CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202860Orig1s000

CLINICAL REVIEW(S)

Clinical Investigator Financial Disclosure Review

Application Number: 202860
Submission Date(s): 23 July 2018
Applicant: Vero Biotech, LLC
Product: Genosyl (nitric oxide) (b) (4)
Reviewer: Shetarra Walker, MD, MSCR
Date of Review: 16 December 2019
Covered Clinical Studies (Name and/or Number): P2010-001 (Pilot) and P2010-002 (PHIANO)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: **24**		
Number of investigators who are sponsor employees (including both full-time and part-time employees): **0**		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **0**		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): ***Not Applicable*** 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 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) **0**		
Is an attachment provided with the reason: *Not Applicable*	Yes ☐	No ☐ (Request explanation from applicant)

The Sponsor has provided adequate certification there are no financial interests or arrangements with clinical investigators to disclose.

Reviewer Comment: *The Sponsor did not provide a new FDA 3454 form in the latest CR Response submission dated 21 June 2019. However, that should not affect approvability because no new clinical studies were conducted or submitted since the 23 July 2018 NDA submission.*

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/

SHETARRA E WALKER
12/16/2019 12:28:28 PM

ALIZA M THOMPSON
12/16/2019 12:51:40 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date:	04 December 2018
From:	Shetarra Walker, MD, MSCR, Clinical Reviewer Division of Cardiovascular and Renal Products/CDER
Through:	Aliza Thompson, MD, Cross Discipline Team Leader Division of Cardiovascular and Renal Products/CDER
Subject:	NDA 202860 Class 2 Resubmission After Complete Response
Sponsor:	Vero Biotech, LLC (Vero)
Proposed Drug Name:	GeNOsyl (b) (4) Delivery System (b) (4) (nitric oxide)

On 23 July 2018, Vero submitted a class 2 NDA resubmission to a complete response for GeNOsyl (b) (4) Delivery System (b) (4) (nitric oxide). GeNOsyl (b) (4) ® (nitric oxide) is a drug-device combination product containing a liquid-based delivery system for inhaled nitric oxide (NO), a pulmonary vasodilator. The proposed indication for GeNOsyl (b) (4) ® (nitric oxide) is (b) (4) pulmonary hypertension (b) (4) near-term neonates (> 34 weeks) with hypoxic respiratory failure in conjunction with ventilator support and other (b) (4). Vero proposes a dose of 20 ppm (b) (4) maintenance (b) (4) for up to 14 days or until (b) (4) wean from (b) (4).

Relevant Regulatory History

NO is currently marketed under the propriety name INOmax® (NO) and approved for the same indication and patient population as that proposed by Vero in this NDA resubmission. On 23 December 1999, FDA approved INOmax®(NO), a gas-based drug-device combination product, under NDA 020845. On 20 March 2012, GeNO LLC (GeNO), now known as Vero, submitted an initial NDA under the 505(b)(2) pathway. GeNO intended to rely on efficacy and safety data from NDA 20845, INOmax® (NO). Because of issues raised by the Office of New Drug Quality Assessment, FDA issued a Refuse-to-File Letter on 18 May 2012. On 30 August 2012, GeNO resubmitted their original NDA. FDA responded with a Complete Response (CR) Letter on 28 June 2013 citing product quality deficiencies. On 28 April 2017, FDA met with GeNO to

Reference ID: 4358836

discuss a path forward for NDA resubmission. In lieu of additional clinical studies, FDA requested that GeNO provide a safety update including an integrated safety summary of the applicant's ongoing clinical studies and any new data in the public domain.

Summary of Clinical Data

In this NDA resubmission, Vero provided clinical data from two sponsor-initiated Phase 2 studies and one investigator-initiated (b) (4) Phase 2 study. In these open-label studies, conducted in adults with pulmonary hypertension or pulmonary arterial hypertension undergoing right heart catheterization (RHC), 51 subjects received either one or two doses of inhaled NO. Inhaled NO doses ranged from 5 ppm to 20 ppm and were delivered by a prior prototype of the GeNOsyl Delivery System. Study durations lasted from 7 minutes to 175 minutes with mean exposure time of 104.6 minutes. Primary endpoints varied among studies and included safety, device performance, and determination of minimally and maximally effective doses (based on change in pulmonary vascular resistance compared to placebo).

Vero provided pooled summary data from all studies in this submission. Fifty (50) out of 51 subjects (98%) completed the studies with one subject discontinuing the study because of an NO_2 alarm that was subsequently deemed false due to operator error. Twelve (12) out of 51 subjects (24%) experienced one or more treatment-emergent adverse events (TEAEs). The most common TEAE reported was pain: back, chest, neck, and at catheter site (eight TEAEs in 5/51 subjects). In almost all instances, pain was reported on the same day as study drug exposure. Other TEAEs included atrial flutter, peripheral edema, infections, headache, contusion, and constipation. Timing related to study drug administration for these TEAES varied, ranging from the same day as study drug exposure to 24 days after study drug.

Out of the 51 subjects in the phase 2 studies, two experienced three serious AEs (SAEs) of cardio-respiratory arrest, acute respiratory failure, and pulmonary edema. A 75-year-old male subject in the (b) (4) Phase 2 study experienced two of the three SAEs, cardio-respiratory arrest and acute respiratory failure. The applicant was unable to obtain narrative information about these SAEs because the study was investigator-initiated. However, based on raw data provided by the sponsor, these SAEs occurred two days after exposure to study drug treatment and on the same day as planned implantation of a left ventricular assist device complicated by bleeding and subsequent cardiac tamponade. The third SAE occurred in a 67-year-old female subject in one of the sponsor-initiated Phase 2 studies. The subject experienced pulmonary edema two days after administration of study drug. Given the pharmacokinetic characteristics and mechanism of action of inhaled NO, it is unlikely that the TEAEs or SAEs were study-drug related. There were no deaths or study withdrawals because of a TEAE and no subject developed methemoglobinemia.

Reviewer Comments:

- *Case Report Forms were not provided by the Applicant.*
- *Under certain circumstances such as pulmonary venous hypertension or left ventricular dysfunction, pulmonary vasodilators can cause pulmonary edema. The subject who experienced the SAE of pulmonary edema had a history of non-ischemic cardiomyopathy and left heart failure. The subject's baseline left ventricular ejection fraction was not available for review, but she was treated with intravenous remodulin the day after exposure to inhaled NO with onset of pulmonary edema within 24 hours after starting*

Reference ID: 4358036

remodulin. Given the timeline of events and underlying cardiac disease, the most likely etiology for pulmonary edema in this subject was initiation of a parenteral prostacyclin.

Although safety findings from these studies do not raise concern, the patient population studied and conditions of use differ from the proposed indication and intended patient population. Furthermore, the drug delivery device used in Phase 2 studies was an earlier prototype that Vero no longer intends to market. Hence, the relevance of these findings to the current application is unclear.

This submission also contains references to articles in the public domain including 45 studies on safety of NO in neonates, 18 studies on efficacy of NO for PPHN, and 12 studies for other indications for which NO has been administered. Review of these data did not raise new safety concerns or identify risks beyond those already included in labeling for the RLD, INOmax® (NO).

Conclusion

The submitted safety data do not raise concern from a clinical perspective. There are, however, outstanding issues (facilities, human factors, and device related) that need to be resolved before this product can be approved.

Reference ID: 4358036

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/

SHETARRA E WALKER
12/04/2018

ALIZA M THOMPSON
12/04/2018

DIVISION OF CARDIOVASCULAR and RENAL PRODUCTS

Divisional Memo

NDA: 202860 GeNOsyl; nitric oxide for pulmonary hypertension in newborns.

Sponsor: GeNO LLC

Review date: 28 June 2013

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

Distribution: NDA 202860

This memo conveys the Division's recommendation to issue a Complete Response letter for this application.

This application has been the subject of review of CMC (Jewell, 19 April 2013) and the device (CDRH reviewer Nguyen; 19 February 2013).

Nitric oxide, a vasodilator, is approved for the treatment of newborns with primary pulmonary hypertension. Its use reduces the need for extracorporeal membrane oxygenation.

The GeNO product GeNOsyl MVG-2000 is a novel drug-device combination consisting of (b) (4) nitrogen dioxide, which is fairly toxic, (b) (4)

The device component is similar to a model with CDRH 510(k) clearance; there are no device-related deficiencies.

CMC issues relate to the release testing of (b) (4) cartridges. These are detailed in an IR letter (21 February 2013) and will be repeated in the CR letter. The site of manufacture of (b) (4) cartridges, (b) (4) is still pending inspection, but an inspection is pointless until the methods of testing are settled. While this creates the possibility that the inspection will uncover problems not addressed in the CR letter, both ODEI and OND Directors have concurred with issuance of a CR letter with this inspection undone.

There are also minor unresolved issues pending with the DMF holder for nitrogen dioxide, conveyed in a letter of 22 February 2013; these are also approvability issues.

Reference ID: 3333528
Reference ID: 4538636

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN L STOCKBRIDGE
06/28/2013