NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	215040
Priority or Standard	Standard
Submit Date(s)	August 14, 2023
Received Date(s)	August 14, 2023
PDUFA Goal Date	February 14, 2024
Division/Office	Division of Hepatology and Nutrition
Review Completion Date	February 13, 2024
Established/Proper Name	acetylcysteine
(Proposed) Trade Name	Legubeti
Pharmacologic Class	Antidote for acetaminophen overdose
Code name	N/A
Applicant	Galephar Pharmaceutical Research Inc.
Dosage form	Powder for oral solution 500 mg and 2.5 g
Applicant proposed Dosing Regimen	The proposed loading dose of Legubeti is 140 mg/kg. Administer a first maintenance dose of 70 mg/kg 4 hours after the loading dose. Repeat 70 mg/kg maintenance dose every 4 hours for a total of 17 maintenance doses.
Applicant Proposed Indication(s)/Population(s)	Indicated as an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen.
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	295124009, Acetaminophen overdose (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Indicated as an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen.
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	
Recommended Dosing Regimen	The recommended loading dose of Legubeti is 140 mg/kg. Administer a first maintenance dose of 70 mg/kg 4 hours after the loading dose. Repeat 70 mg/kg maintenance dose every 4 hours for a total of 17 maintenance doses.

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Abbreviations: CDRH, Center for Devices and Radiological Health; DARS, Division of Applied Regulatory Sciences; DCOA, Division of Clinical Outcome Assessment; DEPI, Division of Epidemiology; DHOT, Division of Hematology Oncology Toxicology; DIIP, Division of Inflammation and Immune Pharmacology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; DPV, Division of Pharmacovigilance; DPMH, Division of Pediatrics and Maternal Health; OB, Office of Biostatistics; OHOP, Office of Hematology and Oncology Products; OPDP, Office of Prescription Drug Promotion; OPMA, Office of Pharmaceutical Manufacturing Assessment; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

Glossary

ADME	absorption, distribution, metabolism, excretion
BA	bioavailability
BLA	biologics license application
BMI	body mass index
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CR	Complete Response
DCOA	Division of Clinical Outcome Assessment
DPMH	Division of Pediatric and Maternal Health
EPC	Established Pharmacologic Class
FDA	Food and Drug Administration
IND	Investigational New Drug
LD	listed drug
NAC	N-acetylcysteine
NDA	new drug application
OPQ	Office of Pharmaceutical Quality
PI	prescribing information
PK	pharmacokinetics
TEAE	treatment-emergent adverse event

1 Executive Summary

1.1. Product Introduction

Legubeti (acetylcysteine) for oral solution is proposed as an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen. It is essential to initiate treatment as soon as possible after the overdose and, in any case, within 24 hrs of ingestion of acetaminophen. Legubeti contains acetylcysteine lysine salt as the active ingredient and is a powder packaged in aluminum packets in 500 mg and 2.5 g strengths.

The proposed dosage regimen in adults and pediatric patients weighing >1 kg is the loading dose of 140 mg/kg followed by a first maintenance dose of 70 mg/kg 4 hrs after the loading dose and repeated every 4 hrs for a total of 17 maintenance doses. The maximum loading and maintenance dose is 15 g and 7.5 g, respectively for patients weighing 100 kg or greater.

Legubeti should be dissolved to form a solution prior to administration. Legubeti is completely dissolved in the recommended volume of liquid for oral administration: water, pediatric electrolyte solution, and caffeine-free Diet Coke. A dosing syringe may be used to administer the oral solution to the pediatric patients. For the patient who is persistently unable to retain the orally administered acetylcysteine, Legubeti may be administered by nasoduodenal tube.

The Applicant proposed to establish the safety and efficacy of Legubeti by relying on the FDA's previous findings of safety and efficacy of Mucomyst (acetylcysteine solution; NDA 13601). Legubeti is a new lysine salt form of acetylcysteine whereas Mucomyst is acetylcysteine free acid in 10% or 20% solution. The proposed indication and the dosage regimen for adult and pediatric patients are the same as those of the listed drug, Mucomyst.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant adequately established the efficacy of Legubeti by relying on FDA's previous findings of efficacy of the listed drug (LD), Mucomyst in adult and pediatric patients. The reliance on Mucomyst was justified by the comparable bioavailability (Study 2021-5140) of acetylcysteine and the similar tolerability and palatability (Study 2024-5442) between Legubeti and oral acetylcysteine solution used in the studies due to discontinuation of Mucomyst. Although acetylcysteine is safe and efficacious, it is known for poor oral tolerability. Given it is essential to initiate treatment as soon as possible after the acetaminophen overdose and Legubeti differs from the LD in salt form (i.e., L-lysine salt), the assurance of tolerability and palatability of Legubeti that is comparable to the LD is needed to further support the reliance on the LD. Lack of adequate data to support tolerability and palatability of Legubeti was one of deficiencies in the Complete Response letter to the original submission of NDA 215040. In this resubmission, the Applicant provided the results of Study 2024-5442 and demonstrated similar tolerability and palatability of Legubeti to that of oral acetylcysteine solution. As such the review team concluded that the efficacy of Legubeti be comparable to that of the LD.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Legubeti (acetylcysteine lysine) has demonstrated safety and effectiveness as an antidote for acetaminophen overdose. In this application, the Applicant relied on FDA's previous findings of efficacy and safety for the listed drug (LD), Mucomyst® (acetylcysteine solution, USP, NDA 013601, currently discontinued not for a reason of safety or efficacy). The recommended dosage regimen is a loading dose of 140 mcg/kg followed by a maintenance dose of 70 mcg/kg every 4 hours starting at 4 hours after the loading dose via oral administration. A total of 17 maintenance doses should be administered. Legubeti may be administered via a nasoduodenal tube in pediatric patients who cannot tolerate Legubeti. The recommended dosage regimen is the same as the dosage regimen of the LD.

To establish a scientific bridge to the LD, the Applicant conducted a relative bioavailability (BA) study 2021-5140, comparing its proposed product to the oral acetylcysteine solution (reference standard, ANDA 072547, AM Regent) and demonstrated equivalent systemic exposure to acetylcysteine between two products. Although the equivalent bioavailability between Legubeti and the acetylcysteine oral solution supported the reliance on the LD, the original NDA 215040, submitted July 6, 2022, received a Complete Response action on May 5, 2023, mainly due to 1) inadequate data to support tolerability and palatability of Legubeti, 2) inadequate information to support the safety of L-lysine administration to pediatric patients weighing down to 1 kg, and 3) citing the prescribing information of Cetylev (NDA 207916) without complying with regulatory requirements.

In this resubmission dated August 14, 2023, the Applicant included 1) the results of a comparative tolerability and palatability study (Study 2023-5442), and 2) publications to resolve deficiencies in the Complete Response (CR) letter.

Acetylcysteine (N-acetylcysteine; NAC) is an N-acetyl derivative of cysteine and approved as an antidote for acetaminophen overdose. Multiple NAC products have been approved for oral or intravenous administration. NAC exerts its action in APAP toxicity by repleting glutathione stores by providing cysteine, binding to toxic metabolites (N-acetyl-p-benzoquinone imine), scavenging free radicals, increasing oxygen delivery to tissues, increasing mitochondrial ATP production, and altering microvascular tone, thus increasing blood flow to the liver and other vital organs. The efficacy of treatment depends on the time interval from when APAP was ingested. NAC administration is most effective within 8 hours of APAP ingestion but may provide clinical benefit even when administration is delayed beyond eight hours. If NAC is started within 24 hours of APAP overdose, the mortality rate is 0.7%.

The most common adverse reactions with orally administered NAC include nausea, vomiting, diarrhea, and other gastrointestinal symptoms. Other adverse reactions include rash, urticaria, and fever. Anaphylactoid reactions have also been documented with oral NAC but are more common with intravenous (IV) NAC. Safety data from the BA study (study 2021-5140), the tolerability and palatability study (study 2023-5442),

published literature review, and analysis of databases of post-marketing safety reports in the United States, did not identify any new safety issues with oral NAC.

Acetylcysteine (N-acetylcysteine; NAC) has an unpleasant smell and taste, and vomiting is common with oral administration. Because Legubeti contains acetylcysteine lysine, a new salt of NAC and the L-Lysine content is approximately 47.25% (w/w) of the active pharmaceutical ingredient (API), there was concern regarding the effect of L-Lysine on tolerability and palatability of Legubeti. An inability to ingest the full dose regimen, either due to inadequate palatability or inadequate tolerability poses significant safety concerns: (1) inability to tolerate full dose NAC regimen or delay in ingestion of doses, may lead to suboptimal efficacy, increasing the risk of APAP hepatotoxicity; and (2) lack of data on the effect L-lysine on gastrointestinal adverse reactions when compared to NAC, as increased risk of vomiting may increase the risk of aspiration in patients, especially in children and those with altered mental status. In the original submission, inadequate data were submitted to support tolerability and palatability of Legubeti at the clinically relevant doses. The relative BA study was conducted at 1 g while the doses can be as high as 15 g based on the recommended dosing. In this resubmission, the tolerability and palatability study (Study 2023-5442) conducted in healthy adults for the loading dose of 140 mg/kg, showed similar palatability and tolerability between Legubeti and acetylcysteine oral solution.

In adults, the daily dose of L-lysine in Legubeti is approximately 8-13 times higher than the recommended daily intake from a regular diet over a three-day regimen Although there are limited human data to support safety of a high dose of L-lysine for a short period, animal data were adequate to support the safety of high dose, short-term L-lysine administration.

Pediatric approval down to 1 kg is granted based on the FDA's previous findings of efficacy and safety for the LD in pediatric patients. In this resubmission, no substantive new safety data were submitted to support the safety of L-lysine content of this product in pediatric patients. Instead, the Applicant submitted one publication on daily intake of L-lysine through formula by infants and the review team further identified that the expected daily lysine intake with use of this product was similar to that expected with daily lysine intake with breastmilk or formula consumption. Analyses of the lysine content of infant formulas and breastmilk coupled with available nonclinical data support the conclusion that the lysine content of Legubeti is reasonably safe at the proposed dosage for administration to pediatric patients down to 1 kg body weight.

In the original submission, the Applicant cited prescribing information of Cetylev to comply with the Physician Labeling Rule (PLR) and the Pregnancy and Lactation Labeling Rule (PLLR) without a proper justification. To resolve this regulatory deficiency cited in the CR letter, the Applicant has updated the label by using nonproduct- specific published literature concerning Lactation, Pregnancy, and Females and Males of Reproductive Potential to comply with PLLR.

To summarize, the Applicant has demonstrated that Legubeti is similar to the LD, from a palatability and tolerability perspective, addressed the safety of lysine administration to pediatric patients weighing down to 1 kg, and updated the label to comply with the PLR and PLLR. The Applicant's response to the Agency's complete response is acceptable and the Agency can conclude a favorable benefit-risk profile for approval of Legubeti.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acetaminophen (N-acetyl-p-aminophenol, APAP) is one of the most widely used pain relievers in use. It has been in use since 1960. • APAP is safe and effective at therapeutic doses. • APAP toxicity: – Hepatotoxicity can occur with acute ingestion of >7.5 g to 10 g (~140 mg/kg), and rarely occur with repeated doses of >3-4 g/day, especially in at-risk populations. – It is the most common cause of acute liver failure (ALF) in the United States (U.S.) and Europe, and the most common indication for liver transplantation for ALF in the U.S. • APAP overdose is responsible for 56,000 emergency department visits, 2,600 hospitalizations, and 500 deaths per year in the United States.	Acetaminophen is a widely used pain reliever. Although safe in therapeutic doses, acute or chronic ingestion can lead to severe liver injury which may result in acute liver failure and death.
Current Treatment Options	• N-acetylcysteine (NAC) is the only approved pharmacological treatment for acetaminophen toxicity. • Several products of NAC are available for oral use. Mucomyst, the listed drug (LD) for this NDA was approved in 1963 as an antidote for APAP toxicity in adult and pediatric patients. It has since been discontinued. Cetylev (acetylcysteine), an effervescent tablet was approved in 2016, but has also been discontinued. There are multiple generic products of NAC, which can be used orally. There is also an intravenous (IV) product of NAC, Acetadote • Oral administration of NAC is complicated by the unpleasant taste and odor of NAC which affects tolerability and palatability of oral NAC products. Patients with APAP toxicity experience nausea and vomiting as presenting symptoms, which combined with the unpleasant taste and odor of NAC can aggravate vomiting and thus make oral NAC intolerable. Patients can also have increased risk of aspiration, especially children and patients with altered mental status.	NAC has been used as an antidote for acetaminophen since 1963 and if given early after overdose of acetaminophen provides a benefit on decreasing the likelihood of severe liver injury as compared with no treatment. NAC products for IV administration and generic products of NAC for oral administration are available.

Benefit	• The Applicant did not conduct any controlled clinical trials of efficacy or safety. The Applicant relies on FDA's previous findings of efficacy for the LD, Mucomyst. • To establish a scientific bridge to the LD, the Applicant conducted a relative bioavailability (BA) study 2021-5140, comparing Legubeti to the Acetylcysteine Oral Solution, the reference standard per the Orange Book, because Mucomyst is currently discontinued, after a single dose of 1000 mg NAC in healthy subjects under fasted conditions. • The equivalent bioavailability was shown between Legubeti and the reference standard at 1000 mg. Because Legubeti is completely dissolved to form a solution prior to oral administration and no evidence that dissociated lysine would affect oral absorption of acetylcysteine, available data also support the comparable systemic exposure between Legubeti and the Acetylcysteine oral solution at doses for the approved body weight range. • Legubeti can be reconstituted in the age-appropriate volume of liquid for oral administration for pediatric patients. • In the current submission, the Applicant has provided results of study 2023-5442, a palatability and tolerability study to address the concerns raised in the complete response letter dated May 5, 2023. The Applicant has demonstrated that Legubeti has a similar palatability and tolerability to the reference drug, acetylcysteine solution.	The Applicant relies on FDA's previous findings of efficacy in adult and pediatric patients for the LD, Mucomyst. The comparable efficacy of Legubeti to the LD can be expected based on the comparable systemic exposure between two products. The Applicant has successfully demonstrated that from a palatability and tolerability perspective, Legubeti is similar to the reference drug, therefore the efficacy of Legubeti will be comparable to the LD.
Risk and Risk Management	Most common adverse reactions with orally administered NAC include nausea, vomiting, diarrhea, and other gastrointestinal symptoms. Rash, urticaria and mild fever have also been observed. Risk of upper gastrointestinal hemorrhage is also included in the Warnings and Precautions section of the LD label. NAC has an unpleasant smell and taste, and vomiting is common with oral administration. Safety data from the BA study 2021-5140, published literature review, and analysis of databases of post-marketing safety reports in the United States, did not identify any new safety issues with oral NAC.	The Applicant relies on FDA's previous findings of safety in adult and pediatric patients for the LD, Mucomyst based on the comparable systemic exposure to NAC. Nonclinical toxicology study and published studies provide a reasonable assurance of safety regarding the amount of L-lysine administered from Legubeti.

	In the palatability and tolerability study which a single dose, double blinded, cross-over study (Study 2023-5442), Legubeti had numerically higher treatment-emergent adverse events (TEAEs) compared to the reference drug, but these TEAEs were mild in severity. Diarrhea, abdominal pain, and nausea were more common with Legubeti compared to the reference drug. No deaths or serious adverse events, or any other significant adverse events were reported in the study. Overall, the tolerability of Legubeti was not substantially worse than the reference drug. For pediatric patients, the maximum daily amount of L-lysine expected to be administered from Legubeti at the proposed dosage is two to four times the daily estimated intake of lysine in enterally fed term neonates. The Applicant was asked to provide information supporting the safety of L-lysine at the level in young pediatric patients down to 1 kg in the complete response for the original submission. The resubmission did not contain substantive new safety data to inform the pediatric risk assessment for the lysine content of this product. Both acetylcysteine and L-lysine have an unpleasant odor and taste, and there were insufficient data in the original submission to ensure the L-lysine salt form did not adversely affect the palatability and tolerability of NAC. To address the tolerability and palatability concerns, the Applicant submitted results from study 2023-5442, a study that assessed the tolerability and palatability of acetylcysteine lysine powder for oral solution in adults. This study used a single weight-based loading dose of Legubeti and the reference drug but did not assess repeat multiple dosing regimens. (b) (4), (b) (5)	(b) (4) pediatric approval down to 1 kg was granted based on the similar palatability and tolerability as well as the FDA's previous findings of efficacy for the LD (see Section 10). Although no new data were submitted to support the safety of L-lysine content of this product in pediatric patients down to 1 kg body weight, analyses of the lysine content of infant formulas and breastmilk coupled with available nonclinical data support the conclusion that the lysine content of Legubeti appears to be reasonably safe at the proposed dosage for administration to pediatric patients down to 1 kg body weight (see Section 10). Study 2023-5442 addresses the safety concern of palatability and tolerability raised in the Agency's complete response dated May 5, 2023, by demonstrating that in adults, the safety, palatability, and tolerability of Legubeti is not substantially different from the reference drug.


(b) (4)

1.4. Patient Experience Data

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

x	**The patient experience data that were submitted as part of the application include:**			**Section of review where discussed, if applicable**
	x	Clinical outcome assessment (COA) data, such as		
		x	Patient reported outcome (PRO)	8.2.6
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

2 Therapeutic Context

2.1. Analysis of Condition

Refer to the Multi-Disciplinary Review and Evaluation of NDA 215040, dated 05/04/2023.

2.2. Analysis of Current Treatment Options

Refer to the Multi-Disciplinary Review and Evaluation of NDA 215040, dated 05/04/2023.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Legubeti is not currently marketed in the U.S.

MUCOMYST (NDA 013601), the LD, was FDA-approved on September 14, 1963, but was withdrawn from the U.S. market on FR Notice Effective March 13, 2009, by the manufacture based on a business decision, and not for reasons of safety or efficacy.

3.2. Summary of Presubmission/Submission Regulatory Activity

- **May 18, 2016:** A Type B Pre-IND meeting for PIND 130190 was held to discuss the contents of an NDA submission utilizing the 505(b)(2) regulatory pathway. During this meeting, the Agency agreed that the Sponsor could submit a 505(b)(2) application as their proposed product would not be a "duplicate" of the LD. Meeting Minutes were sent on May 19, 2016.
- **April 15, 2020:** An Agreed-Initial Pediatric Study Plan letter was issued which provided for a partial waiver for children below 1 kilogram.
- **July 14, 2021:** A request for a Small Business Waiver was granted for NDA 215040.
- **July 7, 2022:** NDA 215040 was submitted via the 505(b)(2) regulatory pathway.
- **September 9, 2022:** Filing Review Issues Identified Letter was issued.
- **September 22, 2022:** The proprietary name request for (b) (4) was denied**.**
- **October 7, 2022:** The Applicant submitted a second proposed proprietary name, LEGUBETI.
- **October 21, 2022:** A draft protocol was submitted to PIND 130190 for a tolerability and palatability study to be conducted to support the pending NDA submission. The Applicant proposed this protocol to address concerns regarding palatability and tolerability raised in the Filing Review Issues Identified Letter dated September 9, 2022.
- **December 16, 2022:** A General Advice Letter was issued containing comments on the draft protocol submitted to PIND 130190.
- **December 29, 2022:** The proprietary name request for LEGUBETI was deemed conditionally acceptable.

- **December 30, 2022:** The Applicant submitted responses to the Filing Review Issues Identified letter dated September 9, 2022.
- **March 7, 2023:** The Applicant submitted a guidance request PIND 130190 regarding the reference product (acetylcysteine oral solution). The Applicant expressed difficulty obtaining acetylcysteine oral solution (America Regent, INC). The Agency did not find acetylcysteine oral solution in shortage at the time and recommended obtaining the reference product.
- **May 5, 2023:** A Complete Response letter was issued.
- **August 14, 2023:** The resubmission was received.
- **October 30, 2023:** The proprietary name request for LEGUBETI was conditionally acceptable.
- **January 18, 2024:** Revised draft labeling was sent to the Applicant with a response received on January 24, 2024; January 25, 2024; and January 31, 2024.
- **January 31, 2024:** Final labeling was agreed upon with the Applicant.

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

4.1. Office of Scientific Investigations

Not applicable.

4.2. Product Quality

During the first cycle review of this application, labeling negotiation with the application was not pursued due to the intended complete response for this application from the clinical perspective. Therefore, in IQA dated April 3, 2023, this application was not recommended for approval from the Office of Pharmaceutical Quality (OPQ) perspective until successful labeling negotiation is conducted and labeling issues are adequately addressed. The Applicant resubmitted this application on August 14, 2023, and responded to the complete response.

This resubmission did not include any chemistry, manufacturing, and controls (CMC) updates and no additional OPQ review for this application except the labeling was needed. During the second cycle review of this application, the labeling negotiation was pursed. The CMC labeling deficiencies that were delineated in the labeling review by the Dr. Caroline Strasinger were communicated to the Applicant. The Applicant has submitted the Prescribing Information (PI) labeling on January 24, 2024, and container closure and carton labels on January 25, 2024, that has adequately addressed all CMC labeling/labels deficiencies.

The manufacturing facilities involved in this application have remained complaint.

Therefore, this application is now recommended for **approval** with an expiration dating period of **24 months**.

4.3.Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Acetylcysteine lysine (also known as nacystelyn or NAL) oral solution is a lysine salt of N-acetylcysteine indicated to prevent or lessen hepatic injury which may occur following ingestion of a hepatotoxic or potentially hepatotoxic amount of acetaminophen. The proposed drug product (Legubeti [acetylcysteine] oral solution) will be packaged in aluminum sachets, with NAL and Povidone (b) (4) as the ingredients. Acetylcysteine (free acid), which is often referred to as N-acetylcysteine (NAC), is an approved drug indicated to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen. The Applicant's NDA is mainly supported by reference to the Agency's previous findings of safety for Mucomyst, available publications of nonclinical studies of acetylcysteine (free acid), and original reports of genotoxicity studies conducted with acetylcysteine lysine (NAL or nacystelyn) that were all previously reviewed and summarized (Multi-Disciplinary Review and Evaluation of NDA 215040 dated 05/04/2023). The reference drug is Mucomyst (NDA 013601), which has been discontinued from marketing. Mucomyst is a 10% or 20% solution of NAC for inhalation when used as a mucolytic agent, with the 20% solution also indicated for oral administration in the treatment of acetaminophen overdose. The proposed labeling (Sections 8.1 and 13.1) contains nonclinical data from publications. Most of the same data is included in the label for Mucomyst (NDA 013601). The Applicant has only designated Mucomyst for reliance on the Agency's findings of safety to support approval of their marketing application as a 505(b)(2) NDA.

The nonclinical assessment of this application was conducted previously under the original NDA review and primarily focused on the safety assessment of lysine exposure from the drug product and the specified impurities in drug substance and drug product. NAL was negative in each of the submitted genotoxicity studies (Multi-Disciplinary Review and Evaluation of NDA 215040 dated 05/04/2023).

The Applicant proposes "antidote" as the Established Pharmacologic Class (EPC) to be stated in the Highlights section of the package insert. Since "antidote" is one of the EPCs shown for acetylcysteine in the Pragmatic Regulated Product Labeling Listing and Registration System (https://elist.fda.gov/prpllr/), the Applicant's proposal is acceptable.

Because Legubeti contains lysine as the counter ion in the active pharmaceutical ingredient, large amounts of lysine will be delivered by the drug product when it is used in accordance with

the dosing recommendations. The Agency's Complete Response letter dated 05/05/2023 identified a safety concern for the daily amount of L-lysine that will be administered in pediatric patients weighing down to 1 kg. This concern was raised by the team from the Division of Pediatric and Maternal Health (DPMH). In the current submission (Complete Response), the Applicant provided publications showing that young piglets are an appropriate model for evaluating intestinal absorption in human neonates and infants. The piglet model demonstrated that only one third of the amino acids (including lysine) can be absorbed via the intestinal mucosa in young piglets (Shulman et al. 1988), (Stoll et al. 1998). To address the safety concern in the Complete Response letter, the Applicant proposes that (b) (4) . We defer to the Medical and DPMH teams for evaluation of this issue.

5.2. Referenced NDAs, BLAs, DMFs

NDA 013601 and NDA 207916.

5.3. Pharmacology

No studies were submitted in the Complete Response or the original NDA.

5.4. ADME/PK

No studies were submitted in the Complete Response or the original NDA.

5.5. Toxicology

No studies were submitted in the Complete Response. For relevant information, refer to Section 5.5 of the Multi-Disciplinary Review and Evaluation of NDA 215040 dated 05/04/2023.

6 Clinical Pharmacology

6.1. Executive Summary

In the original submission, the Applicant conducted a relative BA study (2021-5140) to establish a scientific bridge to the LD, Mucomyst. The study showed that Legubeti provided comparable bioavailability to the approved oral acetylcysteine solution at 1 g of dose. Therefore, the pharmacokinetics (PK) bridging study in combination with the solubility data was able to support reliance of efficacy of acetylcysteine on the LD. However, the relative BA study conducted at 1 g acetylcysteine was not sufficient to justify the reliance on the LD for safety due to the unresolved tolerability/palatability issues that may prevent the timely dosing of the full doses and lead to suboptimal efficacy. Refer to the Multi-Disciplinary Review and Evaluation of NDA 215040 dated 05/04/2023.

In the current resubmission dated 08/14/2023, the Applicant submitted the results of a palatability and tolerability study (under PIND 130190) that was recommended by the Agency in the complete response letter to address the lack of tolerability/palatability data at clinically relevant doses. The palatability and tolerability study (No. 2023-5442) was a phase 1, double-blind, randomized, single-dose, crossover study in healthy adults where the primary objective was to assess the palatability of Legubeti as compared to the approved oral acetylcysteine solution. No PK samples were collected from this study. The study conducted at 140 mg/kg of dose (up to 15 g) showed that the palatability and tolerability of Legubeti were comparable to those of the oral acetylcysteine solution. Refer to Section 8.2 for details.

Therefore, the comparable palatability and tolerability study data can support the reliance of safety of Legubeti on the LD. In conclusion, the clinical bridging between the proposed Legubeti and the LD is now deemed established from a clinical pharmacology standpoint.

The Applicant also submitted original publication information corroborating the proposed labeling language that are not based on the listed drug. This clinical pharmacology review focused on the relevance and accuracy of the annotated references for the label language proposed in the Section 12 Clinical Pharmacology.

Based on our review, the original publication information corroborating the proposed labeling language in the Section 12 Clinical Pharmacology is deemed acceptable from a clinical pharmacology standpoint and there are no remaining clinical pharmacology issues.

6.2. Summary of Clinical Pharmacology Assessment

Dosage and Administration

The Applicant proposed to include a statement. (b) (4) ” in Dosage and Administration Section of the labeling. (b) (4) Therefore, it could create confusion and potential dosing errors with the proposed statement. As such, the corresponding statement proposed in the label of Legubeti was deleted from Subsection 2.3 Recommended Dosage and Preparation and Administration Instructions in Adults and Pediatrics for Acute Acetaminophen Ingestion (refer to Section 11 for additional comments).

Absorption

The Applicant cited PK data from the results of the BA study (No. 2021-5140) that the Applicant conducted to establish a bridge between Legubeti and the LD. The reviewer considers it acceptable.

Distribution

For the proposed label language of "*The protein binding for acetylcysteine ranges from 66% to 87%*.", the Applicant did not provide any original literature information to support this language. Nevertheless, it is noted that the protein binding was reported in other publications (Sahasrabudhe et al. 2023), (Smaga et al. 2021).

Elimination

Metabolism

The label proposes that *"Acetylcysteine (i.e., N-acetylcysteine) undergoes extensive first pass metabolism and is postulated to form cysteine and disulfides (N,N-diacetylcysteine and N-acetylcysteine). Cysteine is further metabolized to form glutathione and other metabolites."* The Applicant did not indicate any specific public or literature information supporting the label contents. The reviewer considers the proposed label contents to be general public information and also considers it acceptable.

Excretion

The proposed label language of *"After a single oral dose of [^{35}S]-acetylcysteine 100 mg, between 13 to 38% of the total radioactivity administered was recovered in urine within 24 hours."* is cited as one of references in the paper by (Borgström et al. 1986). The cited reference is (Rodenstein et al. 1978).

The label contents composing of "In *a separate study, renal clearance was estimated to be approximately 30% of total body clearance*" is supported by the reference of (Borgström et al. 1986).

The rest of label language proposing *"In healthy subjects given a single oral dose of 1 gram of LEGUBETI, the mean (CV%) terminal plasma half-life ($T_{1/2}$) was 3.30 (25%) hours."* is supported by the results of the Applicant's BA study (No. 2021-5140).

Specific Populations

Hepatic Impairment

Following a 600 mg intravenous dose of acetylcysteine to subjects with mild (Child Pugh Class A, n=1), moderate (Child-Pugh Class B, n=4) or severe (Child-Pugh Class C; n=4) hepatic impairment and 6 healthy matched controls, mean $T_{1/2}$ increased by 80%. Also, the mean CL decreased by 30% and the systemic acetylcysteine exposure (mean AUC) increased 1.6-fold in subjects with hepatic impairment compared to subjects with normal hepatic function. These changes are not considered to be clinically meaningful.

For the label language in the hepatic impairment, the Applicant referenced literature written by (Jones et al. 1997), and the reviewer confirmed the contents and considers it acceptable.

Renal Impairment

Hemodialysis may remove some of total acetylcysteine.

For the label proposed for renal impairment, the Applicant referenced literature written by (Hernandez et al. 2015), and the reviewer confirmed the contents and considers it acceptable.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The Applicant did not conduct any controlled clinical trials of efficacy or safety. To establish a scientific bridge to the LD, the Applicant conducted a relative BA study, 2021-5140, comparing the proposed acetylcysteine lysine product to the LD (Refer to the Multi-Disciplinary Review and Evaluation of NDA 215040 dated 05/04/2023).

In this resubmission, in response to the Agency's CR, the Applicant submitted results from a palatability and tolerability study, which was proposed during the review cycle of the original submission. See Section 3.2 for regulatory history and refer to the Multi-Disciplinary Review and Evaluation of NDA 215040 dated 05/04/2023.

Table 1. Description of Palatability and Tolerability Study of Legubeti (Acetylcysteine) Powder for Oral Solution Vs. the Reference-Listed Drug Acetylcysteine Solution in Healthy Adults (2023-5442)

Trial Identity	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers and Countries
2023-5442	Double-blinded, single-dose, randomized, two-period, two-treatment, two-sequence, crossover	Single dose trial, oral 140 mcg/kg up to 15 g	Primary Endpoint • Evaluation of subject preference* between Legubeti (acetylcysteine) POS and the acetylcysteine solution. Secondary Endpoints • Evaluation of subject preference to volume and appearance of drug product. • Safety-profile assessment includes treatment-emergent adverse events, physical examination, chemistry, and hematology parameters.	Single dose of Legubeti and LD separated by a washout period of ≥7 days	24	Healthy Adults	One center study outside the United States.

Source: Reviewer generated from clinical study report for study 2023-5442 in module 5.
* Using the adapted British Nutrition Foundation's Sensory Evaluation 5-point Hedonic scale

7.2. Review Strategy

The Applicant relies on FDA's previous findings of efficacy for the Mucomyst (acetylcysteine solution, USP, NDA 013601), and has not conducted clinical efficacy studies in the target population. The review strategy for the original submission is described in the Multi-Disciplinary Review and Evaluation of NDA 215040 dated 05/04/2023.

For this resubmission, only the palatability and tolerability study submitted in response to the complete response dated 05/04/2023 is reviewed (Section 8).

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The Applicant did not conduct controlled clinical trials of efficacy or safety. The Applicant relies on FDA's previous findings of efficacy for the listed drug, Mucomyst® (acetylcysteine solution, USP, NDA 013601). To establish a scientific bridge to the LD, the Applicant conducted a relative BA study 2021-5140, comparing its proposed product to a reference standard per the Orange Book after a single dose of 1000 mg in healthy subjects under fasted conditions. This study was reviewed at the time of the original submission. (Refer to the Multi-Disciplinary Review and Evaluation of NDA 215040 dated 05/04/2023). Refer to Section 6.

In response to the complete response dated May 5, 2023, the Applicant submitted data from study 2023-5442 in this resubmission. Study 2023-5442 is a palatability study which does not inform efficacy. This study was conducted in response to the Agency's concern regarding the impact of addition of L-Lysine on palatability of Legubeti, which was a safety issue in the complete response letter. Refer to the Multi-Disciplinary Review and Evaluation of NDA 215040 dated 05/04/2023.

Study 2023-5442 was conducted in Canada without an IND although the study protocol was submitted to PIND 130190 for the Agency's comments. The Applicant used Acetylcysteine Solution, USP (200 mg/mL; Fresenius Kabi USA, LLC; ANDA 203853) in Study 2023-5442 due to difficulty obtaining the reference standard used in the relative BA study per the Orange Book (American Regent; INC; ANDA 72547). The use of Acetylcysteine Solution, USP by Fresenius Kabi is acceptable for the comparison of tolerability and palatability because (1), it is like the LD, MUCOMYST, Acetylcysteine Solution, USP contains edetate disodium, sodium hydroxide, and water as inactive ingredients[1]; and (2), the LD is an oral solution without taste masking. Therefore, the palatability and tolerability of acetylcysteine following oral administration of

[1]Prescription Information for Acetylcyeine Injection (Fresenius Kabi USA, LLC) https://nctr-crs.fda.gov/fdalabel/services/spl/set-ids/8d81039e-20ef-5144-e053-2a95a90a89fd/spl-doc?hl=acetylcysteine

Acetylcysteine Solution, with the same inactive ingredients, is expected to be similar to that of the LD.

8.1.1.A Phase 1 Study to Evaluate the Palatability of Legubeti (Acetylcysteine) Powder for Oral Solution Vs. the Reference-Listed Drug Acetylcysteine Solution in Healthy Adults (2023-5442)

Trial Design

This was a double-blinded, single-dose, randomized, two-period, two-treatment, two-sequence, crossover, palatability study.

In each period, subjects received one of the following two treatments as per the treatment sequence in Table 2.

1. Treatment A
    a. Test Product: Legubeti reconstituted as oral solution in caffeine-free Diet Coke® administered after an overnight fast of at least 10 hours.
    b. Dose: 140 mg/kg.
2. Treatment B
    a. Reference Product: Acetylcysteine Solution, USP (200 mg/mL; Fresenius Kabi USA, LLC) mixed with caffeine-free Diet Coke® administered after an overnight fast of at least 10 hours.
    b. Dose: 140 mg/kg.

Table 2. Treatment Sequence for Palatability Study 2023-5442*

	Treatment	
Sequence	**Period 1**	**Period 2**
AB	A	B
BA	B	A

Source: Reviewer generated from Table 2 in Study 2023-5442 protocol.
* A 7-day (±3 hours) washout between drug administrations.

A single dose of the assigned drug product was administered according to the randomization scheme. The dose was based on the weight of the subject (140 mg/kg up to a maximum of 15 g).

Study Endpoints

Primary Endpoint

Evaluation of subject preference between Legubeti (acetylcysteine) and the reference drug, acetylcysteine solution (Fresenius Kabi) using the adapted British Nutrition Foundation's Sensory Evaluation 5-point hedonic scale.

Secondary Endpoints

1. Evaluation of subject preference to volume and appearance of drug product.
2. Safety-profile assessment includes treatment-emergent adverse events (TEAEs), physical examination, chemistry, and hematology parameters.

Statistical Analysis Plan

No formal statistical analysis plan was submitted, but the study report mentions that statistical analysis was performed on quality assured data from subjects in the palatability population.

The treatment difference in response scores for the questions on the Hedonic scale were evaluated by a non-parametric approach (Wilcoxon signed rank test). The formulation attributes were compared between the two treatments, and it was determined if there were statistically significant differences ($p<0.05$). See Section 8.2.6 for more details regarding the Hedonic scale and clinical outcome assessment analyses.

Study Population

Healthy, non-smoking, male, and female volunteers, 18 years of age or older, with a body mass index (BMI) of ≥19 and ≤35 kg/m2 with at least 30% of the subjects having a BMI ≥30 kg/m2.

8.1.2. Study Results

Compliance With Good Clinical Practices

The study report mentions that study 2023-5442 was performed in compliance with the most current International Council for Harmonisation Good Clinical Practice.

Financial Disclosure

Financial disclosure forms were submitted in module 5 for this resubmission in accordance with 21CFR Part 54. No conflicts of interest were noted for the principal investigators or sub-investigators.

Patient Disposition

Twenty-four (24) subjects were enrolled, and all the subjects completed the study.

Protocol Violations/Deviations

No protocol deviations were reported.

Table of Demographic Characteristics

Table 3 displays the demographic information for the study population. Of the 24 enrolled subjects, 63% were female, with a median age of 46 years, and with most subjects between 41 and 64 years (67%). The median BMI was 31.5 kg/m^2 with the highest BMI of 35 kg/m^2. Approximately 46% of the population was White, 38% were Black or African American, and 13% identified as Asian. Eighty percent of the population were not of Hispanic or Latino ethnicity.

Table 3. Demographic Characteristics in Study 2023-5442

Characteristic	Safety Dataset N=24
Sex, n (%)	
Female	15 (62.5)
Male	9 (37.5)
Age (years)	
Mean (SD)	46 (14)
Median (range)	52 (21-62)
Age group, n (%)	
18-40	8 (33.3)
41-64	16 (66.7)
65-75	0 (0.0)
>75	0 (0.0)
Weight (kg)	
Mean (SD)	86.9 (10.1)
Median (range)	87.5 (66-105.8)
Height (cm)	
Mean (SD)	168 (8.1)
Median (range)	167.9 (152.1-183.6)
BMI (kg/m²)	
Mean (SD)	30.7 (3.1)
Median (range)	31.5 (23-35)
Race, n (%)	
Asian	3 (12.5)
Black or African American	9 (37.5)
Multi-racial	1 (4.2)
White	11 (45.8)
Ethnicity, n (%)	
Hispanic or Latino	5 (20.8)
Not Hispanic or Latino	19 (79.2)

Source: Modified from Table 11-1 in Applicant submitted report for study 2023-5442 (module 5.3.1.2)
Abbreviations: BMI, body mass index; N, number of subjects included in each dataset; n, number of subjects in respective categories; SD, standard deviation

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Qualified clinic staff ensured that all study drugs were administered according to the protocol and the randomization scheme. Treatment compliance in the administration of the test and reference products was assured by the presence of the investigator or designate, and by adherence to the study procedures.

The Applicant specifies in the clinical study report study-specific restrictions. These are in Table 4 below.

Table 4. Study 2023-5442 Restrictions

Restriction	Prior to Drug Administration	Until
Medication (prescription or over-the-counter)*	14 days	End of Period 2 confinement
Herbal/natural products	14 days	End of Period 2 confinement
Oral and injectable nutritional supplements and vitamins	14 days	End of Period 2 confinement
Alcohol and alcohol-containing products	72 hours	End of confinement in each Period

Restriction	Prior to Drug Administration	Until
Caffeine-containing and xanthine-containing products	72 hours	End of confinement in each Period
Grapefruit and grapefruit-containing products	48 hours	End of confinement in each Period
Chewing gum	Throughout confinement	
Strenuous activity	Throughout confinement	

Source: Table 9-5 in clinical study report for study 2023-5442 submitted to module 5.
* Exceptions were to be made for: hormonal contraceptives; non-systemic and/or topically applied products (prescription or otherwise); and the occasional use of common analgesics.

8.1.3. Integrated Assessment of Effectiveness

Not applicable.

8.2. Review of Safety

8.2.1. Safety Review Approach

In the original submission, the clinical review of safety for Legubeti focused on FDA's previous findings of safety for the Mucomyst, safety data from the BA study 2021-5140, information from published literature, and information from the FDA Adverse Event Reporting System database for the LD (Refer to the Multi-Disciplinary Review and Evaluation of NDA 215040 dated 05/04/2023). In this resubmission, safety data from study 2023-5442, was reviewed.

8.2.2. Review of the Safety Database

Overall Exposure

Twenty-four (24) subjects were enrolled, all the subjects completed the study, receiving a 140 mg/kg dose of acetylcysteine in each of the two periods.

Adequacy of the Safety Database

Assessment of safety for Legubeti relies on FDA's previous findings on safety for the LD, Mucomyst. Data from this single dose trial assessing palatability of Legubeti is supportive of safety as it addresses the palatability and tolerability concerns raised in the complete response letter dated May 5, 2023.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The quality of the overall submission met the requirement for clinical safety assessment. There are no issues with data integrity that precluded the analysis and conclusions.

Categorization of Adverse Events

The process for recording, coding, and categorizing adverse events and safety analyses were reasonable and appropriate.

Routine Clinical Tests

Overall, laboratory and scheduled visit safety assessments were reasonable and adequate in this study.

8.2.4. Safety Results

Deaths

There were no deaths reported in the palatability and tolerability study.

Serious Adverse Events

There were no serious adverse events reported in the palatability and tolerability study.

Treatment-Emergent Adverse Events and Adverse Reactions

All TEAEs are classified according to version 26.0 of the Medical Dictionary for Regulatory Activities and reported with respect to severity, duration, relationship to study drug(s), and action taken to treatment.

Twenty-four subjects were enrolled, and all the subjects completed the study, receiving a 140 mg/kg dose of acetylcysteine in each of the two periods.

Table 5 displays the summary of all TEAEs for each treatment. Overall, a numerically higher number of subjects (79.2%) in the Legubeti arm (treatment A) reported TEAEs compared to the reference product, acetylcysteine solution, USP 20% (62.5%). Most of these TEAEs were mild in severity and resolved prior to end of the study except for one TEAE of abdominal pain (assessed as mild in severity) in one subject. This subject was lost to follow-up.

Table 5. Summary of All Treatment-Emergent Adverse Events for Each Treatment

	Proportion of Adverse Events* by Treatment Group n (%)		
Severity of TEAEs	**A N=24**	**B N=24**	**Total N=24**
Subjects With TEAEs	19 (79.2)	15 (62.5)	24 (100)
Mild	19 (79.2)	15 (62.5)	24 (100)
Moderate	0 (0)	0 (0)	0 (0)
Severe	0 (0)	0 (0)	0 (0)

Source: Modified by reviewer from Table 12-1 in study 2023-5442 report submitted to module 5
* Adverse event terms are classified according to Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0
Note: Treatment A- Test Product: Legubeti (Acetylcysteine)
Note: Treatment B- Reference Product: Acetylcysteine solution, USP 20% (200 mg/mL)
Abbreviations: N, number of subjects dosed; n, number of subjects in respective categories; TEAE, treatment-emergent adverse event

Table 6 displays the proportion of subjects who reported TEAEs by system organ class for each treatment. Gastrointestinal disorders and nervous system disorders were reported in higher proportion for Legubeti compared to the referent product.

Table 6. Summary of All Treatment-Emergent Adverse Events by System Organ Class for Each Treatment

	Proportion of Adverse Events* by Treatment Group n (%)		
System Organ Class	**A N=24**	**B N=24**	**Total N=24**
Cardiac disorders	0 (0)	1 (4.2)	1 (4.2)
Gastrointestinal disorders	19 (79.2)	14 (58.3)	24 (100)
Investigations	0 (0)	1 (4.2)	1 (4.2)
Nervous system disorders	3 (12.5)	2 (8.3)	4 (16.7)
Product issues	1 (4.2)	0 (0)	1 (4.2)
Vascular disorders	0 (0)	1 (4.2)	1 (4.2)

Source: Extracted by reviewer from Table 12-2 in study 2023-5442 report submitted to module 5
* Adverse event terms are classified according to Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0
Note: Treatment A- Test Product: Legubeti (Acetylcysteine)
Note: Treatment B- Reference Product: Acetylcysteine solution, USP 20% (200 mg/mL)
Note: Subjects having 2 or more adverse events under the same treatment are counted only once within a category. The same subject may appear in different categories and treatments.
Abbreviations: N, number of subjects dosed; n, number of subjects in respective categories; TEAE, treatment-emergent adverse event; SOC, system organ class

Table 7 displays the most common TEAEs reported in study 2023-5442. Diarrhea, abdominal pain, and nausea were reported in higher frequency in the Legubeti arm compared to reference product (58.3 versus 45.8%, 50% versus 20.8%, 41.7% versus 29.2%, respectively).

Table 7. Common Treatment-Emergent Adverse Events for Each Treatment

	Proportion of Adverse Events* by Treatment Group n (%)		
Adverse Event	**A N=24**	**B N=24**	**Total N=24**
Diarrhea	14 (58.3)	11 (45.8)	19 (79.2)
Abdominal pain**	12 (50)	5 (20.8)	16(66.7)
Nausea	10 (41.7)	7 (29.2)	13 (54.2)
Headache	2 (8.3)	2 (8.3)	3 (12.5)
Constipation	1 (4.2)	0 (0)	1 (4.2)
Vomiting	1 (4.2)	0 (0)	1 (4.2)
Somnolence	1 (4.2)	0 (0)	1 (4.2)
Product after taste	1 (4.2)	0 (0)	1 (4.2)
Dizziness	1 (4.2)	1 (4.2)	1 (4.2)
Palpitations	0 (0)	1 (4.2)	1 (4.2)
Flatulence	0 (0)	1 (4.2)	1 (4.2)
Neutrophil count decreased	0 (0)	1 (4.2)	1 (4.2)
White blood cell count decreased	0 (0)	1 (4.2)	1 (4.2)
Hypertension	0 (0)	1 (4.2)	1 (4.2)

Source: Extracted by reviewer from Table 12-2 in study 2023-5442 report submitted to module 5
* Adverse event terms are classified according to Medical Dictionary for Regulatory Activities (MedDRA) Version 26.0
** Abdominal pain includes the related terms abdominal discomfort, abdominal distension, and abdominal pain upper
Note: Treatment A- Test Product: Legubeti (Acetylcysteine)
Note: Treatment B- Reference Product: Acetylcysteine solution, USP 20% (200 mg/mL)
Note: Subjects having 2 or more adverse events under the same treatment are counted only once within a category. The same subject may appear in different categories and treatments.
Abbreviations: N, number of subjects dosed; n, number of subjects in respective categories; TEAE, treatment-emergent adverse event

Concomitant Therapy

No concomitant drug therapy or non-drug therapy were administered during this study.

Laboratory Findings

Hematology, biochemistry, and urinalysis tests were conducted at end-of-study. One subject (Subject (b) (6)) experienced neutropenia (lowest value 0.9 x10^9/L) and leukopenia (lowest value of 3.0 x 10^9/L). Although no narrative was submitted by the Applicant, besides neutropenia and leukopenia, this subject had normal labs, vital signs, electrocardiogram, and physical examination. These reductions in neutrophils and white blood cell counts were not considered significant, and subject was asked to follow up with family doctor (source: Appendix 16.2.8.2 in module 5). Other abnormal laboratory values submitted in the study report were not clinically significant. It is unlikely that Subject (b) (6)'s asymptomatic neutropenia and leukopenia are related to the study drug.

Vital Signs

Abnormalities noted on vital signs measurements were minor and not clinically significant. One subject was noted to have hypertension which was reported as a TEAE but was mild in severity and resolved before the study ended. This TEAE of hypertension was unlikely related to the study drug.

Electrocardiograms

No clinically significant abnormalities on electrocardiogram were noted.

Physical Examination

No abnormalities on physical examination were noted.

8.2.5. Analysis of Submission-Specific Safety Issues

Evidence regarding L-Lysine safety from published literature was discussed in the original submission review as a submission-specific safety issue. Refer to the Multi-Disciplinary Review and Evaluation of NDA 215040 dated 05/04/2023.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Palatability/Tolerability

Regulatory History

The Agency previously asked the Sponsor to reach agreement with the Division of Clinical Outcome Assessment (DCOA) before embarking on tolerability and palatability studies to ensure the patient reported outcome measure used is valid (FDA 2023b). The Sponsor did not request a meeting with the Agency to discuss their measurement strategy prior to conducting their palatability and tolerability study.

Palatability Questionnaire

The Palatability Questionnaire (a.k.a. the adapted British Nutrition Foundation's Sensory Evaluation 5-point Hedonic Scale) is an 8-item patient reported outcome measure assessing overall palatability of the drug product [1 item], taste [3 items: mouth feel, initial taste,

aftertaste], smell [1 item: overall likeability], appearance [2 items: color, appearance], and dose volume [1 item] using a 5-point verbal rating scale (Like very much; Like; Neither like nor dislike; Dislike; Dislike very much). Each item on the palatability questionnaire is scored separately (i.e., do not contribute to a total score) and scores were dichotomized for the palatability evaluation (i.e., "Dislike very much" and "Dislike" are categorized as Negative Acceptability; "Like very much" and "Like" are categorized as Positive Acceptability; "Neither like nor dislike" is categorized as Neutral Acceptability). Refer to 16.2.1.

Palatability Analyses

In Study 2023-5442, there was no statistically significant difference for any of the palatability item scores between Legubeti and the reference drug, acetylcysteine solution. For both treatment arms, the largest proportion of subjects rated overall palatability, mouth feel, initial taste, aftertaste, overall likeability and volume per dose of drug product as negative acceptability. Similarly, the largest proportion of subjects in both treatment arms rated appearance of the drug product as neutral. The same proportion of subjects rated color of Legubeti as neutral or positive whereas most subjects rated color of the reference drug as neutral.

Analyses are displayed in Section 16.2.2.

Conclusion

There was no statistically significant difference between treatment arms for any of the Palatability Questionnaire item scores. However, there was insufficient evidence to support the intended use of the Palatability Questionnaire as a preference measure. Specifically, the Palatability Questionnaire is not a true assessment of subject preference as it does not directly query respondents on their preference for LEGUBETI™ compared to the reference drug, acetylcysteine solution. Furthermore, evidence was not provided to support that the Palatability Questionnaire captures the most important and relevant attributes of palatability that are meaningful to patients.

8.2.7. Safety Analyses by Demographic Subgroups

No subgroup analyses were conducted for study 2023-5442.

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Refer to the Multi-Disciplinary Review and Evaluation of NDA 215040 dated 05/04/2023.

Human Reproduction and Pregnancy

Refer to the Multi-Disciplinary Review and Evaluation of NDA 215040 dated 05/04/2023.

Pediatrics and Assessment of Effects on Growth

As outlined in the Multi-Disciplinary Review and Evaluation of NDA 215040 dated 05/04/2023, there were concerns regarding the benefit risk profile of Legubeti in the pediatric age group. The Applicant had not provided adequate information to support the safety of L-lysine administration to pediatric patients weighing down to 1 kg. This was conveyed in the Agency's complete response dated May 5, 2023. The Applicant response to this complete response was reviewed by DPMH for this resubmission. Please see DPMH (pediatrics) review for further discussion in Section 10.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Refer to the Multi-Disciplinary Review and Evaluation of NDA 215040 dated 05/04/2023.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Refer to the Multi-Disciplinary Review and Evaluation of NDA 215040 dated 05/04/2023.

8.2.10. Integrated Assessment of Safety

The Applicant relies on FDA's previous findings of safety for the LD, Mucomyst, and has not conducted clinical studies with Legubeti in the target population. To establish a scientific bridge to the LD, the Applicant conducted a relative BA study 2021-5140 which was reviewed at the time of the original submission (Refer to the Multi-Disciplinary Review and Evaluation of NDA 215040 dated 05/04/2023).

During the original submission, safety of acetylcysteine, which has been in use since 1963 for acetaminophen toxicity, was reviewed. However, because this is a new salt of acetylcysteine with L-lysine, there was concern regarding use of high dose Legubeti, especially whether L-Lysine would impact tolerability and palatability. In the original submission, there were insufficient data regarding the tolerability and palatability of the proposed Legubeti doses. This was considered a safety issue and this concern was conveyed to the Applicant during the review cycle. To address tolerability and palatability concerns, the Applicant proposed a trial to assess the tolerability and palatability of acetylcysteine lysine for oral solution in adults. The Applicant submitted the protocol for this trial to the PIND 130190. An advice letter with the Agency's recommendations and concerns regarding this study was sent on December 16, 2022.

Given that this was a significant safety issue, but the study results were not available during the original review cycle, a complete response was issued on May 5, 2023. Refer to the Multi-Disciplinary Review and Evaluation of NDA 215040 dated 05/04/2023.

In response to the Agency's complete response, the Applicant's resubmission included the results of study 2023-5442, a phase 1 study to evaluate the palatability of Legubeti versus the reference drug, acetylcysteine solution in healthy adults. During this resubmission review, DCOA was consulted to review the instrument used to measure palatability because during the original submission, DCOA had raised concerns as to whether the Hedonic scale, the instrument

planned for use in the study, was fit-for-purpose. During the original review cycle, the Applicant did not respond to DCOA's concerns and proceeded to complete study 2023-5442 with their proposed instrument. In this resubmission, even though DCOA recommendations were not followed, and insufficient evidence was submitted for assessment of fitness-for-purpose of the palatability questionnaire, this questionnaire measures similar aspects of palatability that were used in the survey to support approval of (b) (4) (see Section 8.2.6).

The results of the study indicate that Legubeti was at least as palatable as the reference drug when assessed on the basis of taste, likeability, mouth feel, aftertaste and overall palatability (see Section 8.2.6).

From a tolerability and safety perspective, Legubeti had numerically higher TEAEs compared to the reference drug, but these TEAEs were mild in severity. Diarrhea, abdominal pain, and nausea were more common with Legubeti compared to the reference drug. No deaths or serious adverse events, or any other significant adverse events were reported in the study. Overall, the tolerability of Legubeti was not substantially worse than the reference drug.

In summary, the Applicant has successfully addressed the palatability and tolerability concerns regarding Legubeti that were raised in the original submission.

8.3. Conclusions and Recommendations

In this resubmission the Applicant has addressed the deficiencies related to palatability and tolerability of Legubeti which were raised in the original submission. Study 2023-5442 demonstrated that the palatability and tolerability of Legubeti is similar to the reference drug, acetylcysteine solution. Therefore, the clinical review team has concluded Legubeti can be approved as a 505(b)(2) new drug indicated as an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen.

9 Advisory Committee Meeting and Other External Consultations

Not applicable

10 Pediatrics

The Applicant originally submitted a new drug application, (NDA) on July 7, 2022, under the 505(b)(2) pathway, relying on Mucomyst, NDA 013601, as the LD. The Division issued a CR to the original NDA due to the following deficiencies:

- Lack of data demonstrating "the tolerability of Legubeti, the lysine salt of acetylcysteine, for the full range of loading and maintenance doses for patients with all body weights proposed in labeling."
- Lack of "adequate information to support the safety of L-lysine administration to pediatric patients weighing down to 1 kg."

The Applicant's resubmission contained the results from a palatability and tolerability study in adults and additional information supporting the safety of the L-lysine exposure anticipated at the proposed dosage in pediatric patients down to 1 kg for the proposed indication (FDA 2023a).

The results of the palatability and tolerability study in adults showed an overall similarity between Legubeti and the reference product (acetylcysteine 20% solution, USP; Fresenius Kabi USA, LLC, USA). (b) (4)

The Applicant met the bioequivalence standard to bridge to FDA's findings of safety and effectiveness of the LD to support pediatric approval of this product and to fulfill its Pediatric Research Equality Act requirements for this application. Although the NDA resubmission did not contain substantive new safety data to inform the pediatric risk assessment for the lysine content of this product, the review team identified that the expected daily lysine intake with use of this product was similar to that expected with daily lysine intake with breastmilk or formula consumption. There are limited published data estimating that breastfed and formula-fed infants routinely receive lysine levels above 200 mg/kg/day as part of their diet.

The daily lysine intake expected with use of this product, at the proposed dosage, is 502.6 mg/kg/day on Day 1 and 313 mg/kg/day on Days 2 and 3. The safety of this amount of lysine exposure is supported by nonclinical data from one publication, (Flodin 1997), which summarized a chronic toxicity study in which rats were fed high supplemental levels of lysine for a 2-year period at levels 170% more than the lysine content of un-supplemented feeds with no observed adverse clinical, hematological or pathological effects.

(b) (4)

(b) (4), findings from the completed palatability study in adults alone should not preclude pediatric approval of this product, particularly if other oral NAC products approved for the same indication, including the LD, were not removed from marketing for safety reasons and this product otherwise meets the bioequivalence standard for approval.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Prescribing Information

A summary of the Division's labeling recommendations and edits in the Legubeti (acetylcysteine) Prescribing Information are included. These edits are made to ensure that the PI is a useful communication tool for healthcare providers and uses clear, concise language; is based on regulations and guidances; and conveys the essential scientific information needed for the safe and effective use of Legubeti.

Table 8 provides a summary and rationale of the proposed changes to the Full Prescribing Information from the proposed PI submitted by the Applicant on August 14, 2023.

Table 8. Summary and Rationale of Proposed Changes to the Full Prescribing Information

Full Prescribing Information Sections[1]	Rationale for Major Changes Incorporated Into the Finalized Prescribing Information[2]
1 INDICATIONS AND USAGE	Applicant's proposed indication statement: (b) (4) Therefore, under Section 1, the indication was revised to: *"LEGUBETI is indicated to prevent, or lessen hepatic injury, which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen, in adults and pediatric patients."*

Full Prescribing Information Sections[1]	**Rationale for Major Changes Incorporated Into the Finalized Prescribing Information[2]**
2 DOSAGE AND ADMINISTRATION	In addition, the use of the term (b) (4) Also refer to Section 6.2. Therefore, the following sentence was deleted from Subsection 2.3 Recommended Dosage and Preparation and Administration Instructions in Adults and Pediatrics for Acute Acetaminophen Ingestion: (b) (4)
4 CONTRAINDICATIONS	None
5 WARNINGS AND PRECAUTIONS	Applicant's proposed Subsection 5.1 Hypersensitivity Reactions: (b) (4) This sentence was revised to include symptoms of anaphylactoid reactions. Although less frequently observed with IV administration, anaphylactoid reactions have been reported with oral N-acetylcysteine (NAC). *"Generalized urticaria, angioedema, bronchospasm, pruritus, flushing, other rash, chest tightness, and hypotension have been observed in patients receiving oral acetylcysteine for acetaminophen overdose."*
6 ADVERSE REACTIONS	Applicant's proposed language in Section 6 Adverse Reactions: (b) (4) This section was revised to include the postmarketing caveat statement and delete words that may be vague, misleading, or promotional in tone (e.g., (b) (4) *"The most common adverse reactions have been identified from clinical studies or post marketing reports of acetylcysteine. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The most common adverse reactions were nausea, vomiting, other gastrointestinal symptoms, and rash with or without fever."*
7 DRUG INTERACTIONS	This section was omitted and not included as part of the PI submitted for review.

Full Prescribing Information Sections[1]	**Rationale for Major Changes Incorporated Into the Finalized Prescribing Information[2]**
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	8.1 Pregnancy and 8.2 Lactation: These sections have been revised to be consistent with revised draft guidance for industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (July 2020). 8.4 Pediatric Use: Applicant's proposed language for this subsection: (b) (4) Therefore, the subsection was revised to: *"Legubeti is indicated in pediatric patients as an antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen. There is no recommended dosage for pediatric patients weighing less than 1 kg [see Dosage and Administration (2.3)]."* 8.5 Geriatric Use: (b) (4). Therefore, the following statement was deleted: (b) (4)
9 DRUG ABUSE AND DEPENDENCE	This section was omitted and not included as part of the PI submitted for review.
10 OVERDOSAGE	This section was omitted and not included as part of the PI submitted for review. (b) (4)
12 CLINICAL PHARMACOLOGY	Subsection 12.2 Pharmacodynamics was added in accordance with 21 CFR 201.57(c)(13)(i)(B) to describe known Exposure-Response (E-R) relationships or include a statement about the lack of this information.

Full Prescribing Information Sections[1]	Rationale for Major Changes Incorporated Into the Finalized Prescribing Information[2]
	The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of acetylcysteine have not been fully characterized.
13 NONCLINICAL TOXICOLOGY	Information pertaining to lysine salt of N-acetylcysteine was added to Subsection 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility. *Carcinogenesis* *Carcinogenicity studies in laboratory animals have not been performed with acetylcysteine lysine (active ingredient in LEGUBETI) or with acetylcysteine.* *Mutagenesis* *Acetylcysteine lysine was negative in the bacterial reverse mutation (Ames) assay, the in vitro mouse lymphoma cell gene mutation assay, and the in vivo mouse micronucleus test. Acetylcysteine was negative in the Ames test.* *Impairment of Fertility* *No fertility studies have been performed with acetylcysteine lysine.*
14 CLINICAL STUDIES	This section was omitted and not included as part of the PI submitted for review.
17 PATIENT COUNSELING INFORMATION	Included the standard FDA-approved patient labeling statement at the beginning of Section 17 and information that a healthcare provider should convey to a patient regarding the risk of hypersensitivity reactions. *Advise the patient to read the FDA-approved patient labeling (Patient Information).* *Hypersensitivity Reactions* *Advise patients that hypersensitivity reactions, including generalized urticaria may occur and to report any signs or symptoms to their healthcare provider immediately [see Warnings and Precautions (5.1)].*
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	The dosage form was revised to read “For Oral Solution” and upon consultation with OPQ, the packaging term "(b) (4)" was revised to "packet" throughout the label and labeling. Sections 3, 11, and 16 were revised to improve readability.

Source: Reviewer’s summary
Abbreviations: FPI, full prescribing information

12 Risk Evaluation and Mitigation Strategies

Not applicable.

13 Postmarketing Requirements and Commitment

None.

14 Division Director (Clinical) Comments

See Section 15.

15 Office Director (or Designated Signatory Authority) Comments

This 505(b)(2) application, NDA 215040, for Legubeti, initially received a CR on May 5, 2023. Legubeti is indicated as an antidote to prevent or lessen hepatic injury which may occur following ingestion of a large quantity of acetaminophen, which can lead to hepatic injury. The CR was issued for several reasons of which the most important was the lack of available evidence for oral tolerability of the new product. Oral preparations of N-acetylcysteine are known to be safe and effective but are poorly tolerated due to their unpleasant taste and odor. The Applicant relied on the safety and effectiveness of NDA013601, the LD for acetylcysteine solution (Mucomsyt®). Consequently, the issue with the initial submission was whether Legubeti offered at least the same palatability as the LD. However, data to address this issue were not available at the end of the initial ten-month review cycle.

The Applicant resubmitted its 505(b)(2) application as a Class 2 product on August 14, 2023. Contained in the submission were data from the Applicant's palatability and tolerability study. The results of this study indicated that Legubeti was at least as well-tolerated as the LD. The review team considered these data as similar to the LD. At the time of the initial review DCOA raised concerns as to whether the instruments planned for use in the tolerability study were fit-for-purpose. However, following the Class 2 resubmission, the DCOA consultants found that the instruments used by the Applicant were acceptable and provided the necessary data to gauge tolerability and palatability.

The review team concluded the Applicant successfully completed the required palatability/tolerability study. Also, the Applicant included the necessary references of originally published studies to support what the Applicant borrowed from the Cetylev label (NDA 207916). The review team concluded that the Applicant offered a complete response to the May 2023 CR action, and recommended approving Legubeti as an oral formulation of NAC for the treatment of hepatoxicity due to acetaminophen overdose. As the Signatory Authority for this NDA, I agree with this regulatory decision.

16 Appendices

References

Borgström, L, B Kågedal, and O Paulsen, 1986, Pharmacokinetics of N-acetylcysteine in man, Eur J Clin Pharmacol, 31(2):217-222.
FDA, 2023a, DPMH Memorandum Resubmission NDA-215040 Legubeti (acetylcysteine lysine) entered in DARRTS 12/11/2023, accessed, https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80710b55
FDA, 2023b, NDA 215040 Complete Response letter dated May 5, 2023, accessed, https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af806c9ab3.
Flodin, NW, 1997, The metabolic roles, pharmacology, and toxicology of lysine, J Am Coll Nutr, 16(1):7-21.
Hernandez, SH, M Howland, TD Schiano, and RS Hoffman, 2015, The pharmacokinetics and extracorporeal removal of N-acetylcysteine during renal replacement therapies, Clin Toxicol (Phila), 53(10):941-949.
Jones, AL, DR Jarvie, D Simpson, PC Hayes, and LF Prescott, 1997, Pharmacokinetics of N-acetylcysteine are altered in patients with chronic liver disease, Aliment Pharmacol Ther, 11(4):787-791.
Rodenstein, D, A DeCoster, and A Gazzaniga, 1978, Pharmacokinetics of oral acetylcysteine: absorption, binding and metabolism in patients with respiratory disorders, Clin Pharmacokinet, 3(3):247-254.
Sahasrabudhe, SA, MR Terluk, and RV Kartha, 2023, N-acetylcysteine Pharmacology and Applications in Rare Diseases-Repurposing an Old Antioxidant, Antioxidants (Basel), 12(7).
Shulman, RJ, SJ Henning, and BL Nichols, 1988, The miniature pig as an animal model for the study of intestinal enzyme development, Pediatr Res, 23(3):311-315.
Smaga, I, M Frankowska, and M Filip, 2021, N-acetylcysteine as a new prominent approach for treating psychiatric disorders, Br J Pharmacol, 178(13):2569-2594.
Stoll, B, J Henry, PJ Reeds, H Yu, F Jahoor, and DG Burrin, 1998, Catabolism dominates the first-pass intestinal metabolism of dietary essential amino acids in milk protein-fed piglets, J Nutr, 128(3):606-614.

16.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): 2023-5442

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 6		
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)): 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) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

16.2. Additional Clinical Outcome Assessment Analyses

16.2.1. Palatability Questionnaire

Figure 1. Palatability Questionnaire, Study 2023-5442

Overall Palatability of the Drug Product

1. Rate the overall palatability of the drug product:

☐ Like very much ☐ Like ☐ Neither like nor dislike ☐ Dislike ☐ Dislike very much

Taste

2. Rate the mouth feel of the drug product:

☐ Like very much ☐ Like ☐ Neither like nor dislike ☐ Dislike ☐ Dislike very much

3. Rate the initial taste of the drug product:

☐ Like very much ☐ Like ☐ Neither like nor dislike ☐ Dislike ☐ Dislike very much

4. Rate the after taste of the drug product:

☐ Like very much ☐ Like ☐ Neither like nor dislike ☐ Dislike ☐ Dislike very much

Smell

5. Rate the overall likeability of the drug product:

☐ Like very much ☐ Like ☐ Neither like nor dislike ☐ Dislike ☐ Dislike very much

General Characteristics

Appearance

6. Rate the colour of the drug product:

☐ Like very much ☐ Like ☐ Neither like nor dislike ☐ Dislike ☐ Dislike very much

7. Rate the appearance of the drug product:

☐ Like very much ☐ Like ☐ Neither like nor dislike ☐ Dislike ☐ Dislike very much

Dose Volume

8. Rate the volume per dose of the drug product:

☐ Like very much ☐ Like ☐ Neither like nor dislike ☐ Dislike ☐ Dislike very much

Source: Appendix 1, study 2023-5442 protocol

16.2.2. Study 2023-5442: Palatability Questionnaire Results

Primary Endpoint

Results from analyses of the primary endpoint (items 1-5 of the palatability questionnaire) are displayed in Table 9, Table 10, Table 11, and Table 12 below. See Section 8.2.6 for summary assessment.

Table 9. Summary of the Frequency Distribution of Evaluation Score (Categorized Data) by Treatment

			Evaluation Score (%)		
Question	*Trt*	*N*	*1 = Negative*	*2 = Neutral*	*3 = Positive*
Question 1: Rate overall palatability of product:	A	24	11(45.8%)	6(25.0%)	7(29.2%)
	B	24	13(54.2%)	7(29.2%)	4(16.7%)
		Average (%)	50.0	27.1	22.9
Question 2: Rate the mouth feel of drug product:	A	24	10(41.7%)	4(16.7%)	10(41.7%)
	B	24	11(45.8%)	10(41.7%)	3(12.5%)
		Average (%)	43.8	29.2	27.1
Question 3: Rate initial taste of drug product:	A	24	11(45.8%)	6(25.0%)	7(29.2%)
	B	24	15(62.5%)	7(29.2%)	2(8.3%)
		Average (%)	54.2	27.1	18.8
Question 4: Rate the aftertaste of drug product:	A	24	16(66.7%)	4(16.7%)	4(16.7%)
	B	24	13(54.2%)	9(37.5%)	2(8.3%)
		Average (%)	60.4	27.1	12.5
Question 5: Rate overall likeability of product:	A	24	15(62.5%)	5(20.8%)	4(16.7%)
	B	24	16(66.7%)	5(20.8%)	3(12.5%)
		Average (%)	64.6	20.8	14.6

Source: Appendix 16.2.6

Source: Clinical study report, study 2023-5442

Table 10. Summary of the Frequency Distribution of Evaluation Score by Treatment

			Evaluation Score (%)				
Question	*Trt*	*N*	*1*	*2*	*3*	*4*	*5*
Question 1: Rate overall palatability of product:	A	24	6(25.0%)	5(20.8%)	6(25.0%)	6(25.0%)	1(4.2%)
	B	24	7(29.2%)	6(25.0%)	7(29.2%)	2(8.3%)	2(8.3%)
		Average (%)	27.1	22.9	27.1	16.7	6.3
Question 2: Rate the mouth feel of drug product:	A	24	3(12.5%)	7(29.2%)	4(16.7%)	9(37.5%)	1(4.2%)
	B	24	4(16.7%)	7(29.2%)	10(41.7%)	2(8.3%)	1(4.2%)
		Average (%)	14.6	29.2	29.2	22.9	4.2
Question 3: Rate initial taste of drug product:	A	24	6(25.0%)	5(20.8%)	6(25.0%)	6(25.0%)	1(4.2%)
	B	24	6(25.0%)	9(37.5%)	7(29.2%)	1(4.2%)	1(4.2%)
		Average (%)	25.0	29.2	27.1	14.6	4.2
Question 4: Rate the aftertaste of drug product:	A	24	9(37.5%)	7(29.2%)	4(16.7%)	4(16.7%)	0(0.0%)
	B	24	7(29.2%)	6(25.0%)	9(37.5%)	1(4.2%)	1(4.2%)
		Average (%)	33.3	27.1	27.1	10.4	2.1
Question 5: Rate overall likeability of product:	A	24	6(25.0%)	9(37.5%)	5(20.8%)	3(12.5%)	1(4.2%)
	B	24	5(20.8%)	11(45.8%)	5(20.8%)	2(8.3%)	1(4.2%)
		Average (%)	22.9	41.7	20.8	10.4	4.2

N, Number of non-missing data; Trt, Treatment

Treatment A: Test Product: Legubeti (Acetylcysteine) Sachets of 0.5 g POS, Lot No.: K1422 (Galephar P.R., Inc.)
Treatment A: Test Product: Legubeti (Acetylcysteine) Sachets of 2.5 g POS, Lot No.: K2122 (Galephar P.R., Inc.)
Treatment B: Reference Product: ACETYLCYSTEINE SOLUTION, USP 20% (200 mg/mL), Lot No.:A1340001 (Fresenius Kabi USA, LLC, Lake Zurich, IL 60047 451291B)
Treatment B: Reference Product: ACETYLCYSTEINE SOLUTION, USP 20% (200 mg/mL), Lot No.:A1340002 (Fresenius Kabi USA, LLC, Lake Zurich, IL 60047 451291B)

Evaluation score (Questions 1-5): 1 = Dislike very much; 2 = Dislike; 3 = Neither like nor dislike; 4 = Like; 5 = Like very much

Source: Appendix 16.2.6

Source: Clinical study report, study 2023-5442

Table 11. Descriptive Statistics for Q1-Q5 (Primary Endpoint) Palatability Data Evaluation

Question	*Trt*	*Mean*	*SD*	*CV%*	*Median*	*Minimum*	*Maximum*	*N*
1	A	2.63	1.24	47.41	3.00	1	5	24
	B	2.42	1.25	51.65	2.00	1	5	24
2	A	2.92	1.18	40.34	3.00	1	5	24
	B	2.54	1.02	40.16	3.00	1	5	24
3	A	2.63	1.24	47.41	3.00	1	5	24
	B	2.25	1.03	45.87	2.00	1	5	24
4	A	2.13	1.12	52.50	2.00	1	4	24
	B	2.29	1.08	47.24	2.00	1	5	24
5	A	2.33	1.13	48.40	2.00	1	5	24
	B	2.29	1.04	45.46	2.00	1	5	24

CV%, Coefficient of variation; N, Number of non-missing data; Q, Question; Sbj, Subject; SD, Standard deviation; Trt, Treatment

Q1, Rate overall palatability of drug product; Q2, Rate the mouth feel of drug product; Q3, Rate initial taste of drug product
Q4, Rate the aftertaste of drug product; Q5, Rate overall likeability of drug product

Treatment A: Test Product: Legubeti (Acetylcysteine) Sachets of 0.5 g POS, Lot No.: K1422 (Galephar P.R., Inc.)
Treatment A: Test Product: Legubeti (Acetylcysteine) Sachets of 2.5 g POS, Lot No.: K2122 (Galephar P.R., Inc.)
Treatment B: Reference Product: ACETYLCYSTEINE SOLUTION, USP 20% (200 mg/mL), Lot No.:A1340001 (Fresenius Kabi USA, LLC, Lake Zurich, IL 60047 451291B)
Treatment B: Reference Product: ACETYLCYSTEINE SOLUTION, USP 20% (200 mg/mL), Lot No.:A1340002 (Fresenius Kabi USA, LLC, Lake Zurich, IL 60047 451291B)

Evaluation score (Questions 1-5): 1 = Dislike very much; 2 = Dislike; 3 = Neither like nor dislike; 4 = Like; 5 = Like very much

Source: Appendix 16.2.6
Source: Clinical study report, study 2023-5442

Table 12. Wilcoxon Signed Rank Evaluation for Questions 1-5

Item #. Concept	p-value for Tests for Location (Treatment A Vs. Treatment B)
1. Overall palatability	0.2344
2. Mouth feel (taste)	0.1172
3. Initial taste	0.0781
4. After taste	1.0000
5. Overall likeability (smell)	0.8047

Source: Clinical study report, study 2023-5442
Note: Treatment A- Test Product: Legubeti™ (Acetylcysteine) Sachets
Note: Treatment B- Reference Product: acetylcysteine solution, USP 20% (200 mg/mL)

Secondary Endpoints

Results from analyses of the secondary endpoints (items 6-8 pf the palatability questionnaire) are displayed in Table 13, Table 14, Table 15, and Table 16 below. See Section 8.2.6 for summary assessment.

Table 13. Summary of the Frequency Distribution of Evaluation Score (Categorized Data) by Treatment

			Evaluation Score (%)		
Question	*Trt*	*N*	*1 = Negative*	*2 = Neutral*	*3 = Positive*
Question 6: Rate the colour of the drug product:	A	24	4(16.7%)	10(41.7%)	10(41.7%)
	B	24	2(8.3%)	15(62.5%)	7(29.2%)
		Average (%)	12.5	52.1	35.4
Question 7: Rate the appearance of drug product:	A	24	5(20.8%)	10(41.7%)	9(37.5%)
	B	24	4(16.7%)	11(45.8%)	9(37.5%)
		Average (%)	18.8	43.8	37.5
Question 8: Rate volume per dose of drug produc	A	24	13(54.2%)	5(20.8%)	6(25.0%)
	B	24	13(54.2%)	5(20.8%)	6(25.0%)
		Average (%)	54.2	20.8	25.0

Source: Appendix 16.2.6

Source: Clinical study report, study 2023-5442

Table 14. Summary of the Frequency Distribution of Evaluation Score by Treatment

			Evaluation Score (%)				
Question	*Trt*	*N*	*1*	*2*	*3*	*4*	*5*
Question 6: Rate the colour of the drug product:	A	24	3(12.5%)	1(4.2%)	10(41.7%)	9(37.5%)	1(4.2%)
	B	24	2(8.3%)	0(0.0%)	15(62.5%)	5(20.8%)	2(8.3%)
		Average (%)	10.4	2.1	52.1	29.2	6.3
Question 7: Rate the appearance of drug product:	A	24	2(8.3%)	3(12.5%)	10(41.7%)	8(33.3%)	1(4.2%)
	B	24	2(8.3%)	2(8.3%)	11(45.8%)	6(25.0%)	3(12.5%)
		Average (%)	8.3	10.4	43.8	29.2	8.3
Question 8: Rate volume per dose of drug produc	A	24	4(16.7%)	9(37.5%)	5(20.8%)	5(20.8%)	1(4.2%)
	B	24	4(16.7%)	9(37.5%)	5(20.8%)	5(20.8%)	1(4.2%)
		Average (%)	16.7	37.5	20.8	20.8	4.2

N, Number of non-missing data; Trt, Treatment

Treatment A: Test Product: Legubeti (Acetylcysteine) Sachets of 0.5 g POS, Lot No.: K1422 (Galephar P.R., Inc.)
Treatment A: Test Product: Legubeti (Acetylcysteine) Sachets of 2.5 g POS, Lot No.: K2122 (Galephar P.R., Inc.)
Treatment B: Reference Product: ACETYLCYSTEINE SOLUTION, USP 20% (200 mg/mL), Lot No.:A1340001 (Fresenius Kabi USA, LLC, Lake Zurich, IL 60047 451291B)
Treatment B: Reference Product: ACETYLCYSTEINE SOLUTION, USP 20% (200 mg/mL), Lot No.:A1340002 (Fresenius Kabi USA, LLC, Lake Zurich, IL 60047 451291B)

Evaluation score (Questions 1-5): 1 = Dislike very much; 2 = Dislike; 3 = Neither like nor dislike; 4 = Like; 5 = Like very much

Source: Appendix 16.2.6

Source: Clinical study report, study 2023-5442

Table 15. Descriptive Statistics for Q6-7, Q8 (Secondary Endpoints) Palatability Data Evaluation

Question	*Trt*	*Mean*	*SD*	*CV%*	*Median*	*Minimum*	*Maximum*	*N*
6	A	3.17	1.05	33.14	3.00	1	5	24
	B	3.21	0.93	29.03	3.00	1	5	24
7	A	3.13	0.99	31.74	3.00	1	5	24
	B	3.25	1.07	33.03	3.00	1	5	24
8	A	2.58	1.14	44.09	2.00	1	5	24
	B	2.58	1.14	44.09	2.00	1	5	24

CV%, Coefficient of variation; N, Number of non-missing data; Q, Question; Sbj, Subject; SD, Standard deviation; Trt, Treatment

Q6, Rate the colour of the drug product; Q7, Rate the appearance of drug product; Q8, Rate volume per dose of drug product;

Treatment A: Test Product: Legubeti (Acetylcysteine) Sachets of 0.5 g POS, Lot No.: K1422 (Galephar P.R., Inc.)
Treatment A: Test Product: Legubeti (Acetylcysteine) Sachets of 2.5 g POS, Lot No.: K2122 (Galephar P.R., Inc.)
Treatment B: Reference Product: ACETYLCYSTEINE SOLUTION, USP 20% (200 mg/mL), Lot No.:A1340001 (Fresenius Kabi USA, LLC, Lake Zurich, IL 60047 451291B)
Treatment B: Reference Product: ACETYLCYSTEINE SOLUTION, USP 20% (200 mg/mL), Lot No.:A1340002 (Fresenius Kabi USA, LLC, Lake Zurich, IL 60047 451291B)

Evaluation score (Questions 6-8): 1 = Dislike very much; 2 = Dislike; 3 = Neither like nor dislike; 4 = Like; 5 = Like very much

Source: Appendix 16.2.6

Source: Clinical study report, study 2023-5442

Table 16. Wilcoxon Signed Rank Result for Questions 6-8

Item # Concept	p-value for Tests for Location (Treatment A Vs. Treatment B)
6. Color (appearance)	1.0000
7. Appearance	0.9844
8. Volume	1.0000

Source: Clinical study report, study 2023-5442
Note: Treatment A- Test Product: Legubeti™ (Acetylcysteine) Sachets
Note: Treatment B- Reference Product: acetylcysteine solution, USP 20% (200 mg/mL)

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Ashish Dhawan	OND/OII/DHN	Sections: 1, 2, 7, 8,16	**Select one:** __X_ Authored ___ Approved
	Signature: Ashish Dhawan -S Digitally signed by Ashish Dhawan -S Date: 2024.02.08 14:35:33 -05'00'			
Clinical Team Leader	George Makar	OND/OII/DHN	Sections: 1, 2, 7, 8,16	**Select one:** __X_ Authored __X_ Approved
	Signature: George A. Makar -S Digitally signed by George A. Makar -S Date: 2024.02.08 15:12:35 -05'00'			
Deputy Director Signatory (Clinical)	Frank Anania	OND/OII/DHN	Sections: 12	**Select one:** __X_ Authored __X_Approved
	Signature: Frank A. Anania -S Digitally signed by Frank A. Anania -S Date: 2024.02.08 14:15:03 -05'00'			
Regulatory Affairs Project Manager	Chinedu Ebonine	OND/ORO/OII/DHN	Sections: 3	**Select one:** __X_ Authored ___Approved
	Signature: Chinedu Ebonine -S Digitally signed by Chinedu Ebonine -S Date: 2024.02.08 15:15:26 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology Reviewer	Sung-Yong (Mark) Hwang	OTS/OCP/DIIP	Sections: 6	**Select one:** __X__ Authored ___ Approved
	Signature: Sung-yong Hwang -S Digitally signed by Sung-yong Hwang -S Date: 2024.02.08 16:39:31 -05'00'			
Clinical Pharmacology Team Leader, CDTL	Insook Kim	OTS/OCP/DIIP	Sections: 1, 6 Approved: All except for 15	**Select one:** __X_ Authored __X__ Approved
	Signature: Insook Kim -S Digitally signed by Insook Kim -S Date: 2024.02.08 16:42:21 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Rosalyn Jurjus	OND/OII/DPT-II	Sections: 5	**Select one:** __X__ Authored ___ Approved
	Signature: Rosalyn A. Jurjus -S Digitally signed by Rosalyn A. Jurjus -S Date: 2024.02.08 14:22:57 -05'00'			
Nonclinical Supervisor	David Joseph	OND/OII/DPT-II	Sections: 5	**Select one:** ___ Authored __X__ Approved
	Signature: David B. Joseph -S Digitally signed by David B. Joseph -S Date: 2024.02.08 14:40:20 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
OPQ, Application Technical Lead (ATL)	Hamid Shafiei	CDER/OPQ/ONDP/DNDPII/NDPB4	Sections: 4.2	**Select one:** __X_ Authored _X_ Approved
	Signature: Hamid Shafiei -S Digitally signed by Hamid Shafiei -S Date: 2024.02.08 14:16:20 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
DPMH Reviewer	Ndidi Nwokorie	CDER/OND/ORDPURM/DPMH	Sections: 10	**Select one:** __X__ Authored __ Approved
	Signature: Ndidi N. Nwokorie -S Digitally signed by Ndidi N. Nwokorie -S Date: 2024.02.08 14:29:07 -05'00'			
DPMH Team Leader	Mona Khurana	CDER/OND/ORDPURM/DPMH	Sections: 10	**Select one:** ___ Authored __X__ Approved
	Signature: Mona Khurana -S Digitally signed by Mona Khurana -S Date: 2024.02.08 16:56:35 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Regulatory Affairs Chief, Project Management Staff	Ayanna Augustus Bryant	OND/ORO/OII/DHN	Sections: 3.1, 3.2	**Select one:** ___Authored _X_ Approved
	Signature: Ayanna Augustus -S Digitally signed by Ayanna Augustus -S Date: 2024.02.08 14:53:01 -05'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Associate Director for Labeling	Katherine Won	OND/OII/DHN	Sections: 11	**Select one:** __X__ Authored ___ Approved
	Signature:	Katherine S. Won -S Digitally signed by Katherine S. Won -S Date: 2024.02.08 14:59:18 -05'00'		

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
DCOA Reviewer	Susan Pretko	CDER/OND/ODES/DCOA	Sections: 8.2.6	**Select one:** X Authored ___ Approved
	Signature: Susan M. Pretko -S Digitally signed by Susan M. Pretko -S Date: 2024.02.08 14:35:56 -05'00'			
DCOA Team Leader	Onyekachukwu Illoh	CDER/OND/ODES/DCOA	Sections: 8.2.6	**Select one:** ___ Authored X Approved
	Signature: Onyekachukwu A. Illoh -S Digitally signed by Onyekachukwu A. Illoh -S Date: 2024.02.08 15:47:28 -05'00'			
DCOA Director	David Reasner	CDER/OND/ODES/DCOA	Sections: 8.2.6	**Select one:** ___ Authored X Approved
	Signature: David Reasner -S Digitally signed by David Reasner -S Date: 2024.02.09 16:59:27 -05'00'			

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/

INSOOK KIM
02/13/2024 02:52:22 PM

FRANK A ANANIA
02/13/2024 02:57:51 PM