azurity pharmaceuticals

Committed to making a difference in patients' lives.

Date: 05 March 2021

Norman Stockbridge, MD, PhD
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research
5901-B Ammendale Rd
Beltsville, MD 20705

Re: NDA 208401 QBRELIS (LISINOPRIL) ORAL SOLUTION
DEFERRAL EXTENSION REQUESTED
RESPONSE TO PREA NON-COMPLIANCE LETTER
SN 0058

Dear Dr. Stockbridge:

Reference is made to Azurity Pharmaceuticals' New Drug Application (NDA) 208401 for Qbrelis® (lisinopril) Oral Solution, approved on 29 July 2016 for several indications, including treatment of hypertension in adults and pediatric patients 6 years of age and older.[1]

The purpose of this letter is to respond to the FDA's Notification of Non-Compliance with PREA letter dated 21 January 2021. As discussed below, Azurity is hereby requesting an extension of the deferral for Final Report Submission until 30 June 2026, in order to meet the Post Marketing Requirement (PMR) 3099-1 commitment. During this time, Azurity would like to continue discussions with the agency regarding a feasible study design to satisfy the requirements of the company's PREA obligations with regard to Qbrelis.

Factual Background

Qbrelis PMR 3099-1

The NDA approval letter for Qbrelis describes a deferred PMR under PREA (PMR 3099-1), with the following timelines:

3099-1 An efficacy, safety and dose-finding study of Qbrelis in hypertensive pediatric

[1] At the time of NDA approval and for almost three years after, the Qbrelis NDA was held by Silvergate Pharmaceuticals, Inc. (Silvergate). The NDA is now held by Azurity Pharmaceuticals, Inc. (Azurity) following the acquisition of Silvergate by CutisPharma, Inc. (CutisPharma). CutisPharma was renamed Azurity. Integration of the combined companies required evaluation of drug product portfolios and regulatory commitments.

patients two years to less than six years of age

Final Protocol Submission: 12/2016
Study Completion: 06/2020
Final Report Submission: 12/2020

PMR 3099-1, *A Dose-Ranging, Safety, Tolerability, and Efficacy Study with Qbrelis™ in Hypertensive Pediatric Patients aged 2 Years to Less than 6 Years of Age,* has been designed as a 28-day dose-ranging, multicenter study to evaluate Qbrelis (lisinopril) Oral Solution with a 14-day double-blind placebo control in 156 children 2 years to less than 6 years old with hypertension.

Azurity's predecessor-in-interest, Silvergate, submitted the final protocol for the study on 03 January 2018.[2] Silvergate diligently set about seeking to establish contractual agreements with sites and investigators who would participate in the trial, but found very few opportunities. In January 2018, along with the final protocol, Silvergate requested a waiver of PMR 3099-1 because the study was impossible or impracticable to conduct.[2] As part of the waiver request, Silvergate explained the significant efforts the company had made and the extremely discouraging results it had obtained. In particular, Silvergate communicated to the Division the negative feedback that the company had received from nephrologists at four leading children's hospitals, following discussion of the company's protocol for Study 3099-1. Specifically, these nephrologists told Silvergate that such a study was impossible or impractical to conduct, given the very small patient population, number of required clinical visits and other characteristics of the study design. The nephrologists communicated their belief that only 1 or 2 patients could be recruited per site for such a study.

The Division declined to grant a waiver, stating that the agency "continues[s] to believe that your product could provide a meaningful therapeutic benefit over existing therapies for pediatric patients in this age range, and would likely be used in a substantial number of pediatric patients."[3] The Division also noted that other antihypertensive agents had been studied in this patient population, which led the agency to conclude that study 3099-1 was feasible.[3]

(b) (4)

[redacted]

[2] Letter from Silvergate Pharmaceuticals, Inc. (January 3, 2018).

[3] General Advice Letter from Norman Stockbridge, MD to Silvergate Pharmaceuticals, Inc. (April 11, 2018).

(b) (4)

The Proposed Pediatric Study for Qbrelis Appears Infeasible

Azurity has made reasonably diligent efforts to comply with its PREA obligations., including reaching out to pediatric nephrologists to determine the feasibility of conducting the required study. Azurity continues to believe the patient population of ages 2 to less than 6 years old with hypertension is an extremely small and difficult patient population to study.

Moreover, the current study design for Study 3099-1 appears infeasible. At the time that Azurity agreed to the original iPSP for Qbrelis, the company believed that the study design was feasible. However, after significant effort by the company, we have determined that the complexity of recruiting study sites, patients, and clinical investigators has proven impossible and impractical. These circumstances were not anticipated at the time of the iPSP and Qbrelis approval.

(b) (4)

(b) (4)

Azurity is Exploring Alternative Study Designs to Satisfy its PREA Obligations

Nevertheless, Azurity remains committed to studying the use of Qbrelis in pediatric patients 2 to less than 6 years of age, and to obtaining meaningful data to inform practitioners regarding the use of Qbrelis in this age group. Accordingly, the company has evaluated alternative options that we believe could satisfy the current PREA obligations and lead to meaningful pediatric labeling.

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(b) (4) Azurity believes this study is feasible to conduct and will provide meaningful dosing guidance for the proposed pediatric subpopulation, with adjustments for age/weight strata and other relevant comorbidities.

In addition, we intend to request a Type C meeting to discuss the Qbrelis (b) (4) study designs with the Division during the third quarter of 2021.

Deferral Extension Request

Azurity is committed to working with the FDA in fulfilling the Qbrelis PREA commitment PMR 3099-1. Hence, Azurity is requesting a deferral extension to June 30, 2026 in order to complete the clinical study as outlined above.

The following timelines are proposed:

Final Qbrelis PPK Protocol Submission*	June 30, 2022**
Study Initiation	Nov 30, 2022
Study Completion	Nov 30, 2024
Extension Safety Arm	Nov 30, 2025
Clinical Study Report (CSR) Submission	June 30, 2026

*The draft study design concept will be prepared and negotiated with FDA and will be consistent with the amlodipine synopsis included in this submission (Attachment 1) for the agency's review.

**Azurity anticipates providing a final draft of the Qbrelis study protocol to the FDA for review (b) (4), upon completion of the (b) (4) and full feasibility assessment.

Azurity respectfully requests that public posting of this Response Letter to the Notification of Non- Compliance with PREA be delayed until the request for deferral extension, in accordance with 505B(a)(3)(B)(i), has been evaluated by FDA. All of the data and information contained in the attached materials are privileged and confidential as trade secrets and commercial information of Azurity Pharmaceutical's.

Under no condition is the disclosure of any portion of the attached materials to any person or entity other than the Food and Drug Administrations authorized without prior consent of the applicant.

This application has been prepared in electronic Common Technical Document (eCTD) format in accordance with FDA's *Guidance for Industry: Providing Regulatory Submissions in Electronic Format-Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. This submission has been transmitted via the Electronic Submissions Gateway. A description of the electronic submission is provided.

Additionally, we ask that all communications regarding this application be sent to Korie Osborn and me. Our contact information is provided.

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Sincerely,

Michael C. Beckloff

References