CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209483Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	(see electronic signature)
From	William H. Chong, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 209091 NDA 022350, Suppl 18 NDA 200678, Suppl 18
Applicant	AstraZeneca
Date of Submission	April 27, 2016
PDUFA Goal Date	February 27, 2017
Proprietary Name / Established (USAN) names	**NDA 209091:** QTERN (dapagliflozin and saxagliptin) **NDA 022350:** ONGLYZA (saxagliptin) **NDA 200678:** KOMBIGLYZE XR (saxagliptin and metformin hydrochloride extended release
Dosage forms / Strength	**NDA 209091:** 10 mg/5 mg (dapagliflozin/saxagliptin) tablets **NDA 022350:** 5 mg and 2.5 mg tablets (saxagliptin) **NDA 200678:** 5 mg/500 mg, 5 mg/1000 mg, and 2.5 mg/1000 mg (saxagliptin/metformin HCl extended release) tablets
Proposed Indication(s)	**NDA 20901:** Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [redacted] (b) (4) **NDA 022350:** Not applicable **NDA 200678:** Not applicable
Recommended Indication(s)	**NDA 209091:** Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who have inadequate glycemic control on dapagliflozin or who are already treated with dapagliflozin and saxagliptin **NDA 022350:** Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus **NDA 200678:** 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.
Recommendation:	*Approval*

1. Introduction

AstraZeneca (hereafter referred to as the applicant) submitted a new drug application (NDA) for a fixed combination drug product (FCDP) that combines saxagliptin, a dipeptidyl peptidase4 (DPP4) inhibitor, with dapagliflozin, a sodium glucose cotransporter2 (SGLT2) inhibitor for use in adult patients with type 2 diabetes mellitus (T2DM). The applicant has previously submitted an NDA (b) (4) for this FCDP, but a Complete Response was issued for that application citing a need for more data (b) (4) Rather, the applicant has submitted a new NDA with a different study to support use of this FDCP. This Cross-Discipline Team Leader (CDTL) review will summarize the relevant information from the involved review disciplines and their recommendations. I will discuss the efficacy data and the relevance to the indication as well as safety findings focusing on the additional available data on muscle injury.

2. Background

Type 2 diabetes mellitus is a disease of impaired glucose homeostasis that results in chronic hyperglycemia which in turn leads to an increased risk for microvascular (e.g., retinopathy, nephropathy) and macrovascular (e.g., myocardial infarction, stroke) complications. Based on the results of the Diabetes Control and Complication Trial (DCCT) [1] and the United Kingdom Prospective Diabetes study (UKPDS) [2], improved glycemic control (as measured using hemoglobin A1c [HbA1c]) is believed to result in improved clinical outcomes.

Many patients with T2DM require multiple antidiabetic drugs to achieve the desired degree of glycemic control, and most patients require intensification of therapy (i.e., addition of antidiabetic drugs) as the duration of disease progresses. There are currently 11 classes of antidiabetic drugs with most classes having multiple members (Table 1). Many of these drug products are also available as FCDPs. The FDA has also approved combinations of basal insulin with a GLP1 receptor agonist.

[1] The Diabetes Control and Complications Trial Research Group. "The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus". NEJM, 1993; 329 (14): 977-986.
[2] UK Prospective Study Group. "Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33)". Lancet, 1998; 352 (9131): 837-853.

Table 1: Summary of FDA approved drugs to improve glycemic control in diabetes

Drug Class	Drug Products
Insulin and insulin analogs	Multiple products including basal, prandial, and mixed insulin products
Biguanides	Metformin (as an immediate release and an extended release formulation)
Sulfonylureas	Chlorpropamide, Glimepiride, Glipizide, Glyburide
Thiazolidinediones	Rosiglitazone, Pioglitazone
Meglitinides	Repaglinide, Nateglinide
Alpha glucosidase inhibitors	Acarbose, Miglitol
Dipeptidyl peptidase4 (DPP4) inhibitors	Sitagliptin, Saxagliptin, Alogliptin, Linagliptin
Glucagonlike peptide1 (GLP1) receptor agonists	Exenatide (as a twice daily and as a once weekly), Liraglutide, Albiglutide, Dulaglutide, Lixisenatide
Sodium glucose cotransporter2 (SGLT2) inhibitors	Canagliflozin, Dapagliflozin, Empagliflozin
Amylin analogs	Pramlintide
Bile acid sequestrants	Colesevelam
Dopamine agonists	Bromocriptine
Basal insulin and GLP1 receptor agonist combinations	Insulin glargine and lixisenatide, insulin degludec and liraglutide

The applicant is now proposing to market an FCDP that combines saxagliptin (a DPP4 inhibitor) with dapagliflozin (an SGLT2 inhibitor). The DPP4 inhibitors prolong the circulation of endogenous incretin hormones by preventing DPP4 mediated degradation. This in turn is believed to increase insulin secretion in response to a glucose load and decrease glucagon secretion. The SGLT2 inhibitors block glucose reabsorption in the kidney, thus resulting in an insulin independent reduction in plasma glucose levels. The applicant believes that this FCDP offers patients with T2DM a way to combine two drugs which improve glycemic control through different mechanisms of action in a manner that will be convenient and that may improve compliance.

An NDA for this FCDP was previously submitted (NDA (b) (4)), but a Complete Response was issued for that NDA (b) (4) (see Complete Response Letter issued on October 15, 2015 under NDA (b) (4)). Following receipt of the Complete Response Letter, an End of Review meeting was held on December 17, 2015 to discuss potential paths forward for the FCDP. Options included (b) (4) or submitting a new NDA with data from a study of adding saxagliptin to patients with inadequate glycemic control on dapagliflozin (see Meeting Minutes issued on January 14, 2016). The applicant has opted to do the latter (b) (4)

3. CMC/Device

There is no new Chemistry, Manufacturing, and Controls (CMC) data for NDA 022350 or NDA 200678. For the CMC information of these two drug products, see the currently approved prescribing information. This section will discuss data relevant to NDA 209091.

The Chemistry, Manufacturing, and Controls (CMC) review of the FCDP was previously completed during review of NDA (b) (4) The drug substance and drug product review was completed by John Amartey, the manufacturing process and microbiology review was completed by Daniel Peng, the manufacturing facilities review was completed by Vipul Dholakia, and the biopharmaceutics review was completed by Peng Duan.

The reviewers from the Office of Product Quality recommended Approval of the NDA during review of NDA (b) (4) In the current submission, the applicant has made only minor changes to the CMC information. (b) (4) These changes have been reviewed by the CMC reviewers and were found to be acceptable. The Office of Product Quality recommends Approval for NDA 209091.

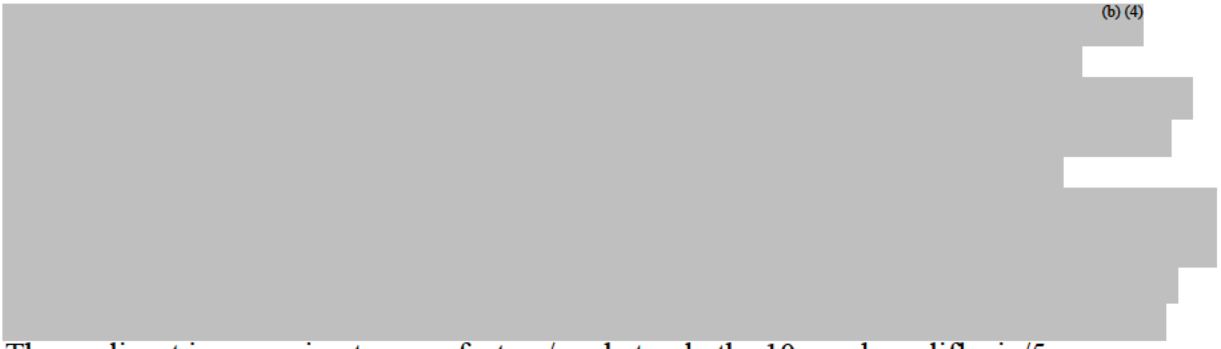
For detailed discussion of the CMC findings, see the completed Quality Review from NDA (b) (4) and the Dr. Amartey's Memorandum for NDA 209091. A brief summary of the CMC data is included below.

The saxagliptin and dapagliflozin FCDP is manufactured as a film coated tablet (b) (4) (see Figure 1).

Figure 1: Saxagliptin and dapagliflozin tablet

(b) (4)

Source: Excerpted from page 11 of the Quality Review for NDA (b) (4)



The applicant is proposing to manufacture/market only the 10 mg dapagliflozin/5 mg saxagliptin dosage strength.

Long-term stability studies were performed with three batches in blister packs and four batches of in high density polyethylene bottles. Based on review of the stability data, the Quality Review concludes that the proposed 36month shelf life is justified.

I agree with the CMC reviewers that the CMC data support Approval.

4. Nonclinical Pharmacology/Toxicology

There is no new nonclinical data for NDA 022350 or NDA 200678. For the nonclinical information of these two drug products, see the currently approved prescribing information. This section will discuss data relevant to NDA 209091.

The nonclinical review for NDA (b) (4) was completed by Dr. Fred Alavi. An updated review for this NDA was completed by Dr. Jeffery Quinn. Both Dr. Alavi and Dr. Quinn recommend Approval. For detailed discussion of the nonclinical findings, see Dr. Alavi's completed review in NDA (b) (4) and Dr. Quinn's completed review in NDA 209091.

The nonclinical data to support the fixed combination drug product is drawn primarily from the individual components (see primary nonclinical reviews under NDA 022350 [saxagliptin] and NDA 202293 [dapagliflozin]). Additional safety findings to support the combination of saxagliptin + dapagliflozin come from a 3 month rat toxicology study and an in vitro human liver microsomal metabolism study. In these two studies, coadministration of the two drugs was studied. The combination of dapagliflozin + saxagliptin did not result in a synergistic effect on the toxicity profile with the exception of increased proteinuria in male rats at doses 6x the maximum recommended human dose. Based on the data reviewed, Dr. Alavi and Dr. Quinn conclude that the nonclinical data support approval of this FCDP.

I agree that the nonclinical data support Approval.

5. Clinical Pharmacology/Biopharmaceutics

There is no new clinical pharmacology data for NDA 022350 or NDA 200678. For the clinical pharmacology information of these two drug products, see the currently approved prescribing information. This section will discuss data relevant to NDA 209091.

The clinical pharmacology review was completed by Dr. S.W. Johnny Lau with additional biopharmaceutics review by Dr. Peng Duan. Based on review of the submitted data, the clinical pharmacology reviewer recommends Approval. For detailed discussion of the clinical pharmacology findings, see Dr. Lau's completed review in NDA (b) (4)

Two clinical pharmacology studies were submitted to support the NDA. The first (study CV181191) was a drug-drug interaction study of dapagliflozin 10 mg and saxagliptin 5 mg. The second (study CV181341) was designed to demonstrate the bioequivalence of the combination tablet with the coadministration of the individual components. This study also included an assessment of food effect. Study CV181341 was reviewed by Biopharmaceutics.

Results from study CV181191 showed that coadministration of dapagliflozin 10 mg and saxagliptin 5 mg does not result in a significant interaction.

An additional clinical pharmacology study (study (b) (4)) was included in the submission for NDA 209091. This study was conducted (b) (4) and was submitted as complementary data for the previously reviewed studies. This study was not reviewed as part of the NDA review.

While the clinical pharmacology reviewer recommends Approval, (b) (4) I agree that the data support Approval. (b) (4) there is sufficient data to support the proposed dosage strength of dapagliflozin 10 mg/saxagliptin 5 mg.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical Efficacy

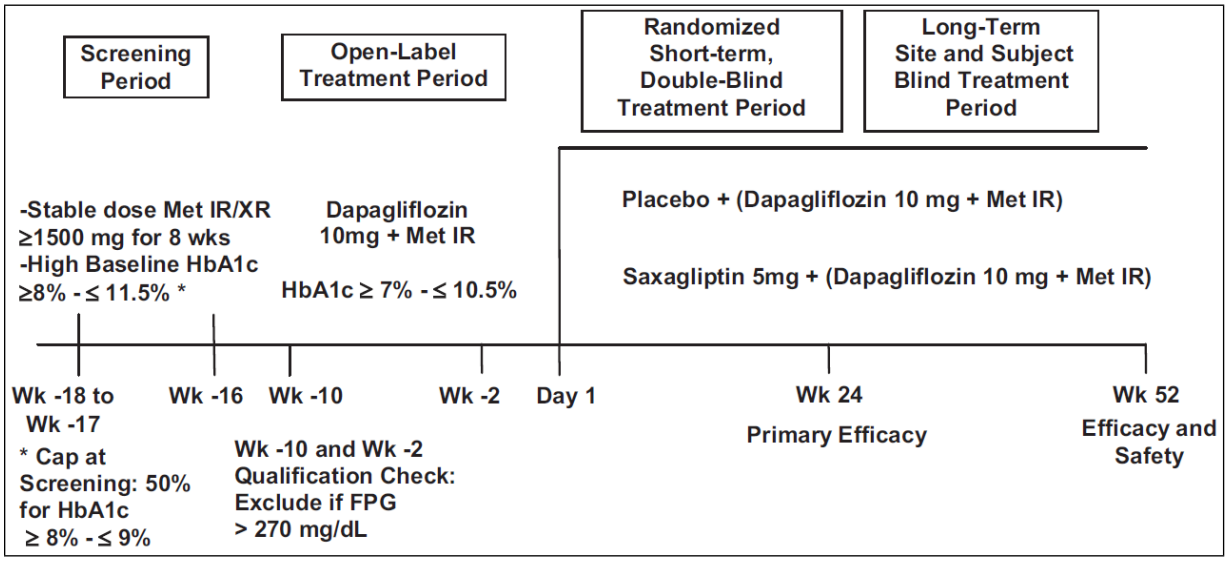
The statistical review of this NDA (and efficacy supplements) was completed by Dr. Anna Kettermann.

The applicant has submitted three clinical studies (study CV181168, study CV181169, and study MB102129) in support of NDA 209091. Each of the studies and the findings will be briefly discussed here. Only one (study CV181168) is proposed for inclusion in labeling to

support the proposed indication. This study has also been submitted to NDA 022350 and NDA 200678 for inclusion in section 14 of the prescribing information. While Dr. Kettermann has reviewed all three studies, my discussion of efficacy will focus on study CV181168.

Study CV181168 was a randomized, double-blind, placebo-controlled study comparing the effect of sequentially adding saxagliptin vs. placebo to a background of dapagliflozin and metformin. The study enrolled patients needing additional glycemic control despite therapy with metformin, treated them with dapagliflozin 10 mg for 8 weeks, and then randomized those patients requiring additional glycemic control to either saxagliptin 5 mg or placebo (Figure 2).

Figure 2: Study schematic for study CV181168



Source: Excerpted from Figure 3.11 of the study report for CV181168

The primary endpoint was change in HbA1c from baseline (i.e., Day 1) to week 24 (i.e., after 24 weeks of saxagliptin or placebo). Secondary endpoints included change in 2hour postprandial glucose, change over time in HbA1c and fasting glucose, and percentage of subjects achieving HbA1c < 7%.

The applicant utilized a longitudinal repeated measures analysis to estimate change from baseline for HbA1c. The primary analysis population consisted of all randomized subjects that received at least one dose of double-blind study drug (i.e., saxagliptin or placebo). Data on HbA1c collected after discontinuation of study drug was excluded from the primary analysis by the applicant.

Dr. Kettermann does not believe that excluding data after discontinuation will yield a realistic estimate of the effect. As such, Dr. Kettermann has conducted analyses including data regardless of adherence which she believes will more appropriately describe real world outcomes.

Both the applicant and Dr. Kettermann conclude that the addition of saxagliptin on top of a background of dapagliflozin and metformin demonstrated a statistically significant greater reduction in HbA1c at week 24 compared to the addition of placebo (Table 2). Dr. Ketterman conducted various analyses using alternative approaches to the handling of missing data examining the difference for change in HbA1c. All analyses supported the conclusion that addition of saxagliptin led to greater reduction in HbA1c than addition of placebo.

Table 2: Summary of HbA1c findings for study CV181168

- Compared addition of saxagliptin vs. addition of placebo in patients inadequately controlled following addition of dapagliflozin 10 mg in patients on metformin therapy

	Difference for change in HbA1c at 24 weeks	95% CI
Applicant's analysis[1]	-0.35%	-0.52, -0.18
FDA analyses		
– MI (J2R)	-0.336	-0.504, -0.166
– MI (CR)	-0.334	-0.505, -0.167
– MI (retrieved dropouts, ANCOVA)	-0.395%	-0.54, -0.233
– MMRM	-0.337	-0.504, -0.171

[1] mixed effect model repeat measurement without data after rescue
MI (J2R) = missing data imputation, jump-to-reference; MI (CR) = missing data imputation, copy reference; MI (retrieved dropouts, ANCOVA) = missing data imputation using retrieved dropouts, analysis of covariance; MMRM = mixed model repeated measures
Source: Adapted from Table 7 and Table 8 of Dr. Kettermann's statistical review

No statistically significant difference was seen for either fasting plasma glucose or 2hour postprandial glucose (Table 3).

Table 3: Summary of fasting glucose and postprandial glucose findings for study CV181168

- Compared addition of saxagliptin vs. addition of placebo in patients inadequately controlled following addition of dapagliflozin 10 mg in patients on metformin therapy

	Difference at 24 weeks	95% CI
Fasting glucose	-3.7 mg/dL	-14.9, 3.1
2-hour postprandial glucose	-5.9 mg/dL	-11, 3.6

Source: Adapted from Table 9 of Dr. Kettermann's statistical review

At week 24, a greater proportion of subjects randomized to receive saxagliptin had an HbA1c < 7% (35.3% vs. 23.1%).

Subgroup analyses were generally consistent with the findings for the population as a whole. While the nonwhite subjects did not demonstrate a statistically significant difference, this is likely due to the small number of nonwhite subjects (nearly 90% of subjects in study CV181168 were classified as white). The treatment difference was smaller for subjects from the North America region (-0.25%, 95% CI [-0.48, -0.01]). Subjects from Latin America had the largest difference (-0.56%, 95% CI [-1.02, -0.1]). Reasons for this are unclear.

Dr. Kettermann concludes that adding saxagliptin to dapagliflozin results in a statistically significantly greater reduction in HbA1c compared to placebo at 24 weeks, and that the efficacy findings support approval of this NDA. I agree with this assessment.

8. Safety

The discussion of safety will primarily focus on the data as it relates to NDA 209091. No new safety concerns relevant to ONGLYZA or KOMBIGLYZE XR were identified from the submitted data for NDA 022350 or NDA 200678.

The safety review was completed by Dr. Frank Pucino. Dr. Pucino did not identify any safety issues which would preclude approval.

The overall safety profile of combining dapagliflozin and saxagliptin is consistent with what would be expected if combining the safety profiles of the individual drug products. Combining dapagliflozin and saxagliptin did not appear to exacerbate any of the previously identified safety concerns for the two drug products. Overall, no concerning findings in terms of deaths or serious adverse events were observed. For a detailed discussion of the safety findings from the development program, see Dr. Pucino's clinical review.

One safety concern which I will discuss here was the potential for muscle injury. During review of the small safety database included with NDA (b) (4) it was noted that the incidence of marked elevation of creatine kinase was higher in the arm which combined dapagliflozin and saxagliptin compared to the individual treatments. There was one event of rhabdomyolysis in the database without a clear explanation. In this NDA, the safety database is expanded to include the long-term safety data from studies CV181168 and MB102129 which adds approximately an additional 100 patient-years of exposure. Additionally, non-serious adverse event data are unblinded for review.

No notable changes were seen when looking at mean changes from baseline for creatine kinase. There remains in imbalance in marked elevations of creatine kinase in subjects treated with both dapagliflozin and saxagliptin compared to subjects treated with either of the components (Table 4). The clinical significance of this is unclear.

Table 4: Summary of Marked Elevations in Creatine Kinase in the Pooled Safety Database

	Dapa + Saxa N=486	Saxa N=334	Dapa N=334
	N (%)	N (%)	N (%)
Creatine kinase > 5x ULRR	7 (1.4)	0	1 (0.3)
Creatine kinase > 10x ULRR	4 (0.8)	0	1 (0.3)

ULRR = upper limit of reference range
Source: Adapted from Table 19 of Dr. Pucino's Clinical Review

The subjects treated with dapagliflozin and saxagliptin did not have an increased incidence of serious adverse events from the 'Musculoskeletal and connective tissue disorders' system organ class (Table 5).

In looking at treatment emergent adverse events from the 'Musculoskeletal and connective tissues disorder' system organ class, subjects treated with dapagliflozin and saxagliptin had a higher incidence than those treated with dapagliflozin but lower than those treated with saxagliptin. During review of NDA (b) (4) these data were not available for review. "Arthralgia' was reported more commonly for subjects treated with the combination of dapagliflozin and saxagliptin compared to the individual components (2.4% dapagliflozin + saxagliptin vs. 1.2% saxagliptin vs. 0.9% dapagliflozin), as was 'Myalgia' (0.8% dapagliflozin + saxagliptin vs. 0.3% saxagliptin vs. 0.9% dapagliflozin). While there is the case of rhabdomyolysis without clear explanation or obvious confounders that was identified previously during review of NDA (b) (4) no additional such cases were identified in review of the expanded safety database.

Table 5: Summary of Treatment Emergent Adverse Events Reported from the 'Musculoskeletal and Connective Tissue Disorders' System Organ Class in the Pooled Safety Database

- Includes events from long-term period

	Dapa + Saxa N=492		Saxa N=336		Dapa N=341	
	N	**%**	**N**	**%**	**N**	**%**
SERIOUS ADVERSE EVENTS	**1**	**(0.2)**	**1**	**(0.3)**	**0**	**(0)**
– ARTHRITIS	0	(0)	1	(0.3)	0	(0)
– RHABDOMYOLYSIS	1	(0.2)	0	(0)	0	(0)
TREATMENT EMERGENT ADVERSE EVENTS	**64**	**(13.0)**	**51**	**(15.2)**	**37**	**(10.9)**
– BACK PAIN	16	(3.3)	12	(3.6)	8	(2.3)
– ARTHRALGIA	12	(2.4)	4	(1.2)	3	(0.9)
– MUSCULOSKELETAL PAIN	6	(1.2)	7	(2.1)	2	(0.6)
– PAIN IN EXTREMITY	5	(1.0)	7	(2.1)	6	(1.8)
– MYALGIA	4	(0.8)	1	(0.3)	2	(0.6)
– MUSCLE SPASMS	3	(0.6)	7	(2.1)	2	(0.6)
– ARTHRITIS	2	(0.4)	1	(0.3)	1	(0.3)
– NECK PAIN	2	(0.4)	5	(1.5)	5	(1.5)
– SPINAL OSTEOARTHRITIS	2	(0.4)	0	(0)	0	(0)
– FLANK PAIN	1	(0.2)	0	(0)	0	(0)
– INTERVERTEBRAL DISC DEGENERATION	1	(0.2)	0	(0)	0	(0)
– INTERVERTEBRAL DISC PROTRUSION	1	(0.2)	0	(0)	0	(0)
MUSCLE FATIGUE	1	(0 2)	0	(0)	0	(0)
– MUSCULOSKELETAL CHEST PAIN	1	(0.2)	0	(0)	0	(0)
– OSTEOARTHRITIS	1	(0.2)	2	(0.6)	0	(0)
– OSTEOCHONDROSIS	1	(0.2)	0	(0)	0	(0)
– PAIN IN JAW	1	(0.2)	0	(0)	1	(0.3)
– PERIARTHRITIS	1	(0.2)	0	(0)	0	(0)
– PERIOSTITIS	1	(0.2)	0	(0)	0	(0)
– RHABDOMYOLYSIS	1	(0.2)	0	(0)	0	(0)
– ROTATOR CUFF SYNDROME	1	(0.2)	0	(0)	0	(0)
– ANKLE IMPINGEMENT	0	(0)	1	(0.3)	0	(0)
– BONE PAIN	0	(0)	1	(0.3)	0	(0)

	Dapa + Saxa N=492		Saxa N=336		Dapa N=341	
	N	%	N	%	N	%
– BURSITIS	0	(0)	1	(0.3)	1	(0.3)
– COSTOCHONDRITIS	0	(0)	0	0	1	(0.3)
– INTERVERTEBRAL DISC DISORDER	0	(0)	0	(0)	1	(0.3)
– JOINT SWELLING	0	(0)	1	(0.3)	0	(0)
– OSTEOPENIA	0	(0)	0	(0)	1	(0.3)
– SPINAL PAIN	0	(0)	0	(0)	1	(0.3)
– TENDONITIS	0	(0)	0	(0)	1	(0.3)
– TRIGGER FINGER	0	(0)	1	(0.3)	1	(0.3)

Source: Reviewer generated based on review of adae.xpt file in module 5.3.5.3 st-lt-pool – Pooled datasets short term plus long term

The lack of additional cases of rhabdomyolysis without an apparent alternative etiology is reassuring given the additional patient-years of exposure in the updated safety database. The absence of a clear imbalance in muscle related treatment emergent adverse events also provides some reassurance that an effect on muscle tissue (if any) is not likely to be substantial or of severe. There remains some uncertainty, however, due to the continued observation of a higher incidence of marked increases in creatine kinase with dapagliflozin + saxagliptin compared to what was seen with the individual treatment with saxagliptin or dapagliflozin.

9. Advisory Committee Meeting

Not applicable. No Advisory Committee Meeting was convened to discuss this NDA.

10. Pediatrics

The applicant has requested a full waiver for pediatric studies. This request was discussed with the Pediatric Review Committee on October 5, 2016. A full waiver for pediatric studies was granted as appropriate studies to inform the use of this FDCP in the pediatric population would be impossible or highly impracticable.

11. Other Relevant Regulatory Issues

Not applicable.

12. Labeling

The proposed proprietary name (QTERN) was reviewed and found acceptable.

The applicant proposed the following indication:

"Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4)"

I do not believe that study CV181168 is sufficient to support this indication. I recommend granting the following indication:

"Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who have inadequate glycemic control on dapagliflozin or who are already treated with dapagliflozin and saxagliptin"

Given the increased incidence of marked elevations in creatine kinase and case of rhabdomyolysis without clear explanation, I recommend including a discussion of this finding in section 6 of the prescribing information.

The presentation of safety information should be updated to be consistent with recent Safety Labeling Changes and safety findings not captured in the FDCP development program but associated with the two individual drug products should be included in the prescribing information.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

I recommend approval for NDA 209091 and the associated supplemental NDAs.

- Risk Benefit Assessment

Safety findings from the studies of combining dapagliflozin and saxagliptin were generally consistent with what would be expected if one combined these two products. No substantial safety concerns were identified which would preclude or contraindicate combining dapagliflozin with saxagliptin. The addition of saxagliptin to patients with inadequate glycemic control while being treated with dapagliflozin 10 mg demonstrated a statistically significant greater reduction in HbA1c compared to the addition of placebo. Overall, the benefit of additional glycemic control weighs favorably when compared to the safety profile of these two drugs.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

I do not recommend a Risk Evaluation and Management Strategy.

- Recommendation for other Postmarketing Requirements and Commitments

I do not recommend any Postmarketing Requirements of Commitments.

- Recommended Comments to Applicant

None.

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/s/

WILLIAM H CHONG
02/27/2017

JEAN-MARC P GUETTIER
02/27/2017
I concur.