sNDA 210,854/S-21; sNDA 214410/S-07: Baloxavir marboxil
Melisse Baylor, M.D.

Clinical, Cross-Discipline Team Leader, and Division Director Review

Date	December 2, 2024
From	Melisse Baylor, MD Aimee Hodowanec, MD (CDTL) Yodit Belew, MD (Associate Director for Therapeutic Review)
Subject	Clinical Review / Team Leader Review

Supplemental NDA #	210854 / Supplement 021 214410 / Supplement 007
Applicant	Genentech, Incorporated
Date of Submission	July 2, 2024
PDUFA Goal Date	May 2, 2025
Proprietary Name/ Established (USAN) names	Xofluza® / baloxavir marboxil
Dosage forms / Strength	Oral tablets: (b) (4) and 40 mg (b) (4) Granules for solution
Dosing Regimen(s)	Administered as a single oral dose by weight: Less than 20 kg: 2 mg/kg 20 kg to less than 80 kg: 40 mg At least 80 kg: 80 mg
Proposed indication(s)	No change in indication requested
Recommendation on Regulatory Action	Approval

1. Executive Summary

This combined Clinical, Cross Discipline Team Leader (CDTL), and Division Director Review provides an overview of the submitted clinical data, describes the conclusions and recommendations, and provides an overall risk-benefit assessment of baloxavir marboxil use in the treatment of acute, uncomplicated influenza in pediatric patients (b) (4) of age.

Baloxavir marboxil (Xofluza®) is currently indicated for:

- Treatment of acute uncomplicated influenza in patients 5 years of age and older who have been symptomatic for no more than 48 hours and who are otherwise healthy or at high risk of developing influenza-related complications.
- Post-exposure prophylaxis (PEP) of influenza in patients 5 years of age and older following contact with an individual who has influenza.

The data reviewed for this supplement were the final Clinical Study Report (CSR) for Study CP40559, a safety, pharmacokinetic (PK), and efficacy trial of baloxavir marboxil in otherwise healthy pediatric patients from birth to less than one year of age who had influenza-like symptoms. Study CP40559 was initiated prior to review of the pediatric efficacy trial for baloxavir marboxil, which enrolled subjects from 12 months to < 12 years of age. After the review of those data, the indication for baloxavir marboxil was limited to patients 5 years of age

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and older due to increased incidence of treatment-emergent resistance-associated substitutions (TE-RAS) observed in pediatric patients younger than 5 years of age. (b) (4)

2. Background

2.1 Baloxavir marboxil

Baloxavir marboxil (Xofluza®), a polymerase acidic endonuclease inhibitor, was approved for the treatment of acute uncomplicated influenza in patients 12 years of age and older who have been symptomatic for no more than 48 hours on October 24, 2018. Baloxavir was subsequently approved for the treatment of influenza in adults and adolescents ≥ 12 years of age who are at high risk of influenza complications in October 2019. On August 11, 2022, baloxavir was approved for the treatment of acute, uncomplicated influenza in otherwise healthy children ≥ 5 years of age. Baloxavir marboxil was not approved for the treatment of influenza in pediatric patients from 1 to < 5 years of age because of the increased frequency of TE-RAS observed in pediatric patients. In pediatric clinical trials, the incidence of virus with treatment-emergent substitutions associated with reduced susceptibility to baloxavir (resistance) was higher in pediatric subjects from 12 months to < 5 years of age (43%, 36/83) than in pediatric subjects ≥ 5 years to < 12 years of age (16%, 19/117) or subjects ≥ 12 years of age (7%, 60/842). (See the review of the Complete Response Letter, 214410/Original 2 and 210854/S-05, 09, entered into DARRTS on August 5, 2022).

The Applicant submitted this supplemental NDA (sNDA) on July 2, 2024, to fulfill three postmarketing commitments related to Study CP40559. The Applicant did not propose revision of the current Xofluza indication. The three PREA PMRs are:

> 3503-1: Conduct a single-arm, open-label clinical trial to evaluate pharmacokinetics, safety, and antiviral activity of baloxavir marboxil in pediatric subjects from birth to less than 12 months of age with acute uncomplicated influenza. Include characterization of baloxavir-resistant substitutions in viral isolates from subjects with prolonged viral shedding.
>
> 3984-1: Conduct a single-arm, open-label clinical trial to evaluate pharmacokinetics, safety, and antiviral activity of baloxavir marboxil in pediatric subjects from birth to less than 12 months of age with acute uncomplicated influenza. Include characterization of baloxavir-resistant substitutions in viral isolates from subjects with prolonged viral shedding.
>
> 3961-1: Submit the clinical study reports including the pharmacokinetic / pharmacodynamic modeling data and the supporting PK, safety and efficacy data from all the relevant studies in adult and pediatric patients to extrapolate efficacy of baloxavir marboxil in pediatric subjects from birth to less than 12 months of age for the prevention of influenza as post-exposure prophylaxis in household contacts of an index case. Include characterization of baloxavir-resistant substitutions including supporting datasets.

After review of the results of Study CP40559, the Clinical Review Team agrees with the applicant that this submission fulfills all three postmarketing commitments.

2.2 Study Conduct

The Applicant submitted the sNDA in accordance with FDA guidelines. The quality and integrity of the submission were adequate, and the material was reviewable as submitted.

According to the Applicant, Study 40559 was conducted in conformance with Good Clinical Practice standards, the Declaration of Helsinki, and applicable local regulatory requirements and laws regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

3. CMC

A new formulation was not developed for use in this trial. As a result, no new product information regarding drug substance or manufacturing was submitted. Please refer to the original review of NDA 214,410 for additional CMC information regarding the granule formulation and to the review of NDA 210,854 regarding the tablet formulation of baloxavir marboxil.

4. Nonclinical Pharmacology / Toxicology

No new Pharmacology/Toxicology data were submitted for review. Please refer to the original reviews of NDA 210,854 and NDA 214,410.

5. Clinical Microbiology

The virology review of this supplement focused on resistance-associated substitutions (RAS) identified in influenza isolates from Study CP40559. A total of 13 subjects in Study CP40559 had post-baseline sequence data obtained (5 A/H1N1, 6 A/H3N2, and 2 B virus infections). Of these, 2 subjects (15.4%) had treatment-emergent RAS.

Please see Dr. Ince‘s review of this NDA supplement for additional details.

6. Clinical Pharmacology / Biopharmaceutics

There were no proposed revisions made to Section 2, **Dosing and Administration** or to Section 12.3, **Pharmacokinetics**, of the baloxavir marboxil package insert. The indication of baloxavir marboxil was not revised and baloxavir continues to be only indicated for use in pediatric patients 5 year of age and older. Please see the Clinical Pharmacology review for NDA 214,410.

7. Clinical / Statistical – Efficacy

Study CP40559 was a single arm, uncontrolled study. Statistics were descriptive. Therefore, there is no biostatistical review of this supplement.

Overview of Trial Design

Study Objectives:

The primary objective of the study was to evaluate the safety of a single dose of baloxavir marboxil in pediatric patients less than 12 months of age.

The key secondary efficacy objective was to evaluate the efficacy of baloxavir marboxil in pediatric patients less than 12 months of age.

Other secondary objectives included evaluation of the virological activity of baloxavir marboxil and of the polymorphic and treatment-emergent amino acid substitutions and drug susceptibility in patients with evaluable virus. Please see Dr. Ince’s Virology review for a discussion of RAS endpoints and results.

Study Design

Study CP40559 was a single arm, uncontrolled, open-label study in otherwise healthy pediatric patients < 12 months of age who had influenza-like symptoms. Influenza-like symptoms were defined as a clinical suspicion of influenza and the presence of either cough or coryza; symptom onset must have been within 96 hours of enrollment. Patients with influenza signs and symptoms were prescreened on Day 1 with an influenza test performed at the local study site, either a Rapid Influenza Diagnostic Test (RIDT) or Polymerase Chain Reaction (PCR). Patients with a positive influenza test in the previous 48 hours could also be enrolled. Study subjects with a positive local influenza test were dosed by age cohort as shown in the following table. All subjects also had a nasal swab obtained at the central laboratory to confirm the diagnosis of influenza.

Table: Age Cohort and Baloxavir Marboxil Dose

Cohort	Age	Minimum Number of Subjects	Dose
I	≥ 3 months to < 12 months	8	2 mg/kg
II	≥ 4 weeks to < 3 months	4	1 mg/kg
III	< 4 weeks	3	1 mg/kg

Source: Study protocol for CP40559, page 26.

Baloxavir marboxil was supplied as granules to the study site and was administered after reconstitution with water as a suspension.

Electronic devices to use as study diaries (eDiaries) were distributed on Day 1. The eDiary contained the Canadian Acute Respiratory Illness and Flu Scale (CARIFS) questionnaire. The CARIFS questionnaire was also used in the study of baloxavir marboxil in pediatric patients from 1 to < 12 years of age and in the study of oseltamivir in pediatric patients. CARIFS is a parental questionnaire with 18 questions covering three domains: symptoms (e.g., cough), function (e.g., play), and parental impact (e.g., clinginess). The CARIFS score is calculated as the sum of all 18 items. However, only three questions on the CARIFS score were used as part of the efficacy endpoint: presence and severity of cough, presence and severity of nasal symptoms (items 14 and 15 of the CARIFS), and a question regarding return to normal daily activity. Parents/guardians were to complete the diary daily until Day 29. Parents/guardians recorded the subjects' symptoms of influenza in the dairy twice daily from Day 1 to Day 9 and once daily from Day 10 to 15. Subject temperature was measured and recorded four times a day (morning, noon, evening, and bedtime) until Day 3, twice daily from Day 4 to Day 9, and once daily on Days 10 to 15.

If influenza symptoms were so severe that the subjects needed "rescue therapy", subjects were permitted to take acetaminophen for the relief of fever or pain. Parents/guardians were to record the date and time of each acetaminophen dose in the subject eDiary.

Nasopharyngeal swabs from each nostril were collected at each study visit and were sent for RT-PCR for influenza as well as viral phenotyping and genotyping.

Each subject had a minimum of 6 study visits. Efficacy was measured until Day 15. All subjects were to be followed until Day 29 for safety follow-up.

Study Population:

Inclusion criteria:

The trial enrolled males and females younger than 12 months of age who had influenza-like symptoms according to the investigator; the influenza symptoms had to include either cough or coryza. Each subject had to have a positive test for influenza (RAT or PCR) that was performed locally and also a negative RAT or PCR test for COVID-19 (SARS-CoV-2). The time interval between the onset of symptoms and screening was ≤ 96 hours; onset of symptoms was defined as the time when body temperature first exceeded 97.5° F.

Exclusion criteria:
Patients were excluded from study participation for any of the following:

- Preterm neonates (born at < 37 weeks);
- Weight < 2.5 kg at screening;
- Weight ≤ 4.5 kg for infants at sites in countries in which there are volume limits for blood draws of 1% of total blood volume over 24 hours and/or 3% of total blood volume over 30-day period;
- Hospitalization for complications of influenza or significant co-morbidities;
- Concurrent infection(s) requiring systemic antiviral therapy at screening;
- Receipt of peramivir, laninamivir (not approved in U.S.), oseltamivir, zanamivir, peramivir, or amantadine during 2 weeks prior to screening;
- Receipt of a live/attenuated influenza vaccine during the 2 weeks prior to screening;
- Concomitant treatment with steroids or other immunosuppressive therapy;
- Uncontrolled renal, vascular, neurologic or metabolic disease (e.g., diabetes, thyroid disorders, adrenal disease), hepatitis, cirrhosis, or pulmonary disease or patients with known chronic renal failure; or
- Active cancer or history of organ transplant.

Prohibited medications:
The use of the following drugs was prohibited from after administration of baloxavir marboxil on Day 1 until study completion:

- Systemic antiviral drugs,
- Antipyretics/analgesics except acetaminophen,
- Corticosteroids in injection, oral, or inhalation formulation, and
- Immunosuppressants

Safety Monitoring:
Subjects were seen at the study site on Days 1, 2, 4, 6, 10, 15, and 29. The study visit on Day 15 was an optional visit for subjects with prolonged symptoms. A single dose of baloxavir marboxil was administered on Day 1.

Medical history and vital signs (blood pressure, heart rate, respiratory rate, and tympanic temperature) were obtained on Day 1. A physical examination was obtained at each visit *if* the subject was symptomatic or at the investigator's discretion. Vital signs were obtained at all visits except the Day 29 visit. Clinical laboratory tests were obtained on Days 1 and 6 and included a complete blood count with differential and platelets; chemistry tests (electrolytes, ALT, AST, alkaline phosphatase, direct and total bilirubin, total protein, albumin, BUN, and creatinine); and dipstick urinalysis. A rapid test for SARS-CoV-2 was obtained on Day 1.

Information on adverse events was collected at each study visit. Adverse events were classified by system organ class and preferred term using the MedDRA dictionary. Adverse events were graded using the Common Terminology Criteria for Adverse Events (CTCAE).

Information on adverse events of special interest (AESIs) was collected at each study visit. AESIs were to be reported to the investigator within 24 hours of learning about the event. The AESI for this study was increases in ALT, AST, and / or bilirubin that met the criteria for Hy's law.

Abnormal laboratory test results were defined as those with a value outside the reference range. Laboratory test results were reported as an adverse event if they met any of the following criteria, the abnormal laboratory value:

- was accompanied by clinical symptoms,
- resulted in a change in treatment,
- resulted in a medical intervention or change in a concomitant medication, or
- was clinically significant in the investigator's judgement.

Study Endpoints:
The primary endpoint was the incidence, severity, and timing of adverse events, serious adverse events, vital sign measurements, and clinical laboratory tests.

The secondary efficacy endpoint was the time to alleviation of influenza signs and symptoms, defined as the length of time taken from the start of baloxavir marboxil to the point at which all of the following criteria were met and remained so for at least 21.5 hours:

- A score of 0 (no problem) or 1 (minor problem) for cough and nasal symptoms (items 14 and 15 of the CARIFS),
- A "yes" response to the following question on the CARIFS: "Since the last assessment has the subject been able to return to day care/school, or resume his or her normal daily activity in the same way as performed prior to developing the flu?" and
- Return to afebrile state (tympanic temperature ≤ 37.2° C).

Select Secondary efficacy endpoints included:

- Duration of fever;
- Duration of symptoms, and
- Time to return to normal health and activity.

Statistical Analysis:
CP 40559 was a single arm, uncontrolled study of baloxavir marboxil in pediatric patients younger than 12 months of age. The study was conducted in an open-label design. All statistical analyses were descriptive.

Thirty subjects were to be enrolled, but no formal sample size calculations were performed.

The analysis populations for this trial were as follows:

- The intent-to-treat population included all subjects who received at least one dose of baloxavir marboxil regardless of whether the subject had any follow-up.
- The intent-to-treat population influenza-infected population (ITTi) included all subjects in the ITT population who had a confirmed diagnosis of influenza virus infection based on RT-PCR results from a nasal swab collected at any time point during study population. The ITTI population was the primary population for all efficacy analyses.
- The safety population included all subjects is the same as the ITT population.

Study Results:

Reference ID: 5492506

Subject Disposition

The first subject was enrolled on January 23, 2019, and the last subject completed the study on April 3, 2023. A total of 49 subjects were enrolled in the study. The subject disposition is shown in the following table.

Table: Subject Disposition

Subject Disposition	**Number of Subjects (%)**
Enrolled	49
Received baloxavir marboxil (Safety Population)	48 (98%)
Prematurely discontinued	3 (6%)
Death	1 (2.0%)
Consent withdrawn	1 (2.0%)
Erroneous enrollment (did not receive baloxavir)	1 (2.0%)
Completed study	46 (94%)

Source: NDA 214410, SDN 0413, CSR SP40559, Table 8, page 40.

Of the 49 subjects enrolled, 48 (98%) received a single dose of baloxavir marboxil. One subject was enrolled but did not meet the entry criteria. Overall, three subjects (6%) were withdrawn from the study prematurely. That subject did not receive baloxavir marboxil and was withdrawn from the study. Another two subjects discontinued the study prematurely after receiving baloxavir marboxil. One subject died on Day 4 as a result of choking; this death is described in the safety section of this review. The parents/guardian of another subject withdrew their consent for study participation. Overall, the majority (94%) of subjects completed the study and there were few premature study discontinuations.

The study was conducted at 15 study sites in seven countries. The number of sites and subjects enrolled in the study are shown in the following table.

Table: Number of Sites by County and Number of Subjects Enrolled by Country

Country	**Number of Sites**	**Number of Subjects Enrolled**
South Africa	4	25 (51%)
United States	6	13 (27%)
Costa Rica	1	6 (12%)
Mexico	1	2 (4%)
Finland	1	1(2%)
Spain	1	1 (2%)
Poland	1	1(2%)

Source: NDA 214410, SDN 0413, CSR CP40559, text page 39.

As shown in the table, the majority of subjects (51%) were enrolled in South Africa. Twenty-seven percent of subjects were enrolled at sites in the U.S. and 12% were enrolled in Costa Rica. Either one or two subjects were enrolled in the other countries enrolling subjects in CP40559.

The demographics and baseline characteristics are shown in the following table.

Demographics and Baseline Characteristics

Demographic and baseline characteristics for the ITT population are shown in the following table.

Reference ID: 5492506

Table : Demographic Characteristics of the Intent-to-Treat Infected Population

Demographic Parameters	**Baloxavir marboxil** (N=48) n (%)
Sex	
Male	25 (52%)
Female	23 (48%)
Age	
Mean days (SD)	206.5 (106.08)
Median (days)	184
Min, max (days)	23, 365
Age Group by Cohort	
Cohort I: 3 months to 12 months	39 (81%)
Cohort II: 4 weeks to 3 months	8 (17%)
Cohort III: Birth to 4 weeks	1 (2%)
Race	
Black or African American	26 (54%)
White	21 (44%)
American Indian or Alaskan Native	1 (2%)
Ethnicity	
Hispanic or Latino	15 (31%)
Not Hispanic or Latino	22 (46%)
Unknown or not reported	11 (23%)
Weight at Baseline	
Mean weight (kg) (SD)	7.31 (1.77)
Min, Max (kg)	50, 80 (40%)

Source: NDA 214410, SDN 0413, CSR CP40559, Table 11, page 45.

The majority of subjects were enrolled in Cohort I and were 3 months to 12 months of age. The study had difficulties enrolling subjects < 4 weeks of age; the study was designed to enroll three subjects younger than 4 weeks of age and only enrolled one.

> *Reviewer comment*: In this reviewer's opinion, the sponsor's effort to enroll subjects younger than 4 weeks was sufficient. The study was conducted over a four-year period at multiple study sites. Although the study was designed to enroll 30 subjects, the study remained open to enroll more subjects in Cohort III; as a result, 49 subjects were enrolled. In addition, pediatric patients younger than 6 weeks of age may be protected by maternal antibodies due to recent or past infection due to maternal immunization, and a substantial number of patients less than 4 weeks of age may not be infected with influenza due to maternal antibodies, making it difficult to enroll of infants less than 6 weeks into trials.

Slightly more than one-half of the subjects were Black or African American, which is consistent with the number of subjects enrolled at South African study sites. Thirty-three percent of subjects were Hispanic or Latino, which may reflect the number of subjects enrolled at Costa Rican sites. The mean weight at baseline was 7.31 kg, which is consistent with the age of pediatric patients enrolled.

Ten of the subjects (21%) had received an influenza vaccine.

Fifteen subjects (31%) were positive for influenza by RT-PCR analyzed at the central laboratory and were included in the Intent-to-Treat, Influenza-Population. The influenza virus subtypes identified by viral subtyping are shown in the following table.

Table: Influenza Virus Types and Subtypes Identified by RT-PCR

Influenza Virus Type or Subtype	**Baloxavir marboxil (N=48) n (%)**
A/H1_2009	5 (33%)
A/H3	7 (47%)
B	2 (13%)
Unknown	1 (7%)

Source: NDA 214410, SDN 0413, CSR CP40559, Table 11, page 45.

The predominant influenza strains identified were influenza A subtypes A/H1, 2019 pandemic strain and the A/H3 subtype. Only one type B influenza virus was identified.

Please see Dr. Ince's Virology review for additional discussion of influenza subtypes.

Efficacy Results for the Primary Endpoint

The assessment of efficacy was a secondary endpoint. In addition, this was a single arm, open-label study, so the statistical analysis of the secondary efficacy was descriptive. The secondary efficacy endpoint was the time to alleviation of influenza signs and symptoms, defined as the length of time taken from the start of baloxavir marboxil to the point at which the subject had either no cough or nasal symptoms or minor symptoms, was able to return to day care/school or to resume normal daily activity and was afebrile.

Fifteen subjects (30%) had influenza confirmed by RT-PCR at the study's central laboratory. Only nine subjects (18% of all study subjects) had an evaluable efficacy endpoint, e.g., had completed the study diary to allow evaluation of the efficacy endpoint. For these nine subjects, the median time to alleviation of symptoms was 163.7 hours (lower 95% confidence interval was 122.5 hours and upper CI was not evaluable).

The applicant previously conducted a randomized, active controlled efficacy and safety trial in pediatric patients from 1 to < 12 years of age. In that trial (Trial CP40563), the median time to alleviation of symptoms in the baloxavir marboxil arm (N=80) was 138 hours (95% CI: 116, 163) and in the oseltamivir arm (N=43) was 150 hours (95% CI: 112, 164). The median time to alleviation of symptoms in hours for infants < 12 months of age are slightly longer than those reported in older pediatric patients. This could be related to the small number of evaluable subjects in Study CP40559. The median time to alleviation of symptoms was shorter than reported in reports of untreated infants in the scientific literature. The median time to alleviation of symptoms of influenza in infants was approximately 192 hours in a report by Mattila et al (https://doi.org/10.1111/irv.12820) and was 253.5 hours in infants with influenza A infections in another report (doi: 10.1111/irv.12862).

Efficacy Results for Selected Secondary Efficacy Endpoints

The median duration of fever was 23.1 hours (95% CI: 22.3, 44.6). The median duration of symptoms was 163.7 hours (lower 95% CI of 71.0 hours and not evaluable for upper CI). The median return to normal health and activity was 140.7 hours (lower 95% CI of 72.2 hours and not evaluable for upper CI).

The median duration of fever was 23.1 hours or less than one day. Fever in infants can lead to a workup for infection, so the short duration of fever is clinically meaningful. However, since this is an uncontrolled study, it is difficult to determine whether baloxavir marboxil affected the duration of fever in this population. The median duration of symptoms was slightly longer than the median time to return to normal health and activity; the results for both endpoints were similar to the results for the primary efficacy endpoint.

Efficacy Summary and Conclusions
Study CP40559 enrolled 49 subjects < 12 months of age with influenza-like symptoms. The evaluation of efficacy, as assessed by the median time to alleviation of symptoms, was limited by the small number of subjects (N=9) who had influenza confirmed by the central laboratory and who had sufficient diary entries to assess the efficacy endpoint and by the single arm, open label study design. Of note, the median duration of fever was considerably shorter, 23.1 hours than the time to alleviation of symptoms, which is particularly beneficial in this age group, in that it may prevent a workup for infection.

8. Safety

Adverse Events
In Study CP40559, adverse events (AEs) were collected through Day 29. AEs were classified by System Organ Class and Preferred Terms of the MedDRA system. The severity of AEs was categorized according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

The overall summary of adverse events with the numbers of each type of AE is shown in the following table.

Table 16: Overall Summary of Adverse Events (Safety Population)

	Baloxavir Marboxil N=48
Number (%) of subjects with any AE	23 (50%)
Number (%) of subjects with any baloxavir-marboxil-related AE	2 (4%)
Number of deaths	1 (2%)
Number (%) of subjects with SAE	2 (4%)

Source: NDA 214410, SDN 0413, CSR CP40559, Table 13, page 50.

As shown in the table, 50% of subjects experienced an adverse event during the 29-day follow-up period. Only 2 subjects had AEs (4%) that were considered related to baloxavir marboxil. Serious adverse events were reported in 2 subjects (4%). There was one death.

Deaths and Other Serious Adverse Events
There was one death, 10-month-old Black male; this adverse event was also reported as a serious adverse event. The subject was previously healthy. On enrollment, he had moderate nasal congestion, severe cough, and a temperature of 39.8° C. He received a single dose of baloxavir on Day 1. His NP swab from Day 1 was negative for influenza at the central

laboratory. The subject was seen at the study site on Day 2; at that visit, his temperature was 37.3° C and his nasal symptoms and cough had improved. On Day 4, the subject choked while eating porridge and died. No further details were reported, and no autopsy was performed. The death was judged by the investigator as not related to baloxavir marboxil.

One other serious adverse event was reported. A 4-month-old Black male subject was diagnosed with a lower respiratory tract infection on Day 2. This subject had symptoms of rhinorrhea, nasal congestion, and diarrhea at enrollment. He received a single dose of baloxavir marboxil and had a NP swab for influenza obtained on Day 1. RT-PCR performed at the central laboratory was negative for influenza. At the study visit on Day 2, the subject had developing trouble breathing with a temperature of 39° C. His chest radiograph showed a lower respiratory tract infection (LRTI). He was started on amoxicillin at that time. The subject was seen at the study site on Day 3 for a follow-up visit and was hospitalized at that time for treatment of his LRTI. The reason for hospitalization and his treatment in hospital were not provided. He was discharged from hospital on Day 5 and finished 10 days of amoxicillin as an outpatient. This SAE was judged as not related to baloxavir marboxil.

> *Reviewer comment:* Although there is limited information regarding the death of the 10-month-old male in the study, the subject was improving prior to his death and his death was temporally related to a choking incident. Another subject was hospitalized with a LRTI, his hospitalization appears to be related to his underlying disease. This reviewer agrees that neither adverse event was related to baloxavir marboxil.

Adverse Events with Severe or Life-threatening Intensity

Grade 3 AEs were reported for two subjects, there were no Grade 4 adverse events, and there was one Grade 5 AE (death). One of the Grade 3 AEs was reported as an SAE; that subject and the subject who died are described in the previous section of this review. The other subject with a Grade 3 AE was a subject with Grade 3 decreased lymphocyte count reported post-dose on Day 1; according to the Applicant, the lymphocyte count resolved by Day 9.

Common Adverse Events

Adverse events of any causality

The following table displays all adverse events reported in at least 1% of subjects who received baloxavir marboxil in Trial T0832. There were no treatment-emergent adverse events reported in more than 5% of subjects in any arm in the pivotal trials.

Table 18: Number and Percentage of Subjects with Treatment-Emergent Adverse Events (Reported in ≥ 2 Subjects, Safety Population)

	Baloxavir Marboxil N=48
Diarrhea	8 (17%)
Vomiting	6 (13%)
Lower respiratory tract infection	2 (4%)
Otitis media	2 (4%)
Pyrexia	2 (4%)
Cough	2 (4%)
Productive cough	2 (4%)
Nasal congestion	2 (4%)
Genital candidiasis	2 (4%)

Source: NDA 214410, SDN 0413, CSR CP40559, Table 14, page 52-53.

The only adverse events reported in more than 2 subjects were diarrhea, which was reported in 8 subjects (17%) and vomiting, which was reported in 6 subjects (13%). This is consistent with the results of Trial CP40563, which enrolled subjects > 12 months to < 12 years. In Trial CP40563, vomiting and diarrhea were the most frequently reported AEs and were reported in 6% and 5%, respectively, of subjects who received baloxavir. In addition, diarrhea and vomiting are more common in pediatric patients with influenza compared to older children and adults. In one study of children hospitalized with influenza A, diarrhea was reported in 18.4% of children < 5 years of age and in 8.4% of children 5 years of age and older. (Wang et al. Clinical characteristics of children with influenza A virus infection requiring hospitalization. Journal of Microbiology, Immunology, and Infection. 2003 Jun;36(2):111-116. PMID: 12886962). In another study of children hospitalized with influenza B, vomiting was reported in 38% and diarrhea in 33% of children younger than 3 years of age. (Liou Y-S, et al. Children hospitalized with influenza B infection. The Pediatric Infectious Disease Journal 6(6):p 541-543, June 1987). Overall, the adverse events are consistent with previous studies of baloxavir marboxil and with influenza symptoms in young children.

The only adverse event considered related to study drug was Grade 1 diarrhea, which was reported in two subjects. Drug-related AEs were infrequently reported in other studies of baloxavir marboxil. The one drug related AE of diarrhea is consistent with Xofluza labeling.

Clinical Laboratory Evaluation

Four subjects had abnormal laboratory values that were reported as adverse events. These included three subjects with Grade 1 laboratory abnormalities: increased lymphocyte count, decreased neutrophil count, and increased platelet count. All Grade 1 abnormalities occurred on Day 7, and all resolved. None were judged as related to baloxavir marboxil. The fourth laboratory abnormality was Grade 3 decrease in lymphocyte count, which was reported on Day 1. This was also judged as not related to baloxavir marboxil and resolved.

Laboratory results were not assessed using a grading toxicity. Laboratory test results assessed as high or low were reported in 32 subjects. The most common laboratory abnormality was increased platelets, which was reported in 23 subjects. High platelet counts ranged from 417 to 856 x 10^9/L (normal range of 200 to 400 x 10^9/L). This finding is not concerning because thrombocytosis is common in pediatric patients with viral infections (Elber-Dorozko S et al. The clinical significance of thrombocytosis in children with viral respiratory tract infections. Euro Resp Journal 2022: 60:2742. https://doi.org/10.1183/13993003.congress-2022.274). Eight subjects had a high lymphocyte count, and one had a low lymphocyte count. These abnormalities are consistent with viral infections in young pediatric patients. Abnormal neutrophil counts were only reported in three subjects.

Overall, few laboratory abnormalities were reported as adverse events. In addition, most abnormalities were those typically observed in young pediatric patients with viral infections.

Safety Summary

The safety results from Study CP40559 are consistent with safety results from the pediatric trial CP40563 and with adverse events described in the package insert. Adverse events are also similar to symptoms of infants who have influenza. There was one death in a 10-month-old male who choked while feeding and died. The investigator assessed the death as not related to baloxavir marboxil, and this reviewer agrees with that assessment. Overall, no new safety

concerns were identified in this trial of pediatric patients younger than 12 months of age, and no safety information from this trial will be added to the Xofluza package insert.

9. Pediatrics

This application contains pediatric data for subjects from < 12 months of age. This sNDA did not trigger PREA because it was not submitted for a new dosing regimen, a new dosage form, a new active ingredient, or a new route of administration.

The Clinical Study Report for Study CP40559 was submitted in response to three PREA PMRs. With this submission, the applicant has fulfilled all three PREA PMRs.

3503-1: Conduct a single-arm, open-label clinical trial to evaluate pharmacokinetics, safety, and antiviral activity of baloxavir marboxil in pediatric subjects from birth to less than 12 months of age with acute uncomplicated influenza. Include characterization of baloxavir-resistant substitutions in viral isolates from subjects with prolonged viral shedding.

Study Completion:	08/2023 (revised date)
Final Report Submission:	12/2023 (deferral extension date)

3984-1: Conduct a single-arm, open-label clinical trial to evaluate pharmacokinetics, safety, and antiviral activity of baloxavir marboxil in pediatric subjects from birth to less than 12 months of age with acute uncomplicated influenza. Include characterization of baloxavir-resistant substitutions in viral isolates from subjects with prolonged viral shedding.

Study Completion:	08/2023 (revised date)
Final Report Submission:	12/2023 (deferral extension date)

3961-1: Submit the clinical study reports including the pharmacokinetic / pharmacodynamic modeling data and the supporting PK, safety and efficacy data from all the relevant studies in adult and pediatric patients to extrapolate efficacy of baloxavir marboxil in pediatric subjects from birth to less than 12 months of age for the prevention of influenza as post-exposure prophylaxis in household contacts of an index case. Include characterization of baloxavir-resistant substitutions including supporting datasets.

Final Report Submission: 02/2024 (deferral extension date)

10. Outstanding Issues

There are no outstanding issues.

11. Recommendations / Risk Benefit Assessment

Study CP40559 was a single arm study and was not designed to demonstrate efficacy. Efficacy in pediatric patients < 12 months of age was to be extrapolated from pediatric patients from 12 months to < 12 years of age based on similar baloxavir exposures between the pediatric subjects in Study CP40559 and those enrolled in the pediatric efficacy trial CP40563, as well as in the pivotal trials of baloxavir in adults and adolescents. However, baloxavir marboxil is *not* approved in pediatric patients from 12 months to < 5 years of age because of the increased incidence of resistance in that age group. Because of the risk of resistance in younger age groups, which is considered a safety concern, use of baloxavir cannot be extrapolated from pediatric patients > 12 months of age to pediatric patients < 12 months of age.

The baloxavir marboxil package insert was revised to include the incidence of TE-RAS in subjects < 12 months of age and to state that the safety and efficacy of baloxavir marboxil has not been established in pediatric patients < 5 years of age, (b) (4)

12. Baloxavir Marboxil Labeling

The baloxavir marboxil labeling has been updated to update the percentage of pediatric patients with treatment-emergent RAS and to include neonates in pediatric populations. The changes with this efficacy supplement affected the following sections.

The percentage of subjects younger than 5 years of age who had treatment-emergent resistance was revised in Section 5.2 and in Section 12.4 of the baloxavir marboxil package insert (see final revised language below).

> **5.2** Increased Incidence of Treatment-Emergent Resistance in Patients Less Than 5 Years of Age
> XOFLUZA is not indicated in patients less than 5 years of age due to increased incidence of treatment-emergent resistance in this age group. In clinical trials, the incidence of virus with treatment-emergent substitutions associated with reduced susceptibility to baloxavir (resistance) was higher in pediatric subjects younger than 5 years of age (b) (4) than in pediatric subjects ≥ 5 years to < 12 years of age (16%, 19/117) or subjects ≥ 12 years of age (7%, 60/842). The potential for transmission of resistant strains in the community has not been determined [see Indications and Usage (1), Use in Specific Populations (8.4), and Microbiology (12.4)].
>
> **12.4 Microbiology**, Clinical studies in pediatric subjects < 5 years of age
> The highest frequencies of treatment-emergent resistance have been observed in pediatric subjects < 5 years of age. In treatment trials in subjects < 5 years of age, treatment-emergent amino acid substitutions associated with reduced susceptibility to baloxavir occurred in (b) (4) of influenza A/H1N1, A/H3N2, and B virus infections, respectively, in pooled data from (b) (4) pediatric treatment trials.

The Pediatric Use section was revised to specify that safety and effectiveness had not been established in neonates.

> **8.4 Pediatric Use,** Pediatric Subjects (< 5 Years of Age)
> The safety and effectiveness of XOFLUZA for treatment and post-exposure prophylaxis of influenza in pediatric subjects less than 5 years of age, (b) (4) have not been established [see Warnings and Precautions (5.2) and Microbiology (12.4)].

Recommendation for Postmarketing Risk Evaluation and Management Strategies
None

Recommendation for Other Postmarketing Requirements and Commitments
None

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