mg QAM and placebo treated subjects

that have been subsequently reported after the cutoff date for the 120-day safety update for NDA 22350.
During the completed ST + LT treatment period, SAEs occurred in 5.6% of patients in the 5 mg saxagliptin QPM arm, 10.8% of patients in the 5 mg QAM arm and 6.8% of patients in the placebo arm.

Table 31 Serious adverse events by System organ class ST+LT study CV181038 (treated subjects)

	Saxagliptin 5 mg QPM N= 72	Saxagliptin 5 mg QAM N= 74	Placebo N= 74
SAEs n, (%)	4 (5.6)	8 (10.8)	5 (6.8)

The new SAEs reported in the saxagliptin 5 mg QPM treatment group, saxagliptin 5mg QAM and placebo arm were single cases in different SOCs. There was no clustering of SAEs in any particular SOC to raise safety concerns.

Table 32 New SAEs not included in the interim study report for CV181038 (treated subjects)

	Saxagliptin 5 mg QPM N= 72	Saxagliptin 5 mg QAM N= 74	Placebo N= 74
Metabolism and nutrition	1	1	1 *
Hypoglycemia, n	1	1	1 *
Neoplasm benign, cysts, polyps	1	0	0
Rectal polyp	1	0	0
Nervous system	0	0	1
Transient Ischemic attack	0	0	1
Cardiac disorders	0	1	2
Acute MI	0	0	1
Angina pectoris	0	1	0
Coronary artery disease	0	0	1
Injury	0	2	0
Femoral neck fracture	0	1	0
Ligament fracture	0	1	0
Investigational	1	0	1 *
Ly count decreased	1	0	0
Lymphocytopenia	0	0	1 *
Hepatobiliary	1	1	0
ALT>5XULN	0	1	0
Cholecystitis	1	0	0
Renal and Urinary	0	1	1
Nephrolithiasis	0	1	0
Calculus ureteric	0	0	1
Total SAEs	4	6	5

* SAEs in one subject

Subjects CV11038-55-781, was 72 years male with history of type 2 diabetes, stable angina, obesity. The subject had exacerbation of chronic cholecystitis on day 338, with pain in epigastrium and right hypochondrium. On day 345 hi laboratory tests showed AST 119 U/L, ALT 403 U/L, total bilirubin 2.4 mg/dL. white blood count was elevated at 14,600 c/µL (normal

range 4,100-12,300 c/μL, baseline 6,00 c/μL. On day 350 an abdominal ultrasound reviled multiple 5-10 mm gallstones. On day 351 the patient was hospitalized and study medication was stopped. On day 357 Cholecystectomy was performed. The study medication was resumed on day 361.

The summary of the narratives of the patients with SAEs in the saxagliptin 5 mg QPM arm, which are relevant to the use of saxagliptin in PM as part of FDC, reported after interim long-term report are described below. I also provide the narrative for the patient with ALT >5x ULN reported in the saxagliptin 5 mg qAM arm because liver is an adverse event of interest for saxagliptin.

Subject CV1810138-47-178, was a 76 year old female with history of type 2 diabetes mellitus and hypothyroidism treated with saxagliptin 5 mg QPM. The subject had baseline lymphocyte count of $1.17X10^3$c/μL. On day 11 of the study patient was diagnosed with urinary tract infection. On day 43 the lymphocyte count was $0.69X10^3$c/μL. The study medication was interrupted on day 46 (lymphocyte count $1.16X10^3$c/μL). The lymphocyte count returned to normal on day 46 suggesting spontaneous improvement despite continued treatment of saxagliptin on Days 43-45. The study medication was resumed on day 50 (lymphocyte count reported for day 57 of $0.9X10^3$c/μL, day 67 of $1.28X10^3$c/μL, and day 71 of $0.9X10^3$c/μL. She felt fatigue and had dizziness that continued until day 75. The patient withdrew consent on day 85 (lymphocyte count $1.18X10^3$c/μL).

Subject CV181038-60-486,was a 46 year old male with history of type 2 diabetes, hypertension, hepatic steatosis who was treated with saxagliptin 5 mg QPM. On day 356 of the study the subject presented with nausea and pain in the hypochondrium and was hospitalized with cholecystitis and erosive gasrtroduodenitis. ALT was 172 U/L (baseline 25 U/L), AST was 85 U/L (baseline 39 U/L), and WBC 18,100 c/ μL (baseline 6, 100 c/ μL). Concomitant medication was prindopril. He was treated with cefotaxime, famotidine, metimazole, papaverine, and sodium chloride. The condition improved. Study medication was not interrupted. On day 441 AST was 27 U/L, WBC count 7,600 c/ μL, and ALT was 52 U/L. Information about amylase or lipase levels at the time of event were not provided.

Subject CV 181038-78-867, was a 53 year old female with history of type 2 diabetes on saxagliptin 5 mg QPM treatment who had grade 2 polyp of the rectum diagnosed on Day 413 of the study. The patient had polypectomy on day 419 of the study. Study drug was interrupted between Day 419 and 425.

Subject CV181038-89-584 was a 64 year old male with history of type 2 diabetes mellitus, who was on saxagliptin 5 mg QPM treatment. The patient had hypoglycemic symptoms on day 254 of the study with a fingerstick glucose of 70 mg/dl. On day 345 with sweating and confusion and glucose level of 64 mg/dl, and on day 412 with glucose level of 42 mg/dl. There were no other hypoglycemic medications administered. The subject managed the hypoglycemic episodes by himself. Study medication was not interrupted. Additional information about timing of food intake and exercise preceding the hypoglycemic events was not provided.

Study CV181039

The study compared the safety of initial treatment with saxagliptin 5 mg + metformin, saxagliptin 10 mg + metformin, saxagliptin 10 mg, and metformin alone.

Table 33 Serious Adverse Events during the ST + completed LT period (treated subjects) CV181039

	saxagliptin 5 mg + met N= 320	saxagliptin 10 mg+ met N=323	saxagliptin 10 mg N=335	met N= 328
Total SAEs, n (%)	16 (5)	22 (7)	16 (5)	15 (4.6)

The SAEs were single cases distributed in different SOCs and were suggestive of no particular safety risk. Most of the reported SAEs were reviewed with NDA 22350. The SAEs that were reported after the ST report and the interim long-term CSR (new SAEs cases) are summarized in the table below. The saxagliptin 5 mg + metformin arm showed slightly better profile in regard to SAEs compared to metformin. The SAEs were single cases in different SOCs with the exception of the cardiovascular SOC where saxagliptin 5 mg + metformin showed favorable profile compared to metformin treatment arm.

Table 34 SAEs since the interim LT CSR reporting period (treated subjects) CV1810139

	saxagliptin 5 mg + met N= 320	saxagliptin 10 mg + met N=323	saxagliptin 10 mg N=335	met N= 328
Total SAEs, n (%)	12	22	16	14
Cardiac disorders	2 ***	5	2	4
Atrial fibrillation	1	1	0	1
Acute MI	1 ***	2	0	2
Cardiac failure	0	1	0	1
Nervous	1***	1	2	2
Syncope vascular	0	0	0	1
Cerebrovascular accident	1	0	0	1
General	1	2	0	1
pyrexia	0	1	0	0
Sudden death	0	1	0	1
Hepatobiliary	1 **	0	1	3 *
Cholecystitis acute *	0	0	0	1 *
Pancreatitis	0	0	0	1
Cholecystitis	1	0	0	1
Pancreatitis acute	0	1	0	0
Neoplasm	2	1	0	1 *
Pancreatic neoplasm *	0	0	0	1 *
Skin Disorders	1	1	0	1
Rosacea	0	0	0	1
Gastrointestinal	2	3	1	2
Food poisoning	0	0	0	1
Infectious	3	2	2	1
Upper respiratory tract infection	0	0	0	1
Renal and urinary	2	1	1	1
Nephrolithiasis	0	0	1	1
Creatinine increased	2	0	0	0
Blood and lymphatic	2 **	1	1	0
Lymphopenia	2 **	2	5	0
Skin	1	1	0	0
Skin ulcer	1	0	0	0
Musculoskeletal	1	0	1	0
Back pain	1	0	0	0
Injury	1	0	0	0
Rib fracture	1	0	0	0

* SAEs in one patient
** SAEs in one subject
*** SAEs in one subject

I have reviewed the narratives of the patients with SAEs reported in this study since the interim long-term CSR.

There were several cases of transient lymphopenia reported in all saxagliptin treatment arms. Most of these patients were asymptomatic. The saxagliptin 10 mg + metformin arm had 5 new

cases and the saxagliptin 10 mg alone arm and the saxagliptin 5 mg + metformin arm each had 2 new cases. Investigators did not stop the study medication except for one of these patients and almost all cases recovered spontaneously or had nadir on-treatment lymphocyte counts that were comparable to pretreatment values. Narratives are provided below.

Subject CV181039-243-1390 was a 46 year old patient with type 2 diabetes on saxagliptin 5 mg + metformin. He was noted to have lymphopenia on day 214 of treatment ($0.7X10^3$c/uL, normal 1-$3.3X10^3$c/uL). No action was taken. On day 235 the sample showed lymphocytes in normal range ($2.6X10^3$c/uL).
Subject CV181039-185-1382, was a 57 year old female with type 2 diabetes on saxagliptin 5 mg + metformin who was noted to have lymphocytopenia on day 128 of treatment ($0.9X10^3$c/uL). The patient had normal lymphocyte count on screening ($1.6X10^3$c/uL), but decreased lymphocyte count on day – 7 before treatment ($0.9X10^3$c/uL). The study medication was not discontinued. On day 142 sample lymphocyte count was in normal range($1.6X10^3$c/uL, 1-$3.3X10^3$c/uL normal). The lymphocyte count was below normal on day 443 sample ($0.7X10^3$c/uL) which was the last day of study drug administration. No further information was reported although the lymphocyte count nadirs are comparable to the Day -7 measurement.
Subject CV181039-181-1053, was a 66 year old male with history of type 2 diabetes on saxagliptin 10 mg + metformin. The patient was noted to have decreased lymphocyte count on day 100 of the study ($0.7X10^3$c/uL) after having normal value at screening ($2.7X10^3$c/uL). The study medication was not discontinued. The lymphocyte count was normal on day 113 sample ($2.3X10^3$c/uL).
Subject CV181039-119-2712 was a 76 year old female with history of type 2 diabetes on treatment with saxagliptin 10 mg + metformin. On day 86 the patient was noted to have lymphocytopenia ($0.7X10^3$c/uL). Her lymphocyte count was normal at screening ($1.5X10^3$c/uL). She experienced chills on day 88-92 and was administered Ambromox (bromhexin metabolite, expectorant). The study medication was not discontinued. On day 100 the lymphocyte count was normal ($1.8X10^3$c/uL).
Subject CV1810139-248-2940 was a 62 year old male with history of type 2 diabetes on saxagliptin 10 mg + placebo. She was noted to have low lymphocyte count on day 357 ($0.9X10^3$c/uL) and day 447 ($0.8X10^3$c/uL) of treatment after having normal lymphocyte count on screening ($1.4X10^3$c/uL). The study medication was not discontinued. On day 482 the lymphocyte count was back to normal range ($1.8X10^3$c/uL).
Subject CV181039-147-542 was a 75 year old female with history of type 2 diabetes on saxagliptin 10 mg + placebo. She was noted to have low lymphocyte count on day 443 of study drug administration after having normal screening value ($1.7X10^3$c/uL). The study drug was interrupted and started again on day 470 (further lymphocyte counts are not provided).
Subject CV181039-180-504 was a 53 year old male with type 2 diabetes on saxagliptin 10 mg + placebo. On day 364 he was noted to have low lymphocyte count ($0.4X\ 10^3$c/uL , normal 1-$3.3X10^3$c/uL). The patient had normal values at screening ($2X10^3$c/uL). The study medication was not discontinued. On day 371 the lymphocyte count was normal ($1.8X10^3$c/uL).
Subject CV181039-254-2525 was a 60 year old female with history of type 2 diabetes. The patient was noted to have lower than normal lymphocyte count at screening ($0.6X10^3$c/uL), but was enrolled in the study. On day 12 she had pharyngitis and low lymphocyte count on day 15

sample ($0.6X10^3$c/uL). During day 22-37 she was hospitalized due to "diabetic decompensation", which was not clarified in the narratives. The patient was treated with Cefotaxime and expectorant. The lymphocyte count was back to normal at day 51 sample ($1.3X10^3$c/uL). On day 100 and Day 114 the lymphocyte count was low ($0.9X10^3$c/uL and $0.6X10^3$c/uL, respectively). Respiratory tract infection was reported for Day 110. On day 120 the lymphocyte count was normal ($1.2X10^3$c/uL), but decreased again on day 142 of the study ($0.9X10^3$c/uL). The lymphocyte count was normal at day 156 sample ($1X10^3$c/uL, but very close to the LLN). Second respiratory tract infection was reported on day 185 and lymphocyte count was noted to be low one day prior on day 184 ($0.7X10^3$c/uL). On day 225 the patient was hospitalized due to decompensation caused by respiratory tract infection. Long acting insulin was added on day 226 (40 units/daily required to achieve normal glucose levels) and study medication and pioglitazone was discontinued on day 240.
Subject CV181039-76-981, was a 64 year old female with type 2 diabetes on saxagliptin 10 mg + placebo. The patient was noted to have low lymphocyte count on day 113, after having normal value on screening ($1.6X10^3$c/uL). The lymphocyte count was normal at day 130 sample. Study medication was not interrupted.

Subject CV181039- 156-751, was a 71 year old female with history type 2 diabetes and hypertension who was treated with saxagliptin 5 mg + metformin. On day 269 the patient discontinued the treatment due to lack of efficacy and pioglitazone rescue was started. On day 294 myocardial infarction was reported. On chest x-ray pulmonary congestion with pleural effusion was diagnosed, CK-MB was increased to 34 U/L (normal 0-25) and positive troponin I developed on day 295. The patient was treated with isosorbide dinitrate, acetylsalicylic acid, digoxin, spironolactone, furosemide, losartan, citicoline, carvedilol, insulin. On Day 295 the subject experienced a cerebral infarction. Although the sponsor stated these events are not related to the study medication, relatedness cannot be ruled out given the long duration of treatment.
Subject CV181039-213-2757, was a 55 year old male with history of type 2 diabetes and hypertension who was treated with saxagliptin 5 mg + metformin. On day 217 of the study he reported chest pain and he was diagnosed with angina pectoris. On day 281 the subject was hospitalized with atrial fibrillation and high blood pressure. No sufficient clinical information was submitted. Relatedness to study drug cannot be ruled out although there has not been a signal for myocardial ischemic events with saxagliptin to date..
Subject CV181039-243-2527, was a 46 year old patient with history of type 2 diabetes, who was treated with saxagliptin 5 mg + metformin. On day 404 of the study he had a traffic accident in which he suffered rib fractures. The blood sugar level was not measured on the day of accident, the subject had in his log record a low blood sugar level on day 173 of 58 mg/dl. Therefore, hypoglycemia cannot be excluded. The rib fracture is probably related to the trauma from the accident but saxagliptin may partially have played a role given the small imbalance in fractures not favoring saxagliptin reported in the NDA.
Subject CV181039-243-1390, was a 46 year old male with history of type 2 diabetes, who was on saxagliptin 5 mg + metformin treatment. On day 449 the patient had ALT 296 U/L and AST 299 U/L (>5X ULN), bilirubin was 1.1 mg/dL (normal 0.2 -1.2). Patient tested "negative" for hepatitis A. The study medication was continued. Three days latter the ALT was 83 U/L and AST 45 U/L. This was the second transient elevation of LFTs for this patient. The first one was

on Day 264 of smaller magnitude with ALT of 121 U/L (3XULN) and AST 94 U/L, no bilirubin was measured. The event was labeled not related to drug treatment but causality cannot be ruled out.

Study CV181056

Study CV181056 did not have a LT period. The safety data was available November 17, 2009, after the cut-off date for the 120-day safety update report for NDA 22350 (June 20, 2008) and is considered new safety data. A total of 1.7% of patients in the saxagliptin + metformin treatment arm reported an SAE compared to 1.3% in the sitagliptin + metformin arm. However, the SAEs were single cases in different SOCs and did not show any particular safety concern. Saxagliptin + metformin treatment did not cause any hypoglycemic SAEs.

Table 35 SAEs in CV181056 (treated subjects)

	saxagliptin 5 mg + met N= 403	sitagliptin (DPP4i) 100 mg + met N= 398
Total SAEs, n (%)	7 (1.7)	5 (1.3)
General	2 (0.5)	0
Chills	1 (0.2)	0
Ulcer hemorrhage	1 (0.2)	0
Cardiac disorders	1 (0.2)	1 (0.3)
Supraventricular tachycardia	1 (0.2)	1 (0.3)
Gastrointestinal disorder	1 (0.2)	0
Fecaloma	1 (0.2)	0
Injury	1 (0.2)	1 (0.3)
Traffic accident	1 (0.2)	0
Fall	0	1 (0.3)
Metabolism	1 (0.2)	2 (0.5)
Hyperglycemia	1 (0.2)	0
Hypoglycemia	0	1 (0.3)
Hypoglycemic unconsciousness	0	1 (0.3)
Neoplasm	1 (0.2)	0
Endometrial cancer	1 (0.2)	0
Respiratory tract disorders	1 (0.2)	0
Asthma	1 (0.2)	0
Vascular	0	1 (0.3)
Aortic aneurysm	0	1 (0.3)

Subject D1680C00002-3507-3507214 was a 35 year old female with type 2 diabetes on saxagliptin 5 mg + plus metformin. Her car collided which resulted in fracture of left distal radius. The event was reported as injury and not related to the tested medication. There was no report of hypoglycemia at the time of the event. Although there is no information about severity of the collision, the fracture could be at least partly related to the saxagliptin treatment as fractures are one on the AEs of interest for saxagliptin.

Study 1810166

There were no SAEs reported for study CV181066.

Study CV1810164

The study reported numerically more patients with infections (4 vs. 1) and fracture (2 vs. 0) SAEs in the saxagliptin + metformin arm (which is consistent with the data reviewed for NDA 22350) compared to placebo + metformin arm although numbers were very low.

Table 36 SAEs during study CV181064 (24 weeks)

	Saxagliptin + met N= 283	Placebo + met N=287
Total SAEs, n (%)	8 (3)	1 (0.3)
Infections	4 (1)	1 (0.3)
Anal abscess	1 (0.4)	0
Appendicitis	1 (0.4)	0
Hepatitis B	1 (0.4)	0
Pulmonary tuberculosis	1 (0.4)	0
Urinary tract infection	0	1 (0.3)
Injury	2 (0.7)	0
Ankle fracture	1 (0.4)	0
Clavicle fracture*	1 (0.4)	0
Rib fracture*	1 (0.4)	0
Hepatobiliary disorder	1 (0.4)	0
Cholecystitis acute	1 (0.4)	0
Nervous system	1 (0.4)	1 (0.3)
Cerebral infarction	1 (0.4)	1 (0.3)
Metabolism	0	1 (0.3)
Diabetic foot	0	1 (0.3)

***** same patient

Select narratives from this trial are summarized below:

D1680C00006-3604-3604636 was a 44 year old female with history of type 2 diabetes on saxagliptin 5 mg + metformin. The patient was admitted in hospital on day 122 of study drug administration with cough and fever. Chest CT and sputum smears were done and patient was diagnosed with pulmonary tuberculosis. Rifampicin, isoniazide, pyrazinamide and ethambutol were started. The study drug was discontinued. The pulmonary tuberculosis was ongoing at the time of the report. For this subject lymphocytopenia was not reported.

Subject D1680C00006-3611-36111610, was a 64 year old female with history of type 2 diabetes on saxagliptin 5 mg + metformin. On day 11 of study drug administration the patient sprained her left ankle. There is no data reported regarding symptoms of hypoglycemia accompanying the accident. X-ray taken revealed fracture of the fibula. The patient continued the study.

Study D1680C00006-3622-3622635, was a 43 year old male with history of type 2 diabetes on saxagliptin 5 mg + metformin. On day 43 after initiation of the study treatment, patient slipped and fell when he was going down the stairs. There were no signs of hypoglycemia at the time of accident. The patient was hospitalized with left clavicular fracture and left fifth rib fracture. The patient continued the study medication.

Subject D168000006-3626-3626640 was a 51 year old female with history of type 2 diabetes on saxagliptin 5 mg + metformin treatment. On day 125 of treatment she was hospitalized with difficulty to walk. She was diagnosed with multiple cerebral infarctions. After twelve days the patient restarted the study medication.

Ongoing studies

Study CV181054

The unblinded data from the completed year 1 of the study was received with the clinical study report for CV181054 and safety information for the ongoing blinded LT period was submitted in the 120 day safety report. In the ST period, the incidence of SAEs was 9.1% with saxagliptin and 7.8% with glipizide This small imbalance was due mainly to a larger number of SAEs in the cardiovascular SOC (12 cases for saxagliptin 5 mg + metformin vs. 7 cases for glipizide + metformin), in the infectious disorders SOC (4 cases compared to 2 cases for glipizide + metformin treatment) and in the neoplasm SOC (4 cases for saxagliptin + metformin vs. no reported neoplasm for glipizide + metformin). The SAEs were mostly single cases reported with different PTs which do not highlight any particular safety risk.

Table 37 SAEs CV181054 (treated subjects) for ST (52 weeks).

	saxagliptin 5 mg + met N=428	glipizide (SU) 5-20 mg + met N=430
Total SAEs, n (%)	39 (9.1)	32 (7.4)
SAEs in areas of interest		
Cardiovascular	12 (2.8)	7 (1.6)
Atrial fibrillation	2 (0.5)	1 (0.2)
Coronary artery disease	2 (0.5)	0
Angina pectoris	1 (0.2)	0
AV block complete	1 (0.2)	0
Cardiac failure	1 (0.2)	1 (0.2)
Coronary artery stenosis	1 (0.2)	0
MI	1 (0.2)	0
Supraventricular tachycardia	1 (0.2)	0
Ventricular fibrillation	1 (0.2)	0
Angina unstable	0	1 (0.2)
Arteriosclerosis coronary artery	0	1 (0.2)
Bradycardia	0	1 (0.2)
Coronary artery occlusion	0	1 (0.2)
Infections	4 (0.9)	2 (0.5)
Anal abscess	1 (0.2)	0
Pneumonia	1 (0.2)	0
Pulmonary tuberculosis	1 (0.2)	0
Pyelonephritis	1 (0.2)	0
Helicobacter gastritis	0	1 (0.2)
Super infection	0	1 (0.2)
Neoplasm	4 (0.9)	0
Bladder cancer	1 (0.2)	0
Colon cancer	1 (0.2)	0
Metastasis to liver	1 (0.2)	0
Salivary gland neoplasm	1 (0.2)	0

Study CV181014
Unblinded safety data of saxagliptin 2.5, 5, 10 mg plus metformin was reviewed (final ST and interim LT period) as part of Onglyza NDA 22350. The LT period of the study is still ongoing. For the purpose of this review I will discuss the data for saxagliptin 5 mg + metformin, placebo + metformin treatment arms, saxagliptin 2.5 mg + metformin, and saxagliptin 10 mg + metformin.

Focusing on the new data presented since the 120 day safety update for NDA 22350, all of the saxagliptin arms had a numerically greater number of SAEs (n=6-8) than did the placebo arm (n=1). However, as shown in the table below, the SAEs are distributed across various preferred terms and do not point to one particular safety risk

Table 38 New data for SAEs reported for CV181014 since 120- day safety update for Onglyza NDA

SAEs, n	saxagliptin 5 mg + met N=191	placebo + met N=179	saxagliptin 2.5 mg + met N=192	saxagliptin 10 mg + met N= 181
Total, n	8	1	8	6
Cardiovascular	3	1	0	0
Cardiac failure	1	1	0	0
Oedema peripheral	1	0	0	0
Bundle branch block	1	0	0	0
Coronary artery insufficiency	0	0	1	0
Nervous	1	0	0	1
Transient ischemic attack	1	0	0	0
Cerebrovascular accident	0	0	0	1
Neoplasm	3	0	0	0
Multiple myeloma	1	0	0	0
Breast cancer	1	0	0	0
Skin cancer	1	0	0	0
Infectious	1	0	0	0
Staphylococcal infection	1	0	0	0
Pneumonia	0	0	2	0
Periumbilical abscess	0	0	1	0
Gastrointestinal			0	1
Abdominal hernia	0	0	0	1
Blood and lymphatic			0	1
Lymphocytopenia	0	0	2	1
Anemia			1	0
Renal	0	0	1	2
Renal failure	0	0	0	1
Nephrolithiasis	0	0	0	1

Subject CV181014-159-1188 was a 55 year old male with type 2 diabetes with history of hypertension on saxagliptin 5 mg + metformin treatment. On day 957 he experienced fatigue, dyspnea, chills. On day 958 the subject was hospitalized in the ICU with a diagnosis of congestive heart failure and bilateral, multifocal pneumonia. The study medication was discontinued. The subject's condition improved after 25 days hospital treatment.

Because there is an imbalance in this trial in the number of SAEs reported since NDA 22350 review, I discuss below the total number of SAEs (previously reported + new SAEs) during the ST + LT treatment period to see if the imbalance exists when the data is viewed in totality.

Table 39 SAEs during ST + LT period of study CV181014

	saxagliptin 5 mg + met N=191	placebo + met N=179	saxagliptin 2.5 mg + met N=192	saxagliptin 10 mg + met N= 181
Total, n	27	15	23	21
Infections	4	1	10	4
Pneumonia	1	1	2	0
Diverticulitis	1	0	1	0
Urinary tract infection	1	0	0	1
Appendicitis	0	0	1	0
Appendicitis perforated	0	0	1	0
Breast abscess	0	0	1	0
Cellulitis	0	0	1	0
Clostridium defficile colitis	1	0	0	0
Erysipelas	0	0	0	1
Meningitis tuberculous *	0	0	0	1
Periumbilical abscess	0	0	1	0
Pyelonephritis	0	0	0	1
Scrotal abscess	0	0	1	0
Sinusitis	0	0	0	1
Sinusitis bacterial	0	0	0	1
Urosepsis	1	0	0	0
Cardiac disorders	7	6	1	4
Coronary artery disease	4	0	0	2
Cardiac failure congestive	3	2	0	0
Coronary artery insufficiency	0	0	1	0
Myocardial infarction	1	3	0	0
Myocardial ischemia	0	0	0	1
Supraventricular tachycardia	0	0	0	1
Angina pectoris	0	1	0	0
Angina unstable	0	1	0	0
Carcinogenic shock	0	1	0	0
Neoplasms	3	2	2	4
Basal cell carcinoma0	1	0	1	
Brest cancer	1	0	0	0
Gastrointestinal carcinoma	0	0	0	1
Lung neoplasm	0	0	0	1
Multiple melanoma	1	0	0	0
Neurilenomma	0	0	0	1
Non-Hodgkin's lymphoma	0	0	1	0
Prostate cancer	0	0	1	0
Uterine Cancer	1	0	0	0
Breast cancer recurrent	0	1	0	0
Injury	4	0	3	1
Ankle fracture	1	0	0	1
Incisional hernia	1	0	1	0
Fall	1	0	0	0
Hip fracture	0	0	1	0
Limb injury	1	0	0	0
Road traffic accident	1	0	0	0

Skin laceration	1	0	0	0
Upper limb fracture	0	0	1	0
Gastrointestinal	1	0	4	2
Abdominal hernia	0	0	1	0
Abdominal pain	1	0	0	0
Diarrhoea	1	0	0	0
Food poisoning	0	0	0	1
GI haemorrhage	0	0	1	0
Intestinal obstruction	0	0	1	0
Stomach granuloma	0	0	1	0
Vomiting	1	0	0	0
Nervous	3	0	1	3
Cerebrovascular accident	0	0	1	3
Altered state of consciousness	1	0	0	0
Dizziness	1	0	0	0
Headache	0	0	0	1
Somnolence	0	0	0	1
Transient Ischemic attack	1	0	0	0
Hepatobiliary disorders	2	1	1	3
Cholecystitis	1	0	0	1
Cholecystitis acute	0	0	1	1
Cholelithiasis	0	1	1	1
Biliary colic	1	0	0	0
Renal	2	1	1	1
Nephrolithiasis	1	1	0	1
Calculus Ureteric	1	0	0	0
Calculus urinary	1	0	0	0
Renal failure acute	0	0	1	0
Blood and lymphatic	0	0	1	2
Anaemia	0	0	1	2
General disorders	0	0	1	2
Chest pain	0	0	1	0
Hernia	0	0	0	1
Pelvic mass	0	0	0	1
Respiratory	1	0	0	2
Pulmonary embolism	1	0	0	1
Asthma	0	0	0	1
Reproductive	0	1	2	0
Dysfunctional uterine bleeding	0	0	1	0
Prostatitis	0	0	1	0
Cystocele	0	1	0	0
Rectocele	0	1	0	0
Vascular	1	0	0	1
Hypertensive crisis	0	0	0	1
Varicose vein	1	0	0	0
Metabolism	1	0	0	0
Dehydratation	1	0	0	0

* same patient discontinued the study due to SAE

Subject CV181014-171-1380 was a 56 year old female with history of type 2 diabetes on saxagliptin 10 mg + metformin. She was reported with high blood pressure 150/100mmHg, headache on day 537. On day 541 she had headache, postprandial vomiting, fever, and nuchal rigidity. With CT subarachnoid hemorrhage was diagnosed on day 541. Study medication was not interrupted. After lumbar puncture on day 914 diagnosis of tuberculosis meningitis was established. The patient was treated with rifampin, isoniazide, pyrazinamide, and prednisone. On day 926 the ALT was 247 U/L, AST 46 U/L. The change was attributed to isoniazide and treatment with it was disrupted. Study medication was discontinued on day 946.

When the whole set of reports for SAEs are reviewed for the ST + LT period the imbalance in the number of SAEs still exists. The SAEs were single cases in different SOC, reported with different PT with exception of imbalance of 4 reports of coronary artery disease in saxagliptin + metformin arm vs. o reports in placebo + metformin arm.
coronary artery disease
Recently initiated
Studies CV181085, CV181086, CV181089, and CV181090 were recently initiated. As of the cut-off date (January 30, 2010) there was small number of patients enrolled (63, 43, 46 and 130, respectively).

7.3.3 Dropouts and/or Discontinuations: AEs leading to discontinuation

The incidence of AEs leading to discontinuation was the same or very similar for saxagliptin + metformin treatment, compared to metformin, sitagliptin + metformin, glipizide + metformin. As monotherapy saxagliptin 5 mg QPM and saxagliptin 5 mg + metformin XR showed favorable results to placebo and placebo + metformin XR, respectively. The only study that showed more AEs leading to discontinuation was when saxagliptin 5 mg + metformin were compared to placebo + metformin in Study CV181014 (results are from St and interim report, the LT extension is still ongoing), although this imbalance was not seen in the other studies where saxagliptin was co-administered with metformin.

Figure 3 Summary table of AEs leading to discontinuation in the studies reviewed for this NDA

CV181038	5 mg saxagliptin QPM	Placebo
AEs leading to discontinuation, n (%)	1 (1.4)	3 (4.1)
CV181039	5 mg saxagliptin + met	met
AEs leading to discontinuation	14 (4)	14 (4)
CV181056	5 mg saxagliptin + met	100 mg sitagliptin (DPP4i) + met
AEs leading to discontinuation	9 (2)	9 (2)
CV181066	saxagliptin 5 mg + met XR N= 46	Placebo + met XR N= 47
AEs leading to discontinuation	0	1 (2.1)
CV 181054	5 mg saxagliptin + met	5 – 20 mg glipizide (SU) + met
AEs leading to discontinuation	18 (4.2)	19 (4.4)
CV181014	5 mg saxagliptin + met	Placebo + met
AEs leading to discontinuation	18 (9.4)	9 (5)

Completed studies

Study CV181038

The AEs leading to dropout were single cases in different SOCs, that did not lead to concerns for a safety signal. Nevertheless saxagliptin 5 mg QPM presented better that saxagliptin 5 mf QAM and placebo.

Table 40 Adverse events leading to discontinuation from entire ST + LT study period of CV181038 study by SOC and PT

	saxagliptin 5 mg QPM N= 72	saxagliptin 5 mg QAM N= 74	Placebo N= 74
Total subjects with AEs leading to discontinuation	1 (1.4)	2 (2.7)	3 (4.1)
GI disorders	0	1 (1.4)	0
dry mouth	0	1 (1.4)	0
Investigations	0	1 (1.4)	0
hematology test abnormal	0	1 (1.4)*narrative	0
Skin and subcutaneous	0	1 (1.4)	0
contact dermatitis	0	1 (1.4)	0
Eye disorder	1 (1.4)	0	0
eye pain	1 (1.4)	0	0
Nervous system	1 (1.4)	0	0
headache	1 (1.4)	0	0
Cardiac disorder	0	0	1 (1.4)
Acute MI	0	0	1 (1.4)
Metabolism	0	0	1 (1.4)
hypoglycemia	0	0	1 (1.4)

*The subject CV181038-78-754 was a 58 year old female with type 2 diabetes and history of hypercholesterolemia on treatment with saxagliptin 5 mg QAM. On day 455 of the study ALT was 209 U/L and AST 103 U/L with normal bilirubin of 0.5 mg/dL. On day 470 the bilirubin was elevated to 2.5 mg/dL, but ALT was 23 U/L and AST 23 U/L. On day 473 the patient was diagnosed with calculus cholecystitis. The study mediation was not discontinued.

Study CV181039

The incidence of discontinuation due to AEs was the same in the saxagliptin 5 mg + metformin arm (4%) and in the metformin alone treatment arm. The events reported during ST + LT treatment period were single cases in different SOCs except in the investigations SOC where there were 3 cases of ALT increased (0.9%) in the saxagliptin + metformin treatment group compared to 1 case (0.3%) in the metformin arm. The narratives of the cases were reviewed under NDA 22350. There were no subjects in the saxagliptin 5 mg + metformin arm who had ALT >3XULN and total bilirubin > 1.5X ULN, compared to 1 case (0.3 %) in the metformin treatment arm.

Table 41 AEs leading to discontinuation during ST + LT (old and new data) of study CV1810139

	saxagliptin 5 mg + met N= 320	met N= 328	saxagliptin 10 mg N=335	saxagliptin 10 mg + met N=323
AE leading to discontinuation, n (%)	14 (4)	14 (4)	14 (4)	10 (3)

Study CV181056

During the 18 week period the incidence of AEs leading to discontinuation was the same in the saxagliptin + metformin arm (2 %) as in the sitagliptin + metformin treatment arm (2%). The AEs were single cases in different SOCs and did not raise any particular safety concerns.

Table 42 AEs leading to discontinuation during 18 week treatment period of study CV181056

	saxagliptin 5 mg + met N= 403	sitagliptin + met N= 398
AE leading to discontinuation, n (%)	9 (2)	9 (2)

From the AEs that led to discontinuation case D1680C00002-3507-3507214, was a 35 year old female with type 2 diabetes on saxagliptin 5 mg and metformin 1500 mg, who had a fracture of the left radius on Day 28 of treatment during a traffic accident. There is no information about severity of the accident and relation to the study drug cannot be excluded. The rest of the AEs that lead to discontinuation were dyspnea, gastritis, nausea, hyperglycemia, dizziness, tremor, endometrial cancer, and dyspnea.

Study CV181066

There were no AEs leading to discontinuation in the saxagliptin 5 mg + metformin XR arm. There was one AE (nausea and dizziness) that led to discontinuation in the placebo + metformin XR arm of the study.

Figure 4 AEs leading to discontinuation in study CV181066 (treated subjects)

	saxagliptin 5 mg + met XR N= 46	Placebo + met XR N= 47
AE leading to discontinuation, n (%)	0	1 (2.1)

Study CV1810164

A numerically greater number of patients discontinued due to AEs in the saxagliptin + metformin treatment group (6 cases, 2.1%) compared to the placebo + metformin treatment (3 cases, 1%).

Table 43 Subjects who discontinued due to AEs during 24 week study CV181064

	saxagliptin + met N=283	placebo + met N=287
Total, n (%)	6 (2.1)	3(1)
Infections	2 (0.7)	1 (0.3)
Hepatitis B	1 (0.4)	0
Pneumonia	1 (0.4)	0
Pulmonary tuberculosis	1 (0.4)	0
Urinary tract infection	0	1 (0.3)
Blood	1 (0.4)	0
Lymphocytopenia	1 (0.4)	0
Gastrointestinal	1 (0.4)	1 (0.3)
Abdominal discomfort	1 (0.4)	1 (0.3)
Hepatobiliary	1 (0.4)	0
Hepatic function abnormal	1 (0.4)	0
Investigation	1 (0.4)	1 (0.3)
Blood glucose increased	1 (0.4)	1 (0.3)

D1680C00006-3604-3604636 is the previously described patient treated with saxagliptin 5 mg + metformin who was diagnosed with pulmonary tuberculosis.
Subject D1680C00006-3618-3618609 was a 40 year old female with type 2 diabetes on saxagliptin 5 mg + metformin. The subject reported bilateral eyelid oedema on day 25 of treatment that resolved after 2 days latter without treatment. Two months after starting of the treatment the patient had discontinued the study due to increased ALT 67U/L. The drug was stopped and no follow-up ALT or total bilirubin values were reported.
Subject D1680C00006-3608-3608605 was a 45 year old male with type 2 diabetes on saxagliptin 5 mg + metformin. The first time he had low lymphocyte values was 3 days after initiation of treatment ($0.4X10^3$c/uL). Treatment was stopped for 11 days, which normalized the lymphocyte count ($1.1X10^3$c/uL). There was second temporary stop of the study medication 100 days after treatment was initiated. Lymphopenia was reported $<0.7X10^3$c/uL on day 4, 8, 86, 113, 141, 144,

147, 150, and 155 of the study. Study medication was stopped 162 days after the treatment was started.

Ongoing studies

Study CV181054

The incidence of AEs leading to discontinuation was similar for the saxagliptin + metformin arm and glipizide + metformin arm.

Figure 5 AEs leading to discontinuation during 52 weeks (ST) of the CV181054 study

	saxagliptin 5 mg + met N=428	glipizide + met N= 430
AE leading to discontinuation, n	18	19

Study CV181014

The incidence of discontinuation due to AEs was greater in the saxagliptin 5 mg + metformin arm compared to the placebo + metformin arm.

Figure 6 AEs leading to discontinuation during ST + LT treatment (new events) of CV181014 study

by SOC, PT	saxagliptin 5 mg + met N= 191	placebo + met N= 179	saxagliptin 2.5 mg + met N=192	saxagliptin 10 mg +met N=181
AEs leading to discontinuation, n (%)	18	9	11	13
Investigations	3	3	4	3
Blood creatinine increase	1	1	3	2
Blood creatine phosphate increase	0	0	0	1
ALT increased	1	0	1	0
Lymphocyte count decrease	0	1	0	0
Weight increased	1	1	0	0
Blood and lymphatic	3	0	0	2
Anemia	3	0	0	2
Lymphopenia	1	0	0	1
Thrombocytemia	1	0	0	0
General	0	0	1	2
Astenia	0	0	0	1
Fatigue	0	0	0	1
Oedema peripheral	0	0	1	1
Infections	2	0	2	2
Meningitis tuberculous	0	0	0	1
Staphylococcal infection	0	0	0	1
Diverticulitis	0	0	1	0
Pneumonia	1	0	0	0
Urosepsis	1	0	0	0
Viral infection	0	0	1	0
Neoplasm	2	0	1	2
GI carcinoma	0	0	0	1
Lung neoplasm	0	0	0	1
Brest cancer	1	0	0	0
Non-Hodgkin lymphoma	1	0	1	0
Uterine cancer	1	0	0	0
Nervous	0	1	0	2
Cerebrovascular accident	0	0	0	1
Dizziness	0	0	0	1
Headache	0	1	0	0
Eye disorders	0	0	0	1
Eye pain	0	0	0	1
GI	0	0	0	1
Abdominal pain upper	0	0	0	1
Abdominal pain	1	0	0	0
Diarrhoea	1	0	0	0
Nausea	1	0	0	0
Psychiatric disorders	1	1	1	1
Psychiatric symptom	0	0	0	1
Depression	0	1	0	0

Major depression	0	0	0	0
Schizophrenia	1	0	0	0
Renal	0	1	1	1
Renal failure acute	0	0	1	1
Renal disorder	0	1	0	0
Respiratory	0	1	0	1
Dyspnoea excertional	0	0	0	1
Throat irritation	0	0	0	1
Gough	0	1	0	0
Cardiac disorders	2	1	0	0
Cardiac failure	0	1	0	0
Cardiac failure congestive	1	0	0	0
Coronary artery disease	1	0	0	0
Immune system	1	0	0	0
Sarcoidosis	1	0	0	0
Musculoskeletal	0	0	1	0
Pain in extremity	0	0	1	0
Skin	3	2	0	0
Drug eruption	0	1	0	0
Pigmentation disorder	1	0	0	0
Rash	1	0	0	0
Rash generalized	0	1	0	0
Rash papular	1	0	0	0

Subject CV181014-164-1416 was a 53 year old female with history on saxagliptin 10 mg+ metformin with pioglitazone added as rescue therapy on day 351. The patient had lymphocytopenia on day 1170 of study drug administration ($0.8X10^3$c/μL) that resolved on day 1261. The study medication was not stopped.
Subject CV181014-202-369 was a 59 year old female with history of type 2 diabetes on saxagliptin 2.5 mg + metformin, with pioglitazone 15 mg added as rescue on day 663 of study drug treatment. Lymphopenia was noted on day 1150 of the study ($0.6X10^{3c}$/μL) that resolved on day 1156 without treatment. The study medication was not stopped.
Subject CV181014-171-1380 was a 56 year old female with history of type 2 diabetes on saxagliptin 10 mg + metformin. She was reported with high blood pressure 150/100mmHg, headache on day 537. On day 541 she had headache, postprandial vomiting, fever, and nuchal rigidity. With CT subarachnoid hemorrhage was diagnosed on day 541. Study medication was not interrupted. After lumbar puncture on day 914 diagnosis of tuberculosis meningitis was established. The patient was treated with rifampin, isoniazide, pyrazinamide, and prednisone. On day 926 the ALT was 247 U/L, AST 46 U/L. The change was attributed to isoniazide and treatment with it was disrupted. Study medication was discontinued on day 946.

Recently initiated
Studies CV181085, CV181086, CV181089, and CV181090 were recently initiated with small number of patients and will not be reviewed under this NDA

7.3.4 Significant Adverse Events (adverse events of interest)

Hypoglycemia
Regarding hypoglycemia saxagliptin as monotherapy and in combination with metformin showed safety profile comparable with placebo and favorable compared to active comparator (sitagliptin).

Completed studies

Study CV181038

AEs of hypoglycemia were identified by matching reported AEs to a predefined list of preferred terms (MedDRA v10.1) that could reflect a diagnosis of hypoglycemia (hypoglycemia, blood glucose decreased, and blood glucose abnormal). For the purpose of the study "confirmed" hypoglycemia was defined as fingerstick glucose value ≤ 50 mg/ dL in the presence of symptoms. same approach was used in all other studies.

The saxagliptin 5 mg QPM had the same number of confirmed hypoglycemic events as placebo and saxagliptin 5 mg QAM treatment arm. The hypoglycemia observed in the saxagliptin 5 mg QPM and QAM arms were mild and the one observed in the placebo group was moderate. In all treatment arms the hypoglycemia resolved after treatment with juice/snack. All cases of hypoglycemia were observed in patients younger than 65 years.

Table 44 Confirmed hypoglycemia by predefined PT during the ST + LT treatment period (new + old data) study CV181038

	saxagliptin 5 mg QPM N=74	saxagliptin 5 mg QAM N=72	placebo N=74
Hypoglycemia	1 (1.4)	1 (1.4)	1 (1.4)

Study CV181039

There were no cases of confirmed hypoglycemia in the saxagliptin 5 mg + metformin arm and two cases in the placebo+ metformin treatment group.

Table 45 Confirmed hypoglycemia - by PT during ST + LT treatment period (old + new data)

	saxagliptin 5 mg + met N= 320	met N= 328
Hypoglycemia	0	2 (0.6)

Study CV181056

The incidence of hypoglycemia was slightly higher in the saxagliptin + metformin treatment arm (3.2%) compared to the sitagliptin + metformin arm (2.8%). No cases of hypoglycemia were observed in saxagliptin + metformin arm, compared to one case of hypoglycemia with lost consciousness in the sitagliptin + metformin arm.

Table 46 Hypoglycemic adverse events by PT of study CV181056

	saxagliptin + met N=403	sitagliptin + met N=398

Total hypoglycemic events, n (%)	13 (3.2)	11 (2.8)
Hypoglycemia	13 (3.2)	10 (2.5)
Hypoglycemic unconsciousness	0	1 (0.3)

Study CV181066

There were no cases of hypoglycemia in the saxagliptin + metformin XR arm, compared to one case of hypoglycemia in the placebo + metformin XR arm.

Table 47 Hypoglycemic adverse events by PT in CV181066

	saxagliptin 5 mg + met XR N= 46	placebo + met XR N= 47
Hypoglycemia, n (%)	0	1 (2.1)

Ongoing studies

Study CV181054

The second year of the study is ongoing. The data was presented for the first year. In regard of hypoglycemia caused by medication, saxagliptin + metformin administration showed favorable results, hypoglycemic events were only 3 %, compared to the glipizide + metformin treatment which showed hypoglycemia of 36 %. There were no subjects experiencing hypoglycemia in the saxagliptin + metformin arm compared to 2 % of the subjects on glipizide + metformin experiencing a severe hypoglycemia adverse event.

Table 48 Reported hypoglycemic adverse events by PT during ST treatment period in CV181054 study

	saxagliptin + met N=428	glipizide + metformin N= 430
Hypoglycemia	13 (3)	156 (36)

No subjects with hypoglycemia on saxagliptin + metformin treatment required medical assistance, compared to 1 % of the patients on glipizide + metformin, who needed medical assistance.

Study CV181014

There is one new case of hypoglycemia that was reported after the interim LT report for NDA 22350.

Subject CV181014-31-435 was a 48 year old female with type 2 diabetes treated with saxagliptin 5 mg who had a hypoglycemic event on day 568 with a fingerstick glucose value of 48 mg/dL. The event did not require medical treatment and occurred after physical activity. The study drug was not discontinued.

Recently initiated

Studies CV181085, CV181086, CV181089, and CV181090 were recently initiated with small number of patients and will not be reviewed under this NDA

Skin disorders

Completed studies

Study CV181038

There was only one new case of skin disorder (skin ulcer) in the saxagliptin 5 mg QPM arm and no cases reported in the saxagliptin 5 mg QAM and placebo arms.

Table 49 Skin disorders by PT during ST + LT period (new data) of study CV181038

	saxagliptin 5 mg QPM N= 72	saxagliptin 5 mg QAM N= 74	Placebo N= 74
skin ulcer, n (%)	1 (1)	0	0

Study CV181039

The saxagliptin 5 mg + metformin treatment arm had the same incidence of 7AEs of skin disorders SOC as the metformin arm.

Table 50 Skin disorders by PT during the ST + LT treatment period (old + new data) of study CV1810138

	saxagliptin 5 mg + met N= 320	met N=328
total skin disorders AEs	1 (0.3)	1 (0.3)
skin ulcer	1 (0.3)	0
lip ulceration	0	1 (0.3)

Study CV181056

There were no cases with skin disorder AEs in the saxagliptin + metformin treatment arm, compared to 1 case (0.3%) in sitagliptin + metformin arm, which was sore on right earlobe (patient D1680C00002-3509-3509206, 52 year old male).

Study CV181066

In the skin disorder SOC, there was a single AE (case of scalp seborrhea) in the saxagliptin + metformin XR arm, compared to no cases in placebo + metformin XR arm.

Table 51 Skin disorders by PT in study CV1810166

	saxagliptin 5 mg + met XR N= 46	placebo + met XR N= 47
scalp seborrhea	1 (2.2)	0

Ongoing studies

Study CV181054

There were no AEs of skin disorders SOC reported for saxagliptin + metformin arm and two cases (0.5%), which were scab and skin ulcer in the glipizide + metformin arm reported during the 1 year ST-period.

There were no skin disorder AEs reported by PT for the still blinded LT period of CV181054.

Study CV181014

Table 52 Skin disorders (new data) study CV181014

	saxagliptin 5 mg + met N= 191	placebo + met N= 179
Newly reported	5 (3)	2 (1)

The narratives of two SAE of skin disorders SOC newly reported were provided:

Subject CV181014-172-517, was a 51 year old female with history of type 2 diabetes on treatment with saxagliptin 5 mg + metformin 1500 mg who experienced a rash involving a single dermatome on day 835. She was diagnosed with herpes zoster and treated with acyclovir from day 839 to day 858. On day 858 the event was reported resolved. Same subject experienced AE of biliary colic on day 779. The patient was treated with scopolamine and study medication was interrupted. On day 926 Cholecystectomy was performed. Study medication was resumed on day 929.
Subject CV181014-171-1384 was a 62 year male with history of type 2 diabetes on treatment with saxagliptin 5 mg and metformin 2500 mg. He had leg edema and was diagnosed with pyoderma of the right ankle on day 969 of the study. He was treated with topical bacitracin/neomycin, followed by ampicillin, ciprofloxacin and fusidate without improvement. On day 1080 skin ulcer of right ankle developed. Callagenase was added to the treatment on day 1081. The study medication was not discontinued.

Recently initiated
Studies CV181085, CV181086, CV181089, and CV181090 were recently initiated with small number of patients and will not be reviewed under this NDA

Localized edema

In Studies CV181038, CV181056, CV181066, and CV181054 there were no cases (old + new data) of localized edema related to saxagliptin administration as monotherapy or in combination with metformin.

Completed studies
Study CV181038
There were no cases reported (old + new data) in saxagliptin 5 mg QPM and QAM arm of localized edema in ST + LT treatment period of study CV181018. This compares favorably to the placebo arm, where one case of pedal edema (1.4%) was reported.

Study CV181039
Saxagliptin 5 mg + metformin presented less favorably than metformin in relationship to localized edema with 3 cases (old + new data) vs. 2 cases. The difference of 1 case is very small to draw any conclusions.

Table 53 Localized edema AEs by PT during ST + LT treatment (old + new data) period of study CV181039

	saxagliptin 5 mg + met N= 320	met N= 328
Localized edema total, n (%)	3 (0.9)	2 (0.6)
Pedal edema	0	1 (0.3)
Edema fingers	1 (0.3)	0
Edema palpebral	1 (0.3)	0
Pedal edema	1 (0.3)	0
Orbital edema	0	1 (0.3)

The narrative for the case of palpebral edema was submitted and reviewed under NDA 22350.

Study CV181056

There were no edema related AEs reported during randomized treatment period.

Study CV181066

There were no AEs of localized edema in the saxagliptin 5 mg + metformin XR treatment group. There were one case (2.1 %), which was pedal edema in the placebo + metformin XR arm.

Ongoing studies

Study CV181054

There were no cases of localized edema reported during the first year of the study.

Study CV181014

Saxagliptin 5 mg + metformin treatment arm had slightly more cases of localized edema (3%), compared to the placebo + metformin treatment arm (2%). The difference of 2 cases is too small to draw any conclusions.

Figure 7 Localized edema AE during ST + LT period of study CV181014

	saxagliptin 5 mg + met N= 191	placebo + met N= 179
Total subjects with AE, n (%)	6 (3)	4 (2)
Foot edema	2 (1)	0
Eye swelling	1 (0.5)	0
Pedal edema	1 (0.5)	2 (1)
Swelling of feet	1 (0.5)	0
Scrotum swelling	1 (0.5)	0
Hands swelling	0	2 (1)

Subject CV181014-171-1384 was a 62 year old male with type 2 diabetes on saxagliptin 5 mg + metformin with a history of leg edema. On day 743 of study drug administration the patient was noted to have a varicocele.

Subject CV181014-164-1416 was a 53 year old female with type 2 diabetes on saxagliptin 10 mg + metformin, and rescue therapy of pioglitazone since day 351. He was noted to have face edema on day 397 and 617 and lymphopenia on day 1170 and 1261 (0.8X103c/µL). The lymphocytopenia resolved on day 1282 without treatment. No additional data is provided about the face edema.

The rest of the narratives for localized edema were submitted and reviewed under NDA22350.

Recently initiated

Studies CV181085, CV181086, CV181089, and CV181090 were recently initiated with small number of patients and will not be reviewed under this NDA.

Infections

In regard to the incidence of infections during treatment with saxagliptin as monotherapy or in combination with metformin the results of the studies reviewed under this NDA are inconclusive with regard to whether saxagliptin increases the risk of infection. Three of the studies (CV181038, CV181066, and CV181054 first year data) showed greater incidence of infections after treatment with saxagliptin relative to comparators. Two of the studies (CV181056 and CV 181014- LT ongoing) showed the same incidence of infections for saxagliptin and comparators. One study (CV1810139) showed lower incidence of infections in saxagliptin 5 mg + metformin arm compared to the metformin monotherapy arm.

Completed studies

Study CV181038

In the completed ST+LT period, the incidence of infections was higher in the saxagliptin 5 mg QPM (39%) and saxagliptin 5 mg QAM (42%) arms compared to the placebo arm (24 %). The most common AEs in the infectious disorder SOC in the saxagliptin 5 mg QPM arm were Upper respiratory tract infections (15%), nasopharyngitis (7%), and urinary tract infections (6%). The data show a numerically increased risk of infections when saxagliptin is administered with no clear difference between AM and PM dosing.

Table 54 AEs of interest: Infections during the ST + LT period (old + new data) study CV1810138

Infections	saxagliptin 5 mg QPM N=72	saxagliptin 5 mg QAM N= 74	Placebo N= 74
Infections total, n (%)	28 (39)	31 (42)	18 (24)
Upper respiratory infections	11 (15)	10 (14)	7 (10)
Nasopharyngitis	5 (7)	4 (5)	3 (4)
Urinary tract infection	4 (6)	3 (4)	2 (3)
Sinusitis	0	3 (4)	3 (4)
Gastroenteritis	1 (1)	5 (7)	0
Bronchitis	1 (1)	1 (1)	0
Lower respiratory tract infection	0	3 (4)	0
Influenza	0	3 (4)	1 (1)
Rhinitis	0	1 (1)	1(1)
Viral infection	2 (3)	1 (1)	0
Tenia pedis	1 (1)	1 (1)	0
Cellulitis	0	1 (1)	1 (1)
Folliculitis	0	1 (1)	0
Gastroenteritis viral	0	0	1 (1)
Onychomycosis	0	1 (1)	0
Paronychia	0	1 (1)	0
Acute sinusitis	1 (1)	0	1 (1)
Acute tonsillitis	0	1 (1)	0

Chronic sinusitis	0	1 (1)	0
Cystitis	1 (1)	0	0
Laryngitis	0	1 (1)	0
Pharyngitis streptococcal	0	1 (1)	0
Skin Candida	2 (3)	0	0
Tonsillitis	1 (1)	0	0
Tooth abscess	2 (3)	0	0
Vaginal infection	0	1 (1)	0
Abdominal wall abscess	1 (1)	0	0
Bacteriuria	0	1 (1)	0
Cellulitis of male external genitalia	0	1 (1)	0
Chikungunya virus infection	1 (1)	0	0
Foruncle	0	1 (1)	0
Pneumonia	0	1 (1)	0
Pyelonephritis chronic	0	1 (1)	0
Pyoderma	0	1 (1)	0
Respiratory tract infection			
Tenia infection	0	1 (1)	0
Tenia versicolor	1 (1)	0	0
Tracheitis	0	1 (1)	1 (1)
Tracheobronchitis	0	1 (1)	0
Herpes ophthalmic	0	0	1 (1)
Rash pustular	0	0	1 (1)
Tenia cruris	0	0	1 (1)

Study CV181039

The overall incidence of infections was lower in the saxagliptin 5 mg + metformin arm compared to the metformin arm.

Table 55 The most common AEs of Infections SOC (incidence > 2 %) (old + new data) by PT during study CV181039

	saxagliptin 5 mg + met n= 320	met N= 328
Total AEs Infections, n (%)	99 (31)	114 (35)
Nasopharyngitis	29 (9)	19 (6)
Urinary tract infection	13 (4)	25 (8)
Influenza	20 (6)	19 (6)
Upper respiratory tract infection	15 (5)	10 (3)
Bronchitis	14 (4)	4 (1)
Pharyngitis	7 (2)	9 (3)
Gastroenteritis	8 (3)	3 (1)
Rhinitis	4 (1)	2 (1)
Viral infection	4 (1)	7 (2)

Study CV181056
Regarding the AEs of infectious SOC, the saxagliptin + metformin treatment arm had the same incidence (25 %) as the comparator arm of sitagliptin + metformin.
The most common AE of the infectious SOC by PT were influenza, urinary tract infection, nasopharyngitis, and upper respiratory tract infection.

Table 56 AEs of interest of Infections SOC during study CV181056

	saxagliptin + met N= 403	sitagliptin + met N= 398
Total Infections	101 (25)	100 (25)
Influenza	23 (6)	23 (6)
Urinary tract infection	23 (6)	21 (5)
Nasopharyngitis	16 (4)	16 (4)
Upper respiratory tract infection	9 (2)	4 (1)

Study CV181066
The infections were more common in the saxagliptin 5 mg + metformin arm (9%) compared to the placebo + metformin arm (2%). However, because of small sample sizes, this difference is driven by only 3 excess cases of infection in the saxagliptin arm compared to the placebo arm.

Table 57 Most common AEs of interest of Infections SOC during study CV 181066

	saxagliptin 5 mg + met XR	placebo + met XR
Infections, n (%)	4 (9)	1 (2)
Urinary tract infection	2 (4)	0
Nasopharyngitis	1 (2)	0
Pyelonephritis	1 (2)	0

Ongoing studies
Study CV181054
The data from first year of the study showed a slightly bigger incidence of infections in the saxagliptin + metformin arm (33%) compared to the glipizide + metformin arm (29%). However, review of the individual PTs did not identify a particular AE leading to this difference.

Table 58 Most common AEs of interest of Infection SOC during study CV181054

	saxagliptin + met N= 428	glipizide + met N= 430
Infections, n (%)	139 (33)	125 (29)
Nasopharyngitis	41 (10)	37 (9)
Upper respiratory tract infection	21 (5)	13 (3)
Bronchitis	13 (3)	15 (4)
Influenza	11 (3)	11 (3)
Urinary tract infection	8 (2)	12 (3)

Study CV181014
With the 120 Day safety update for NDA 200678 the data submitted for AEs of Infections SOC for saxagliptin 5 mg + metformin arm (57 %) is comparable with that for placebo + metformin

(58%). The most common AEs > 2% incidence for the Infection SOC are shown in the table below.

Figure 8 AEs of interest By PT in infection SOC ST + LT (includes new data after Onglyza 120 day safety update) study CV181014

	saxagliptin 5 mg + met N= 191	placebo + met N= 179
Total infections, n (%)	109 (57)	103 (56)
Influenza	31 (16)	27 (15)
Nasopharyngitis	28 (15)	25 (14)
Upper respiratory tract infection	19 (10)	17 (10)
Urinary tract infection	16 (8)	15 (8)
Bronchitis	19 (10)	13 (7)
Sinusitis	14 (7)	8 (5)
Gastroenteritis	6 (3)	4 (2)
Furuncle	4 (2)	0
Viral gastroenteritis	4 (2)	2 (1)
Tooth infection	6 (3)	3(2)
Tooth abscess	4 (2)	1 (1)

Recently initiated
Studies CV181085, CV181086, CV181089, and CV181090 were recently initiated with small number of patients and will not be reviewed under this NDA.

Fractures
There was an incidence of 1 % fractures in the saxagliptin 5 mg + metformin treatment arms (study CV181039 and CV181014), compared to no fractures in metformin monotherapy and placebo + metformin treatment arms, respectively. All the rest of the studies reviewed for this NDA show no fractures in the treatment arms.
Completed studies
Study CV181038
There were no fractures reported for study CV181038 since the data review for NDA 22350.

Study CV181039
There were 3 fractures (1%) reported since the data review for NDA 22350, which were rib fracture, tibia fracture, and upper limb fracture in the saxagliptin 5 mg + metformin arm compared to no fractures in the metformin treatment arm.

Study CV181056
There were no fractures reported in study CV1811056 and Study CV181066 since the data review for NDA 22350.
Ongoing studies
Study CV181054 there were no fractures reported since the review for NDA 22350.

Study CV181014 there are 2 cases of fractures (1%) in the saxagliptin 5 mg + metformin arm reported since the review for NDA 22350, which were rib fracture and stress fracture, compared to no fractures in the placebo + metformin arm.

Recently initiated

Studies CV181085, CV181086, CV181089, and CV181090 were recently initiated with small number of patients and will not be reviewed under this NDA.

Pancreatitis

There was only one case of pancreatitis (0.3%) in the saxagliptin 5 mg + metformin arm and one case in the saxagliptin 10 mg + metformin arm in study CV181039, and two cases (0.6%), which were pancreatitis and pancreatitis chronic, in the metformin arm. All other studies reviewed for this NDA (**CV181038, CV181056, CV181064, CV181066, CV181054,** CV181014**)** did not report any cases of pancreatitis.

Hypersensitivity related AEs

Hypersensitivity reaction was identified using a list of predefined preferred and lower level terms.

In regard to the hypersensitivity related AEs, saxagliptin 5 mg QPM presented comparably to placebo (CV181038), and saxagliptin + metformin presented comparably to the active comparators sitagliptin + metformin (CV181056) and glipizide + metformin (CV181054). Saxagliptin 5 mg + metformin, saxagliptin + metformin XR, and saxagliptin + metformin presented less favorably than metformin (CV181039), placebo + metformin XR (CV181066), and placebo + metformin (CV181014), respectively.

Completed studies

Study CV181038

There were 4 new cases since NDA22350 was reviewed (6%) of hypersensitivity related AEs in the saxagliptin 5 mg QPM arm (which were rash, dermatitis, rash papular, and swelling face - narrative submitted and reviewed under NDA 22350), 10 cases (14%) of hypersensitivity related cases in saxagliptin 5mg QAM arm, compared to 5 cases (7%) of hypersensitivity AEs with placebo.

Study CV181039

The incidence of hypersensitivity related AEs since the review for NDA 22350 was 6% (19 cases, which were pruritus, dermatitis, eczema, and rash) in the saxagliptin 5 mg + metformin arm and 4% (13 cases) in the metformin arm.

Study CV181056

There were no hypersensitivity related AE reported in the saxagliptin + metformin or sitagliptin + metformin treatment arms.

Study CV181066

There was one case (2%) of seborrheic dermatitis in the saxagliptin + metformin XR treatment arm and no cases in the placebo + metformin XR arm.

Ongoing studies

Study CV181054

No hypersensitivity related AEs were reported in the saxagliptin + metformin arm, compared to 0.5 % incidence of hypersensitivity related AEs in the glipizide + metformin arm.

Study CV181014

The incidence of hypersensitivity related AEs was 16 % in the saxagliptin + metformin treatment (most common were rash, rash papular, pruritus) and 13 % in the placebo + metformin treatment arm.

Recently initiated

Studies CV181085, CV181086, CV181089, and CV181090 were recently initiated with small number of patients and will not be reviewed under this NDA.

Acute cardiovascular events

Saxagliptin 5 mg QPM as monotherapy and saxagliptin 5 mg in combination with metformin had numerically fewer cardiovascular events compared to placebo (CV181038), metformin (CV181039), placebo + metformin (CV181014) and active comparator (sitagliptin, glipizide) + metformin (CV181056 and CV181054). Saxagliptin 5 mg in combination with metformin XR had a similar incidence of cardiovascular events as the combination of placebo and metformin XR (CV181066). The sponsor is conducting a required postmarketing trial to definitively assess the cardiovascular safety of saxagliptin.

Completed studies

Study CV181038

There were no cardiovascular events reported for the saxagliptin 5 mg QPM and saxagliptin 5 mg QAM arms since the review for NDA 22350 compared to a 4.1 % incidence of cardiovascular events reported with placebo.

Study CV181039

The incidence of new cardiovascular events since the review for NDA 22350 in the saxagliptin 5 mg + metformin treatment arm was 0.3% (which were acute myocardial infarction and cerebral infarction), compared to metformin with 2.1 % incidence of cardiovascular events.

Study CV181056

There were no cardiovascular events in the saxagliptin 5 mg + metformin arm and 2 cases (0.5% incidence) of cardiovascular events in the sitagliptin + metformin arm.

Study CV181066

There were no cardiovascular events reported during the study.

Ongoing studies

Study CV181054

The incidence of cardiovascular events was 1.9 % in the saxagliptin + metformin arm and 2.1 % in the glipizide + metformin arm.

Study CV181014
The saxagliptin 5 mg + metformin treatment arm had a similar incidence of cardiovascular events 8.9%, reported since the data review for NDA 22350 (17 cases, most common were coronary artery disease and cardiac failure), compared to 9.5 % (17 cases) in the placebo + metformin arm. There is only one case of congestive cardiac failure in the saxagliptin 5 mg + metformin arm (CV181014-159-1188) that is a new case reported after the interim LT report of Onglyza NDA.
Recently initiated
Studies CV181085, CV181086, CV181089, and CV181090 were recently initiated with small number of patients and will not be reviewed under this NDA.

Decreased lymphocyte count (reported as an adverse event)
The incidence of Lymphocytopenia (reported as an AE by investigators) was low in all studies (<3%). Saxagliptin 5 mg QPM, saxagliptin 5 mg + metformin, and saxagliptin 5 mg + metformin XR had same incidence as placebo (CV181038), sitagliptin + placebo (CV181056), and placebo + metformin XR (CV181066), respectively. Saxagliptin 5 mg + metformin had a lower numerical incidence of Lymphocytopenia compared to metformin (CV181039) and glipizide + metformin (CV181054). Only in study CV181014, LT period of which is ongoing, the incidence of lymphocytopenia was greater with saxagliptin + metformin treatment than in the placebo + metformin arm.
Completed studies
Study CV181038
The incidence of lymphopenia AEs was 3 % (2 cases) for both the saxagliptin 5 mg QPM and placebo treatment arms.
Study CV181039
Thee were no AEs of lymphopenia in the saxagliptin + metformin treatment arm, compared to one case (0.3%) in the metformin arm.

Study CV181056
There were no AEs of lymphopenia during this study.
Study CV181066
No AEs of lymphopenia were reported**.**
Ongoing studies
Study CV181054
There were no cases of lymphopenia in the saxagliptin + metformin arm and one case (0.2%) in the glipizide + metformin treatment arm.
Study CV181014
The incidence of Lymphocytopenia was greater (2.1%) in the saxagliptin 5 mg + metformin arm compared to the placebo + metformin arm (0.6%). All cases of lymphopenia in the saxagliptin 5 mg + metformin arm were reported previously and reviewed under the Onglyza NDA. The 42 month LT period of the study is still ongoing.
Recently initiated
Studies CV181085, CV181086, CV181089, and CV181090 were recently initiated with small number of patients and will not be reviewed under this NDA.

Decreased platelet count
The incidence of thrombocytopenia reported as an AE in the saxagliptin 5 mg QPM or saxagliptin in combination with metformin arms was equal or very similar to that in the comparator arms. Any differences were small and not expected to have clinical relevance. No bleeding issues related to thrombocytopenia were reported.
Completed studies
Study CV181038
No cases of thrombocytopenia reported since the data reviewed for NDA 22350.
Study CV181039
There were no cases of thrombocytopenia in the saxagliptin 5 mg + metformin arm identified since the data review for NDA 22350 and the incidence of thrombocytopenia in the metformin arm was 0.3%.

There were no cases of thrombocytopenia reported in study CV181056 and Study CV181066.

Ongoing studies
Study CV181054
The incidence of thrombocytopenia in the saxagliptin + metformin arm was low (one case) and there were no cases of thrombocytopenia in the glipizide + metformin arm.
Study CV181014
The incidence of thrombocytopenia was low (one case) in the saxagliptin 5 mg + metformin arm and no cases were reported in the placebo + metformin arm.
Recently initiated
Studies CV181085, CV181086, CV181089, and CV181090 were recently initiated with small number of patients and will not be reviewed under this NDA.

Liver function test abnormalities
There were no saxagliptin-treated subjects with ALT and AST > 3X ULN and total bilirubin > 1.5 ULN.

7.3.5 Submission Specific Primary Safety Concerns

Submission Specific Primary Safety Concerns were hypoglycemia, skin disorders, localized edema, infections, fractures, hypersensitivity, pancreatitis, cardiovascular events, lymphopenia, thrombocytopenia, and liver toxicity. Data addressing these concerns were reviewed in section 7.3.4.

7.4 Supportive Safety Results

The sponsor conducted several clinical pharmacology studies to bridge the FDC formulation to coadministered components. This section of my review will focus on whether any concerning major safety signals were identified in these small studies.

Study CV181060 was a bioequivalence study of the fixed dose combination of 5 mg saxagliptin and 500 mg metformin XR relative to 5 mg of saxagliptin and 500 mg metformin XR coadministered to healthy subjects in fed condition.
There were no deaths or SAEs reported. There was 1 discontinuation due to pyrexia in the saxagliptin 5 mg + metformin XR 500 mg fed treatment group. The incidence of AEs was 29 % in the saxagliptin 5 mg+ metformin XR 500 mg arm (most common of which was somnolence), 26 % in the saxagliptin 5 mg/metformin XR 500 mg FDC fed arm (most common AEs were somnolence and headache), and 30 % in the saxagliptin 5 mg/metformin XR 500 mg FDC fasted (most common was somnolence).

Study CV181074 was a bioequivalence study of a metformin XR 1X1000 mg tablet relative to metformin XR 2X 500 mg tablets in healthy subjects in a fed condition. Wash out period was 4-7 days. There were no deaths, SAEs or discontinuations from the study due to AEs.

Study CV181076 was a bioequivalence study of the fixed dose combination of 5 mg saxagliptin and 1000 mg metformin XR tablet relative to a 5 mg saxagliptin tablet and a 1000 mg metformin XR tablet co-administered to healthy subjects in a fed condition. There was 7 days wash out period between treatment periods. There were no deaths, SAEs or discontinuations due to AEs.

Study CV138098 was a bioequivalence study of a metformin XR 500 mg tablet manufactured in Mt. Vernon, IN, USA relative to a metformin XR 500 mg tablet manufactured in Evansville, IN, USA in healthy subjects in the fasted state and fed state.
A: metformin XR 500 mg (Evansville) fasted
B: metformin XR 500 mg (Mt Vernon) fasted
C: metformin XR 500 mg (Evansville) fed
D: metformin XR 500 mg (Mt Vernon) fed
There were no deaths or SAEs. There was one subject who discontinued in each of the treatments A, B, and C (3.8%, 3.7 %, and 3.7%, respectively). The case that led to discontinuation in treatment A was due to hepatic enzymes increased (subject 00029, ALT values ranged from 66 to 75 UI/L with normal total bilirubin). The case that led to discontinuation in treatment B (subject 00041, 35 years old male) reported AE vomiting, orthostatic hypotension, disorientation, and confused state.
The case that led to discontinuation in treatment C (subject 00030, 41 years old female) reported cough, rhinorrhea, fatigue. Note that only metformin was tested in this study.

Study 138100 was a bioequivalence study of a metformin XR 1000 mg tablet manufactured in Mt Vernon, IN, USA relative to a metformin XR 1000 mg tablet manufactured in Evansville, IN, USA in healthy subjects in the Fasted state and fed state.
A: metformin XR 1000 mg (Evansville) fasted
B: metformin XR 1000 mg (Mt Vernon) fasted
C: metformin XR 1000 mg (Evansville) fed

D: metformin XR 1000 mg (Mt Vernon) fed

There were no deaths or SAEs. There were 2 cases of hematochezia in treatment A and B.
The subject 00015 (26 years old male), under treatment A reported after dosing cramping, nausea, diarrhea. After 7 days he had positive test for fecal occult blood. The subject discontinued the study on day 1.
The subject 00023(29 years old male) was on study B complained of cramping and diarrhea after dosing. Five days after dosing he had positive test for fecal occult blood. Note that only metformin was tested in this study.

7.4.1 Common Adverse Events (AEs)

In all studies reviewed for this NDA the AEs with higher incidence among saxagliptin-treated patients were in the infectious SOC (upper respiratory tract infection, nasopharyngitis, urinary tract infection and influenza), although the incidence order was slightly different in the different studies. Infection-related AEs are discussed in more detail in Section 7.3.4 above. There were no new common AEs identified.

Completed studies

Study CV181038

Most common AEs in the saxagliptin 5 mg QPM arm reported since the review for NDA 22350 were upper respiratory tract infection (15 %), nasopharyngitis (7%) and urinary tract infections (6%). The incidence of the same AEs in the placebo group was 10%, 4 %, and 3%, respectively.

Study CV181039

Most common AEs reported for saxagliptin 5 mg + metformin since the review for NDA 22350 were nasopharyngitis 9% (vs 6 % in the placebo arm), Influenza 6 % (vs. 6 % in placebo arm), and upper respiratory tract infection 5% (vs 3 % in the placebo arm).

Study CV181056

Most common AEs in the saxagliptin 5 mg + metformin arm were influenza with incidence of 6% and urinary tract infection with incidence of 6%, which were with same (6%) and similar (5%) incidence in sitagliptin + metformin arm, respectively.

Ongoing studies

Study CV181054

Most common AEs reported in the saxagliptin 5 mg + metformin arm were nasopharyngitis with incidence 10% (vs. 9% in the glipizide + metformin arm) and upper respiratory tract infection with incidence 5 % (vs. 3% in comparator's group).

Study CV181014

The most common AEs in this study are the infectious SOC disorders, pedal edema and hypertension but these events were well balanced between treatment groups.

Table 59 Most common AEs with incidence > 5 % during study CV181014

	saxagliptin 5 mg + met N= 191	placebo + met N= 179
Infectious disorders	109 (57)	103 (58)
Influenza, n (%)	31 (16)	27 (15)

Nasopharyngitis	28 (15)	25 (14)
Upper respiratory tract infection	19 (10)	17 (10)
Urinary tract infection	15 (8)	16 (8)
Bronchitis	19 (10)	13 (7)
Musculoskeletal disorders	65 (34)	59 (33)
Arthralgia	21 (11)	13 (7)
Back pain	16 (8)	19 (11)
Gastrointestinal disorders	65 (34)	62 (35)
Diarrhoea	19 (10)	23 (13)
General disorders	15 (8)	12 (7)
Pedal edema	15 (8)	12 (7)
Vascular disorders	23 (12)	17 (10)
Hypertension	14 (7)	13 (7)

Recently initiated
Studies CV181085, CV181086, CV181089, and CV181090 were recently initiated with small number of patients and will not be reviewed under this NDA.

7.4.2 Laboratory Findings

AEs of lymphocytopenia have been discussed above. This section focuses on markedly low lymphocyte counts and markedly low platelet counts based on the sponsor's prespecified criteria similar to those used in NDA 22350.

There were 2 cases of lymphocytopenia (< 0.7 X 10^3c/µL) in saxagliptin 5 mg + metformin and 2 cases in placebo + metformin arm (CV1810114) and 2 cases in saxagliptin 5 mg QPM and 1 case in placebo arm (CV1810138).

There was one case of thrombocytopenia (< 50X10^9c/L) in saxagliptin 5 mg + metformin and no cases in placebo + metformin arm (CV181014) and one case of thrombocytopenia in saxagliptin + metformin and no cases in glipizide + metformin arm (CV181054).

7.4.3 Vital Signs

No clinically significant changes in vital signs from baseline were observed.

7.4.4 Electrocardiograms (ECGs)

There were some shifts from normal at baseline to abnormal ECG. The changes observed at different studies varied and did not point to a concern for any particular cardiac disorder.
Completed studies
Study CV181038

The incidence of shift from normal at baseline to abnormal at week 76 (new data since the review for NDA 22350) was 25 % in the saxagliptin 5 mg QPM arm, 26 % in the saxagliptin 5 mg QAM arm, and 39 % in the placebo treated arm.

Study CV181039

The incidence of shift from normal at baseline to abnormal at visit 76 (new data since the review for NDA 22350) was 14 % in both the saxagliptin 5 mg + metformin arm and the metformin alone arm. The number of patients in the arms was small to draw conclusions.

Study CV181056

The incidence of shift to abnormal ECG was 4 % in both the saxagliptin + metformin arm and the sitagliptin + metformin arm.

Study CV181066

There were 3 cases (7%) of non-specific ST/T changes (CV181066-10-147, CV181066-17-74, and CV181066-17-160), one case (2%) with left ventricular hypertrophy, and one case (2%) of sinus tachycardia in the saxagliptin 5 mg + metformin XR arm.

Ongoing studies

Study CV181054

The incidence of change from baseline from normal to abnormal at week 52 was 7 % for the saxagliptin + metformin arm and 6 % for the glipizide + metformin arm.

Recently initiated

Studies CV181085, CV181086, CV181089, and CV181090 were recently initiated with small number of patients and will not be reviewed under this NDA.

7.5 Other Safety Explorations

Drug-Disease Interactions

Saxagliptin has been studied in a randomized controlled trial in patients with renal impairment. The results of this study are currently under review as an Efficacy supplement for NDA 22350.

Drug-Drug Interactions

See the clinical pharmacology review conducted for the original saxagliptin NDA and for this FDC NDA. Data from a study evaluating the effect of saxagliptin on a combined oral contraceptive containing ethinyl estradiol and norgestimate is currently under review as a supplement to NDA 22350.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There are no new concerns for carcinogenicity based on the clinical data included in this NDA.

7.6.2 Human Reproduction and Pregnancy Data

No data are available from well controlled studies in pregnant women A listing of all pregnancies from each study was planned to be provided as part of SAEs listing. There were no pregnancies reported in CV181014, CV181038, CV181054, CV181056, CV181064, and CV181066.

7.6.3 Pediatrics and Assessment of Effects on Growth

This NDA does not include pediatric data. (b) (4) We consider that (b) (4) the pediatric program for saxagliptin/metformin XR FDC that the pediatric requirements should be deferred (b) (4) The sponsor has also been asked to assess the swallowability of the large tablets by children. The sponsor has also been asked to submit the full protocol of the saxagliptin efficacy and safety study with sufficient time for review prior to initiating the study to ensure that it will provide adequate supportive data for the FDC.

8 Post-market Experience

At the time of Onglyza approval 3 clinical trials were required as postmarketing requirements under 505 (o), which are ongoing. Two of them were epidemiologic studies to compare the risk of severe hepatic events and severe hypersensitivity and Cutaneous reactions among patient exposed to saxagliptin and those exposed to other antidiabetic medications. The third study was with goal to estimate the incidence of major adverse cardiovascular events in patients with type 2 diabetes. There were two non-clinical PMR studies to evaluate the teratogenecity when saxagliptin and metformin are co-administered. I defer to pharmacology/toxicology as to whether the sponsor can be released from these non-clinical PMRs.

9 Appendices

9.1 Labeling Recommendations

I recommend that saxagliptin/metformin XR FDC is labeled as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate. The label for saxagliptin/metformin XR in Section 4 “Contraindications”, Section 5 “ Warning and precautions” should contain all elements of approved saxagliptin and metformin XR label.

9.2 Advisory Committee Meeting

This FDC NDA was not taken to advisory committee meeting. There were no new issues identified that rose to the level of needing input from an advisory committee.

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

/s/

ARLET NEDELTCHEV-PENEVA
09/28/2010

HYLTON V JOFFE
09/28/2010
Please see CDTL memorandum.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 200678 **Applicant: Bristol-Myers Squibb** **Stamp Date: 12/29/09**

Drug Name: (b) (4) **NDA/BLA Type: 505(b)(1)** **strengths: 5/500, 5/1000, 2.5/1000 mg**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	YES			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	YES			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	YES			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	YES			
5.	Are all documents submitted in English or are English translations provided when necessary?	YES			
6.	Is the clinical section legible so that substantive review can begin?	YES			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	YES			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	YES			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	YES			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	YES			
11.	Has the applicant submitted a benefit-risk analysis for the product?	YES			CV181066 Clinical protocol page 205/883
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	505 (b) (1)			505 (b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	YES			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1 CV181066 Phase 3	YES			duration=4 weeks subjects=46 (Saxa 5 mg+ Met ≥ 1500 mg/d) subjects=47(Saxa 5 mf+

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Indication: treatment T2DM CV181038 Pivotal Study #2 Indication: treatment T2DM Reviewed for NDA 22350 approval	YES			Met ≥ 1500 mg/d) duration= 24 weeks subjects=365 (Saxa 2.5-5mg/d, 5 mg qAM, 5 mg qPM) subjects=272 placebo
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	YES			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	YES			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		NO		n subjects =93 US sites subjects=43
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	YES			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	YES			CV181032 QTc study reviewed with NDA 22350
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	YES			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	YES			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			NA	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	YES			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	YES			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested			NA NA	Death=0 SAEs=0

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	by the Division)?	YES			AEdropouts=1 (Placebo+Met), CV181066
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	YES			Bioequivalence studies
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			NA	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	YES			(b) (4) [redacted]
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			NA	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		NO		
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	YES			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	YES			eCTD
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	YES			
34.	Are all datasets to support the critical safety analyses available and complete?	YES			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	YES			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	YES			Module 5.3.1.2.24.1 deaths=0 SAEs=0 AE dropouts=1(Placebo+Met)
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	YES			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	YES			Module 1.3.4
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	YES			CV181066 Final clinical study report page 56

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____YES____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Arlet V. Nedeltcheva

Reviewing Medical Officer Date

Hylton Joffe

Clinical Team Leader Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200678	ORIG-1	BRISTOL MYERS SQUIBB	(b) (4) (saxagliptin + metformin XR) Tablets

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

/s/

ARLET NEDELTCHEV-PENEVA
02/16/2010

HYLTON V JOFFE
02/17/2010

I concur with Dr. Nedeltcheva that the NDA is fileable from a clinical perspective. The pivotal efficacy and safety trials were reviewed under the saxagliptin NDA. The current NDA includes additional safety data.