CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219122Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	219122
Priority or Standard	Standard
Submit Date(s)	01/04/2024
Received Date(s)	01/04/2024
PDUFA Goal Date	11/04/2024
Division/Office	DDLO/OND
Reviewer Name(s)	Lauren Wood Heickman, MD
Review Completion Date	11/1/2024
Established/Proper Name	Sitagliptin oral solution, 25 mg/mL
(Proposed) Trade Name	Brynovin
Applicant	Azurity Pharmaceuticals, Inc.
Dosage Form(s)	Oral liquid
Applicant Proposed Dosing Regimen(s)	The Applicant is seeking approval of an oral liquid solution 25 mg/mL strength
Applicant Proposed Indication(s)/Population(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

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Glossary

AC	advisory committee
AE	adverse event
BE	bioequivalence
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CGMP	Current Good Manufacturing Practice
CMC	chemistry, manufacturing, and controls
CSR	clinical study report
DPP4	dipeptidyl peptidase-4
ECG	electrocardiogram
FDA	Food and Drug Administration
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
IND	Investigational New Drug Application
LD	listed drug
NDA	new drug application
	(b) (4)
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigation
PD	pharmacodynamic
PK	pharmacokinetic
PMC	postmarketing commitment
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
REMS	risk evaluation and mitigation strategy
SGLT2	Sodium-glucose cotransporter-2
T2DM	type 2 diabetes mellitus

1. Executive Summary

1.1. Product Introduction

Sitagliptin is an DPP-4 enzyme inhibitor, approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). It inhibits the metabolism and elimination of incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), prolonging endogenous incretin actions in glucose homeostasis, and lowers plasmas glucose levels. Sitagliptin was initially approved by the US FDA in 2006 under the brand name Januvia.

On January 4, 2024, Azurity Pharmaceuticals, Inc., herafter referred to as the Applicant, submitted a New Drug Application (NDA) under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act seeking approval for Sitagliptin Hydrochloride Oral Solution, 25 mg/mL to improve glycemic control in adults with type 2 diabetes mellitus. In this 505(b)(2) NDA, the Applicant proposed to rely on FDA's finding of safety and effectiveness for Januvia (sitagliptin phosphate monohydrate tablet, NDA 021995), marketed by Merck Sharp & Dohme Corp.

The Applicant has developed sitagliptin oral liquid solution as a new formulation intended to address the needs of patients with difficulty swallowing sitagliptin tablets. The sitagliptin drug substance for the sitagliptin oral solution is the hydrochloride monohydrate salt rather than the phosphate monohydrate salt (Januvia). The proposed trade name for the product is Brynovin. The Applicant has proposed a single strength of sitagliptin oral solution, 25 mg/mL. The proposed dosing regimen is 4 mL (100 mg) orally once daily with or without food.

The development program for this application is based on demonstration of bioequivalence (BE) to the listed drug Januvia. The Applicant conducted a single pivotal clinical pharmacology study, Study AZ17.001, a relative bioavailability study comparing administration of sitagliptin oral solution, 25 mg/mL administered under fasting and fed conditions, using Januvia tablets as the reference product. The Applicant has proposed that a demonstration of BE, in conjunction with its CMC data package, constitutes an adequate scientific bridge to the listed drug to support reliance on FDA’s finding of safety and effectiveness for Januvia.

The applicant is proposing the following indication:
“BRYNOVIN is a dipeptidyl peptidase-4 (DPP-4) inhibitor indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.”

1.2. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Type 2 diabetes mellitus (T2DM) is a serious chronic medical condition, which has been increasing in prevalence in the United States, and can lead to secondary complications such as retinopathy, neuropathy, nephropathy, and cardiovascular disease. Abnormal glucose homeostasis from insulin resistance and impaired glucose metabolism results in hyperglycemia in patients with T2DM. Improved glycemic control, measured by change from baseline hemoglobin A1c (A1C), is recognized by FDA as a surrogate endpoint, as studies have shown that improved glycemic control reduces the risk of microvascular disease (retinopathy, nephropathy, neuropathy). There are multiple classes of approved pharmacologic treatments for T2DM, including biguanides, sulfonylureas, insulin and insulin analogs, glucagon-like peptide-1 (GLP-1) analogs, dipeptidyl peptidase-4 (DPP4) inhibitors, and sodium-glucose linked transporter-2 (SGLT2) inhibitors, including oral and subcutaneous dosage forms. Several diabetes medications are also available as oral liquid formulations for patients who have difficulty swallowing tablets (including metformin, and colesevelam) but to date, no DPP-4 inhibitors are available as an oral liquid formulation.

Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) enzyme inhibitor, approved for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. It inhibits the metabolism and elimination of incretin hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), prolonging endogenous incretin actions in glucose homeostasis, and lower plasma glucose levels.

The Applicant has submitted an NDA under the 505(b)(2) pathway for sitagliptin oral solution (25 mg/mL) using Januvia, NDA 021995 (sitagliptin tablets) as the reference listed drug (LD). The sitagliptin oral solution product differs from the LD by dosage form (oral solution vs oral tablet) and salt form (sitagliptin hydrochloride vs sitagliptin phosphate). The Applicant conducted a bioequivalence study to bridge sitagliptin oral solution (25 mg/mL) to the reference product, Januvia. The Applicant included a food-effect arm as part of the relative BA study, to assess the effect of food on the PK and relative BA of a 100 mg dose of Azurity Sitagliptin HCl Oral Solution 25 mg/mL under fed versus fasted conditions because Januvia is given once daily with or without food.

The reference product Januvia has been approved in the US since 2006, and its safety and effectiveness have been well-characterized. The benefit-risk assessment for Brynovin is based on the assessment that the data and information submitted constitute an adequate scientific bridge to the reference product, such that reliance on the safety and effectiveness of Januvia is justified.

The relative bioavailability (BA) study met the prespecified endpoints to demonstrate BE under fasted conditions; although the relative BA study did not demonstrate BE under fed conditions, in conjunction with the CMC data, the clinical pharmacology review concluded that the results of the relative BA study constitute an adequate scientific bridge to the listed drug to justify reliance on FDA's previous finding of safety and effectiveness for Januvia. There were no deficiencies in the application related to safety, efficacy, drug substance, drug product, manufacturing process, labeling, and microbiology sections of this application.

There were product quality concerns related to a facility inspection which did not meet Current Good Manufacturing Practice (CGMP) standards. As a result, the Office of Pharmaceutical Quality (OPQ) review team did not recommend approval of oral sitagliptin solution, 25 mg/mL (and I concur) until the Applicant addresses the facilities issue outlined in the complete response letter.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Type 2 diabetes mellitus (T2DM) is a disease characterized by hyperglycemia, insulin resistance, and relative impairment of insulin secretion. • Within the U.S., an estimated 38.1 million adults have diabetes mellitus, with T2DM comprising about 90 to 95% of cases.[1] • T2DM is often associated with other metabolic derangements, such as dyslipidemia, hypertension, and obesity. • Chronic complications of T2DM include cardiovascular disease, retinopathy, nephropathy, and neuropathy.	T2DM is a serious, life-threatening condition that can lead to serious morbidity and mortality if left untreated.

[1] Centers for Disease Control and Prevention. National Diabetes Statistics Report 2021. https://www.cdc.gov/diabetes/php/data-research/index.html. [Accessed October 1, 2024].

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• Treatment options for T2DM includes lifestyle modifications, usually followed by the addition of one or multiple different medications. • There are currently multiple classes of pharmacologic treatments for T2DM, including biguanides, sulfonylureas, insulin and insulin analogs, glucagon-like peptide-1 (GLP-1) analogs, dipeptidyl peptidase-4 (DPP4) inhibitors, and sodium-glucose linked transporter 2 (SGLT-2) inhibitors. • There are several available as oral liquid formulations (metformin, and colesevelam hydrochloride) but to date, no DPP4 inhibitors are available as a liquid formulation. • Sitagliptin is currently only available in tablet form, which cannot be crushed.	There are multiple effective treatment options available for the treatment of T2DM.
Benefit	• Brynovin is a liquid formulation of sitagliptin, which could allow use in patients with difficulty swallowing	If approved, sitagliptin oral solution (25 mg/mL) would be the first oral liquid form of a DPP4 inhibitors on the market, which could offer the potential for use in populations with difficulty swallowing pills.
Risk and Risk Management	• The safety of Brynovin is expected to be similar to that of the reference drug Januvia	The data and information submitted comprise an adequate scientific bridge between Brynovin and Januvia such that reliance on the safety and effectiveness of Januvia is justified.

1.3. Patient Experience DataNot applicable.

2. Therapeutic Context

2.1. Analysis of Condition

T2DM is a disease of impaired glucose homeostasis resulting in chronic hyperglycemia that is associated with significant morbidity and mortality due to microvascular and macrovascular pathologies, and is a major cause of hospitalization, blindness, renal failure, amputations and cardiovascular (CV) disease. Patients have varying degrees of insulin resistance and are unable to maintain euglycemia with endogenous insulin secretion.

2.2. Analysis of Current Treatment Options

There is no cure for T2DM, but therapies aimed at improving glycemic control are available. Currently approved therapies in T2DM aim to improve glycemic control by improving insulin resistance, enhancing insulin secretion, or increasing glucose excretion.

Several classes of drugs are currently approved for the treatment of T2DM, used either alone or in combination. These drug classes include:

- Biguanides (i.e. metformin)
- Sulfonylureas
- Thiazolidinediones (TZDs)
- Meglitinides
- DPP-4 inhibitors
- Glucagon-like peptide-1 receptor agonists (GLP-1 RA)
- GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) co-agonist (i.e. tirzepatide)
- Sodium-glucose cotransporter-2 (SGLT2) inhibitors
- Alpha-glucosidase inhibitors
- Amylin-mimetics
- Dopamine agonist (i.e. bromocriptine)
- Insulin and insulin analogues
- Bile acid sequestrants (i.e. colesevelam hydrochloride)

Despite the relatively large number of drugs available for the treatment of T2DM, a substantial proportion of patients either remain under poor glycemic control or experience

deterioration of glycemic control after an initial period of successful treatment with an anti-diabetic drug.

Sitagliptin is a DPP-4 inhibitor that is widely used both alone and in combination with a range of other oral hypoglycemic agents for treatment of T2DM. There are currently four approved DPP-4 inhibitors in the US market, of which Januvia (sitagliptin) was the first, approved in October 2006. There are no oral liquid forms of sitagliptin or other DPP-4 inhibitors.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Table 1 Related Regulatory History Summary

Drug	Regulatory Event	Approval Date
Januvia (sitagliptin)	IND 065495 opened 08/12/2002 (Merck and Co Inc)	
	NDA 021995 opened 12/16/2015	Approved 10/16/2006 as Januvia (Merck and Co Inc)
Sitagliptin hydrochloride oral liquid formulation (25 mg/mL)	IND 155653 opened on 01/25/2021 (VistaPharm, Inc.)	
	NDA 219122 submitted on 01/04/2024 (Azurity Pharmaceuticals, Inc.)	

3.2. Summary of Presubmission/Submission Regulatory Activity

3/16/2021 The Agency issued an Exempt letter informing VistaPharm, LLC (the prior sponsor) that the planned comparative bioavailability study met all the requirements for exemption from the investigational new drug (IND) regulations and, therefore, an IND is not required to conduct the investigation.

6/11/2021 VistaPharm submitted a combined type B Pre-IND meeting request and meeting background package to IND 155653 to receive advice on the regulatory requirements and their overall development program to support submission of a 505(b)(2) new drug application (NDA) for their proposed product.

8/10/2021 Type B Written Response Only (WRO) meeting minutes for PIND 155653

- The Agency agreed that the 505(b)2 regulatory pathway would be appropriate for their sitagliptin oral liquid product (with a proposed new dosage form and a new salt form).
- The Agency recommended the Sponsor modify the proposed relative bioavailability (BA) study comparing the maximally tolerated dose intended for Brynovin (100 mg) in the oral liquid form to the equivalent dose of the listed drug Januvia to include both fasting and fed conditions and agreed that a study of this design would be sufficient to establish a pharmacokinetic bridge.
- The Agency agreed that the Sponsor's proposal to not include a co-packaged dosing device was reasonable
- Due to the change in the salt form of sitagliptin from sitagliptin phosphate monohydrate to sitagliptin hydrochloride and the change in the dose form to liquid formulation, Brynovin would be subject to PREA requirements.

7/12/2022 The Sponsor notified the Agency of a change in ownership from VistaPharm, Inc. to Azurity Pharmaceuticals, Inc.

04/14/2022 – Type D WRO meeting to obtain FDA CMC feedback regarding a proposed registration stability package and registration facility inspection

- The Agency agreed that 6 months accelerated and 12 months long-term stability data from three finished product batches produced as registration batches at the current drug product manufacturing facility (b) (4) along with 3 months of stability data (long term and accelerated conditions) from three finished product batches produced as supporting registration batches from the new finished product manufacturing facility (Delpharm Montreal Inc.) was reasonable. However, if the 3-month stability data indicate any trend, additional stability data may be required.

- The Agency indicated that the Sponsor's general approach for pre-approval inspection at Delpharm as the supporting registration and intended commercial manufacturing facility (due to the planned closure of the (b) (4) facility during the review period) appeared reasonable but that the need for preapproval inspection coverage at the commercial manufacturer would be evaluated during NDA review.

4/25/2023 Agreement was issued for the initial Pediatric Study Plan (iPSP) with partial waivers for pediatric assessment studies for the age groups 1) from birth to less than 10 years of age as studies would be impossible or highly impracticable to conduct for the proposed indication in this age group, and 2) from 10 years to 17 years (inclusive) of age based on evidence strongly suggesting that the drug would be ineffective in this age group.

3.3. Foreign Regulatory Actions and Marketing History

Brynovin is not yet approved for marketing in any country.

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

4.1. Office of Scientific Investigations (OSI)

Because the submission did not include clinical data other than the bioequivalence study, OSI was not involved in the review of NDA 219122. Instead, the Office of Study Integrity and Surveillance (OSIS) was consulted regarding the bioequivalence study. OSIS determined new on-site inspections were not needed for the clinical or analytic sites. ORA had previously inspected the clinical study site (Worldwide Clinical Trials, San Antonio) and OSIS had previously conducted a Remote Regulatory Assessment (RRA) of the analytical site (b) (4) in (b) (4) under NON-RESPONSIVE. Based on the previous ORA inspection and the previous RRA, OSIS determined that inspections are not needed for either site for NDA 219122. Please refer to the OSIS review memo [CONSULT REV-DSI-05 (Bioequivalence Establishment Inspection Report Review)] by Felecia Hagood dated 4/29/2024 for more details.

4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ) Review team assessed the Chemistry, Manufacturing, and Controls (CMC) information for the NDA 219122 submission and determined that standards were not met to support the approval of the drug product from a quality perspective, and recommended a complete response. The issue leading to the decision to not support approval was that a manufacturing facility did not meet Current Good Manufacturing Practice (CGMP) standards. Other than the facilities deficiency, there were no other CMC deficiencies identified on OPQ review of drug substance, drug product, manufacturing process, labeling, and microbiology sections of this application.

Sitagliptin oral solution, 25 mg/mL is a clear, colorless to nearly colorless aqueous solution filled in a 125 mL amber glass bottle. The recommended storage condition for the drug product is 2°C to 8°C. The drug product is intended for administration using an oral dosing syringe. The drug substance is the hydrochloride monohydrate salt form of sitagliptin, whereas the listed drug (LD) product, Januvia sitagliptin tablets (NDA 021995) contains the phosphate monohydrate salt form of sitagliptin.

The manufacturing process for sitagliptin oral solution, 25 mg/mL involves species that could potentially form nitrosamine impurities, including, (b) (4) (b) (4) During the review cycle the drug product specifications

were modified to include monitoring of (b) (4) which was present in all drug product batches manufactured by both (b) (4) (the original drug product manufacturer) and Delpharm (the current drug product manufacturer).

The quantification of and control for (b) (4) during product stability was an important focus of the quality review. (b) (4) (b) (4) (b) (4) the drug product (b) (4) levels, which controls for a stability acceptance limit of (b) (4) ng/day when the oral liquid formulation is dosed at 100 mg/day (maximum daily dose), were found to be acceptable at release and during shelf-life through 12 months storage at refrigerated conditions. Therefore, the OPQ review found that once the facilities deficiency is resolved, a shelf-life of 12 months can be assigned to sitaglitpin oral solution 25 mg/mL based on the available data.

Below is the nomenclature, molecular structure, molecular formula, and molecular weight for the sitagliptin drug substance.

Sitagliptin Hydrochloride

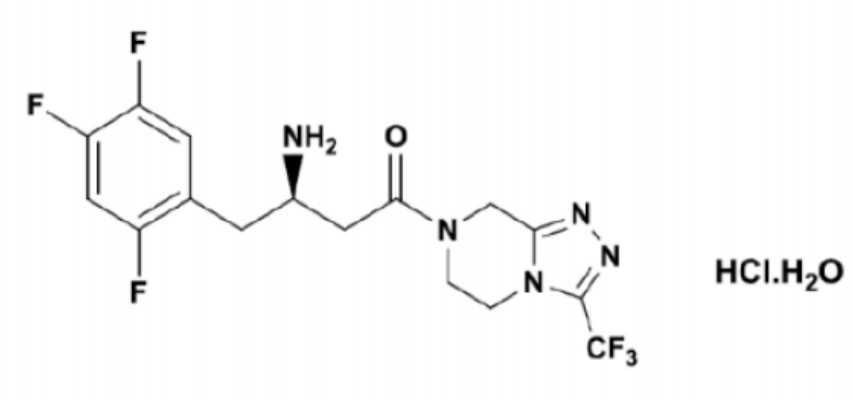
Chemical Names: 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine HCl monohydrate.

General properties:

[2] (b) (4) (b) (4)

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

4.1. Figure 1: Chemical Structure of Sitagliptin Hydrochloride



Source: from CMC review

Molecular Formula: $C_{16}H_{15}F_6N_5O \bullet HCl.H_2O$

Molecular weight: 461.79 g/mol

For more details on the product quality review please refer to REV-QUALITY-25 (Integrated Quality Review) dated 09/25/2024 and amended on 10/10/2024 by Dr. Muthukumar Ramaswamy.

4.2. Clinical Microbiology

Not applicable.

4.3. Nonclinical Pharmacology/Toxicology

The Applicant did not conduct any new nonclinical pharmacology or toxicology studies for sitagliptin oral solution, 25 mg/mL, and is relying on the nonclinical information for Januvia. The proposed oral suspension for sitagliptin has a novel formulation, and uses a different salt form of sitagliptin (hydrochloride instead of phosphate) but does not contain any new excipients. Dr. Amit Chaudhary, the nonclinical reviewer, evaluated the safety of the excipients at the proposed concentrations, along with any potential drug product impurities, specifically extractable or leachable compounds from the liquid suspension.

The review concluded that, based on these findings, the safety concerns regarding the presence of the nitrosamine impurity (b) (4) were adequately addressed in the NDA submission.

Please refer to the Nonclinical review memo by Dr. Amit Chaudhary dated 10/8/2024 for more details.

4.4. Clinical Pharmacology

The Applicant conducted a single bioequivalence study, which was an open-labeled, randomized, single-dose, three treatment, three-period, crossover study which compared the bioavailability of 100 mg of sitagliptin oral solution 25 mg/mL (4 mL) under both fed and fasted conditions to administration of a single 100 mg Januvia sitagliptin phosphate oral tablet under fasted conditions.

In study AZ17.001, healthy adult subjects were given (A) a single dose of 4 mL (100 mg) of 25 mg/mL sitagliptin hydrochloride oral liquid solution after an overnight fast, (B) a single dose of 4 mL (100 mg) of 25 mg/mL sitagliptin hydrochloride oral liquid solution after a high fat, high calorie meal, or (C) a single dose of 100 mg sitagliptin phosphate tablet (Januvia) given after an overnight fast.

The Clinical Pharmacology review concludes that the submitted pharmacokinetic (PK) results of the relative BA study performed by the Sponsor are acceptable to support approval from a clinical pharmacology perspective.

The main conclusions were:

- Study AZ17.001 showed that 100 mg of Azurity Sitagliptin hydrochloride Oral solution 25 mg/mL (4 mL) is bioequivalent to Merck's Januvia 100 mg under fasted conditions, based on the 90% CI of the geometric mean ratios (GMRs) of the proposed sitagliptin hydrochloride oral solution product to LD product (Januvia) for primary PK endpoints (Cmax, AUC_{last} and AUC_{inf}) were within the FDA-defined BE acceptance criteria of 80 – 125%, as shown in Table 1 below.

Table 1. PK Parameters for Sitagliptin Oral Solution (25 mg/mL) and Sitagliptin oral tablet (Januvia) After a Single Oral Dose of 100 mg under fasted conditions

Dependent Variable	GeoMean[a] Test	GeoMean[a] Ref	Ratio (%)[b] (T/R)	90% CI[c] Lower	90% CI[c] Upper	ANOVA CV%
C_{max}	361	356	101.46	93.37	110.25	17.78
AUC_{last}	3280	3260	100.62	97.98	103.32	5.59
AUC_{inf}	3390	3330	101.65	99.19	104.17	5.07

Treatment A (Test): Azurity Sitagliptin HCl Oral Solution 4 mL (100 mg), fasted
Treatment C (Reference): Januvia (sitagliptin phosphate) 100 mg Tablet, fasted
[a] Geometric Mean based on Least Squares Mean
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval

Source: Table 8 of Study AZ17.001 CSR

- The results of Study AZ17.001 also indicate that 100 mg of Azurity Sitagliptin hydrochloride Oral solution 25 mg/mL (4 mL) is bioequivalent to Merck's Januvia 100

mg under fed conditions, based on the 90% CI of the geometric mean ratios (GMRs) of the proposed sitagliptin hydrochloride oral solution product to LD product (Januvia) since the AUC-based primary PK endpoints (AUC_{last} and AUC_{inf}) were within the FDA-defined BE acceptance criteria of 80 – 125%.

In Study AZ17.001, the oral sitagliptin solution was noted to have a decreased Cmax (~28%) and delayed Tmax by 2.5 hours (from 1.5 hrs to 4 hrs) under fed conditions compared with Januvia under fasted conditions. This is different than for Januvia, where there is no noted effect of food on the PK exposures (both Cmax and AUC) of sitagliptin. To evaluate whether the PK differences in Cmax contribute to clinically meaningful differences in efficacy, the clinical pharmacology team evaluated dose response data from NDA 021995 (Januvia) and the Applicant's generated PK simulations on steady-state PK exposure of sitagliptin. The clinical pharmacology team concluded that the reduced Cmax would not have a significant impact on clinical efficacy since simulated steady-state PK for the oral sitagliptin liquid (25 mg/mL) have previously shown that mean concentration (Cavg) at steady-state during the 24 hour dosing period remains above levels expected to inhibit plasma DPP4 activity and sitagliptin PK studies conducted for Januvia have previously shown that despite 50% lower plasma Cmax with 50 mg twice daily dosed sitagliptin phosphate tablets (i.e. a different dose forms of Januvia), that a similar A1C-lowering treatment effect was observed as 100 mg sitagliptin dosed once daily. The clinical pharmacology team also concluded that the delayed Tmax of sitagliptin oral liquid solution under fed conditions would not have a significant impact on clinical efficacy as the PK-PD relationship of sitagliptin and inhibition of plasma dipeptidyl peptidase-4 (DPP4) activity from NDA 021995 (Januvia) inhibition of plasma DPP4 activity is primarily due to plasma steady-state sitagliptin concentration alone (Cavg) and was independent of time (Clinical pharmacology review of Januvia) and, therefore delayed Tmax is not expected to influence efficacy.

Based on the reviewed clinical pharmacology data, which support the bioequivalence of Sitagliptin Oral Solution (25 mg/mL) with Januvia under fasted conditions, the clinical pharmacology review team concluded that an adequate scientific bridge with Januvia was established and support the approval of Sitagliptin Oral Solution (25 mg/mL). Please refer to the Clinical Pharmacology review dated 9/24/2024 by Dr. Lin Zhou for more details.

4.5. Devices and Companion Diagnostic Issues

Not applicable

4.6. Consumer Study Reviews

The Division of Medication Error Prevention and Analysis (DMEPA) proprietary name review found the proposed proprietary name, Brynovin, is conditionally acceptable. Please review to Proprietary Name Reviews dated March 15, 2024 (amended April 2, 2024) by Dr. Vraj Patel.

5. Sources of Clinical Data and Review Strategy

5.1. Review Strategy

The Applicant has proposed to rely on FDA's finding of safety and effectiveness for Januvia (NDA 021995) in this 505(b)(2) application. The clinical program involved a single clinical pharmacology relative BA study, study AZ17.001, intended to bridge the proposed Brynovin product to Januvia, the listed drug. To justify the reliance, the Applicant demonstrated bioequivalence of Brynovin to Januvia under fasted conditions. The clinical review of NDA 219122 is therefore limited to review of the adverse event, clinical laboratory, and vital sign data from study AZ17.001 to confirm that no clinical safety issues were observed that would preclude the conclusion of safety based on the reliance on Januvia.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Table of Clinical Studies

Table 2 Summary of Clinical Studies

Trial Identity	Trial Design	Regimen	Treatment Duration/ Follow Up	# enrolled (completed)	Study Population
AZ17.001 Bioequivalence and food effect study	Open label, randomized, single-dose, three-period, three-way crossover, balanced, oral bioequivalence study in healthy adult human subjects	Reference (R) product: Januvia (sitagliptin phosphate 100mg tablet) Test (T) product: Brynovin (sitagliptin oral liquid 25 mg/mL solution, 4 mL)	single-dose, 48 hour observation post-dose 5 day washout period between the R and T product dosing	30 (26)	Healthy adults age 18 to 55 with BMI 18.5 to 35.0 kg/m^2

Source: Reviewer Generated

6.2. Assessment of Efficacy Across Trials

Efficacy is based on FDA's previous findings of safety and effectiveness for Januvia. See the Clinical Pharmacology review by Dr. Lin Zhou for discussion of the adequacy of study AZ17.001 to comprise a scientific bridge.

7. Review of Safety

7.1. Safety Review Approach

Results of Study AZ17.001 were submitted with this NDA application, to establish a scientific bridge between Brynovin and the reference listed drug, Januvia. Study AZ17.001 was a Phase 1, open label, randomized, three-period, three-treatment, three-sequence, crossover, balanced, single dose study in 30 healthy adults, age 20-55 years. This study compared Azurity's Sitagliptin Oral Solution to the listed Drug (LD), Januvia, at a dose of 100 mg in fasting and fed (high-fat) conditions.

In study AZ17.001, healthy adult subjects were given a single dose of 4 mL (100 mg) of 25 mg/mL sitagliptin hydrochloride oral liquid solution after an overnight fast (Azurity fasted group), a single dose of 4 mL (100 mg) of 25 mg/mL sitagliptin hydrochloride oral liquid solution after a high fat, high calorie meal (Azurity fed group), or a single dose of 100 mg sitagliptin phosphate tablet (Januvia) given after an overnight fast. It should be noted that bioequivalence studies are not generally intended for independent evaluation of safety outside of showing BE to a product that is known to be safe, however there was a limited amount of safety data collected study AZ17.001, including laboratories, vital signs, electrocardiograms (ECG) and adverse events (AEs). I reviewed the safety findings including all treatment-emergent AEs (TEAE) in this study.

7.2. Safety Results

No safety-focused clinical studies were performed by the applicant in support of this application. Review of treatment emergent adverse events (TEAEs) from the single-dose crossover BE study was conducted. Of the 30 healthy volunteers who enrolled in the study, there were no serious adverse events (SAE), and no deaths. One subject was withdrawn from the study by the investigator due to being lost to follow up after receiving the Azurity sitagliptin liquid product in both fasted and fed conditions, and one was withdrawn by the investigator after an adverse event of right antecubital peripheral swelling (reported as "peripheral swelling") occurred the day of Azurity sitagliptin administration under fasted conditions. A total of 9 TEAEs were reported by 8/30 (26.7%) of subjects over the course of study AZ17.001, including peripheral swelling, pain in extremity, conjunctivitis, conjunctivitis allergic, eye irritation, feeling hot, arthropod bite, alopecia, and anxiety. The reported severity was mild in 7/8 (88%) of subjects, with a single moderate severity TEAE in a subject in the Azurity fed arm

with reported AE 'conjunctivitis allergic' which occurred 5 days after dosing. There was an imbalance in the proportion of subjects with TEAE in Azurity arms (10.7% of Azurity fasted (3/28) and 18.5% of Azurity fed (5/27)) versus placebo (3%, 1/29). Eye-related AEs were the most common type of AE reported. Two subjects in the Azurity fed group and one in the Azurity fasted group reported eye-related AEs. On looking into the individual PTs, the three eye-related adverse events of 'eye irritation', 'conjunctivitis' and 'conjunctivitis allergic' did not appear to be temporally related to the dosing, occurring 10 and 23 hours, and 5 days after dosing. I concluded upon review that each event was unlikely to be related to the study drug based on the timing of the events and event descriptions. There were no AEs related to clinically significant out-of-range laboratories or vital signs. ECG were performed at screening and at the end of study visit. No clinically significant abnormalities in ECGs were observed.

In conclusion, no new safety concerns arose in the BE study.

7.3. Safety in the Postmarket Setting

7.3.1. Safety Concerns Identified Through Postmarket Experience

Brynovin is not approved in any country.

7.3.2. Expectations on Safety in the Postmarket Setting

The safety of Brynovin is expected to be similar to the safety of the reference product Januvia.

7.4. Integrated Assessment of Safety

No new safety concerns arose in the BE study and the events observed are all consistent with the labeling of the reference product.

I conclude that Brynovin is safe in adults with T2DM, based on a reliance on FDA's previous finding of safety for Januvia in adults with T2DM. The reliance is justified by the scientific bridge between Brynovin and Januvia established by the demonstration of BE under fasted conditions. No safety data collected in BE study AZ17.001 preclude this conclusion.

8. Advisory Committee Meeting and Other External Consultations

Not applicable.

9. Labeling Recommendations

9.1. Prescription Drug Labeling

The applicant submitted a label based on the label of the reference drug, Januvia. In view of the recommendations for a Complete Response, the final labeling review is deferred until the next review cycle.

9.2. Nonprescription Drug Labeling

Not applicable.

10. Risk Evaluation and Mitigation Strategies (REMS)

No REMS was recommended for this application.

11. Postmarketing Requirements and CommitmentsNo postmarketing requirements or commitments are recommended for this application.

12. Appendices

12.1. References

None.

12.2. Financial Disclosure

The bioequivalence study was conducted at a single site, with only one investigator.

Covered Clinical Study (Name and/or Number): AZ17.001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): Form 3455 not submitted because Sponsor stated it was not applicable		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be		

influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LAUREN K WOOD HEICKMAN
11/01/2024 11:43:50 AM

PATRICK ARCHDEACON
11/01/2024 02:02:56 PM