CLINICAL REVIEW

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Reviewer Name(s)	Mari Suzuki, MD
Review Completion Date	See stamp date
Established/Proper Name	Saxagliptin, saxagliptin and metformin hydrochloride extended-release
(Proposed) Trade Name	Onglyza, Kombiglyze XR
Applicant	AstraZeneca
Dosage Form(s)	tablet
Applicant Proposed Dosing Regimen(s)	Saxagliptin (Onglyza) 2.5mg and 5mg Saxagliptin-metformin XR (Kombiglyze XR) 5mg/500mg, 5mg/1000mg, and 2.5mg/1000mg
Applicant Proposed Indication(s)/Population(s)	Not applicable
Recommendation on Regulatory Action	Approval; PMR 3199-1 Fulfilled
Recommended Indication(s)/Population(s) (if applicable)	Not applicable

Table of Contents

Glossary 7

1. Executive Summary 9
   1.1. Product Introduction 9
   1.2. Conclusions on the Substantial Evidence of Effectiveness 9
   1.3. Benefit-Risk Assessment 10
   1.4. Patient Experience Data 15

2. Therapeutic Context 15
   2.1. Analysis of Condition 16
   2.2. Analysis of Current Treatment Options 17

3. Regulatory Background 21
   3.1. Marketing History 21
   3.2. Summary of Presubmission/Submission Regulatory Activity 21

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety 25
   4.1. Office of Scientific Investigations (OSI) 25
   4.2. Product Quality 26
   4.3. Clinical Microbiology 26
   4.4. Nonclinical Pharmacology/Toxicology 26
   4.5. Clinical Pharmacology 26
   4.6. Devices and Companion Diagnostic Issues 26
   4.7. Consumer Study Reviews 27

5. Sources of Clinical Data and Review Strategy 27
   5.1. Table of Clinical Studies 27

6. Review of Relevant Individual Trials 27
   6.1. Study Design 27
      6.1.1. Study Results 37

7. Integrated Review of Effectiveness 50

7.1. Assessment of Efficacy Across Trials 50
7.1.1. Primary Endpoints 50
7.2. Additional Efficacy Considerations 50
7.2.1. Considerations on Benefit in the Postmarket Setting 50
7.3. Integrated Assessment of Effectiveness 50

8. Review of Safety 51
8.1. Safety Review Approach 51
8.2. Review of the Safety Database 52
8.2.1. Overall Exposure 52
8.2.2. Relevant characteristics of the safety population: 55
8.2.3. Adequacy of the safety database: 55
8.3. Adequacy of Applicant's Clinical Safety Assessments 56
8.3.1. Categorization of Adverse Events 56
8.3.2. Routine Clinical Tests 57
8.4. Safety Results 58
8.4.1. Overall Adverse Events 59
8.4.2. Deaths 60
8.4.3. Serious Adverse Events 60
8.4.4. Dropouts and/or Discontinuations Due to Adverse Effects 63
8.4.5. Significant Adverse Events 63
8.4.6. Treatment Emergent Adverse Events and Adverse Reactions 64
8.4.7. Laboratory Findings 69
8.4.8. Vital Signs 69
8.4.9. QT 69
8.4.10. Immunogenicity 69
8.5. Analysis of Submission-Specific Safety Issues 69
8.5.1. Hypoglycemic Events 69
8.5.2. Other Adverse Events of Special Interest 70
8.6. Safety Analyses by Demographic Subgroups 71
8.7. Specific Safety Studies/Clinical Trials 72

8.7.1. Safety Concerns Identified Through Postmarket Experience 72
8.8. Additional Safety Explorations 73
8.8.1. Human Carcinogenicity or Tumor Development 73
8.8.2. Human Reproduction and Pregnancy 73
8.8.3. Pediatrics and Assessment of Effects on Growth 73
8.9. Integrated Assessment of Safety 73
9. Advisory Committee Meeting and Other External Consultations 73
10. Labeling Recommendations 74
10.1. Prescription Drug Labeling 74
7.2 Concomitant Use with Insulin or Insulin Secretagogues....76
10.2. Nonprescription Drug Labeling....82
11. Risk Evaluation and Mitigation Strategies (REMS) 82
12. Postmarketing Requirements and Commitments 83
13. Appendices 83
13.1. Financial Disclosure 83

Table of Tables

Table 1. Summary of Available Non-Insulin Therapies for Pediatric Type 2 Diabetes.....18
Table 2. Glycemic Criteria for Initiation of Rescue Medication 33
Table 3. Protocol Amendments Related to Changes in Study Conduct.....36
Table 4. T2NOW Study Disposition.....38
Table 5. Relevant Protocol Deviations During the ST Period in Randomized Population.....39
Table 6. Demographics and Baseline Characteristics of Randomized Population.....41
Table 7. Primary endpoint analysis of A1c (%) Change from Baseline at Week 26 45
Table 9. Pooled Treatment Comparison: Primary and Secondary Analysis of A1c and FPG Change from Baseline at Week 26 49
Table 9. T2NOW ST period Exposure.....53
Table 10. T2NOW LT Period Exposure for Saxagliptin and Placebo re-randomized to saxagliptin 53
Table 12. Overall Exposure in ST and LT Periods 54
Table 13. T2NOW Study Clinical Assessments.....57
Table 14. T2NOW Study Short-term Procedural Outline.....57
Table 14. SAEs in T2NOW study 60
Table 17. T2NOW study Excluded SAEs 62
Table 18. T2NOW study Severe Adverse Events in ST and LT Periods.....63
Table 19. T2NOW ST Period TEAEs 67
Table 20. LT Period TEAEs.....68
Table 21. Hypoglycemic Events in Pooled Saxagliptin vs Placebo During ST Period, Regardless of Rescue 70
Table 24. Number of Patients with AEoSIs for Saxagliptin and Placebo During the ST + LT period 71
Table 25. Onglyza (saxagliptin) PI updates 74
Table 26. Kombiglyze (saxagliptin-metformin hydrochloride extended release) PI updates.....78

Table of Figures

Figure 1. Study Design Schematic for T2NOW.....28
Figure 2. Primary efficacy results on HbA1c change at Week 6, Week 12, Week 20, and Week 26 among pooled saxagliptin and placebo arms with corresponding number of available subjects 45
Figure 3. Forest plot of change from baseline in A1c (%) by subgroup between overall saxagliptin and placebo at week 26, regardless of rescue - ANCOVA MI-WO method (Randomized Subjects Data Set).....46
Figure 4. Forest plot of subgroup analyses for Age, Sex, and Race: placebo-adjusted HbA1c change from baseline at Week 26 47

Glossary

A1c	hemoglobin A1c (or HbA1c)
AC	advisory committee
ADA	American Diabetes Association
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CVOT	Cardiovascular Outcomes Trial
DPP4	dipeptidyl-peptidase-4 (DPP-4) inhibitor
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
EMA	European Medicines Agency
EMA PDCO	European Medicines Agency Paediatric Committee
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GIP	gastric inhibitory polypeptide
GCP	good clinical practice
GLP-1	glucagon-like peptide-1
GRMP	good review management practice
ICH	International Council for Harmonization

IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MI-WO	multiple-imputation washout
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PT	preferred term for adverse event
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SD	Standard Deviation
SGE	special government employee
SOC	system organ class for adverse event
T2D	type 2 diabetes mellitus
T2NOW	Study D1680C00019
TEAE	treatment emergent adverse event
USPI	United States Prescribing Information
WR	Written Request under Best Pharmaceuticals for Children Act (BPCA)
WRO	Written Response Only

1. Executive Summary

1.1. Product Introduction

Saxagliptin is a dipeptidyl-peptidase-4 (DPP-4) inhibitor. DPP-4 inhibitors lower blood glucose in adults with type 2 diabetes (T2D) by preventing the enzymatic breakdown of the incretin hormones, glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), leading to enhancement of incretin-stimulated insulin-release and glucagon suppression. Saxagliptin is available as Onglyza tablets (saxagliptin, NDA 022350/S-026), and Kombiglyze XR tablets (saxagliptin and metformin hydrochloride extended release, NDA 200678/S-028). These products are indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2D.

Pursuant to the Pediatric Research Equity Act (PREA), and initially in response to a Written Request (WR) of the Best Pharmaceuticals for Children Act (BPCA), the Applicant has conducted a pediatric postmarketing study D1680C00019 (T2NOW study) to assess the safety and efficacy of saxagliptin and dapagliflozin for the glycemic control indication in pediatric patients aged 10 years and older with type 2 diabetes. As effectiveness of saxagliptin was not demonstrated in T2NOW, the Applicant is not requesting expansion of the glycemic control indication for Onglyza or Kombiglyze XR to pediatric patients aged 10 years and older. However, the Applicant has submitted proposed updates to the U.S. Prescribing Information (USPI) for Onglyza and Kombiglyze XR to describe the pediatric study results to fulfill the requirements under PREA.

This study was determined to fulfill the Pediatric Research Equity Act Postmarketing Requirement (PMR) 3399-1 under a different review (NDA 202293/S-031 Farxiga and NDA 205649/S-022 Xigduo XR contained the final report for PMR 3199-1, as did NDA 022350/S-026 Onglyza and NDA 200678/S-028. The June 12, 2024 approval of S-031 and S-022 included fulfilment of PMR 3199-1).

T2NOW study was conducted to meet the terms of Written Request, issued on March 4, 2019 and amended October 29, 2021, in accordance with the Best Pharmaceuticals for Children Act (BPCA). (b) (4)

1.2. Conclusions on the Substantial Evidence of Effectiveness

T2NOW was an adequate and well controlled study. T2NOW featured a randomized, double blinded, and concurrent placebo control. T2NOW also employed a validated surrogate primary endpoint (A1c), enrolled a population reasonably congruent with the US population, and submitted them to trial practices which reasonably aligns with US clinical practice. FDA was

made aware of protocol amendments throughout the planning and execution of this protocol; there were no objectionable design elements.

Effectiveness of saxagliptin to improve glycemic control in pediatric patients with T2D was not established in this adequate and well-controlled study. After 26 weeks, treatment with saxagliptin did not demonstrate statistically significant improvement in A1c (hemoglobin A1c) compared to placebo [placebo-adjusted treatment difference -0.44% (95% CI -0.93 to 0.05; p-value 0.078) in T2NOW study.

1.3. Benefit-Risk Assessment

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Benefit-Risk Integrated Assessment

The incidence and prevalence of pediatric type 2 diabetes mellitus (T2D) has been increasing in the United States over the past two decades [1], with racial and ethnic groups that have historically experienced healthcare disparities disproportionately affected. Emerging data suggests pediatric patients may experience more rapid progression of disease and accelerated development of diabetes complications and comorbidities as compared to adults with T2D. Treatment options for pediatric T2D are limited, including only one oral therapy (metformin hydrochloride), several injectable glucagon-like peptide-1 (GLP-1) receptor agonists, and insulin products. There is an unmet need for additional treatment options for pediatric patients with T2D.

Astra Zeneca AS ("the Applicant") submitted supplemental new drug applications (sNDAs) for Onglyza (saxagliptin) and Kombiglyze XR (fixed dose combination product of saxagliptin and metformin hydrochloride extended release), proposing updates to the U.S. Prescribing Information (USPI) to describe results of a single adequate and well-controlled pediatric phase 3 study, T2NOW study (D1680C00019). T2NOW was a 26-week, double-blind, randomized, placebo-controlled study with a safety extension period of an additional 26 weeks in 245 pediatric T2D subjects aged 10 to 17 years. Subjects were randomized 1:1:1 to dapagliflozin 5mg, saxagliptin 2.5mg, or placebo over 26 weeks. Subjects in either the dapagliflozin 5mg or saxagliptin 2.5mg groups who failed to achieve A1c<7.0% at week 12 underwent a second randomization at week 14 to either remain on the same dose or increase dosage, e.g. to saxagliptin 5mg or dapagliflozin 10mg. Subjects in the placebo group were re-randomized at week 32 or 40 to either saxagliptin 5mg or dapagliflozin 10mg or continue placebo treatment.

In T2NOW, the average age was 14.6 years, the average duration of T2D was 1.64 years, and the mean A1c (HbA1c) was 8.0%. Most subjects (87.8%) were treated with background metformin and 48.8% were treated with insulin. Approximately 50% were white, 47% were Hispanic/Latino ethnicity; 28.7% were Asian, 11.6% were American Indian/Alaska Native, 4.3% were black or African American, and 1.8% were native Hawaiian. The majority were obese with mean body mass index (BMI) 30.0 kg/m2.

The primary efficacy endpoint of T2NOW study was change from baseline in A1c at 26 weeks, tested for the pooled saxagliptin dosing group (included all subjects who received saxagliptin at any dose) versus placebo. Based on the primary efficacy analysis (which was adjusted for treatment, baseline A1c, and baseline age group), treatment with saxagliptin did not result in a statistically significant improvement in A1c compared to placebo [Applicant reported placebo-adjusted treatment difference -0.44% (95% CI -0.93, 0.05; p=0.078)]. The mean A1c in subjects treated with saxagliptin rose by 0.25 (SE 0.244) above baseline by 52 weeks. Subgroup analyses for age, sex, BMI, race, geographic region and background antidiabetic therapy were generally consistent with the overall study population.

No clinically meaningful changes were seen in exploratory analyses of key secondary endpoints (including fasting plasma glucose, or portion of subjects achieving A1c thresholds, body weight, or blood pressure).

The most likely treatment effect (e.g., the point estimate) was near traditionally accepted values, but did not meet pre-specified statistical parameters for approval. T2NOW A1c trend suggests saxagliptin treatment effect attenuates over time. Overall, the data submitted from the T2NOW study does not support the effectiveness of saxagliptin in pediatric patients with T2D. These results are consistent with recently completed trials for other DDP-4 inhibitors (e.g. alogliptin, linagliptin, sitagliptin) in which pediatric efficacy was also not established.

The safety profile of saxagliptin in pediatric subjects with T2D in the T2NOW study was similar to the known and labeled safety profile in adults with T2D. Serious adverse events (SAEs) occurred in 3 (3.4%) saxagliptin group and 2 (2.6%) in placebo group in the 26-week treatment and 4 (4.5%) subjects treated with saxagliptin during the safety-extension period; none were assessed as treatment-related. An increased risk of hypoglycemia was not seen in this trial with saxagliptin therapy, with background insulin treatment, though it is part of saxagliptin's labeled safety profile for adult patients with T2D. No clinically significant changes in vital signs or laboratory studies were noted.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The prevalence of pediatric type 2 diabetes (T2D) is increasing in the U.S., with disproportional consequences on racial and ethnic groups that have historically experienced healthcare disparities • Although the pathophysiology of T2D is similar to adults, pediatric patients may experience more rapid disease progression and earlier pancreatic beta-cell dysfunction compared with adults with T2D • Pediatric patients also appear to have accelerated development of diabetes complications and comorbidities as compared to adults with T2D	T2D in the pediatric population is a serious, chronic condition with increasing prevalence that disproportionately affects minority racial and ethnic groups. Pediatric T2D is characterized by more rapid disease progression, accelerated pancreatic beta cell function decline, and accelerated development of diabetes complications, compared to adults with T2D. Given these

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		differences in disease process between adults and children with T2D, full extrapolation of efficacy from adults is not appropriate.
Current Treatment Options	• Metformin, empagliflozin, dapagliflozin, GLP-1 receptor agonists: liraglutide, exenatide (extended release), dulaglutide, and insulin are currently labeled therapeutic options for pediatric T2D. • Metformin, empagliflozin, and dapagliflozin are the only available oral therapies.	There are limited treatment options for pediatric patients with T2D
Benefit	• In the T2NOW study, at 26-weeks, saxagliptin treatment did not provide a significant A1c improvement compared to placebo [placebo-adjusted treatment different -0.44% (95% CI -0.93, 0.05; p=0.078). • Subgroup analyses for the treatment effect based on age (including subjects aged <15 years), sex, race, region and background medication were generally consistent with the overall population. • No significant differences were seen in key secondary endpoints (fasting plasma glucose, proportion of subjects achieving A1c thresholds, body weight, or blood pressure)	Saxagliptin with or without baseline metformin and/or baseline insulin therapy was not superior to placebo for glycemic lowering at 26 weeks in pediatric patients with T2D. Differences between the pediatric and adult treatment response are likely due to more rapid disease progression in pediatric T2D subjects.
Risk and Risk Management	• No deaths occurred in the study • SAEs were infrequent and consistent with expectations of population under study (e.g., diabetes related sequelae, appendicitis, abdominal pain, COVID-19) • AESIs were consistent with the known safety profile in adults • There was no treatment difference in hypoglycemia events between the two treatment arms.	In the T2NOW study, the overall safety profile of saxagliptin in pediatric T2D subjects was generally similar to the safety profile in adults with T2D that is currently described in the USPI.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• No clinically significant changes in vital signs or laboratory studies were noted. • There were no detected differences in pubertal progression and growth between treatment arms; the study data was limited due to the small number of subjects in early stages of pubertal development, absence of relevant pre-study information regarding growth patterns and growth potential, and possible misclassification of pubertal stage.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☒	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

The incidence of pediatric type 2 diabetes mellitus (T2D) has been increasing over the past 2 decades [1]. As of 2017, the U.S. prevalence of pediatric T2D was estimated at 28,000, however, if current trends continue, the prevalence is projected to reach 220,000 by 2060 [2]. The prevalence of pediatric T2D appears to be higher in certain racial and ethnic groups (including non-Hispanic Blacks, Hispanics, Asians/Pacific Islanders and American Indians) and in adolescent girls (with a 60% higher prevalence rate than boys)[3]. Nearly 80 to 90% of youth with T2D have overweight and obesity. The onset of pediatric T2D often coincides with pubertal insulin resistance and it is rarely diagnosed in patients below 10 years of age.

The pathophysiology of pediatric T2D is similar to that in adults, involving non-autoimmune pancreatic β-cell failure occurring on a background of insulin resistance. However, there are several differences in disease process and progression in pediatric versus adult T2D. The degree of insulin resistance in pediatric T2D appears to be more profound than in adults, even at the same degree of adiposity [4, 5]. According to the TODAY study, nearly 50% of pediatric patients on metformin monotherapy failed glycemic control over a 4-year follow up with a median time to insulin of 11 months, far greater than the rates of glycemic failure reported in adults on metformin monotherapy [6]. Data from the TODAY study also suggests that some youth with T2D may experience more rapid deterioration of pancreatic β-cell function as compared to adults [7], while others may exhibit more durable glycemic control on metformin monotherapy [8]. The predictors of treatment response in pediatric T2D are not fully understood and are currently under study. TODAY study participants who failed to maintain glycemic control had significantly lower pancreatic β-cell function, higher fasting glucose concentration, higher A1c at randomization, and higher HbA1c after a short course of metformin compared to those who did not fail [7, 9, 10]. Diabetic ketoacidosis at the time of diagnosis of pediatric T2D also appears to predict greater β-cell decline over time [11].

Youth with T2D also have accelerated development of diabetes complications and co-morbidities. Based on U.S. and Canadian registry studies, there is a higher prevalence of diabetic kidney disease, hypertension, retinal disease, and peripheral nerve disease in youth with T2D as compared to type 1 diabetes [12, 13]. Compared to adults with T2D, diabetes-related complications appear early in youth with T2D and accumulate more rapidly. According to a longitudinal follow up study of youths with T2D[13], at a mean time of 13.3 years since diagnosis (and mean age of 26.4 years), the incidence of diabetic kidney disease was 54.8%, the incidence of nerve disease was 32.4%, and the prevalence of retinal disease (including more advanced stages) was as high as 51% within a 1-year period. At least 1 diabetes-related complication occurred in 60.1% of participants, at least two complications occurred in 28.4% of participants, and serious cardiovascular events occurred despite the young age of participants.

The higher incidence of complications in youth-onset T2D may relate to more rapid disease progression, sub-optimal response to currently approved treatments, and additional age and socioeconomic-related challenges.

2.2. Analysis of Current Treatment Options

There is an unmet need for additional treatment options for pediatric T2D.

Oral antidiabetic agents to treat pediatric T2D include empagliflozin (Jardiance, approval for pediatric patients age 10 and above on June 20, 2023), dapagliflozin (Farxiga) and dapagliflozin-metformin XR (Xigduo XR, approval for pediatric patients aged 10 and above on June 12, 2024), and glucophage (metformin hydrochloride, approval for pediatric patients aged 10 years and above in 2002). A metformin extended-release product, Riomet ER (metformin hydrochloride extended-release oral suspension) was also approved in 2019 but is no longer marketed.

Injectable options include insulin and glucagon-like peptide-1 (GLP-1) receptor agonists. In the past several years, 3 injectable GLP-1 receptor agonist products have been approved for use in pediatric T2D: liraglutide (pediatric approval in 2019), exenatide extended release (pediatric approval in 2021) and dulaglutide (pediatric approval in 2022). Some of the insulin products that have an indication "to improve glycemic control in adults and children with diabetes mellitus" are Humulin R (insulin human), Novolin R (insulin human), Humulin N (isophane insulin human), Novolin N (isophane insulin human), Novolin 70/30 (isophane insulin human and insulin human), Humulin R U-500 (insulin human), Apidra (insulin glulisine), Fiasp (insulin aspart), Humalog (insulin lispro), Levemir (insulin detemir), Novolog (insulin aspart), Ryzodeg (insulin degludec and insulin aspart), Toujeo (insulin glargine), Tresiba (insulin degludec), and Lyumjev (insulin lispro-aabc). No insulin product labels include any pediatric T2D efficacy trial data.

A summary of non-insulin therapies approved for pediatric T2D is in Table 1.

Table 1. Summary of Available Non-Insulin Therapies for Pediatric Type 2 Diabetes

Product (s) Name	Year of Approval	Currently Marketed (Yes/No)	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
Glucophage (metformin hydrochloride)	2000	No* (several ANDAs available)	Oral, twice daily Dosage: 500 mg twice daily to be increased in 500 mg increments to a maximum of 2000mg per day in divided doses	In a double-blind placebo-controlled study in pediatric patients, FPG change of-42.9 mg/dL in metformin group compared to + 21.4 mg/dL in placebo group (p<0.0001).	Common AEs: diarrhea, nausea, vomiting, flatulence, asthenia, indigestion, abdominal discomfort and headache. Warnings/Precautions: lactic acidosis, vitamin B12 deficiency, hypoglycemia with concomitant use with insulin and insulin secretagogues.
Riomet (metformin hydrochloride oral suspension)	2003	No			
Riomet ER (metformin hydrochloride extended-release oral suspension)	2019	No	Oral, once daily Dosage: 500 mg once daily to be increased in 500 mg increments to maximum of 2000 mg per day.	Pediatric approval was based on 1) establishing similarity between Riomet ER and Glucophage XR (via a bioequivalence study), 2) similar efficacy, safety and pharmacokinetics between Glucophage XR and Glucophage IR in adults, and 3) similar efficacy, safety and pharmacokinetics between Glucophage IR in adults and pediatrics.	
Victoza (liraglutide)	2019	Yes	SC injection, once daily Dosage: 0.6 mg daily to be increased to 1.2mg and to 1.8 mg in weekly increments.	In a 26-week, double-blind, placebo-controlled clinical trial in 134 pediatric T2D patients aged 10 to 17 years, estimated treatment difference in HbA1c reduction from baseline between liraglutide and placebo was -1.06% (95% confidence interval of -1.65% to -0.46%)	Common AEs: nausea, diarrhea, vomiting, decreased appetite, dyspepsia, constipation, and immunogenicity-related events (including urticaria). Warnings/Precautions: thyroid C-cell tumors (contraindicated in patients with a personal or family history of MTC or MEN2), pancreatitis, renal impairment, hypersensitivity and acute gallbladder disease, hypoglycemia regardless of concomitant insulin therapy in pediatric patients only*
Bydureon (exenatide)	2021	Yes	SC injection, weekly	In a 24-week double-blind,	Common AEs: nausea, diarrhea, vomiting,

			Dosage: 2 mg once weekly	placebo-controlled trial in 82 pediatric T2D patients aged 10 to 17 years, estimated treatment difference in HbA1c reduction from baseline between exenatide and placebo was -0.71% (95% confidence interval of -1.42% to 0%, p<0.05)	constipation, headache, dyspepsia, injection-site nodule, injection site pruritis. Warnings/Precautions: thyroid C-cell tumors (contraindicated in patients with a personal or family history of MTC or MEN2), acute pancreatitis, acute kidney injury, gastrointestinal disease, hypersensitivity reactions, drug-induced immune mediated thrombocytopenia, serious injection site reactions, immunogenicity-associated decreased glycemic control, acute gallbladder disease, hypoglycemia with concomitant use of insulin secretagogues or insulin.
Trulicity (dulaglutide)	2022	Yes	SC injection, once weekly Dosage: 0.75 mg once weekly, may increase to 1.5 mg once weekly after 4 weeks	In a 26-week double-blind, placebo-controlled trial of 154 pediatric T2D patients aged 10 years and older, estimated treatment difference in HbA1c reduction from baseline between pooled dulaglutide arms (0.75 mg and 1.5 mg) versus placebo was -1.4% (95% confidence interval of -1.9% to -0.8%).	Common AEs: nausea, diarrhea, vomiting, abdominal pain, decreased appetite, and injection site reactions (in pediatric patients only). Warnings/Precautions: thyroid C-cell tumors (contraindicated in patients with a personal or family history of MTC or MEN2), pancreatitis, hypoglycemia with concomitant use of insulin or insulin secretagogue, hypersensitivity reactions, acute kidney injury, severe gastrointestinal disease, diabetic retinopathy complications, acute gallbladder disease
Empagliflozin (Jardiance)	2023	Yes	Oral, once daily Dosage: 10mg and 25mg once daily	In a 26-week, randomized, placebo-controlled, double-blind, parallel-group study (DINAMO) in 157 pediatric T2D patients aged between 10 and 17 years, treatment different in A1c (HbA1c) reduction between empagliflozin and placebo was -0.84% (95% confidence interval -1.50 to -0.19, p=0.0116)].	Common AEs: urinary tract infections and female genital mycotic infections, and hypoglycemia with or without insulin or insulin secretagogues (in pediatric patients only) Warnings/Precautions: diabetic ketoacidosis in patients with T1D and other ketoacidosis, volume depletion, urosepsis and pyelonephritis, hypoglycemia risk increased when used in combination with insulin secretagogues or insulin (risk higher in pediatric patients regardless of concomitant

					insulin use), necrotizing fasciitis of the perineum (Fournier's gangrene), genital mycotic infections, lower limb amputation, hypersensitivity reactions.
Dapagliflozin (Farxiga) and dapagliflozin-metformin XR (Xigduo XR)	2024	Yes	Oral, once daily Dosage: 5mg or 10mg once daily	In a 26-week randomized, double-blind, placebo-controlled, parallel-group study (T2NOW) in 245 pediatric T2D patients aged between 10 and 17 years, treatment difference in A1c (HbA1c) reduction between dapagliflozin (pooled dosages of 5mg and 10mg) and placebo was -1.03% (95% CI -1.57 to -0.49; $p < 0.001$).	Common AEs: urinary tract infections and female genital mycotic infections, and hypoglycemia with or without insulin or insulin secretagogues (in pediatric patients only) Warnings/Precautions: diabetic ketoacidosis in patients with T1D and other ketoacidosis, volume depletion, urosepsis and pyelonephritis, hypoglycemia risk increased when used in combination with insulin secretagogues or insulin (risk higher in pediatric patients regardless of concomitant insulin use), necrotizing fasciitis of the perineum (Fournier's gangrene), genital mycotic infections, lower limb amputation, hypersensitivity reactions.

Source: Adapted from NDA 201280/S-027, NDA 201281/S-035, NDA 208206/S-024 (linagliptin) and NDA 202293-S031, NDA 205649/S-022 (dapagliflozin) clinical reviews.
Abbreviations: XR, ER= extended release, T2D= type 2 diabetes, FPG= fasting plasma glucose, A1c= hemoglobin A1c, AE= adverse events, MTC= medullary thyroid carcinoma, MEN2= multiple endocrine neoplasia type 2, SC= subcutaneous, ANDA= Abbreviated New Drug Application
*in adults treated with liraglutide, increased risk of hypoglycemia was seen only with concomitant insulin or insulin secretagogue therapy

3. Regulatory Background

3.1. Marketing History

Onglyza tablets (saxagliptin, NDA 022350) was approved in the United States on July 31, 2009 for the indication as an adjunct to diet and exercise and to improve glycemic control in adults with T2D. Fixed dose combination products with saxagliptin and metformin hydrochloride (Kombiglyze XR tablets, NDA 200678) were subsequently approved November 5, 2010 for adults as an adjunct to diet and exercise to improve glycemic control.

As of July 30, 2023, saxagliptin (Onglyza) 2.5mg is approved for the treatment of T2D in adult patients in 75 countries and saxagliptin 5mg is approved in 83 countries worldwide, including the European Union, for the treatment of adult T2D patients. As of July 30, 2023, saxagliptin/metformin FDC is approved in 98 countries for T2D treatment.

3.2. Summary of Presubmission/Submission Regulatory Activity

July 31, 2009: The approval letter for saxagliptin (Onglyza, NDA 022350) waived pediatric study requirements for 0 to 9 years of age under the Pediatric Research Equity Act (PREA) (21 USC 355c), because necessary studies would be impossible or highly impracticable with too few children in this age range with type 2 diabetes mellitus to study. Additionally, FDA deferred submission of pediatric studies for 10 to 16 years of age (inclusive) for this NDA application because this product was ready for approval for use in adults and the pediatric studies have not been completed. The following pediatric assessments were required:

> PMR 1493-1: Deferred randomized and controlled pediatric study under PREA to evaluate efficacy, safety, and pharmacokinetics of saxagliptin for the treatment of type 2 diabetes mellitus in pediatric patients ages 10 to 16 years.
>
> Final Report Submission: by June 30, 2015

November 5, 2010: The approval letter issued for Kombiglyze XR (NDA 200678) waived

requirements for 0 to 9 years of age under PREA, because necessary studies would be impossible or highly impractical with too few children in this age range with type 2 diabetes mellitus to study. Pediatric study for ages 10 to 16 years was deferred. The following pediatric assessments were required:

> PMR 1703-1: A clinical pharmacology study in pediatric patients with type 2 diabetes comparing the pharmacokinetics of Kombiglyze XR to co-administered saxagliptin and metformin immediate-release tablets. As part of this study, you must evaluate whether pediatric patients can safely swallow the large Kombiglyze XR tablets.
>
> Final Protocol Submission: by October 31, 2011
> Trial Completion: by January 31, 2013
> Final Report Submission: by December 2013
>
> PMR 1703-2: A 52-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of saxagliptin vs. placebo, both as add-on therapy to metformin in pediatric patients with inadequate glycemic control on metformin alone. Approximately one-half of the patients must be on metformin extended-release therapy at the time of randomization to add-on saxagliptin vs. add-on placebo. As part of this study, you must evaluate whether pediatric patients can safely swallow the large metformin extended-release tablets.
>
> Final Protocol Submission: by June 30, 2011
> Trial Completion: by April 30, 2015
> Final Report Submission: by December 31, 2015

November 14, 2013: FDA releases the Applicant from PMR 1703-1 to evaluate swallowability of Kombiglyze XR tablets in pediatric patients, as Kombiglyze XR for pediatric patients is identical to the formulation marketed for adults, which has precedent bridging to individual components in an adult bioequivalent study, and the size and dimensions of Kombiglyze XR are not very different from metformin extended-release, for which swallowability (of metformin extended release) will be evaluated in the pediatric efficacy and safety study for Kombiglyze XR.

June 29, 2015: Pediatric PMR 1703-2 was released and reissued as 1703-3, to incorporate requirement to evaluate the swallowability of metformin extended-release in at least half of pediatric patients in the pediatric safety and efficacy study.

> 1703-3 Conduct a 52-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of saxagliptin vs. placebo, both as add-on therapy to metformin in pediatric patients with inadequate glycemic control on metformin alone.

Approximately one-half of the patients must be on metformin extended release therapy at the time of randomization to add-on saxagliptin vs. add-on placebo.

The timetable will remain unchanged from the PMR 1703-2 deferral extension granted letter from May 30, 2013 and apply to this newly issued PMR 1703-3:

Final Report Submission: June 30, 2018

The Applicant initially pursued a path of conducting separate pediatric clinical development programs to satisfy respective post-marketing requirements (PMR) for pediatric studies under the PREA. These were PMR 1493-1 for Onglyza and PMR 1703-3 for Kombiglyze XR (and PMR 2121-2 for Farxiga or dapagliflozin). The initially agreed-upon PMR pediatric studies for ONGLYZA® and KOMBIGLYZE™ XR, studies CV181058 and CV181147, experienced severe difficulty with patient recruitment.

September 14, 2015: The Applicant communicated that their proposed multi-arm pediatric study – Study CV181375 - (b) (4) will provide adequate clinical information for pediatric T2DM to fulfill the PREA PMRs for Onglyza, Kombiglyze XR (and Farxiga). In Written Response Only, FDA communicated agreement in concept, that efficacy and safety of saxagliptin and dapagliflozin can be evaluated in one study with a shared placebo control.

March 24, 2016, The Applicant submitted a draft protocol for a new pediatric study D1680C00019 (synonymous with clinical protocol CV181375) and henceforth referred to as T2NOW, to study pediatric patients aged 10 to 17 years (inclusive) in which both saxagliptin and dapagliflozin were proposed to be studied with a common placebo arm. This initial protocol for T2NOW is titled, "A 26 Week, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel Group, Phase 3 Trial with a 26 Week Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 5 and 10 mg, and Saxagliptin 2.5 and 5 mg in Pediatric Patients with Type 2 Diabetes Mellitus who are between 10 and below 18 years of age."

- T2NOW is intended as a single global pediatric study to satisfy PREA PMRs applicable to both saxagliptin-containing and dapagliflozin-containing products, specifically PMR 1493-1 (NDA 022350 (Onglyza [saxagliptin]), PMR 1703-3 NDA 200678 (Kombiglyze XR [saxagliptin and metformin XR]), and PMR 2121-2 for NDA 202293 (Farxiga [dapagliflozin]) and NDA 205649 (Xigduo XR [dapagliflozin-metformin hydrochloride extended release).

June 17, 2016: FDA advice is sent on the proposed new pediatric study, with recommendation to have a second randomization for pediatric patients who have A1c greater than 7% at 12 weeks, to either continue current dose of drug or double the dosage.

April 24, 2017: A PREA PMR release and reissue letter and Acknowledge Final Protocol for Postmarketing Requirements was issued, following the November 9, 2016 submission of protocol T2NOW Amendment 3. FDA agreed that this single clinical protocol could satisfy the PREA-required pediatric assessments for Onglyza (NDA 022350, saxagliptin), Kombiglyze XR (NDA 200678 saxagliptin/metformin XR), Farxiga and Xigduo XR.

As the protocol for T2NOW differed in several substantive ways from the original PMRs, FDA issued a Release for Postmarketing Requirements for PMR-1493-1 (NDA 022350, saxagliptin), PMR-1703-3 (NDA 200678, saxagliptin/metformin XR) and PMR-2121-2 (dapagliflozin). A New Postmarketing Requirement was reissued for all four applications as follows:

> PMR 3199-1: Conduct a 26-week randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of the monotherapies saxagliptin and dapagliflozin for the treatment of pediatric patients ages 10 to <18 years with T2D, followed by a 26-week site and subject-blinded safety extension period (weeks 26 to 52). Background therapy will consist of either metformin, insulin, or metformin plus insulin. A second randomization will take place at week 14, with up-titration of dose (saxagliptin may be increased from 2.5 mg to 5 mg; dapagliflozin from 5 mg to 10 mg) for approximately half of the subjects with a A1C greater than or equal to 7%.
>
> Study Completion: December 2021
> Final Report Submission: April 2022

November 17, 2021: Teleconference (tcon) was held between the Applicant and the FDA clinical and statistical teams to discuss the power re-estimation requested by FDA for T2NOW. (b) (4) T2NOW was noted to have an SD of 1.71 (higher than the assumed SD of 0.9 used for study sample size estimation). (b) (4) Based upon review and discussion of this data, the following additional protocol related proposals were agreed upon by the FDA during the meeting:

1. The pediatric effect size assumption will be increased to 0.75 (b) (4)
2. The SD assumption increased to 1.7 (instead of 0.9)
3. The primary analysis will be changed to all dapagliflozin (5 mg and 10 mg doses combined) versus placebo treatment arm, and all saxagliptin doses (2.5 mg and 5 mg combined) versus placebo treatment arm (instead of subgroup analysis based on titration doses).

4. The full alpha (0.05) will be used for each primary comparison (instead of a split alpha of 0.025 previously proposed), to align with FDA's guidance for industry *COVID-19: Master Protocols Evaluating Drugs and Biological Products for Treatment or Prevention* (May 2021), which states, "Applicants do not need to perform multiplicity adjustments for the multiple comparisons of different investigational drugs to the comparator group to ensure control of the overall familywise type I error rate."
5. FDA agreed that the percentage of US patients required in the study may be reduced to 11% (instead of 15%).

The Applicant was advised that all changes discussed should be incorporated into the study protocol and SAP prior to data base lock/unblinding.

(b) (4)

December 20, 2022: FDA issued Written Responses Only (WRO) for Type B pre-sNDA meeting Request for dapagliflozin. The following key topics were discussed. FDA added advice that, based on accumulating experiences reviewing completed pediatric trials of antihyperglycemic agents in patients with T2D, FDA recommended that the (b) (4)

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Scientific Investigations (OSI) was consulted to conduct a routine[2] inspection of the clinical investigators for this study, given that the results from this study support expansion of the labeled population for dapagliflozin drug products. The multidisciplinary team (including

[1] (b) (4)

[2] The biostatistics reviewer and the clinical reviewer did not identify any data quality or integrity issues that would prompt a for-cause inspection

the clinical review team, statistical review team, and OSI reviewer) identified three clinical sites[3] for a detailed inspection, based upon large enrollment numbers of study subjects, high proportion of treatment responders, and lack of an inspection history. Based on the overall inspection results of these three clinical sites and the regulatory assessments, the OSI review verified data generated by these clinical investigator sites. The primary efficacy endpoint of the change from baseline in A1C at Week 26 was verified using the source records with no notable discrepancies. Safety data including AEs and SAEs were appropriately documented. T2NOW appears to have been conducted adequately and the clinical data submitted by the Applicant appear to be acceptable. For additional details of these audits, see the Clinical Inspection Summary by Dr. Ling Yang dated April 29, 2024.

4.2. Product Quality

No new product quality information was submitted with these supplements. The CMC review team recommends approval.

4.3. Clinical Microbiology

No new microbiology data were submitted with these supplements.

4.4. Nonclinical Pharmacology/Toxicology

No new nonclinical data were submitted with these supplements.

4.5. Clinical Pharmacology

This review references the primary review authored by Dr. Dong Guo and concurred by clinical pharmacology team leader Dr. Edwin Chow. The Applicant did not conduct Additional PK/PD study in pediatric patients, as efficacy was not demonstrated for saxagliptin in pediatric T2DM patients and the Applicant is not seeking a pediatric indication. As no new clinical pharmacology information was submitted to update saxagliptin product PIs, a detailed clinical pharmacology review was not conducted. See Dr. Dong Guo's clinical pharmacology memo, June 21, 2024, DARRTS reference ID: 5399071.

4.6. Devices and Companion Diagnostic Issues

Not applicable to these submissions.

[3] one domestic clinical site (Dr. Audre Lee Jones [Site #7852, Texas] enrolled 7 subjects) and two international clinical sites (Dr. Raymundo Garcia-Reza [Site # 4904, Mexico] enrolled 12 subjects; Dr. Rosa Isela Luna Ceballos [Site # 4905, Mexico] enrolled 13 subjects)

4.7. Consumer Study Reviews

Not applicable. No consumer study was submitted with these supplements.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The analyses used to formulate conclusions regarding efficacy in this review are derived from the biostatistics review.

Refer to the Office of Biometrics Division DBII Review (Dr. Yoonhee Kim, NDA 022350/S-26 and NDA 200678/S-28 saxagliptin statistical review, August 26, 2024, DARRTS ID: 5435880) for more detailed discussion of efficacy analyses.

6. Review of Relevant Individual Trials

6.1. Study Design

The study under review is also known as "T2NOW," D1680C00019, or CV181375 and has a National Clinical Trial ID of NCT03199053. The results of this trial, as analyzed and summarized by the Applicant or the Applicant's designees, are available to the public (DOI: 10.1056/EVIDoa2300210).

Study Title: A 26-Week, Multicenter, Randomized, Placebo-Controlled, Double-Blind, Parallel Group, Phase 3 Trial with a 26-Week Safety Extension Period Evaluating the Safety and Efficacy of Dapagliflozin 5 and 10 mg, and Saxagliptin 2.5 and 5 mg in Pediatric Patients with Type 2 Diabetes Mellitus Who Are Between 10 and Below 18 Years of Age.

Primary Objective: To determine if there will be a greater mean reduction from baseline in A1c achieved after 26 weeks of dapagliflozin (5 mg or 10 mg [all doses and regimens combined]) or saxagliptin (2.5 mg or 5 mg [all doses and regimens combined]) compared to a common placebo group in pediatric subjects with T2D.

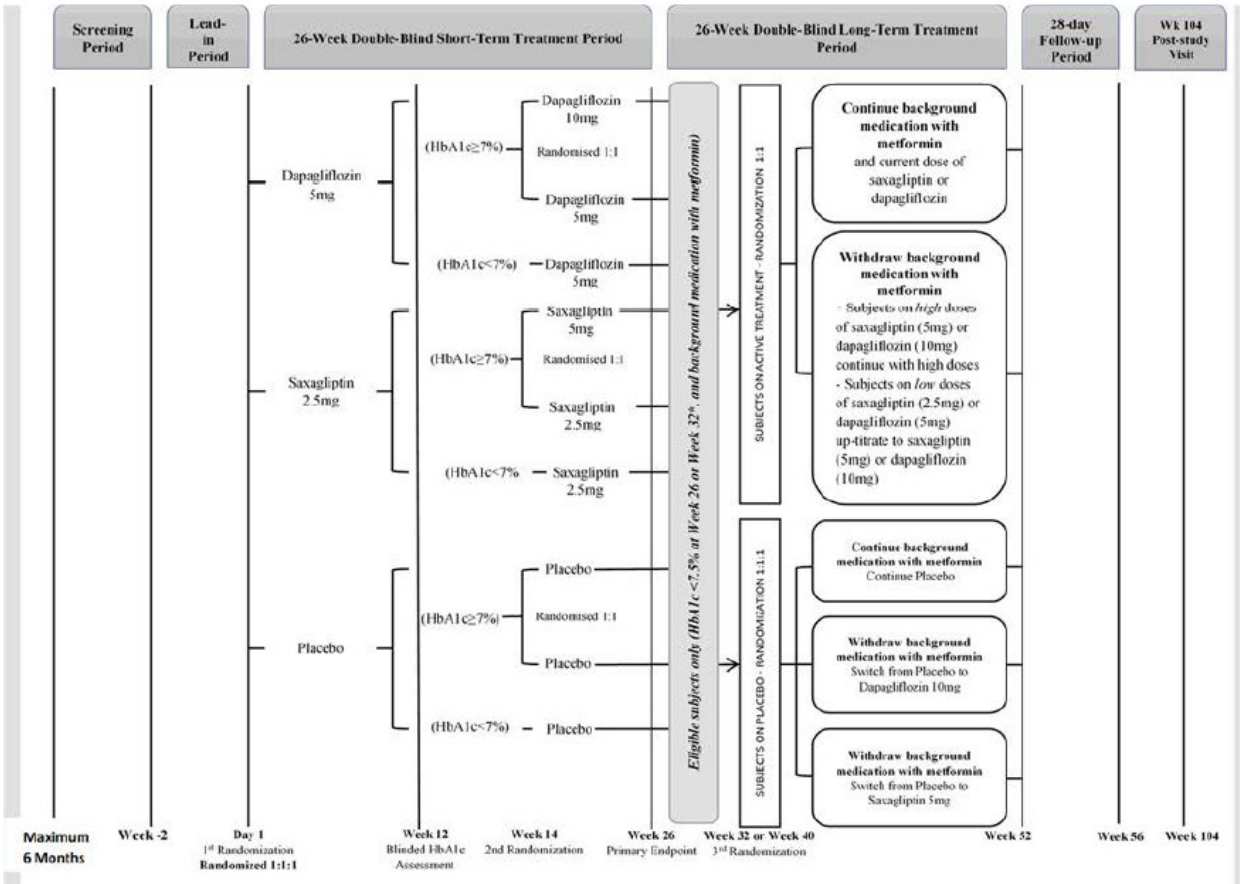
Trial Design

T2NOW was a global phase 3 umbrella study designed to investigate the efficacy and safety of dapagliflozin and saxagliptin as add on to standard of care (metformin, insulin, or both) compared to a shared placebo group for the treatment of pediatric patients with T2D (Figure 1). T2NOW included a 26-week randomized, double-blind, placebo-controlled, parallel-group

short-term (ST) treatment period. The ST period was followed by a 26-week site and subject-blind long-term (LT) extension (Weeks 26 to 52). Eligible subjects had A1c ≥ 6.5% and ≤ 10.5% on a diet and exercise program and stable background therapy of metformin (minimum dose 1,000 mg of metformin immediate release [IR] or extended release [XR]), insulin, or metformin (IR or XR) plus insulin.

The study was conducted at 123 clinical sites in 23 countries (Argentina, Australia, Brazil, Canada, Chile, Colombia, England, Finland, India, Israel, Italy, Malaysia, Mexico, New Zealand, Philippines, Poland, Russia, South Korea, Taiwan, Thailand, Turkey, Ukraine, and United States).

Figure 1. Study Design Schematic for T2NOW



Source: T2NOW Clinical Study Protocol Figure 3

Study Procedures

Following the 2-week lead-in period, subjects who meet the eligibility criteria were randomly assigned by the Interactive Web/Voice Response System (IXRS) at the Day 1 Randomization visit, to one of the following three double-blind treatment arms in a 1:1:1 ratio: low-dose

treatment with dapagliflozin 5 mg, saxagliptin 2.5 mg, or placebo. Randomization was stratified based on baseline antidiabetic medication (metformin vs insulin vs metformin + insulin), sex (male vs female), and age (10 to below 15 years vs 15 to below 18 years). All subjects were given two identical tablets (their assigned treatment and a placebo tablet).

A blinded A1c assessment occurred at Week 12, and subjects with values ≥ 7% ("non-responders") underwent a 2nd randomization (1:1) to either continue low dose (dapagliflozin 5 mg or saxagliptin 2.5 mg) or up-titrate to a higher dose (dapagliflozin 10 mg or saxagliptin 5 mg) beginning Week 14. Non-responders assigned to the placebo group continued placebo. To maintain blinding of treatments and A1c results, all placebo subjects and all responders at Week 12 underwent a dummy second randomization process indistinguishable from the actual 2nd randomization and at Week 14, and all subjects were instructed to take 3 tablets daily (their assigned treatment and 2 placebo tablets). The primary efficacy endpoint was change in A1c from baseline at Week 26 for the pooled saxagliptin dose groups (i.e., responders on 2.5 mg, non-responders remaining on 2.5 mg, and non-responders up-titrated to 5 mg) vs placebo. The second randomization was done per FDA recommendation (IND 063634, saxagliptin, advice June 17, 2016) in order to address the scientific question of whether patients who have insufficient A1c should remain at the current dose or have a dose increase.

Reviewer comment: T2NOW study's second randomization was acceptable as it aligned with actual clinical practice to target glycemic goal with antidiabetic treatment. This study design with second randomization was at the behest of FDA. The 26-week treatment comparison included a mix of subjects who were (1) controlled at week 12 and remained on saxagliptin 2.5 mg, (2) subjects who were uncontrolled at week 12 and were randomly assigned to remain on saxagliptin 2.5 mg or (3) uncontrolled subjects who were randomly up-titrated to saxagliptin 5 mg. The pooling of the 3 treatment groups introduces heterogeneity in the estimated treatment effect.

Following the primary efficacy assessment at Week 26, subjects entered the double-blind, 26-week LT treatment extension period. In the LT period, subjects on saxagliptin and receiving background therapy with metformin alone and achieving A1c values <7.5% underwent a 3rd randomization (1:1),[4] to either continue current therapy or undergo withdrawal of metformin to assess the efficacy of monotherapy with dapagliflozin through Week 52. For eligible subjects randomized to withdrawal of metformin, those on saxagliptin 2.5 mg were up titrated to saxagliptin 5 mg, and those on saxagliptin 5 mg remained on the 5 mg dose. Subjects on placebo receiving background therapy with metformin alone and achieving A1c values < 7.5% were randomized (1:1:1) to remain on placebo with metformin, or withdraw metformin and begin dapagliflozin 10 mg, or withdraw metformin and begin saxagliptin 5 mg. Subjects who were receiving background medication with insulin only or insulin and metformin (and

[4] Subjects were assessed for eligibility for the third randomization at week 26 or week 32, and if eligible, underwent the third randomization on week 32 or week 40, respectively

therefore not eligible for the 3rd randomization) continued with their randomized study drug assigned after the 12-week assessment during the double-blind LT treatment period. Following Week 52 assessments, investigational products were discontinued, and study subjects were placed on standard of care therapy to maintain glycemic control. Subjects returned for a 28-day safety follow-up visit. A final post-treatment safety follow-up visit will occur at Week 104.

Reviewer comment: *As outlined in the pre-submission history, T2NOW was designed and modified via multiple communications with FDA* (b) (4) *The study duration and design, including 3 separate randomizations, were all agreed upon by FDA prior to study initiation. The incorporation of 2nd randomization at week 14 for subjects who did not achieve A1c target of < 7% was intended to investigate the effect of continued treatment with saxagliptin 2.5mg vs up-titration to saxagliptin 5 mg in the subset of non-responders, to estimate the incremental benefit of dose escalation in subjects who are non-responders. The planned 3rd randomization for withdrawal of metformin in the subset of subjects who achieved A1c < 7.5% during the LT treatment period was intended to assess the treatment effect of monotherapy with saxagliptin. Interpretability of A1c reduction after 3rd randomization is limited however, as it deviates from standard of care.*

Key Inclusion Criteria

- T2D by World Health Organization/American Diabetes Association (ADA) criteria
- A1c ≥ 6.5% and ≤ 10.5% obtained during the 6-month screening period
- Treated with diet and exercise on a stable dose of at least 1000 mg/day metformin (IR or XR), or stable dose of insulin, or a stable combination of at least 1000 mg/day metformin (IR or XR) and insulin for a minimum of 8 weeks prior to Day 1
- Male and female aged 10 to <17 years with at least 30% between 10-14 years and one-third but no more than two-thirds female
- Women of childbearing potential using highly effective birth control methods

Key Exclusion Criteria

- Pre-existing diagnosis of T1D
- Positive at screening for autoantibodies to glutamic acid decarboxylase (GAD) or islet cell antigen (IA-2) AND abnormally low levels of C-peptide
- Previous diagnosis of monogenic etiology of T2D
- Diabetic ketoacidosis within 6 months of screening
- Current use of anti-diabetes medications other than metformin and/or insulin use within 16 weeks of screening
- Initiation or discontinuation of prescription or non-prescription weight loss drugs within 8 weeks of screening (use of weight loss drugs required to be stable during the study)
- Medical history and concurrent diseases:
  - Pregnancy or planned pregnancy or lactation during the trial

- Unstable or rapidly progressive renal disease
- Unresolved vesico-ureteral reflux
- Acute or chronic pancreatitis
- Recurrent hemolysis or hemoglobinopathy with exception of sickle cell trait or thalassemia
- Malignancy within 5 years of screening except treated basal cell or squamous cell carcinoma
- Immunosuppression or current treatment for cancer
- Replacement or chronic systemic corticosteroid therapy (i.e. > 4 weeks within 3 months of Day 1 study visit)

- Physical and lab findings:
  - Estimated glomerular filtration rate (eGFR) calculated by the Schwartz Formula < 80 mL/min/1.73 m_2 (1.33 mL/s)
  - Abnormal TSH with abnormal free T4
  - Hematuria
  - Alanine transaminase (ALT) or aspartate transaminase (AST) or alkaline phosphatase > 2 x upper limit of normal (ULN) or clinically significant hepatic disease including active infectious hepatitis
  - Anemia (hemoglobin < 10.7 g/dL for females, < 11.3 g/dL for males)
  - Volume depletion
  - Abnormal electrocardiogram (ECG)
- Known allergies or adverse drug reactions to study drug or excipients
- Other exclusion criteria:
  - Alcohol or substance abuse within 6 months of screening
  - Prisoners or involuntary incarcerated patients
  - Patients who were compulsorily detained for treatment of psychiatric or physical illness
  - Participants in other clinical study within 3 months

Reviewer comment: In general, the eligibility requirements appear to be reasonable. The study included a broad range for A1c eligibility of 6.5% to 10.5%. It is more difficult to demonstrate a treatment effect with a baseline A1c closer to the normal range. However, to ease recruitment challenges that have been historically associated with pediatric trials for T2D, this broad range of A1c has typically been accepted. The rate of disease progression and resulting glycemic deterioration has been noted to be more rapid in pediatric patients with T2D compared to adult T2D patients; therefore, it can be anticipated that the need for rescue for hyperglycemia will be greater for subjects assigned to placebo, particularly with A1c levels at the higher range of eligibility. The study was designed to compare treatment with saxagliptin vs placebo, and all study subjects were required to be receiving standard of care background therapy with metformin and/or insulin. Although trials with placebo comparator for 6 months duration have generally been considered acceptable for pediatric subjects with

T2D, provided that acceptable rescue criteria are in place for the safety of study subjects, T2D trials being initiated today in this population vulnerable to rapid glycemic deterioration are more likely to incorporate an active comparator such as an approved GLP-1 receptor agonist or SGLT2 inhibitor, as some of these are now approved in pediatric patients above age 10. This may challenge recruitment, if patients have well controlled glycemia on these potent antidiabetic therapies; alternatively if GLP-1 receptor agonists or SGLT2 inhibitors are used as an active comparator, it may make it difficult for an investigational drug to prove superiority. DPP-4 inhibitors may be administered up to eGFR<45 mL/min/1.73m2 but T2NOW eligibility criteria was above eGFR 80 mL/min/1.73m2, which may be reasonable given the pediatric population may not be expected to have significant renal decline. Transaminitis with ALT/AST >2x ULN were exclusion criteria, which may have hampered patient recruitment. Metabolic dysfunction-associated steatotic liver disease (MASLD) is comorbid with obesity and/or T2D, and as such, permissive transaminitis up to 5x ULN may have been permitted and helped with patient recruitment and been representative of pediatric T2D patients.

Investigational Drug Dosing

- Doses of saxagliptin (2.5 mg and 5 mg) and dapagliflozin (5 mg and 10 mg), which are approved for the glycemic control indication for adults with T2D, were administered once daily. All study subjects were given two identical tablets (i.e., their assigned treatment and a matching placebo tablet). To maintain blinding with the 2nd randomization, eligible subject underwent randomization and ineligible subjects underwent dummy randomization. All subjects were then instructed to take 3 tablets daily (their assigned treatment and 2 placebo tablets).

- Down-titration of blinded study drug and/or background metformin was not allowed at any time during the study. Patients on background insulin treatment who experienced multiple or severe episodes of hypoglycemia could down-titrate insulin treatment during the study at the Investigator's discretion.

Concomitant Medications

Once consented, subjects were:

- not to receive any prescription antihyperglycemic medication other than study drug, metformin and/or insulin
- not to begin treatment with any systemic corticosteroid therapy lasting > 5 days (subjects who require systemic corticosteroid therapy were to be discussed with the medical monitor prior to starting therapy whenever possible)
- not to commence or modify therapy with any prescription or over-the-counter weight loss medications
- not to undergo any bariatric surgery

- to comply with their prescribed dosing regimen to preserve study integrity and ensure subject safety

Discontinuation of Investigational Product

Subjects who discontinued study drug before the end of the study treatment period were to enter a non-treatment, follow-up phase, in which subjects followed their visit schedules with modified assessments until study completion. Subjects are to also attend a post-study visit at Week 104, for assessment of measures of growth and maturity.

Rescue Medication

During the trial, subjects were eligible for the addition of open-label rescue medication to their blinded treatment regimen to treat ongoing hyperglycemia. Insulin could be used as rescue, at the Investigator's discretion. Subjects who were already taking insulin at the start of the study could be switched to a flexible insulin dose following a Rescue Visit. For subjects on baseline insulin, persistently increased doses of insulin 20% or more above baseline dose, despite advice and counsel to keep the insulin dose stable, could be considered another potential manifestation of poor glycemic control, and such subjects were to be evaluated for rescue. Only insulin could be used as rescue medication, but subjects could be rescued without the use of medication.

The criteria for initiation of glycemic rescue are summarized in Table 2. Subjects who met rescue criteria were to first complete the Rescue Visit procedures before receiving open-label rescue medication to ensure that important trial endpoint measurements were collected. Rescued subjects were to then continue in the study according to their original visit schedule.

Table 2. Glycemic Criteria for Initiation of Rescue Medication

Week 6 visit up to and not including Week 26 visit	FPG > 240 mg/dL based on 3 consecutive fasting SMBG values followed by a confirmatory central laboratory FPG or Single central laboratory FPG followed by a confirmatory central laboratory FPG
Week 26 visit up to and not including Week 52 visit	FPG >180 mg/dL based on SMBG for 3 consecutive days followed by a confirmatory central laboratory FPG or Single central laboratory FPG followed by a confirmatory central laboratory FPG or A1c >8.0% (while A1c values will remain blinded throughout the study, sites will be notified to allow rescue if values exceed this threshold)

Abbreviations: FPG= fasting plasma glucose, SMBG= self-monitored blood glucose
Source: Clinical Protocol Table 3.5.2-1

Reviewer comment: In general, the study blinding procedures related to investigational drug products appear to have been acceptable to minimize bias. The criteria for initiation of glycemic rescue were also reasonable to maintain subject safety when persistent hyperglycemia occurred.

Study Endpoints

Primary Endpoint

- Change from baseline in A1c (%) at Week 26

Secondary Efficacy Endpoints

- Change from baseline in FPG at Week 26
- Incidence of A1c < 7.0% at Week 26

Safety Endpoints

- Incidence of AEs, SAEs, discontinuations due to AEs
- Hypoglycemic events
- Marked clinical laboratory abnormalities
- Vital signs
- Tanner staging, measures of growth and maturation
- DKA events

Reviewer comment: The primary efficacy endpoint for T2NOW is change from baseline in A1c at Week 26. A1c is a well-validated surrogate marker for the risk of long-term microvascular complications of diabetes mellitus and is therefore an acceptable surrogate clinical endpoint. The timing of this assessment is also appropriate because it allows 12 weeks of exposure at a stable saxagliptin dose following the 2nd randomization (dose adjustment) for non-responders at Week 14. A1c is derived from the average of the blood glucose fluctuation in the preceding 3 months and therefore, approximately 12 weeks of exposure to a new dose is necessary to demonstrate the treatment effect.

Statistical Analysis Plan

Sample Size Estimation

Assuming a -0.75% treatment effect difference between the active treatment group and the placebo group and a 1.7% standard deviation (SD), a sample size of 81 subjects per initial randomized treatment arm (162 subjects in total) would provide 80% power at a two-sided alpha level of 0.05. In the study, 88 subjects on saxagliptin and 76 subjects on placebo were randomized and treated. From study results, the pooled standard error (SE) for the saxagliptin

and the placebo groups was 1.54%, and the estimated placebo-adjusted treatment effect was – 0.44% for saxagliptin.

Estimand

The key components of the pre-specified estimand from the SAP are summarized as follows based on the statistical approaches used for the primary efficacy analysis:

Population & Analysis Set:

The primary population for analysis was the modified intent-to-treat (mITT) population, defined as all randomized subjects who received at least one dose of study drug, regardless of treatment adherence or rescue medication.

Handling of Missing Data:

Missing data was handled by multiple imputation based on placebo washout. Specifically, missing data from the placebo arm were imputed with a sequential linear regression constructed based on observed A1c values from the placebo arm, measured at baseline, Week 6, 12, 20 and 26. Missing data from the treatment arm were imputed with a sequential linear regression constructed based on the observed A1c values from the placebo arm, measured at baseline and Week 26. Two hundred imputed datasets were generated, and Rubin's Rule was used to combine the analysis results.

Primary Efficacy Analysis

The primary hypothesis test was performed based on an ANCOVA, with A1c change from baseline at Week 26 as the response variable, and treatment, baseline A1c, sex, baseline age stratum (<15 years vs 15 to <18 years), and background antidiabetic medication (metformin only vs insulin + metformin) as covariates.

Sensitivity Analysis

To assess the robustness of the primary analysis result, return-to-baseline (RTB) approach to handle missing data was performed as a sensitivity analysis. The same ANCOVA model as the primary efficacy analysis was fitted to 200 imputed datasets, and Rubin's Rule was applied to combine the analysis results.

Protocol Amendments

All amendments to the study protocol were discussed and agreed upon with FDA. Table 3 provides a summary of key modifications. Additional details of the discussions between the Applicant and FDA pertaining to the protocol are recorded in the presubmission history in

Section 3.2.

Table 3. Protocol Amendments Related to Changes in Study Conduct

Number	Date	Key Changes
1	10/11/2016	• The original study design was entirely revised in accordance with FDA-specified preferred study objectives and design.
2	4/4/2017	• Protocol revised to reflect cessation of Bristol-Myers Squibb's involvement in the study • Specified preferred objectives and procedures following EMA and FDA discussions. • A post-treatment visit was added at Week 104 to assess growth and maturity.
3	10/4/2018	• Per recommendations from FDA: o addition of randomized withdrawal of background medication in a subset of eligible patients from the active treatment groups o randomized withdrawal of background medication or switch to active treatment in a subset of eligible patients in the placebo group • Collection of vital status removed.
4	4/27/2019	• Revised to reflect modifications in study design: o extension of the screening period and change in the screening/retesting design, o update of safety concerns and monitoring of AEs of interest o revision of fasting blood glucose, growth, bone and maturation marker measurements, as well as Tanner staging schedules in patients who discontinued study drug early o clarification of initiation or up-titration of insulin at the Rescue Visit o AE/SAE collection until study completion o correction of the study drug dispensation schedule

5	9/24/2020	• Because of some study delays related to the COVID-19 pandemic: o flexibility was granted in the timing of scheduled assessments to maintain an interval of at least 12 weeks between the Week 14 and Week 26 visits and between the third randomization visit and the Week 52 visit. o Short- and long-term period study visits could be delayed by a maximum of 11 months in total. o If the duration of study drug administration was longer than 52 (+1) weeks, the safety follow-up period was to be shortened such that the complete study duration did not exceed 104 weeks.
6	2/7/2022	• To allow for flexibility in scheduling, the window period for the Week 104 post-dose visit was modified from "± 7 days" to "-28 days to +7 days" from the original scheduled date. • Based on discussions with FDA: o the primary objective was modified to assess the effect of all doses and regimens combined for each drug vs placebo o accordingly, the primary and secondary objectives were reordered and updated to make overall analysis (all doses for each treatment) as the primary objective o corresponding to the change in primary objective, the primary analysis was updated as: "The primary analysis will be performed using an analysis of covariance (ANCOVA)" o the analyses were updated to use a full alpha of 0.05 to test each drug vs placebo rather than the current split into 0.025 o for power analysis, the assumption of an effect size of 0.75% rather than 0.5% was used.

Source: Reviewer generated from CSR Table 10

6.1.1. Study Results

Compliance with Good Clinical Practices

The Applicant attested that T2NOW was performed in accordance with the ethical principles of the Declaration of Helsinki, in accordance with International Council of Harmonization (ICH) /Good Clinical Practice (GCP) guideline, and in accordance with applicable regulatory requirements and the AstraZeneca policy on Bioethics.

Financial Disclosure

The Applicant has adequately disclosed financial arrangements. There do not appear to be conflicts of interest that would compromise data integrity. Refer to the Financial Disclosure information in Section 13.2.

Patient Disposition

There were 509 subjects screened. 234 (46%) subjects failed to meet enrollment criteria, and 11 subjects were excluded due to being part of site 4910 (site in Mexico, legal issues precluded access to source trial data).

A total of 245 subjects were randomized from 94 sites in 21 countries: 88 to the saxagliptin group, 81 to the dapagliflozin group, and 76 to the placebo group. All randomized subjects received at least one dose of study drug. Two subjects treated with placebo were discontinued from study visit up to Week 26 but were evaluated for A1c at Week 26. See Table 4 for details.

Of the 88 subjects who were initially randomized to saxagliptin 2.5 mg group, in the ST period there were 13 discontinuations: 5 in saxagliptin treatment arm (1 parent/guardian withdrawal, 4 subject withdrawals) and 8 in placebo (1 lost to followup, 1 parent/guardian withdrawal, 6 subject withdrawals). Seven subjects prematurely discontinued study drug or study before week 14, 5 subjects missed the week 12 A1c assessment. In the saxagliptin treatment arm, 52 (57.1% of ITT population) achieved A1c <7% at 12 weeks. This left 39 "non-responder" subjects (42.9% of ITT population), who underwent a second randomization to either continue saxagliptin 2.5mg or uptitrate to saxagliptin 5mg.

Table 4. T2NOW Study Disposition

T2NOW Study Disposition

	Placebo (N=76)	Total Saxagliptin (N=88)	Total (N=164)
Randomized			
Y	76 (100.0)	88 (100.0)	164 (100.0)
Discontinuations in ST Period (up to week 26)			
LOST TO FOLLOW-UP	1 (1.3)	0	1 (0.6)
WITHDRAWAL BY PARENT/GUARDIAN	1 (1.3)	1 (1.1)	2 (1.2)
WITHDRAWAL BY SUBJECT	6 (7.9)	4 (4.5)	10 (6.1)
Discontinuations in LT Period			

T2NOW Study Disposition

	Placebo (N=76)	Total Saxagliptin (N=88)	Total (N=164)
LOST TO FOLLOW-UP	1 (1.3)	1 (1.1)	2 (1.2)
OTHER	2 (2.6)	0	2 (1.2)
WITHDRAWAL BY PARENT/GUARDIAN	1 (1.3)	0	1 (0.6)
WITHDRAWAL BY SUBJECT	3 (3.9)	3 (3.4)	6 (3.7)
Completed 26 weeks	68 (89.5)	83 (94.3)	151 (92.1)
Completed 52 weeks	43 (56.6)	53 (60.2)	96 (58.5)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y', TR01AG3 = 'Total Saxagliptin' or 'Placebo'.
Randomized - Dataset: Demographics; Filter: SAFFL = 'Y', TR01AG3 = 'Total Saxagliptin' or 'Placebo'.
Discontinuations in ST Period (up to week 26) - Dataset: Demographics; Filter: SAFFL = 'Y', TR01AG3 = 'Total Saxagliptin' or 'Placebo', EOP01STT = 'DISCONTINUED'.
Discontinuations in LT Period - Dataset: Demographics; Filter: SAFFL = 'Y', TR01AG3 = 'Total Saxagliptin' or 'Placebo', EOP02STT = 'DISCONTINUED'.
Completed 26-week A1c - Dataset: Demographics; Filter: SAFFL = 'Y', TR01AG3 = 'Total Saxagliptin' or 'Placebo', BGINLTFL = 'Y'.
Completers up to week 52 - Dataset: Demographics; Filter: SAFFL = 'Y', TR01AG3 = 'Total Saxagliptin' or 'Placebo', COMPLFL = 'Y'.

Reference: Clinical reviewer generated in Analysis Studio

Reviewer comment:
In comparison to contemporaneous pediatric glycemic control studies, there was good study retention and compliance. A high proportion of subjects continued to receive treatment at week 26 (148 of 161, 92%). Disposition was relatively balanced between the treatment arm, but it is notable that nominally fewer subjects in the saxagliptin treatment arm discontinued treatment or study participation than the placebo arm at both weeks 26 and 52.

Protocol Violations/Deviations

Relevant protocol deviations were defined as deviations that could potentially affect the interpretability of the study results and are summarized in Error! Reference source not found.. Over the ST period, of the 245 subjects randomized, 59 (24.1%) had at least one relevant protocol deviation: 18 (22.2%) in the dapagliflozin group, 15 (17.0%) in the saxagliptin group, and 26 (34.2%) in the placebo group. The most common reason for relevant protocol deviation was treatment compliance <80% or >120% during the ST treatment period (8 [9.1%] in the saxagliptin group, and 9 [11.8%] in the placebo group).

Table 5. Relevant Protocol Deviations During the ST Period in Randomized Population

	Number (%) of patients

Relevant protocol deviation [a] Exclusion type	Total saxagliptin (N = 88)	Placebo (N = 76)	Total (N = 245)
ST Period			
Number of patients with at least 1 relevant deviation	15 (17.0)	26 (34.2)	59 (24.1)
Number of patients with at least 1 complete exclusion	11 (12.5)	14 (18.4)	39 (15.9)
Number of patients with at least 1 partial exclusion	5 (5.7)	16 (21.1)	28 (11.4)
Randomised patients not satisfying the target population baseline antihyperglycaemic therapy requirement (metformin [IR or XR], or insulin, or metformin [IR or XR] plus insulin)			
Complete exclusion	3 (3.4)	3 (3.9)	11 (4.5)
Randomised patients with randomisation strata error - age, sex, background medication			
Complete exclusion	0	2 (2.6)	3 (1.2)
Randomised patients who used antihyperglycaemic medication (other than protocol allowed medication) for 7 or more consecutive days during the ST period			
Partial exclusion	0	3 (3.9)	3 (1.2)
Randomised patients who were treated with any systemic corticosteroid therapy for ≥ 5 consecutive days initiated or changed during ST period, or within 5 days prior to randomisation			
Partial exclusion	1 (1.1)	0	2 (0.8)
Randomised patients whose background metformin dose was not stable and/or background insulin dose increases or decreases 20% or more above baseline dose and/or there is a gap of greater than 14 days of background metformin or insulin during the ST treatment period			
Partial exclusion	1 (1.1)	11 (14.5)	15 (6.1)
Randomised patients with treatment compliance < 80% or > 120% during the ST treatment period			
Complete exclusion	8 (9.1)	9 (11.8)	28 (11.4)
Randomised patients who receive no double-blind medication for 14 or more consecutive days during the ST treatment period			
Partial exclusion	3 (3.4)	2 (2.6)	8 (3.3)
Randomised patients who received incorrect study drug for 14 or more consecutive days during the ST treatment period			
Partial exclusion	0	1 (1.3)	1 (0.4)

A patient may have had more than 1 relevant protocol deviation and can be counted in more than 1 category.

Percentages are based on the total number of patients in the treatment group (N).

IR, immediate release; LT, long-term; N, number of patients in the treatment group or regimen in the analysis set; ST, short-term

Reference: Clinical reviewer adaptation of Table 12 from Applicant's CSR

Reviewer comment: While other protocol deviations were generally balanced between the treatment groups, glycemic rescue was considered a protocol deviation, with an imbalance between the two treatment groups which favored the placebo treatment arm.

Table of Demographic Characteristics

Table 6Table 6. Demographics and Baseline Characteristics of Randomized Population

Demographics and Baseline Characteristics of T2NOW study Randomized Population

	Placebo (N=76)	Total Saxagliptin (N=88)	Total (N=164)
Sex			
F	44 (57.9)	53 (60.2)	97 (59.1)
M	32 (42.1)	35 (39.8)	67 (40.9)
Age			
Mean (SD)	14.7 (1.64)	14.5 (1.75)	14.6 (1.70)
Median (Min, Max)	15.0 (11, 17)	15.0 (10, 17)	15.0 (10, 17)
Age categories			
>= 10 to < 15	32 (42.1)	40 (45.5)	72 (43.9)
>= 15 to < 18	44 (57.9)	48 (54.5)	92 (56.1)
Race			
AMERICAN INDIAN OR ALASKA NATIVE	12 (15.8)	7 (8.0)	19 (11.6)
ASIAN	24 (31.6)	23 (26.1)	47 (28.7)
BLACK OR AFRICAN AMERICAN	3 (3.9)	4 (4.5)	7 (4.3)
NATIVE HAWAIIAN OR OTHER PACIFIC ISLANDER	3 (3.9)	0	3 (1.8)
OTHER	2 (2.6)	4 (4.5)	6 (3.7)
WHITE	32 (42.1)	50 (56.8)	82 (50.0)
Ethnicity			
HISPANIC OR LATINO	34 (44.7)	43 (48.9)	77 (47.0)
NOT HISPANIC OR LATINO	42 (55.3)	45 (51.1)	87 (53.0)
Geographic Region			
Asia/Pacific	23 (30.3)	26 (29.5)	49 (29.9)
Europe	17 (22.4)	15 (17.0)	32 (19.5)
Latin America	23 (30.3)	35 (39.8)	58 (35.4)
North America	13 (17.1)	12 (13.6)	25 (15.2)
Baseline BMI (z-score)			
Mean (SD)	1.5 (0.83)	1.8 (0.70)	1.6 (0.77)
Median (Min, Max)	1.6 (-1.65, 3.01)	1.9 (-0.56, 2.98)	1.7 (-1.65, 3.01)
A1c at Baseline (%)			
Mean (SD)	8.0 (1.63)	8.0 (1.43)	8.0 (1.52)
Median (Min, Max)	7.7 (5.2, 12)	7.7 (5.5, 12.2)	7.7 (5.2, 12.2)

Demographics and Baseline Characteristics of T2NOW study Randomized Population

	Placebo (N=76)	Total Saxagliptin (N=88)	Total (N=164)
eGFR at baseline (%)			
Mean (SD)	112.7 (20.69)	115.4 (26.21)	114.1 (23.78)
Median (Min, Max)	111.3 (67.3, 166.4)	108.4 (67.3, 199.6)	110.2 (67.3, 199.6)
Background Diabetes Medications			
INS	8 (10.5)	12 (13.6)	20 (12.2)
MET	39 (51.3)	45 (51.1)	84 (51.2)
MET+INS	29 (38.2)	31 (35.2)	60 (36.6)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y', TR01AG3 = 'Total Saxagliptin' or 'Placebo'.
Sex - Dataset: Demographics; Filter: None.
Age - Dataset: Demographics; Filter: AGE = '10' - '17'.
Age categories - Dataset: Demographics; Filter: SAFFL = 'Y'.
Race - Dataset: Demographics; Filter: SAFFL = 'Y'.
Ethnicity - Dataset: Demographics; Filter: SAFFL = 'Y'.
Geographic Region - Dataset: Demographics; Filter: SAFFL = 'Y'.
Baseline BMI (z-score) - Dataset: Demographics; Filter: SAFFL = 'Y'.
A1c at Baseline (%) - Dataset: Demographics; Filter: SAFFL = 'Y'.
eGFR at baseline (%) - Dataset: Demographics; Filter: SAFFL = 'Y'.
Background Diabetes Medications - Dataset: Demographics; Filter: SAFFL = 'Y'.
SD = Standard Deviation.

Reference: Clinical Reviewer generated in OCS Studio

Reviewer Comment:
All enrolled T2NOW study subjects had A1c (%) values between 6.5-10.5% during screening. Subjects were not assessed for eligibility based on A1c criteria at the randomization visit. Thus, both saxagliptin and placebo treatment arm groups had A1c values falling below or above the eligibility thresholds, as the screening visit may occur up to 6 months prior to randomization. Both treatment arms included a sizable proportion of subjects with baseline A1c below 6.5% with saxagliptin 8% (7/88) and placebo 17.1% (13/76), and A1c greater than 10.5% with saxagliptin 4.5% (4/88) and placebo 9.2% (7/76). While the mean A1c values were similar between saxagliptin and placebo (8.02% vs 7.96%), the standard deviation was higher for the placebo group (saxagliptin A1c SD 1.431 vs. placebo A1c SD 1.629). Despite this broad A1c distribution for the pediatric T2D study, A1c was not a stratification factor.

The "typical" pediatric T2D patient was a 14-15 year old, white, obese female, with moderately uncontrolled A1c (8.0%), on metformin treatment alone. Generally, the saxagliptin and placebo treatment arms are well-balanced for baseline disease characteristics (A1c, BMI z-score, eGFR), demographics (age, geographic region), and background anti-diabetes medications. There is good representation of male and female subjects using basal insulin +/- metformin. The saxagliptin treatment arm had more females, and there was a higher proportion of white patients in the saxagliptin treatment arm and more ethnic Hispanics. There was a small number of black or African American patients in both treatment arms, despite there being a high prevalence of pediatric T2D in this racial group. Overall though, the study population was diverse with enrollment of multiple racial groups and

T2NOW study's racial and ethnic study population is akin to other pediatric T2D studies, including those that enrolled more heavily from the US population.

While the Applicant cannot exclude the possibility of observed imbalances due to lower enrollment in the US population, or differences due to ethnic differences in study populations, general trends from subgroup analyses were consistent with the primary analyses, and the T2NOW study findings are consistent with other pediatric T2D studies with DPP-4 inhibitor drug class. Overall, this lends confidence that T2NOW findings are generalizable to the US population.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

During T2NOW, subjects were considered compliant with their investigational drug treatment regimen if their adherence rates (assessed by drug tablet counts) was between 80-120%. Most patients met treatment compliance during the ST study with overall 87.8% during the ST period and 85.3% during the ST+LT period. During the ST period, the saxagliptin treatment arm had 90.9% compliance, compared to 88.2% compliance in placebo treated arm. During the ST+LT period, the saxagliptin arm had 87.5% compliance, compared to 86.8% compliance with placebo.

Concomitant Medications

The most common treatment emergent non-diabetes medications used in the ST period by subjects were anilide drugs (e.g. paracetamol, chlorphenamine) with total treatment group rate 15.9% (39/245) and Vitamin D analogues with total treatment group rate 8% (21/245). There were no notable imbalances between treatment arms that would be considered to contribute to any between-treatment arm differences in safety or efficacy.

Rescue Medications

The proportion of subjects who required glycemic rescue medication or discontinued study drug due to lack of efficacy was lower in the saxagliptin treated arm than in the placebo treated arm during the ST period. There were 6.8% (6/88) of saxagliptin treated subjects who discontinued due to lack of efficacy and 14.5% (11/76) in the placebo treated arm. For the ST+LT period, the saxagliptin treatment arm had lower rates than placebo: saxagliptin had 38.6% (34/88) and placebo had 46.1% (35/76) subjects discontinue due to lack of efficacy and requiring glycemic rescue medication.

Reviewer comment:
The primary efficacy analysis was based on A1c change, regardless of rescue treatment (i.e. treatment policy estimand). This would not penalize the placebo treatment arm for glycemic rescue. Rescued subjects are still considered to be on the placebo treatment regimen, regardless of efficacy strength of rescue therapy. An estimand strategy which focused on a "true" placebo control (i.e., a hypothetical estimand where rescue therapy did not occur) would likely reveal a larger treatment effect.

Efficacy Results – Primary Endpoint

A significant difference was not found between saxagliptin treatment compared to placebo at Week 26 (see Table 7). At baseline, all patients are randomized and treated with saxagliptin 2.5mg (low dose). While a significant A1c reduction was seen at week 6 and week 12 compared

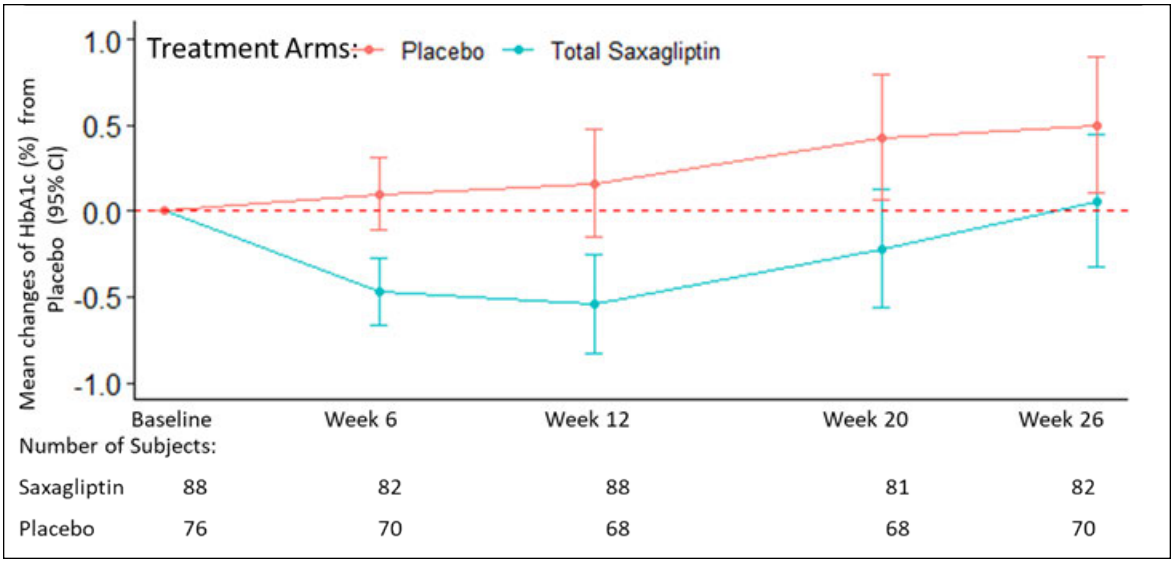
to placebo, this A1c reduction effect was not sustained after the second randomization. After the second randomization, no significant A1c reduction is observed at week 20 nor week 26 (primary efficacy endpoint). See Figure 2:

Table 7. Primary endpoint analysis of A1c (%) Change from Baseline at Week 26

Efficacy endpoint statistic	Saxagliptin [pooled 2.5 mg and 5 mg] QD N=88	Placebo N=76
Baseline, Mean (SD)	8.02 (1.43)	7.96 (1.63)
Week 26 Missing, n (%)	6 (6.8)	6 (7.9)
Change from baseline to Week 26, LS Mean (SE)	0.06 (0.19)	0.50 (0.20)
Difference from Placebo[1]		
LS Mean difference (95% CI)		-0.44 (-0.93, 0.05)
Two-sided P-value		0.078

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error
[1]Primary efficacy analysis is based on multiple imputations using placebo wash-out model. 200 datasets were generated, and each dataset was analyzed with ANCOVA using treatment, sex, age group (10-14/15-<18), background antidiabetic medication (metformin only/insulin+metformin), baseline HbA1c as covariates. The analysis was performed in the mITT using all observed data.
Source: Statistical Reviewer's Analysis Table 5 and the T2NOW clinical study report (CSR) page 131

Figure 2. Primary efficacy results on HbA1c change at Week 6, Week 12, Week 20, and Week 26 among pooled saxagliptin and placebo arms with corresponding number of available subjects



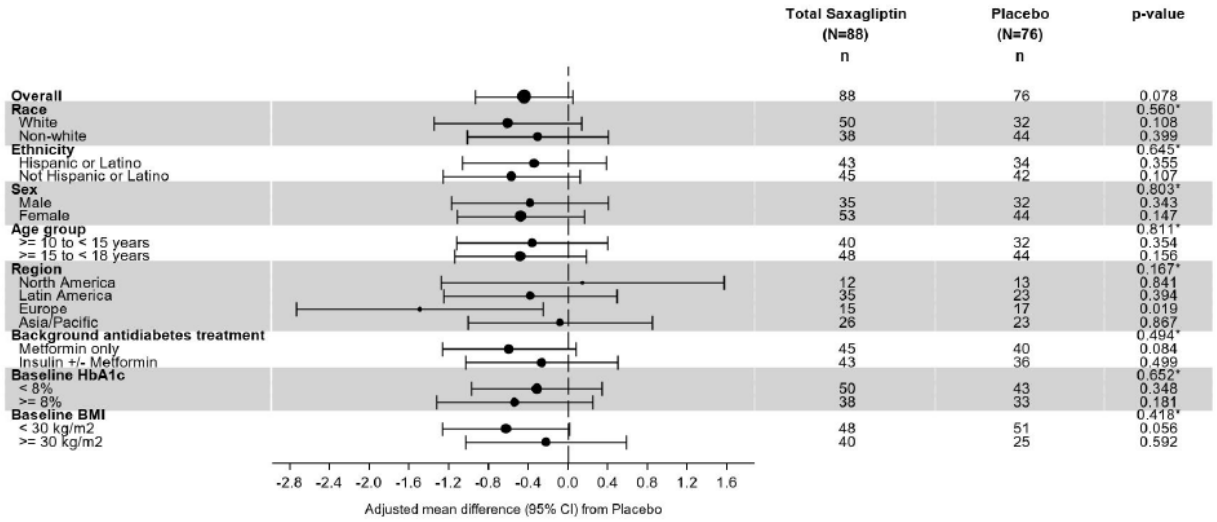
Reference: Statistical Reviewer's Analysis and the Applicant's CSR Figure 12

The degree of missing data was low. The Applicant's primary analysis method was multiple imputation using placebo-washout (MI-WO) method. For the Applicant's sensitivity analysis, subjects from the excluded site 4910 were included.

Reviewer comment:
In saxagliptin treated subjects, a non-significant numeric treatment difference in change in A1c compared to placebo was observed. However, this treatment difference was in the context of rapid glycemic worsening, such that the change from baseline in A1c at 26 weeks was close to null.

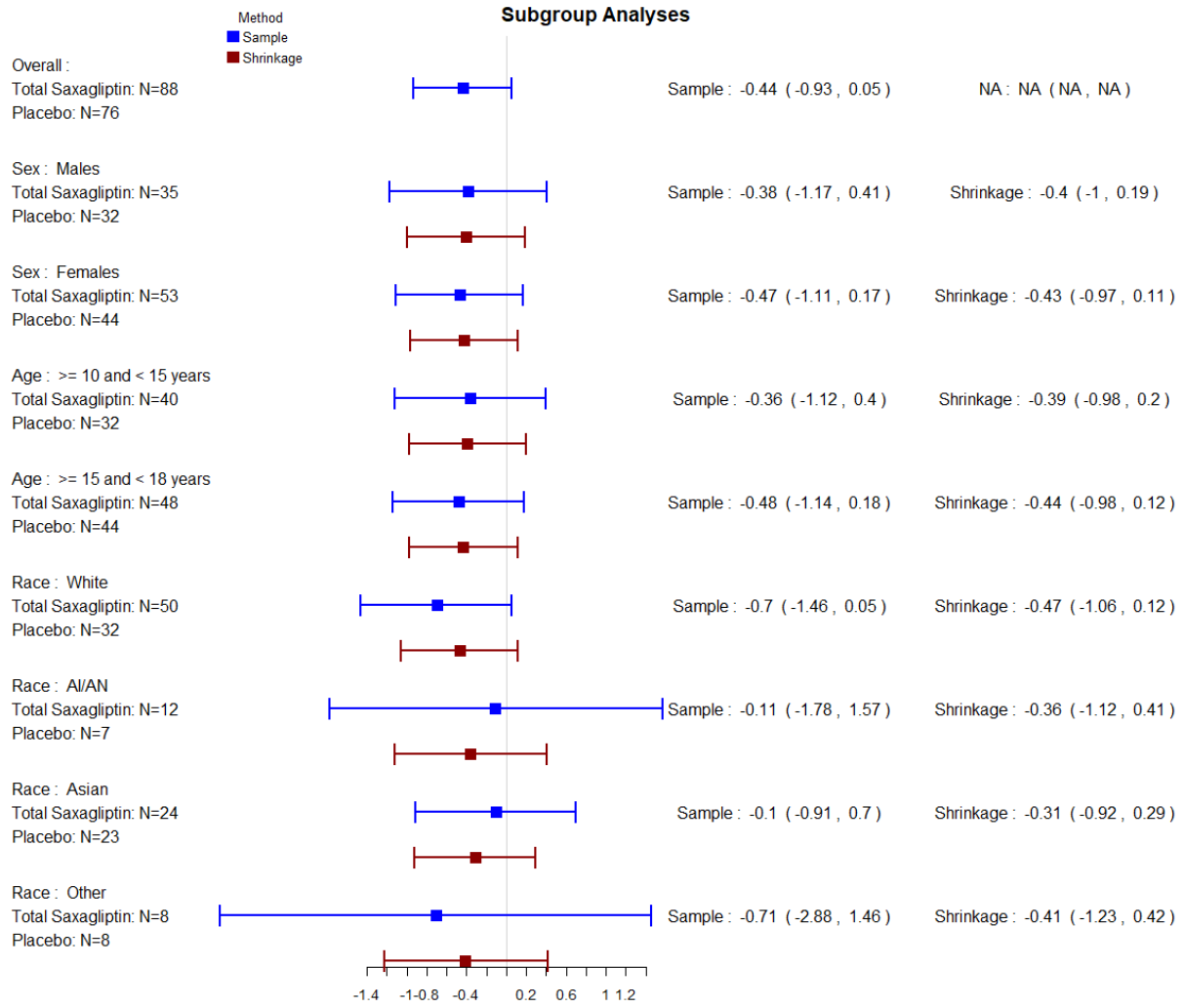
Subgroup Analyses for the Primary Efficacy Endpoint
The Applicant's primary analysis results were consistent across subgroups: age at randomization (≤10 to <15 years, ≥15 years to <18 years), baseline A1c, geographic region, sex, race, ethnicity, and background antidiabetic medication. See Figure 3 and Figure 4 for details.

Figure 3. Forest plot of change from baseline in A1c (%) by subgroup between overall saxagliptin and placebo at week 26, regardless of rescue - ANCOVA MI-WO method (Randomized Subjects Data Set)



Reference: Applicant's Figure 14.2.2.2.9.b

Figure 4. Forest plot of subgroup analyses for Age, Sex, and Race: placebo-adjusted A1c change from baseline at Week 26



Abbreviations: AI/AN = American Indian or Alaska Native
Values on the negative side favor saxagliptin, values on the positive side favor placebo.
Source: Statistical Reviewer's Analysis and CSR; adls.xpt, adeff.xpt

Reviewer Comment:
These subgroup findings alone would not be able to define a subgroup for which saxagliptin may have better efficacy, and would not conclude there is sustained efficacy over time. Past DPP-4 inhibitor drug class studies in pediatric T2D suggest an attenuation of effect in glycemic control over time, with peak efficacy observed at 12 weeks in most pediatric T2D populations. Longer term glycemic control study in these subgroup populations will likely show

attenuation of effect.

Data Quality and Integrity

Based on the clinical inspections conducted at two study sites (see Section 4.1), the primary efficacy endpoint, change in A1c (%) from baseline to end of 26 weeks, was verified using the source records, with no discrepancies noted.

Efficacy Results – Secondary and other relevant endpoints

Secondary analyses included FPG change from baseline and proportion of patients with baseline A1c ≥ 7% who achieved an A1c level < 7% ("responders") at Week 26. These secondary analyses demonstrated non-significant treatment effect, supporting the conclusion that the benefit of saxagliptin in treating T2D in pediatric patients (10 to 17 years old) was not established in this T2NOW study.

T2NOW analyses were conducted with hierarchical testing, with stopping of all subsequent endpoints after the first endpoint with p-value>0.05 to control for type I error. The secondary analyses for saxagliptin were conducted after the primary endpoint (p-value 0.078). Descriptions of their findings follow, which support non-superiority of saxagliptin over placebo.

Assessment of Dose-Response Relationship for Efficacy

Of the 88 subjects who were initially randomized to saxagliptin, 22% (36/164) achieved a A1c<7.0% at week 12. This left 52 "non-responder" subjects (32%, 52/164), who underwent a second randomization to either continue saxagliptin 2.5mg (n=26) or increase their treatment dosage to saxagliptin 5mg (n=26).

The change in A1c from baseline at week 26 between the low-dose/high-dose treatment regimen and placebo was with weighted ANOVA MI-WO analysis -0.51 (-1.05, 0.04, p-value 0.067). This secondary endpoint did not find superiority with saxagliptin, consistent with the primary efficacy findings.

Fasting Plasma Glucose at week 26

Additional results of the secondary efficacy analysis, change from baseline in FPG at Week 26, are presented in Error! Reference source not found.. There was not a significant difference noted between the saxagliptin pooled group and the placebo group in FPG change from baseline at 26 weeks. This result supports the finding of lack of efficacy of saxagliptin in the primary analysis.

The degree of missing endpoint data was low (10% and under) and generally balanced between the saxagliptin and placebo treatment arms.

Table 8. Pooled Treatment Comparison: Primary and Secondary Analysis of A1c and FPG Change from Baseline at Week 26

	Pooled Saxagliptin treatment (2.5mg and 5mg) daily N=88	Placebo N=76
Primary Efficacy Analysis (Change from Baseline A1c)		
Baseline, mean (SD)	8.02 (1.431)	7.96 (1.629)
Week 26 missing, n (%)	6 (6.8%)	6 (7.9%)
Change from baseline to week 26, LS mean (SE)	0.06 (0.19)	0.50 (0.20)
Comparison to Placebo LS mean difference (95% CI) Two sided p-value	-0.44 (-0.93, 0.05), 0.078	
Secondary Analysis (Change from Baseline in Fasting Plasma Glucose)		
Baseline(mg/dL), mean (SD)	172.25 (154.09)	152.02 (57.18)
Week 26 missing, n (%)	8 (9.1%)	8 (10.5%)
Change from baseline to week 26, LS mean (SE)	-1.16 (7.13)	2.65 (7.56)
Comparison to Placebo LS mean difference (95% CI)	-3.81 (-22.19, 14.58)	

Formal evaluation of each endpoint is made at the two-sided 0.05 alpha level (with corresponding 95% CIs). After the first endpoint with p-value >0.05 formal evaluation of all subsequent endpoints stops due to controlling for family-wise error.

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error, QD = daily
Reference: Derived from Dr. Yoonhee Kim's NDA 022350 and NDA 200678 Statistical Review, August 26, 2024 and Applicant's Tables 14.2.2.2.1.b, 14.2.2.2.5.b, 14.2.3.3.1.b

Reviewer comment:
For saxagliptin treated subjects, glycemic reduction generally increased in magnitude up to week 12, with eventual reduction in this effect by week 26 nearing baseline A1c values. This effect was similarly seen in other DDP-4 inhibitor class drugs studied in pediatrics (sitagliptin, NDA 021995/S-47; linagliptin, NDA 201280/S-27). These findings support the conclusion that DDP-4 inhibitor drug class demonstrates a weak treatment effect in pediatric T2D patients that attenuates over time, thought to be due to rapid progression of underlying T2D disease. Saxagliptin's lack of superiority to placebo in pediatric T2D, aligned with findings from other DDP-4 inhibitor drugs, gives further confidence that saxagliptin's failure to demonstrate

superiority over placebo is due to weak DPP-4 inhibitor drug effect, rather than insufficient study sample size of T2NOW.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

This section is not applicable to the review.

7.1.1. Primary Endpoints

This section is not applicable to the review.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

This section is not applicable to the review.

7.3. Integrated Assessment of Effectiveness

T2NOW study was a 26-week, double-blind, randomized, placebo-controlled, parallel group study, with a double-blind active treatment safety extension period of an additional 26 weeks. The study enrolled pediatric subjects aged 10 to 17 years old with inadequately controlled type 2 diabetes mellitus (A1c 6.5 to 10.5%), including those treated with metformin, with or without insulin therapy. Subjects were randomized 1:1:1 to receive dapagliflozin 5mg, saxagliptin 2.5mg, or placebo over 26 weeks. Subjects in the saxagliptin 2.5mg group who failed to achieve A1c<7.0% at week 12 ("non-responders") underwent a second randomization at week 14, to either remain on the saxagliptin 2.5mg dose or increase to 5mg; subjects in the saxagliptin 2.5mg group who achieved an A1c < 7.0% ("responders") at week 12 did not undergo a second randomization. Subjects on placebo were re-randomized at week 32 or 40 to either saxagliptin 5mg or dapagliflozin 10mg. The primary efficacy endpoint was the change from baseline in A1c at 26 weeks, to be evaluated concurrently for the pooled dapagliflozin, saxagliptin, and placebo treatment arms. Key secondary efficacy endpoints included change from baseline in fasting plasma glucose at week 26 and percentage of subjects with baseline A1c≥7% who achieve an A1c level <7.0% at week 26.

A total of 245 subjects were treated with either saxagliptin (2.5 or 5mg; n=88), dapagliflozin (5 or 10mg; n=81), or placebo (n=76). Background therapies included metformin (51.2%), a combination of metformin and insulin (36.6%), and insulin (12.2%). The mean A1c at baseline was 8.1% and the mean duration of type 2 diabetes mellitus was 2.5 years. The mean age was 14.6 years (range: 10-17 years) and 56.1% were aged 15 years and older. Approximately 50% were White, 28.7% were Asian, 4.3% were black or African American, and 11.6% were American Indian. Approximately 47% reported being Hispanic/Latino. The mean BMI was 30 kg/m2 and mean BMI z-score was 1.6. Subjects with an eGFR less than 80mL/min/1.73m2 were not enrolled in the study. Approximately 20.3% of the study population had microalbuminuria or macroalbuminuria.

Overall saxagliptin added on to diet and exercise did not significantly improve glycemic control compared with placebo in pediatric T2DM patients aged 10 to 17 years who had a A1c level of 6.5% to 10.5%. For the primary analysis (ITT population), the adjusted mean change in A1c from baseline to Week 26 between the overall saxagliptin compared with placebo was -0.44% (95% CI -0.93 to 0.05), p = 0.078. The results of the predefined subgroups and the key secondary analyses were consistent with the primary endpoint.

Overall, there appears to have been a weak glycemic effect of saxagliptin observed early on in treatment that was not sustained. Sensitivity analyses, subgroup analyses of the primary endpoint, and exploratory analyses of secondary endpoints were consistent with overall primary efficacy findings. These saxagliptin findings are consistent with recently completed trials for other DPP-4 inhibitors (e.g. alogliptin, linagliptin, sitagliptin) in which pediatric efficacy was also not established. Differences in demonstrated treatment response in adult and pediatric trials of saxagliptin and other DPP-4 inhibitors may reflect more rapid disease progression in the pediatric T2D trial population.

8. Review of Safety

8.1. Safety Review Approach

The safety of saxagliptin has been well characterized in adult subjects with T2D. The USPI for saxagliptin-containing products includes Warnings and Precautions regarding the risks of pancreatitis, hypoglycemia with concomitant use of insulin or insulin secretagogues, hypersensitivity reactions, arthralgia, bullous pemphigoid and heart failure. The most common adverse events (AEs with >2% incidence) were nasopharyngitis, diarrhea, and cough.

The safety review focused primarily on previously identified risks of saxagliptin observed in adult studies, but also evaluated for potential risks that may be specific to pediatric patients. For T2NOW, the Applicant prespecified several adverse events of special interest (AESIs) based on the known safety profile of saxagliptin, with pediatric-specific safety issues including effects on growth, bone development, and puberty. (b) (4) .

The primary safety analysis is based on the 26-week placebo-controlled assessment period of T2NOW of subjects who received at least one dose of study drug (i.e. treated patients' data set). This included consideration of AEs after rescue therapy or treatment discontinuation, as an on-study analysis. Safety data for this period is reported for the pooled saxagliptin arm (i.e., all subjects who received saxagliptin at any dose from baseline to week 26) and placebo arm. Saxagliptin dosages (2.5mg and 5mg) are not considered separately, given the small number of subjects in each dose treatment group precluding meaningful comparisons, and study design where a portion of subjects re-randomized to higher saxagliptin dose if they did not achieve A1c<7% at week 12.

Safety review of the 26-week ST period included 88 subjects on saxagliptin and 76 patients on placebo. This permitted adequate interpretation of TEAEs. FDA safety analyses for the pooled saxagliptin vs placebo treatment arms generally corroborated the Applicant's CSR results.

The ST+LT period was evaluated for serious adverse events and TEAEs leading to study discontinuation, with brief synopses in the following sections. Safety analysis of T2NOW in entirety, consisting of the ST+LT periods is complicated by antidiabetic treatment modifications that were carried out in the LT period, such as fourth re-randomization at week 32 or 40, where 6 placebo treated subjects switch to saxagliptin (n=3) or dapagliflozin (n=3). The Applicant performed a weighted analysis to account for this, where AEs in subjects who continued their ST period treatment were weighted more greatly to have similar denominator counts for comparison.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

T2NOW was composed of a 26-week short term (ST) period for efficacy evaluation and a 26 - week long term (LT) treatment period for additional safety evaluation.

ST period
The duration of exposure through Week 24 is described in Table 9. The long term (LT)

treatment period (i.e. weeks 26 to 52) exposure is detailed in Table 10.

Table 9. T2NOW ST period Exposure

T2NOW Study: Exposure During ST Period by Treatment Received

	Total Saxagliptin (N=88)	Placebo (N=76)	Total (N=164)
Duration of Exposure (Months)			
Mean (SD)	6.1 (0.80)	5.8 (1.34)	6.0 (1.09)
Median (Min, Max)	6.0 (2.6, 12)	6.0 (0.2, 9.5)	6.0 (0.2, 12)
Duration of Exposure Grouping by Month			
>0 to 1 month	0	2 (2.6)	2 (1.2)
>2 to 3 months	1 (1.1)	1 (1.3)	2 (1.2)
>3 to 4 months	0	3 (3.9)	3 (1.8)
>4 to 5 months	0	2 (2.6)	2 (1.2)
>5 to 6 months	59 (67.0)	46 (60.5)	105 (64.0)
>6 to 7 months	25 (28.4)	17 (22.4)	42 (25.6)
>7 to 8 months	2 (2.3)	2 (2.6)	4 (2.4)
>8 to 9 months	0	2 (2.6)	2 (1.2)
>9 to 10 months	0	1 (1.3)	1 (0.6)
>11 to 12 months	1 (1.1)	0	1 (0.6)

Source: OCS Analysis Studio, Custom Table Tool. Table generated by OCS Clinical Services.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y', TR01AG3 = 'Total Saxagliptin' or 'Placebo'; Column Variable 1 TR01AG3 (Actual Pooled Treatment 3 for Period 01):.
Duration of Exposure (Days) - Dataset: Demographics; Filter: None; Row Variable 1: EXPDYTO1 (Exposure (days) - ST).
Duration of Exposure (Months) - Dataset: Demographics; Filter: None; Row Variable 1: EXPMOTO1 ().
Duration of Exposure Grouping by Month - Dataset: Demographics; Filter: None; Row Variable 1: EXPCATM1 ().
SD = Standard Deviation.

Table 10. T2NOW LT Period Exposure for Saxagliptin and Placebo re-randomized to saxagliptin

	Total Saxagliptin (N=82)	Placebo to Saxagliptin (N=3)	Placebo (N=60)
Duration of Exposure (Months)			
Mean (SD)	5.8 (1.10)	6.3 (0.55)	5.8 (1.48)
Median (Min, Max)	6.0 (1.4, 8.4)	6.0 (5.9, 6.9)	6.0 (1, 9.3)
Duration of Exposure Grouping by Month			
>0 to 1 month	0	0	1 (1.7)
>1 to 2 months	2 (2.4)	0	3 (5.0)
>2 to 3 months	3 (3.7)	0	1 (1.7)
>3 to 4 months	1 (1.2)	0	0
>4 to 5 months	2 (2.4)	0	1 (1.7)
>5 to 6 months	46 (56.1)	2 (66.7)	30 (50.0)
>6 to 7 months	24 (29.3)	1 (33.3)	19 (31.7)
>7 to 8 months	2 (2.4)	0	2 (3.3)
>8 to 9 months	2 (2.4)	0	2 (3.3)
>9 to 10 months	0	0	1 (1.7)

Source: OCS Analysis Studio, Custom Table Tool. Table generated by OCS clinical services.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y', EOT01STT = 'COMPLETED' or 'ONGOING'; Column Variable 1: TRTSEQA (Actual Sequence of Treatments).
Duration of Exposure (Days) - Dataset: Demographics; Filter: None; Row Variable 1: EXPDYTO2 (Exposure (days) - LT).
Duration of Exposure (Months) - Dataset: Demographics; Filter: None; Row Variable 1: EXPMOTO2 ().
Duration of Exposure Grouping by Month - Dataset: Demographics; Filter: None; Row Variable 1: EXPCATM2 () .
SD = Standard Deviation.

Additional custom variables added were EXPMOTO2 (duration of exposure in LT period in months) and EXCATM2 (exposure range in months).
In addition to the Safety Analysis Flag, "End of Treatment Status in Period 01" (E0T01STT) was used to select "completed" status participants, as 10 placebo subjects discontinued and 6 saxagliptin subjects discontinued.

Overall Exposure (ST+LT) Periods:
The mean duration of overall exposure (ST+LT treatment periods) was 349 days for saxagliptin, or 49.8 weeks. Additionally, during the LT period, 3 subjects on placebo were re-randomized to saxagliptin 5mg treatment and their mean exposure duration was 190 days. See Table 11 for details.

Th ST+LT exposure analysis differs from the general approach to safety analyses described in Section 8.1, in order to describe the overall exposure of ST+LT period for subjects who continuously received saxagliptin over these periods vs placebo, and separately reports the exposure of "switchers," those ST Period placebo participants (n=3) who were re-randomized at week 32 (or 40) to treatment with saxagliptin 5mg (or dapagliflozin 10mg).

The switchers were re-randomized during LT Period (week 32 or 40); 6 participants who were treated on placebo in ST period were re-randomized to saxagliptin 5mg (n=3) and dapagliflozin 10mg (n=3). Most of the placebo re-randomizations occurred at week 32, except for 1 participant. The switchers' placebo treated duration (i.e. from study initiation to week 32/40) is summarized in a separate column from placebo treated arm in Table 11. In general, the overall exposures to saxagliptin and comparator placebo arm are substantive enough to permit adequate adverse event analyses in pediatric T2D subjects.

Table 11. Overall Exposure in ST and LT Periods

T2NOW Study: Exposure During ST & LT Period by Treatment Received with Switchers

	Total Saxagliptin (N=88)	Placebo to Saxagliptin (N=3)	Placebo to Dapagliflozin (N=3)	Placebo (N=76)	Total (N=170)
Duration of Exposure (Days)					
Mean (SD)	349.2 (65.25)	190.3 (17.04)	173.3 (4.73)	316.5 (104.14)	328.7 (89.79)
Median (Min, Max)	364.0 (78, 611)	181.0 (180, 210)	175.0 (168, 177)	363.0 (6, 475)	364.0 (6, 611)
Duration of Exposure (Months)					
Mean (SD)	11.5 (2.14)	6.3 (0.55)	5.7 (0.17)	10.4 (3.43)	10.8 (2.95)
Median (Min, Max)	12.0 (2.6, 20.1)	6.0 (5.9, 6.9)	5.8 (5.5, 5.8)	11.9 (0.2, 15.6)	12.0 (0.2, 20.1)
Duration of Exposure Grouping by Month					
>0 to 1 month	0	0	0	2 (2.6)	2 (1.2)
>2 to 3 months	1 (1.1)	0	0	1 (1.3)	2 (1.2)
>3 to 4 months	0	0	0	3 (3.9)	3 (1.8)

T2NOW Study: Exposure During ST & LT Period by Treatment Received with Switchers

	Total Saxagliptin (N=88)	Placebo to Saxagliptin (N=3)	Placebo to Dapagliflozin (N=3)	Placebo (N=76)	Total (N=170)
>4 to 5 months	0	0	0	1 (1.3)	1 (0.6)
>5 to 6 months	3 (3.4)	2 (66.7)	3 (100.0)	3 (3.9)	11 (6.5)
>6 to 7 months	2 (2.3)	1 (33.3)	0	5 (6.6)	8 (4.7)
>7 to 8 months	1 (1.1)	0	0	3 (3.9)	4 (2.4)
>8 to 9 months	3 (3.4)	0	0	2 (2.6)	5 (2.9)
>9 to 10 months	2 (2.3)	0	0	1 (1.3)	3 (1.8)
>10 to 11 months	1 (1.1)	0	0	1 (1.3)	2 (1.2)
>11 to 12 months	48 (54.5)	0	0	33 (43.4)	81 (47.6)
>12 to 13 months	22 (25.0)	0	0	14 (18.4)	36 (21.2)
>13 to 14 months	3 (3.4)	0	0	2 (2.6)	5 (2.9)
>14 to 15 months	1 (1.1)	0	0	2 (2.6)	3 (1.8)
>15 to 16 months	0	0	0	3 (3.9)	3 (1.8)
>20 months	1 (1.1)	0	0	0	1 (0.6)

Source: OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y', TRTNEW = 'Total Saxagliptin' or 'Placebo' or 'Placebo to Saxagliptin' or 'Placebo to Dapagliflozin'; Column Variable 1: TRTNEW().
Duration of Exposure (Days) - Dataset: Demographics; Filter: None; Row Variable 1: EXPDYTT2 ().
Duration of Exposure (Months) - Dataset: Demographics; Filter: None; Row Variable 1: EXPMOTOT ().
Duration of Exposure Grouping by Month - Dataset: Demographics; Filter: None; Row Variable 1: EXPCATMT ().
SD = Standard Deviation.

The placebo treatment arm (n=76) in Table 11 includes those who were re-randomized to drug product treatment in LT period ("switchers", n=6).

Reference: Table generated by OCS Clinical Services.

8.2.2. Relevant characteristics of the safety population:

The characteristics of the safety population for the primary safety analysis (i.e. ST treatment period through week 26) have already been described in Section 6.1.1.

8.2.3. Adequacy of the safety database:

Because the safety profile of saxagliptin was previously evaluated in adult patients with type 2 diabetes mellitus, the exposure and size of the safety database in T2NOW is considered generally adequate to identify common adverse drug reactions. The exposure duration is similar to other recently completed pediatric trials (e.g. liraglutide, extended release exenatide,

dulaglutide, empagliflozin). (b) (4)

8.3. Adequacy of Applicant's Clinical Safety Assessments

The overall quality of the data submitted was acceptable. Based on clinical inspections conducted at two study sites (see Section 4.1), no discrepancies were noted in the source records for any of the safety data including adverse events, serious adverse events, laboratory tests and physical exam results.

8.3.1. Categorization of Adverse Events

Protocol definitions for AEs, SAEs, and severity of AEs were acceptable. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 25.1. All AEs and AESIs were collected from the period of informed consent through the end of the study. After completion of the study, only related SAEs and related AESIs which the investigator subsequently became aware of were collected. Treatment-emergent adverse events (TEAEs) were defined as all AEs occurring between start of a placebo lead-in period until the week 104 post-study visit. All non-serious adverse events are followed until resolution, stabilization, or subject is lost to follow-up.

Error! Reference source not found. T2NOW protocol initially defined a comprehensive list of adverse events of special interest (AESIs) for dapagliflozin and saxagliptin. Those pertinent to saxagliptin were:

- Hypoglycemia
- Pancreatitis
- Hypersensitivity reactions
- severe cutaneous adverse reactions (including bullous pemphigoid)
- arthralgia
- decreased lymphocyte and/or thrombocyte counts
- cardiac failure

Hypoglycemia was reported by subjects and family members in patient diaries, based on hypoglycemic symptoms. Subjects were encouraged to measure their blood glucose values if experiencing hypoglycemia symptoms and to carry ingestible forms of carbohydrate for treatment. The Investigator was responsible for questioning subjects about all symptoms reported on the hypoglycemia reports in the diary. Then the Investigator would adjudicate hypoglycemia diary entries, based on hypoglycemia symptoms and/or blood glucose values that met hypoglycemia definition. Unless fulfilling a Serious Adverse Event, signs and symptoms of hypoglycemia, hypoglycemia episode or discontinuation due to hypoglycemia would not be reported as an AE. Hypoglycemia AEs were defined by ADA criteria [14] and by International Society for Pediatric and Adolescent Diabetes (ISPAD) criteria [15].

8.3.2. Routine Clinical Tests

T2NOW clinical assessments are summarized below in Table 12 and Table 13:

Table 12. T2NOW Study Clinical Assessments

		Baseline	6w	12w	20w	26w	32w	40w	46w	52w
ECG		X				X				X
Clinical Laboratory*	(CBC), biochemistry, urinalysis (with microscopy, creatinine albumin, glucose)	X	X	X	X	X		X		X
Urine HCG		X	X	X	X	X	X	X	X	X
Clinical exam	Targeted physical exam, height, body weight, orthostatic blood pressure and heart rate	X	X	X	X	X	X	X		X
Growth, bone, maturation markers	TSH, FT4, LH, FSH, estradiol, total testosterone, IGF-1, IGFBP-3, calcitonin, 25-hydroxy vitamin D, bone alkaline phosphatase, osteocalcin, PTH and CTX-1	X				X				X
Tanner staging		X				X				X

Reference: Clinical reviewer prepared based on T2NOW Clinical Study Report
*estimated glomerular filtration rate according to the Schwartz formula

Table 13. T2NOW Study Short-term Procedural Outline

Procedure	Day 1	Day 2	Day 6	Day 12	Day 14	Day 20	Wk 26/ETD (early	Notes

							discontinuation of IP)/Rescue	
Fasting Plasma Glucose (FPG)	X		X	X		X	X	On Day 1, the FPG sample will be collected pre-dose only. At the Wk 6, 12, 20 and 26 visits FPG samples will be collected pre-dose and approximately 2 hours post-dose (1 hour) All samples will be drawn in the fasting condition.
HbA1c	X		X	X		X	X	Results masked following IP administration on Day 1 until after study completion
Pregnancy Test (WOCBP only)	X		X	X	X	X	X	WOCBP must have a negative serum or urine pregnancy test within 24 hours prior to the start of study drug. Home pregnancy kits will be provided.
Spot Urine Glucose	X		X	X		X	X	Results blinded to the Sponsor, Investigator, site, and subject for the duration of the study following IP administration on Day 1 until after study completion
Growth, bone and maturation markers	X						X	Thyroid-stimulating hormone (TSH), free thyroxine, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, total testosterone, insulin-like growth factor-1 (IGF-1), insulin-like growth factor binding protein-3 (IGFBP-3), calcitonin, 25-hydroxy vitamin D, bone alkaline phosphatase, osteocalcin, parathyroid hormone (PTH) and carboxyterminal cross-linked telopeptide of Type 1 collagen (CTX-1)

Reference: Adapted from Applicant's T2NOW study Clinical Study Protocol Amendment 6 (February 7, 2022)

8.4. Safety Results

The study design of T2NOW involved 3 initial treatment arms with saxagliptin, dapagliflozin, or placebo in the short-term treatment period. Doses of saxagliptin or dapagliflozin were increased for "non-responders" (i.e. patients with A1c above goal) at week 14. At week 26, there was a third randomization. Going into LT period, generally the study drug treatment remained consistent, while metformin was withdrawn for responders at entry into LT period (b) (4) to conduct investigations with study drug monotherapy. In the LT safety extension, the placebo treatment arm was re-randomized at weeks 32 or 40 to continue placebo or switch to dapagliflozin or saxagliptin. This created a new subgroup of patients, "switchers" (n=6) who were on placebo treatment in the ST period, then re-randomized to saxagliptin (n=3) and dapagliflozin (n=3) in LT period. The adverse events of switchers were evaluated separately, to ensure their adverse events don't get misclassified under placebo treatment group (which was the switchers' original treatment group in ST period).

8.4.1. Overall Adverse Events

An overview of the TEAEs that occurred during T2NOW (i.e. ST+LT periods) is presented below (based on Applicant's analysis). Pertinent AEs are discussed in respective subsections.

During the ST+LT periods, the percentage of patients reporting any AE was similar in the total saxagliptin group and placebo groups (69.3% and 71.1%). The reported exposure-adjusted incidence rate per 100 patient years was lower in the total saxagliptin group than in the placebo treated group (148.62 vs. 182.69 patient years). Overall, the incidence of the broad AE categories over 52-weeks of T2NOW was generally balanced between saxagliptin and placebo treated groups.

Table 14.3.2.1.3.b Number of subjects with AEs in any category for saxagliptin and placebo during the ST+LT period, regardless of rescue (Treated Subjects Data Set)

	Total Saxagliptin (N=88)			Placebo (N=76)		
AE category	Number (%) of subjects[a]	Number of events	Incidence rate adjusted for exposure time (per 100 patient years)[b]	Number (%) of subjects[a]	Number of events	Incidence rate adjusted for exposure time (per 100 patient years)[b]
Any AE	61 (69.3)	187	147.62	54 (71.1)	218	182.69

Any hypoglycaemia event	26	(29.5)	133	38.45	22	(28.9)	161	41.49
Any AE or hypoglycaemia event	70	(79.5)	320	209.50	58	(76.3)	379	225.27
Any SAE	7	(8.0)	8	8.71	5	(6.6)	5	7.46
Any hypoglycaemia SAE	0		0	0	0		0	0
Any adjudicated DKA SAE	0		0	0	1	(1.3)	1	1.47
Any AE leading to discontinuation of study medication	1	(1.1)	1	1.19	1	(1.3)	1	1.45
Any SAE leading to discontinuation of study medication	0		0	0	0		0	0
Any hypoglycaemia SAE leading to discontinuation of study medication	0		0	0	0		0	0

AE = Adverse event. AEOSI = Adverse event of special interest. DKA = Diabetic ketoacidosis. IP = Investigational product. N = Number of subjects in the treatment group or regimen in the analysis set. SAE =Serious Adverse Event. ST+LT = Short term + Long term.

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories.

[b] Number of subjects with AEs divided by the sum of the minimum of exposure time or time to event per subject across all subjects multiplied by 100.

Includes AEs with an onset date on or after the date of first dose of ST IP and up to and including 4 days (30 days in case of SAEs) following the date of last dose of ST+LT IP, regardless of rescue medication initiation.

Related AEs are per investigator assessment.

Percentages are based on the total number of subjects in the treatment group (N).

Program: t_saeanyyrs.sas

Reference: Applicant's Table 14.3.2.1.3.b

8.4.2. Deaths

There were no reported deaths in T2NOW.

8.4.3. Serious Adverse Events

Serious Adverse Events (SAEs) that occurred in T2NOW (inclusive of ST+LT periods) is depicted in Table 14. Overall, there are no concerning trends or isolated observations. The serious adverse events appear consistent with expectations for the enrolled population.

Table 14. SAEs in T2NOW study

Summary of Serious Adverse Events in ST+LT Period

System Organ Class Preferred Term	**Pooled Saxagliptin** **N = 88** **n (%)**	**Placebo** **N = 76** **n (%)**
Any AE	7 (8.0)	5 (6.6)
Gastrointestinal disorders	**2 (2.3)**	**1 (1.3)**
Abdominal pain lower	1 (1.1)	0 (0.0)
Abdominal pain upper	0 (0.0)	1 (1.3)
Gastritis	1 (1.1)	0 (0.0)
Infections and infestations	**2 (2.3)**	**0 (0.0)**
Appendicitis	1 (1.1)	0 (0.0)

Summary of Serious Adverse Events in ST+LT Period

System Organ Class Preferred Term	Pooled Saxagliptin N = 88 n (%)	Placebo N = 76 n (%)
Any AE	7 (8.0)	5 (6.6)
Covid-19	1 (1.1)	0 (0.0)
Investigations	**1 (1.1)**	**0 (0.0)**
Transaminases increased	1 (1.1)	0 (0.0)
Metabolism and nutrition disorders	**2 (2.3)**	**3 (3.9)**
Diabetic ketoacidosis	0 (0.0)	1 (1.3)
Hyperglycaemia	2 (2.3)	2 (2.6)
Nervous system disorders	**0 (0.0)**	**1 (1.3)**
Presyncope	0 (0.0)	1 (1.3)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "SAXA2.5_2.5" or "SAXA2.5_2.5*" or "SAXA2.5_5" or "SAXA2.5" and SAFFL = "Y" (Pooled Saxagliptin); TRT01A = "PLAC" or "PLACPLAC" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" and ITTFL = "Y" and ASER = "Y" (Adverse Events).
The table above does not distinguish switchers (n=3), ST period placebo treated patients who are re-randomized to saxagliptin in LT period. They are counted as part of the placebo group, although the table above is for ST and LT periods, as switchers did not experience any SAEs in LT period.

Summary of all SAE narratives:

(b) (6): 15/F/metformin/saxagliptin 2.5mg, who is hospitalized for right lower abdominal pain, 80 days into treatment. The severity was moderate intensity and resolved by end of study. Not related to study drug.

(b) (6) 16/M/metformin/saxagliptin 5mg with COVID-19. Subject recovered. SAE not related to study treatment.

(b) (6) 14/F/insulin/saxagliptin 2.5mg, with transaminases increased on Day 23 from treatment start. There is incidentally an urinary tract infection adverse event that occurs 5 days later. Both are with causality not study drug related. In T2NOW, subject tolerated 357 days on treatment.

(b) (6) 14/M/metformin/saxgliptin 5mg with acute gastritis, 367 days after randomization and on treatment. Patient presented to emergency room with 2 day history of reduced oral intake, emesis, epigastric pain. Clinical improvement and hospital discharge. Not drug related.

(b) (6) 16/M/metformin/saxagliptin 2.5mg with appendicitis, 366 days into treatment. S/p appendectomy and discharge from hospital. Not study drug related.

(b) (6) 15/M/metformin/insulin/saxagliptin 2.5mg with hyperglycaemia. Not study drug related.

(b) (6) 16/M/metformin/insulin/saxagliptin 2.5mg with hyperglycaemia. Not drug related.

LT SAE narrative at excluded study site 4910:
(b) (6) 16/F/metformin XR/insulin/placebo who had suicide attempt on study day 215. The subject recovered and the causality was determined to be not related to study treatment.

There were 3 SAEs due to hospitalization, that were not part of the on treatment timeframe (and therefore not mentioned above) which were reviewed and the reviewer agrees with the Applicant's causality assessments of not related. See Table 15.

Table 15. T2NOW study Excluded SAEs

SAE associated with saxagliptin	SAE summary	Clinical reviewer assessment of relatedness to study treatment/comments
Diabetes mellitus inadequate control	(b) (6) 13 year old Asian male on saxagliptin 2.5mg + metformin + insulin, with uncontrolled diabetes involving hospitalization at Week 104 followup. Reported as moderate intensity severity, resolved, not related.	Not related
Local swelling	(b) (6) 13 year old female with oropharyngeal pain and swelling, with natal cleft swelling involving hospitalization weeks before beginning study treatment. Mild severity intensity, not related. With resolution.	Not related
Ureterolithiasis	(b) (6) 16 year old Asian female on saxagliptin 5mg + metformin + insulin with worsening ureteral stone at week 104 followup involving hospitalization, moderate	Not related

	intensity, resolved, not related.	

Reference: Applicant's T2NOW narratives

8.4.4. Dropouts and/or Discontinuations Due to Adverse Effects

There were 2 subjects who discontinued study treatment due to possible drug-related AE: 1 in the saxagliptin treatment arm and 1 in the placebo treatment arm. One peripheral sensory neuropathy adverse event was reported for a subject who had been on 352 days of saxagliptin treatment. The subject discontinued study treatment. One non-serious urinary tract infection was reported for a placebo-treated subject. The patient discontinued study treatment.

Reviewer comment:
Peripheral neuropathy is described as a microvascular complication for diabetes [16], but generally DDP-4 inhibitors are not known to have an effect on microvascular complications. It is most likely that the subject with peripheral sensory neuropathy experienced symptoms due to T2D disease progression.

8.4.5. Significant Adverse Events

Severe adverse events are characterized in Table 16 but none indicate possible new safety signals or relatedness to study treatment.

Table 16. T2NOW study Severe Adverse Events in ST and LT Periods

Summary of TEAEs with Severe Intensity in ST and LT Periods

System Organ Class Preferred Term	Pooled Saxagliptin N = 88 n (%)	Placebo N = 76 n (%)
Any AE	3 (3.4)	3 (3.9)
Gastrointestinal disorders	**1 (1.1)**	**0 (0.0)**
Toothache	1 (1.1)	0 (0.0)
Investigations	**1 (1.1)**	**0 (0.0)**
Transaminases increased	1 (1.1)	0 (0.0)
Metabolism and nutrition disorders	**1 (1.1)**	**2 (2.6)**
Diabetic ketoacidosis	0 (0.0)	1 (1.3)
Hyperglycaemia	1 (1.1)	1 (1.3)
Nervous system disorders	**0 (0.0)**	**1 (1.3)**
Presyncope	0 (0.0)	1 (1.3)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "SAXA2.5_2.5" or "SAXA2.5_2.5*" or "SAXA2.5_5" or "SAXA2.5" and SAFFL = "Y" (Pooled Saxagliptin); TRT01A = "PLAC" or "PLACPLAC" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" and ITTFL = "Y" and AESEV = "SEVERE" and APERIOD = 1 to 2 (Adverse Events).

Reference: Reviewer generated in Analysis Studio.

8.4.6. Treatment Emergent Adverse Events and Adverse Reactions

During the T2NOW duration (i.e. ST + LT period), a similar percentage of patients experienced

TEAES in the total saxagliptin and placebo treated arms [61 (69.3%) vs 54 (71.1%)].

ST period TEAEs:
For the ST period (see Table 17), TEAEs were generally balanced between saxagliptin and placebo treatment arms. The SOC of Infections and Infestations had the greatest number of AEs for both saxagliptin and placebo groups. The most common PTs in this SOC were influenza, upper respiratory tract infection, and urinary tract infection. There were slightly more reported events for the saxagliptin treatment groups. This is congruous with findings from adult patient studies with saxagliptin. Gastrointestinal disorders SOC contained the next most events with abdominal pain and diarrhea being the most common PTs, however reported more commonly with placebo treated patients. The third most common SOCs was Metabolism and nutrition disorders, with Vitamin D deficiency being the most common PT term. A forest plot in

Table 17 of common ST period TEAEs (≥5% of subjects) depicts the general balance between saxagliptin and placebo treatment arms.

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Table 17. T2NOW ST Period TEAEs

Summary of TEAEs by SOC and PT Occurring in ≥5% of Subjects in ST Period

System Organ Class Preferred Term	Pooled Saxagliptin N = 88 n (%)	Placebo N = 76 n (%)	Risk Difference RD (95% CI)	Forest Plot
Any AE	49 (55.7)	47 (61.8)	-6.16 (-21.23, 8.91)	
Gastrointestinal disorders	**10 (11.4)**	**9 (11.8)**	-0.48 (-10.31, 9.36)	
Abdominal pain	2 (2.3)	4 (5.3)	-2.99 (-8.90, 2.92)	
Diarrhoea	1 (1.1)	4 (5.3)	-4.13 (-9.61, 1.36)	
General disorders and administration site conditions	**1 (1.1)**	**5 (6.6)**	-5.44 (-11.44, 0.56)	
Infections and infestations	**28 (31.8)**	**27 (35.5)**	-3.71 (-18.22, 10.80)	
Influenza	5 (5.7)	4 (5.3)	0.42 (-6.55, 7.39)	
Upper respiratory tract infection	3 (3.4)	4 (5.3)	-1.85 (-8.15, 4.44)	
Urinary tract infection	5 (5.7)	4 (5.3)	0.42 (-6.55, 7.39)	
Injury, poisoning and procedural complications	**6 (6.8)**	**4 (5.3)**	1.56 (-5.72, 8.83)	
Investigations	**3 (3.4)**	**11 (14.5)**	-11.06 (-19.84, -2.29)	
Metabolism and nutrition disorders	**9 (10.2)**	**16 (21.1)**	-10.83 (-21.97, 0.31)	
Vitamin d deficiency	5 (5.7)	6 (7.9)	-2.21 (-9.97, 5.54)	
Musculoskeletal and connective tissue disorders	**2 (2.3)**	**4 (5.3)**	-2.99 (-8.90, 2.92)	
Nervous system disorders	**4 (4.5)**	**4 (5.3)**	-0.72 (-7.36, 5.93)	
Respiratory, thoracic and mediastinal disorders	**3 (3.4)**	**5 (6.6)**	-3.17 (-9.91, 3.57)	
Skin and subcutaneous tissue disorders	**5 (5.7)**	**4 (5.3)**	0.42 (-6.55, 7.39)	

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "SAXA2.5_2.5" or "SAXA2.5_2.5*" or "SAXA2.5_5" or "SAXA2.5" and SAFFL = "Y" (Pooled Saxagliptin); TRT01A = "PLAC" or "PLACPLAC" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" and APERIOD = 1 to 1 and ITTFL = "Y" (Adverse Events).
Percent Threshold: Any Column ≥ 5%.
Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).
Includes mITT population: those who received at least 1 dose of study drug based on actual treatment received regardless of any intercurrent events.
Included are patients who reported at least one event (if one patient had two events it was only counted once).

Reference: Reviewer generated in Analysis Studio.

LT period TEAEs:

In the LT period (see Table 18), the most common SOC was Infections and infestations with most common PT terms of COVID-19, upper respiratory tract infection, urinary tract infection, and nasopharyngitis. There were more subjects in the saxagliptin treatment arm with these events. The second most common SOC was Gastrointestinal disorders. Third most common was

metabolism and nutrition disorders.

The investigations SOC AEs were predominantly in the placebo group (28 AEs vs 38 in saxagliptin treatment arms). The majority of investigations SOC consisted of 12 transaminitis AEs (9 in placebo and 3 in saxagliptin treatment group).

Table 18. LT Period TEAEs

Summary of TEAEs by SOC and PT Occurring in ≥5% of Subjects in the LT period

System Organ Class Preferred Term	Pooled Saxagliptin N = 88 n (%)	Placebo N = 76 n (%)	Risk Difference RD (95% CI)	Forest Plot
Any AE	38 (43.2)	32 (42.1)	1.08 (-14.10, 16.25)	
Gastrointestinal disorders	**7 (8.0)**	**6 (7.9)**	0.06 (-8.23, 8.35)	
Infections and infestations	**22 (25.0)**	**20 (26.3)**	-1.32 (-14.73, 12.10)	
Covid-19	5 (5.7)	1 (1.3)	4.37 (-1.11, 9.84)	
Nasopharyngitis	2 (2.3)	4 (5.3)	-2.99 (-8.90, 2.92)	
Upper respiratory tract infection	5 (5.7)	1 (1.3)	4.37 (-1.11, 9.84)	
Urinary tract infection	4 (4.5)	5 (6.6)	-2.03 (-9.11, 5.04)	
Investigations	**2 (2.3)**	**8 (10.5)**	-8.25 (-15.82, -0.68)	
Metabolism and nutrition disorders	**5 (5.7)**	**5 (6.6)**	-0.90 (-8.28, 6.48)	

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "SAXA2.5_2.5" or "SAXA2.5_2.5*" or "SAXA2.5_5" or "SAXA2.5" and SAFFL = "Y" (Pooled Saxagliptin); TRT01A = "PLAC" or "PLACPLAC" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" and APERIOD = 2 to 2 and ITTFL = "Y" (Adverse Events).
Percent Threshold: Any Column ≥ 5%.
Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).
Reference: Reviewer generated in Analysis Studio.

Switchers:
There were 3 adverse events in the 3 placebo-treated patients switched to saxagliptin 5mg in the LT treatment period. Only 2 adverse events occurred in the LT treatment period, after the third randomization (one AE with a subject on saxagliptin 5mg and one AE with a subject on dapagliflozin 10mg).

TEAE narrative for placebo-to-saxagliptin treatment switcher subject:
[E0716002] 17 year old white male from Latin America, re-randomized to saxagliptin 5mg monotherapy from placebo treatment, had adverse event of “Vitamin D deficiency.” The adverse event was categorized with mild severity, with recovery. The AE causality was not related to study drug.

8.4.7. Laboratory Findings

There were no clinically notable mean changes observed in clinical chemistry or hematology parameters.

8.4.8. Vital Signs

No clinically meaningful changes were observed in vital signs.

8.4.9. QT

Thorough QT study was assessed in original review.

8.4.10. Immunogenicity

No immunogenicity assessments occurred during this study.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Hypoglycemic Events

Hypoglycemia is a commonly occurring adverse event with concomitant anti-diabetes medications. The risk of hypoglycemia with concomitant anti-diabetes medication (e.g. insulin) is described in the Prescribing Information, under Warnings and Precautions: (b) (4)

During T2NOW, participants were provided blood glucose meters for self-monitoring, with blood glucose measurement at least once per day and for any hypoglycemic or hyperglycemic symptoms. The American Diabetes Association (ADA) hypoglycemia criteria were used to categorize hypoglycemia events during the study:

- Level 1 - Glucose <70 mg/dL and ≥54 mg/dL
- Level 2 - Glucose <54 mg/dL
- Level 3 - A severe hypoglycemic event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia, irrespective of glucose level.

In the ST period, 22 (25.0%) subjects in the saxagliptin treatment arm experienced 71 hypoglycemia events, compared to 20 (26.3%) of placebo subjects who experienced 81

hypoglycemia events. None of the hypoglycemia events were SAEs. Treatment with saxagliptin did not adversely affect the incidence or rate of hypoglycemia compared to placebo.

Table 19 characterizes the hypoglycemia event types in the ST period between saxagliptin and placebo treatment arms. An analysis of the ST and LT periods (data not shown) reveals similar trends.

Table 19. Hypoglycemic Events in Pooled Saxagliptin vs Placebo During ST Period, Regardless of Rescue

	Total Saxagliptin (n=88)		Placebo (n=76)	
ADA classification	No. (%) patients^	No. events	No. (%) patients^	No. events
Any hypoglycemia event	22 (25.0)	71	20 (26.3%)	81
Level 1	10 (11.4)	46	13 (17.1)	65
Level 2	12 (13.6)	18	6 (7.9)	9
Level 3	3 (3.4)	6	4 (5.3)	4
Not classified	1	1	2	3

^Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than 1 category are counted once in each of those categories. Percentages are based on the total number of patients in the treatment group (N).
Excludes 4 hypoglycaemic events which were not classified in 3 subjects (1 subject on saxagliptin with 1 hypoglcaemic event not classified and 2 subjects on placebo with 3 hypoglycaemic events not classified).
References: Clinical reviewer generated table with analysis using JMP 15.2.1 on ADHYPO dataset, with adaptation from Applicant's week 56 CSR Table 14.3.6.4.2.b

8.5.2. Other Adverse Events of Special Interest

Adverse events of special interest for saxagliptin originally outlined in the study protocol were: hypoglycemia, pancreatitis, hypersensitivity, severe cutaneous adverse reactions including bullous pemphigoid, arthralgia, decreased lymphocyte count. Generally, there were no significant imbalances with these adverse events with saxagliptin (see Table 20):

Table 20. Number of Patients with AEoSIs for Saxagliptin and Placebo During the ST + LT period

	Total saxagliptin (N = 88)		**Placebo (N = 76)**	
AEoSI category	Number (%) of patients [a]	Number of events	Number (%) of patients [a]	Number of events
Changes in growth	No AEoSIs			

Severe cutaneous adverse reactions (including bullous pemphigoid)	0	0	1 (1.3)	1
Genital mycotic infections	1 (1.1)	2	2 (2.6)	2
Urinary tract infections (including urosepsis/pyelonephritis)	7 (8.0)	10	8 (10.5)	12
Pancreatitis	No AEoSIs			
Hypoglycaemic events	1 (1.1)	3	0	0
Ketoacidosis	0	0	1 (1.3)	2
Malignancies (including bladder cancer)	No AEoSIs			

Reference: T2NOW clinical study report

Includes AEs with an onset date on or after the date of first dose of ST study drug and up to and including 4 days (30 days in case of SAEs) following the date of last dose of ST + LT study drug, regardless of rescue medication initiation.

Percentages are based on the total number of patients in the treatment group (N).

AE, adverse event; AEoSI, adverse event of special interest; N, number of patients in the treatment group or regimen in the analysis set; SAE, serious adverse event; ST, short-term; ST + LT, short-term + long-term

Looking at ST+LT periods together, there were more urinary tract infections, genital mycotic infections, stomatitis, volume depletion/syncope, bone fracture, hyperlipidemia, arthralgia in placebo arm. This is different than in the ST period alone, though the difference between the groups is not significant.

There were no AE for changes in growth, bullous pemphigoid, necrotizing fasciitis of the perineum (Fournier's gangrene), opportunistic infections, decreased lymphocyte and/or thrombocyte counts, pancreatitis, heart failure, and acute kidney injury.

8.6. Safety Analyses by Demographic Subgroups

The Applicant analyzed the incidence of any AE by age group (≥10 and <15 years, ≥15 and <18 years), race, ethnicity, sex, age group, region, background antidiabetic medication, baseline A1c, and baseline BMI. There were small differences in the percentages of patients reporting AEs between the saxagliptin and placebo groups for some of the subgroups (region, race, and ethnicity), these were not considered meaningful both because of the limited sample size and magnitude of imbalance.

The clinical review team did not further explore drug safety by demographic subgroups because (a) the safety profile observed in the pediatric study is broadly consistent with the safety profile in adults, (b) The original NDA medical reviews of the large, adult, premarket databases did not identify a meaningful treatment interaction with demographic subgroups, despite being adequately powered and (c) the pediatric safety database is generally inadequate

to identify marginal treatment differences in adverse events, let alone treatment interactions by patient subgroups such as race, gender, or age.

8.7. Specific Safety Studies/Clinical Trials

8.7.1. Safety Concerns Identified Through Postmarket Experience

On August 22, 2023 FDA Written Response (Reference ID: 5229297), FDA agreed to the Applicant's plan to submit the annual periodic benefit-risk evaluation report (PBRER) with cumulative data for both saxagliptin and saxagliptin/metformin FDC (Onglyza and Kombiglyze XR) with data lock of July 30, 2023, in lieu of a separate document for 4-month safety update (4MSU), with inclusion of safety signals from any ongoing clinical investigations regardless of population or investigational indication.
The most recent saxagliptin PBRER submission to FDA was on September 29, 2023 (covering dates July 31, 2022 to July 30, 2023). In total, an estimated 38,578 patients and/or healthy volunteers have been enrolled into clinical development programs, of which 22,691 subjects received saxagliptin. No significant actions related to safety were taken or proposed during the reported period. No safety-related changes were made to the Core Data Sheet (CDS) during the reporting period.

The Applicant reports on April 11, 2024 that there is no new safety information. There are no ongoing clinical studies, with T2NOW being the only ongoing clinical study at the time of supplemental NDA submission (December 2023). Preliminary results for 104-week data (i.e. non-treatment safety followup) became available and the Applicant reports no safety signals.

In alignment with updates to the metformin (Glucophage, MAH Merck), the CDS update dated 17 April 2023 included the following safety related changes:

- An addition was made to section 4.4 Special Warnings and Special Precautions of the CDS on Vitamin B12 decrease/deficiency.
- The adverse drug reaction 'Vitamin B12 deficiency' was re-defined as 'Vitamin B12 decrease/deficiency' and the frequency category was updated from 'very rare' to 'common' and the related footnote was deleted in section 4.8 of the CDS.

In summary, there is no new safety information presented in the PBRER reporting for Onglyza or Kombiglyze XR.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Not applicable to this submission.

8.8.2. Human Reproduction and Pregnancy

Not applicable to this submission. No reports of pregnancy occurred during the conduct of T2NOW.

8.8.3. Pediatrics and Assessment of Effects on Growth

The Applicant's CSR summary for the markers of growth, maturation, and bone health, including Tanner scores and puberty status during the ST + LT period, reports that no safety concerns were raised with saxagliptin treatment. The design of T2NOW includes a posttreatment visit at Week 104 for a final assessment of measures of growth and maturity. Although the requirement of this final study visit was removed (b) (4) the Applicant agreed to submit an addendum to the CSR with the full analyses of these measures once all study subjects complete the final visit.

8.9. Integrated Assessment of Safety

No deaths occurred in T2NOW. SAEs occurred in 8% (7/88) saxagliptin treated subjects and 6.6% (5/76) placebo treated subjects. None of the SAEs were assessed as related to saxagliptin treatment. Common TEAEs (infections, gastrointestinal disorders) were generally consistent with the reported saxagliptin safety profile in adult T2D. No clinically meaningful changes in vital signs (e.g. heart rate, blood pressure) or laboratory parameters were noted.

The assessment of safety in the pediatric population is limited by the size of the safety database (N=164), which is generally sufficient only to identify treatment differences in common adverse events. However, review of T2NOW did not reveal any concerning and/or unexpected treatment differences in safety outcomes, besides those already well-studied and labeled from adult studies.

9. Advisory Committee Meeting and Other External Consultations

No issues arose during the review which required the input of an advisory committee.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Prescribing information is being addressed in internal labeling meetings and labeling negotiations with the Applicant at the time of this review filing. We recommend Section 8.4 for Onglyza and Kombiglyze XR USPI be updated with a pediatric use statement clarifying that safety and effectiveness has not been established in pediatric T2D patients, with brief summary of T2NOW.
PI sections with updates during this review are below (Table 21 and Table 22):

Table 21. Onglyza (saxagliptin) PI updates

Section	PI section update	
1 Indications and Usage	Limitations of Use ONGLYZA is not *recommended* for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis	▪ Update to LOU language, for consistency with other DPP-4 inhibitors
2 Dosage and Administration	The recommended dosage of Onglyza is 2.5mg or 5mg *orally* once daily *Do* not cut, crush, or chew Onglyza tablets	▪ Addition of route of administration "orally" ▪ Revision to command language ▪ Addition for instructions with missed dose, to not to take extra dose
2.4 Concomitant Use with an Insulin Secretagogue (e.g. Sulfonylurea) or with Insulin		▪ Removal of this section, as it does not refer to dosage and administration. Moved this information to Section 7.
3 Dosage Forms and Strengths		▪ Revisions for brevity and clarity with removal of drug name and tablets descriptor
5 Hypoglycemia with Concomitant Use	Revised to Hypoglycemia with Concomitant Use of Insulin or Insulin Secretagogues ~~Sulfonylurea or Insulin~~	▪ Addition of insulin secretagogues

5.7 Macrovascular Outcomes	~~5.7 Macrovascular Outcomes There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with ONGLYZA.~~	▪ Removal of this section, as not found in other DDP-4 inhibitor USPI and a CVOT with saxagliptin did not find increase in risk, nor a risk reduction.
6.1 Clinical Trials Experience	~~Adverse Reactions with Concomitant Use with Insulin~~ ~~In the add-on to insulin trial [see *Clinical Studies (14.1)*], the incidence of adverse reactions, including serious adverse reactions and discontinuations due to adverse reactions, was similar between ONGLYZA and placebo, except for confirmed hypoglycemia [see *Adverse Reactions (6.1)*].~~ Hypersensitivity Reactions Hypersensitivity-reactions ~~related events~~, such as urticaria and facial edema, in the 5-~~study~~ trial pooled analysis up to Week 24 were reported in 1.5%, 1.5%, and 0.4% of patients who received ONGLYZA 2.5 mg, ONGLYZA 5 mg, and placebo, respectively.	▪ Removal of redundant section "Adverse Reactions with Concomitant Use with Insulin" for hypoglycemia risk with concomitant insulin use, as this is repeated in Hypoglycemia section which follows. Additionally this information is relocated to Section 7 Drug Interactions ▪ Revision of hypersensitivity-related events to hypersensitivity reactions for clarity ▪ Specification of metformin as metformin HCl salt form
7.2 Concomitant Use with Insulin or Insulin Secretagogues	7.2 Concomitant Use with Insulin or Insulin Secretagogues Insulin and insulin secretagogues are known to cause hypoglycemia.	▪ Creation of section 7.2 with relocation of content which was previously in section 2

	Coadministration of ONGLYZA with insulin or an insulin secretagogue may require lower dosages of insulin or the insulin secretagogue to reduce the risk of hypoglycemia [see Warnings and Precautions (5.3)].	
8.4 Pediatric Use	The safety and effectiveness of ONGLYZA as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus have not been established in pediatric patients. Effectiveness of ONGLYZA was not demonstrated in a 26-week, placebo-controlled, double-blind randomized clinical study with a 26-week safety extension (NCT03199053) in 245 pediatric patients aged 10 to 17 years with inadequately controlled type 2 diabetes mellitus.	Update based on findings from T2NOW and fulfillment of PMR 3199-1. Language for this section is written to align with other DDP-4 inhibitors which have completed pediatric studies.
8.5 Geriatric Use	No overall differences in safety or effectiveness were observed between patients 65 years of age and older and younger adult patients. ~~subjects ≥65 years old and younger subjects. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some~~	▪ Revision for consistency with draft guidance for industry: *Geriatric Information in Human Prescription Drug and Biological Product Labeling* (September 2020).

	~~older individuals cannot be ruled out.~~	
10 Overdosage	In the event of an overdose, initiate appropriate supportive treatment as dictated by the patient's clinical status. Saxagliptin and its active metabolite are removed by hemodialysis (23% of dose over 4 hours). Contact the Poison Help Line, (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations.	▪ Revised to add new contact recommendations from America's Poison Centers
14 Clinical Studies	In these trials, the mean age was 54 years, and 71% of patients were White ~~Caucasian~~, 16% were Asian, 4% were ~~B~~black or African American, and 9% were of other racial groups.	▪ Updated descriptors for race and ethnicity
17 Patient Counseling Information		▪ Removal of language here for Medication Guide, written for HCP as there is already reference to this ▪ Removal of laboratory tests section which encompasses standard of care for glycemic control

Table 22. Kombiglyze (saxagliptin-metformin hydrochloride extended release) PI updates

Revisions to Kombiglyze XR are aligned with recommendations made for Onglyza. The table below captures the distinct PI updates to Kombiglyze XR, primarily for the metformin HCl component.

Section	PI section update	

1 Indications and Usage	KOMBIGLYZE XR 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~~	▪ Updated language for consistency with other DDP-4 inhibitor and metformin combination drugs
2 Dosing		▪ Revisions for clarity
4.4 Special Warnings and Special Precautions		▪ Vitamin B12 decrease/deficiency
5.4 Vitamin B12 Concentrations	In controlled clinical trials of metformin of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, may be associated with anemia but appears to be rapidly reversible with discontinuation of metformin or vitamin B_{12} supplementation. Certain individuals (those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. Measure hematologic parameters on an annual basis and vitamin B_{12} at 2- to 3-year intervals in patients on KOMBIGLYZE XR and	▪ Edits to align with Xigduo XR USPI.

	manage any abnormalities [*see Adverse Reactions (6.1)*].	
6 Adverse Reactions	• Lactic Acidosis *[see Boxed Warning and Warnings and Precautions (5.1)]* • Vitamin B_{12} Concentrations *[see Warnings and Precautions (5.4)]*	▪ Updated adverse reactions that are described elsewhere in labeling. ▪ The adverse drug reaction 'Vitamin B12 deficiency' was re-defined as 'Vitamin B12 decrease/deficiency' and the frequency category was updated from 'very rare' to 'common'
6.1 Clinical Trials Experience	*Vitamin B_{12} Concentrations* *Metformin hydrochloride* In metformin clinical trials of 29-week duration, a decrease to subnormal levels of previously normal serum vitamin B_{12} levels was observed in approximately 7% of patients.	▪ Edits to align with Xigduo XR PI. ▪ Removal of recommendation to perform hematologic parameters on an annual basis.
Section 7.6 Drugs Affecting Glycemic Control	Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These medications include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs	▪ Edits to align with Xigduo XR PI for readability.

	are administered to a patient receiving KOMBIGLYZE XR, observe the patient closely for loss of blood glucose control. When such drugs are withdrawn from a patient receiving KOMBIGLYZE XR, observe the patient closely for hypoglycemia.	
8.4 Pediatric Use	The safety and effectiveness of KOMBIGLYZE XR as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus have not been established in pediatric patients. Effectiveness of saxagliptin was not demonstrated in a 26-week, placebo-controlled, double-blind randomized clinical study with a 26-week safety extension (NCT03199053) in 245 pediatric patients aged 10 to 17 years with inadequately controlled type 2 diabetes mellitus.	▪ Update based on findings from T2NOW and fulfillment of PMR 3199-1. (See Onglyza PI updates in above section.)
8.5 Geriatric Use	*Metformin hydrochloride* Controlled clinical studies of metformin did not include sufficient numbers of elderly patients to determine whether they respond differently than younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater	▪ Edits to align with Xigduo XR PI.

	frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy and the higher risk of lactic acidosis. Assess renal function more frequently in elderly patients [*see Warnings and Precautions (5.1)*].	
12.3 Pharmacokinetics	*KOMBIGLYZE XR* Bioequivalence and food effect of KOMBIGLYZE XR was characterized under low calorie diet. The low calorie diet consisted of 324 kcal with meal composition that contained 11.1% protein, 10.5% fat, and 78.4% carbohydrate. The results of bioequivalence studies in healthy subjects demonstrated that KOMBIGLYZE XR combination tablets are bioequivalent to coadministration of corresponding doses of saxagliptin (ONGLYZA®) and metformin hydrochloride extended-release as individual tablets under fed conditions.	▪ Update to remove "Glucophage XR", as discontinued from US market.
14 Clinical Studies	~~There have been no clinical efficacy or safety studies conducted with KOMBIGLYZE XR to characterize its effect on A1C reduction. Bioequivalence of KOMBIGLYZE XR with coadministered saxagliptin and metformin hydrochloride~~	▪ Recommend removal of disclaimer that there were no studies conducted with Kombiglyze XR, as covered in section 12 and not likely to be relevant to HCP's consideration for safety and efficacy of

	~~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.~~	drug.

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

No REMS are considered necessary.

12. Postmarketing Requirements and Commitments

This application is in response to PREA PMR 3199-1. The Division met with the PeRC and recommended the PMR be fulfilled. The PeRC agreed (PeRC Meeting Minutes, 8/20/2024).

13. Appendices

13.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): D1680C00019

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 394		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒ *	No ☐ (Request explanation from Applicant)

* [redacted] The Applicant reports that [redacted] in error, did not complete a financial disclosure form during [redacted] time on the study and was therefore not added to the FDA 1572 equivalent. The Applicant's attempts to contact [redacted] study site email or phone number or via social media (LinkedIn and Twitter on June 6, 2023) were also unsuccessful. The site enrolled [redacted]
The absence of financial disclosure for this investigator does not raise concerns as it is unlikely

that the data from (b) (6) would affect the validity of study results.

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/s/

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