

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

CLINICAL REVIEW

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Reviewer Name(s)	Kim Shimy, M.D.
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Established/Proper Name	Alogliptin, alogliptin and metformin hydrochloride
(Proposed) Trade Name	Nesina, Kazano
Applicant	Takeda
Dosage Form(s)	tablets
Applicant Proposed Dosing Regimen(s)	Nesina: 25 mg once daily Kazano: twice daily, not to exceed maximum recommended dose of 25 mg alogliptin and 2000 mg metformin hydrochloride
Applicant Proposed Indication(s)/Population(s)	Not Applicable
Recommendation on Regulatory Action	Approval; PMR 2009-1, PMR 2007-2, PMR 2007-3 Fulfilled
Recommended Indication(s)/Population(s) (if applicable)	Not Applicable

Table of Contents

Glossary.....	7
1. Executive Summary	11
1.1. Product Introduction.....	11
1.2. Conclusions on the Substantial Evidence of Effectiveness	11
1.3. Benefit-Risk Assessment	11
1.4. Patient Experience Data.....	16
2. Therapeutic Context	16
2.1. Analysis of Condition.....	17
2.2. Analysis of Current Treatment Options	18
3. Regulatory Background	22
3.1. U.S. Regulatory Actions and Marketing History.....	22
3.2. Summary of Presubmission/Submission Regulatory Activity	22
3.3. Foreign Regulatory Actions and Marketing History.....	26
4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety.....	27
4.1. Office of Scientific Investigations (OSI)	27
4.2. Product Quality	27
4.3. Clinical Microbiology.....	27
4.4. Nonclinical Pharmacology/Toxicology	27
4.5. Clinical Pharmacology	27
4.6. Devices and Companion Diagnostic Issues	30
4.7. Consumer Study Reviews.....	30
5. Sources of Clinical Data and Review Strategy	30
5.1. Table of Clinical Studies.....	30
5.2. Review Strategy.....	31
6. Review of Relevant Individual Trials Used to Support Efficacy	31
6.1. Study SYR-322_309	31
6.1.1. Study Design.....	31
CDER Clinical Review Template	2
Version date: March 8, 2019 for all NDAs and BLAs	

6.1.2. Study Results.....	45
7. Integrated Review of Effectiveness	69
7.1. Assessment of Efficacy Across Trials	70
7.1.1. Primary Endpoints.....	70
7.1.2. Secondary and Other Endpoints	70
7.1.3. Subpopulations	70
7.1.4. Dose and Dose-Response.....	70
7.1.5. Onset, Duration, and Durability of Efficacy Effects	70
7.2. Additional Efficacy Considerations.....	70
7.2.1. Considerations on Benefit in the Postmarket Setting	70
7.2.2. Other Relevant Benefits.....	70
7.3. Integrated Assessment of Effectiveness	71
8. Review of Safety	72
8.1. Safety Review Approach	72
8.2. Review of the Safety Database	72
8.2.1. Overall Exposure	72
8.2.2. Relevant characteristics of the safety population:	73
8.2.3. Adequacy of the safety database:	73
8.3. Adequacy of Applicant’s Clinical Safety Assessments.....	73
8.3.1. Issues Regarding Data Integrity and Submission Quality	73
8.3.2. Categorization of Adverse Events.....	73
8.3.3. Routine Clinical Tests	75
8.4. Safety Results	77
8.4.1. Deaths	77
8.4.2. Serious Adverse Events.....	77
8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects	80
8.4.4. Significant Adverse Events.....	82
8.4.5. Treatment Emergent Adverse Events and Adverse Reactions	88
8.4.6. Laboratory Findings	92
8.4.7. Vital Signs	103

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

8.4.8. Electrocardiograms (ECGs).....	104
8.4.9. QT	104
8.4.10. Immunogenicity	104
8.5. Analysis of Submission-Specific Safety Issues	104
8.6. Safety Analyses by Demographic Subgroups	104
8.7. Specific Safety Studies/Clinical Trials	105
8.8. Additional Safety Explorations	105
8.8.1. Human Carcinogenicity or Tumor Development	105
8.8.2. Human Reproduction and Pregnancy	105
8.8.3. Pediatrics and Assessment of Effects on Growth	105
8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound	109
8.9. Safety in the Postmarket Setting.....	109
8.9.1. Safety Concerns Identified Through Postmarket Experience	109
8.9.2. Expectations on Safety in the Postmarket Setting	110
8.9.3. Additional Safety Issues From Other Disciplines	110
8.10. Integrated Assessment of Safety.....	110
9. Advisory Committee Meeting and Other External Consultations.....	111
10. Labeling Recommendations	111
10.1. Prescription Drug Labeling	111
10.2. Nonprescription Drug Labeling.....	111
11. Risk Evaluation and Mitigation Strategies (REMS)	111
12. Postmarketing Requirements and Commitments.....	111
13. Appendices	112
13.1. References	112
13.2. Financial Disclosure	112
13.3. Demographic Subgroup Safety Analyses.....	113

Table of Tables

Table 1: Summary of Available Non-Insulin Therapies for Pediatric Type 2 Diabetes	19
Table 2: Key Meetings and Regulatory Interactions Regarding the Pediatric Phase 3 Study SYR-322_309	23
Table 3: Hepatic Function Criteria for Study Treatment Discontinuation in Study SYR-322_309	37
Table 4: Disposition of Randomized and Treated Subjects in Study SYR-322_309	47
Table 5: Reasons for Exclusion from Per-Protocol Set among Treated Subjects, Study SYR-322_309	48
Table 6: Protocol Deviations in All Treated Subjects, Study SYR-322_309.....	49
Table 7: Demographic Characteristics of Treated Subjects, Study SYR-322_309.....	52
Table 8: Baseline Characteristics of Treated Subjects, Study SYR-322_309.....	53
Table 9: Baseline Characteristics Relating to T2D, All Treated Subjects, Study SYR-322_309	55
Table 10: Study SYR-322_309 Medication Compliance by Study Week.....	57
Table 11: Number of Treated Subjects with Change in Total Daily Dose of Metformin Compared with Total Daily Dose at Randomization, Study SYR-322_309	59
Table 12: Number of Treated Subjects with Change in Total Daily Dose of Insulin Compared to Total Daily Dose at Randomization.....	60
Table 13: Primary Efficacy Analysis for HbA1c (%) Change from Baseline to Week 26, Study SYR-322_309	62
Table 14: HbA1c (%) Change from Baseline to Week 26, Sensitivity Analysis, Study SYR-322_309	63
Table 15: HbA1c (%) Change from Baseline to Week 12, 18, 29 and 52, Study SYR-322_309.....	66
Table 16: HbA1c (%) Change from Baseline to Week 39 and week 52 by Antidiabetic Drug Use at Screening, Study SYR-322_309	68
Table 17: Study Treatment Exposure, Study SYR-322_309	73
Table 18: Clinical Laboratory Testing in Study SYR-322_309.....	76
Table 19: Treatment-emergent SAEs in Study SYR-322_309.....	77
Table 20: TEAEs leading to Treatment Discontinuation in Study SYR-322_309	80
Table 21: Lab Testing for Subject (b) (6)	81
Table 22: TEAEs considered to be AESIs by SOC and PT in Study SYR-322_309.....	83
Table 23: Narrow FDA Medical Query for Viral Infections and Hepatic Injury.....	85
Table 24: Broad FDA Medical Query for Viral Infection, Anaphylactic Reaction, Pancreatitis and Hepatic Injury.....	86
Table 25: Hypoglycemia Event Analysis, Study SYR-322_309	87
Table 26: Incidence of Hypoglycemia Events in Subjects With and Without Background Insulin Therapy While on Study Treatment, Study SYR-322_309	88
Table 27: TEAEs by SOC occurring in > 5% of Alogliptin-Treated Subjects in Study SYR-322_309	89
Table 28: TEAEs by PTs occurring with Selected SOC*s that Occurred in > 5% of Alogliptin-treated subjects, Study SYR-322_309	90

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Table 29: TEAEs by PT occurring in > 3% of Alogliptin-Treated Subjects in Study SYR-322_309 .	91
Table 30: Baseline eGFR, Study SYR-322_309	92
Table 31: Renal Impairment (based on eGFR) Shift Table from Baseline to Week 52	93
Table 32: Urine Albumin/Creatinine Shift Table from Baseline to Week 52	94
Table 33: Listing of Alogliptin-Treated Subjects in Temple's Corollary, Study SYR-322_309	96
Table 34: Change from Baseline in Growth-Hormone Dependent Factors among Subjects Baseline Tanner stage (Breast/Genitalia) < 5*	100
Table 35: Change from Baseline to Week 52 in Markers of Bone Metabolism	101
Table 36: Number and Percentage of Subjects with Markedly Abnormal Laboratory Values, Study SYR-322_309	103
Table 37: Baseline Tanner Stage (Breast) among Female Subjects, Study SYR-322_309	106
Table 38: Baseline Tanner Stage (Genitalia) among Male Subjects, Study SYR-322_309	106
Table 39: Baseline Tanner Stage (Pubic Hair), Study SYR-322_309	106
Table 40: Shift Table for Tanner Stage for Breast/Genitalia from Baseline to Week 52	107
Table 41: Change from Baseline in Height (cm) in Subjects with Baseline Tanner Stage (Breast/Genitalia) <5	108
Table 42: TEAEs by SOC and PT based on Age, Study SYR-322_309	113
Table 43: TEAEs by SOC and PT based on Race, Study SYR-322_309	114
Table 44: TEAEs by SOC and PT based on Sex, Study SYR-322_309	116

Table of Figures

Figure 1: Box plots of dose-normalized C _{max} (left panel) and AUC (0-inf) (right panel) of alogliptin following single oral administration of alogliptin 12.5 or 25 mg in children, adolescents and adults with type 2 diabetes.	29
Figure 2: Summary of pharmacodynamic parameter estimates of DPP-4 Inhibition following a single oral administration of alogliptin 12.5 or 25 mg tablets to children, adolescents and adults with type 2 diabetes.	29
Figure 3: SYR-322_309 Study Design	33
Figure 4: Participant Flow Diagram for Study SYR-322_309.....	46
Figure 5: Time to First Hyperglycemic Rescue Event during Double Blind Treatment Period (full analysis set).....	61
Figure 6: Forest Plot of Subgroup Analyses for Sex, Age and Race: Placebo-adjusted HbA1c (%) Change from Baseline at Week 26, Study SYR-322_309	64
Figure 7: Forest Plot of Subgroup Analyses for Geographic Region, Schedule of Antidiabetic Therapy Status, Ethnicity and COVID-19: Placebo-adjusted HbA1c (%) Change from Baseline at Week 26, Study SYR-322_309	65
Figure 8: HbA1c (%) Change from Baseline by Study Week, Study SYR-322_309.....	67
Figure 9: Hepatocellular DILI Screening Plot through Week 52, Study SYR-322_309.....	95
Figure 10: Hepatic Function Labs for Subject (b) (6) Study SYR-322_309	96
Figure 11: Hepatic Function Labs for Subject (b) (6) Study SYR-322_309	97
Figure 12: Hepatic Function Labs for Subject (b) (6) Study SYR-322_309	98
Figure 13: Hepatic Function Labs for Subject (b) (6) Study SYR-322_309	99

Glossary

AC	advisory committee
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AR	adverse reaction
AST	aspartate aminotransferase
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CEC	clinical event committee
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CMQ	custom MedDRA query
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
CTX	C-terminal telopeptide
DBP	diastolic blood pressure
DKA	diabetic ketoacidosis
DMC	data monitoring committee
DSMB	data safety monitoring board
DPP-4	dipeptidyl peptidase-4
ECG	electrocardiogram
eCTD	electronic common technical document
eGFR	estimated glomerular filtration rate
ETASU	elements to assure safe use
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

FDASIA	Food and Drug Administration Safety and Innovation Act
FPG	fasting plasma glucose
GCP	good clinical practice
GIP	gastric inhibitory polypeptide
GLP-1	glucagon-like peptide-1
GRMP	good review management practice
HbA1c	hemoglobin A1c
HDL	high density lipoprotein
HHF	hospitalization for heart failure
ICH	International Council for Harmonization
IGF-1	insulin-like growth factor 1
IGFBP-3	insulin-like growth factor binding protein 3
IND	Investigational New Drug Application
IR	information request
IRT	interactive response technology
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
LDL	low density lipoprotein
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed models for repeated measures
MI	myocardial infarction
mITT	modified intent to treat
NAFLD	nonalcoholic fatty liver disease
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NGSP	National Glycohemoglobin Standardization Program
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
PeRC	Pediatric Review Committee
PPG	postprandial glucose
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

PP	per protocol
PPI	patient package insert
PPS	per protocol set
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PTE	pretreatment event
RBC	red blood cells
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SE	standard error
SD	standard deviation
SGE	special government employee
SGLT2	sodium glucose co-transporter-2
SMQ	standardized MedDRA query
sNDA	supplemental new drug application
SOC	standard of care
T2D	type 2 diabetes
T1D	type 1 diabetes
TEAE	treatment emergent adverse event
TSH	thyroid stimulating hormone
ULN	upper limit of normal
USPI	U.S. prescribing information
WBC	white blood cells
WR	written request

1. Executive Summary

1.1. Product Introduction

Alogliptin (trade name: Nesina) 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. Alogliptin is available as Nesina tablets (alogliptin, NDA 022271) and Kazano tablets (alogliptin and metformin hydrochloride, NDA 203414)¹. These products are indicated to improve glycemic control in adults with T2D. Pursuant to the Pediatric Research Equity Act (PREA), Takeda ("the Applicant") has conducted a pediatric postmarketing study (Study SYR-322_309) to assess the safety and efficacy of alogliptin for the glycemic control indication in pediatric patients aged 10 years and older with type 2 diabetes. Based on the results of Study SYR-322_309 in which the effectiveness of alogliptin was not demonstrated, the Applicant is not requesting an expansion of the glycemic control indication for Nesina or Kazano to pediatric patients aged 10 years and older. However, the Applicant has submitted proposed updates to the U.S. Prescribing Information (USPI) for Nesina and Kazano to describe the pediatric study results and to fulfill the requirements under PREA.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Effectiveness of alogliptin to improve glycemic control in pediatric patients with T2D was not established in an adequate and well-controlled study. After 26 weeks, treatment with alogliptin did not demonstrate significant improvement in hemoglobin A1c (HbA1c) compared to placebo [placebo-adjusted treatment difference -0.18% (95% CI -0.84 to 0.49; p=0.60).

In addition, Study SYR-322_309 fulfills the Pediatric Research Equity Act Postmarketing Requirements (PMRs) 2009-1, 2007-2 and 2007-3.

1.3. Benefit-Risk Assessment

¹ Alogliptin is also available as Oseni tablets (alogliptin and pioglitazone, NDA 022426), however, the pediatric study requirement under PREA was waived for this product.

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 decades¹, 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 T2D². Treatment options for pediatric T2D have been limited compared to adults, and until recently, only included metformin hydrochloride and insulin products. In the past few years, several injectable glucagon-like peptide-1 (GLP-1) receptor agonists, and recently, drug products containing the sodium glucose cotransporter-2 (SGLT2) inhibitor empagliflozin, were approved for use in pediatric T2D patients. However, there remains an unmet need for additional treatment options for pediatric patients with T2D.

Takeda ("the Applicant") has submitted supplemental new drug applications (sNDAs) for Nesina (alogliptin) and Kazano (fixed dose combination product of alogliptin and metformin hydrochloride) proposing updates to the U.S. Prescribing Information (USPI) to describe the results of a single, adequate and well-controlled pediatric phase 3 study, Study SYR-322_309. Study SYR-322_309 was a 52-week, double-blinded, placebo-controlled study in 151 pediatric T2D subjects aged 10 to 17 years with inadequately controlled T2D [(hemoglobin A1c (HbA1c) 6.5% (or 7.0% for those on insulin) to 11%]. Eligible subjects were randomized in a 1:1 ratio to receive alogliptin 25 mg or matching placebo daily for 52 weeks. The average age was 14.2 years, the average duration of T2D was 1.6 years and the mean HbA1c was 8.1%. The majority of subjects were treated with background metformin (72.9%), 33.1% were treated with insulin, and 19.2% were not on background antidiabetic medication. Approximately 58.3% were white, 16.6% were American Indian or Alaska Native, 21.2% were Black or African American and 20.1% were of Hispanic or Latino ethnicity (however, ethnicity was not reported for 52.3% of study participants). The mean body mass index (BMI) percentile was 96.2%.

The primary efficacy endpoint of Study SYR-322_309 was change from baseline in HbA1c at 26 weeks. Based on the primary efficacy analysis (which was adjusted for treatment assignment, background antidiabetic medication, and baseline HbA1c), treatment with alogliptin did not result in a statistically significant improvement in HbA1c compared to placebo [placebo-adjusted treatment difference -0.18% (95% CI -0.84 to 0.49; p=0.60)]. A large proportion of missing data for the primary endpoint was observed (18.7% for alogliptin, 17.1% for placebo); mean treatment compliance was also < 80% in both treatment arms (78.8% for alogliptin, 72.7% for placebo). Subgroup analyses for age, gender, race, ethnicity, geographic region and background antidiabetic medication were consistent with the primary analysis results. No significant differences were seen in secondary endpoints including HbA1c change at other study weeks or fasting plasma glucose at Week 26.

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

The safety profile of alogliptin in pediatric T2D subjects in Study SYR-322_309 was similar to the known and labeled safety profile in adults with T2D. No deaths occurred in the study. Serious adverse events (SAEs) occurred in 2 (2.7%) subjects treated with alogliptin and in 3 (4.0%) subjects treated with placebo; none were assessed as treatment related. Adverse events of special interest (AESI) were generally consistent with those reported in adult studies, and included hepatic enzyme elevation and infections. No severe hypoglycemia events occurred, and no imbalance in hypoglycemia events was observed with alogliptin treatment as compared to placebo. The majority of the trial population were in advanced puberty at baseline, limiting evaluation of treatment-related effects on growth and puberty.

In summary, the data submitted from Study SYR-322_309 do not support the effectiveness of alogliptin in pediatric T2D patients. Due to larger than anticipated standard deviation and small effect size, the study was underpowered to compare alogliptin to placebo. However, failure to demonstrate superiority of alogliptin to placebo is most likely the result of inadequate efficacy rather than of insufficient sample size. A smaller magnitude of glycemic lowering was observed in pediatric T2D subjects treated with alogliptin as compared to that observed in adults, consistent with the results of other recently completed pediatric T2D studies of dipeptidyl-peptidase-4 (DPP-4) inhibitors. Differences in the demonstrated treatment response in adult and pediatric studies of alogliptin may reflect more rapid disease progression in the pediatric T2D study population.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none">• The prevalence of pediatric type 2 diabetes (T2D) is increasing in the U.S., with racial and ethnic groups that have historically experienced healthcare disparities disproportionately affected.• Although the pathophysiology of T2D is similar to adults, pediatric patients may experience more rapid disease progression and earlier 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.	<p>T2D in the pediatric population is a serious, chronic condition with increasing prevalence that disproportionately affects minority racial and ethnic groups.</p> <p>Pediatric T2D is characterized by more rapid disease progression, accelerated beta cell function decline, and accelerated development of diabetes complications, compared to adults with T2D. Given these differences in disease</p>

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		process between adults and children with T2D, full extrapolation of efficacy from adults is not appropriate.
Current Treatment Options	<ul style="list-style-type: none"> Metformin, insulin, liraglutide, exenatide-extended release, dulaglutide, empagliflozin, and a fixed-dose combination of empagliflozin and metformin, are currently labeled therapeutic options for pediatric T2D. Metformin and empagliflozin are the only available oral therapies. 	There are limited treatment options for pediatric patients with T2D as compared to adults with T2D.
Benefit	<ul style="list-style-type: none"> In Study SYR-322_309, at week 26, treatment with alogliptin did not result in a statistically significant improvement in HbA1c compared to placebo [placebo-adjusted treatment difference -0.18% (95% CI -0.84 to 0.49; p=0.60)]. A large proportion of missing data for the primary endpoint was observed (18.7% for alogliptin, 17.1% for placebo); mean treatment compliance was also < 80% in both treatment arms (78.8% for alogliptin, 72.7% for placebo). Due to larger than anticipated standard deviation and small effect size, the study was underpowered to compare alogliptin versus placebo. Subgroup analyses for age, gender, race, ethnicity, geographic region and background antidiabetic medication were consistent with the primary analysis results. No significant differences were seen in secondary endpoints including HbA1c change at other study weeks or fasting plasma glucose at Week 26. 	Alogliptin 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 to alogliptin are likely due to more rapid disease progression in pediatric T2D subjects.

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	<ul style="list-style-type: none">• No deaths occurred in the study.• SAEs occurred in 2.7% of alogliptin-treated subjects; none were assessed as treatment related. AESIs were consistent with the known safety profile in adults and included hepatic enzyme elevations and infections.• No severe hypoglycemia events occurred, and no imbalance in other hypoglycemia events was observed with alogliptin as compared to placebo.• The majority of the trial population were in advanced puberty at baseline, limiting evaluation of treatment-related effects on growth and puberty.	In Study SYR-322_309, the overall safety profile of alogliptin in pediatric T2D subjects was generally similar to the safety profile adults with T2D that is currently described in the USPI.

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

1.4. Patient Experience Data

This section is not relevant to the application.

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

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

2. Therapeutic Context

2.1. Analysis of Condition

The incidence of pediatric T2D has been increasing over the past 2 decades¹. 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 2060³. 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)⁴. 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^{5,6}. 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 monotherapy⁷. Data from the TODAY study also suggest that some youth with T2D may experience more rapid deterioration of β -cell function as compared to adults⁸, while others may exhibit more durable glycemic control on metformin monotherapy⁹. The predictors of treatment response in pediatric T2D are not fully understood and currently under study. TODAY study participants who failed to maintain glycemic control had significantly lower β -cell function, higher fasting glucose concentration, higher HbA1c at randomization, and higher HbA1c after a short course of metformin compared to those who did not fail^{8,10,11}. Diabetic ketoacidosis at the time of diagnosis of pediatric T2D also appears to predict greater β -cell decline over time¹².

Youth with T2D also have accelerated development of diabetes complications and co-morbidities. Based 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^{2,13}. 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, 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

challenges²Error! Bookmark not defined.

2.2. Analysis of Current Treatment Options

There is an unmet need for additional treatment options for pediatric T2D. Current treatment options (other than insulin) approved for pediatric T2D are listed in Table 1. Glucophage (metformin hydrochloride) was approved for use in pediatric patients aged 10 years and older in 2000². A metformin extended-release product, Riomet ER (metformin hydrochloride extended-release oral suspension), was also approved in 2019 but is no longer marketed. In the past several years, three injectable glucagon-like peptide-1 (GLP-1) receptor agonist products have been approved for use in pediatric T2D: liraglutide (pediatric approval in 2019), exenatide (pediatric approval in 2021) and dulaglutide (pediatric approval in 2022). Up until recently, metformin hydrochloride was the only oral antihyperglycemic agent approved for use in pediatric T2D, however, several oral drug products containing empagliflozin, an SGLT2 inhibitor, were approved for the treatment of pediatric T2D on June 20, 2023. Many other oral antihyperglycemic agents available to adults with T2D (including other SGLT2 inhibitors and the commonly used drug classes of sulfonylureas, DPP-4 inhibitors, and thiazolidinediones) are not approved for use in children. Recent pediatric trials of DPP-4 inhibitors have failed to demonstrate efficacy in pediatric T2D patients, despite the established efficacy in adults. The difference in pediatric versus adult efficacy for DPP-4 inhibitors may relate to the comparatively weaker glycemic lowering of DPP-4 inhibitors (as compared to the GLP-1 receptor agonists and empagliflozin) in the setting of a more progressive underlying disease. 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.

² Glucophage is no longer marketed; however, generic metformin hydrochloride products are available for use in pediatric T2D patients.

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

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	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).	<p><u>Common AEs:</u> diarrhea, nausea, vomiting, flatulence, asthenia, indigestion, abdominal discomfort and headache.</p> <p><u>Warnings/Precautions:</u> lactic acidosis, vitamin B12 deficiency, hypoglycemia with concomitant use with insulin and insulin secretagogues.</p>
Riomet (metformin hydrochloride oral suspension)	2003	No	Dosage: 500 mg twice daily to be increased in 500 mg increments to a maximum of 2000 mg per day in divided doses		
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	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%)	<p><u>Common AEs:</u> nausea, diarrhea, vomiting, decreased appetite, dyspepsia, constipation, and immunogenicity-related events (including urticaria).</p> <p><u>Warnings/Precautions:</u> 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*.</p>
Bydureon (exenatide)	2021	Yes	SC injection, weekly	In a 24-week double-blind,	<u>Common AEs:</u> nausea, diarrhea, vomiting,

CDER Clinical Review Template

Version date: March 8, 2019 for all NDAs and BLAs

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

			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 bydureon 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. <u>Warnings/Precautions:</u> 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 to 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 trulicity arms (0.75 mg and 1.5 mg) versus placebo was -1.4% (95% confidence interval of -1.9% to -0.8%).	<u>Common AEs:</u> nausea, diarrhea, vomiting, abdominal pain, decreased appetite, and injection site reactions (in pediatric patients only). <u>Warnings/Precautions:</u> 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
Jardiance (empagliflozin) and Synjardy (empagliflozin and metformin hydrochloride)	2023	Yes	Oral Jardiance: 10 mg and 25 mg once daily Synjardy: twice daily, 10 to 25 mg total daily dose of empagliflozin; 1000 to 2000 mg total daily dose of metformin	In a 26-week double-blind, placebo-controlled trial of 157 pediatric T2D patients aged 10 years and older, empagliflozin was superior to placebo in reducing HbA1c from baseline to week 26 [placebo-adjusted treatment difference – 0.84% (95% confidence interval -1.50 to -0.19, p=0.0116)].	<u>Common AEs with empagliflozin:</u> urinary tract infection and female genital mycotic infections (>5% of patients), also increased urination, male genital mycotic infections, nausea <u>Warnings/Precautions for empagliflozin:</u> ketoacidosis, volume depletion, urosepsis and pyelonephritis, necrotizing fasciitis of the perineum (Fournier's Gangrene), genital mycotic infections, hypersensitivity reactions, hypoglycemia regardless of concomitant insulin therapy * pediatric patients only

**in adults, increased risk of hypoglycemia was seen only with concomitant insulin or insulin secretagogue therapy.*

CDER Clinical Review Template

Version date: March 8, 2019 for all NDAs and BLAs

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Source: Reviewer Created. Abbreviations: XR, ER= extended release, T2D= type 2 diabetes, FPG= fasting plasma glucose, HbA1c= hemoglobin A1c, AE= adverse events, MTC= medullary thyroid carcinoma, MEN2= multiple endocrine neoplasia type 2, SC= subcutaneous, ANDA= Abbreviated New Drug Application

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Nesina tablets (alogliptin, NDA 022271) and Kazano tablets (alogliptin and metformin hydrochloride, NDA 203414) were approved on January 25, 2013. Both products are indicated as adjuncts to diet and exercise to improve glycemic control in adults with T2D.

3.2. Summary of Presubmission/Submission Regulatory Activity

Pursuant to the PREA, the NDA approval letters for Nesina and Kazano issued on January 25, 2013, specified the following postmarketing study requirements to assess the safety and efficacy of alogliptin for the claimed indication in pediatric patients:

NDA 022271 (Nesina)

PMR 2007-1: A clinical pharmacology study in pediatric patients with T2DM to evaluate the pharmacokinetics (PK) of alogliptin and to determine the dose(s) for the subsequent phase 3 studies that will be conducted under the Pediatric Research Equity Act (PREA) to evaluate the efficacy and safety of alogliptin for the treatment of T2DM in pediatric patients ages 10 to 17 years (inclusive). At least 25% of randomized subjects will be 10 to 13 years of age.

PMR 2007-2: A 52-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of alogliptin when added on to metformin in pediatric patients ages 10 to 17 years (inclusive) with type 2 diabetes mellitus. At least 30% of randomized subjects will be 10 to 14 years of age, and at least one-third and not more than two-thirds of subjects in both age subsets (10-14 years and 15-17 years) will be female.

PMR 2007-3: A 52-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of alogliptin in pediatric patients ages 10 through 17 years (inclusive) with type 2 diabetes mellitus. At least 30% of randomized subjects will be 10-14 years of age, and at least one-third and not more than two-thirds of subjects in both age subsets (10-14 years and 15-17 years) will be female.

NDA 203414 (Kazano)

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

PMR 2009-1: A 52-week, randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of alogliptin when added on to metformin in pediatric patients ages 10 to 17 years (inclusive) with type 2 diabetes mellitus. At least 30% of randomized subjects will be 10 to 14 years of age and at least one-third and not more than two-thirds of subjects in both age subsets (10-14 years and 15-17 years) will be female.

A phase 1, single dose clinical pharmacology study of alogliptin in adult and pediatric subjects with T2D (Study SYR-322_104) was designed to satisfy PMR-2007-1. Following discussions with the Agency, PMRs 2007-2 and 2007-3 (NDA 022271) and PMR 2009-1 (NDA 203414) were combined into a single phase 3 study (Study SYR-322_309) designed to assess the safety and efficacy of alogliptin in the pediatric population.

The clinical study report for the pharmacokinetic (PK) Study SYR-322_102 was initially submitted on June 24, 2014 (see Section 4.5 for details). On December 14, 2014, the Agency issued an information request (IR) requesting subject level electronic data for alogliptin PK and pharmacodynamics (PD) with standard demographic information from Study SYR-322_104. On January 16, 2015 Takeda submitted the requested information; PMR 2007-1 was fulfilled on 21 January 2016.

Key regulatory interactions relating to the design of the phase 3 study SYR-322_309 are presented in Table 2.

Table 2: Key Meetings and Regulatory Interactions Regarding the Pediatric Phase 3 Study SYR-322_309

Date	Meeting/Submission	Comments
October 1, 2013	Written Request issued	The written request specified completion of two clinical studies to evaluate the efficacy and safety of alogliptin monotherapy and alogliptin as an add on to metformin in pediatric patients aged 10 to 17 years with T2D ³ .
December 12, 2014	Written Responses to Type C Meeting Request submitted September 30, 2014	The Agency agreed to the proposed dose (25 mg), proposed patient population (i.e., treatment-naïve subjects, subjects receiving metformin, and subjects receiving metformin in combination with insulin), and HbA1c inclusion criteria (i.e., 6.5% to 10% for subjects on metformin only or treatment naïve subjects and 7 to 11% for subjects on insulin). The Agency recommended that the study design include a double-blind treatment period

³ Following subsequent interactions with the Agency, Takeda opted pursue a single clinical study of alogliptin rather than the two clinical studies specified in the written request. A written request amendment does not appear to have been pursued; and a request for pediatric exclusivity was not submitted with this sNDA.

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

		up to 52 weeks with hyperglycemic rescue starting from day 1, and that the primary efficacy endpoint be assessed at 24 to 26 weeks followed by a blinded placebo-controlled safety extension. The Agency also noted that the proposed sample size (100 patients per arm) may be inadequate to demonstrate differences between treatment and placebo in subsets of subjects receiving alogliptin and metformin versus alogliptin alone. The Agency also recommended that Takeda conduct assessment of swallowability for the alogliptin/metformin combination product, or alternatively, provide a justification for not including an assessment.
March 3, 2015	Advice Letter/Information Request (IR), issued in response to clarifying questions submitted by Takeda on January 16, 2015, in follow up to the Agency's December 12, 2014 Type C Meeting Written Responses	The Agency reiterated/clarified prior advice that the study be adequately powered to demonstrate efficacy of alogliptin administered as monotherapy and alogliptin administered as an add-on to metformin, as required by PMRs 2007-2 and 2007-3 and the Written Request, that hyperglycemia rescue criteria should be in place throughout the study, and that a primary endpoint measured at 24 to 26 weeks is required by PMRs 2007-2, 2007-3 and the October 1, 2013 Written Request, and that a pediatric swallowability assessment or justification for not conducting such an assessment be provided for the alogliptin/metformin combination product.
July 21, 2015	Written Responses to Type C Meeting Request submitted on May 8, 2015	Due to low prevalence of untreated pediatric T2D subjects, Takeda proposed a novel study design evaluating alogliptin as an add-on to standard-of-care (i.e., subjects receiving a background of metformin and/or insulin). The Agency noted that while this study would not satisfy the requirement to assess alogliptin as monotherapy as specified in PMR 2007-3, if during review it is determined that the study provides adequate information to inform use of alogliptin in the pediatric population, it may be possible to release Takeda from the requirement for a second study. The Agency also recommended strengthening the hyperglycemia rescue criteria using more stringent thresholds. The Agency also clarified that an assessment of swallowability of the tablet was no longer necessary.

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

July 31, 2025	Final protocol submission for SYR-322_309.	Protocol title: "A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Alogliptin Compared with Placebo in Pediatric Subjects with Type 2 Diabetes Mellitus"
August 27, 2015	IR regarding protocol SYR0322_309	Agency requested additional clarification regarding the proposed hyperglycemic rescue criteria, including a rationale for selecting a glucose level > 300 mg/dL as the sole level in considering the need for rescue based on a self-monitored blood glucose (SMBG). The Agency raised concerns that this proposed threshold may be too lax, and may also introduce confusion given that SMBGs may include fasting and non-fasting values. The Agency also requested clarification as to whether all measured SMBG values need to be > 300 mg/dL over a 2-day period to meet the proposed criteria for rescue.
May 16, 2016- November 8, 2017	Protocol amendments 1-3 for Study SYR-322_309	See Section 6.1.1 for detailed listing of protocol amendments.
December 4, 2019	Deferral extension granted/Deferral extension denied	<p>The Agency agreed to Takeda's October 25, 2018 request for a deferral extension for PMRs 2007-2 and 2009-1, however the proposed revised milestone due dates were modified by the Agency to align with the timeline in the Written Request, as follows:</p> <ul style="list-style-type: none"> - Study completion: November 2020 - Final report submission: May 2021 <p>A deferral extension was denied for PMR 2007-3 as the current timelines aligned with the timeline in the Written Request.</p>
November 8, 2019	Deferral Extension granted	<p>The Agency agreed to Takeda's September 26, 2019 request for a deferral extension for PMRs 2007-2, 2007-3 and 2009-1. The revised milestone due dates were agreed to as follows:</p> <ul style="list-style-type: none"> - Study completion: October 2021 - Final report submission: April 2022

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

August 14, 2020	Protocol amendment 9 for Study SYR-322_309	See section 6.1.1 for detailed listing of protocol amendments.
November 17, 2020	Deferral extension denied	The Agency denied Takeda's October 21, 2020 request for a deferral extension for PMRs 2007-2, 2007-3 and 2009-1 due to COVID-19 related delays, stating that the request was premature and a new request should be submitted 6 months prior to the current final report submission deadline (April 2022) if still required.
December 10, 2021	Deferral extension granted	<p>The Agency granted Takeda's October 28, 2021 request for a deferral extension for PMRs 2007-2, 2007-3 and 2009-1. The revised milestone due dates were agreed to as follows:</p> <ul style="list-style-type: none">- Study completion: February 2022- Final Report Submission: September 2022

Source: Reviewer Created based on review of DARRTs and regulatory history provided in the submissions

Reviewer Comment: PMR 2009-1 (for Kazano, NDA 203414) and PMR-2007-2 (for Nesina, NDA 022271) both specified a trial evaluating alogliptin as an add-on therapy to metformin; while PMR 2007-3 (for Nesina, NDA 022271) specified a trial evaluating alogliptin monotherapy. During the pediatric phase 3 program development, the Division agreed with the Applicant's proposal not to conduct an alogliptin monotherapy trial because alogliptin was unlikely to be utilized as a monotherapy in clinical practice, and given anticipated recruitment challenges for a second trial. In subsequent communications regarding the PMRs, the timelines for all three pediatric PMRs were unified around a single pediatric phase 3 study, Study SYR-322_309, which was designed to assess the safety and efficacy of alogliptin administered as monotherapy and on the background of metformin and/or insulin. As detailed in Sections 6.1.1 and 6.1.2, Study SYR-322_309 enrolled pediatric subjects who received alogliptin both as monotherapy and as add-on therapy to metformin; in addition, results of exploratory analyses of the primary efficacy results in these subpopulations were consistent with that of the overall trial. Thus, the Division considers the study design adequate to fulfill all three PMRs; the PeRC concurred with the Division's conclusion on June 27, 2023.

3.3. Foreign Regulatory Actions and Marketing History

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

As of April 15, 2023⁴, Alogliptin has been authorized for use as a treatment for T2D in 73 countries and is available in dosages of 6.25 mg, 12.5 mg or 25 mg for oral administration. A fixed-dose combination of alogliptin with metformin has been authorized for use as a treatment for T2D in 68 countries and is available as oral tablets containing either 12.5 mg or 25 mg of alogliptin with either 500 mg, (b) (4) or 1000 mg of metformin.

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

4.1. Office of Scientific Investigations (OSI)

Following consultation with OSI, no sites were found to have any outstanding good-clinical practice (GCP) concerns. Although a high rate of protocol deviations occurred in the study (see Section 6.1.2), the sites with the highest number of protocol deviations only enrolled 1 to 2 subjects, and several sites were international. Since the Applicant is not seeking to expand the indication due to the negative efficacy result, site inspections were not conducted for this application.

4.2. Product Quality

There are no new chemistry, manufacturing and controls (CMC) or sterility data.

4.3. Clinical Microbiology

There are no new data with regard to microbiology information in the submission.

4.4. Nonclinical Pharmacology/Toxicology

There are no new data with regard to pharmacology/toxicology information in the submission.

4.5. Clinical Pharmacology

Study SYR-322_104

Study SYR-322_104 was conducted to meet the clinical pharmacology pediatric assessment as required by PMR 2007-1 in the approval letter for NDA 022271 issued on January 25, 2013. A study report entitled, "A Comparative, Randomized, Open-Label, Multi-center, Single Dose Pharmacokinetic, Pharmacodynamic and Safety Study of Alogliptin (12.5 mg and 25 mg)

⁴ Periodic Benefit-Risk Evaluation report, April 16, 2022 through April 15, 2023, submitted to NDAs for Nesina, Kazano and Oseni.

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

between Children, Adolescents and Adults with Type 2 (Non-Insulin Dependent) Diabetes Mellitus” was submitted on June 24, 2014; additional information requested by the Agency was submitted on January 16, 2015. These submissions were reviewed by Dr. Sang Chung in the clinical pharmacology review submitted on June 26, 2015 under NDA 022271. Findings from Dr. Chung’s review are briefly summarized below.

Single doses⁵ of alogliptin 12.5 mg or 25 mg were administered to adult and pediatric subjects with T2D, who could be treated with stable doses of concomitant metformin. Blood samples and urine for measurement of alogliptin concentrations were collected pre-dose and up to 72 hours post-dose. Blood samples for measurement of DPP-4 inhibition and GLP-1 concentrations were collected pre-dose and up to 24 hours post-dose. A total of 46 participants were enrolled in and completed the study, including 9 subjects aged 10 to < 14 years (5 received alogliptin 12.5 mg, 4 received alogliptin 25 mg), 15 subjects aged 14 to < 18 years (8 received alogliptin 12.5 mg, 7 received alogliptin 25 mg) and 22 adults (all received alogliptin 25 mg). The majority of participants in each age and dosing group were female (71 to 80%).

According to the results, extent of exposure as measured by the maximum concentration (C_{max}) and area under the concentration time curve (AUC (0-inf)) was lower in pediatric subjects than in adult subjects, with differences that ranged from 23% to 29% after a single oral administration of alogliptin 25 mg (Figure 1). The mean apparent clearance of alogliptin after oral administration was 37% higher in pediatric than in adult subjects. Administration of alogliptin resulted in rapid DPP-4 inhibition in both pediatric and adult subjects (Figure 2). The Applicant also simulated steady state PK and PD (DPP-4 inhibition) data in the pediatric and adult patients with T2D using a population PK/PD model built based on data from Study 104. Based on the results, the Applicant concluded that pediatric subjects with T2D require a 25 mg dose of alogliptin to achieve alogliptin exposures and DPP-4 inhibition similar to those in adults with T2D. The Applicant also concluded that there was no meaningful difference in AUC and C_{max} among subject groups or between sexes.

According to Dr. Chung’s review, although exposure tended to be lower following single doses of alogliptin in pediatric subjects as compared to adults, the exposure difference between the two populations was relatively small, and there were no apparent differences in urinary PK characteristics or DPP-4 inhibition. Although Dr. Chung generally agreed with the Applicant’s conclusions, he noted that there are “no clear factor(s) that explain the lower systemic alogliptin exposure in pediatric groups than adults” and that this lowered exposure cannot fully be explained by differences in body weight. Overall, the study was deemed acceptable to satisfy PMR 2007-1 and the results supported evaluating the adult 25 mg dose of alogliptin in the pediatric phase 3 study.

⁵ According to Dr. Chung’s review, single doses were chosen because in adults, alogliptin pharmacokinetics was linear with time and there was no known active metabolite.

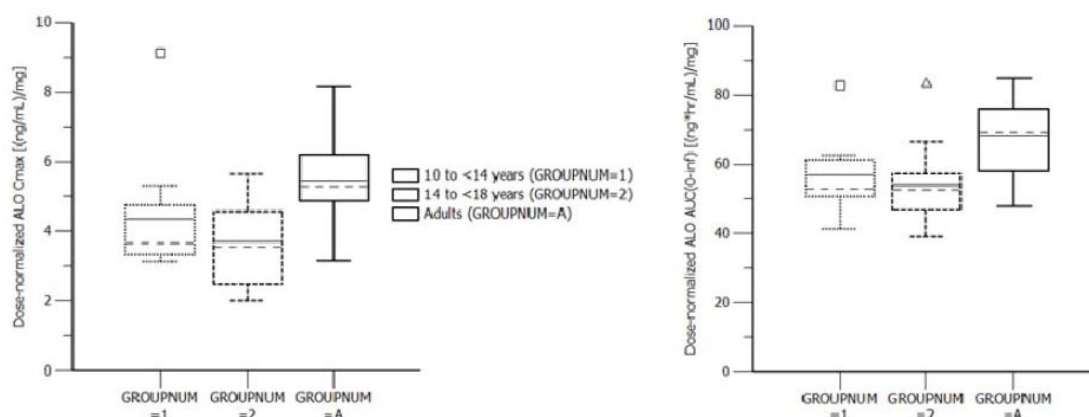
Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Figure 1: Box plots of dose-normalized Cmax (left panel) and AUC (0-inf) (right panel) of alogliptin following single oral administration of alogliptin 12.5 or 25 mg in children, adolescents and adults with type 2 diabetes.



Note: The lower and upper boundaries of the box indicate the 25th and 75th percentiles, respectively; the solid and dashed lines within the box indicate the mean and median, respectively; the whiskers show the lowest data value within 1.5 IQR of the lower quartile, and the highest value within 1.5 IQR of the upper quartile, where IQR is the interquartile range (the difference between the third and first quartiles, the middle 50%).

Source: Adapted from Figure 11.b from CSR for study SYR-322_104.

Figure 2: Summary of pharmacodynamic parameter estimates of DPP-4 Inhibition following a single oral administration of alogliptin 12.5 or 25 mg tablets to children, adolescents and adults with type 2 diabetes.

Treatment	Group	N	Statistic	Time to Emax (hr) (a,b)	Emax (%)	AUEC(0-24) (%·hr)	E24 (%)
ALO 12.5 mg	10 to <14 years	5	Mean	4.05	83.7	1570	52.0
			%CV	2.00, 4.08	5	7	20
	14 to <18 years	7	Mean	4.00	81.6	1558	55.4
			%CV	2.00, 4.03	7	12	16
ALO 25 mg	10 to <14 years	4	Mean	2.08	89.3	1699	57.4
			%CV	2.00, 4.00	3	4	9
	14 to <18 years	7	Mean	4.00	90.4	1854	70.4
			%CV	3.97, 4.12	2	3	8
	Adults	22 (c)	Mean	2.00	92.7	1890	72.8
			%CV	2.00, 4.07	2	4	7

ALO= alogliptin

(a) Median is presented for Time to Emax instead of mean.

(b) Minimum, maximum is presented for Time to Emax instead of %CV.

(c) N=21 for E24.

Source: Adapted from Figure 11.h from CSR for study SYR-322_104.

PK data from Study SYR-322 309

CDER Clinical Review Template

Version date: March 8, 2019 for all NDAs and BLAs

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Population PK Model: According to a population PK analysis conducted by the Applicant using PK data from Study SYR-322_104 and Study SYR-322_309, apparent clearance of alogliptin was 26% lower in adult as compared to pediatric subjects for the two studies. However, the apparent clearance in pediatric subjects from Study SYR-322_104 alone was 21% lower than that estimated in the analysis using data from both studies. Body weight was found to be a significant predictor of alogliptin PK; however other factors including background antidiabetic therapies, sex, race, dose and estimated glomerular filtration rate had no influence on the PK. The predicted exposures in pediatrics were approximately 25% lower than the corresponding exposures in adults for the same doses, consistent with the higher clearance estimated in pediatrics.

Reviewer Comment: Poor adherence to study treatment in study SYR-322_309 (as discussed in Section 6.1.2) could explain the higher apparent clearance in pediatric subjects in the population PK analysis using data from studies SYR-322_309 and SYR-322_104 as compared to the PK analysis using data from SYR-322_104 alone. Though exposure differences were noted between pediatric and adult subjects with T2D, the magnitude of the difference was not considered clinically meaningful (falling within the 80 to 125% bioequivalence criteria) and there was no difference in pharmacodynamic effect based on DPP-4 inhibition. See Dr. Guo's clinical pharmacology review for this supplement for additional details⁶.

4.6. Devices and Companion Diagnostic Issues

This section is not applicable to the submission.

4.7. Consumer Study Reviews

This section is not applicable to the submission.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

⁶ See review submitted on 6/9/2023 under NDA 022271.

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

The primary efficacy and safety data are based on a single adequate and well-controlled phase 3 study, Study SYR-322_309.

5.2. Review Strategy

The primary documents reviewed were submitted under NDAs 022271/S-015 and 203414/S-016. The review of efficacy focused on the Applicant's analyses and confirmatory analyses conducted by the statistician, Dr. Sung Hee Kim. The review of safety was based on analyses of safety data within the submitted datasets and review of the Applicant's safety analyses, where applicable.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study SYR-322_309

6.1.1. Study Design

Overview and Objective

Study Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Alogliptin Compared With Placebo in Pediatric Subjects With Type 2 Diabetes Mellitus

Overview: The purpose of this trial was to evaluate the efficacy and safety of alogliptin 25 mg once daily in pediatric patients aged 10 to 17 years with inadequately controlled type 2 diabetes. Alogliptin was compared to placebo, as monotherapy or when added onto a background of metformin and/or insulin.

Study Objectives:

Primary objective: To evaluate the efficacy of alogliptin 25 mg daily compared to placebo when administered as monotherapy, or when added to a background of metformin alone, insulin alone or a combination of metformin and insulin, as measured by HbA1c change from baseline to week 26 in pediatric subjects with T2DM.

Secondary objectives:

- To evaluate HbA1c change from baseline after treatment with alogliptin as compared with placebo at weeks 12, 18, 39 and 52
- To evaluate the safety of alogliptin as compared to placebo at weeks 26 and 52 with respect to:
 - o Incidence of hypoglycemic events

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

- Treatment-emergent adverse events (TEAEs)
- Clinical laboratory parameters
- Electrocardiogram (ECG) readings
- Physical examinations and vital signs
- Effects on biomarkers of bone turnover (bone specific alkaline phosphatase and C-terminal telopeptide (CTX)
- CD26 surface antigen levels⁷

Exploratory Objectives

- To evaluate clinically meaningful levels⁸ of response to HbA1c at weeks 26 and 52.
- To evaluate 2-hour post-prandial glucose (PPG) at weeks 26 and 52.
- To evaluate incidence and time to hyperglycemic rescue.
- To evaluate fasting plasma glucose (FPG) change from baseline at weeks 12, 26 and 52.
- To evaluate changes from baseline in lipids (including total cholesterol, high- and low-density lipoprotein cholesterol and triglycerides at weeks 12, 26 and 52.
- To evaluate changes in body weight, height, and body mass index (BMI) at weeks 26 and 52.
- To evaluate plasma concentrations of alogliptin using sparse sampling approach.

Study Design

Study SYR-322_309 (Figure 3) was a multicenter, randomized, double-blind, placebo-controlled 52-week study evaluating treatment of alogliptin versus placebo in pediatric subjects aged 10 to 17 years with inadequately controlled type 2 diabetes. At the time of recruitment, subjects may have been naïve to treatment or on background treatment with metformin and/or insulin. During a 2-week screening period, subjects were assessed for eligibility based on inclusion criteria, exclusion criteria and randomization criteria. Subjects who met all eligibility criteria were allowed to proceed directly to randomization, while subjects who did not meet the additional randomization criteria were allowed to enter a pre-randomization stabilization period (further described below). Eligible subjects were randomized in a 1:1 ratio to one of two treatment groups, 25 mg alogliptin daily or a matching placebo for a 52-week double blind treatment period. Randomization was stratified by the background antidiabetic regimen that subjects had received for the 12 weeks prior to the screening period, with treatment-naïve subjects grouped under “Schedule A” and subjects who had receiving metformin and/or insulin grouped under “Schedule B”. Following randomization, doses of background antidiabetic therapy were to be maintained through the first 26 weeks of the double-blind treatment period. During the double-blind treatment period, study visits (in person or via telephone)

⁷ CD26 is another name for DPP-4. This objective relates to an exploratory evaluation of potential immune effects of treatment, by evaluating changes in DPP-4 positive cells in relation to changes in CD4 and CD8 positive T-cells

⁸ “Clinically meaningful levels” of HbA1c response are meant to indicate HbA1c below various glycemic thresholds (i.e., 6.5%, 7.0% and 7.5%) and HbA1c decrease $\geq 0.5\%$ and $\geq 1.0\%$ (see section on Study Endpoints).

Clinical Review

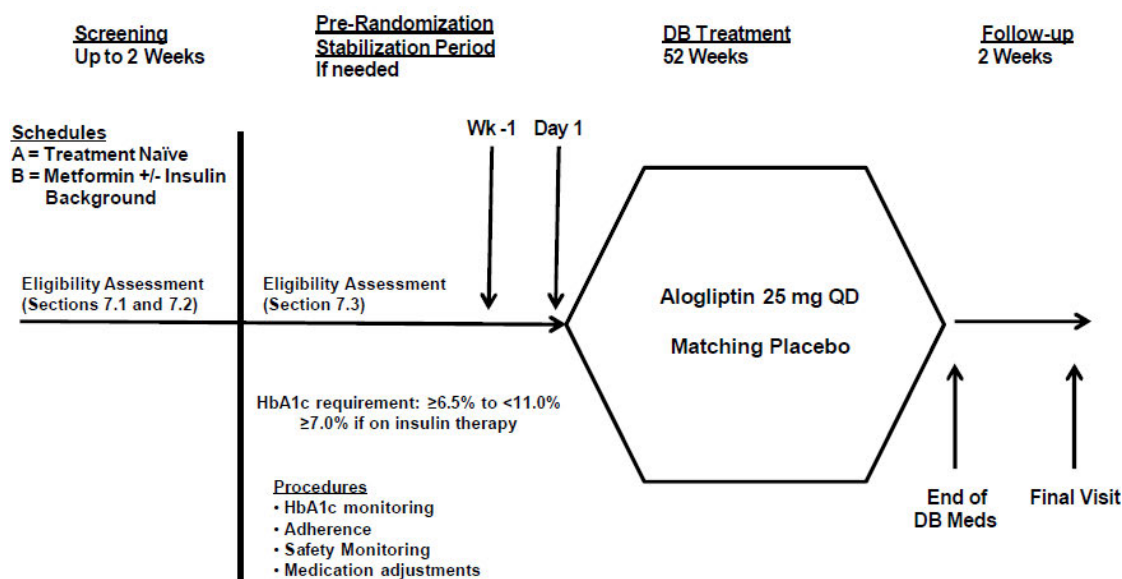
Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

occurred at weeks 4, 12, 18, 26, 32, 39, and 45, followed by an end of treatment visit at week 52. A post-treatment follow-up visit occurred at week 54.

Figure 3: SYR-322_309 Study Design



Abbreviations: DB: double blind; HbA1c: hemoglobin A1c

Source: SYR-322_309 protocol

Pre-Randomization Stabilization Period: The pre-randomization stabilization period was designed to allow for the following:

- Washout of exclusionary medications.
- Adjustment of anti-hypertensive treatment to meet blood pressure eligibility criteria.
- Evaluation of underlying etiology and persistence of elevated alanine aminotransferase (ALT).
- Increase in metformin dose (treatment goal of 1000 mg twice daily or maximum tolerated dose without treatment-related side effects) for metformin-treated subjects who are not already at the maximum tolerated dose for at least 2 months.
- Initiation of insulin therapy in subjects treated with maximally tolerated metformin and HbA1c levels $> 11.0\%$
- Reduction or discontinuation of insulin dose for subjects treated with insulin alone or in combination with maximally tolerated metformin who are able to maintain HbA1c $< 8.0\%$ (stable dose of insulin required before proceeding to randomization).
- Initiation of insulin therapy for subjects with HbA1c $\geq 11\%$ on maximally tolerated

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

- metformin (stable dose of insulin required before proceeding to randomization.
- Exclusion of subjects who exhibit deterioration in glycemic control despite other measures.

During the pre-randomization stabilization period, study visits occurred at least every 3 months and 1 week prior to randomization.

Reviewer Comment: The study was designed to maximize subject enrollment by allowing subjects to enter a pre-randomization stabilization period prior to meeting key eligibility criteria relating to HbA1c and other factors that were required for randomization to study treatment. During the pre-randomization stabilization period, efforts were made to wean subjects off insulin and to maximize metformin treatment; however, insulin initiation was also permitted for subjects who exhibited worsening glycemic control. Despite these measures, less than half of the subjects who entered the pre-randomization period were ultimately randomized for double blind treatment (see Section 6.1.2).

The Applicant's designations of "Schedule A" and "Schedule B" reflect pre-trial antidiabetic therapy, not the background therapy actually received during the double-blind treatment period. According to the protocol, treatment naïve subjects who entered the pre-randomization period may have been initiated on metformin and/or insulin prior to randomization; and subjects who received insulin may have had the insulin dose reduced or discontinued prior to randomization. This issue is further discussed in Section 6.1.2.

Study Location and Administrative Structure: Study SYR-322_309 was conducted across 37 sites in 6 countries, including 22 sites in North America, 1 site in South America, 1 site in the European Union and 13 sites in other countries⁹. An independent data monitoring committee (DMC) comprised of 2 clinicians and a biostatistician with experience in the management of T2D patients and in the conduct and monitoring of randomized clinical trials, was established to review study safety data periodically. Clinical research organizations (CROs) were used to provide study services including site selection, study management and monitoring, data management, statistical and pharmacokinetic analysis.

Key Inclusion Criteria:

- Confirmed diagnosis of T2D based on American Diabetes Association (ADA) and World Health Organization (WHO) criteria
- Able to swallow study medication tablet
- Use of adequate contraception (for female subjects of childbearing potential who are

⁹ United States (22 sites randomized 73 subjects), Brazil (1 site randomized 1 subject), Italy (1 site randomized 1 subject), Israel (1 site randomized 1 subject), Russian Federation (2 sites randomized 3 subjects), Mexico (10 sites randomized 73 subjects).

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

sexually active with a male partner, or for male subjects sexually active with a female partner of childbearing potential).

Key Exclusion Criteria:

- Hypersensitivity or allergy to alogliptin, DPP-4 inhibitors, metformin, insulin or related compounds
- Confirmed diagnosis with type 1 diabetes mellitus or maturity-onset diabetes of the young
- Hemoglobin level < 11.0 g/dL for males or < 10.0 g/dL for females
- History of hemoglobinopathy that may impact HbA1c levels
- History of bariatric surgery
- Proliferative diabetic retinopathy within 6 months prior to Screening
- 1 or more episode of diabetic ketoacidosis (DKA) at any time after T2D diagnosis
- History of > 1 episode of pancreatitis
- Serum creatinine \geq 1.5 mg/dL for males or \geq 1.4 mg/dL for females, or creatinine clearance < 60 mL/min
- Female subjects who are pregnant or planning to become pregnant
- History of human immunodeficiency virus or chronic active viral hepatitis
- History of unstable endocrine, psychiatric or severe rheumatic disorder or major illness or debility that may prohibit study participation/completion or may impact interpretability of efficacy/safety data.

Additional Randomization Criteria (to be met following screening and/or after completion of the pre-randomization stabilization period):

- HbA1c \geq 6.5% or < 11.0% if the subject is treatment naïve or on metformin monotherapy, or \geq 7.0% to < 11.0% if the subject is on insulin alone or in combination with metformin.
- No treatment with any antidiabetic agent other than metformin or insulin within 12 weeks prior to randomization
- No treatment with oral or parenteral steroids for more than 3 weeks (cumulatively) within 6 months prior to randomization or a course of oral or parenteral steroids within the 2 months prior to randomization
- Systolic blood pressure (SBP) < 160 mmHg and diastolic pressure < 100 mmHg (antihypertensive medications allowed)
- Alanine aminotransferase (ALT) < 3 x upper limit of normal (ULN) or ALT < 5x ULN with confirmed diagnosis of nonalcoholic fatty liver disease (NAFLD).
- Male and female subjects, aged 10 to 17 years of age (inclusive) at time of randomization
- For subjects with T2D diagnosis < 1 year or for those who are taking insulin prior to randomization, the following additional criteria must be met:

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

- Fasting C-peptide concentration > 0.6 ng/mL (>0.20 nmol/L) drawn at least 1 week after treatment for ketosis or acidosis, if applicable
- No presence of autoantibodies as documented by glutamic acid decarboxylase (GAD) 65 and islet antigen (IA-2) antibodies below the ULN reference ranges
- Body mass index (BMI) > 85th percentile

Reviewer Comment: Notably, several criteria relating to confirming the diagnosis and expected phenotype of T2D (e.g., presence of pancreatic autoantibodies, elevated BMI, minimum fasting C-peptide concentration) were limited to subjects who were either recently diagnosed or requiring treatment with insulin. Most likely, the rationale for this approach was to minimize additional testing given that subjects who are not treated with insulin > 1 year after diagnosis are less likely to have underlying type 1 diabetes (T1D). However, according to clinical practice guidelines¹⁰, pancreatic autoantibody testing should be done in all youth with the clinical diagnosis of T2D because of the high frequency of islet autoimmunity¹¹. Youth with hyperglycemia and the presence of islet autoantibodies are best classified as having T1D, as the presence of antibodies predicts rapid development of insulin requirement as well as risk for development of other autoimmune disorders.

Dose Selection: The dose of alogliptin used in Study SYR-322_309 (25 mg) was the same dose approved for use in adults with T2D. The selection of the alogliptin 25 mg dose was based on results of Study SRY-322_104, described in Section 4.5,

Study Treatments:

Possible study treatments included alogliptin 25 mg tablets or matching placebo tablets.

Discontinuation Criteria:

Possible reasons for permanent discontinuation of study treatment included:

- Pretreatment event (PTE) or adverse event (AE) that imposed an unacceptable risk to the subject's health or made the subject unwilling to continue study treatment
- Significant protocol deviation (e.g., subject failed to meet protocol entry criteria or did not adhere to the protocol's requirements) such that continued participation posed an unacceptable risk to the subjects' health.
- Lost to follow up.
- Voluntary withdrawal.
- Study termination.

¹⁰ Shah AS, Zeitler PS, Wong J, Pena AS, Wicklow B, Arslanian S, Chang N, Fu J, Dabadghao P, Pinhas-Hamiel O, Urakami T, Craig ME. ISPAD Clinical Practice Consensus Guidelines 2022: Type 2 diabetes in children and adolescents. *Pediatr Diabetes*. 2022 Nov;23(7):872-902. doi: 10.1111/pedi.13409. Epub 2022 Sep 25. PMID: 36161685.

¹¹ 10 to 20% of youth with T2D phenotype have present pancreatic autoantibodies, ISPAD Clinical Practice Consensus Guidelines 2022

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

- Pregnancy
- At the discretion of the principal investigator
- Discontinuation based on changes in liver function (Table 3)
- Pancreatitis withdrawal criteria
 - Suspected pancreatitis, or
 - Serum amylase $\geq 2\times$ ULN, or
 - Serum lipase $\geq 2\times$ ULN
- If a subject did not have renal impairment at screening or randomization and later developed renal impairment confirmed by a repeat test within a maximum of 7 days by a central laboratory AND a creatinine clearance < 60 mL/min (using Schwartz formula¹⁷).

Table 3: Hepatic Function Criteria for Study Treatment Discontinuation in Study SYR-322_309

Subject Baseline Aminotransferases	Criteria for Discontinuation of Study Treatment
Normal or Elevated ALT or AST (all subjects)	<ul style="list-style-type: none">• ALT or AST $> 8 \times$ ULN
Normal ALT and AST	<ul style="list-style-type: none">• ALT or AST $> 5 \times$ ULN and persists for more than 2 weeks• ALT or AST $> 3 \times$ ULN in conjunction with elevated total bilirubin $> 2 \times$ ULN or INR > 1.5• ALT or AST $> 3 \times$ ULN with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia ($> 5\%$)
Elevated ALT or AST	<ul style="list-style-type: none">• ALT or AST $> 5 \times$ ULN AND 2-fold increases above baseline values and persists for more than 2 weeks• ALT or AST $> 5 \times$ ULN AND 2-fold increases above baseline values in conjunction with elevated total bilirubin > 2 ULN or INR > 1.5• ALT or AST $> 5 \times$ ULN AND 2-fold increases above baseline values with appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia ($> 5\%$)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; INR: international normalized ratio; ULN: upper limit of normal.

Source: Study SYR-322_309 protocol

Background Therapy: Metformin and/or insulin were allowed as background antidiabetic therapy during the double-blind portion of the study. Treatment with other antidiabetic agents (including DPP-4 inhibitors or GLP-1 receptor agonists) were not allowed within the 12 weeks before screening and through the completion of the week 52 end-of treatment visit, except for subjects who required hyperglycemic rescue medications. Subjects receiving background metformin or insulin were required to maintain the same dose throughout the first 26 weeks of the double-blind treatment period. Insulin or increased doses of insulin could be provided to treat acute metabolic decompensations but if the supplemental use extended beyond 2 weeks, the subject would be considered to have met the hyperglycemic rescue criteria.

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Reviewer Comment: The protocol stated that doses of background metformin and insulin should remain “stable” prior to the primary endpoint assessment at week 26, but did not provide any further details on how this would be defined for subjects receiving insulin therapy. In their March 31, 2023 response to an Information Request (IR), the Applicant clarified that decisions on specific antidiabetic medications changes were made at the individual investigator’s discretion.

Hyperglycemic Rescue criteria

The following hyperglycemic criteria were used to designate subjects to be rescued with antihyperglycemic agents

- Subjects with HbA1c values <7.0% at the Baseline Visit will be rescued if their HbA1c remains at >8.0% confirmed by a second sample drawn at the next scheduled visit and analyzed by the central laboratory.
- Subjects with HbA1c values > 7.0% at the Baseline Visit will be rescued if their HbA1c values increase by >1.0% as determined by the central laboratory AND confirmed by a second sample drawn at the next scheduled visit and analyzed by the central laboratory.

Reviewer Comment:

The protocol did not specify which antidiabetic agents would be used for hyperglycemic rescue. In their March 31, 2023 response to an IR, the Applicant clarified that specific antidiabetic medications used for hyperglycemic rescue were at the individual investigator’s discretion.

Treatment Compliance

Compliance was calculated based on counts of study medication containers and unused medications at site visits. Compliance (%) was calculated as the (number of tablets dispensed - number of tablets returned)/number of tablets dispensed * 100. The compliance threshold¹² for the Per-protocol set was defined as < 70% or > 124%.

Study Procedures: Subject monitoring was conducted as per the following schedule of events, taken from the protocol:

¹² According to a memo dated April 7, 2022 attached to the statistical analysis plan, it was noticed that the non-compliance threshold defined in the SAP (i.e., <80% or >120%) was inconsistent with that defined in the protocol (i.e., <70% or >125%). The Applicant stated that for consistency, the definition in the protocol was used to define the Per-protocol set.

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Assessment	Screening	Pre-Randomization Stabilization Period (if needed)		Double-Blind Treatment Period Weeks 1- 52 After Randomization (a)								End-of-Treatment Visit	Follow-Up Visit
	Screening Visit (b)	At Least Every 3 Months (b)	Week -1	Baseline Visit (Day 1)	4 (b)	12	18 (c)	26	32 (b)	39	45 (b)	52 (a)	54 (a,b)
Visit windows (days)	(Up to 14 Days)				±2	±7	±7	±7	±7	±7	±7	±7	±2
Informed consent and assent	X												
Inclusion/exclusion	X	X (d)	X (d)										
Demographics; medical history (including medication history and concurrent conditions)	X												
8-hour fast (e)	X		X	X				X				X	
Diabetes education (f)	X	X		X	X	X		X					
Randomization				X									
Complete physical examination	X			X				X				X	
Brief physical examination (g)						X				X			
Vital signs	X	X	X	X		X		X		X		X	
Temperature	X			X								X	
Body weight and height	X			X				X				X	
12-lead ECG	X			X				X				X	
Issue subject diary and glucometer		X (h)		X									
Review diaries and glucometer readings		X	X	X		X		X		X		X	
Review concomitant medications and PTE/AEs	X (i)	X	X	X	X	X		X	X	X	X	X	X(i)
Hematology, serum chemistry	X		X	X		X		X				X	
FPG (j)	X		X	X		X		X				X	
Lipid panel	X			X		X		X				X	
Amylase/lipase (k)				X									
Urinalysis	X			X				X (l)				X	
2-hour PPG (m)				X				X				X	
C-peptide (n)	X		X										

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Assessment	Screening	Stabilization Period (if needed)		Double-Blind Treatment Period Weeks 1- 52 After Randomization (a)								Treatment Visit	-Up Visit
	Screening Visit (b)	At Least Every 3 Months (b)	Week -1	Baseline Visit (Day 1)	4 (b)	12	18 (c)	26	32 (b)	39	45 (b)	52 (a)	54 (a,b)
Visit windows (days)	(Up to 14 Days)				±2	±7	±7	±7	±7	±7	±7	±7	±2
eGFR (o)	X			X				X				X	
HbA1c	X	X	X (p)	X		X	X	X		X		X	
Tanner Stage scoring				X				X				X	
Serum pregnancy test (q)	X			X		X		X				X	
Urine (dipstick) pregnancy test (q)		X	X							X			
PK collection (r)				X		X		X		X			
In-clinic dosing				X		X		X		X (s)		X (t)	
Access IVRS/TWRS	X			X		X		X		X		X	
Dispense blinded study drug (u)				X		X		X		X			
Document drug accountability						X		X		X		X	
CD26 surface antigen				X				X				X	
Biomarker labs (v)				X				X				X	
GAD 65 and/or IA-2 (w)	X		X										
IGF-1 and IGF-BP3				X				X				X	

(a) Subjects who complete the 52-Week double-blind treatment period will complete an End-of-Treatment Visit and Follow-Up Visit, 2 weeks after the last dose of study drug. Subjects who terminate study drug prematurely will complete an End-of-Treatment Visit and a Follow-Up Visit 2 weeks later and will continue to be followed for the 52-Week duration of the study and complete a Projected Week 52 Visit. The same procedures should be conducted at the Projected Week 52 Visit as the End-of-Treatment Visit for subjects who prematurely discontinue the study. For sites not able to conduct onsite visits due to unavoidable circumstances (eg, a widespread disease outbreak such as the COVID-19 pandemic or natural disaster), acceptable alternatives to assess subject safety and overall clinical status may include, but are not limited to, visits as per protocol schedule conducted by delegated site staff speaking directly with the subject by telephone or other medium (eg, a computer-based video communication), or sites may send site staff to subjects to conduct study assessments, contingent upon local regulations.

The End-of-Treatment Visit should be performed in person. Alternative methods of data collection may be considered for this visit when it is not possible for the subject to come to the study site. Under such circumstances, a preferred alternative for the visit would be for site staff to go to the subject's residence and conduct the protocol-specified procedures in that location. Assessments collected at subjects' residence should comply with applicable local regulations. If neither option is available with sponsor or designee approval, sites may conduct end-of-treatment procedures remotely as is feasible.

During contact with the subject by an alternative method, the study site physician or other qualified site staff should also, at minimum, conduct the following assessments within the visit: AE assessments, documentation of concomitant medication, drug accountability, and assessment of clinical symptoms. Other study assessments may be collected remotely as is feasible and may involve audio or video recording. Assessments that cannot be completed during the protocol-specified window will be considered missing data, and such departures will be recorded in the study records. Alternatively, sites may seek approval to extend the visit window up to 3 times the protocol-specified window in order to conduct an onsite visit. The interval between successive visits when clinical laboratory tests and vital sign measurements are performed may not be longer than 8 weeks.

(b) The Screening Visit will be scheduled within 2 weeks prior to Day 1 or prior to the start of the Pre-Randomization Stabilization Period. During the Pre-Randomization Stabilization period, subjects will visit the study center at regular intervals according to the

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

investigator's discretion but at least every 3 months and at Week -1 prior to randomization. The Week 4, 32, 45, and 54 visits will be conducted only via telephone call to the subject. A follow-up visit will be conducted via telephone with the subject 2 weeks after the End-of-Treatment Visit.

(c) The Sponsor or its designee will decide whether the Week 18 Visit will be conducted as an in-clinic visit, or optionally, as a home health visit.

(d) The randomization criteria listed in Section 7.3 will be assessed at the visits before Week -1 and all inclusion and exclusion criteria will be assessed at Week -1 prior to randomization.

(e) Subjects who have had the diagnosis of T2DM for less than 1 year and/or who are taking insulin at the time of randomization will be required to fast for at least 8 hours prior to the Screening or Week -1 visit for the assessment of fasting c-peptide. Subjects who are participating in postprandial glucose testing (refer to section 9.1.9.1) will be required to fast for at least 8 hours prior to the visits indicated in the Schedule of Procedures.

(f) Subjects will be instructed on proper nutrition and exercise, how to recognize signs and symptoms of hypoglycemia, and the use of the glucometer.

(g) The brief physical exam will consist of the following body systems: (1) respiratory system; (2) cardiovascular system;

(3) nervous system (4) dermatologic system; and (5) gastrointestinal system.

(h) During the Pre-Randomization Stabilization Period, the site will supply a glucometer to subjects who do not have one or cannot obtain access to one. Subjects who do not enter the Pre-Randomization Stabilization Period should receive their glucometer (if needed) and diary at the Day 1 Visit.

(i) At the Screening visit, review only concomitant medications. At the Follow-up Visit, review only AEs.

(j) Collected only from those subjects who arrive at the clinic in a fasted state.

(k) Serum amylase and serum lipase to be performed at Day 1 (Baseline Visit) for all subjects, and at an Unscheduled Visit for any subject who experiences persistent nausea and/or vomiting for ≥ 3 days with or without abdominal pain.

(l) The Week 26 urinalysis will only include quantitative assessments.

(m) 2-hour PPG test will be optional and completed on subjects at selected sites only.

(n) Required prior to randomization only for subjects who have had the diagnosis of T2DM for less than 1 year and/or who are taking insulin.

(o) Calculated by the central laboratory.

(p) HbA1c concentration should be $\geq 6.5\%$ to $<11.0\%$ or $\geq 7.0\%$ to $<11.0\%$ if the subject is on insulin. If this criterion is not met, the assessment may be repeated every 3 months.

(q) To be completed on all female subjects. If a urine pregnancy test yields a positive result, a serum pregnancy test must also be collected at the same visit and submitted to the central laboratory for confirmation of results.

(r) A total of five 3 mL pharmacokinetic samples will be collected from each subject during the course of the study. At Baseline (Day 1) and Weeks 12, 26, and 39, one postdose sample will be obtained as instructed in Section 9.1.14.1. At Week 26, one predose trough sample will be obtained approximately 24 to 36 hours after the previous dose of study medication plus 1 sample following dosing in the clinic as instructed in Section 9.1.14.1.

(s) Subjects may be dosed in the clinic if dose was not self-administered at home.

(t) Only subjects participating in PPG testing will be dosed in the clinic at Week 52.

(u) Subjects who meet the criteria for rescue will continue double-blind study medication, and continue to participate in the duration of the study.

(v) The following labs will be collected at Baseline and at Weeks 26 and Week 52/End-of-Treatment: Bone specific alkaline phosphatase and C-terminal telopeptide.

(w) Collected once prior to randomization for subjects who have had the diagnosis of T2DM for less than 1 year and/or who are taking insulin at time of randomization.

Source: Study SYR-322_309 protocol

Study Endpoints

Primary Endpoint:

- HbA1c change from baseline to week 26

Secondary Efficacy Endpoints:

- HbA1c change from baseline at weeks 12, 18, 39 and 52.

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Safety Endpoints:

- Physical examination findings
- Vital sign measurements
- 12-lead ECG abnormalities
- Adverse events (AEs)
- Incidence of infections (total, urinary and respiratory tract infections) and hypersensitivity reactions
- Incidence of hypoglycemia
- Clinical laboratory evaluations (hematology¹³, serum chemistry¹⁴, urinalysis)
- Change from baseline in bone specific alkaline phosphatase and CTX at weeks 26 and 52
- Change from baseline in CD26 surface antigen levels⁷ at weeks 26 and 52.

Exploratory Endpoints:

- Clinical response endpoints including:
 - Incidence of HbA1c $\leq 6.5\%$ at weeks 26 and 52
 - Incidence of HbA1c $\leq 7.0\%$ at Weeks 26 and 52.
 - Incidence of HbA1c $\leq 7.5\%$ at Weeks 26 and 52.
 - Incidence of HbA1c decrease from Baseline $\geq 0.5\%$ at Weeks 26 and 52.
 - Incidence of HbA1c decrease from Baseline $\geq 1.0\%$ at Weeks 26 and 52
- Change from Baseline in 2-hour PPG at Weeks 26 and 52.
- Incidence of and time to hyperglycemic rescue events.
- Change from Baseline in FPG at Weeks 12, 26, and 52.
- Change from Baseline in lipids, including total cholesterol, HDL-C, LDL-C, and triglycerides at Weeks 12, 26, and 52.
- Change from Baseline in body weight at Weeks 26 and 52.
- Change from Baseline in height at Weeks 26 and 52.
- Change from Baseline in BMI Z-scores at Weeks 26 and 52.
- Change from Baseline in Tanner Stage score findings at Weeks 26 and 52.
- Changes from Baseline in microalbuminuria, insulin-like growth factor-1 (IGF-1), and IGF-binding protein 3 (IGFBP-3) at Weeks 26 and 52.
- Evaluation of trough and post-dose plasma concentrations of alogliptin.

¹³ White blood cell count with auto-differential, platelet count, hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin

¹⁴ albumin, alkaline phosphatase, aspartate aminotransferase, blood urea nitrogen, bicarbonate, calcium, magnesium, chloride, creatinine, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, direct bilirubin (only if total bilirubin is elevated), total protein, uric acid, gamma glutamyl transferase, total cholesterol, high density lipoprotein, low density lipoprotein, triglycerides, amylase, lipase, glucose

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Statistical Analysis Plan

The Statistical Analysis Plan (SAP) defined the following analysis sets:

Full Analysis Set (FAS): all randomized subjects who took at least 1 dose of the study medication. The FAS was to be used for the primary efficacy analysis.

Per Protocol Set (PPS): all FAS subjects who had no major protocol deviations. Major protocol deviations included any violations of study inclusion criteria; exclusion criteria 1, 3, 4, 8, 9, 10; drug compliance¹²; receiving incorrect randomized treatment, not completing the Week 26 assessment (including HbA1C value). The PPS was used for supportive analyses of the primary and secondary endpoints.

PK Set: All randomized subjects who had at least one blood draw taken for PK assessments.

Primary efficacy analysis: The Applicant used a mixed model for repeated measure (MMRM)¹⁵ based on FAS for the primary endpoint analysis. A sensitivity analysis of handling dropouts or missing data by washout imputation was also performed using 20 imputed datasets.

Secondary and exploratory efficacy analyses: The Applicant analyzed each secondary endpoint using the MMRM analysis specified for the primary efficacy analysis, along with summary and descriptive statistics. For clinical response endpoints, logistic regression modeling adjusted for incidence, randomized treatment, antidiabetic therapy (yes/no) and baseline HbA1c. The time to the first hyperglycemic rescue event was analyzed using Cox proportional hazards regression modeling, adjusting for baseline HbA1c and antidiabetic therapy (yes/no).

Reviewer Comment: The SAP did not define any specific estimands and did not address how intercurrent events (e.g., hyperglycemic rescue) would be handled for the primary efficacy analysis. For the primary efficacy analysis presented in the CSR, the Applicant excluded subjects who received hyperglycemic rescue and therefore did not utilize the preferred “intention-to-treat” strategy. Additionally, according to Dr. Kim’s primary statistical review, the primary efficacy analysis specified in the SAP is considered insufficient from a regulatory perspective, as MMRM assumes that missing data are missing at random which is unlikely in the context of a clinical trial. The Agency had previously recommended a multiple imputation method instead of MMRM; however, the Applicant did not change the primary analysis method and instead performed placebo washout imputation as a sensitivity analysis. On November 16, 2022, an IR was issued to the Applicant to revise the primary endpoint analysis to use the placebo washout imputation with 100 imputed datasets and to include subjects

¹⁵ In this MMRM model, change from Baseline in HbA1c will be the response variable; randomized treatment, scheduled visit (Weeks 12, 18, 26, 39, and 52), antidiabetic therapy (Y/N also known as Schedule B/A), and visit-by-treatment interaction will be fixed categorical effects; and baseline HbA1c and visit-by-baseline HbA1c interaction will be continuous covariates

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

who received hyperglycemic rescue before week 26. This is discussed further in Section 6.1.2.

Protocol Amendments

The following table lists substantial protocol amendments submitted to the Agency¹⁶:

Date	Amendment Number/Region	Key Changes
May 16, 2016	1/Global	<ul style="list-style-type: none">• Modified study entry criteria including broadening HbA1c and hepatic enzyme criteria to allow for subjects with non-alcoholic fatty liver disease (NAFLD) to be enrolled.• Reduced schedules of assessments to simplify the study design.• Added the pre-randomization stabilization period for subjects who have not yet been stabilized on current antidiabetic therapy or who have not yet met certain entry criteria.• Revisions to guidance for hepatic safety monitoring and withdrawal criteria to reflect potential inclusion of subjects with non-alcoholic fatty liver disease (NAFLD).• Removed assessment of retinopathy via fundus photography, given that diabetic retinopathy may be less likely in pediatric subjects with T2D.• Home glucose management and hyperglycemic rescue language were clarified to allow for individualized glucose management based on the needs of the subject and local guidance.
November 30, 2016	2/Global	<ul style="list-style-type: none">• Removed assessment of dual-energy X-ray absorptiometry scans, as DPP-4 inhibitors were not found to have an impact on bone density in clinical studies.• The length of time for maintenance of stable anti-hyperglycemic therapy during the pre-randomization stabilization period was increased from 1 month to 2 months.• Clarified that inclusion criteria regarding C-peptide, autoantibodies, age and BMI apply at randomization and

¹⁶ Amendment 3 was a non-substantial global amendment with editorial changes and to provide updated contact information. Non-US specific substantial amendments not listed here included amendment 4 (Italy), amendment 5 (Germany), amendment 6 (Germany), amendment 7 (Brazil), amendment 8 (Russia).

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

		<p>that C-peptide, autoantibodies and BMI criteria apply to subjects with the diagnosis of T2D < 1 year and/or who are taking insulin.</p> <ul style="list-style-type: none">• eGFR calculations were modified to be based on the Schwartz formula¹⁷ rather than the Cockcroft-Gault formula.• Increased HbA1c entry criterion to $\geq 7\%$ for subjects on insulin to minimize risk of hypoglycemia with additional therapy.• Added chronic steroid use as an exclusionary medication
August 14, 2020	9/Global	<ul style="list-style-type: none">• Sample size was decreased from 100 subjects per arm to 75 subjects per arm per FDA recommendation given that sample size estimation in the original protocol appeared to be inflated.• Updated measures in the protocol for unavoidable circumstances (including COVID-19).• Added sensitivity analysis excluding subjects affected by COVID-19 to the primary endpoint.

Source: Reviewer created based on DARRTs review, Table A-1 from the status of post marketing study commitments and requirements submitted by the Applicant, and study SYR-322_309 CSR

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant affirms that the studies were conducted in accordance good clinical practice (GCP) standards and considerations for the ethical treatment of human participants.

Financial Disclosure

None of the 182 principal investigators and sub-investigators who participated in the study declared any financial interests or arrangements with the Applicant (see Appendix 13.2).

¹⁷ The bedside Schwartz formula ($\text{eGFR} = 0.413 \times \text{height (cm)} / \text{Serum creatinine (mg/dL)}$) is preferred for estimating eGFR in a pediatric population > 1 year of age.

Clinical Review

Kim Shimy, MD

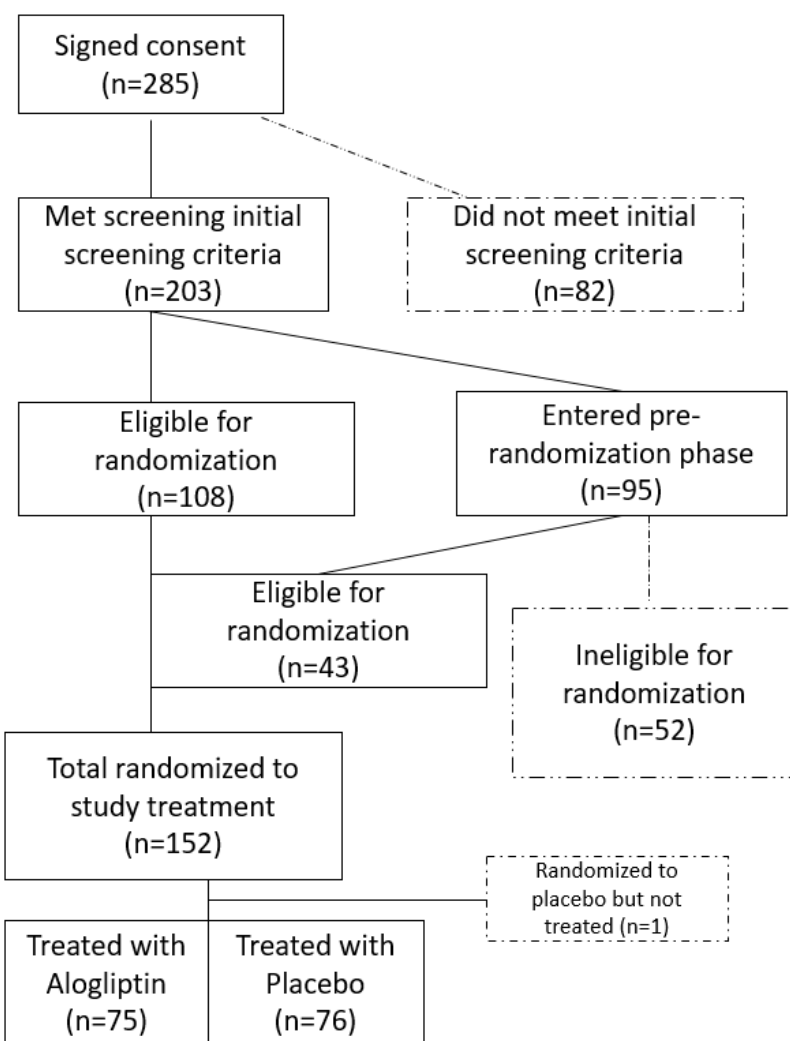
NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Patient Disposition

A total of 285 subjects signed consent, and 152 subjects were randomized to study treatment (see Figure 4). Among the 52 subjects who were excluded following the pre-randomization phase, the most common reason for ineligibility was based on not meeting entrance criteria for the double-blind treatment period (41 subjects, out of which 37 were excluded due to ineligible HbA1c), followed by voluntary withdrawal (5 subjects), loss to follow up (3 subjects), and other unspecified reasons (2 subjects). Of the 37 subjects excluded after the pre-randomization phase due to having an ineligible HbA1c, 17 (45.9%) had an HbA1c above the eligibility range while 20 (54.1%) had an HbA1c below the eligibility range.

Figure 4: Participant Flow Diagram for Study SYR-322_309



Source: Reviewer created

Reviewer Comment: According to the design of Study SYR-322_309, subjects who entered the pre-randomization phase were those who did not meet the “additional randomization criteria” which included the HbA1c eligibility criterion (i.e., HbA1c \geq 6.5 to 11% for subjects not treated with insulin; HbA1c \geq 7 to 11% for subjects treated with insulin). Among subjects who entered the pre-randomization phase, around 50% were eventually excluded due to having too low an HbA1c (i.e., HbA1c < 6.5% for those not treated with insulin and <7.0% for those treated with insulin). As discussed above in Section 2.1, the subset of the pediatric T2D population that exhibits more durable glycemic control appear to have lower baseline HbA1c; these subjects were likely excluded from Study SYR-322_309. Therefore, as a result of the study design feature of the pre-randomization stabilization period, Study SYR-322_309 may have been further enriched with pediatric T2D subjects likely to experience rapid disease progression.

The disposition of randomized and treated subjects is described below in Table 4. The rate of study treatment discontinuation was slightly higher in subjects treated with alogliptin versus placebo (17.3% vs. 15.6% through week 52; 9.3% vs. 5.3% through week 26). Only 36.0% of alogliptin-treated subjects and 23.4% of placebo-treated subjects were in the PPS. Reasons for exclusion from the PPS among are detailed in Table 5. Among treated subjects excluded from the PPS, the most common reason for exclusion was a major protocol deviation. Two (2) subjects in each treatment arm discontinued the study or study treatment due to adverse events; these events are discussed in Section 8.4.3.

Table 4: Disposition of Randomized and Treated Subjects in Study SYR-322_309

	Alogliptin (N=75) n (%)	Placebo (N=76) n (%)
Full analysis set (FAS)	75 (100.0)	76 (100.0)
Per-protocol set (PPS)	27 (36.0)	18 (23.4)
Completed study treatment	62 (82.7)	64 (84.2)
Discontinued study treatment prior to week 52	13 (17.3)	12 (15.6)
Discontinued study prior to week 52	12 (16.0)	10 (13.0)
Discontinued study or study treatment due to an adverse event	2 (2.6)	2 (2.6)

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Discontinued study treatment prior to week 26	7 (9.3)	4 (5.3)
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Source: Reviewer created based on review of *adsl.xpt* dataset and study SYR-322_309 CSR.

Table 5: Reasons for Exclusion from Per-Protocol Set among Treated Subjects, Study SYR-322_309

	Alogliptin 25 mg QD (N=48)	Placebo (N=58)
Drug compliance < 70% or > 125%	2 (4.2)	6 (10.3)
Drug compliance < 70% or > 125%/Not completed Week 26 assessment (including HbA1C value)	1 (2.1)	0
Drug compliance < 70% or > 125%/Subject has titration of antidiabetic therapy while on study treatment	2 (4.2)	2 (3.4)
Not completed Week 26 assessment (including HbA1C value)	4 (8.3)	3 (5.2)
Subject has major protocol violation	17 (35.4)	20 (34.5)
Subject has major protocol violation/Drug compliance < 70% or > 125%	6 (12.5)	10 (17.2)
Subject has major protocol violation/Drug compliance < 70% or > 125%/Not completed Week 26 assessment (including HbA1C value)	0	4 (6.9)
Subject has major protocol violation/Drug compliance < 70% or > 125%/Not completed Week 26 assessment (including HbA1C value)/Subject has titration of antidiabetic therapy while on study treatment	0	1 (1.7)
Subject has major protocol violation/Drug compliance < 70% or > 125%/Subject has titration of antidiabetic therapy while on study treatment	1 (2.1)	3 (5.2)
Subject has major protocol violation/Not completed Week 26 assessment (including HbA1C value)	5 (10.4)	0
Subject has major protocol violation/Subject has titration of antidiabetic therapy while on study treatment	7 (14.6)	3 (5.2)
Subject has titration of antidiabetic therapy while on study treatment	3 (6.2)	6 (10.3)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool.

Columns - Dataset: Demographics; Filter: SAFFL = 'Y', PPROTFL = 'N'.

Table Section 1 - Dataset: Demographics; Filter: SAFFL = 'Y'.

Reviewer Comment: The rate of study treatment discontinuation was slightly higher in alogliptin-treated subjects as compared to placebo-treated subjects. Only 36% of alogliptin-treated subjects and 23.4% of placebo-treated subjects were in the PPS; with most subjects being excluded due to major protocol deviations. Due to the small number of subjects, results from analyses of the PPS are likely to be uninformative; these analyses are not discussed in the review.

Protocol Violations/Deviations

Protocol deviations in treated subjects in study SYR-322_309, as categorized by the Applicant, are detailed below in Table 6. Important protocol deviations occurred in 57.3% of alogliptin-treated subjects and in 61.8% of placebo-treated subjects. The most common category of

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

important protocol deviations in both treatment arms was deviations related to study drug treatment, predominantly relating to poor treatment compliance. The issue of treatment compliance within Study SYR-322_309 is discussed later in this review.

Protocol deviations relating to inclusion criteria in the alogliptin arm included 1 subject who turned 18 years prior to randomization, and 1 subject treated with insulin who was randomized despite having a BMI percentile of 84%. Protocol deviations relating to inclusion criteria in the placebo arm included 1 subject with inappropriately low HbA1c who was subsequently withdrawn from the study, 1 subject who did not have pancreatic autoantibody test results drawn prior to randomization and for whom the IA-2 antibody later tested was noted to be 0.1 U/mL above the reference range, and 1 subject with out-of-range blood pressure due to not taking blood pressure medications on the day of the screening visits. Protocol deviations relating to exclusion criteria occurred in 1 subject in the placebo arm who had more than 1 episode of DKA after diagnosis of T2D. One (1) subject in the placebo arm was initiated on new background antidiabetic therapies including insulin and lixisenatide outside of hyperglycemic rescue. Protocol deviations relating to informed consent occurred with similar frequency in the alogliptin and placebo arms. Two (2) subjects within the alogliptin arm had protocol deviations relating to incorrect stratification relating to schedule A/B. As discussed above, the Applicant's designations of schedule A/B were based on background antidiabetic therapy at screening rather than background antidiabetic therapy at randomization; the Applicant provided additional data regarding background antidiabetic therapy at randomization which is discussed in more detail later in this review. Protocol deviations with respect to the safety assessments occurred with greater frequency in the placebo as compared to the alogliptin arms, mostly related to issues with laboratory testing. Protocol deviations that were described as being related to the COVID-19 pandemic occurred in 3 subjects (4.0%) in the alogliptin arm, and in 7 subjects (9.2%) in the placebo arm¹⁸.

Table 6: Protocol Deviations in All Treated Subjects, Study SYR-322_309

	Alogliptin (N=75)	Placebo (N=76)
Subjects with Non-Important PDs	73 (97.3)	74 (97.4)
Subjects with Important PDs	43 (57.3)	47 (61.8)
Subjects with Important PDs by Category		
01- Inclusion Criteria	2 (2.7)	3 (3.9)
Age > 18	1	
BMI < 85 for subject on insulin	1	
bp out of range		1
Ineligible HbA1c		1
positive pancreatic autoantibody		1

¹⁸ Protocol deviations relating to the COVID-19 pandemic were determined via a manual review and count of the term "COVID" within the description provided in the variable DVTERM within the addv.xpt dataset

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

randomized prior to autoantibody testing		1
02 - Exclusion Criteria		1
> 1 episode DKA since diagnosis		1
03 - Study Drug	20 (26.7)	22 (28.9)
change in background anti-diabetic medication	1	1
compliance < 70%/non-compliance	9	14
compliance > 125%	2	1
no detail provided*	1	1
Issue with study drug storage temperature		1
study drug not taken	4	1
unable to determine compliance/loss of study drug bottles	4	3
04 - Assessment Safety	12 (16.0)	18 (23.7)
glucose monitoring not performed/not reviewed	4	6
hyperglycemic rescue- inappropriate	1	
hyperglycemic rescue-not done		2
hypoglycemia events not recorded	1	
lab not reported/not done/mis-reported	7	10
study drug not taken	1	
study procedures not done		3
05 - Lab/Endpoint Data	3 (4.0)	1 (1.3)
lab not reported/not done/mis-reported	1	1
Lab/study procedures not done	2	
06 - Visit Window	6 (8.0)	5 (6.6)
Lab performed outside of visit window		1
study procedures done outside of visit window	6	4
07 - Informed Consent	11 (14.7)	11 (14.5)
Informed consent for sub-study obtained late		1
Informed consent for sub-study not obtained		1
Informed consent incomplete	4	3
Informed consent obtained late	1	2
Informed consent -other	1	
Informed consent-other	3	5
Not reconsented	3	2
08 - Prohibited Co-Medication		1
new antidiabetic therapy initiated		1 (1.3)
10 - Other	13 (17.3)	9 (11.8)
other- AE recording	1	
other- delayed reporting of SAE	1	
other-delayed assessment of critical lab		1

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

other-stratification	2	
other-study procedures	9	9

*Source: reviewer created based on review of addv.xpt dataset. Categorization of important protocol deviation was performed by the Applicant and recorded within the DVDECOD variable; further classification of protocol deviations within each category was performed by the reviewer based on review of information provided in the DVTERM1 through DVTERM 6 variables. *no information regarding protocol deviation was provided in DVTERM1.*

Reviewer Comment: Important protocol deviations occurred in more than half of enrolled subjects, though the numbers of protocol deviations were generally well balanced between treatment arms. The most common type of protocol deviation was low compliance with study treatment. Overall, there did not appear to be any imbalance in protocol deviations that would materially impact interpretation of study results.

Table of Demographic Characteristics

A summary of the demographic characteristics of the study population is provided in Table 7. The majority of enrolled subjects (68.9%) were female, the mean age was 14.2 years, and 52.3% of enrolled subjects were within the age range of 10 to 14 years. Among subjects aged 10-14 years, 24.1 % were male; among subjects aged 15 to 17 years, 38.9 % were male. With regard to race, 58.2% of subjects were White, 21.2% were Black or African American, and 16.6% were American Indian or Alaska Native. Ethnicity was not recorded for any subjects enrolled outside of the United States (i.e., 52.3% of the study population). Subjects from the United States comprised 47.7% of the study population.

Table 7: Demographic Characteristics of Treated Subjects, Study SYR-322_309

	Alogliptin (N=75)	Placebo (N=76)	Total (N=151)
Age (years)			
Mean (SD)	14.2 (1.92)	14.2 (2.21)	14.2 (2.06)
Median (Min, Max)	14.0 (10, 17)	14.0 (10, 17)	14.0 (10, 17)
Age Range			
10-14 years	40 (53.3)	39 (51.3)	79 (52.3)
> 14 years	35 (46.7)	37 (48.7)	72 (47.7)
Sex			
Female	53 (70.7)	51 (67.1)	104 (68.9)
Male	22 (29.3)	25 (32.9)	47 (31.1)
Race			
AMERICAN INDIAN OR ALASKA NATIVE	11 (14.7)	14 (18.4)	25 (16.6)
ASIAN	0	1 (1.3)	1 (0.7)
BLACK OR AFRICAN AMERICAN	16 (21.3)	16 (21.1)	32 (21.2)
MULTIPLE	4 (5.3)	1 (1.3)	5 (3.3)
WHITE	44 (58.7)	44 (57.9)	88 (58.3)
Ethnicity			
NOT RECORDED	40 (53.3)	39 (51.3)	79 (52.3)
HISPANIC OR LATINO	9 (12.0)	6 (7.9)	15 (9.9)
NOT HISPANIC OR LATINO	26 (34.7)	31 (40.8)	57 (37.7)
Geographic Region			
BRAZIL	1 (1.3)	0	1 (0.7)
ISRAEL	1 (1.3)	0	1 (0.7)
ITALY	0	1 (1.3)	1 (0.7)
MEXICO	36 (48.0)	37 (48.7)	73 (48.3)
RUSSIA	2 (2.7)	1 (1.3)	3 (2.0)
USA	35 (46.7)	37 (48.7)	72 (47.7)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool.
Columns - Dataset: Demographics; Filter: SAFFL = 'Y'. Age (years) - Dataset: Demographics; Filter: None., Age Range 10-14 years - Dataset: Demographics; Filter: AGE = '10' - '14'. Age Range > 14 years - Dataset: Demographics; Filter: AGE = '15' - '17'. Sex - Dataset: Demographics; Filter: None. Race - Dataset: Demographics; Filter: None.
Ethnicity - Dataset: Demographics; Filter: None., Geographic Region - Dataset: Demographics; Filter: None., SD = Standard Deviation.

Reviewer Comment: The demographics of the study population with regard to age and sex (i.e., mean age of around 14 years and majority female) were generally similar to other recently completed pediatric trials of antihyperglycemic therapies. The PREA PMRs 2007-2, 2009-1, and 2007-3 specified the inclusion of at least 30% of subjects aged 10 to 14 years, and that at least one third but not more than two thirds of subjects in both age subsets (10-14 years and 15-17 years) would be female (i.e., at least one third of subjects in both age subsets should be male). In Study SYR-322_309, 24.1 % of subjects aged 10-14 years were male and 38.9 % of subjects aged ≥ 15 years were male, therefore slightly less than one third of subjects were male within the 10-to-14-year age group. The prevalence of pediatric T2D is known to be higher in females as compared to males; additionally, the onset of pediatric type 2

diabetes often coincides with pubertal insulin resistance which may be expected to occur slightly later in males versus females given physiologic differences in the timing of pubertal development. Given these factors, it is not unexpected that a slightly lower percentage of males in the 10-to-14-year age range were enrolled as compared to the 15-to-17-year age range. The percentage of male subjects enrolled in recently completed pediatric T2D trials of other therapeutic agents has ranged from 29 to 38%. Overall, DDLO considers the enrollment of male subjects in Study SYR-322_309 was generally appropriate; the PeRC concurred with this conclusion on June 27, 2023.

With regard to race, 21.2% of the study population were Black or African American, and 16.6% were American Indian or Alaska Native. Ethnicity was not recorded for any non-U.S. subjects; however, among the 72 subjects enrolled from the U.S., 15 subjects (20.8%) were of Hispanic or Latino ethnicity. Based on U.S. prevalence estimates from 2002 to 2017, the representation of ethnic and racial minorities among youths with T2D has increased rapidly, particularly among non-Hispanic black and Hispanic youths¹⁹.

A summary of other baseline characteristics of treated subjects is provided in Table 8. The majority of the study population was obese, with a mean BMI percentile of 96.2%, and 35.1% had BMI percentile > 99%. One (1) subject in each treatment arm had a BMI < 85th percentile (subject (b) (6) in the alogliptin arm, and subject (b) (6) in the placebo arm). Among these subjects, only subject (b) (6) had testing of pancreatic autoantibodies which were negative. Subject (b) (6) did not undergo testing of pancreatic autoantibody or baseline C-peptide; this subject had a baseline HbA1c of 8.0%, was treated with metformin at baseline, and had been diagnosed with T2D for 1 year and 1 month prior to randomization. This subject eventually was initiated on insulin degludec for hyperglycemic rescue at week 4. The majority of the study population were in mid to late puberty based on Tanner staging; this is discussed in more detail in Section 8.8.3.

Table 8: Baseline Characteristics of Treated Subjects, Study SYR-322_309

	Alogliptin (N=75)	Placebo (N=76)	Total (N=151)
Height (cm)			
Mean (SD)	163.1 (8.79)	164.7 (9.54)	163.9 (9.18)
Median (Min, Max)	162.0 (142, 184)	164.0 (144, 187)	163.0 (142, 187)

¹⁹ Lawrence JM et al. Trends in Prevalence of Type 1 and Type 2 Diabetes in Children and Adolescents in the US, 2001-2017. JAMA. 2021;326(8):717-727. Per Supplementary eTable 2, estimated prevalence of T2D per 1000 youth aged 10-14 years in 2017 was 0.10 (white females), 0.03 (white males), 1.36 (black females), 0.60 (black males), 0.51 (Hispanic females), 0.26 (Hispanic males), 0.37 (Asian/pacific islander females), 0.26 (Asian/pacific islander males), 0.70 (American Indian females), 0.57 (American Indian males). Estimated prevalence of T2D per 1000 youth aged 15 -19 years in 2017 was 0.33 (white females), 0.31 (white males), 3.48 (black females), 1.81 (black males), 1.94 (Hispanic females), 1.44 (Hispanic males), 1.09 (Asian/pacific islander females), 0.65 (Asian/pacific islander males), 3.52 (American Indian females), 1.78 (American Indian males).

Clinical Review
Kim Shimy, MD
NDA 022271/S-015, NDA 203414/S-016
Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

	Alogliptin (N=75)	Placebo (N=76)	Total (N=151)
Weight (kg)			
Mean (SD)	90.7 (28.82)	92.2 (26.83)	91.5 (27.75)
Median (Min, Max)	85.4 (54, 185.5)	85.7 (48, 165.9)	85.4 (48, 185.5)
BMI (kg/m2)			
Mean (SD)	33.7 (8.7)	33.6 (7.9)	33.7 (8.2)
Median (Min, Max)	32.4 (18.8, 68.1)	31.2 (20.6, 56.3)	31.7 (18.8, 68.1)
BMI Percentile			
Mean (SD)	95.9 (7.6)	96.5 (4.8)	96.2 (6.4)
Median (Min, Max)	98.4 (39.3, 99.9)	98.4 (68.8, 99.9)	98.4 (39.3, 99.9)
BMI Percentile Categories			
<85%	1 (1.3)	1 (1.3)	2 (1.3)
85% - <95%	19 (25.3)	17 (22.4)	36 (23.8)
95% - <99%	30 (40.0)	30 (39.5)	60 (39.7)
>= 99%	25 (33.3)	28 (36.8)	53 (35.1)
Tanner Stage Genitalia/Breast Score			
1	0	1 (1.3)	1 (0.7)
2	5 (6.7)	3 (3.9)	8 (5.3)
3	11 (14.7)	12 (15.8)	23 (15.2)
4	26 (34.7)	18 (23.7)	44 (29.1)
5	33 (44.0)	41 (53.9)	74 (49.0)
Missing	0	1 (1.3)	1 (0.7)

Source: OCS Analysis Studio, Custom Table Tool., Columns - Dataset: Demographics; Filter: SAFFL = 'Y'. BMI (kg/m2) - Dataset: Demographics; Filter: None.. BMI Percentile - Dataset: Demographics; Filter: None. BMI Percentile Categories - Dataset: Demographics; Filter: None. Tanner Stage Genitalia/Breast Score - Dataset: Demographics; Filter: None., Height (cm) - Dataset: Demographics; Filter: None., Weight (kg) - Dataset: Demographics; Filter: None., SD = Standard Deviation.

Reviewer Comment: The majority of the study population were obese with BMI > 95th percentile. As discussed in Section 6.1.1, several eligibility criteria including BMI > 85th percentile and testing of pancreatic autoantibodies were only required for subjects with T2D duration < 1 year or for subjects treated with insulin prior to study entry. Two subjects (one in each treatment arm) were enrolled with a normal BMI; one of these subjects (in the placebo arm) had negative pancreatic autoantibody testing. The subject with normal BMI in the empagliflozin arm had T2D onset 1 year and 1 month prior to study entry and therefore was not tested for pancreatic autoantibodies; this subject was subsequently initiated on insulin therapy for hyperglycemic rescue 1 month into the trial. However, even if this one subject was misdiagnosed as having T2D, the overall study conclusions are unlikely to have been impacted.

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 9 displays the baseline characteristics relating to T2D²⁰. The mean HbA1c was 8.1% and the mean duration of T2D was 1.6 years. As previously discussed, the Applicant had categorized subjects as Schedule A or Schedule B according to background antidiabetic use at screening. Baseline HbA1c was higher among subjects categorized as Schedule B as compared to Schedule A (mean HbA1c 8.3% vs. 7.2%), likely reflecting more advanced disease in subjects who required background antidiabetic therapy at screening.

As discussed earlier, due to the presence of a pre-randomization stabilization period, background antidiabetic therapy could have changed between screening and randomization. To determine whether the rate of background antidiabetic therapy differed at screening versus randomization, on February 22, 2023, an IR was sent to the Applicant requesting details regarding background antidiabetic use at randomization. Based on the Applicant's response, among subjects designated as "Schedule A" (i.e., treatment naïve at screening), 2 out of 14 subjects in the placebo-arm (14.3%) and 2 out of 13 subjects in the alogliptin arm (15.3%) were actually receiving metformin at the time of randomization; among subjects designated as "Schedule B" (i.e., on background insulin and/or metformin at screening), 3 out of 62 subjects in the placebo arm (4.8%) and 3 out of 62 subjects in the alogliptin arm (4.8%) were actually not receiving any background antidiabetic therapy at the time of randomization.

At randomization, background antidiabetic therapy included metformin alone in 47.7% of subjects, metformin and insulin in 25.2% of subjects, insulin alone in 7.9% of subjects, and 19.2% of subjects did not receive any background antidiabetic therapy. Among subjects receiving background insulin at randomization, the mean total daily dose was 45.5 units/day; 62% of subjects received basal insulin only and 22% received both basal and mealtime insulin. Among subjects treated with background metformin at randomization, 73.6% received a total daily dose of 1500 mg or higher.

The most common concurrent medical conditions (>10%) reported in the study population included obesity (22.5%), asthma (13.9%), attention deficit hyperactivity disorder and acanthosis nigricans (12.6% each) and hypertension (11.3%).

Table 9: Baseline Characteristics Relating to T2D, All Treated Subjects, Study SYR-322_309

	Alogliptin (N=75)	Placebo (N=76)	Total (N=151)
HbA1c (%)			
Mean (SD)	8.2 (1.51)	8.1 (1.33)	8.1 (1.42)
Median (Min, Max)	7.7 (6.3, 11.5)	7.7 (5.7, 11.3)	7.7 (5.7, 11.5)
HbA1c (%) Range (n, %)			

²⁰ Data regarding fasting C-peptide is not displayed; since only subjects who had T2D diagnosed < 1 year or were receiving insulin had C-peptide levels drawn at screening.

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

	Alogliptin (N=75)	Placebo (N=76)	Total (N=151)
≤7.0	23 (30.7)	21 (27.6)	44 (29.1)
>7.0 to < 8.5	26 (34.6)	23 (30.3)	49 (32.5)
≥8.5%	26 (34.7)	32 (46.1)	58 (38.4)
Duration of T2D Diagnosis (years)			
Mean (SD)	1.6 (1.4)	1.5 (1.8)	1.6 (1.6)
Median (Min, Max)	1.3 (5.9, 0.0)	0.8 (7.8, 0.1)	1.1 (7.8, 0.0)
Antidiabetic Therapy at Screening			
Schedule A (treatment naïve at screening)	13 (17.3)	14 (18.4)	27 (17.9)
Schedule B (metformin and/or insulin at screening)	62 (82.7)	62 (81.6)	124 (82.1)
Baseline HbA1c among Schedule B			
Mean (SD)	N=62 8.3 (1.57)	N=62 8.3 (1.28)	N=124 8.3 (1.43)
Median (Min, Max)	8.1 (6.3, 11.5)	8.4 (6.2, 11.3)	8.2 (6.2, 11.5)
Baseline HbA1c among Schedule A			
Mean (SD)	N=13 7.4 (0.87)	N=14 7.1 (1.07)	N=27 7.2 (0.97)
Median (Min, Max)	7.3 (6.3, 9.7)	6.8 (5.7, 10.3)	7.1 (5.7, 10.3)
Antidiabetic Therapy at Randomization			
Insulin only	8 (10.7)	4 (5.3)	12 (7.9)
Metformin and insulin	19 (25.3)	19 (25.0)	38 (25.2)
Metformin only	34 (45.3)	38 (50.0)	72 (47.7)
None	14 (18.7)	15 (19.7)	29 (19.2)
Insulin users (at randomization)			
	N=27	N=23	N=50
Total Daily Insulin Dose (units/day)			
Mean (SD)	40.4 (25.5)	51.4 (39.9)	45.5 (33.0)
Min, Max	13, 150	10, 176	10, 176
Insulin Regimen, n (% of insulin users)			
Basal only	20 (74.1)	11 (47.8)	31 (62.0)
Mealtime only	3 (11.1)	5 (21.7)	8 (16.0)
Basal + mealtime	4 (14.8)	7 (30.4)	11 (22.0)
Metformin users (at randomization)			
	N=53	N=57	N=110
Metformin > 1500 mg/day, n (% of metformin users)	32 (60.4)	40 (70.2)	72 (65.5)
Metformin = 1500 mg/day, n (% of metformin users)	5 (9.4)	4 (7.0)	9 (8.2)
Metformin < 1500 mg/day, n (% of metformin users)	16 (30.2)	13 (22.8)	29 (26.4)

Source: Reviewer Created based on OCS Analysis Studio, Custom Table Tool, HbA1c ranges added by Reviewer based on review of adsl.xpt dataset and Antidiabetic therapy at randomization and details regarding insulin dose, insulin regimen and metformin dose added by Reviewer based on Applicant's submission in response to Agency's IR issued on 2/22/23. Columns - Dataset: Demographics; Filter: SAFFL = 'Y'. HbA1c (%) - Dataset: Demographics; Filter: None.

T2D duration (days) - Dataset: Medical History; Filter: SAFFL = 'Y', MHDECOD = 'Type 2 diabetes mellitus'.

Antidiabetic Therapy - Dataset: Demographics; Filter: None.

SD = Standard Deviation.

Reviewer Comment: The average baseline HbA1c, proportion of subjects within HbA1c ranges, and average duration of T2D were generally similar between treatment arms. Subjects treated with background antidiabetic therapy had a higher baseline HbA1c as compared to subjects who did not receive background antidiabetic therapy; a finding that has

CDER Clinical Review Template

56

Version date: March 8, 2019 for all NDAs and BLAs

been observed in other pediatric T2D trials²¹ and is suggestive of more rapid disease progression at baseline in subjects receiving background antidiabetic therapy. As discussed earlier, the Applicant's designations of "Schedule A" and "Schedule B" reflected antidiabetic therapy at screening. A total of 6 subjects (3 subjects in each treatment arm) designated as Schedule B (i.e., received metformin and/or insulin at screening) actually did not receive any background antidiabetic therapy at randomization, and a total of 4 subjects (2 subjects in each treatment arm) designated as Schedule A (i.e., treatment naïve at screening) had been initiated on background antidiabetic medication at randomization. When considering the background antidiabetic therapy at randomization, 19.2% of the study population received alogliptin as monotherapy and 72.9% of the study population received alogliptin as add-on therapy to metformin.

As discussed in Section 3.2, during the development of the pediatric phase 3 program, the Applicant and DDLO jointly agreed that a separate alogliptin monotherapy trial would not be conducted, due to ongoing recruitment challenges in pediatric type 2 diabetes trials and because alogliptin was unlikely to be used as monotherapy given current standard of care in which metformin is first-line treatment. Given that alogliptin was administered both as monotherapy and as add-on therapy to standard of care in Study SYR-322_309, the Division considers the study design adequate to fulfill all three PMRs; the PerC agreed with the Division's conclusion on June 27, 2023.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

Treatment compliance was assessed as (number of tablets dispensed - number of tablets returned) / ([number of tablets dispensed]*100%).

Through the entire study, the mean (SD) compliance percentage was 78.8% and 72.7% for alogliptin and placebo, respectively. Compliance rates were generally consistent throughout the study, though the mean compliance from weeks 26 to 52 (84.1% in alogliptin and 80.2% in placebo) was higher than from weeks 0 to 26 (77.6% in alogliptin and 71.7% in placebo); which may reflect increased withdrawal or drop-out of subjects with reduced compliance towards the end of the study (Table 10).

Table 10: Study SYR-322_309 Medication Compliance by Study Week

Compliance (%)	Alogliptin 25 mg QD (N = 75)	Placebo (N = 76)
Weeks 0 to 26		

²¹ See primary clinical review for the DINAMO study, under NDA 204629/S-042

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

n	75	76
Mean (SD)	77.56 (11.608)	71.74 (13.872)
Median	77.71	73.43
Minimum, maximum	30.3, 100.0	23.3, 98.9
Weeks 26 to 52		
n	65	66
Mean (SD)	84.10 (16.456)	80.17 (18.193)
Median	86.67	84.76
Minimum, maximum	7.6, 100.0	30.5, 100.0
Week 12		
n	75	76
Mean (SD)	81.05 (12.661)	72.51 (16.304)
Median	80.00	76.67
Minimum, maximum	29.5, 100.0	12.4, 100.0
Week 26		
n	72	73
Mean (SD)	71.40 (18.069)	69.54 (16.439)
Median	70.36	70.00
Minimum, maximum	0.7, 100.0	2.9, 100.0
Week 39		
n	68	71
Mean (SD)	80.85 (16.262)	77.48 (20.203)
Median	85.71	82.86
Minimum, maximum	19.0, 100.0	0.0, 100.0
Week 52		
n	65	66
Mean (SD)	84.10 (16.456)	80.17 (18.193)
Median	86.67	84.76
Minimum, maximum	7.6, 100.0	30.5, 100.0

Source: Applicant submission of 5/19/2023 in response to Agency IR issued on 5/8/2023. Note: Treatment compliance (%) was calculated as (number of tablets dispensed - number of tablets returned) / (number of tablets dispensed)*100.

Reviewer Comment: The mean treatment compliance was < 80% in both treatment arms in Study SYR-322_309, significantly lower than that reported in the pediatric trials of the DPP-4 inhibitors sitagliptin and linagliptin in which the mean treatment compliance was > 90%²². The impact of poor compliance on the primary efficacy results is further discussed below.

²² See primary clinical reviews submitted under NDA 021995/S-047 and NDA 201280/S-027

Concomitant Medications

Background antidiabetic medication at randomization was previously described in Table 9. According to the protocol, the doses of background antidiabetic medication (i.e., metformin and/or insulin) were to remain stable through week 26; unless changes were made for the purposes of hyperglycemic rescue. Table 11 and Table 12 display information regarding changes in background metformin and insulin therapy, respectively, that occurred during the double-blind treatment period, including from weeks 0 to 26 and from weeks 26 to 52.

Through week 26, 1 subject in the alogliptin arm experienced an increase in total daily dose of metformin in the context of hyperglycemic rescue; metformin dose was decreased in 1 subject in the alogliptin arm and in 2 subjects in the placebo arm. Through week 26, the insulin dose was increased in 7 alogliptin-treated subjects and in 3 placebo-treated subjects; these changes were related to hyperglycemic rescue in 5 of the 7 alogliptin-treated subjects and in all placebo-treated subjects. Through week 26, insulin dose was decreased in 2 subjects treated with alogliptin and in 1 subject treated with placebo.

From week 26 to 52, changes in background metformin dose occurred in 6 subjects treated with alogliptin and in 5 subjects treated with placebo; changes in background insulin dose occurred in 16 subjects treated with alogliptin and in 8 subjects treated with metformin. Overall, a greater number of subjects in the alogliptin arm (14 subjects) experienced an increase in the background insulin dose as compared to subjects in the placebo arm (5 subjects).

Table 11: Number of Treated Subjects with Change in Total Daily Dose of Metformin Compared with Total Daily Dose at Randomization, Study SYR-322_309

	Weeks 0 to 26		Weeks 26 to 52	
	Alogliptin (N = 53)	Placebo (N = 57)	Alogliptin (N = 47)	Placebo (N = 53)
Number (%) of treated subjects with increase in total daily dose of metformin compared with total daily dose at randomization	1 (1.9)	0 (0.0)	2 (4.3)	2 (3.8)
Number (%) of treated subjects with increase in total daily dose of metformin compared with total daily dose at randomization, relating to hyperglycemic rescue.	1 (1.9)	0 (0.0)	2 (4.3)	1 (1.9)
Number (%) of treated subjects with decrease in total daily dose of metformin compared with total daily dose at randomization	1 (1.9)	2 (3.5)	4 (8.5)	3 (5.7)

Source: Applicant's analysis, submitted in response to the Agency's IR issued on 3-10-2023

Table 12: Number of Treated Subjects with Change in Total Daily Dose of Insulin Compared to Total Daily Dose at Randomization

	Weeks 0 to 26		Weeks 26 to 52	
	Alogliptin (N = 27)	Placebo (N = 23)	Alogliptin (N = 25)	Placebo (N = 21)
Number (%) of treated subjects with increase in insulin dose ^a compared with insulin dose at randomization	7 (25.9)	3 (13.0)	14 (56.0)	5 (23.8)
Number (%) of treated subjects with increase in insulin dose ^a compared with insulin dose at randomization, relating to hyperglycemic rescue.	5 (18.5)	3 (13.0)	10 (40.0)	4 (19.0)
Number (%) of treated subjects with decrease in insulin dose ^a compared with insulin dose at randomization	2 (7.4)	1 (4.3)	2 (8.0)	3 (14.3)

^aIncrease or decrease in insulin dose defined as > 10% change. Source: Applicant's analysis, submitted in response to the Agency's IR issued on 3-10-2023

Reviewer Comment: Through week 26, few changes in background metformin dose occurred. An increase in insulin dose occurred in 7 alogliptin-treated subjects and in 3 placebo-treated subjects; however, these changes were mostly related to hyperglycemic rescue. Changes in the dose of background metformin and insulin were more frequent from weeks 26 to 52. Notably, a greater number of subjects in the alogliptin arm as compared to the placebo arm (14 vs. 5 subjects, respectively) experienced increases in the background insulin dose from weeks 26 to 52. It is uncertain whether this imbalance in adjustment of background insulin could account for the differences in the estimated treatment effect of alogliptin vs. placebo observed from weeks 26 to 52 (see discussion below) as compared to that observed from baseline to week 26.

Rescue Medication

A total of 39 out of 151 treated subjects received hyperglycemic rescue while on study treatment, including 22 out of 76 subjects in the placebo arm (28.9%) and 17 out of 75 subjects in the alogliptin arm (22.7%). Insulin was predominantly used for hyperglycemic rescue therapy, though metformin was also used in some patients. The majority of subjects who received rescue therapy completed the study. Two (2) subjects in the alogliptin arm who received rescue therapy discontinued the study (one due to an adverse event, another due to pregnancy) and 1 subject in the placebo arm was withdrawn at the discretion of the principal investigator. According to exploratory analyses conducted by the Applicant, no statistically significant differences between treatment groups was observed for the incidence of hyperglycemic rescue events over any time points during the treatment period²³. In addition, no differences were

²³ See section 11.4.2.3.3 of CSR for Study SYR-322_309.

Clinical Review

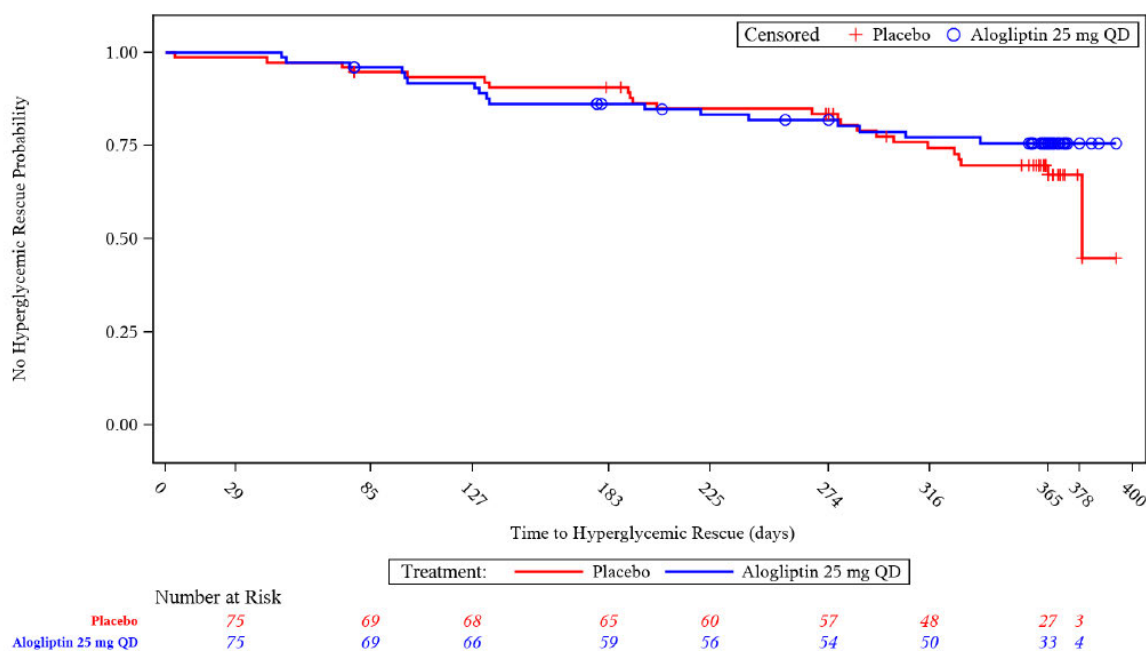
Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

observed for the time to first hyperglycemic rescue event (alogliptin vs placebo hazard ratio [95% CI]: 0.75 [0.40, 1.41]; p-value = 0.370) (Figure 5).

Figure 5: Time to First Hyperglycemic Rescue Event during Double Blind Treatment Period (full analysis set)



Source: Figure 11.b from Study SYR-322_309 CSR; QD: once daily

Reviewer Comment: No significant differences were observed in the rate of rescue therapy in subjects treated with alogliptin as compared to placebo.

Efficacy Results – Primary Endpoint

The primary endpoint was the change in HbA1c (%) from baseline to the end of 26 weeks. As discussed above, the analysis of the primary efficacy endpoint specified in the SAP (i.e., MMRM) was not preferred by the Agency. In the primary efficacy analysis presented in the CSR, Applicant also excluded subjects who had received hyperglycemic rescue which did not reflect the preferred “intention-to-treat” approach. Following an IR issued on November 16, 2022, the Applicant revised the primary endpoint analysis using placebo washout imputation (with 100 imputed datasets) and including subjects who received hyperglycemic rescue prior to week 26. The results of the primary efficacy analysis performed by the statistical reviewer (Dr. Kim), and by the Applicant in response to the November 16, 2022 IR are displayed below in Table 13. The

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

primary analysis was performed with an analysis of covariance (ANCOVA) adjusted for treatment, schedule (A/B), and baseline HbA1c. The efficacy of alogliptin versus placebo was not established, with a non-significant placebo-adjusted treatment effect of -0.18% change in HbA1c from baseline (95% confidence interval -0.84 to 0.49, with p-value of 0.60) according to Dr. Kim's analysis.

Table 13: Primary Efficacy Analysis for HbA1c (%) Change from Baseline to Week 26, Study SYR-322_309

	Alogliptin 25 mg QD N=75	Placebo N=76
Baseline, Mean (SD)	8.16 (1.51)	8.11 (1.33)
Week 26 Missing, n (%)	14 (18.7)	13 (17.1)
Change from baseline to Week 26, LS Mean (SE)	0.02 (0.25)	0.20 (0.23)
Comparison to Placebo ¹		
LS Mean difference (95% CI)	-0.18 (-0.84, 0.49)	
Two-sided P-value	0.60	
Comparison to Placebo ²		
LS Mean difference (95% CI)	-0.12 (-0.75, 0.51)	
Two-sided P-value	0.70	

Source: Dr. Kim's primary statistical review (Table 5). Abbreviations: CI= confidence interval, LS= least square, SD= standard deviations, SE= standard error. Primary efficacy analysis is based on multiple imputation placebo wash-out model. 100 datasets were generated, and each dataset was analyzed with ANCOVA using treatment, schedule (A/B), baseline HbA1c as covariates. The analysis was performed in the mITT using all observed data.

¹ Dr. Kim's analysis ² Applicant's analysis in IR response dated November 30, 2022.

Reviewer Comment: Superiority of alogliptin to placebo was not established based on the primary efficacy analysis. The magnitude of the observed treatment effect (placebo-adjusted HbA1c change of -0.18%) at 26 weeks is comparatively lower than that described in adult studies of alogliptin (placebo-adjusted HbA1c change ranging from -0.4% to -0.6% in various studies of alogliptin including when administered as monotherapy or add-on therapy).

As noted previously, the rate of study treatment compliance in Study SYR-322_309 was <80%. While it is possible that poor compliance may have contributed to the failed efficacy of alogliptin, other studies of DPP-4 inhibitors in pediatric T2D subjects have also failed to demonstrate superiority over placebo with respect to glycemic lowering, with a comparatively lower treatment effect than that demonstrated in adult studies. In pediatric T2D studies of sitagliptin, non-significant placebo-adjusted HbA1c changes of -0.17% (monotherapy study) and -0.33% (add-on therapy study) were observed after 20 weeks of treatment²⁴. In a pediatric T2D study of linagliptin, a non-significant placebo-adjusted HbA1c

²⁴ See primary clinical review under NDA 021995/S-047

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

change of -0.34% was observed after 26 weeks of treatment²⁵. Differences in the demonstrated treatment response in adult and pediatric trials of DPP-4 inhibitors may reflect more rapid disease progression in the pediatric T2D study population.

Dr. Kim also performed a sensitivity analysis for the primary endpoint using the return-to-baseline approach to impute missing data (Table 14), which revealed similar results to the primary efficacy analysis.

Table 14: HbA1c (%) Change from Baseline to Week 26, Sensitivity Analysis, Study SYR-322_309

	Alogliptin 25 mg QD N=75	Placebo N=76
Baseline, Mean (SD)	8.16 (1.51)	8.11 (1.33)
Change from baseline to Week 26, LS Mean (SE)	-0.00 (0.24)	0.16 (0.23)
Comparison to Placebo		
LS Mean difference (95% CI)		-0.16 (-0.82, 0.50)
Nominal two-sided P-value		0.63

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error

Primary efficacy analysis is based on multiple imputation return-to-baseline model. 100 datasets were generated, and each dataset was analyzed with ANCOVA using treatment, schedule (A/B), baseline HbA1c as covariates. The analysis was performed in the mITT using all observed data.

Source: Statistical Reviewer's Analysis

Subgroup Analyses for the Primary Efficacy Endpoint

Dr. Kim conducted subgroup analyses for sex, age (< 14 years vs. ≥14 years) and race (Black/African American vs. White vs. other races) which are displayed in Figure 6; and for geographic region (U.S. vs. non-U.S.), antidiabetic therapy status (Schedule A vs. Schedule B), ethnicity (Hispanic or Latino vs. not Hispanic or Latino) and COVID-19 (Affected vs. Not affected) which are displayed in Figure 7. The subgroup analyses were generally consistent with the overall trial results.

²⁵ See primary clinical review under NDA 201280/S-027

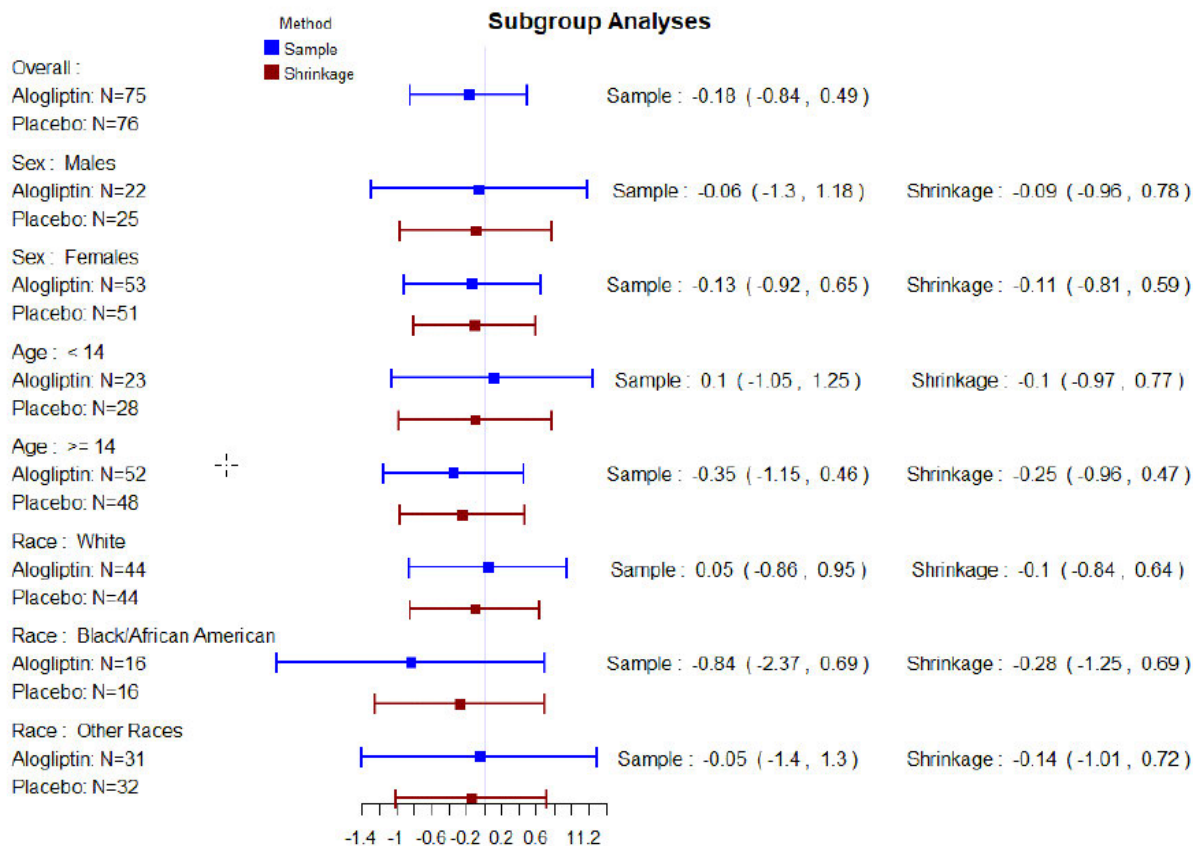
Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Figure 6: Forest Plot of Subgroup Analyses for Sex, Age and Race: Placebo-adjusted HbA1c (%) Change from Baseline at Week 26, Study SYR-322_309



Values on the negative side favor alogliptin, values on the positive side favor placebo.

Other races include American Indian or Alaska Native (n=32), Asian (n=1), or multiple races (n=5). For the American Indian or Alaska Native race, the mean baseline HbA1c was 7.89 and 8.40 for alogliptin (n=16) and placebo (n=16) arms, respectively. The mean change from baseline to Week 26 in HbA1c was 0.35 and -0.07 for alogliptin and placebo arms, respectively. For the multiple races, the mean baseline HbA1c was 7.98 and 7.50 for alogliptin (n=4) and placebo (n=1) arms, respectively. The mean change from baseline to Week 26 in HbA1c was 1.30 and 2.9 for alogliptin and placebo arms, respectively.

Source: Statistical Reviewer's Analysis

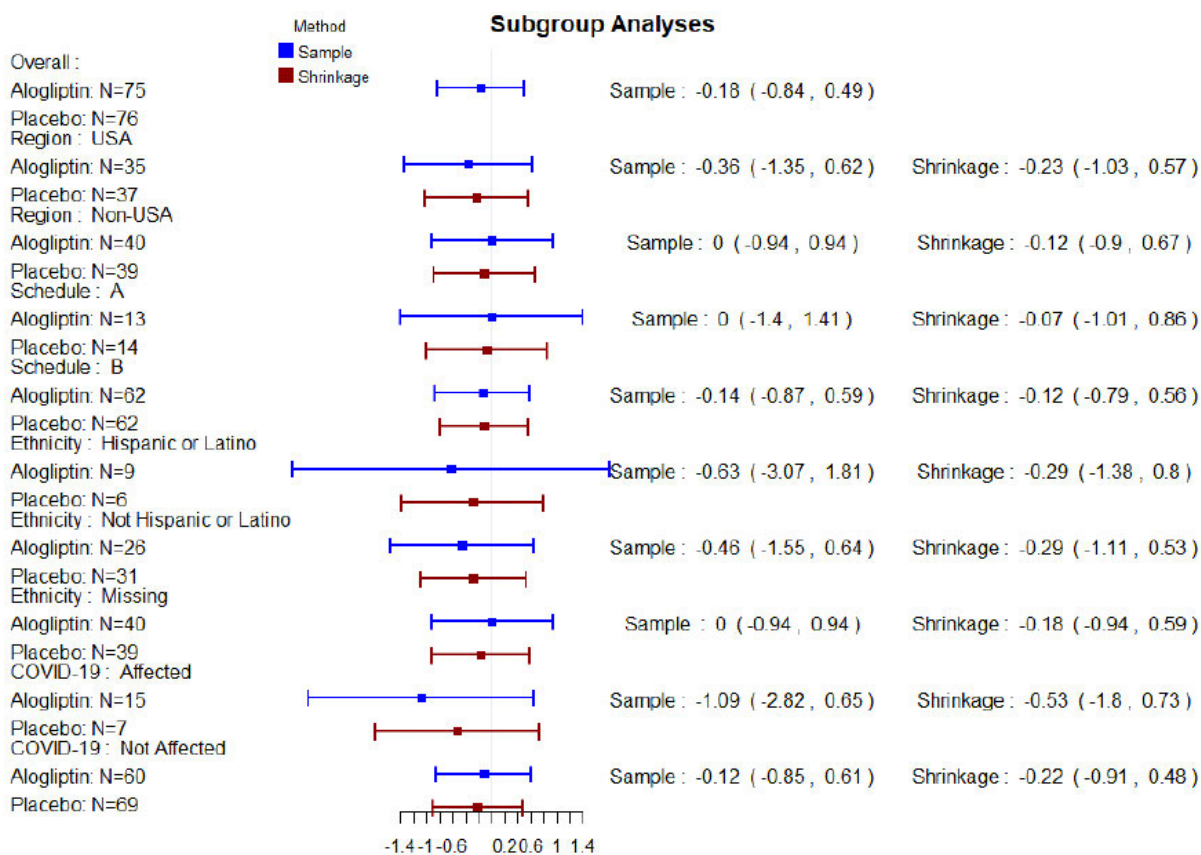
Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Figure 7: Forest Plot of Subgroup Analyses for Geographic Region, Schedule of Antidiabetic Therapy Status, Ethnicity and COVID-19: Placebo-adjusted HbA1c (%) Change from Baseline at Week 26, Study SYR-322_309



Values on the negative side favor alogliptin, values on the positive side favor placebo.

Source: Statistical Reviewer's Analysis

Reviewer Comment: Exploratory subgroup analyses for subjects who received alogliptin as monotherapy versus those who received alogliptin as add-on therapy to metformin and/or insulin were consistent with the primary results for the full study population showing absence of efficacy. The Division considers these analyses adequate to fulfill the PMRs; the PeRC concurred with the Division's conclusions on June 27, 2023.

Data Quality and Integrity

There were no potential issues concerning the submitted data quality or integrity identified during the review of the efficacy results.

Efficacy Results – Secondary and other relevant endpoints

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

The secondary efficacy endpoints included HbA1c (%) change from baseline at week 12, 18, 39 and 52. Dr. Kim's analyses of the secondary efficacy endpoints are detailed in Table 15, and are represented graphically in Figure 8 showing change from baseline in HbA1c by study week. Subjects in both treatment arms experienced a small decrease in HbA1c from baseline to week 12, however HbA1c progressively rose above baseline thereafter in both treatment arms. After week 26, subjects in the placebo arm experienced more rapid rise in HbA1c as compared to subjects in the alogliptin arm, resulting in a non-significant numerical treatment difference of -0.42% and -0.56% at week 39 and week 52, respectively.

Table 15: HbA1c (%) Change from Baseline to Week 12, 18, 29 and 52, Study SYR-322_309

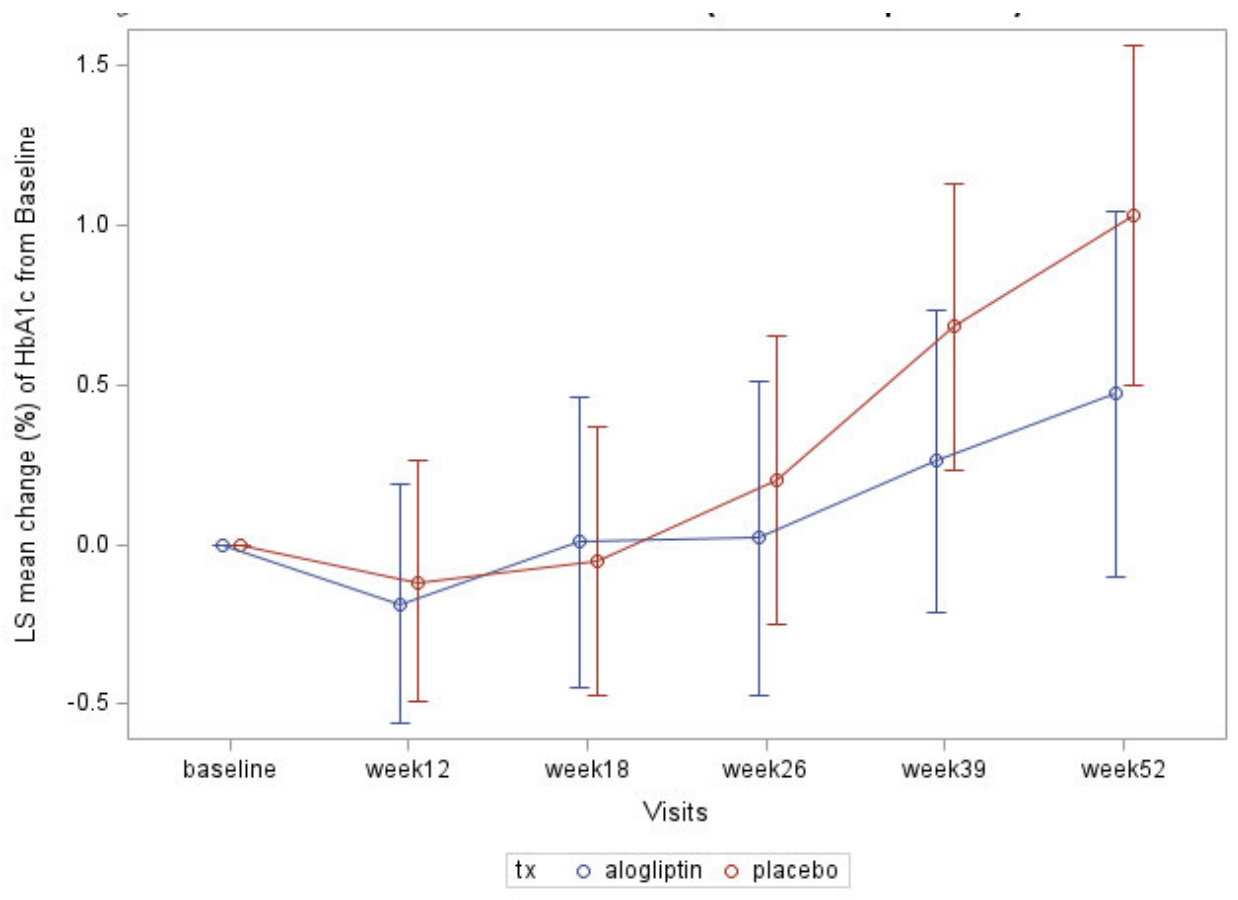
Endpoint		Alogliptin 25 mg QD N=75	Placebo N=76
At Week 12	Change from baseline to Week 12, LS Mean (SE)	-0.19 (0.19)	-0.12 (0.19)
	Comparison to Placebo		
	LS Mean difference (95% CI)		-0.07 (-0.57, 0.43)
	Nominal two-sided P-value		0.78
At Week 18	Change from baseline to Week 18, LS Mean (SE)	0.00 (0.23)	-0.05 (0.22)
	Comparison to Placebo		
	LS Mean difference (95% CI)		0.05 (-0.57, 0.68)
	Nominal two-sided P-value		0.86
At Week 39	Change from baseline to Week 39, LS Mean (SE)	0.26 (0.24)	0.68 (0.23)
	Comparison to Placebo		
	LS Mean difference (95% CI)		-0.42 (-1.07, 0.24)
	Nominal two-sided P-value		0.21
At Week 52	Change from baseline to Week 52, LS Mean (SE)	0.47 (0.29)	1.03 (0.27)
	Comparison to Placebo		
	LS Mean difference (95% CI)		-0.56 (-1.35, 0.22)
	Nominal two-sided P-value		0.16

Abbreviations: CI = confidence interval, LS = least square, SD = standard deviation, SE = standard error

Secondary efficacy analysis is based on multiple imputation placebo wash-out model. 100 datasets were generated, and each dataset was analyzed with ANCOVA using treatment, schedule (A/B), baseline HbA1c as covariates. The analysis was performed in the mITT using all observed data.

Source: Statistical Reviewer's Analysis

Figure 8: HbA1c (%) Change from Baseline by Study Week, Study SYR-322_309



Courtesy: Dr. Sunghee Kim. Abbreviation: LS= least square.

Reviewer Comment: The numerical treatment effect progressively increased at week 39 and 52, which is an unexpected finding. Possible reasons for this pattern are discussed further in the review. However, it is important to note that after week 26, HbA1c increased compared to baseline in both treatment arms; this increase was more pronounced in the placebo arm which resulted in the numerical treatment effect. The progressive rise from baseline in HbA1c among alogliptin-treated subjects (mean HbA1c increase of 0.47% by week 52) does not suggest meaningful glycemic benefit.

The statistical review team conducted exploratory analyses for change from baseline HbA1c beyond week 26 based on Schedule A/B status (i.e., Schedule A: no antidiabetic therapy at screening, vs. Schedule B: metformin and/or insulin at screening), displayed in Table 16. At week 39, the placebo-adjusted treatment effect was 0.02% for Schedule A and -0.44% in Schedule B; at week 52, the placebo-adjusted treatment effect was -0.17% in Schedule A and -

0.60% in Schedule B.

Table 16: HbA1c (%) Change from Baseline to Week 39 and week 52 by Antidiabetic Drug Use at Screening, Study SYR-322_309

	Schedule A		Schedule B	
Endpoint	Alogliptin 25 mg (N=13)	Placebo (N=14)	Alogliptin (N=62)	Placebo (N=62)
HbA1c at Week 39				
LS mean change from baseline (SE)	-0.25 (0.51)	-0.27 (0.41)	0.41 (0.27)	0.85 (0.26)
Placebo adjusted treatment effect (95% CI)	0.02 (-1.28, 1.31)		-0.44 (-1.18, 0.29)	
Nominal P-value	0.98		0.23	
HbA1c at Week 52				
LS mean change from baseline (SE)	-0.66 (0.56)	-0.49 (0.41)	0.74 (0.33)	1.34 (0.32)
Placebo adjusted treatment effect (95% CI)	-0.17 (-1.56, 1.21)		-0.60 (-1.50, 0.31)	
Nominal P-value	0.81		0.20	

Source: Dr. Kim's Mid-Cycle Meeting Slides, analysis conducted using placebo washout imputation by antidiabetic drug use at screening (Schedule A: no antidiabetic drug use at screening, Schedule B: metformin and/or insulin use at screening). CI= confidence interval, SE= standard error, LS= least square.

Reviewer Comment: Exploratory analyses conducted by statistical review team suggested that the nominal difference in mean HbA1c change between alogliptin vs. placebo arm at week 39 and week 52 was driven by the subgroup of patients in Schedule B (i.e., subjects who received metformin and/or insulin at screening). As discussed earlier, subjects in schedule B had higher baseline HbA1c as compared to subjects in schedule A and therefore may have had more progressive disease as baseline. At week 39 and at week 52, all subjects in Schedule B experienced a rise in HbA1c from baseline, however, this rise was more pronounced in Schedule B subjects treated with placebo which resulted in the calculated treatment effect. By Week 52, alogliptin-treated subjects in Schedule B experienced a 0.74% increase in HbA1c from baseline.

As discussed earlier, the protocol required stable dosing of background antidiabetic therapy only through week 26 of the study. However, as presented in Table 12, insulin dose increases (including those unrelated to hyperglycemic rescue) occurred with higher frequency among insulin-treated subjects in the alogliptin arm as compared to the placebo arm from week 26 to 52. Therefore, imbalances in background insulin dosing beyond week 26 in Schedule B subjects represents one possible explanation for the observed numerical treatment effect at Weeks 39 and 52 .

Dr. Kim's analyses of fasting plasma glucose and body mass index score at week 26 also revealed no significant treatment-related differences. With regard to fasting plasma glucose, the least mean square change from baseline to week 26 for alogliptin versus placebo was -3.52 mg/dL (95% confidence interval -26.94 to 19.0, p-value 0.77, see statistical review for further details).

The Applicant's analyses of other exploratory efficacy endpoints using the FAS (including the incidence of HbA1c less than or equal to 6.5%, 7.0%, and 7.5% and HbA1c decrease from baseline $\geq 0.5\%$ and $\geq 1.0\%$ at Weeks 26 and 52, change from baseline in 2-hour post-prandial glucose excursion at weeks 26 and 52 and time to hyperglycemic rescue events) did not reveal any significant differences between alogliptin versus placebo.

Dose/Dose Response

The dose and exposure-response relationship were previously discussed in Section 4.5. As discussed above, the effectiveness of alogliptin 25 mg was not established in the primary efficacy analysis.

Durability of Response

A significant treatment response was not observed at week 26; the numerical increase in treatment response observed beyond week 26 was previously discussed and is unlikely related to alogliptin treatment.

Persistence of Effect

Persistence of effect was not assessed in Study SYR-322_309.

Additional Analyses Conducted on the Individual Trial

No additional analyses were conducted for study SYR-322_309.

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.

7.1.2. Secondary and Other Endpoints

This section is not applicable to the review.

7.1.3. Subpopulations

This section is not applicable to the review.

7.1.4. Dose and Dose-Response

This section is not applicable to the review.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

This section is not applicable to the review.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Current understanding of pediatric T2D suggests that there may be two subgroups of patients, those who are able to achieve durable glycemic control on metformin monotherapy and those who fail to respond to metformin and rapidly develop glycemic failure. As discussed in Section 6.1.2, Study SYR-322_309 may have been enriched with pediatric T2D subjects who were more likely to experience rapid disease progression, as around 50 % of subjects who entered the pre-randomization phase were excluded due to having too low an HbA1c. An unanswered question is whether the efficacy outcome may have been different if alogliptin were studied in the subgroup of pediatric T2D patients who do not develop rapid disease progression. However, given that this subgroup typically achieves an HbA1c well below glycemic treatment goals on metformin monotherapy, there would not be an indication to seek additional treatment unless the patient was unable to tolerate metformin.

7.2.2. Other Relevant Benefits

Up until recently, metformin was the only approved oral antihyperglycemic agent for pediatric

T2D with all other therapeutic options (liraglutide, extended-release exenatide, dulaglutide and insulin) involving subcutaneous injection, which can be a less convenient route of administration in pediatric patients. However, new oral options containing empagliflozin were recently approved for treatment of pediatric T2D, with comparable glycemic efficacy to adults. Considering the risk of rapid disease progression among pediatric T2D patients, additional oral therapies with significant glycemic lowering effect are needed.

7.3. Integrated Assessment of Effectiveness

Study SYR-322_309 was a 52-week, double-blind, randomized, placebo-controlled study in pediatric T2D subjects aged 10 to 17 years with inadequately controlled T2D (HbA1c 6.5% to 11% for those not on insulin, 7.0% to 11% for those on insulin). Eligible subjects were randomized in a 1:1 ratio to receive alogliptin 25 mg or matching placebo daily for 52 weeks.

A total of 151 subjects were treated with either alogliptin (N=75) or placebo (N=76). Background therapies at randomization included metformin alone (47.7%), a combination of metformin and insulin (25.2%), insulin alone (7.9%) or none (19.2%). The mean HbA1c was 8.1% and the mean duration of T2D was 1.6 years. The mean age was 14.2 years and 52.3% were aged 10 to 14 years. Approximately 58.3% were white, 16.6% were American Indian or Alaska Native, 21.2% were Black or African American. Ethnicity was not reported for 52.3% of study participants. The mean body mass index (BMI) percentile was 96.2%.

The primary analysis was performed with an ANCOVA using treatment, antidiabetic therapy (yes/no), and baseline HbA1c as covariates. The efficacy of alogliptin versus placebo was not established, with a non-significant placebo-adjusted treatment effect of -0.18% change in HbA1c from baseline (95% confidence interval -0.84 to 0.49, with p-value of 0.60). Sensitivity analyses, subgroup analyses of the primary endpoint, and exploratory analyses of secondary endpoints were consistent with overall primary efficacy result for alogliptin.

Secondary endpoints included HbA1c change from baseline at Weeks 12, 18, 39 and 52. Based on descriptive analyses, there was a numerical increasing treatment difference of HbA1c change at Week 39 and 52, driven primarily by a larger increase in HbA1c in the placebo arm as compared to the alogliptin arm (HbA1c increase at week 52 of 1.03% in the placebo arm vs. 0.47% in the alogliptin arm). Imbalances in the adjustment of insulin doses between the alogliptin and placebo arms from weeks 26 to 52 may account for this finding. Exploratory analyses did not reveal any imbalances in hyperglycemic rescue between the treatment arms. No clinically meaningful differences were observed in fasting plasma glucose at week 26.

Overall, the evidence from Study SYR-322_309 does not support the effectiveness of alogliptin in pediatric patients with T2D. At 26 weeks, a small, non-significant treatment effect was observed, notably lower than that described in adult studies of alogliptin (HbA1c lowering

ranging from 0.4 to 0.6% in monotherapy and add-on therapies). Due to larger than anticipated standard deviation and smaller effect size, the study was underpowered to compare alogliptin to placebo. However, given the smaller magnitude of treatment effect in the pediatric T2D population, the failure to demonstrate superiority of alogliptin to placebo is most likely the result of inadequate efficacy rather than of insufficient sample size. Differences in the demonstrated treatment response in adult and pediatric trials of alogliptin and other DPP-4 inhibitors may reflect more rapid disease progression in the pediatric trial population.

8. Review of Safety

8.1. Safety Review Approach

The safety of alogliptin has been well-characterized in adult subjects with T2D. In adult studies of alogliptin, the most common adverse events (AEs with > 4% incidence) were nasopharyngitis, headache and upper respiratory tract infection. The USPI for alogliptin-containing products also describes 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 safety review focused primarily on previously identified risks of alogliptin observed in adult studies, but also evaluated for potential risks that may be specific to pediatric patients. For Study SYR-322_309, the Applicant prespecified several AESIs based on the known safety profile of alogliptin, and pediatric-specific safety issues including effects on growth, bone development and puberty.

The safety analysis is based on the 52-week placebo-controlled assessment period. For the safety review of adverse events and selected laboratory data, I conducted my own analysis of the submitted tabulations and datasets using OCS Analysis Studio or JMP 16.0, followed by a review of the Applicant's safety data presented in the CSR to verify the findings in my analyses. For other safety data, I reviewed the Applicant's safety analyses in the CSR (or as provided in response to an information request) and conducted my own analyses from the datasets when appropriate.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The duration of exposure in Study SYR-322_309 is described in Table 17. The mean duration of

Clinical Review
Kim Shimy, MD
NDA 022271/S-015, NDA 203414/S-016
Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

exposure to alogliptin was 41.6 weeks.

Table 17: Study Treatment Exposure, Study SYR-322_309

	Placebo (N = 76)	Alogliptin 25 mg QD (N = 75)
Duration of exposure (weeks)		
n	76	75
Mean (SD)	41.20 (12.248)	41.55 (13.274)
Median	39.90	40.00
Minimum, maximum	0.1, 53.9	0.1, 56.1
Duration of exposure (categorized)		
0 - <12 weeks	3 (3.9)	6 (8.0)
12 - <26 weeks	2 (2.6)	1 (1.3)
≥26 weeks	71 (93.4)	68 (90.7)

Source: Study SYR-322_309 CSR, Table 12.a

8.2.2. Relevant characteristics of the safety population:

The characteristics of the safety population have already been described in Section 6.1.2 (see Table 7, Table 8 and Table 9).

8.2.3. Adequacy of the safety database:

Because the safety profile of alogliptin has been previously evaluated in adults, the exposure and size of the safety database in the DINAMO study is considered generally adequate and is similar to exposures for other recently completed pediatric trials (e.g., liraglutide, extended-release exenatide, dulaglutide, empagliflozin) that supported expanding the indication of these products to pediatric T2D patients aged 10 years and older.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The overall quality of the data submitted was acceptable.

8.3.2. Categorization of Adverse Events

According to the SAP, a pretreatment event (PTE) was defined as any untoward medical occurrence prior to administration of any study medication. An adverse event (AE) was defined as any untoward medical occurrence on or after the first administration date of the study medication. Definitions for severity of PTEs and AEs included mild (transient event easily

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

tolerated by the subject), moderate (the event causes subject discomfort and interrupts the subject's usual activities) and severe (the event causes considerable interference with the subject's usual activities). Worsening or complications of PTEs occurring after administration of study medication were recorded as AEs. A treatment emergent adverse event (TEAE) was defined as any untoward medical occurrence whose onset date is on or after the first study drug dose date through the 14 days after last dose of study drug. AE verbatim reported terms were coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.

Reviewer comment: Based on the adae.xpt dataset, 12 AEs occurring on day 1 of study treatment were flagged as treatment-emergent events, but were also described as "pretreatment events". Since the definition of treatment-emergent adverse events did not incorporate whether the event occurred prior to or following study drug administration, events that occurred prior to study drug administration but on the same day of the first study drug appear to have been classified as treatment-emergent.

The protocol-specified criteria for defining SAEs included any untoward medical occurrence that at any dose

1. Results in death
2. Is life threatening
3. Requires inpatient hospitalization or prolongation of existing hospitalization
4. Results in persistent or significant disability or incapacity
5. Is a congenital anomaly or birth defect
6. Is an important medical event that
 - a. Requires intervention to prevent criteria 1-5 above
 - b. May expose the subject to danger even if the event is not immediately life-threatening or fatal or does not result in hospitalization
 - c. Includes any event or synonym described in the Takeda medically significant AE list²⁶.

PTEs that fulfilled any of these criteria were also considered SAEs.

Prespecified adverse events of special interest (AESIs) included serious hepatic abnormalities, pancreatitis, infections (including urinary tract infections), and severe hypersensitivity reactions including angioedema, anaphylaxis and Stevens-Johnson syndrome.

²⁶ Acute respiratory failure/acute respiratory distress syndrome, torsade de pointes/ventricular fibrillation/ventricular tachycardia, malignant hypertension, convulsive seizure, agranulocytosis, aplastic anemia, toxic epidermal necrolysis/Stevens-Johnson syndrome, neuroleptic malignant syndrome/malignant hyperthermia, spontaneous abortion/stillbirth and fetal death, hepatic necrosis, acute liver failure, anaphylactic shock, acute renal failure, pulmonary hypertension, pulmonary fibrosis, confirmed or suspected endotoxin shock, confirmed or suspected transmission of infectious agent by a medicinal product, COVID-19-related-disease, COVID-19 pneumonia

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Reviewer Comment: Although not specified in the SAP or protocol, the Applicant appears to have classified other AEs occurring simultaneously with the prespecified AESIs also as AESIs (e.g., For an AESI of “alanine aminotransferase increased” that occurred on day 180 in Subject (b) (6) a simultaneous AE of “blood glucose increased” that also occurred on Day 180 was classified and reported as an AESI). This issue is discussed further in Section 8.4.4.

Hypoglycemia events were defined as follows:

Mild to Moderate Hypoglycemia Criteria:

Blood glucose <60 mg/dL (3.33 mmol/L) in the presence of symptoms, or

Blood glucose <50 mg/dL (2.78 mmol/L) with or without symptoms.

Severe Hypoglycemia Criterion:

Any episode requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions, associated with a documented blood glucose <60 mg/dL (3.33 mmol/L) (unless the clinical situation makes obtaining a blood glucose difficult [eg, it involves coma or seizure]).

Reviewer Comment: The definitions of hypoglycemia events used in Study SYR-322_309 are not consistent with current American Diabetes Association (ADA) definitions of hypoglycemia events²⁷. The ADA definition for severe (Level 3) hypoglycemia is similar to that used in Study SYR-322_309 but does not require a documented blood glucose < 60 mg/dL. The definitions used in Study SYR-322_309 for mild hypoglycemia (blood glucose < 60 mg/dL with symptoms) and moderate hypoglycemia (blood glucose < 50 mg/dL with or without symptoms) together likely provided a reasonable representation of ADA Level 2 events (defined as blood glucose < 54 mg/dL). However, Study SYR-322_309 likely did not adequately capture ADA Level 1 events (defined as blood glucose ≥54 mg/dL and < 70 mg/dL). ADA Level 1 events are typically used as an alert value at which patients should take action to avoid continued decline in blood glucose and for that reason may not be as clinically relevant as ADA Level 2 and Level 3 events. Overall, the definitions for hypoglycemia used in Study SYR-322_309 are likely adequate to capture clinically meaningful hypoglycemia events.

8.3.3. Routine Clinical Tests

Clinical laboratory tests monitored during Study SYR-322_309 are detailed below. Laboratory

²⁷ According to ADA, Level 1 hypoglycemia is glucose < 70 mg/dL and >54 mg/dL; Level 2 hypoglycemia is glucose < 54 mg/dL, Level 3 hypoglycemia is a severe event characterized by altered mental and/or physical status requiring assistance. *ADA Glycemic Targets: Standards of Medical Care in Diabetes- 2022. Diabetes Care. 2022 Jan 1:45 (Suppl 1): S83-S96*

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

testing was monitored according to the schedule detailed in Section 6.1.2.

Table 18: Clinical Laboratory Testing in Study SYR-322_309

Hematology	Serum Chemistry	Urinalysis (a)
White blood cell count with autodifferential	Albumin	Qualitative:
Platelet count	Alkaline phosphatase	Appearance
Hemoglobin	Alanine aminotransferase	Color
Hematocrit	Aspartate aminotransferase	pH
Red blood cell count	Blood urea nitrogen	Specific gravity
Mean corpuscular volume	Bicarbonate	Ketones
Mean corpuscular hemoglobin	Calcium	Protein (albumin)
Mean corpuscular hemoglobin concentration	Magnesium	Glucose
Other	Chloride	Nitrite
HbA1c	Creatinine	Urobilinogen
CD26 surface antigen	Lactate dehydrogenase	Blood
Bone specific alkaline phosphatase	Phosphorus	Quantitative: (e)
CTX	Potassium	Albumin
FPG (b)	Sodium	Creatinine
	Total bilirubin	Albumin/creatinine ratio
	Direct bilirubin (only if Total bilirubin is elevated)	
	Total protein	
	Uric acid	
	GGT	
	Lipid panel (total cholesterol, high-density lipoproteins, low-density lipoproteins (direct), and triglycerides) (c)	
	Serum amylase (d)	
	Serum lipase (d)	
	Glucose	
Diagnostic Screening:		
Serum	Urine	
C-peptide (f)	hCG	
hCG	(female subjects) (g)	
(female subjects) (g)		
eGFR (h)		
2-hour postprandial glucose (i)		
IGF-1 (j)		
IGF-BP3 (j)		
GAD 65 (f)		
IA-2 (f)		

hCG=human chorionic gonadotropin.

(a) It is recommended that a follow-up urine culture be obtained within 7 days of clinical recovery from all urinary tract infections.

(b) Collected only from those subjects who arrive at the clinic in a fasted state. Always drawn in a separate tube for this study.

(c) Collect only at the visits specified in the schedule of assessments

(d) Serum amylase and serum lipase to be performed at Day 1 (Baseline Visit) for all subjects and at an

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Unscheduled Visit for any subject who experiences persistent nausea and/or vomiting for ≥ 3 days with or without abdominal pain.

(e) The Week 26 urinalysis will only include quantitative assessments.

(f) Collected once prior to randomization only in subjects who have had the diagnosis of T2DM for less than 1 year

and/or who are taking insulin.

(g) To be completed on all female subjects. If a urine pregnancy test yields a positive result, a serum pregnancy test must also be collected at the same visit and submitted to the central laboratory for confirmation of results.

(h) Calculated at Screening and Baseline and at Weeks 26 and 52 by the central laboratory using the Schwartz formula.

(i) Select sites only.

(j) Collected at Baseline and at Weeks 26 and 52.

Source: Study SYR-322_309 protocol

8.4. Safety Results

8.4.1. Deaths

No deaths occurred in Study SYR-322_309.

8.4.2. Serious Adverse Events

In total, there were 16 SAEs reported by the Applicant. Of these, 4 SAEs were not considered relevant to the safety analysis, including 2 pre-treatment SAEs (dyslipidemia and asthma exacerbation) and 2 post-treatment SAEs of hyperglycemia and ketonuria that occurred more than 3 months after discontinuation of study drug in a single subject. After excluding these events, a total of twelve (12) treatment-emergent SAEs occurred in 5 subjects, including 5 SAEs in 2 alogliptin-treated subjects, and 7 SAEs in 3 placebo-treated subjects. A summary of these SAEs is provided in Table 19.

Table 19: Treatment-emergent SAEs in Study SYR-322_309

System Organ Class - Preferred Term	Alogliptin 25 mg QD	Placebo
	(N=75) n (%)	(N=76) n (%)
Infections and infestations	1 (1.3)	1 (1.3)
Cellulitis	0 (0.0)	1 (1.3)
Periorbital cellulitis	0 (0.0)	1 (1.3)
Septic shock	1 (1.3)	0 (0.0)
Injury, poisoning and procedural complications	1 (1.3)	2 (2.6)
Forearm fracture	0 (0.0)	1 (1.3)
Gunshot wound	1 (1.3)	0 (0.0)
Lip injury	0 (0.0)	1 (1.3)

CDER Clinical Review Template

Version date: March 8, 2019 for all NDAs and BLAs

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

System Organ Class - Preferred Term	Alogliptin 25 mg QD (N=75) n (%)	Placebo (N=76) n (%)
Metabolism and nutrition disorders	1 (1.3)	0 (0.0)
Diabetic ketoacidosis	1 (1.3)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (1.3)
Knee deformity	0 (0.0)	1 (1.3)
Nervous system disorders	1 (1.3)	0 (0.0)
Brain oedema	1 (1.3)	0 (0.0)
Psychiatric disorders	0 (0.0)	1 (1.3)
Suicidal ideation	0 (0.0)	1 (1.3)
Vascular disorders	1 (1.3)	1 (1.3)
Hypertensive urgency	0 (0.0)	1 (1.3)
Hypovolemic shock	1 (1.3)	0 (0.0)

Source: Reviewer generated in OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Alogliptin 25 mg QD" and SAFFL = "Y" (Alogliptin 25 mg QD); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" and AESER = "Y" (Adverse Events).

Narratives for SAEs that occurred in alogliptin-treated subjects were reviewed and are summarized below.

SAEs occurring in Alogliptin-treated subjects:

- Subject (b) (6) SAEs of **gunshot wound, septic shock, hypovolemic shock** occurred in a 14-year-old- Caucasian male subject with T2D and congenital hypothyroidism. Approximately 10 months and 24 days after starting study treatment with alogliptin, he sustained a gunshot wound to the chest and was hospitalized during which time he had removal of 70 cm of bowel, lost 2 liters of blood and was found to have electrolyte imbalance and peritonitis. Study drug was discontinued at that time. Two days later he had septic shock and hypovolemic shock that was classified as grade IV.

Reviewer Comment: These SAEs appear unrelated to study treatment with alogliptin.

- Subject (b) (6) SAEs of **brain edema and diabetic ketoacidosis (DKA)** occurred in a 14-year-old Caucasian male subject with T2D, high blood pressure and coarctation of the aorta who was treated with insulin glargine, insulin lispro, metformin, losartan, and cholecalciferol at baseline. The subject's baseline HbA1c was 7.2%, which had risen to 9.2% by week 12 and to 15.5% on week 18 (day 127). On (b) (6) (study day 105) he developed a headache unresponsive to acetaminophen or ibuprofen, as well as nausea, vomiting, hyperglycemia and moderately high ketones. The study medical officer on call administered Lantus, Humalog, metformin and the study drug. Ketones had declined to small-trace the next day, but vomiting and headache had continued. After 3 to 4 days of vomiting, (b) (6) the subject presented to the emergency

room with a blood glucose of 750 mg/dL, pH of 7.13, bicarbonate 14, and elevated BUN/creatinine (38/2.19), moderate serum and urine ketones. According to the reports, no insulin doses had been missed, although the narrative states that noncompliance cannot be fully ruled out. Normal saline bolus as administered, and the subject was started on intravenous fluids and IV insulin drip (0.05 U/kg/hr). About 3 to 4 hours after arrival to the emergency room, the subject developed altered mental status (intermittent decreased consciousness) and complained of severe headache. A subsequent head computed tomography (CT) showed diffuse mild cerebral edema. Hypertonic saline was administered, and intravenous (IV) antibiotics were given for presumed sepsis though were subsequently discontinued after negative blood and urine cultures. He was transited back to his home regimen (b) (6) and was discharged 2 days later following resolution of headaches and normalization in BUN/creatinine. On (b) (6) the subject was withdrawn from study treatment at the principal investigator's discretion.

Reviewer Comment: Based on the subject's HbA1c trend during the study, which markedly increased from 7.2% at baseline to 15.5% by week 18, non-compliance with background antidiabetic medications, including insulin, appears likely prior to the onset of these SAEs. The subject appears to have met diagnostic criteria for DKA given the report of hyperglycemia, ketones and acidosis, however the severity of acidosis would be categorized as moderate based on the pH of 7.13²⁸. Additionally, other features including marked hyperglycemia (blood glucose > 600 mg/dL) and significant volume depletion (as evidenced by the elevated BUN and creatinine consistent with acute kidney injury) are somewhat more consistent with hyperglycemic hyperosmolar state (HHS). Cerebral edema has been described in 1% of episodes of DKA in children, and has also been reported in some cases of HHS²⁹. Risk factors for the development of cerebral edema in children include severe acidosis and increased BUN at presentation. According to the narrative, although only moderate acidosis was present, this subject had significant elevation in BUN (38). The narrative does not report the rate or composition of IV fluids administered following the normal saline bolus to correct fluid deficits upon the subject's initial presentation to the emergency room. The role of intravenous fluids in causing or contributing to the risk of cerebral edema and cerebral injury in children with DKA has been a source of controversy, however, recent studies have suggested no difference in neurologic outcomes when fluid deficits between 5 to 10% of body weight are replaced over 24 to 48 hours using fluids with a sodium content between 0.45% to

²⁸ Glaser N, Fritsch M, Priyambada L, et al. ISPAD Clinical Practice Consensus Guidelines 2022: Diabetic Ketoacidosis and Hyperglycemic Hyperosmolar State. *Pediatr Diabetes* 2022.

²⁹ Glaser N, Barnett P, et al; Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. Risk factors for cerebral edema in children with diabetic ketoacidosis. *The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. N Engl J Med.* 2001 Jan 25;344(4):264-9. doi: 10.1056/NEJM200101253440404. PMID: 11172153.

0.9% NaCl³⁰. Although the pathogenesis of DKA-related cerebral injury remains incompletely understood, recent evidence suggests that abnormalities in cerebral perfusion and the hyperinflammatory state caused by DKA play important roles, and that variations in fluid treatment likely have minimal effects²⁸. Overall, the SAE of DKA appears to be most likely related to non-compliance with diabetes medication and/or concomitant infection and the SAE of cerebral edema was most likely secondary to DKA and significant volume depletion, rather than related to alogliptin treatment per se.

The SAEs occurring in the placebo arm were also briefly reviewed. The SAE of hypertensive emergency and suicidal ideation occurred in a 15-year-old female subject (b) (6) with a prior history of hypertension treated with amlodipine and hydrochlorothiazide and a prior history of visual and auditory hallucinations. The SAEs of forearm fracture, cellulitis, periorbital cellulitis and knee deformity (genu valgum) occurred in a 12-year-old female subject with a history of genu valgum. The forearm fracture was the result of a motor vehicle accident, the SAE of cellulitis was more consistent with a second degree burn from touching a hot pan and the SAE of periorbital cellulitis occurred following the subject's attempts to "pop a pimple" near the eye. An SAE of a lip laceration occurred in a 12-year-old female subject relating to an accident.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

TEAEs leading to treatment discontinuation are summarized in Table 20. Two (2) subjects in the alogliptin arm and 2 subjects in the placebo arm experienced treatment emergent adverse events leading to treatment discontinuation.

Table 20: TEAEs leading to Treatment Discontinuation in Study SYR-322_309

Preferred Term	Alogliptin 25 mg QD (N=75) n (%)	Placebo (N=76) n (%)
Alanine aminotransferase increased	1 (1.3)	1 (1.3)
Aspartate aminotransferase increased	0 (0.0)	1 (1.3)
Glycosylated hemoglobin increased	0 (0.0)	1 (1.3)
Gunshot wound	1 (1.3)	0 (0.0)
Hypovolemic shock	1 (1.3)	0 (0.0)
Septic shock	1 (1.3)	0 (0.0)

Source: Reviewer generated using OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Alogliptin 25 mg QD" and SAFFL = "Y" (Alogliptin 25 mg QD); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" and AEACN = "DRUG WITHDRAWN" (Adverse Events).

³⁰ Kuppermann N, et al; PECARN DKA FLUID Study Group. Clinical Trial of Fluid Infusion Rates for Pediatric Diabetic Ketoacidosis. N Engl J Med. 2018 Jun 14;378(24):2275-2287. doi: 10.1056/NEJMoa1716816. PMID: 29897851; PMCID: PMC6051773.

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Narratives for TEAES leading to discontinuation in the alogliptin arm were reviewed in detail and are summarized below:

- SAEs of septic shock, gunshot wound, and hypovolemic shock occurred in subject (b) (6) and were described above in Section 8.4.2. These SAEs are unlikely related to treatment.
- The TEAE of alanine aminotransferase (ALT) increased occurred in subject (b) (6). This subject was a 15-year-old female with T2D since 2017, nonalcoholic fatty liver disease (NAFLD), anxiety, depression and dysmenorrhea, with a reported race of American Indian or Alaska native and Hispanic ethnicity. Concomitant medications were metformin, bupropion hydrochloride and sertraline hydrochloride. The subject had elevated AST, ALT and GGT at baseline (Table 21). On study day 180 (at the time of the week 26 assessment), the subject was noted to have an ALT > 4 x upper limit of normal (ULN), which was captured as an AE of alanine aminotransferase increased. On the same day, the subject also experienced AEs of non-fasting and fasting hyperglycemia, hypertriglyceridemia, gamma-glutamyltransferase increased, and urine albumin present. Relevant laboratory tests are displayed in Table 21. The elevation in ALT remained ongoing and lead to discontinuation of treatment on day 300, after which the subject was lost to follow up; no follow up liver function tests were available after treatment discontinuation. Hepatic function labs for this subject are also discussed in more detail in Section 8.4.6. The subject appeared to have evidence of mild albuminuria at baseline which progressed to microalbuminuria on day 180. The subject appears to also have experienced worsening in glycemic control over the course of the study with HbA1c rising to 8.8% at week 26 as compared to 6.5% at baseline, which may also explain the rise in triglycerides compared to baseline.

Table 21: Lab Testing for Subject (b) (6)

Visit/Study Day	AST (normal range: 11.0-41.0 U/L)	ALT (normal range: 5.0- 30.0 U/L)	Fasting Plasma Glucose (normal range: 3.6- 5.8 mmol/L)	GGT (normal range: 4-24 U/L)	HbA1c	Triglycerides (mg/dL)	Urine Albumin (mg/dL) (normal range up to 2 mg/dL)	Urine Albumin/ creatinine (mg/mmol)* (normal range up to 1.6 mg/mmol)
Screening/Day - 17	52 H	64 H	7.99 H	43 H	6.5	253 H	2.33 H	1.61 H
Baseline/Day 1	45 H	49 H	6 H	36 H	6.5	293 H	5.12 H	
Week 12/Day 105	40	61 H	6.55 H	40 H	6.6	228 H	NA	

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Week 26/Day 180	82 H	134 H, MA	15.88 H	77 H	8.8	503 H	4.98 H	3.24 H
Unscheduled/Day 189	92 H	118 H, MA	14.38 H	69 H	NA	438 H	NA	
Unscheduled/Day 292	109 H	136 H, MA	15.6 H	62 H	9.2	372 H	NA	

Abbreviations: ALT: alanine aminotransferase; GGT: gamma-glutamyltransferase; H: high, HbA1c: hemoglobin A1C; MA: markedly abnormal; mg: milligrams; mmol/L: millimoles per liter; mm/dL: milligrams per deciliter; NA: not applicable; U/L: units per liter.

*urine albumin/creatinine ratio 3 to 30 mg/mmol = microalbuminuria, >30 mg/mmol = macroalbuminuria

Source: adapted from Applicant-provided Narrative

Reviewer Comment: Two (2) alogliptin-treated subjects discontinued therapy due to TEAEs. TEAEs leading to discontinuation in 1 alogliptin-treated subject were unlikely related to treatment as they occurred following a gunshot wound. Another alogliptin-treated subject with a pre-existing history of NAFLD and baseline mild elevation in ALT discontinued treatment due to a TEAE of ALT increased to 4 x ULN that was first noted at week 26 and persisted for 16 weeks. The evaluation of treatment-relatedness of this event is limited by the absence of any follow up labs after treatment discontinuation. However, given that hepatic effects are a labeled warning and precaution for alogliptin, it is reasonable to consider this event as related to treatment. This event is discussed in more detail in Section 8.4.6.

8.4.4. Significant Adverse Events

As discussed previously, the Applicant prespecified the following AESIs: serious hepatic abnormalities; pancreatitis; infections (including urinary tract infections); and severe hypersensitivity reactions (including angioedema, anaphylaxis, and Stevens-Johnson Syndrome). No AESIs relating to pancreatitis or severe hypersensitivity reactions occurred in the trial. AESIs relating to hepatic events occurred in 1 subject (1.3%) treated with alogliptin and in 2 subjects (3.6%) treated with placebo. AESIs relating to infections occurred in 8 subjects (10.6%) treated with alogliptin and in 9 subjects (11.8%) treated with placebo.

A summary of AESIs (as categorized in the datasets) is provided in Table 22. As noted previously, the Applicant flagged several TEAEs as AESIs due to their simultaneous occurrence with other AESIs in single subject treated with alogliptin (subject (b) (6)); these AESIs are indicated with a (*) in Table 22.

Table 22: TEAEs considered to be AESIs by SOC and PT in Study SYR-322_309

System Organ Class - Preferred Term	Alogliptin 25 mg QD (N=75) n (%)	Placebo (N=76) n (%)
Infections and infestations	8 (10.7)	9 (11.8)
Ear infection	0 (0.0)	1 (1.3)
Gastroenteritis	2 (2.7)	2 (2.6)
Pharyngitis	0 (0.0)	2 (2.6)
Pharyngitis streptococcal	2 (2.7)	1 (1.3)
Pharyngotonsillitis	0 (0.0)	2 (2.6)
Upper respiratory tract infection	4 (5.3)	3 (3.9)
Investigations	1 (1.3)	2 (2.6)
Alanine aminotransferase increased	1 (1.3)	2 (2.6)
Albumin urine present*	1 (1.3)	0 (0.0)
Aspartate aminotransferase increased	0 (0.0)	1 (1.3)
Blood glucose increased*	1 (1.3)	0 (0.0)
Gamma-glutamyltransferase increased	1 (1.3)	0 (0.0)
Metabolism and nutrition disorders	1 (1.3)	0 (0.0)
Hyperglycemia*	1 (1.3)	0 (0.0)
Hypertriglyceridemia*	1 (1.3)	0 (0.0)

Source: Reviewer generated using OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Alogliptin 25 mg QD" and SAFFL = "Y" (Alogliptin 25 mg QD); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" and AESIFL = "Y" (Adverse Events).

*TEAE's flagged by the Applicant as AESIs due to simultaneous occurrence with AESI of alanine aminotransferase increase in subject (b) (6)

Narratives of AESIs occurring in alogliptin-treated subjects were reviewed in detail; these are summarized below:

AESI	Subject ID/Background information	Details	Study drug changed/interrupted
gastroenteritis	(b) (6) a 10-year-old female on background metformin.	AE occurred 238 days after starting alogliptin. The subject was treated with oral esomeprazole 40 mg daily x 8 days and the event resolved after 3 days.	No
gastroenteritis	(b) (6) 15-year-old female on background metformin and insulin glargine, also treated	AE occurred 325 days after starting alogliptin and resolved within 5 days. The subject was treated with oral	No

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

	with bezafibrate for hypertriglyceridemia.	cefixime. No changes in study drug occurred.	
Pharyngitis, streptococcal	(b) (6) a 15-year-old female on background metformin, also with a history of asthma, allergic rhinitis, essential HTN and on concomitant treatment with cefdinir, medroxyprogesterone and loratadine.	AE occurred 20 days after starting alogliptin and resolved in 9 days. The subject was treated with azithromycin.	No. The subject voluntarily withdrew from the study on day 384, unrelated to this AE.
Upper respiratory tract infection	(b) (6) an 11-year-old female on background metformin, also with a history of allergic rhinitis, seasonal allergies, cough-variant asthma, acute sinusitis, strep throat and sore throat, and on concomitant treatment with epinephrine, cetirizine and salbutamol sulfate.	AE occurred 116 days after starting alogliptin and was treated with amoxicillin with clavulanate and potassium benzonatate.	No
Pharyngitis, streptococcal	(b) (6) 15-year-old male on background metformin, also with a history of asthma and hypertension treated with lisinopril and salbutamol sulfate, respectively.	AE occurred 75 days after starting alogliptin and was treated with amoxicillin	No
Upper respiratory tract infection	(b) (6) a 13-year-old female on background	AE occurred 152 days after starting alogliptin, treated with oral	No

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

	metformin.	bromphen- pseudophen-DM	
Alanine aminotransferase increased, gamma glutamyltransferase increase	(b) (6) a 15-year-old female on background metformin, also with history of non-alcoholic fatty liver disease and also treated with bupropion hydrochloride and sertraline hydrochloride.	AE occurred 179 days after starting alogliptin and occurred concomitantly with other AEs including elevated urine albumin, headache, blood glucose increase/hyperglycemia (> 240 mg/dL), hypertriglyceridemia (> 500). Lab details are provided in Section 8.4.3	Yes

Source: Reviewer created based on review of AESI narratives.

An FDA Medical Query (FMQ) was also run to investigate relevant safety signals for alogliptin, as displayed in Table 23 and Table 24. The results of the FMQ analysis were similar to the results from the analysis of AESIs, and overall did not reveal any notable imbalances between treatment arms.

Table 23: Narrow FDA Medical Query for Viral Infections and Hepatic Injury

Narrow FDA Medical Queries and Terms			
FDA Medical Query	Alogliptin 25 mg QD (N = 75)	Placebo (N = 76)	Risk Difference for Alogliptin 25 mg QD over Placebo
Viral Infection	13 (17.3%)	7 (9.2%)	0.08 (-0.03, 0.19)
Influenza	7 (9.3%)	2 (2.6%)	0.07 (-0.01, 0.14)
SARS-CoV-2 test positive	2 (2.7%)	0 (0%)	0.03 (-0.01, 0.06)
Gastroenteritis viral	2 (2.7%)	1 (1.3%)	0.01 (-0.03, 0.06)
Dengue fever	1 (1.3%)	0 (0%)	0.01 (-0.01, 0.04)
Asymptomatic COVID-19	0 (0%)	1 (1.3%)	-0.01 (-0.04, 0.01)
Viral infection	0 (0%)	1 (1.3%)	-0.01 (-0.04, 0.01)
COVID-19	1 (1.3%)	3 (3.9%)	-0.03 (-0.08, 0.02)
Hepatic Injury	1 (1.3%)	4 (5.3%)	-0.04 (-0.1, 0.02)
Alanine aminotransferase increased	1 (1.3%)	3 (3.9%)	-0.03 (-0.08, 0.02)
Aspartate aminotransferase increased	0 (0%)	3 (3.9%)	-0.04 (-0.08, 0)

Source: Reviewer created, JMP clinical

Table 24: Broad FDA Medical Query for Viral Infection, Anaphylactic Reaction, Pancreatitis and Hepatic Injury

Broad FDA Medical Queries and Terms			
FDA Medical Query	Alogliptin 25 mg QD (N = 75)	Placebo (N = 76)	Risk Difference for Alogliptin 25 mg QD over Placebo
Viral Infection	17 (22.7%)	12 (15.8%)	0.07 (-0.06, 0.19)
Influenza	7 (9.3%)	2 (2.6%)	0.07 (-0.01, 0.14)
SARS-CoV-2 test positive	2 (2.7%)	0 (0%)	0.03 (-0.01, 0.06)
Upper respiratory tract infection	4 (5.3%)	3 (3.9%)	0.01 (-0.05, 0.08)
Gastroenteritis viral	2 (2.7%)	1 (1.3%)	0.01 (-0.03, 0.06)
Dengue fever	1 (1.3%)	0 (0%)	0.01 (-0.01, 0.04)
Respiratory tract infection	1 (1.3%)	1 (1.3%)	0 (-0.04, 0.04)
Asymptomatic COVID-19	0 (0%)	1 (1.3%)	-0.01 (-0.04, 0.01)
Otitis media	0 (0%)	1 (1.3%)	-0.01 (-0.04, 0.01)
Viral infection	0 (0%)	1 (1.3%)	-0.01 (-0.04, 0.01)
COVID-19	1 (1.3%)	3 (3.9%)	-0.03 (-0.08, 0.02)
Anaphylactic Reaction	0 (0%)	1 (1.3%)	-0.01 (-0.04, 0.01)
Drug hypersensitivity	0 (0%)	1 (1.3%)	-0.01 (-0.04, 0.01)
Pancreatitis	0 (0%)	1 (1.3%)	-0.01 (-0.04, 0.01)
Lipase increased	0 (0%)	1 (1.3%)	-0.01 (-0.04, 0.01)
Hepatic Injury	1 (1.3%)	4 (5.3%)	-0.04 (-0.1, 0.02)
Gamma-glutamyltransferase increased	1 (1.3%)	2 (2.6%)	-0.01 (-0.06, 0.03)
Alanine aminotransferase increased	1 (1.3%)	3 (3.9%)	-0.03 (-0.08, 0.02)
Aspartate aminotransferase increased	0 (0%)	3 (3.9%)	-0.04 (-0.08, 0)

Source: Reviewer created, JMP clinical

Reviewer Comment: No AESIs relating to pancreatitis or severe hypersensitivity reactions occurred in Study SYR-322_309. AESIs relating to infections occurred in 8 subjects (10.6%) treated with alogliptin and in 9 subjects (11.8%) treated with placebo. One (1) subject treated with alogliptin experienced an AESI relating to hepatic event which also led to treatment discontinuation (as previously discussed in Section 8.4.3). Overall, the AESIs occurring in alogliptin-treated subjects in Study SYR-322_309 were consistent with the safety signals identified in adult studies.

Hypoglycemia Events:

An analysis hypoglycemia events occurring on study treatment was completed based on a review of the adhypo.xpt dataset, using the Applicant's pre-specified definitions for hypoglycemia as described in Section 8.3.2. No severe hypoglycemia events occurred in Study SYR-322_309. Overall, alogliptin treatment did not appear to be associated with an increased risk of hypoglycemia as compared to placebo.

Table 25: Hypoglycemia Event Analysis, Study SYR-322_309

Hypoglycemia Event	Alogliptin (N=75) Events n (%)	Placebo (N=76) Events n(%)
Any hypoglycemia event	15 events 4 (5.3%)	13 events 5 (6.5%)
Blood glucose < 60 mg/dL with symptoms	0 events 0 (0%)	7 events 4 (5.3%)
Blood glucose < 50 mg/dL with or without symptoms	15 events 4 (5.3%)	6 events 3 (3.9%)
Severe event	0 events 0 (0%)	0 events 0 (0%)

Source: Reviewer generated based on review of *adhypo.xpt* dataset.

According to Table 15.3.4.7.1 in the CSR, only 2 placebo-treated subjects were reported to have experienced a blood glucose < 60 mg/dL with symptoms³¹. However, the incidence of blood glucose < 60 mg/dL with symptoms in the alogliptin arm, blood glucose < 50 mg/dL with or without symptoms in both treatment arms, and any hypoglycemia event in both treatment arms reported in the CSR were consistent with the reviewer-completed analysis.

The current USPI for alogliptin products contains a Warning and Precaution regarding an increased risk of hypoglycemia with concomitant treatment with insulin and/or insulin sulfonylureas. To determine whether a similar safety signal exists in pediatric T2D subjects, an IR was sent to the Applicant requesting additional data regarding the rate of hypoglycemia events occurring in subjects treated with background insulin as compared to those not treated with background insulin at randomization. Based on the Applicant's response (summarized in Table 26) hypoglycemia events occurred in 3 out of 23 (13.0%) placebo-treated subjects and in 3 out of 27 (11.1%) alogliptin-treated subjects who received background insulin. Among subjects who did not receive background insulin, hypoglycemia events occurred in 2 out of 53 (3.8%) placebo-treated subjects and in 1 out of 48 (2.1%) alogliptin treated subjects. Overall, there did not appear to be an imbalance in hypoglycemia events associated with alogliptin treatment in subjects who received background insulin or in subjects who did not receive background insulin.

³¹ Based on my review of the *adhypo.xpt* datasets, the following placebo-treated subjects experienced blood glucose < 60 mg/dL with symptoms: (b) (6)

Table 26: Incidence of Hypoglycemia Events in Subjects With and Without Background Insulin Therapy While on Study Treatment, Study SYR-322_309

	Subjects on Background Insulin ^a			Subjects Not on Background Insulin ^a		
	Placebo (N=23)	Alogliptin (N=27)	Total (N=50)	Placebo (N=53)	Alogliptin (N=48)	Total N=101
One or more hypoglycemia episodes	3	3	6	2	1	3
Subjects with blood glucose < 60 mg/dL with symptoms	2	2	4	2	1	3
Subjects with severe hypoglycemia	0	0	0	0	0	0
Average hypoglycemic events per day during the treatment	0.0066	0.0283	0.0156	0.0137	0.024	0.0202
Total number of days having >1 event during the treatment	7	5	12	3	5	8

Source: SAS Table 4, [Appendix A](#).^a Subjects who received insulin treatment at the time of randomization are classified as being on background insulin therapy.

Reviewer Comment: No severe hypoglycemia events occurred in Study SYR-322_309. As discussed earlier, the definitions of hypoglycemia used in Study SYR-322_309 differed from current ADA definitions of hypoglycemia events; however, the definitions used for mild hypoglycemia (blood glucose < 60 mg/dL with symptoms) and moderate hypoglycemia (blood glucose < 50 mg/dL with or without symptoms) together likely provided a reasonable representation of ADA Level 2 events (defined as blood glucose < 54 mg/dL) which are considered clinically relevant hypoglycemia events. Overall, mild and moderate hypoglycemia events as defined in Study SYR-322_309 occurred in 5.3% of alogliptin-treated subjects and in 6.5% of placebo-treated subjects. Hypoglycemia events were more likely to occur in subjects who received background insulin therapy as compared to those who did not receive background insulin therapy, but there did not appear to be any imbalance in hypoglycemia events associated with alogliptin treatment as compared to placebo. In adult studies of alogliptin, an increased risk of hypoglycemia was also not observed with monotherapy or with add-on therapy to insulin or glyburide, however, a Warning and Precaution regarding the risk of hypoglycemia with concomitant insulin or sulfonylurea was added to the product label based on safety findings observed in other trials of DPP4 inhibitors.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

A total of 431 TEAEs occurred in the safety population, including 205 events in 60 out of 75 (80.0%) subjects who received alogliptin, and 226 events in 58 out of 76 (76.3%) subjects who received placebo. In terms of severity, the majority of TEAEs were considered mild (153 and 158 TEAEs in the alogliptin and placebo arms, respectively), 45 TEAEs in the alogliptin arm and 64 TEAEs in the placebo arm were moderate, while 7 AEs in the alogliptin arm and 4 AEs in the placebo arm were severe. A summary of TEAEs by system organ class (SOC) occurring in > 5%

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

of alogliptin-treated subjects is provided in Table 27. TEAEs occurred more frequently within the SOC of nervous system disorders, general disorders and administration site conditions, reproductive system and breast disorders and renal and urinary disorders in subjects who received alogliptin versus placebo. A summary of PTs occurring within these selected SOC is provided in Table 28. The imbalance in the SOC of nervous system disorders was driven by the PT of headache. Apart from the PT of dysmenorrhea which occurred in 5 alogliptin-treated subjects as compared to 2 placebo-treated subjects, no other imbalance in PTs within the SOC of reproductive system and breast disorders was evident.

Table 27: TEAEs by SOC occurring in > 5% of Alogliptin-Treated Subjects in Study SYR-322_309

System Organ Class	Alogliptin 25 mg QD (N=75) n (%)	Placebo (N=76) n (%)	Risk Difference	
			RD (95% CI)	Forest Plot
Gastrointestinal disorders	15 (20.0)	17 (22.4)	-2.37 (-15.40, 10.66)	
General disorders and administration site conditions	9 (12.0)	2 (2.6)	9.37 (1.18, 17.56)	
Infections and infestations	28 (37.3)	26 (34.2)	3.12 (-12.16, 18.41)	
Injury, poisoning and procedural complications	6 (8.0)	8 (10.5)	-2.53 (-11.76, 6.71)	
Investigations	11 (14.7)	11 (14.5)	0.19 (-11.06, 11.45)	
Metabolism and nutrition disorders	17 (22.7)	23 (30.3)	-7.60 (-21.61, 6.42)	
Musculoskeletal and connective tissue disorders	5 (6.7)	6 (7.9)	-1.23 (-9.51, 7.06)	
Nervous system disorders	17 (22.7)	11 (14.5)	8.19 (-4.15, 20.54)	
Renal and urinary disorders	5 (6.7)	3 (3.9)	2.72 (-4.42, 9.86)	
Reproductive system and breast disorders	7 (9.3)	3 (3.9)	5.39 (-2.52, 13.29)	
Respiratory, thoracic and mediastinal disorders	5 (6.7)	4 (5.3)	1.40 (-6.15, 8.96)	
Skin and subcutaneous tissue disorders	5 (6.7)	7 (9.2)	-2.54 (-11.15, 6.07)	

Source: Reviewer generated in OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Alogliptin 25 mg QD" and SAFFL = "Y" (Alogliptin 25 mg QD); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" (Adverse Events).

Percent Threshold: Aloglip in 25 mg QD ≥ 5%.

Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Table 28: TEAEs by PTs occurring with Selected SOCs* that Occurred in > 5% of Alogliptin-treated subjects, Study SYR-322_309

System Organ Class - Preferred Term	Alogliptin 25 mg QD (N=75) n (%)	Placebo (N=76) n (%)
General disorders and administration site conditions	9 (12.0)	2 (2.6)
Chest discomfort	0 (0.0)	1 (1.3)
Chest pain	0 (0.0)	1 (1.3)
Fatigue	1 (1.3)	1 (1.3)
Inflammation	1 (1.3)	0 (0.0)
Influenza like illness	2 (2.7)	0 (0.0)
Injection site pain	1 (1.3)	0 (0.0)
Malaise	1 (1.3)	0 (0.0)
Pain	0 (0.0)	1 (1.3)
Peripheral swelling	1 (1.3)	0 (0.0)
Pyrexia	2 (2.7)	1 (1.3)
Nervous system disorders	17 (22.7)	11 (14.5)
Amnesia	0 (0.0)	1 (1.3)
Brain oedema	1 (1.3)	0 (0.0)
Dizziness	3 (4.0)	2 (2.6)
Headache	14 (18.7)	8 (10.5)
Hyperesthesia	1 (1.3)	0 (0.0)
Somnolence	0 (0.0)	1 (1.3)
Syncope	1 (1.3)	0 (0.0)
Tremor	0 (0.0)	1 (1.3)
Renal and urinary disorders	5 (6.7)	3 (3.9)
Albuminuria	2 (2.7)	0 (0.0)
Bladder spasm	0 (0.0)	1 (1.3)
Ketonuria	1 (1.3)	0 (0.0)
Microalbuminuria	1 (1.3)	1 (1.3)
Proteinuria	1 (1.3)	1 (1.3)
Reproductive system and breast disorders	7 (9.3)	3 (3.9)
Amenorrhea	1 (1.3)	0 (0.0)
Dysmenorrhea	5 (6.7)	2 (2.6)
Menstruation delayed	0 (0.0)	1 (1.3)
Menstruation irregular	0 (0.0)	1 (1.3)
Ovarian cyst	1 (1.3)	0 (0.0)

Source: Reviewer generated in OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Alogliptin 25 mg QD" and SAFFL = "Y" (Alogliptin 25 mg QD); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" (Adverse Events).

* TEAEs occurred more frequently within the SOCs of nervous system disorders, general disorders and administration site conditions, reproductive system and breast disorders and renal and urinary disorders in subjects who received alogliptin versus placebo.

Table 29 displays the incidence of TEAEs by preferred term that occurred in > 3% of alogliptin-treated subjects. The most common AE in alogliptin-treated subjects was headache (18.7%), followed by hyperglycemia (12.0%), diarrhea (9.3%) and influenza (9.3%).

Table 29: TEAEs by PT occurring in > 3% of Alogliptin-Treated Subjects in Study SYR-322_309

Preferred Term	Alogliptin 25 mg QD (N=75)	Placebo (N=76)	Risk Difference	
	n (%)	n (%)	RD (95% CI)	Forest Plot
Diarrhea	7 (9.3)	7 (9.2)	0.12 (-9.13, 9.38)	
Dizziness	3 (4.0)	2 (2.6)	1.37 (-4.34, 7.08)	
Dysmenorrhea	5 (6.7)	2 (2.6)	4.04 (-2.66, 10.73)	
Glycosylated hemoglobin increased	3 (4.0)	4 (5.3)	-1.26 (-7.96, 5.44)	
Headache	14 (18.7)	8 (10.5)	8.14 (-3.06, 19.34)	
Hyperglycemia	9 (12.0)	9 (11.8)	0.16 (-10.18, 10.50)	
Influenza	7 (9.3)	2 (2.6)	6.70 (-0.80, 14.20)	
Nausea	3 (4.0)	5 (6.6)	-2.58 (-9.70, 4.54)	
Type 2 diabetes mellitus	3 (4.0)	5 (6.6)	-2.58 (-9.70, 4.54)	
Upper respiratory tract infection	4 (5.3)	3 (3.9)	1.39 (-5.32, 8.10)	
Vomiting	4 (5.3)	6 (7.9)	-2.56 (-10.47, 5.35)	

Source: Reviewer generated in OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Alogliptin 25 mg QD" and SAFFL = "Y" (Alogliptin 25 mg QD); TRT01A = "Placebo" and SAFFL = "Y" (Placebo); TRTEMFL = "Y" (Adverse Events).

Percent Threshold: Aloglip in 25 mg QD ≥ 3%.

Risk Difference calculated by comparing the left column (Group 1) to the right column (Group 2).

As discussed in Section 8.3.2, due to the definition of TEAEs as all AEs occurring on the first day of study treatment, AEs that may have occurred prior to the first dose of medication but on the first day of study treatment were included in the TEAEs represented in Table 27, Table 28, and Table 29. Therefore, a separate analysis was conducted to determine which TEAEs occurred prior to the first dose of study treatment: among alogliptin-treated subjects these included the TEAEs of bundle-branch block left in 1 subject, upper respiratory tract infection in 1 subject, C-telopeptide increased in 2 subjects, and proteinuria in 1 subject. These findings do not change any conclusions regarding the safety findings for alogliptin from the overall TEAE analyses.

Reviewer Comment: The most common TEAEs in alogliptin-treated subjects were headache,

hyperglycemia, diarrhea and influenza. Common adverse reactions (4% or greater incidence) in the adult studies of alogliptin included nasopharyngitis, headache and upper respiratory tract infection. Overall, no new safety signals were identified based on analysis of TEAEs in Study SYR-322_309.

8.4.6. Laboratory Findings

The safety review of laboratory findings included the entire double-blind treatment period (through week 52). Laboratory findings through week 26 were also reviewed, but only discussed if any relevant differences were noted as compared to the analysis through week 52.

Renal Function Parameters:

Overall, the mean baseline eGFR was 143.6 mL/min/1.73 m² in the trial population (Table 30).³² As discussed earlier, subjects with eGFR <60 mL/min/1.73 m² were not enrolled in the study. However, it appears that 1 subject (b) (6) in the placebo arm with a baseline eGFR < 60 was enrolled. Upon further review, this subject had an eGFR of 79 mL/min/1.73 m² at the time of screening, however the eGFR had declined to 52.7 mL/min/1.73 m² at baseline measurement, and subsequently rose to 158 mL/min/1.73 m² by week 52.

Table 30: Baseline eGFR, Study SYR-322_309

	Alogliptin 25 mg QD (N=75)	Placebo (N=76)	Total (N=151)
eGFR (mL/min/1.73 m ²)			
Mean (SD)	147.3 (36.96)	139.9 (40.54)	143.6 (38.85)
Median (Min, Max)	137.9 (79, 246)	134.2 (52.7, 305)	135.5 (52.7, 305)

Source: Reviewer generated in OCS Analysis Studio, Custom Table Tool.

Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.

Table Section 1 - Dataset: Laboratory; Filter: PARAM = 'Glomerular Filtration Rate (mL/min/1.73m²)', AVISIT = 'Baseline'.

SD = Standard Deviation.

No clinically meaningful changes in mean serum creatinine, urine albumin/creatinine ratio or estimated GFR occurred in subjects treated with alogliptin from baseline to week 52.

A shift table for renal impairment based on eGFR is displayed in Table 31. One (1) subject in each treatment arm had a rise in serum creatinine > 0.25 mg/dL by week 52; the alogliptin-treated subject (b) (6) with rise in serum creatinine had a corresponding decrease in eGFR and is discussed below.

One alogliptin-treated subject (b) (6) shifted from mild renal impairment at baseline to moderate renal impairment by week 52. This subject a baseline eGFR of 79 mL/min/1.73 m², an

³² This finding likely reflects the phenomenon of hyperfiltration, which may be seen in up to 50% of pediatric T2D subjects (Bjornstad P, Cherney DZ. Renal Hyperfiltration in Adolescents with Type 2 Diabetes: Physiology, Sex Differences, and Implications for Diabetic Kidney Disease. Curr Diab Rep. 2018 Mar 19;18(5):22).

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

eGFR of 71.1 mL/min/1.73 m² at week 26, and an eGFR of 58.6 mL/min/1.73 m² at week 52 (no follow up labs available after treatment discontinuation). This subject also had evidence of macroalbuminuria at baseline (urine albumin to creatinine ratio of 43.55 mg/mmol, i.e., > 30 mg/mmol) which worsened by week 52 (155.86 mg/mmol). This subject had an AE of Dengue fever on study day 181 but no renal-related AEs, and received concomitant medications of metformin and insulin throughout the trial.

Two (2) placebo-treated subjects and 1 alogliptin-treated subject shifted from normal renal function to mild-renal impairment by week 52. The alogliptin treated had a baseline eGFR of 117 mL/min/1.73 m² which decreased to 87.8 mL/min/1.73 m² by week 52.

Table 31: Renal Impairment (based on eGFR) Shift Table from Baseline to Week 52

Treatment Arm	Baseline Renal Impairment	Final Renal Impairment		
		None	Mild	Moderate
Alogliptin 25 mg QD (N = 51)	None	48 (94.1%)	1 (2.0%)	0
	Mild	1 (2.0%)	0	1 (2.0%)
	Moderate	0	0	0
Placebo (N = 57)	None	53 (93.0%)	2 (3.5%)	0
	Mild	1 (1.8%)	0	0
	Moderate	1 (1.8%)	0	0

Source: Reviewer generated in OCS Analysis Studio, Kidney Function Tool.

None: ≥90 mL/min/1.73 m²; Mild: 90-60 mL/min/1.73 m²; Moderate: ≤60 mL/min/1.73 m².

Percentage based on population of a given treatment arm.

End of Treatment: AVISIT = Week 52 (Day 365).

Reviewer Comment: One alogliptin-treated subject who had mild renal impairment at baseline shifted to moderate renal impairment by the end of the study. This subject most likely had progression of underlying diabetic nephropathy, based on evidence of baseline macroalbuminuria that also worsened over the course of the trial. As displayed in Table 28, no AEs relating to renal impairment occurred in alogliptin-treated subjects.

Based on a review of the adlb.xpt dataset, 92 out of 151 treated subjects had a baseline urine albumin-to-creatinine ratio measurement; of these subjects, 37 subjects had evidence of microalbuminuria, and 2 subjects had evidence of macroalbuminuria. According to a shift table for urine albumin/creatinine ratio through week 52 (Table 32), 4 alogliptin-treated subjects and 3 placebo-treated subjects shifted from normoalbuminuria to microalbuminuria by week 52. No subjects in either treatment arm shifted from normoalbuminuria or microalbuminuria to

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

macroalbuminuria. A small percentage of subjects in both treatment arms who had microalbuminuria at baseline reverted back to normoalbuminuria by week 52, a phenomenon that has been previously reported in patients with diabetes³³.

Table 32: Urine Albumin/Creatinine Shift Table from Baseline to Week 52

Treatment Arm	Baseline Renal Impairment	Final Albuminuria		
		Normoalbuminuria	Microalbuminuria	Macroalbuminuria
Alogliptin 25 mg QD (N = 29)	Normoalbuminuria	15 (51.7%)	4 (13.8%)	0
	Microalbuminuria	1 (3.4%)	8 (27.6%)	0
	Macroalbuminuria	0	0	1 (3.4%)
Placebo (N = 24)	Normoalbuminuria	9 (37.5%)	3 (12.5%)	0
	Microalbuminuria	6 (25.0%)	5 (20.8%)	0
	Macroalbuminuria	0	0	1 (4.2%)

Source: Reviewer generated using OCS Analysis Studio, Kidney Function Tool.

Normoalbuminuria: ≤ 3 mg/mmol; Microalbuminuria: 3–30 mg/mmol; Macroalbuminuria: ≥ 30 mg/mmol.

Percentage based on population of a given treatment arm.

End of Treatment: AVISIT = Week 52 (Day 365).

Reviewer Comment: At least 39 subjects enrolled in Study SYR-322_309 (representing 25.8% of the overall study population) had microalbuminuria or macroalbuminuria at baseline, despite a mean duration of T2D of 1.6 years. This finding is consistent with that reported in other recently completed pediatric T2D trials³⁴, and likely reflects the early-onset of diabetes-related complications that has been reported in children with T2D.

Hepatic Function Parameters:

A hepatocellular drug-induced liver injury (DILI) plot analysis was conducted (Figure 9) for the duration of the placebo-controlled period. No hepatic event fulfilled Hy's law criteria (i.e., AST or ALT $\geq 3 \times$ ULN and total bilirubin $\geq 2 \times$ ULN). Four (4) subjects in the alogliptin arm (Table 33) and 7 subjects in the placebo arm were in the quadrant for Temple's Corollary (i.e., AST or ALT $\geq 3 \times$ ULN). This information slightly differs from that reported in the Applicant's analysis of

³³ de Boer IH, et al (2011) Long-term renal outcomes of patients with type 1 diabetes mellitus and microalbuminuria: an analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort. Arch Intern Med 171:412–420

³⁴ In the DINAMO study of empagliflozin and linagliptin in pediatric T2D subjects, nearly a quarter of the trial population also had microalbuminuria or macroalbuminuria at baseline. See clinical review for NDA 204629/S-042 and NDA 201280/S-027.

Clinical Review

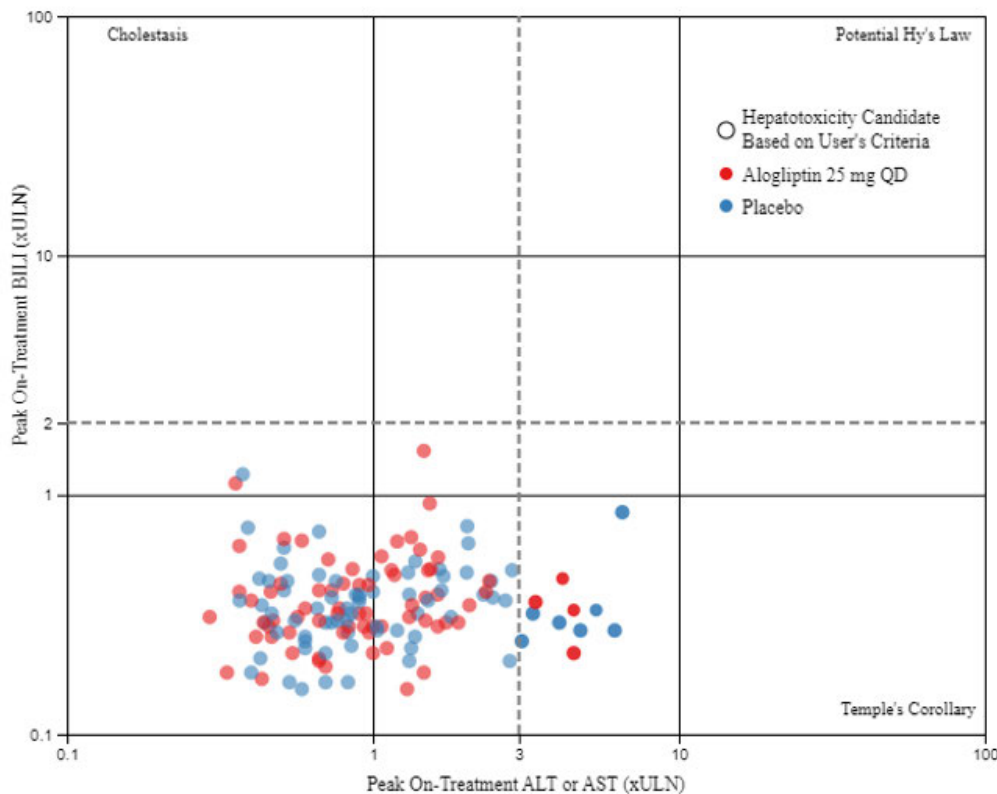
Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

markedly abnormal laboratory values (Table 36), in which ALT elevations $\geq 3 \times \text{ULN}$ were reported in 4/72 (5.6%) of alogliptin-treated subjects and in 8/75 (10.7%) of placebo-treated subjects, and AST elevations $\geq 3 \times \text{ULN}$ were reported in no alogliptin-treated subjects and in 2/75 (2.7%) of placebo-treated subjects. Hepatic function data for the 4 alogliptin-treated subjects meeting Temple's Corollary as displayed in Figure 9 were individually reviewed.

Figure 9: Hepatocellular DILI Screening Plot through Week 52, Study SYR-322_309



Source: Reviewer generated using OCS Analysis Studio, Hepatic Explorer.

Filters: None.

*Hepatotoxicity Candidates: ALT or AST $\geq 3 \times \text{ULN}$; BILI $\geq 2 \times \text{ULN}$ (0-30 days forward); ALP $< 2 \times \text{ULN}$ (0-999 days backward).

*Results missing ULN values were imputed using the weighted mean of the lab code.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BILI, bilirubin;

DILI, drug-induced liver injury; ULN, upper limit of normal.

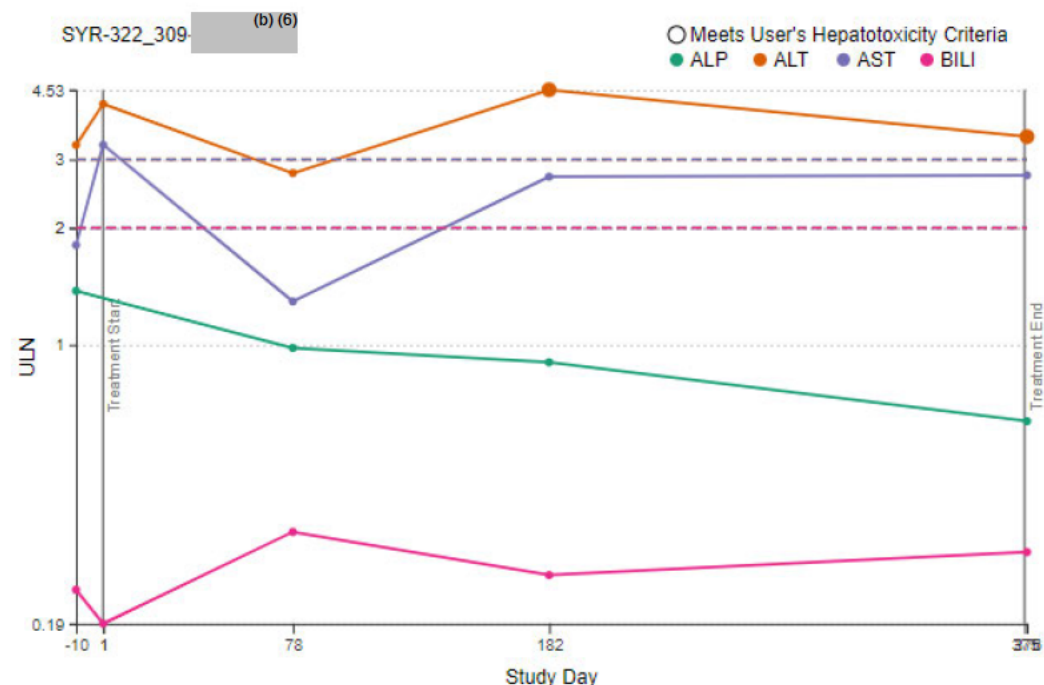
Table 33: Listing of Alogliptin-Treated Subjects in Temple's Corollary, Study SYR-322_309

Subject		Treatment Arm	Peak ALT or AST (xULN)	Peak BILI (xULN)	Baseline ALT or AST > ULN
SYR-322_309-	(b) (6)	Alogliptin 25 mg QD	4.5333	0.3298	Y
SYR-322_309-	(b) (6)	Alogliptin 25 mg QD	4.1667	0.4468	Y
SYR-322_309-	(b) (6)	Alogliptin 25 mg QD	3.4	0.3564	Y
SYR-322_309-	(b) (6)	Alogliptin 25 mg QD	4.5333	0.2181	Y

Source: Reviewer generated using OCS analysis studio, Hepatic explorer

Subject (b) (6) This subject had a pre-treatment history of NAFLD and had elevated ALT and AST at baseline [125 U/L (4x ULN) and 134 U/L (3.3x ULN), respectively] which declined after initiating treatment, subsequently increased but remained below baseline values. The final ALT and AST measurements after treatment discontinuation at week 54 were 103 and 112 U/L (Figure 10). This subject had no hepatic-related TEAEs.

Figure 10: Hepatic Function Labs for Subject (b) (6) Study SYR-322_309



Source: Reviewer generated using OCS analysis studio, hepatic explorer

Clinical Review

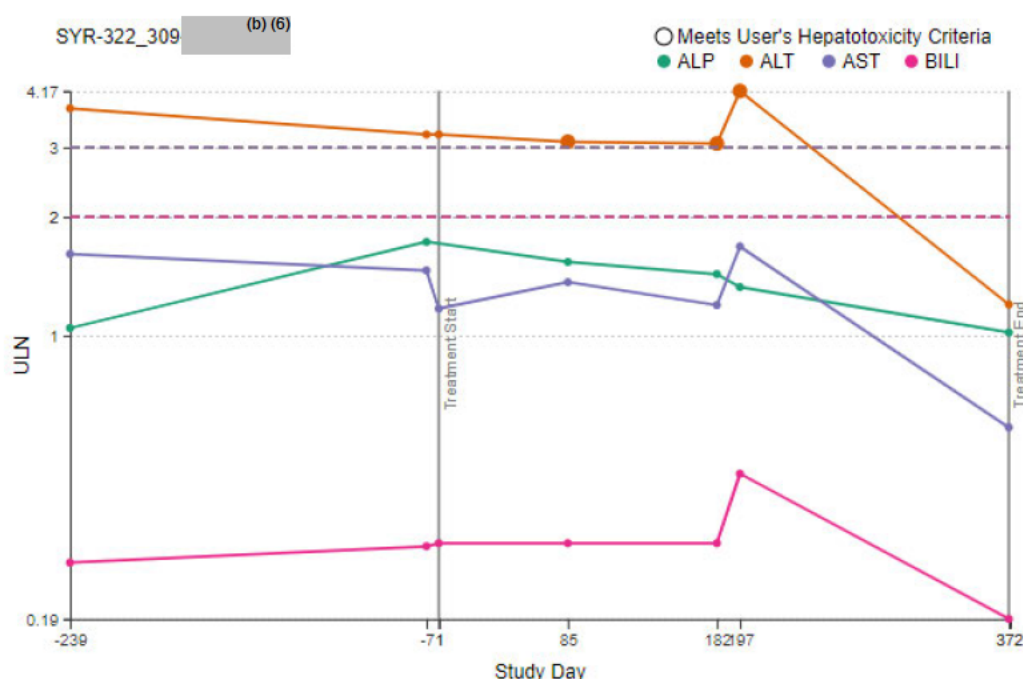
Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

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Subject (b) (6) This subject had elevated ALT (97 U/L) and AST (48 U/L) at baseline. ALT and AST both increased at study day 197 to 125 U/L and 69 U/L, respectively, and subsequently declined by the end of the study, though ALT remained slightly above normal (Figure 11). This subject was also briefly treated with loperamide and omeprazole for AEs of diarrhea and gastritis that occurred on study day 166, however AST and ALT measurements on day 182 after exposure to these concomitant medications were relatively stable. This subject had no hepatic-related AEs.

Figure 11: Hepatic Function Labs for Subject (b) (6) **Study SYR-322_309**



Source: Reviewer generated using OCS Analysis studio hepatic explorer.

Subject (b) (6) This subject had normal AST and ALT at the initial screening, however, both ALT and AST increased prior to randomization with ALT measured at 58 U/L at baseline. ALT and AST peaked on study day 84 (measured at 102 and 52 U/L, respectively) but declined thereafter to normal values without interruption in treatment. This subject had no hepatic-related AEs.

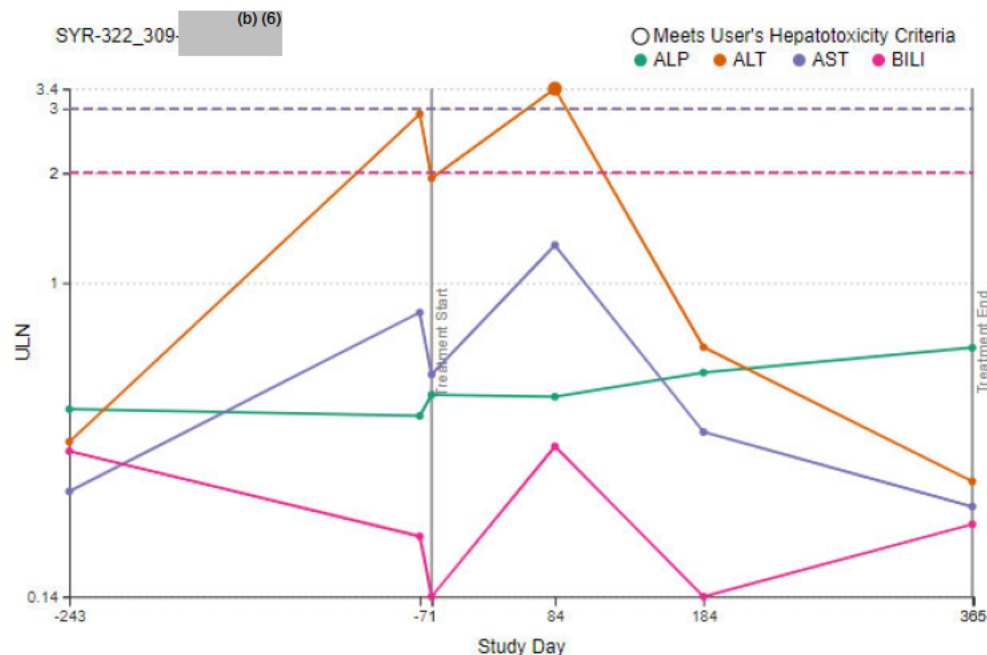
Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

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Figure 12: Hepatic Function Labs for Subject (b) (6) Study SYR-322_309

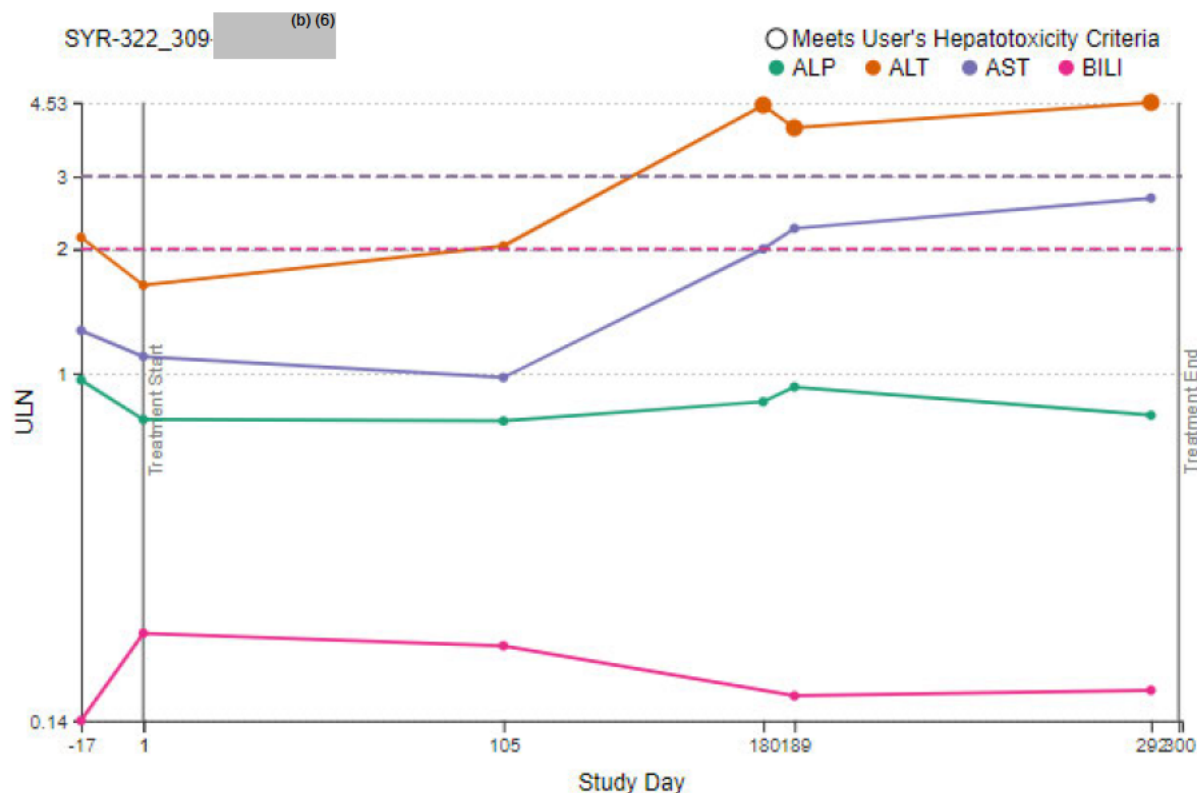


Source: Reviewer generated using OCS analysis studio, Hepatic explorer

Subject (b) (6) This subject, a 15-year-old female (previously discussed in Section 8.4.3), had a pre-trial history of NAFLD, anxiety, depression and dysmenorrhea, and was treated with concomitant medications of metformin, sertraline hydrochloride and bupropion hydrochloride. Baseline hepatic function laboratories were notable for mildly elevated ALT and AST (49 U/L and 45 U/L, respectively), mildly elevated gamma-glutamyltransferase (36 U/L; upper limit of normal 26 U/L), and normal alkaline phosphatase (125 U/L). On study day 180, the subject had ALT measured at 134 U/L ($> 4 \times$ ULN) which was captured in an AE of alanine aminotransferase increased³⁵. AST was also elevated to $2 \times$ ULN (82 U/L). Follow up unscheduled laboratory tests on study day 189 and at study day 292 revealed ongoing ALT elevation (118 U/L and 136 U/L, respectively) and AST elevation (92 U/L and 109 U/L, respectively). The subject discontinued treatment on study day 300 and follow up AST and ALT were not obtained (Figure 13). Alkaline phosphatase and bilirubin remained normal throughout.

³⁵ On the same day, the subject also experienced AEs of albumin urine present, blood glucose increased, gamma-glutamyltransferase increased, hyperglycemia and hypertriglyceridemia (see Section 8.4.3 for additional discussion regarding these AEs).

Figure 13: Hepatic Function Labs for Subject (b) (6) Study SYR-322_309



Reviewer Comment: No subject met criteria for Hy's law in Study SYR-322_309. Overall, a lower percentage of alogliptin-treated subjects experienced AST or ALT ≥ 3 x ULN as compared to those treated with placebo (4 alogliptin-treated subjects (5.6%) vs. 7 placebo-treated subjects (9.2%) based on a reviewer-completed analysis). Among the 4 alogliptin-treated subjects who experienced peak AST or ALT > 3 x ULN, all had baseline elevations in transaminases and none of the events were accompanied by elevations in bilirubin. One alogliptin-treated subject (b) (6) with pre-existing non-alcoholic fatty liver disease and baseline ALT 1.6 x ULN experienced an ALT elevation of 4.5 x ULN after 26 weeks of treatment, not accompanied by changes in bilirubin or alkaline phosphatase, which persisted for 16 weeks and eventually led to study treatment discontinuation³⁶. Although follow up laboratories were not obtained after treatment discontinuation, it is reasonable to consider this event as treatment-related considering that hepatic effects are a known and labeled safety issue for alogliptin currently described in Section 5 (Warnings and Precautions) based on postmarketing reports of fatal and nonfatal hepatic failure in patients taking alogliptin in

³⁶ The prespecified discontinuation criteria for study SYR-322_309, detailed in Table 3 were consistent with that recommended in the FDA's 2009 Drug-Induced Liver Injury: Premarketing Clinical Evaluation guidance for industry. Of note, this subject did not technically meet discontinuation criteria which required AST or ALT elevation > 5 x ULN for more than 2 weeks.

which causality could not be excluded. In adult glycemic control trials of alogliptin, serum ALT elevations greater than 3xULN were reported in 1.3% of alogliptin-treated subjects as compared to 1.7% of subjects treated with placebo or active comparators. In the cardiovascular outcome trial of alogliptin in adults with T2D and increased cardiovascular risk, increases in serum ALT 3x ULN occurred in 2.4% of alogliptin-treated subjects and in 1.8% of placebo-treated subjects.

Growth-hormone dependent factors and markers of bone metabolism:

An analysis of changes in growth-hormone dependent factors (i.e., IGF-1 and IGFBP-3) was conducted excluding subjects who were Tanner stage 5 at baseline, as these subjects may have been expected to have already completed linear growth. In general, for subjects who are in puberty and who have not yet completed linear growth, IGF-1 and IGF-BP3 would be expected to increase over time. Overall, there was significant variability in the mean and median change from baseline in both IGF-1 and IGF-BP-3 in both treatment arms, with some subjects experiencing large increases while others experiencing large decreases. Additionally, there was variability in the mean and median change from baseline to week 26 as compared to week 52 for both IGF-1 and IGF-BP3. In alogliptin-treated subjects, a mean increase from baseline in IGF-1 and IGF-BP3 was observed at week 26, but a mean decrease at baseline was observed at week 52. Similar variability occurred in placebo-treated subjects. In addition, the magnitude of calculated changes (whether representative of an increase or a decrease) in mean or median IGF-1 and IGFBP-3 were not clinically significant.

Table 34: Change from Baseline in Growth-Hormone Dependent Factors among Subjects Baseline Tanner stage (Breast/Genitalia) < 5*

	Alogliptin 25 mg QD (N=42)	Placebo (N=35)	Total (N=77)
IGF-1 (ug/L) Change at Week 26			
Mean (SD)	13.5 (70.82)	6.5 (75.95)	10.3 (72.68)
Median (Min, Max)	-3.4 (-100.1, 197.1)	2.2 (-120.9, 201.4)	-1.3 (-120.9, 201.4)
IGF-1 (ug/L) change at Week 52			
Mean (SD)	-9.7 (84.84)	-17.9 (70.62)	-13.8 (77.43)
Median (Min, Max)	-17.9 (-139.5, 184.9)	-21.5 (-155.4, 112.6)	-18.6 (-155.4, 184.9)
IGFBP-3 (ug/L) Change at Week 26			
Mean (SD)	79.5 (650.76)	-23.8 (653.22)	32.1 (648.51)
Median (Min, Max)	7.5 (-1043.5, 1482)	51.5 (-1144.5, 1027.5)	38.0 (-1144.5, 1482)
IGFBP-3 (ug/L) Change at Week 52			
Mean (SD)	-14.0 (746.04)	21.3 (666.11)	3.6 (700.72)
Median (Min, Max)	36.0 (-1551.5, 1483.5)	20.5 (-1081.5, 1449.5)	26.0 (-1551.5, 1483.5)

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Alogliptin 25 mg QD (N=42)	Placebo (N=35)	Total (N=77)
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Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool.

Columns - Dataset: Demographics; Filter: SAFFL = 'Y', TSSBSL = '1' or '2' or '3' or '4' or 'Missing'.

IGF-1 (ug/L) Change at Week 26 - Dataset: Laboratory; Filter: PARAM = 'Insulin-like Growth Factor-1 (ug/L)', AVISIT = 'Week 26 (Day 183)'.

IGF-1 (ug/L) change at Week 52 - Dataset: Laboratory; Filter: AVISIT = 'Week 52 (Day 365)', PARAM = 'Insulin-like Growth Factor-1 (ug/L)'.

IGFBP-3 (ug/L) Change at Week 26 - Dataset: Laboratory; Filter: PARAM = 'Insulin-Like Growth Factor Binding Prot3 (ug/L)', AVISIT = 'Week 26 (Day 183)'.

IGFBP-3 (ug/L) Change at Week 52 - Dataset: Laboratory; Filter: PARAM = 'Insulin-Like Growth Factor Binding Prot3 (ug/L)', AVISIT = 'Week 52 (Day 365)'.

SD = Standard Deviation.

* This analysis included 1 placebo-treated subject with missing baseline Tanner stage; this subject was recoded as having Tanner stage 5 at week 26 therefore it is uncertain whether they had completed linear growth at baseline or whether they may have had a Tanner stage < 5 at baseline that progressed to Tanner stage 5 by week 26. , This analysis also included 1 placebo-treated subject with baseline Tanner stage 1 who was recorded as Tanner stage 2 for breast/genitalia at week 26, suggesting that this subject had entered puberty during the trial.

Unit conversion: IGFBP-3 unit 1000 ug/L = 1 ug/mL; IGF-1 1 ug/L = 1 ng/mL

Reviewer Comment: In general, increases in IGF-1 and IGF-BP3 would be expected to occur over a 12-month period in pubertal children who have not yet completed growth; however, based on an analysis of the subgroup of subjects with baseline Tanner stage for genital/breast below 5, this pattern was not consistently observed in either the alogliptin or placebo arms. Given the overall variability in IGF-1 and IGFBP-3 measurements during the study, it is difficult to draw any conclusions regarding the impact of alogliptin treatment.

Table 35 displays the change from baseline to week 52 in bone specific alkaline phosphatase and in type 1 collagen C-telopeptides. Overall, no treatment-related effects were evident in the markers of bone metabolism, or in changes from baseline to week 52 in calcium and phosphate (data not shown).

Table 35: Change from Baseline to Week 52 in Markers of Bone Metabolism

	Alogliptin 25 mg QD (N=75)	Placebo (N=76)	Total (N=151)
Bone specific alkaline phosphatase (U/L)			
Mean (SD)	-15.4 (22.50)	-14.4 (18.00)	-14.9 (20.15)
Median (Min, Max)	-8.6 (-88.6, 16.9)	-8.9 (-58.8, 19.1)	-8.9 (-88.6, 19.1)
Type 1 Collagen C-Telopeptides (ng/L)			
Mean (SD)	-100.3 (337.68)	-153.3 (252.13)	-129.1 (293.90)
Median (Min, Max)	-52.0 (-886, 771)	-116.0 (-965, 439)	-81.0 (-965, 771)

Source: reviewer generated using OCS Analysis Studio, Custom Table Tool.

Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.

Bone specific alkaline phosphatase (U/L) - Dataset: Laboratory; Filter: AVISIT = 'Week 52 (Day 365)', PARAM = 'Bone Specific Alkaline Phosphatase (U/L)'.

Type 1 Collagen C-Telopeptides (ng/L) - Dataset: Laboratory; Filter: PARAM = 'Type 1 Collagen C-Telopeptides (ng/L)', AVISIT = 'Week 52 (Day 365)'.

SD = Standard Deviation.

Lipids:

As discussed in Section 6.1.1, change from baseline in lipids was an exploratory endpoint. Based on a reviewer-completed analysis, no clinically meaningful differences between treatment groups were observed in LDL, HDL, total cholesterol and triglycerides for mean change from baseline to week 26 or week 52 (data not shown); the Applicant's analyses revealed similar results.

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Hematology:

According to the Applicant's analysis, no clinically meaningful differences between treatment groups were observed in results of hematology evaluations for mean changes from baseline or markedly abnormal values. These data were reviewed, and I concur with the Applicant's conclusions. Results of a reviewer-completed analysis for mean changes in baseline for hematocrit, hemoglobin, leukocytes, neutrophils and platelets revealed similar results (data not shown).

As discussed in Section 6.1.1, an exploratory endpoint, change from baseline in CD26 surface antigen levels, was assessed based on an evaluation of change from baseline in the ratio of CD4-positive T-cells to CD26-positive T-cells, and in the ratio of CD8-positive T-cells to CD26-positive T-cells. According to a reviewer-conducted analysis (data not shown), no clinically meaningful differences were observed in this endpoint at weeks 26 or 52. The Applicant's analysis revealed similar results.

Serum Chemistry:

According to the Applicant's analyses, no clinically meaningful differences between treatment groups were observed with respect to mean change from baseline or shifts out of the normal range in serum chemistry values. Table 36 displays the incidence of subjects who had markedly abnormal laboratory values according to the Applicant's analysis in the CSR. Data regarding hypoglycemia and hepatic function changes have been previously discussed; no other clinically meaningful imbalances in markedly abnormal laboratory values were apparent.

Table 36: Number and Percentage of Subjects with Markedly Abnormal Laboratory Values, Study SYR-322_309

	n/M (%) ^b	
	Placebo (N = 76)	Alogliptin 25 mg QD (N = 75)
Alanine aminotransferase (U/L)		
≥3 × ULN	8/75 (10.7)	4/72 (5.6)
Aspartate aminotransferase (U/L)		
≥3 × ULN	2/75 (2.7)	0
Cholesterol (mmol/L)		
>7.72 mmol/L	1/75 (1.3)	1/72 (1.4)
Gamma glutamyltransferase (U/L)		
≥3 × ULN	2/75 (2.7)	5/72 (6.9)
Glucose (mmol/L)		
<2.8 mmol/L	10/75 (13.3)	15/73 (20.5)
>19.4 mmol/L	8/75 (10.7)	10/73 (13.7)
Potassium (mmol/L)		
<3.0 mmol/L	0	1/72 (1.4)
>6.0 mmol/L	0	0
Phosphate (mmol/L)		
<0.52 mmol/L	0	0
>2.00 mmol/L	0	1/72 (1.4)
Sodium (mmol/L)		
<130 mmol/L	1/75 (1.3)	0
>150 mmol/L	0	0
Triglycerides (mmol/L)		
>2.5 × ULN	5/75 (6.7)	1/72 (1.4)

Source: Study SYR-322_309 CSR. Abbreviations: QD: once daily, ULN: upper limit of normal.

^a at least 1 postbaseline markedly abnormal result. During study was defined as being from date of first dose of study treatment to 7 days after the last dose of study treatment.

^b the denominator M is the number of subjects with nonmissing data at the timepoint, n is the number of subjects with markedly abnormal values at the time point, postbaseline.

Reviewer Comment: Overall, no new safety signals were observed based on the safety analysis of laboratory parameters in pediatric T2D subjects aged 10 years and older in Study SYR-322_309.

8.4.7. Vital Signs

Based on a reviewer-completed analysis, there were no clinically meaningful changes in mean systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, pulse rate, or respiratory rate from baseline to week 26 or to week 52 in subjects treated with alogliptin (data not shown).

8.4.8. Electrocardiograms (ECGs)

Based on review of the adeg.xpt dataset, through week 26, 2 alogliptin-treated subjects and 5 placebo-treated subjects experienced ECG changes considered to be worsening from baseline; through week 52, 3 alogliptin-treated subjects and 6 placebo-treated subjects experienced ECG changes considered to be worsening from baseline. Based on the Applicant's analyses of clinically significant shifts in ECG parameter, 2 alogliptin-treated subjects experienced a shift to abnormal clinically significant at weeks 26 and 52.

Only 1 ECG-related AE occurred in an alogliptin-treated subject: an AE of bundle-branch block (subject (b) (6)). This AE occurred on the day of randomization and was therefore classified as treatment-emergent; however, it occurred prior to the first dose of study medication and therefore was unrelated to alogliptin-treatment (see Section 8.3.2 regarding the Applicant's definition of TEAEs).

Reviewer comment: Overall, no imbalance in ECG changes was observed with alogliptin treatment.

8.4.9. QT

This section was evaluated as part of the original NDA review.

8.4.10. Immunogenicity

Immunogenicity was not assessed in Study SYR-322_309.

8.5. Analysis of Submission-Specific Safety Issues

Submission-specific safety issues are discussed throughout Section 8.4 of this review, with the exception of puberty and growth assessments which are described in Section 8.8.3

8.6. Safety Analyses by Demographic Subgroups

The Applicant did not assess AEs in relation to any demographic subgroups, as this was not prespecified in the SAP. An analysis of the impact of background antidiabetic medication on hypoglycemia risk was conducted and previously described (see Section 8.4.4). Common TEAEs by SOC and PT occurring in >5 % of treated subjects based on age (10-14 years vs. > 14 years), sex (female vs. male) and race (white race vs. all other races) are displayed in the Appendix Section 13.3 (see Table 42, Table 43 and Table 44). Subgroup analysis based on ethnicity was not conducted as > 50% of the study population was missing an ethnicity designation. Overall, no meaningful differences were observed in the incidence of TEAEs based on age, sex or race. Minor imbalances are most likely due to chance, considering the small number of subjects within these subgroups.

8.7. Specific Safety Studies/Clinical Trials

No additional specific safety studies are being conducted.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

There is no information relevant to this section of the review in the submission.

8.8.2. Human Reproduction and Pregnancy

One subject (b) (6) receiving alogliptin became pregnant and was discontinued from the study with the last dose of study drug administered on (b) (6) (study day 209). This subject was a 15-year-old female who was treated with concomitant metformin and had a prior history of NAFLD. According to a review of the datasets, a serum hCG test performed on study day 190 was negative. The subject received insulin glargine on study day 198 for hyperglycemic rescue. The subject discontinued study treatment on study day 209 and initiated folic acid and iron amino acid chelate on study day 212. A healthy baby boy was born by cesarian delivery on (b) (6) with no reported issues.

Reviewer Comment: Based on negative hCG testing on study day 190 prior to the discovery of pregnancy on study day 209, the subject most likely was exposed to alogliptin for a few weeks in the first trimester of pregnancy. Based on non-clinical studies of alogliptin, no adverse developmental effects were observed when alogliptin was administered to pregnant rates during organogenesis at high multiples of exposure to the clinical dose.

8.8.3. Pediatrics and Assessment of Effects on Growth

Puberty:

Tanner staging was assessed separately for breast/genitalia and for pubic hair at baseline, week 26 and at week 52. As discussed in Section 6.1.2, the majority of the trial population (78.1%) had Tanner stage 4 to 5 for breast/genitalia at baseline. Baseline Tanner stage for breast/genitalia for female and male subjects are displayed separately in Table 37 and Table 38; baseline Tanner stage based on pubic hair development for all subjects is displayed in Table 39. Overall, 78.8% of female subjects and 76.6% of male subjects were Tanner stage 4 to 5 for breast/genitalia at baseline, and 78.2% of the study population were Tanner stage 4 to 5 for pubic hair at baseline. Very few subjects (19.2% of female subjects and 23.4% of male subjects) were Tanner stage 2 to 3 for breast/genitalia at baseline. One (1) subject in the placebo arm was Tanner stage 1 at baseline; this subject was noted to be Tanner stage 2 by week 26 suggesting interval onset of puberty during the study. One (1) subject in the placebo arm also had missing baseline pubertal status but was subsequently noted to be Tanner stage 5 at week 26.

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Table 37: Baseline Tanner Stage (Breast) among Female Subjects, Study SYR-322_309

	Alogliptin 25 mg QD (N=53)	Placebo (N=51)	Total (N=104)
Tanner Stage (breast)			
1	0	1 (2.0)	1 (1.0)
2	2 (3.8)	1 (2.0)	3 (2.9)
3	7 (13.2)	10 (19.6)	17 (16.3)
4	20 (37.7)	11 (21.6)	31 (29.8)
5	24 (45.3)	27 (52.9)	51 (49.0)
Missing	0	1 (2.0)	1 (1.0)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool.

Columns - Dataset: Demographics; Filter: SAFFL = 'Y', SEX = 'F'.

Table Section 1 - Dataset: Demographics; Filter: None.

Table 38: Baseline Tanner Stage (Genitalia) among Male Subjects, Study SYR-322_309

	Alogliptin 25 mg QD (N=22)	Placebo (N=25)	Total (N=47)
Tanner Stage (genitalia)			
2	3 (13.6)	2 (8.0)	5 (10.6)
3	4 (18.2)	2 (8.0)	6 (12.8)
4	6 (27.3)	7 (28.0)	13 (27.7)
5	9 (40.9)	14 (56.0)	23 (48.9)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool.

Columns - Dataset: Demographics; Filter: SAFFL = 'Y', SEX = 'M'.

Table Section 1 - Dataset: Demographics; Filter: None.

Table 39: Baseline Tanner Stage (Pubic Hair), Study SYR-322_309

	Alogliptin 25 mg QD (N=75)	Placebo (N=76)	Total (N=151)
Tanner Stage (pubic hair)			
1	0	1 (1.3)	1 (0.7)
2	8 (10.7)	6 (7.9)	14 (9.3)
3	7 (9.3)	10 (13.2)	17 (11.3)
4	29 (38.7)	20 (26.3)	49 (32.5)
5	31 (41.3)	38 (50.0)	69 (45.7)
Missing	0	1 (1.3)	1 (0.7)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool.

Columns - Dataset: Demographics; Filter: SAFFL = 'Y'.

Table Section 1 - Dataset: Demographics; Filter: None.

Reviewer Comment: Consistent with other recently completed pediatric T2D phase 3 studies, the majority of the study population, including both male and female subjects, were in advanced puberty (Tanner stage 4-5) at baseline. Given that, any observations regarding the impact of alogliptin treatment on pubertal development are likely to be limited.

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Change from baseline in Tanner stage scores was included among the exploratory endpoints. According to the Applicant's analyses, no statistically significant difference between treatment groups was observed for increased Tanner stage score at week 26 or week 52 for any component of Tanner stage assessments.

Based on a review of the adrs.xpt dataset, a shift table for Tanner stage (breast/genitalia) was generated for subjects who were below Tanner stage 5 at baseline. Most subjects either remained in the baseline Tanner stage or progressed to the next Tanner stage by week 52. One (1) alogliptin-treated subject with baseline Tanner stage 4 was assessed as Tanner stage 3 at week 52, likely reflecting misclassification of either baseline or week 52 Tanner stage. Two (2) subjects in the alogliptin treated arm who were assessed as Tanner stage 3 at baseline advanced to Tanner stage 5 by week 52; no subjects in the alogliptin-treated arm advanced by more than 1 stage.

Table 40: Shift Table for Tanner Stage for Breast/Genitalia from Baseline to Week 52

	Alogliptin				Placebo			
	Week 52				Week 52			
Baseline	Tanner 2	Tanner 3	Tanner 4	Tanner 5	Tanner 2	Tanner 3	Tanner 4	Tanner 5
Tanner 1	0	0	0	0	1	0	0	0
Tanner 2	0	1	2	0	0	0	1	1
Tanner 3	0	4	3	0	0	5	3	2
Tanner 4	0	1	17	4	0	0	11	3

Source: Reviewer generated, based on review of adrs.xpt dataset

Reviewer Comment: Overall, no treatment-related differences in pubertal development were observed in study SYR-322_309; however, the evaluation of pubertal effects was limited by the small numbers of subjects in the early stages of puberty.

Height:

Height was measured at baseline, week 26 and week 52. Given that subjects who have completed linear growth would not be expected to have further increase in height, evaluation of change in height should be restricted to subjects who have not yet completed linear growth. Given the unavailability of bone age or pre-trial growth velocity which would more directly assess further growth potential, and since the end of puberty (i.e., Tanner stage 5) usually coincides with near-completion of linear growth, an analysis of height changes in the subjects

who had baseline Tanner stage for breast/genitalia from 1 to 4 was conducted (Table 41). Overall, a small mean increase in height was reported in both treatment arms from baseline to week 26 and to week 52; however, the magnitude of height increase remains far below what would normally be expected in pubertal subjects over a 6-to-12-month period. Notably, some subjects experienced reported decreases in height ranging from -1 to -3 cm from baseline to week 26 and from baseline to week 52; this finding is most likely the result of measurement error.

Table 41: Change from Baseline in Height (cm) in Subjects with Baseline Tanner Stage (Breast/Genitalia) <5

	Alogliptin 25 mg QD (N=42)	Placebo (N=35)	Total (N=77)
Change from baseline to week 26 in height (cm)			
Mean (SD)	1.2 (2.05)	1.1 (2.02)	1.1 (2.02)
Median (Min, Max)	0.0 (-3, 7)	0.0 (-1, 8)	0.0 (-3, 8)
Change from baseline to week 52 in height (cm)			
Mean (SD)	1.7 (2.70)	2.0 (2.65)	1.8 (2.66)
Median (Min, Max)	0.5 (-3, 9)	1.0 (-1, 10)	1.0 (-3, 10)

Source: Reviewer generated using OCS Analysis Studio, Custom Table Tool.

Columns - Dataset: Demographics; Filter: SAFFL = 'Y', TSSBSL = '1' or '3' or '2' or 'Missing' or '4'.

Change from baseline to week 26 in height (cm) - Dataset: Vital Signs; Filter: PARAM = 'Height (cm)', AVISIT = 'Week 26 (Day 183)'.

Change from baseline to week 52 in height (cm) - Dataset: Vital Signs; Filter: AVISIT = 'Week 52 (Day 365)', PARAM = 'Height (cm)'.

SD = Standard Deviation.

* This analysis included 1 placebo-treated subject with missing baseline Tanner stage; this subject was recoded as having Tanner stage 5 at week 26 therefore it is uncertain whether they had completed linear growth at baseline or whether they may have had a Tanner stage < 5 at baseline that progressed to Tanner stage 5 by week 26. , This analysis also included 1 placebo-treated subject with baseline Tanner stage 1 who was recorded as Tanner stage 2 for breast/genitalia at week 26, suggesting that this subject had entered puberty during the trial.

Reviewer Comment: Because adolescents who have completed linear growth would not be expected to exhibit further changes in height, the safety evaluation for any treatment-related effects on growth should be focused on subjects who have remaining growth potential. Remaining growth potential would have been best assessed either by evaluation of pre-study growth velocity, bone age assessment, and/or information regarding mid-parental height; however, none of this information was collected systematically. Because the end of puberty (i.e., Tanner stage 5) typically correlates with near-completion of linear growth, changes in height in the subgroup of subjects who were below Tanner stage 5 at baseline were explored. However, even within this subgroup, minimal changes in height were observed through week 26 and through week 52, with an overall change in height of 1.8 cm/year. This represents an abnormally low growth velocity for subjects undergoing puberty. This finding may be explained by measurement error given that some subjects in both treatment arms are reported to have experienced a “decrease” in height from baseline to week 26 and to week 52. As these findings were consistent across treatment arms, there is no obvious evidence of any treatment-related impact on growth; however, it is difficult to draw any conclusions given the limitations in the data.

Body Mass Index:

Body mass index was calculated based on measured height and weight, and BMI percentiles

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

and Z-scores were computed using the Centers for Disease Control (CDC) growth chart by age and gender. Based on both reviewer-conducted and Applicant-conducted analyses, no clinically meaningful differences were observed in change from baseline in BMI z-score or BMI percentile.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

This section was evaluated as part of the original NDA review. There are no unique considerations for pediatrics that warrant discussion.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

The Applicant states that the cumulative global post-marketing adult patient exposure to alogliptin monotherapy and to alogliptin as a fixed-dose combination with metformin post-authorization through April 15, 2023 is estimated 9,783,682 and 2,133,749 patient-years, respectively⁴.

Based on post-marketing reports, the warnings and precautions for alogliptin-containing products were updated in 2015 and 2016 to include severe and disabling arthralgia, pancreatitis, fatal and non-fatal hepatic failure and bullous pemphigoid. In April 2016, a warning and precaution regarding heart failure was also added to the product labeling, based on results of the cardiovascular outcome trial (EXAMINE) in which a greater percentage of patients with T2D and recent coronary syndrome who were treated with alogliptin as compared to placebo were hospitalized for congestive heart failure. In March 2022, based on post-marketing reports, “tubulointerstitial nephritis” was added to the post-marketing experience section of the labeling for all alogliptin-containing products³⁷. The Division of pharmacovigilance recently conducted an evaluation of cases of intestinal obstruction associated with DPP-4 inhibitors but concluded that there was insufficient evidence for the addition of intestinal obstruction to the USP for DPP-4 inhibitor products³⁸. The alogliptin USPI presently includes ileus in Section 6.2 postmarketing experience.

Based on the most recent periodic benefit-risk evaluation report for Nesina and Kazano (reporting period from April 16, 2022 through April 15, 2023), no new safety signals were identified³⁹.

³⁷ This action was taken in response to a proposed labeling update by Takeda for all alogliptin-containing products to include the adverse reaction of tubulointerstitial nephritis (TIN) in the postmarketing experience of the prescribing information and was also supported by a pharmacovigilance review of TIN within the DPP-4 inhibitor drug class which recommended the addition of TIN to Section 6.2 for alogliptin and sitagliptin containing products.

³⁸ See October 26, 2022 review by Dr. Ali Niak of DPV-I under NDA 022271.

³⁹ See primary clinical review of the referenced PBRER, submitted 7/5/2023 under NDAs 022271 and 203414

8.9.2. Expectations on Safety in the Postmarket Setting

This section is not relevant since a pediatric indication is not being granted.

8.9.3. Additional Safety Issues From Other Disciplines

No additional safety issues were identified from other disciplines.

8.10. Integrated Assessment of Safety

The risks of alogliptin in adults with T2D are well-characterized, and include pancreatitis, hypoglycemia with concomitant use of insulin or insulin secretagogues, hypersensitivity reactions, arthralgia, bullous pemphigoid and heart failure.

In Study SYR-322_309, the overall safety profile of alogliptin was generally similar to the known and labeled risks in adults with T2D.

No deaths occurred in the study. SAEs occurred in 2 (2.7%) subjects treated with alogliptin and in 3 (4.0%) subjects treated with placebo. No SAEs in alogliptin-treated subjects were assessed as related to treatment. With regard to AESIs, no events relating to pancreatitis or severe hypersensitivity reactions occurred in the trial. AESIs relating to hepatic events occurred in 1 subject (1.3%) treated with alogliptin and in 2 subjects (3.6%) treated with placebo. AESIs relating to infections occurred in 8 subjects (10.6%) treated with alogliptin and in 9 subjects (11.8%) treated with placebo. Overall, the AESIs occurring in alogliptin-treated subjects in Study SYR-322_309 were consistent with the safety signals identified in adult studies. The most common TEAEs in alogliptin-treated subjects were headache, hyperglycemia, diarrhea and influenza.

No severe hypoglycemia events occurred in Study SYR-322_309. Overall, hypoglycemia events occurred in 5.3% of alogliptin-treated subjects and in 6.5% of placebo-treated subjects. Hypoglycemia events were more likely to occur in subjects who received background insulin therapy as compared to those who did not receive background insulin therapy, but there did not appear to be any imbalance in hypoglycemia events associated with alogliptin treatment as compared to placebo. This finding is consistent with that reported in adult studies of alogliptin; however, hypoglycemia with concomitant use of insulin or insulin secretagogues is an identified safety signal for other DPP-4 inhibitors and is described in the alogliptin product label.

One alogliptin-treated subject who had mild renal impairment at baseline shifted to moderate renal impairment by the end of the study. This subject most likely had progression of underlying diabetic nephropathy, based on evidence of baseline macroalbuminuria that also worsened over the course of the trial. With regard to hepatic function, no subject met criteria for Hy's law, and overall, fewer alogliptin treated subjects experienced AST or ALT > 3x ULN as

compared to those treated with placebo (5.6% vs. 9.2%). One alogliptin-treated subject experienced a prolonged ALT elevation of 4.5x ULN; hepatic events have been identified in post-marketing reports and are currently described in Section 5 (Warnings and Precautions) of the alogliptin product label. No clinically relevant changes in other laboratory parameters or vital signs were noted. The majority of the trial population were in advanced puberty at baseline, limiting evaluation of treatment-related effects on growth and puberty.

In summary, based on the submitted data from Study SYR-322_309, no new safety signals were identified in pediatric T2D subjects as compared to those described in adult studies.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not convened for this supplement.

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, labeling negotiations were ongoing). We recommend that Section 8.4 for the USPIs of Nesina and Kazano be updated with an appropriate pediatric use statement clarifying that the safety and effectiveness have not been established in pediatric patients and summarizing the available evidence from the DINAMO study.

10.2. Nonprescription Drug Labeling

This section is not applicable to the submission.

11. Risk Evaluation and Mitigation Strategies (REMS)

No REMS are recommended.

12. Postmarketing Requirements and Commitments

No postmarketing requirements or commitments are applicable to this supplement.

13. Appendices

13.1. References

See references at the end of this document.

13.2. Financial Disclosure

Attached to form FDA 3454, the applicant provided a listing of all investigators and sub-investigators; none disclosed any financial interests or arrangements.

Covered Clinical Study (Name and/or Number): SYR-322-309

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from Applicant)
Total number of investigators identified: <u>182</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
<p>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)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in S</p> <p>Sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		

Clinical Review
Kim Shimy, MD
NDA 022271/S-015, NDA 203414/S-016
Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from Applicant)
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13.3. Demographic Subgroup Safety Analyses

Table 42: TEAEs by SOC and PT based on Age, Study SYR-322_309

System Organ Class - Preferred Term	Alogliptin (≤14 years) (N=40)	Placebo (≤14 years) (N=39)	Alogliptin (>14 years) (N=35)	Placebo (>14 years) (N=37)
	n (%)	n (%)	n (%)	n (%)
Blood and lymphatic system disorders	2 (5.0)	1 (2.6)	1 (2.9)	0 (0.0)
Gastrointestinal disorders	8 (20.0)	9 (23.1)	7 (20.0)	8 (21.6)
Abdominal pain	1 (2.5)	2 (5.1)	1 (2.9)	1 (2.7)
Abdominal pain upper	1 (2.5)	1 (2.6)	0 (0.0)	2 (5.4)
Constipation	2 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhea	5 (12.5)	4 (10.3)	2 (5.7)	3 (8.1)
Nausea	1 (2.5)	3 (7.7)	2 (5.7)	2 (5.4)
Vomiting	2 (5.0)	4 (10.3)	2 (5.7)	2 (5.4)
General disorders and administration site conditions	8 (20.0)	2 (5.1)	1 (2.9)	0 (0.0)
Influenza like illness	2 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pyrexia	2 (5.0)	1 (2.6)	0 (0.0)	0 (0.0)
Immune system disorders	1 (2.5)	2 (5.1)	1 (2.9)	1 (2.7)
Infections and infestations	17 (42.5)	12 (30.8)	11 (31.4)	14 (37.8)
Bronchitis	2 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Covid-19	1 (2.5)	0 (0.0)	0 (0.0)	3 (8.1)
Gastroenteritis	1 (2.5)	0 (0.0)	1 (2.9)	2 (5.4)
Influenza	3 (7.5)	1 (2.6)	4 (11.4)	1 (2.7)
Nasopharyngitis	1 (2.5)	1 (2.6)	1 (2.9)	2 (5.4)
Sinusitis	1 (2.5)	1 (2.6)	0 (0.0)	3 (8.1)
Upper respiratory tract infection	4 (10.0)	2 (5.1)	0 (0.0)	1 (2.7)
Injury, poisoning and procedural complications	4 (10.0)	4 (10.3)	2 (5.7)	4 (10.8)
Contusion	0 (0.0)	0 (0.0)	2 (5.7)	2 (5.4)
Investigations	6 (15.0)	5 (12.8)	5 (14.3)	6 (16.2)
Alanine aminotransferase increased	0 (0.0)	1 (2.6)	1 (2.9)	2 (5.4)
Aspartate aminotransferase increased	0 (0.0)	2 (5.1)	0 (0.0)	1 (2.7)
C-telopeptide increased	1 (2.5)	0 (0.0)	1 (2.9)	2 (5.4)
Gamma-glutamyltransferase increased	0 (0.0)	2 (5.1)	1 (2.9)	0 (0.0)
Glycosylated hemoglobin increased	2 (5.0)	2 (5.1)	1 (2.9)	2 (5.4)
Sars-cov-2 test positive	2 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	11 (27.5)	12 (30.8)	6 (17.1)	11 (29.7)

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

System Organ Class - Preferred Term	Alogliptin (≤14 years) (N=40) n (%)	Placebo (≤14 years) (N=39) n (%)	Alogliptin (>14 years) (N=35) n (%)	Placebo (>14 years) (N=37) n (%)
Diabetes mellitus	2 (5.0)	0 (0.0)	0 (0.0)	2 (5.4)
Hypercholesterolemia	2 (5.0)	0 (0.0)	0 (0.0)	1 (2.7)
Hyperglycemia	6 (15.0)	5 (12.8)	3 (8.6)	4 (10.8)
Hypertriglyceridemia	0 (0.0)	3 (7.7)	2 (5.7)	2 (5.4)
Type 2 diabetes mellitus	2 (5.0)	3 (7.7)	1 (2.9)	2 (5.4)
Vitamin d deficiency	0 (0.0)	1 (2.6)	0 (0.0)	2 (5.4)
Musculoskeletal and connective tissue disorders	3 (7.5)	5 (12.8)	2 (5.7)	1 (2.7)
Arthralgia	0 (0.0)	2 (5.1)	1 (2.9)	1 (2.7)
Nervous system disorders	9 (22.5)	4 (10.3)	8 (22.9)	7 (18.9)
Dizziness	1 (2.5)	0 (0.0)	2 (5.7)	2 (5.4)
Headache	7 (17.5)	4 (10.3)	7 (20.0)	4 (10.8)
Psychiatric disorders	1 (2.5)	2 (5.1)	0 (0.0)	3 (8.1)
Anxiety	0 (0.0)	2 (5.1)	0 (0.0)	0 (0.0)
Renal and urinary disorders	2 (5.0)	1 (2.6)	3 (8.6)	2 (5.4)
Albuminuria	0 (0.0)	0 (0.0)	2 (5.7)	0 (0.0)
Reproductive system and breast disorders	3 (7.5)	2 (5.1)	4 (11.4)	1 (2.7)
Dysmenorrhea	3 (7.5)	1 (2.6)	2 (5.7)	1 (2.7)
Respiratory, thoracic and mediastinal disorders	2 (5.0)	3 (7.7)	3 (8.6)	1 (2.7)
Cough	0 (0.0)	2 (5.1)	0 (0.0)	0 (0.0)
Oropharyngeal pain	0 (0.0)	2 (5.1)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	4 (10.0)	3 (7.7)	1 (2.9)	4 (10.8)

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Alogliptin 25 mg QD" and AGE = 10 to 14 and SAFFL = "Y" (Alogliptin in (≤14 years)); TRT01A = "Placebo" and AGE = 10 to 14 and SAFFL = "Y" (Placebo (≤14 years)); TRT01A = "Alogliptin 25 mg QD" and AGE = 15 to 17 and SAFFL = "Y" (Alogliptin (>14 years)); TRT01A = "Placebo" and AGE = 15 to 17 and SAFFL = "Y" (Placebo (>14 years)); TRTEMFL = "Y" (Adverse Events).

Percent Threshold: Any Column ≥ 5%.

Table 43: TEAEs by SOC and PT based on Race, Study SYR-322_309

System Organ Class - Preferred Term	Alogliptin (White) (N=44) n (%)	Placebo (White) (N=44) n (%)	Alogliptin (Non- White) (N=31) n (%)	Placebo (Non-White) (N=32) n (%)
Gastrointestinal disorders	10 (22.7)	11 (25.0)	5 (16.1)	6 (18.8)
Abdominal pain	2 (4.5)	1 (2.3)	0 (0.0)	2 (6.3)
Constipation	0 (0.0)	0 (0.0)	2 (6.5)	0 (0.0)
Diarrhea	4 (9.1)	5 (11.4)	3 (9.7)	2 (6.3)
Nausea	3 (6.8)	3 (6.8)	0 (0.0)	2 (6.3)
Vomiting	3 (6.8)	4 (9.1)	1 (3.2)	2 (6.3)
General disorders and administration site conditions	4 (9.1)	0 (0.0)	5 (16.1)	2 (6.3)
Pyrexia	0 (0.0)	0 (0.0)	2 (6.5)	1 (3.1)
Immune system disorders	1 (2.3)	0 (0.0)	1 (3.2)	3 (9.4)

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

System Organ Class - Preferred Term	Alogliptin (White) (N=44) n (%)	Placebo (White) (N=44) n (%)	Alogliptin (Non- White) (N=31) n (%)	Placebo (Non-White) (N=32) n (%)
Seasonal allergy	1 (2.3)	0 (0.0)	1 (3.2)	2 (6.3)
Infections and infestations	13 (29.5)	17 (38.6)	15 (48.4)	9 (28.1)
Covid-19	0 (0.0)	3 (6.8)	1 (3.2)	0 (0.0)
Influenza	5 (11.4)	2 (4.5)	2 (6.5)	0 (0.0)
Nasopharyngitis	1 (2.3)	1 (2.3)	1 (3.2)	2 (6.3)
Sinusitis	1 (2.3)	3 (6.8)	0 (0.0)	1 (3.1)
Upper respiratory tract infection	2 (4.5)	2 (4.5)	2 (6.5)	1 (3.1)
Urinary tract infection	0 (0.0)	1 (2.3)	2 (6.5)	0 (0.0)
Injury, poisoning and procedural complications	5 (11.4)	4 (9.1)	1 (3.2)	4 (12.5)
Investigations	6 (13.6)	4 (9.1)	5 (16.1)	7 (21.9)
Albumin urine present	0 (0.0)	0 (0.0)	2 (6.5)	0 (0.0)
Aspartate aminotransferase increased	0 (0.0)	1 (2.3)	0 (0.0)	2 (6.3)
Gamma-glutamyltransferase increased	0 (0.0)	0 (0.0)	1 (3.2)	2 (6.3)
Glycosylated hemoglobin increased	3 (6.8)	0 (0.0)	0 (0.0)	4 (12.5)
Metabolism and nutrition disorders	9 (20.5)	12 (27.3)	8 (25.8)	11 (34.4)
Hyperglycemia	4 (9.1)	4 (9.1)	5 (16.1)	5 (15.6)
Hypertriglyceridemia	0 (0.0)	4 (9.1)	2 (6.5)	1 (3.1)
Type 2 diabetes mellitus	2 (4.5)	2 (4.5)	1 (3.2)	3 (9.4)
Musculoskeletal and connective tissue disorders	2 (4.5)	3 (6.8)	3 (9.7)	3 (9.4)
Nervous system disorders	11 (25.0)	7 (15.9)	6 (19.4)	4 (12.5)
Headache	9 (20.5)	4 (9.1)	5 (16.1)	4 (12.5)
Psychiatric disorders	1 (2.3)	2 (4.5)	0 (0.0)	3 (9.4)
Anxiety	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.3)
Renal and urinary disorders	2 (4.5)	1 (2.3)	3 (9.7)	2 (6.3)
Reproductive system and breast disorders	4 (9.1)	2 (4.5)	3 (9.7)	1 (3.1)
Dysmenorrhea	2 (4.5)	2 (4.5)	3 (9.7)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	2 (4.5)	5 (16.1)	2 (6.3)
Nasal congestion	0 (0.0)	0 (0.0)	2 (6.5)	2 (6.3)
Skin and subcutaneous tissue disorders	3 (6.8)	2 (4.5)	2 (6.5)	5 (15.6)
Hidradenitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.3)

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Alogliptin 25 mg QD" and RACE = "WHITE" and SAFFL = "Y" (Alogliptin (White)); TRT01A = "Placebo" and RACE = "WHITE" and SAFFL = "Y" (Placebo (White)); TRT01A = "Alogliptin 25 mg QD" and RACE = "BLACK OR AFRICAN AMERICAN" or "AMERICAN INDIAN OR ALASKA NATIVE" or "MULTIPLE" or "ASIAN" and SAFFL = "Y" (Alogliptin (Non-White)); TRT01A = "Placebo" and RACE = "BLACK OR AFRICAN AMERICAN" or "AMERICAN INDIAN OR ALASKA NATIVE" or "MULTIPLE" or "ASIAN" and SAFFL = "Y" (Placebo (Non-White)); TRTEMFL = "Y" (Adverse Events).

Percent Threshold: Any Column ≥ 5%.

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

Table 44: TEAEs by SOC and PT based on Sex, Study SYR-322_309

System Organ Class - Preferred Term	Alogliptin (Female) (N=53) n (%)	Placebo (Female) (N=51) n (%)	Alogliptin (Male) (N=22) n (%)	Placebo (Male) (N=25) n (%)
Blood and lymphatic system disorders	3 (5.7)	1 (2.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	10 (18.9)	12 (23.5)	5 (22.7)	5 (20.0)
Abdominal pain upper	1 (1.9)	3 (5.9)	0 (0.0)	0 (0.0)
Diarrhea	5 (9.4)	5 (9.8)	2 (9.1)	2 (8.0)
Nausea	1 (1.9)	3 (5.9)	2 (9.1)	2 (8.0)
Vomiting	1 (1.9)	4 (7.8)	3 (13.6)	2 (8.0)
General disorders and administration site conditions	6 (11.3)	2 (3.9)	3 (13.6)	0 (0.0)
Infections and infestations	21 (39.6)	19 (37.3)	7 (31.8)	7 (28.0)
Influenza	6 (11.3)	1 (2.0)	1 (4.5)	1 (4.0)
Nasopharyngitis	1 (1.9)	3 (5.9)	1 (4.5)	0 (0.0)
Sinusitis	0 (0.0)	2 (3.9)	1 (4.5)	2 (8.0)
Upper respiratory tract infection	3 (5.7)	2 (3.9)	1 (4.5)	1 (4.0)
Injury, poisoning and procedural complications	5 (9.4)	4 (7.8)	1 (4.5)	4 (16.0)
Contusion	2 (3.8)	0 (0.0)	0 (0.0)	2 (8.0)
Investigations	8 (15.1)	7 (13.7)	3 (13.6)	4 (16.0)
Aspartate aminotransferase increased	0 (0.0)	3 (5.9)	0 (0.0)	0 (0.0)
C-telopeptide increased	0 (0.0)	0 (0.0)	2 (9.1)	2 (8.0)
Glycosylated hemoglobin increased	1 (1.9)	2 (3.9)	2 (9.1)	2 (8.0)
Metabolism and nutrition disorders	12 (22.6)	15 (29.4)	5 (22.7)	8 (32.0)
Hyperglycemia	7 (13.2)	6 (11.8)	2 (9.1)	3 (12.0)
Hypertriglyceridemia	1 (1.9)	4 (7.8)	1 (4.5)	1 (4.0)
Type 2 diabetes mellitus	2 (3.8)	2 (3.9)	1 (4.5)	3 (12.0)
Musculoskeletal and connective tissue disorders	3 (5.7)	5 (9.8)	2 (9.1)	1 (4.0)
Nervous system disorders	12 (22.6)	9 (17.6)	5 (22.7)	2 (8.0)
Dizziness	1 (1.9)	0 (0.0)	2 (9.1)	2 (8.0)
Headache	10 (18.9)	8 (15.7)	4 (18.2)	0 (0.0)
Psychiatric disorders	1 (1.9)	5 (9.8)	0 (0.0)	0 (0.0)
Renal and urinary disorders	3 (5.7)	2 (3.9)	2 (9.1)	1 (4.0)
Albuminuria	0 (0.0)	0 (0.0)	2 (9.1)	0 (0.0)
Reproductive system and breast disorders	7 (13.2)	3 (5.9)	0 (0.0)	0 (0.0)
Dysmenorrhea	5 (9.4)	2 (3.9)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	2 (3.8)	4 (7.8)	3 (13.6)	0 (0.0)
Skin and subcutaneous tissue disorders	5 (9.4)	5 (9.8)	0 (0.0)	2 (8.0)

Source: OCS Analysis Studio, Safety Explorer.

Filters: TRT01A = "Alogliptin 25 mg QD" and SEX = "F" and SAFFL = "Y" (Alogliptin (Female)); TRT01A = "Placebo" and SEX = "F" and SAFFL = "Y" (Placebo (Female)); TRT01A = "Alogliptin 25 mg QD" and SEX = "M" and SAFFL = "Y" (Alogliptin (Male)); TRT01A = "Placebo" and SEX = "M" and SAFFL = "Y" (Placebo (Male)); TRTEMFL = "Y" (Adverse Events).

Percent Threshold: Any Column ≥ 5%.

Clinical Review

Kim Shimy, MD

NDA 022271/S-015, NDA 203414/S-016

Nesina (alogliptin) tablets, Kazano (alogliptin and metformin hydrochloride) tablets

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/s/

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