Title Page

A PHARMACOKINETIC STUDY OF ZAVEGEPANT INTRANASAL IN HEALTHY ADULTS COMPARING CONVENTIONAL VENOUS BLOOD SAMPLING WITH PATIENT-CENTRIC SAMPLING

Study Intervention Number:	PF-07930207
Study Intervention Name:	Zavegepant
US IND Number:	134120
EudraCT/EU CT Number:	Not applicable
ClinicalTrials.gov ID:	Not available
Pediatric Investigational Plan Number:	Not applicable
Protocol Number:	C5301022
Phase:	1
Sponsor Legal Address:	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001

Brief Title: A Study to Compare Zavegepant Concentration Using Samples Collected From the Vein Versus Patient-Centric Microsampling

Document History

Document	Version Date
Amendment 1	12 June 2023
Original protocol	10 May 2023

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and IRBs/ECs and any protocol administrative change letter(s).

Protocol Amendment Summary of Changes Table

Amendment 1 (09 June 2023)

Overall Rationale for the Amendment:

Dysgeusia (bad/metallic/bitter taste) has been reported as the most common treatment-emergent adverse event with zavegepant. Because of this adverse event, patients may not adhere to their medications which may limit the effectiveness of treatment with zavegepant. Therefore, understanding this adverse event (eg, time-course, description of the taste sensation) and potential strategies to mask this unpleasant taste could help improve patient experience and adherence. This amendment was mainly considered to add an exploratory objective to this study to evaluate zavegepant-induced dysgeusia and whether eating a butterscotch candy before zavegepant IN administration will help manage dysgeusia. Changes were made to the protocol to support this exploratory objective, along with other editorial changes, as described below.

Description of Change	Brief Rationale	Section # and Name
Substantial Modification(s)		
Added a tertiary (exploratory) objective to the protocol to evaluate the effect of the administration of 10 mg of zavegepant IN with a butterscotch candy on dysgeusia compared to zavegepant IN alone.	Based on data from zavegepant IN clinical trials, dysgeusia (bad/metallic/bitter taste) has been reported as the most common treatment-emergent adverse event with zavegepant. Because of this adverse event, patients may not adhere to their medications which may limit the effectiveness of treatment	1.1 Synopsis 3. Objectives and Endpoints 4.1 Overall Design 6.1.1. Administration

Description of Change	Brief Rationale	Section # and Name
	with zavegepant. Therefore, understanding this adverse event (eg, time-course, description of the taste sensation) and potential strategies to mask the unpleasant taste could help improve patient experience and adherence. As an exploratory objective of this study, we will prospectively evaluate the unpleasant taste sensation and whether eating a butterscotch candy before zavegepant IN administration will help manage dysgeusia.	
Provided rationale for the tertiary objective added	To clarify the reason for adding this objective to the trial.	1.1 Synopsis 2.1 Study Rationale 4.2 Scientific Rationale for Study Design
Added inclusion criterion #5 that requires participants to be willing to consume a butterscotch candy	To support the tertiary objective of evaluating the effect of the administration of 10 mg of zavegepant IN with a butterscotch candy on dysgeusia compared to zavegepant IN alone.	1.1 Synopsis 5.1 Inclusion Criteria
Edited an exclusion criterion to exclude participants who are active smokers or use tobacco or nicotine-containing products within 1 months of screening	Smokers were excluded since smoking causes loss of taste and induces dysgeusia.	1.1 Synopsis 5.1 Exclusion Criteria
Added an exclusion criterion to exclude participants with a condition that affect ability to taste eg, dysgeusia, respiratory infection, cold	To ensure that study participants can provide meaningful and adequate feedback for the taste assessment	1.1 Synopsis 5.1 Exclusion Criteria
Updated the study design by adding one additional	This will support the tertiary objective added, which will	1.1 Synopsis

Description of Change	Brief Rationale	Section # and Name
day/period for running the taste assessment of zavegepant + butterscotch and compare it to zavegepant administration in period 1. Also, updated Section 5.3.2 Meals and Dietary Restrictions to clarify the food restriction prior to the taste assessment questionnaire.	be helpful in better understanding zavegepant-induced dysgeusia and evaluating whether this simple strategy of using butterscotch will be useful in mitigating dysgeusia with minor changes in the study design.	1.3 Schedule of Activities, Table 1 5.3.2. Meals and Dietary Restrictions
Provided text to support the analysis of the taste assessment questionnaire data under the tertiary objective.	To provide clarity on how this data will be analyzed and collected.	1.1 Synopsis 9.2. Analysis Sets 9.3.1 General Considerations 10.11 Appendix 11: Taste Assessment Questionnaire
Added one additional day and period to support the taste assessment evaluation as described for the study's tertiary objective.	To support the tertiary objective added.	1.3 Schedule of Activities, Table 1
Added urine cotinine test to be performed at screening and on Day -1.	To ensure that participants are non-smokers as required by the nonsmoker exclusion criterion	1.3 Schedule of Activities, Table 2 10.2 Appendix 2: Clinical Laboratory Tests
Deleted the original footnote ‘b’ to clarify that blood-to-plasma ratio samples will be collected for all participants regardless of the type of Tasso device used.	This will ensure that we have sufficient blood-to-plasma ratio data in healthy participants, which will support the conversion of zavegepant dried blood concentrations data to their equivalent plasma concentrations for adequate comparison between the Tasso and venous sampling methods.	1.3 Schedule of Activities, Table 2 8.5 Pharmacokinetics
Non-substantial Modification(s)		
Appendix 11 includes the taste assessment	Added for the collection of the data need to fulfil the	10.11 Appendix 11: Taste Assessment Questionnaire

Description of Change	Brief Rationale	Section # and Name
questionnaire that will be used for the tertiary objective of this study	tertiary objective of this study	
Added the taste assessment questionnaire, and consumption of butterscotch candy as placeholders.	To support the tertiary objective added and clarify the SoA related to this objective	1.3 Schedule of Activities, Table 1
Added Days for each period.	To support the tertiary objective added and provide clarity.	1.3 Schedule of Activities, Table 2
Program level changes have been made based on availability of evidence supporting these changes. The majority of the changes include adding information about the unidose nasal device used for administering zavegepant. Information related to the risk assessment of using this device, reporting AE related to the use of this device or what to do in case of a device deficiency.	To ensure consistency within protocols across the zavegepant clinical program and provide more information about the unidose nasal device as required by the protocol template.	2.3.1 Risk assessment 6.1.1 Administration 6.1.2 Medical Devices 8.4.9 Medical Device Deficiencies 10.9 Appendix 9: AEs, ADEs, SAEs, SADEs, USADEs, and Device Deficiencies
Editorial updates to use consistent wording and terminology. Formatting updates.	For clarification and to ensure consistency.	Throughout the protocol

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LIST OF TABLES

1. PROTOCOL SUMMARY

1.1. Synopsis

PROTOCOL TITLE: A Pharmacokinetic Study of Zavegepant Intranasal in Healthy Adults Comparing Conventional Venous Blood Sampling with Patient-Centric Sampling

Brief Title: A Study to Compare Zavegepant Concentration Using Samples Collected From the Vein Versus Patient-Centric Microsampling

Regulatory Agency Identification Number(s):

US IND Number:	134120
EudraCT/EU CT Number:	Not applicable
ClinicalTrials.gov ID:	Not available
Pediatric Investigational Plan Number:	Not applicable
Protocol Number:	C5301022
Phase:	1

Abbreviation: CT = clinical trial; EU = European Union; EudraCT = European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database); ID = identification; IND = Investigational New Drug; US = United States

Rationale:

Zavegepant (PF-07930207) is a high affinity, selective, and structurally unique, small molecule calcitonin gene-related peptide (CGRP) receptor antagonist, which was recently approved by the Food and Drug Administration (FDA) for the acute treatment of migraine with or without aura in adults via intranasal (IN) administration. As a component of zavegepant clinical development, future pediatric studies will be conducted to evaluate the safety, tolerability, and pharmacokinetics (PK) of zavegepant in participants 6 to less than 12 years of age with migraine.

Recruiting and retaining pediatric patients in clinical trials has always been challenging due to a variety of factors, including inconvenience with patient preferences. To overcome some of those challenges, it is essential to prioritize patient-centric approaches that cater to the unique needs of pediatric patients. One such approach is patient-centric sampling (PCS), which aims to reduce the burden on pediatric patients by minimizing the volume of the biological samples required and being less invasive with minimal to no pain compared to the venous phlebotomy collection method, which is particularly beneficial for pediatrics who are fearful of needles. Additionally, PCS offers greater flexibility to pediatric patients and their families by allowing at-home sample collection for those who may have difficulty traveling to clinics.

To allow the use of PCS in zavegepant pediatric studies, a bridging or comparative study comparing the PCS approach with an equivalent conventional sampling technique is needed

as a regulatory expectation to demonstrate the concordance of data from PCS in a controlled environment prior to implementation in large-scale clinical trials. Therefore, the primary objective of this study is to establish the correlation between zavegepant concentration from samples collected using PCS devices compared to conventional venous blood sampling. In addition, if feasible, this study will also determine the PK and safety of zavegepant IN in Japanese participants.

Lastly, based on data from zavegepant IN clinical trials, dysgeusia (bad/metallic/bitter taste) has been reported as the most common treatment-emergent adverse event with zavegepant. Because of this adverse event, patients may not adhere to their medications which may limit the effectiveness of treatment with zavegepant. Therefore, understanding this adverse event (eg, time-course, description of the taste sensation) and potential strategies to mask the unpleasant taste could help improve patient experience and adherence. As an exploratory objective, this study will also evaluate the palatability attributes of zavegepant IN administration and whether eating a butterscotch candy before zavegepant IN administration will help manage dysgeusia.

Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• Characterize the PK profile of zavegepant from samples collected using Tasso Devices (Tasso-Plus and Tasso-M20) vs standard venous phlebotomy following IN administration of 10 mg of zavegepant IN formulation in healthy participants	• Zavegepant concentrations from samples collected using Tasso devices vs standard venous phlebotomy • PK parameters: AUC_{inf} (if data permit), AUC_{last}, C_{max}, T_{max}, $t_{½}$, CL/F and V_z/F, as data permits
Secondary:	**Secondary:**
• Evaluate the safety and tolerability following IN administration of 10 mg of zavegepant IN formulation in healthy participants	• Assessment of TEAEs, and clinical laboratory tests

Abbreviation: AUC_{inf} = area under plasma concentration-time profile from time 0 extrapolated to infinite time; AUC_{last} = area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last}); CL/F = apparent clearance; C_{max}, = maximum plasma concentration; $t_{½}$ = terminal half-life; TEAE = treatment-emergent adverse event; T_{max} = time to C_{max}; V_z/F = apparent volume of distribution

Overall Design:

Brief Summary

This is a Phase 1, non-randomized, open-label study in healthy participants to primarily characterize the PK profile of IN zavegepant from samples collected using Tasso Devices (Tasso-Plus, for liquid blood sample collection and Tasso-M20, for dried blood sample collection) compared to standard venous phlebotomy. Leveraging these data will establish a correlation between the 2 methods and meet regulatory expectations before implementing these patient-centric blood collection devices in future studies. This study consists of 2 periods.

In period 1, 50% (n=7) of the enrolled participants will use Tasso-Plus, and the other 50% (n=7) will use Tasso-M20 to ensure having adequate PK data collected from each device. For each participant, PK samples will be collected after zavegepant administration in period 1 using the assigned Tasso device simultaneously with collecting venous blood samples. In addition, taste assessments will be performed at time intervals of 1 (immediately after dosing), 5, 10 and 20 minutes after zavegepant IN administration. Also, if feasible, 4 Japanese participants will be enrolled among those 14 participants to evaluate the PK and safety of zavegepant IN in Japanese vs. non-Japanese participants.

In period 2, a butterscotch candy will be given 5 minutes before administering the zavegepant IN study intervention. Taste assessment will also be performed after zavegepant IN administration with a butterscotch candy in period 2. For taste assessment, each participant will record the sensory attributes at timed intervals of 1 (immediately after dosing), 5, 10 and 20 minutes after zavegepant administration in each period.

Screening evaluation will occur within 28 days prior to the study drug administration (Day 1). Participants will be admitted to the CRU on Day -1 and will remain in the clinical research unit (CRU) through completion of procedures on Day 3. Participants will receive a 10 mg dose of IN zavegepant on Day 1, and a second dose of 10 mg zavegepant IN 24 hours after administering the first dose. The PK of zavegepant will be characterized following the first dose. A telephone follow-up will be made 28-35 days after the second (last) dose.

In this study, if more than 2 participants prematurely discontinue for reasons unrelated to the safety of the investigational product, participants may be replaced at the discretion of the principal investigator (PI) and sponsor study team.

Number of Participants:

Approximately 14 participants will be enrolled in the study. If feasible, 4 Japanese participants will be enrolled among those 14 participants.

Note: "Enrolled" means a participant’s, or their legally authorized representative’s, agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity. Potential

participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Study Population:

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

Participants must meet the following key inclusion criteria to be eligible for enrollment into the study:

1. Male or female ≥18 years of age and older at the time of signing the informed consent document (ICD).
    - For Japanese participants to be enrolled, they need to meet the following inclusion criteria: Japanese participants must have 4 Japanese grandparents who were born in Japan.
2. Male and female participants who are overtly healthy as determined by medical evaluation.
3. Body max index (BMI) 16.0-32.0 kg/m^2 and body weight ≥45.0 kg (99 lb).
4. Females must not be breastfeeding or lactating and must have a negative urine or serum pregnancy test (minimum sensitivity 25 international units per liter [IU/L] or equivalent units of human chorionic gonadotropin [HCG]) at screening. Woman/women of childbearing potential (WOCBP) must have negative urine or serum pregnancy test at admission.
5. Participants are willing to consume a butterscotch candy.

Exclusion Criteria

Participants with any of the following characteristics/conditions will be excluded:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).
2. Clinically significant history of nasal conditions that may affect the administration or absorption of the nasal product (eg, severe septum deviation or nasal deformity, inflammation, perforation, mucosal erosion, localized infection or ulceration, congestion, polyposis, rhinorrhea, nasal surgery within the previous 6 months, or nasal trauma).

3. Significant history of seizure disorder other than a single childhood febrile seizure (eg, epilepsy) or history of gallstone or cholecystectomy.

4. Any other medical or psychiatric condition, including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions or situations related to coronavirus disease 2019 (COVID-19) pandemic that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

5. Use of organic anion transporting polypeptide 1B3 (OATP1B3) inhibitors within 14 days or 5 half-lives, whichever is longer, before first dosing.

6. Participation in a clinical research study involving the administration of an investigational or marketed drug or device within 30 days prior to investigational product (IP) dosing, administration of a biological product in the context of a clinical research study within 90 days prior to IP dosing, or concomitant participation in an investigational study involving no drug or device administration.

7. Any clinically significant abnormal laboratory test results or positive test found during medical screening. A single repeat for positive drug screen may be allowed at the discretion of the PI.

8. Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination or nasal inspection beyond what is consistent with the target population.

9. Participants with **ANY** of the following abnormalities in clinical laboratory tests at screening:

    - Aspartate aminotransferase (AST) **or** alanine aminotransferase (ALT) level > 1.5 × upper limit of normal (ULN);

    - Total bilirubin level >1.5 × ULN;

    - Estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73m^2.

10. Use of tobacco or nicotine-containing products within 1 month of screening or a positive urine cotinine test (ie, active smokers and those who currently use nicotine-containing products are excluded from participation in this study).

11. Conditions that affect ability to taste eg, dysgeusia, respiratory infection, cold, or other conditions as evaluated by the PI.

12. Presence of piercings or any physical findings in the nose that, in the opinion of the PI, would likely interfere with the successful completion of the dosing procedure.

13. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

14. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit, or 3 ounces (90 mL) of wine).

15. Any reason that, in the opinion of the PI, would prevent the participant from participating in the study.

Study Arms and Duration:

This study consists of 2 periods. In period 1, eligible participants will receive the first IN dose of zavegepant 10 mg via nasal spray. Study staff will administer the IN spray in 1 nostril to each participant. A total of approximately 14 participants will be enrolled, out of which 50% of participants (n=7) will use Tasso-Plus blood collection device, while the other 50% of participants (n=7), will use Tasso-M20 blood collection device. All 14 participants will have 6 PK samples collected using the assigned Tasso device simultaneously with collecting venous blood samples at the following time points, 30 minutes, 1, 2-, 4-, 8-, and 12-hour postdose. In addition, taste assessments will be performed at time intervals of 1 (immediately after dosing), 5, 10 and 20 minutes after zavegepant IN administration. If feasible, 4 Japanese participants will be enrolled among those 14 participants to evaluate the PK and safety of zavegepant IN in Japanese vs non-Japanese participants. For Japanese participants, a total of 12 venous blood samples will be collected at the following time points, 0, 15 minutes, 30 minutes, 1, 1.5-, 2-, 3-, 4-, 6-, 8-, 12-, and 24-hour.

In period 2, a butterscotch candy will be given 5 minutes before administering the zavegepant IN study intervention. As noted earlier, taste assessment will also be performed after zavegepant IN administration with a butterscotch candy in period 2. For taste assessment, each participant will record the sensory attributes at timed intervals of 1 (immediately after dosing), 5, 10 and 20 minutes after zavegepant administration in each period.

Study Intervention	
Intervention Name	Zavegepant
Use	Experimental
IMP or NIMP/AxMP	IMP
Dose Formulation	Nasal spray

Study Intervention	
Unit Dose Strength(s)	10 mg
Route of Administration	IN

Abbreviation: AxMP = auxiliary medicinal product; IMP = investigational medicinal product; IN = intranasal; NIMP = noninvestigational medicinal product

Study Arm(s)	
Arm Title	Zavegepant
Arm Description	All participants will receive zavegepant 10 mg IN spray in period 1 and a butterscotch candy + zavegepant 10 mg IN spray in period 2

Abbreviation: IN = intranasal

Statistical Methods:

There is no statistical hypothesis for this study. Approximately 14 evaluable participants will be enrolled in this study. The sample size determined for this study was based on the established scientific recommendation for having 30 to 40 PK data points at minimum from each method to ensure the adequate comparison between PCS (test) and venous sampling (reference). A sample size of 7 evaluable participants per cohort, with 6 Tasso-venous paired PK samples to be collected from each participant ($7 \times 6 = 42$ data points) will be sufficient to meet the scientific community recommendation for having an adequate Tasso-venous plasma PK bridging study.

For summary statistics by sampling time, the nominal PK sampling time will be used. For individual participant plots by time, the actual PK sampling time will be used. Actual PK sampling times will also be used in the derivation of PK parameters. PK parameters will be estimated using non-compartmental analysis. Box and whisker plots for individual participant parameters (area under plasma concentration-time profile from time 0 extrapolated to infinite time [AUC_{inf}], area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration [AUC_{last}], and maximum plasma concentration [C_{max}]) will be constructed for each of the Tasso devices used (Tasso-Plus and Tasso-M20), by blood collection method, and overlaid with geometric means. For the taste assessment, the data used in the analysis will be transcribed and rescaled to a score from 0 to 100 from the raw measurements on the questionnaire. The sensory attributes (overall liking, bitterness, tongue/mouth burn, throat burn, sour taste, salty taste, and sweet taste) from the taste questionnaires will be listed and descriptively summarized by study intervention in each period, with the main difference being the use of butterscotch in period 2.

Ethical Considerations:

All study intervention risks are communicated through the Investigator's Brochure (IB). Based on the totality of available clinical and nonclinical data and taking into account the

measures to monitor and minimize risk to study participants, the overall benefit/risk profile supports the clinical investigation of zavegepant 10 mg IN administration in healthy adults. There is no anticipated therapeutic benefit for the healthy participants in this study.

1.2. Schema

Not applicable.

1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 12.	**Screen**	**Period 1**		**Period 2**		**Telephone F/U**	**Early Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 30-37**		• All screening should be done ≤28 days before the first dose. • Day relative to start of study intervention (Day 1). • Follow-up may occur via telephone contact and must occur 28-35 days after administration of the final dose of study intervention.
Days within each period		**Day -1**	**Day 1**	**Day 1**	**Day 2**			
Informed consent	X							• Informed consent should be obtained prior to undergoing any study-specific procedures. • See Section 10.1.3 for additional information.
CRU confinement		X	→	→	X			
Inclusion/exclusion criteria	X	X						• See Section 5.1 and Section 5.2.
Demography (including height and body weight)	X							• See Section 8.3.1.
Medical/medication history	X	X						• Medication history will be updated at each visit.
Review alcohol/caffeine/tobacco	X	X						
Physical exam	X	X						• A full physical examination may be done at screening or Day -1; otherwise, brief physical exam is envisioned for findings during previous PE or new/open AEs, at the investigator's discretion.
Nasal inspection		X		X	X		X	• The nasal passages and turbinates will be visually inspected with a nasal speculum and light on Day -1 (to exclude participants with mucosal erythema, congestion, septal defects etc.), and 24 h (± 30 min) postdose to detect evidence of nasal inflammation or edema.

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 12.	Screen	Period 1		Period 2		Telephone F/U	Early Discontinuation	Notes
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Days within each period		**Day -1**	**Day 1**	**Day 1**	**Day 2**			
Taste Assessment Questionnaire			X	X				• Review taste questionnaire and instructions with participants prior to the first taste assessment on Period 1, Day 1. Each participant will record the sensory attributes at timed intervals of 1 (immediately after dosing), 5, 10 and 20 min after administering the study intervention, using a Taste Assessment Questionnaire (see Appendix 11).
Butterscotch candy				X				• A butterscotch candy is to be given to the participants 5 min prior to the administering of 10 mg zavegepant IN on Period 2. • Participants will be instructed not to chew or crush the candy but allow it to dissolve over time.
Vital signs (BP and Pulse Rate)	X							• Supine BP and pulse rate will be performed at screening.
Single 12-Lead ECG	X							• Supine ECGs will be performed at screening.
Safety laboratory	X	X		X			X	• Screening, Day -1, and 24 h (± 30 min) after the first dose. See Appendix 2 for safety laboratory tests in the study. • For period 2, day 1, safety lab samples will be collected prior to dosing. • Participants should fast for at least 4 hours before blood samples for safety labs are drawn.
Pregnancy test (WOCBP only)	X	X			X		X	• Serum or urine β-hCG for female participants of childbearing potential.
Contraception check	X	X				X	X	
FSH	X							• For confirmation of postmenopausal status only. See Section 10.4.3 for the definition of postmenopausal.
Alcohol breath, urine drug screening and urine cotinine testing	X	X						• Alcohol breath test will be performed at the discretion of the investigator. • Urine cotinine (mandatory) will be performed at Screening, and on Period 1 Day -1. This test may be performed at any other time at the discretion of the investigator.

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 12.	**Screen**	**Period 1**		**Period 2**		**Telephone F/U**	**Early Discontinuation**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 3**	**Day 30-37**		• All screening should be done ≤28 days before the first dose. • Day relative to start of study intervention (Day 1). • Follow-up may occur via telephone contact and must occur 28-35 days after administration of the final dose of study intervention.
Days within each period		**Day -1**	**Day 1**	**Day 1**	**Day 2**			
HIV, HBsAg, HBsAb, HBcAb, HCVAb	X							• HBsAb is to be run if HBsAg and/or HBcAb are positive.
Retained Research Sample for Genetics (Prep D1)			X					
Study intervention administration			X	X				
PK blood sampling			X	X			X	• See Table 2 for details. • Period 2 Day 1 PK sample will be 24 hr post dosing in Period 1 Day 1. Sample will be collected for Japanese participants only.
CRU discharge					X			• Discharge from CRU after completing protocol-required activities on the day.
Serious and nonserious AE monitoring	X	→	→	→	X	X	X	• See Section 8.4.3 for follow-up AE and SAE assessments.

Table 2. Pharmacokinetic Sampling Timepoints

Visit Identifier												**Notes**
Study Day	**Day 1**											**Day 2**	Hour 0 = Predose sample collection The predose blood draw will be taken within 1 h before dosing. See Section 8.5 for details of PK sample collection.
Days within each period	**Period 1, Day 1**											**Period 2, Day 1**	
Time Before/After Dose	**0 h**	**0.25 h**	**0.5 h**	**1 h**	**1.5 h**	**2 h**	**3 h**	**4 h**	**6 h**	**8 h**	**12 h**	**24 h**	
Study intervention administration	X												
Venous PK sampling	X[b]	X[b]	X	X	X[b]	X	X[b]	X	X[b]	X	X	X[b]	
Tasso PK sampling[a]			X	X		X		X		X	X		
Blood: plasma ratio				X						X			

a. Tasso PK sampling will be performed using either Tasso-Plus or Tasso-M20 device.
b. To be collected for Japanese participants only.

2. INTRODUCTION

Zavegepant (PF-07930207; formerly BHV-3500) is a selective, high-affinity, small molecule CGRP receptor antagonist that was approved by the FDA on March 9, 2023, for the acute treatment of migraine with or without aura in adults via IN administration.[1] Zavegepant 10 mg nasal spray offers a novel IN CGRP receptor antagonist therapy for the acute treatment of migraine with the potential to address important unmet medical needs in the migraine patient population. IN zavegepant provides rapid onset, durable efficacy without the risk of medication overuse headache and without contraindications or warnings regarding use by patients with cardiovascular disease.

CGRP is an endogenous 37 amino acid peptide contained within pain-signaling nociceptive afferents and is thought to play a causal role in migraine.[2,3] Multiple lines of clinical evidence point to a role for CGRP in migraine pathophysiology: 1) serum levels of CGRP are elevated during migraine;[4] 2) treatment with anti-migraine drugs returns CGRP levels to normal coincident with pain relief;[5] and 3) IV CGRP infusion produces lasting pain in non-migraineurs and migraineurs.[3,6]

Treatment with a CGRP receptor antagonist is thought to relieve migraine by: 1) blocking CGRP-induced neurogenic vasodilation (returning dilated intracranial arteries to normal); 2) halting the cascade of CGRP-induced neurogenic inflammation (which leads to peripheral and central sensitization); and/or 3) inhibiting the central relay of pain signals from the trigeminal nerve to the caudal trigeminal nucleus.[2,7]

2.1. Study Rationale

As a component of zavegepant clinical development, future pediatric studies will be conducted to evaluate the safety, tolerability, and PK of zavegepant in participants 6 to less than 12 years of age with migraine. Recruiting and retaining pediatric patients in clinical trials has always been challenging due to a variety of factors, including inconvenience with patient preferences. To overcome some of those challenges, it is essential to prioritize patient-centric approaches that cater to the unique needs of pediatric patients. One such approach is PCS, which aims to reduce the burden on pediatric patients by minimizing the volume of the biological samples required and being less invasive with minimal pain compared to the venous phlebotomy collection method, which is particularly beneficial for pediatrics who are fearful of needles. Additionally, PCS offers greater flexibility to pediatric patients and their families by allowing at-home sample collection for those who may have difficulty traveling to clinics.

To allow the use of PCS in zavegepant pediatric studies, a bridging or comparative study comparing the PCS approach with an equivalent conventional sampling technique is needed as a regulatory expectation to demonstrate the concordance of data from PCS in a controlled environment prior to implementation in large-scale clinical trials. Therefore, the primary objective of this study is to establish the correlation between zavegepant concentration from samples collected using PCS devices compared to conventional venous blood sampling. In addition, if feasible, this study will also determine the PK and safety of zavegepant IN in Japanese participants.

Lastly, based on data from zavegepant IN clinical trials, dysgeusia (bad/metallic/bitter taste) has been reported as the most common treatment-emergent adverse event with zavegepant. For instance, in a Phase 2/3, double-blind, randomized, placebo-controlled study (BHV3500-201[8,9]), dysgeusia was reported as the most common TEAEs with zavegepant 10 and 20 mg IN and placebo (13.5% to 16.1% vs 3.5%, respectively). Similarly, results from a Phase 3 study of zavegepant IN administration for the treatment of acute migraine BHV3500-301[10] have reported dysgeusia as the most common TEAEs after zavegepant 10 mg IN administration with an incidence rate of 20.5% vs 4.7% in placebo. Because of this adverse event, patients may not adhere to their medications which may limit the effectiveness of treatment with zavegepant. Therefore, understanding this adverse event (eg, time-course, description of the taste sensation) and potential strategies to mask the unpleasant taste could help improve patient experience and adherence. As an exploratory objective, this study will evaluate palatability attributes of zavegepant and whether eating a butterscotch candy before zavegepant IN administration will help manage dysgeusia.

2.2. Background

Migraine is a chronic neurological condition characterized by attacks of headache that usually feature unilateral, throbbing pain accompanied by nausea or sensitivity to light and sound.[11] Migraine affects about 1.04 billion people globally,[12] approximately three-quarters of whom are women. During migraine attacks, most people have functional impairments, often leading to absence from or reduced productivity at work or school and limiting participation in family, social, and leisure activities.[13] Migraine-related disability extends to periods between attacks[14] and can include physical symptoms (gastroparesis), which can slow absorption of oral drugs, and psychological symptoms (anger, anxiety, depression, hopelessness[15]). Persistent stigma about migraine[16] leads many people to understate or under-report the negative effects of migraine and to avoid discussing their condition.[14]

The use of medication for the acute treatment of migraine attacks is ubiquitous.[17,18] For the past 30 years, serotonin receptor agonists (ie, triptans) have been the most widely prescribed class of acute antimigraine medication. All 7 drugs in the triptan class are available for oral administration; two (sumatriptan and zolmitriptan) are available as nasal sprays and only sumatriptan is available for parenteral or rectal administration. Some non-oral therapies have shorter T_{max} than oral therapies;[19] shorter T_{max} values might be associated with a more rapid onset of treatment effects.[20] The recommendation for the use of non-oral triptans is based on favorable pharmacokinetic profiles,[19,20] a small set of comparative studies indicating that, for some agents, nasal formulations outperform tablets,[21,22] and clinical practice experience.[23]

Oral triptans provide a pain-free response in 20%–40% of patients with migraine and consistent benefits in 39%–79%.[18,24,25,26] Yet recurrence rates range from 20% to 40% of patients with migraine, and clinical use is limited by cardiovascular contraindications and precautions, which are most common among men older than 40 years and postmenopausal women.[18,24,25,26] Additionally, medication overuse is a recognized risk that can result in medication-overuse headache and the transformation of episodic migraine into chronic migraine.[25]

Although alternatives to oral triptans have long been available, the findings that CGRP is a key element of migraine pathophysiology[27,28,29] have resulted in the development of highly specific, safe,[30] and effective[31] medications for acute treatment. Two small-molecule CGRP receptor antagonists (gepants) have received regulatory approval for the acute treatment of migraine in the USA: rimegepant, an orally disintegrating tablet, and ubrogepant, an oral tablet. Rimegepant has also been approved for the acute treatment of migraine in the EU and the UK. This new class of agents attempts to address the limitations of acute treatment with traditional migraine medications, but neither drug is available in a non-oral formulation. Zavegepant nasal spray is the first non-oral gepant approved for the acute treatment of migraine.[1] The clinical pharmacology of zavegepant has been well characterized in a comprehensive program based on 10 Phase 1 studies.[32] Efficacy and safety were determined in 2 positive pivotal trials assessing IN administration of zavegepant for the acute treatment of migraine. A favorable safety profile was seen during a 1-year open-label safety study with up to 8 doses per month of IN zavegepant for the acute treatment of migraine.[33]

2.2.1. Nonclinical Overview

A summary of the nonclinical investigational programs can be found in the current IB.

2.2.2. Clinical Overview

2.2.2.1. Safety Overview

In clinical studies, approximately 2,700 participants have been administered zavegepant IN, and approximately 606 participants have been administered oral zavegepant. Administration of zavegepant was well tolerated at 5 mg, 10 mg, and 20 mg as a single IN spray in 1,185 adult participants with migraine (BHV3500-201[8,9]). A similar safety profile was observed in the 629 adult participants administered a single dose of zavegepant 10 mg IN for the acute treatment of migraine (BHV3500-301[10]).

Zavegepant, 10 mg IN, was well tolerated in a completed long-term safety study (up to 8 doses per month) in 603 adult participants with migraine for up to 52 weeks (BHV3500-202[34]). The most frequently occurring adverse events in clinical studies to date have been associated primarily with IN administration (eg, dysgeusia, throat irritation, nasal congestion, nasal discomfort), as well as nausea and back pain, and the majority have been of mild to moderate intensity.

2.2.2.2. Efficacy Overview

In a Phase 2/3, double-blind, randomized, placebo-controlled, dose-ranging study of zavegepant (5 mg, 10 mg, or 20 mg) IN for the acute treatment of migraine, zavegepant doses of 10 mg and 20 mg via IN administration demonstrated statistically significant efficacy on both coprimary endpoints of freedom from pain at 2 hours postdose and freedom from MBS at 2 hours postdose.

A Phase 3 study of zavegepant IN administration for the treatment of acute migraine BHV3500-301[10]) demonstrated statistically significant efficacy for both coprimary endpoints

as well as for 13 of the 17 secondary endpoints, including significant evidence of ultrarapid onset and durability of response.

A Phase 2/3 study of oral zavegepant in the preventive treatment of migraine (BHV3500-302) is currently ongoing.

2.2.2.3. Clinical Pharmacology

Based on the completed clinical studies of IN and PO zavegepant, the following observations were made regarding the zavegepant PK properties. Zavegepant is rapidly absorbed (T_{max}: 0.54 hours) following a single zavegepant 10 mg IN dose. The terminal elimination half-life of zavegepant 10 mg IN dose is approximately 3 hours.[35] While the effective half-life of zavegepant, which is considered more clinically relevant than the elimination half-life as it takes into account the entire plasma concentration-time profile, ranged from approximately 5 to 8 hours across dose levels ranging from 5 to 40 mg IN. Zavegepant exhibits less than dose-proportional increases in exposure following single IN dose administration over the dose range from 1 mg to 40 mg. No evidence of meaningful accumulation was observed across a dose range of 5 to 20 mg zavegepant IN after repeated QD dosing.

The results of the DDI study showed that co-administration of sumatriptan with zavegepant IN does not result in a meaningful change in the PK of sumatriptan or of zavegepant. Co-administration of sumatriptan with zavegepant IN does not cause elevations in mean arterial blood pressure or of systolic or diastolic blood pressure greater than those observed with sumatriptan alone. Lack of a clinically significant effect on the exposures of EE and LNG following co-administration of zavegepant 20 mg IN and oral contraceptive support that zavegepant is not a clinically relevant inhibitor of CYP3A4. Zavegepant may be administered with an oral contraceptive without dose frequency adjustment. A 16% increase in the C_{max} and a 1.9-fold increase in zavegepant AUC were observed in participants with moderate hepatic impairment.

Co-administration of itraconazole (strong CYP3A4 inhibitor and P-gp inhibitor) with IN zavegepant showed no clinically relevant changes in the exposure of zavegepant. However, co-administration of itraconazole with a single dose of zavegepant oral soft gelatin capsule 50 mg increased the AUC and C_{max} of oral zavegepant by approximately 59% and 77%, respectively, suggesting that the increase is likely due to P-gp inhibition of zavegepant efflux transport by itraconazole in the gastrointestinal tract. In addition, coadministration of rifampin, a strong CYP3A inducer and an inhibitor of OATP1B3 and NTCP transporters with oral zavegepant 100 mg, showed an increase in zavegepant AUC by 2.3-fold and C_{max} by 2.2-fold in the presence of rifampin, suggesting that drugs that inhibit the OATP1B3 or NTCP transporters could increase the exposure of zavegepant. Therefore, concomitant administration of zavegepant with inhibitors of OATP1B3 or NTCP transporters should be avoided. Furthermore, it is unlikely that induction of CYP3A would substantially impact zavegepant exposure when zavegepant is administered either IN or oral. The 10 mg IN zavegepant exposures were approximately 17% lower for C_{max} and 10% lower for AUC_{inf} during a migraine attack than in the non-migraine period; however, the decrease in exposure in the migraine state is not clinically meaningful. There was no clinically relevant prolongation of the QTc interval by zavegepant.

2.3. Benefit/Risk Assessment

The safety and tolerability of zavegepant doses greater than 10 mg IN were explored in early clinical development, including single doses of 0.1 mg through 40 mg and daily multiple doses up to 2 weeks ranging from 5 to 40 mg (refer to IB). Across these single and multiple dose ranges, zavegepant was found to be generally safe and well tolerated.

The inclusion and exclusion criteria of this study have been chosen to select participants who are known to be free from any significant illness, history of autoimmune diseases, and any condition that could impact their safety or interfere with meeting the study objectives. The proposed safety screening and monitoring assessments are deemed to be sufficient to monitor the potential risks of zavegepant administration. There is no anticipated therapeutic benefit for the healthy participants in this study.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of zavegepant may be found in the USPI[1] which is the SRSD for this study. Refer to the Study Intervention(s) table in Section 6.1 for a complete description of SRSDs.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention Zavegepant		
Hypersensitivity reactions	Hypersensitivity reactions including facial swelling and urticaria have occurred with zavegepant.	Site staff and participants are instructed throughout protocol and ICD to immediately report all AEs post-dosing for further management instructions.
AEs associated with IN administration, such as dysgeusia, throat irritation, nasal congestion and nasal discomfort.	The potential risks are based on AEs reported in studies of zavegepant IN administration, and the majority have been of mild to moderate intensity.	Eligibility criteria have been selected to ensure that only appropriate participants are included in the study (see Section 5.1). Nasal inspection will be conducted on Day -1 (to exclude participants with mucosal erythema, congestion, septal defects etc), and 24 h (± 30 min) postdose per the SoA. AEs and clinical laboratory results will be monitored on an ongoing basis.
Study Procedures		
The study intervention will be administered intranasally via a liquid spray device.	The IN administration could be affected by some human and operational factors, such as the way of handling the devices and the way of inhalation and exhalation. These may lead to higher variabilities in PK data.	Enhanced site training and participant education in terms of the study intervention administration. For all the study participants, all attempts would be made for study intervention administration performed by no more than 3 study staff members to minimize variability in device handling.
Relatively intensive PK sampling and narrow time window within 1 hour post dose.	Risk of PK sample collection outside the required time window might be higher.	Enhance site communication and training. Actual PK sampling times will be used in the derivation of PK parameters.
Other		
Atypical PK sampling methodology (Tasso devices)	Risk of improper collection procedure that could lead to compromised sample(s)	Enhanced site communication and training on Tasso device collection and handling procedures

2.3.2. Benefit Assessment

Zavegepant is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate pharmacokinetic, safety, and tolerability data in healthy adults. As noted earlier, data from this study will be used to support the future clinical development of zavegepant in pediatrics.

2.3.3. Overall Benefit/Risk Conclusion

Considering all available nonclinical and clinical data regarding the reassuring safety and tolerability of zavegepant to date and measures to monitor and minimize risk to study participants in this study, the overall benefit/risk profile supports the further clinical development of zavegepant in healthy adults.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• Characterize the PK profile of zavegepant from samples collected using Tasso Devices (Tasso-Plus and Tasso-M20) vs. standard venous phlebotomy following IN administration of 10 mg of zavegepant IN formulation in healthy participants	• Zavegepant concentrations from samples collected using Tasso devices vs. standard venous phlebotomy • PK parameters: AUC_{inf} (if data permit), AUC_{last}, C_{max}, T_{max}, $t_{½}$, CL/F and V_z/F, as data permits
Secondary:	**Secondary:**
• Evaluate the safety and tolerability following IN administration of 10 mg of zavegepant IN formulation in healthy participants	• Assessment of TEAEs, and clinical safety laboratory tests
Tertiary/Exploratory:	**Tertiary/Exploratory:**
• Evaluate the effect of the administration of 10 mg of zavegepant IN with a butterscotch candy on dysgeusia compared to zavegepant IN alone	• Taste Assessment Survey Scoring Metrics after study intervention: overall liking, bitterness, tongue/mouth burn, throat burn, sour taste, salty taste, and sweet taste

4. STUDY DESIGN

4.1. Overall Design

This is a single-center, Phase 1, non-randomized, open-label, 2-period study in healthy participants to primarily evaluate the correlation of zavegepant concentration from samples

collected using Tasso Devices (Tasso-Plus and Tasso-M20) compared to standard venous phlebotomy. This study consists of two periods which will include approximately 14 participants.

In period 1, 50% (n=7) of participants will use Tasso-Plus, while the other 50% (n=7) will use Tasso-M20. All 14 participants will have 6 PK samples collected using the assigned Tasso device simultaneously with collecting venous blood samples at the following time points, 30 minutes, 1, 2-, 4-, 8-, and 12-hour postdose, as described in the SoA, Table 2. In addition, taste assessments will be performed at time intervals of 1 (immediately after dosing), 5, 10 and 20 minutes after zavegepant IN administration. Also, if feasible, 4 Japanese participants will be enrolled among those 14 participants to evaluate the PK and safety of zavegepant IN in Japanese vs. non-Japanese participants. For Japanese participants, a total of 12 venous blood samples will be collected at the following time points, 0, 15 minutes, 30 minutes, 1, 1.5-, 2-, 3-, 4-, 6-, 8-, 12-, and 24-hour (refer to SoA, Table 2).

In period 2, a butterscotch candy will be given 5 minutes before administering the zavegepant IN study intervention. Taste assessment will also be performed after zavegepant IN administration with a butterscotch candy in period 2. For taste assessment, each participant will record the sensory attributes at timed intervals of 1 (immediately after dosing), 5, 10 and 20 minutes after zavegepant administration in each period.

Healthy participants will be screened within 28 days prior to the first administration of the study intervention to confirm that they meet the participant selection criteria for the study. Eligible participants will be admitted to the CRU on Day -1 and will be confined in the CRU until Discharge on Day 3 (SoA), approximately 24 hours after the second dose. Enrolled participants will receive a single IN dose of zavegepant 10 mg (0.1 mL) in each period. PK venous blood samples as well as Tasso PK sampling, using Tasso-Plus and Tasso-M20, will be collected at specified intervals as per SoA (Table 2) for PK assessments.

The primary analysis will occur when all participants have PK samples collected. The expected duration of participation from screening until follow-up telephone contact is approximately 9 weeks.

4.2. Scientific Rationale for Study Design

As a component of the clinical development of zavegepant, future pediatric studies will be conducted to evaluate the safety, tolerability, and PK of zavegepant in participants 6 to less than 12 years of age with migraine. Recruiting and retaining pediatric patients in clinical trials has always been challenging due to a variety of factors, including inconvenience with patient preferences. To overcome some of those challenges, it is essential to prioritize patient-centric approaches that cater to the unique needs of pediatric patients. One such approach is PCS, which aims to reduce the burden on pediatric patients by minimizing the volume of the biological samples required and being less invasive with minimal pain compared to the venous phlebotomy collection method, which is particularly beneficial for pediatrics who are fearful of needles. Additionally, PCS offers greater flexibility to pediatric patients and their families by allowing at-home sample collection for those who may have difficulty traveling to clinics.

To allow the use of PCS in zavegepant pediatric studies, a bridging or comparative study comparing the PCS approach with an equivalent conventional sampling technique is needed as a regulatory expectation to demonstrate the concordance of data from PCS in a controlled environment prior to implementation in large-scale clinical trials.[36] Therefore, the primary objective of this study is to establish the correlation between zavegepant concentration from samples collected using PCS devices compared to conventional venous blood sampling. PK sampling time points and duration, as described in SoA, Table 2, were selected to adequately capture the rapid absorption of zavegepant, since it has a T_{max} of 0.54 hours, as well as zavegepant elimination phase. Based on zavegepant PK data, zavegepant has an elimination half-life of ~ 3 hours and an effective half-life of 6.55 hours following a single zavegepant 10 mg IN dose. For Tasso bridging analysis, having PK samples that covers zavegepant relevant concentration up to 12 hours will be sufficient to have adequate concentration-time comparison between the 2 methods. While for the Japanese participants, having PK timepoints up to 24 hours will cover >3 half-lives, which will be sufficient to adequately estimate zavegepant half-life in Japanese. That's why 24 hours PK samples will only be requested for Japanese enrolled participants, as described in SoA, Table 2.

A healthy participant population is considered for the study because healthy participants with no concomitant diseases and using no concomitant medications represent a homogenous population allowing for proper evaluation of the PK, safety, and tolerability of a drug without confounding factors. Six PK samples will be collected from the Tasso devices at the same time of collecting venous blood samples, as described in the SoA, Table 2. Those 6 Tasso-venous paired samples collected in 7 participants for each device ($7 \times 6 = 42$ data points) are sufficient to meet the scientific community recommendation for having an adequate Tasso-venous phlebotomy PK bridging study.[36] Different PK sampling times were selected to cover the concentration-time profile of zavegepant IN. Of note, blood-to-plasma ratio samples will be aliquoted from the same venous blood draw as specified in the SoA, Table 2. These samples will be crucial for determining the blood-to-plasma ratio value for each participant to convert the dried blood concentrations collected using Tasso-M20 to their equivalent plasma concentrations for adequate comparison between the 2 methods.

If feasible, 4 Japanese participants will be enrolled among the 14 participants planned for this study to determine the PK and safety of zavegepant IN in this population since there is no PK and safety data available for the use of zavegepant IN in this population. Leveraging this data will be useful in supporting the development of zavegepant IN in Japan. However, the recruitment of these Japanese participants will be optional, and the completion of this trial will not require their enrollment.

As noted earlier, data from clinical trials of zavegepant IN formulation have shown dysgeusia (bad/metallic/bitter taste) as the most common treatment-emergent adverse event following zavegepant administration (refer to IB). We hypothesize that the mechanism of dysgeusia associated with zavegepant nasal spray administration relates to the postnasal dripping of residual spray into the oral cavity and contact with the posterior tongue and taste buds, triggering the taste receptor cells. To test this hypothesis and better understand this adverse event (its intensity, onset, and duration), a taste assessment questionnaire will be performed at 1 (immediately after dosing), 5, 10 and 20 minutes after zavegepant IN administration.

Previous case studies have shown that simple interventions like sucking butterscotch or drinking a fruit punch–flavored powdered drink have successfully managed dysgeusia following the use of sumatriptan or esketamine nasal sprays, respectively.[37,38] Therefore, finding strategies to mask zavegepant-induced bitter taste can help improve patient experience and adherence. As an exploratory objective, this study will explore whether giving a butterscotch candy before zavegepant IN administration will help manage dysgeusia. To do that, a second dose of 10 mg zavegepant IN will be administered 24 hours after the first dose. Participants will be instructed to eat a butterscotch candy approximately 5 minutes prior to zavegepant IN administration in period 2. Taste assessments will be compared for the 14 subjects after zavegepant administration alone in period 1 vs. zavegepant and butterscotch candy in period 2. Administering a second dose of 10 mg zavegepant IN 24 hours after the first dose is well-supported by zavegepant IN clinical trials data which shows no dose-limiting AEs after administering single doses as high as 40 mg IN and multiple doses of 20 mg for up to 14 days (refer to IB).

4.2.1. Choice of Contraception/Barrier Requirements

Human reproductive safety data is not available for zavegepant, but no evidence of embryo lethality and teratogenicity was found in animal embryofetal development studies in rats and rabbits with zavegepant (refer to IB). Therefore, the use of a highly effective method of contraception is required (see Appendix 4). No data are available on the potential in vivo transfer of zavegepant or its metabolites into human breast milk; therefore, lactating women must not receive zavegepant. Only male and non-pregnant/non-lactating female participants will be included in the study.

4.3. Justification for Dose

The 10 mg IN dose of zavegepant was selected as the optimal therapeutic dose for the acute treatment of migraine as it provided efficacy with minimized systemic exposure of zavegepant. Based on that, this dose was the approved dose by the FDA for the acute treatment of migraine. Therefore, the exposure achieved following 10 mg zavegepant IN is the most relevant for this study and for future pediatric studies. Overall, the data demonstrated that IN zavegepant 10 mg is effective for the acute treatment of migraine.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last scheduled procedure shown in the SoA for the last participant in the trial.

A participant is considered to have completed the study if they have completed all periods of the study, including the last visit.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled, including participants across diverse and representative racial and ethnic backgrounds. If a prescreening tool is utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of a diverse participant population, including, where permitted under local regulations, age, sex, race, and ethnicity. The following eligibility

criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female ≥18 years of age and older at the time of signing the ICD.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants.

    - For Japanese participants to be enrolled, they need to meet the following inclusion criteria: Japanese participants must have 4 Japanese grandparents who were born in Japan.

Other Inclusion Criteria:

2. Male and female participants who are overtly healthy as defined by:

    - the absence of clinically significant illness and surgery within 4 weeks prior to dosing. Participants vomiting within 24 hours Predose will be carefully evaluated for upcoming illness/disease.

    - the absence of clinically significant history of neurological, endocrinal, cardiovascular, pulmonary, hematological (eg, neutropenia), immunologic, psychiatric, gastrointestinal, renal, hepatic, and metabolic disease.

3. BMI 16.0-32.0 kg/m^2 and body weight ≥45.0 kg (99 lb).

4. Females must not be breastfeeding or lactating and must have a negative urine or serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) at screening. WOCBP must have negative urine or serum pregnancy test at admission.

5. Participants are willing to consume a butterscotch candy.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Evidence or history of clinically significant hematological, renal, endocrine, pulmonary, gastrointestinal, cardiovascular, hepatic, psychiatric, neurological, or allergic disease (including drug allergies, but excluding untreated, asymptomatic, seasonal allergies at the time of dosing).

    - Current diagnosis of viral hepatitis or a history of liver disease.

    - History of HIV infection, hepatitis B, or hepatitis C; positive testing for HIV, HBsAg, HBsAb, HBcAb, or HCVAb. Hepatitis B vaccination is allowed.

2. Clinically significant history of nasal conditions that may affect the administration or absorption of the nasal product (eg, severe septum deviation or nasal deformity, inflammation, perforation, mucosal erosion, localized infection or ulceration, congestion, polyposis, rhinorrhea, nasal surgery within the previous 6 months, or nasal trauma).

3. Significant history of seizure disorder other than a single childhood febrile seizure (eg, epilepsy) or history of gallstone or cholecystectomy.

4. Any other medical or psychiatric condition, including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality or other conditions or situations related to COVID-19 pandemic that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

5. Refer to Section 6.9 Prior and Concomitant Therapy. Any of the products taken during the timeframe specified below will be reviewed and evaluated by the principal investigator to determine participant's eligibility:

    - Use of OATP1B3 inhibitors (refer to Appendix 10), within 14 days or 5 half-lives (whichever is longer) prior to the first dosing;

    - Prescription medication within 14 days prior to the first dosing (hormonal contraception allowed);

    - OTC products within 7 days prior to the first dosing;

    - Oxymetazoline (or other nasal spray decongestants) from at least 14 days prior to the first dosing until after the last PK blood sample collection of the study;

- A depot injection or an implant of any drug (other than hormonal contraceptives) within 3 months prior to the first dosing;

- Natural health products (including herbal remedies such as Butterbur root or extracts, homeopathic and traditional medicines, probiotics, food supplements such as vitamins (including ascorbic acid), minerals, amino acids, essential fatty acids, and protein supplements used in sports) within 7 days prior to the first dosing until after the last PK blood sample collection of the study; with the exception of the occasional use of ibuprofen.

Prior/Concurrent Clinical Study Experience:

6. Participation in a clinical research study involving the administration of an investigational or marketed drug or device within 30 days prior to IP dosing, administration of a biological product in the context of a clinical research study within 90 days prior to IP dosing, or concomitant participation in an investigational study involving no drug or device administration.

Diagnostic Assessments:

7. Any clinically significant abnormal laboratory test results or positive test found during medical screening. A single repeat for positive drug screen may be allowed at the discretion of the PI.

8. Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination or nasal inspection beyond what is consistent with the target population.

9. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic) for participants <60 years; and ≥150/90 mm/Hg for participants ≥60 years old, following at least 5 minutes of supine rest. If systolic BP is ≥140 or 150 mm Hg (based on age) or diastolic ≥90 mm Hg, the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

10. Standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results (eg, QTcF >450 ms, complete LBBB, signs of an acute or indeterminate- age myocardial infarction, ST-T interval changes suggestive of myocardial ischemia, second- or third- degree AV block, or serious bradyarrhythmias or tachyarrhythmias). If QTcF exceeds 450 ms, or QRS exceeds 120 ms, the ECG should be repeated twice and the average of the 3 QTcF or QRS values used to determine the participant's eligibility. Computer-interpreted ECGs should be overread by a physician experienced in reading ECGs before excluding a participant.

11. Participants with **ANY** of the following abnormalities in clinical laboratory tests at screening, as assessed by the study-specific laboratory and confirmed by a single repeat test, if deemed necessary:

    - AST **or** ALT level >1.5 × ULN.
    - Total bilirubin level >1.5 × ULN. Participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.
    - eGFR of <60 mL/min/1.73m². eGFR is calculated using the recommended formulas in Section 10.7.2 to determine eligibility and to provide a baseline to quantify any subsequent kidney safety events.

Other Exclusion Criteria:

12. Use of tobacco or nicotine-containing products within 1 month of screening or a positive urine cotinine test (ie, active smokers and those who currently use nicotine-containing products are excluded from participation in this study).

13. Conditions that affect ability to taste eg, dysgeusia, respiratory infection, cold, or other conditions as evaluated by the PI.

14. Presence of piercings or any physical findings in the nose that, in the opinion of the PI, would likely interfere with the successful completion of the dosing procedure.

15. Investigator site staff directly involved in the conduct of the study and their family members, site staff otherwise supervised by the investigator, and sponsor and sponsor delegate employees directly involved in the conduct of the study and their family members.

16. History of alcohol abuse or binge drinking and/or any other illicit drug use or dependence within 6 months of Screening. Binge drinking is defined as a pattern of 5 (male) and 4 (female) or more alcoholic drinks in about 2 hours. As a general rule, alcohol intake should not exceed 14 units per week (1 unit = 8 ounces (240 mL) beer, 1 ounce (30 mL) of 40% spirit, or 3 ounces (90 mL) of wine).

17. Any reason that, in the opinion of the PI, would prevent the participant from participating in the study.

5.3. Lifestyle Considerations

The following guidelines are provided:

5.3.1. Contraception

The investigator or their designee, in consultation with the participant, will confirm that the participant is utilizing an appropriate method of contraception for the individual participant

from the permitted list of contraception methods (see Appendix 4, Section 10.4.4) and will confirm that the participant has been instructed in its consistent and correct use. The investigator or designee will advise the participant to seek advice about the donation and cryopreservation of germ cells prior to the start of study intervention, if applicable.

At time points indicated in SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart. Participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception, considering that their risk for pregnancy may have changed since the last visit.

In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued and document the requirement to use an alternate protocol-specified method, including if the participant will no longer use abstinence as the selected contraception method, or if pregnancy is known or suspected in the participant or partner.

5.3.2. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory, and at least 10 hours prior to taking the study intervention in period 1, Day 1, and in period 2, Day 1.
- Breakfast may be provided in the morning of Day 3.
- Lunch and dinner will be provided at appropriate times.
- An evening snack may be permitted.
- Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to the first dose of study intervention until collection of the final PK blood sample.
- While participants are confined, their total daily nutritional composition should be approximately 55% carbohydrate, 30% fat, and 15% protein. The daily caloric intake per participant should not exceed approximately 3200 kcal.

5.3.3. Caffeine, Alcohol, and Tobacco

- Participants will abstain from caffeine-containing products for 24 hours prior to the start of dosing until the collection of the final PK sample.
- Participants will abstain from alcohol for 24 hours prior (or as specified above for red wine) to admission to the CRU and continue abstaining from alcohol until the collection of the final PK sample. Participants may undergo an alcohol breath test or blood alcohol test at the discretion of the investigator.

- Participants will abstain from the use of tobacco- or nicotine-containing products for more than 1 month prior to screening and during confinement in the CRU.

5.3.4. Activity

- Participants will abstain from strenuous exercise (eg, heavy lifting, weight training, calisthenics, aerobics) for at least 48 hours prior to each blood collection for clinical laboratory tests. Walking at a normal pace will be permitted.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. Screen failure data are collected and remain as source and are not reported on the CRF.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened with the approval of the principal investigator.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational and noninvestigational medicinal products, medical devices, and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

For the purposes of this protocol, study intervention refers to zavegepant.

6.1. Study Intervention(s) Administered

Zavegepant is formulated as 10 mg for IN single-dose administration. The study intervention will be provided in single-use unidose nasal spray devices fully prepared and ready for administration.

Study Intervention(s)	
Intervention Name	Zavegepant
Type	Drug
Use	Experimental
IMP or NIMP/AxMP	IMP
Dose Formulation	Nasal spray
Unit Dose Strength(s)	10 mg
Dosage Level(s)	10 mg
Route of Administration	IN

Study Intervention(s)	
Sourcing	Provided centrally by the sponsor. Refer to the IP manual.
Packaging and Labeling	Study intervention will be provided in unidose nasal spray. Each nasal spray will be labeled according to local regulatory requirements. Study intervention will be provided to the site as bulk labeled nasal spray for dispensing by the pharmacy and administration by site personnel.
SRSD	USPI
Current Name or Alias	Zavegepant

Study Arm(s)	
Arm Title	Zavegepant
Arm Description	All participants will receive zavegepant 10 mg IN spray in period 1 and a butterscotch candy + zavegepant 10 mg IN spray in period 2

6.1.1. Administration

Following an overnight fast of at least 10 hours, on Day 1 of period 1, participants will receive study intervention at approximately 0800 hours (plus or minus 2 hours). Administer study intervention according to the IPM. On Day 1 of period 2, following an overnight fast of at least 10 hours, participants will receive a butterscotch candy followed 5 minutes later by study intervention. Participants will be instructed not to chew or crush the candy but allow it to dissolve over time.

Administration of study intervention will be performed by an appropriately qualified and trained member of the study staff as allowed by local, state, and institutional guidance. Study staff will administer the IN spray in 1 nostril to each participant. Study staff will record which nostril was used for drug administration. After the dose is administered, participants will be asked to remain seated upright for approximately 10 minutes in order to avoid any study intervention leakage. Participants must inform the staff if they sneeze or if the product drips out of their nose during or shortly after the administration. Of note, for all the study participants, all attempts would be made for study intervention administration performed by no more than 3 study staff members to minimize variability in device handling.

Participants must inform the study staff if they believe the device did not function properly, ie, if they believe the device did not dispense a spray content. All occurrences of dose misadministration or unidose nasal spray malfunction should be communicated to the

sponsor as soon as possible. Under no circumstance may a participant be administered a supplementary dose of study medication.

Following administration of study intervention(s), participants will be observed for 10 minutes by an appropriately qualified and trained member of the study staff. Appropriate medication and other supportive measures for management of a medical emergency will be available in accordance with local guidelines and institutional guidelines.

6.1.2. Medical Devices

1. The study intervention, zavegepant (10 mg dose), uses a unitdose nasal spray device constituent for delivery to the intended user population. Instructions for medical device use are provided in the IPM.

2. All medical device deficiencies (including malfunction, use error, and inadequate labeling) for the above-listed medical devices shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.4.9) and appropriately managed by the sponsor.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm that appropriate conditions (eg, temperature) have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, and/or administer study intervention.

3. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented upon return to business.

4. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with actions taken. The site should actively pursue options for returning the study intervention to the labeled storage conditions, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the excursion definition and information to report for each excursion will be provided to the site in the PCRU local/site procedures.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.

6. Study interventions should be stored in their original containers.

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

8. Further guidance and information for the final disposition of unused study interventions are provided in the PCRU's local/site procedures. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery.

6.2.1. Preparation and Dispensing

Within this protocol, preparation refers to the investigator site activities performed to make the study intervention ready for administration or dispensing to the participant by qualified staff. Dispensing is defined as the provision of study intervention, concomitant treatments, and accompanying information by qualified staff member(s) to a healthcare provider, participant, in accordance with this protocol. Local health authority regulations or investigator site guidelines may use alternative terms for these activities.

See the IPM for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

6.3. Assignment to Study Intervention

The investigator will assign participant numbers to the participants as they are screened for the study. Pfizer will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the participant will receive the study treatment regimen assigned to the corresponding randomization number.

6.4. Blinding

This is an open-label study.

6.4.1. Blinding of the Sponsor

As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating PK modeling, and/or supporting clinical development.

6.5. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF.

6.6. Dose Modification

By design, this study only includes the administration of IN dose of zavegepant in each period at a fixed dosage level (10 mg). As such, dose modifications will not be made during the study.

6.7. Continued Access to Study Intervention After the End of the Study

No study intervention will be provided to participants at the end of their study participation.

6.8. Treatment of Overdose

There is no clinical experience with overdose of zavegepant. This is a single and fixed-dose study; thus, the probability of having a treatment overdose is low. For this study, any dose of zavegepant greater than 40 mg (the maximum dose that has been explored to-date) within a 24-hour time period will be considered an overdose.

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**
5. Obtain a blood sample for PK analysis within 2 hours from the last dose of study intervention if requested by the study medical monitor (determined on a case-by-case basis).

6.9. Prior and Concomitant Therapy

Concomitant administration of zavegepant with inhibitors of OATP1B3 may result in a significant increase in zavegepant exposure. Avoid concomitant administration of zavegepant with drugs that inhibit OATP1B3 transporter, as listed in Appendix 10.

Participants will be asked to refrain from using prescription medication, OTC products, or natural health products that may potentially affect their safety and/or the PK profile of the study drug. Any of these products taken during the timeframe specified below will be reviewed and evaluated by the PI in order to determine if they affect a participant's eligibility or continued participation in the study. Product restriction timeframes are as follows:

- Prescription medication within 14 days prior to the first dosing until after the last PK blood sample collection of the study (hormonal contraception allowed);
- OTC products within 7 days prior to the first dosing;
- Oxymetazoline (or other nasal spray decongestants) from at least 14 days prior to the first dosing until after the last PK blood sample collection of the study;
- A depot injection or an implant of any drug (other than hormonal contraceptives) within 3 months prior to the first dosing;
- Natural health products (including herbal remedies such as Butterbur root or extracts, homeopathic and traditional medicines, probiotics, food supplements such as vitamins (including ascorbic acid), minerals, amino acids, essential fatty acids, and protein supplements used in sports) within 7 days prior to the first dosing until after the last PK blood sample collection of the study.

All concomitant treatments taken during the study must be recorded with indication, daily dose, and start and stop dates of administration. All participants will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 28 days before the first dose of study intervention will be documented as a prior treatment. Treatments taken after the first dose of study intervention will be documented as concomitant treatments.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

It may be necessary for a participant to permanently discontinue study intervention. Reasons for permanent discontinuation of study intervention include the following:

- AE (including Grade 3 severity or greater and considered by the investigator to be related to study intervention);
- SAE considered by the investigator to be related to study intervention;

- Requirement for prohibited concomitant medication;
- Study terminated by sponsor;
- Withdrawal by participant or legally authorized representative.

Discontinuation of study intervention does not represent withdrawal from the study. If study intervention is permanently discontinued, the participant should remain in the study to be evaluated for subsequent scheduled assessments. See the SoA for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, further study follow-up, and/or future collection of additional information.

7.1.1. Potential Cases of Acute Kidney Injury

Participants exposed to IMP demonstrating transient or sustained increase in Screat (with decrease in Screat-based eGFR or eCrCL) require expedited evaluation to differentiate AKI from DICI. DICI is defined as transporter-mediated effect related to altered renal tubular creatinine handling without histological injury.

AKI may be due to one or more types of injury, including DIKI. Differentiation of DIKI from other causes of AKI and from DICI may require clinical, radiographic, histopathologic, and laboratory assessments, as well as nephrology consultation.

Follow-up Assessments

The participant should return to the site for evaluation as soon as possible, preferably within 48 hours of awareness of the abnormal results.

Evaluation should include physical examination, laboratory tests, detailed medical and surgical history, review of all medications (including recreational drugs and supplements [herbal]), family history, sexual history, travel history, blood transfusion, and potential occupational exposure to chemicals.

Laboratory assessments should include simultaneous serum cystatin C (Scys) and serum creatinine (Screat) tests. Estimates of eGFR, eCrCl and Screat-based eGFR and combined Screat-Scys-based eGFR should also be derived using the appropriate equation described in Appendix 7.

Assessments of urine albumin-to-creatinine ratio or urine volume may also be performed as appropriate.

If appropriate, nephrology consultation may be recommended to facilitate differentiation of renal parenchymal disease, pre-renal azotemia, and post-renal obstruction.

Differentiating Acute Kidney Injury from DICI

A confirmed Screat increase is defined as:
(i) ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours OR
(ii) confirmed Screat increase ≥1.5 times baseline (known or suspected to have occurred within the prior 7 days).

Based on the assessments performed, suspected AKI (including DIKI) may be differentiated from DICI as follows.

Adult participants

	AKI (including DIKI) **Any one of the below**	**DICI**
Scys & Screat	Simultaneous, confirmed serum cystatin C (Scys) increase and confirmed Screat increase	Confirmed Screat increase without confirmed increase in reflex Scys AND Confirmed Screat-based eGFR decrease without confirmed combined Screat-Scys-based eGFR decrease.
eGFR	Decrease in Screat-based eGFR and combined Screat-Scys-based eGFR (when available)	
Albuminuria or proteinuria	Confirmed albuminuria increase (see Appendix 7 for Grades A1 to A3 quantitation)	
Urine volume	Urine volume <0.5 mL/kg/h for 6 consecutive hours	

Regardless of the presence or absence of increase in Screat, DIKI and other causes of AKI may be suspected if either there is new-onset or worsening albuminuria or proteinuria are detected.

All confirmed cases of clinically relevant decrease in kidney function should be considered potential cases of DIKI if no other reason for the kidney function abnormalities has been found.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at their own request. Reasons for discontinuation from the study include the following:

- Refused further study procedures;

- Lost to follow-up;
- Safety reason
- Death;
- Study terminated by sponsor.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. See the SoA for assessments to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The early discontinuation visit applies only to participants who are enrolled/randomized and then are prematurely withdrawn from the study. Participants should be questioned regarding their reason for withdrawal.

The participant will be permanently discontinued from the study intervention and the study at that time.

If a participant withdraws from the study, they may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see Section 7.2.1 for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with them or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. Counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study;

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative Procedures

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study -specific procedures.

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Participants will be screened within 28 days prior to the administration of the study intervention to confirm that they meet the study population criteria for the study. If the time between screening and dosing exceeds 28 days as a result of unexpected delays (eg, delayed drug shipment), then participants do not require rescreening if the laboratory results obtained prior to first dose administration meet eligibility criteria.

A participant who qualified for this protocol but did not enroll from an earlier cohort/group may be used in a subsequent cohort/group without rescreening, provided laboratory results obtained prior to the first dose administration meet the eligibility criteria for this study. In addition, other clinical assessments or specimen collections, eg, retained research samples, may not need to be repeated, as appropriate.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be

circumstances outside the control of the investigator that make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that they have taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

If an IV catheter is utilized for blood sample collections, ECGs and vital sign assessments (pulse rate and BP) should be collected prior to the insertion of the catheter.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for each individual participant in this study is approximately 85 mL. The actual collection times of blood sampling may change. Additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 56 consecutive days.

To prepare for study participation, participants will be instructed on the information in the Section 5.3 and 6.9 sections of the protocol.

8.2. Efficacy Assessments

Efficacy parameters are not evaluated in this study.

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA. Unscheduled safety measurements may be obtained at any time during the study to assess any perceived safety issues.

8.3.1. Physical Examinations

A complete physical examination will include, at a minimum, head, ears, eyes, nose, mouth, skin, heart and lung examinations, lymph nodes, and gastrointestinal, musculoskeletal, and neurological systems.

A brief physical examination will include, at a minimum, assessments of general appearance, the respiratory and cardiovascular systems, and participant-reported symptoms.

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation.

Height and weight will also be measured and recorded as per the SoA. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only

light clothing remains. They must also remove the contents of their pockets and remain still during the measurement of weight.

Physical examination findings collected during the study will be considered source record and will not be required to be reported, unless otherwise noted. Any untoward physical examination findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.2. Nasal Inspection

The nasal passages and turbinates will be visually inspected with a nasal speculum and light on Day -1 (to exclude participants with mucosal erythema, congestion, septal defects etc.), and 24 hours (± 30 minutes) postdose to detect evidence of nasal inflammation or edema.

8.3.3. Vital Signs

8.3.3.1. Blood Pressure and Pulse Rate

Supine BP will be measured with the participant's arm supported at the level of the heart and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study. Participants should be instructed not to speak during measurements.

The same properly sized and calibrated BP cuff will be used to measure BP each time. The use of an automated device for measuring BP and pulse rate is acceptable; however, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds. When the timing of these measurements coincides with a blood collection, BP and pulse rate should be obtained prior to the nominal time of the blood collection.

Additional collection times, or changes to collection times, of BP and pulse rate will be permitted, as necessary, to ensure the appropriate collection of safety data.

Any untoward vital sign findings that are identified during the active collection period and meet the definition of an AE or SAE (Appendix 3) must be reported according to the processes in Sections 8.4.1 to 8.4.3.

8.3.4. Electrocardiograms

Standard 12-lead ECGs will be collected at times specified in the SoA section of this protocol using an ECG system that automatically calculates the HR and measures PR, QT, QTcF, and QRS intervals. All scheduled ECGs should be performed after the participant has rested quietly for at least 5 minutes in a supine position.

In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality. It is important that leads be placed in the same positions each time in order to achieve precise ECG recordings. If a machine-read QTc value is prolonged, as defined above, repeat measurements may not be necessary if a

qualified medical provider's interpretation determines that the QTcF values are in the acceptable range.

ECG values of potential clinical concern are listed in Appendix 8.

8.3.5. Clinical Safety Laboratory Assessments

See Appendix 2 for the list of clinical safety laboratory tests to be performed and the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically significant changes occurring during the study in the AE section of the CRF. Clinically significant abnormal laboratory test findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significant and abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or study medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See Appendix 6 for suggested actions and follow-up assessments in the event of potential DILI.

See Appendix 7 for instructions for laboratory testing to monitor kidney function and report laboratory test abnormalities.

8.3.6. Pregnancy Testing

A urine or serum pregnancy test is required at screening. Following screening, pregnancy tests may be urine or serum tests, and must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the SoA. Following a negative pregnancy test result at screening, appropriate contraception must be commenced, and a second negative pregnancy test result will be required at the baseline visit prior to starting the study intervention. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected) and at the end of the study. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations.

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of an AE and an SAE can be found in Appendix 3.

AEs may arise from symptoms or other complaints reported to the investigator by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative), or they may arise from clinical findings of the investigator or other healthcare providers (clinical signs, test results, etc.).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study (see Section 7.1).

During the active collection period as described in Section 8.4.1, each participant will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before undergoing any study -related procedure and/or receiving study intervention), through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention.

Follow-up by the investigator continues throughout the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator.

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues study because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the PASS.

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and they consider the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the PSSA.

8.4.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in Section 8.4.1 are reported to Pfizer Safety on the PASS immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of its being available.

8.4.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in Section 8.4.1, will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed, and all spontaneously reported AEs and SAEs reported by the participant.

As part of ongoing safety reviews conducted by the sponsor, any nonserious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

Reporting of AEs and SAEs for participants who fail screening are participant to the CRF requirements as described in Section 5.4.

8.4.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3. Follow-Up of AEs and SAEs

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow--up procedures is provided in Appendix 3.

8.4.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.4.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to the study intervention. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include EDP, EDB, and occupational exposure.

Any such exposures to the study intervention under study are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention inseminates a female partner.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of environmental exposure. Below are examples of environmental EDP:
    - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by ingestion, inhalation, or skin contact.

- A male family member or healthcare provider who has been exposed to the study intervention by ingestion, inhalation, or skin contact then inseminates his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant/participant's partner, the investigator must report this information to Pfizer Safety using the PSSA regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 28 days after the last dose.

- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the PSSA Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a liveborn baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;

- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on

preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.4.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female nonparticipant is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by ingestion, inhalation, or skin contact.

The investigator must report EDB to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the PSSA. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study**,** so the information is not recorded on a CRF. However, a copy of the completed report is maintained in the investigator site file.

An EDB report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accordance with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the EDB.

8.4.5.3. Occupational Exposure

The investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness using the PSSA regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

Not applicable.

8.4.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Not applicable.

8.4.8. Adverse Events of Special Interest

Not applicable.

8.4.8.1. Lack of Efficacy

This section is not applicable because efficacy is not expected in the study population.

8.4.9. Medical Device Deficiencies

Medical devices being provided for use in this study are those listed in Section 6.1.2. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a medical device deficiency can be found in Appendix 9.

Note: AEs and/or SAEs that are associated with a medical device deficiency will follow the same processes as other AEs or SAEs, as outlined in Section 8.4.1 through 8.4.4 and Appendix 3 of the protocol.

8.4.9.1. Time Period for Detecting Medical Device Deficiencies

Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.

Importantly, reportable device deficiencies are not limited to problems with the device itself but also include incorrect or improper use of the device and even intentional misuse, etc.

If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

Refer to Section 10.9.4 for instructions for documenting and reporting medical device deficiencies.

8.4.9.2. Regulatory Reporting Requirements for Device Deficiencies

The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/EC.

Note: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs (ie, an SADE) that must fulfill the legal responsibility to notify

appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a device deficiency.

- The sponsor shall review all device deficiencies and determine and document in writing whether they could have led to an SAE. These shall be reported to the regulatory authorities and IRBs/ECs as required by national regulations.

8.4.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Medication errors are recorded and reported as follows:

Recorded on the Medication Error Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported on the PSSA to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;

- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, such medication errors occurring to a study participant are recorded on the medication error page of the CRF, which is a specific version of the AE page and, if applicable, any associated serious and nonserious AE(s), are recorded on the AE page of the CRF.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Medication errors should be reported to Pfizer Safety within 24 hours on a PSSA **only when associated with an SAE.**

8.5. Pharmacokinetics

Venous blood samples of approximately 4 mL, to provide approximately 1.5 mL plasma, will be collected for measurement of plasma concentrations of zavegepant as specified in the

SoA. Prior to centrifugation of blood samples collected at the time points specified in the SoA, Table 2, a 500 µL portion of the PK blood sample will be aliquoted and used to determine the blood-to-plasma ratio of zavegepant. Determining the blood-to-plasma ratio will be crucial for converting the dried blood concentrations collected using Tasso-M20 to their equivalent plasma concentrations for adequate comparison between the 2 methods. For Tasso sampling, approximately 100 µL of blood will be collected from participants using the Tasso-M20 devices, while for Tasso-Plus, approximately 300-500 µL of blood will be collected to provide approximately 150 - 200 µL serum into appropriately labeled tubes for the measurement of zavegepant concentration as specified in the SoA, Table 2. Of note, both Tasso and venous PK samples will be collected at the same time. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60-minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. This protocol deviation window does not apply to samples to be collected more than 10 hours after dose administration at outpatient/follow-up visits with visit windows.

Samples will be used to evaluate the PK of zavegepant. Samples collected for analyses of zavegepant concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, for metabolite identification and/or evaluation of the bioanalytical method. The data may be used for other internal exploratory purposes. The exploratory results may not be reported in the CSR.

Genetic analyses will not be performed on the collected PK samples unless consent for this was included in the informed consent. Participant confidentiality will be maintained.

Samples collected for measurement of zavegepant concentrations will be analyzed using a validated analytical method in compliance with applicable SOPs.

The PK samples must be processed and shipped as indicated in the instructions provided to the investigator site to maintain sample integrity. Any deviations from the PK sample handling procedure (eg, sample collection and processing steps, interim storage or shipping conditions), including any actions taken, must be documented and reported to the sponsor. On a case-by-case basis, the sponsor may make a determination as to whether sample integrity has been compromised.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The IRB/EC will

be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICD.

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.6.2. Retained Research Samples for Genetics

A 4-mL blood sample optimized for DNA isolation Prep D1 will be collected according to the SoA, as local regulations and IRBs/ECs allow.

Retained Research Samples may be used for research related to the study intervention. Genes and other analytes (eg, proteins, RNA, nondrug metabolites) may be studied using the retained samples.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment of these samples can be found in the laboratory manual and supporting documentation.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in the SAP, which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Statistical Hypotheses

There is no statistical hypothesis for this study.

9.2. Analysis Sets

For purposes of analysis, the following analysis sets are defined:

Participant Analysis Set	Description
Enrolled	"Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.
PK Concentration Analysis Set	All enrolled participants who receive 1 single IN dose of zavegepant and provide at least 1 evaluable plasma concentration.
PK Parameter Analysis Set	All enrolled participants who receive 1 single IN dose of zavegepant and provide at least 1 evaluable PK parameters of interest.
Taste Assessment Set	All participants who receive at least 1 single IN dose of zavegepant and complete the Taste Assessment Questionnaire
Safety Analysis Set	All participants who take at least 1 dose of study intervention. Participants will be analyzed according to the product they actually receive.

9.3. Statistical Analyses

The SAP will be developed and finalized before any analyses are performed and will describe the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.3.1. General Considerations

No formal statistical tests will be performed. Descriptive summaries will be provided for all endpoints by each blood collection method. For the taste assessment in this study, the data used in the analysis will be transcribed and rescaled to a score from 0 to 100 from the raw measurements on the questionnaire. The sensory attributes (overall liking, bitterness, tongue/mouth burn, throat burn, sour taste, salty taste, and sweet taste) from the taste questionnaires (Appendix 11) will be listed and descriptively summarized by study intervention (zavegepant alone vs zavegepant + butterscotch candy) and time points.

Summary statistics (mean and 90% CI) will be calculated for the various questions. Radar plots for each of 4 time points, summarizing all attributes for each intervention will be generated. Boxplots of each attribute will be plotted against the time points. More details will be provided in the SAP.

9.3.2. Pharmacokinetic Analysis

9.3.2.1. Derivation of PK Parameters

Zavegepant PK parameters from samples collected using Tasso and venous phlebotomy will be derived from the concentration-time profile using non-compartmental methods, as detailed in Table 3. Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 3. Plasma PK Parameters for Protocol C5301022

Parameter	Definition	Method of Determination
C_{max}	Maximum plasma concentration	Observed directly from data
AUC_{last}	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{inf}[a]	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}/k_{el})$, where C_{last} is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{1/2}$[a]	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve
CL/F[a]	Apparent clearance	$Dose/AUC_{inf}$
V_z/F[a]	Apparent volume of distribution	$Dose/(AUC_{inf} \times k_{el})$

a. If data permits.

9.3.2.2. Statistical Methods for Pharmacokinetic Data

The plasma concentration of zavegepant will be listed and descriptively summarized by nominal sampling time, for each Tasso device by blood collection method (Tasso and venous), and by race (non-Japanese and Japanese), as data permit. Individual participant and summary profiles (mean and median plots) of the plasma concentration-time data will be plotted using actual and nominal sampling times, respectively. The correlations of paired Tasso-Plus versus venous phlebotomy concentrations and paired Tasso-M20 versus venous phlebotomy concentrations will be reported.

The PK parameters of zavegepant will be listed and summarized descriptively for each Tasso device by blood collection method (Tasso and venous), and by race (non-Japanese and Japanese), as data permits. For AUC_{last}, AUC_{inf}, and C_{max}, box and whisker plots for individual participant parameters will be constructed for each Tasso device by blood collection method and overlaid with geometric means. The PK parameter analysis set will be used.

Additional specifications about the tables, listings, and figures will be outlined in the SAP.

9.3.3. Safety Analyses

All safety analyses will be performed on the safety population.

AEs, ECGs, BP, pulse rate, and safety laboratory data will be reviewed and summarized to evaluate the safety of participants. Any clinical laboratory, ECG, BP, and pulse rate abnormalities of potential clinical concern will be described. Safety data will be presented in tabular and/or graphical format and summarized descriptively, where appropriate.

Medical history and physical examination, and neurological examination information, as applicable, collected during the course of the study, will be considered source data and will not be required to be reported, unless otherwise noted. However, any untoward findings identified on physical and/or neurological examinations conducted during the active collection period will be captured as AEs, if those findings meet the definition of an AE. Data collected at screening that are used for inclusion/exclusion criteria, such as laboratory data, ECGs, and vital signs, will be considered source data, and will not be required to be reported, unless otherwise noted. Demographic data collected at screening will be reported.

9.4. Interim Analyses

No interim analysis will be conducted for this study. As this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, and/or supporting clinical development.

9.5. Sample Size Determination

Approximately 14 evaluable participants will be enrolled (7 for Tasso-Plus and 7 for Tasso-M20). There is no statistical hypothesis for this study. The sample size determination for this study was based on the established scientific recommendation for having 30 to 40 PK data points to ensure adequate comparison between PCS (test) and venous sampling.[36] With a sample size of 7 evaluable participants per each Tasso device, and 6 Tasso-venous paired PK samples collected, there will be sufficient PK data points ($7 \times 6 = 42$ data points from each Tasso device) to meet the scientific community recommendation for having an adequate Tasso-venous phlebotomy PK bridging study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP guidelines that the investigator becomes aware of.

10.1.2. Financial Disclosure

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study. The participant should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each participant is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant is fully informed about their right to access and correct their personal data and to withdraw consent for the processing of their personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the IRB/EC-approved ICD(s) during their participation in the study as required per local regulations.

A copy of the ICD(s) must be provided to the participant. Participants who are rescreened are required to sign a new ICD.

10.1.3.1. Electronic Consent

Participants may be able to experience the informed consent process by electronic means (eConsent). The eConsent process includes an electronic presentation of the informed consent document (eICD), clinical trial educational components (as applicable), and electronic signatures (if allowed by local regulations). The use of eConsent does not replace or alter the ICD content or informed consent process as described above. The eConsent process complies with applicable regulations and sponsor policies to ensure reliability and data privacy.

10.1.4. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The sponsor maintains SOPs on how to respond in the event of unauthorized access, use, or disclosure of sponsor information or systems.

10.1.5. Committees Structure

10.1.5.1. Data Monitoring Committee

This study will not use an E-DMC.

10.1.6. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

Pfizer posts clinical trial results on EudraCT/CTIS for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

Pfizer posts CSR synopses and plain-language study results summaries on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

Pfizer complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

Pfizer provides researchers secure access to participant-level data or full CSRs for the purposes of “bona-fide scientific research” that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirements document.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password-protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source records and documents. This verification may also occur after study completion. It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan maintained and utilized by the sponsor or designee.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

In this study, the CRF will serve as the source document. A document must be available at the investigative site that identifies those data that will be recorded on the CRF and for which the CRF will be the source document.

Definition of what constitutes a source document and its origin can be found in the Source Document Locator, which is maintained by the sponsor's designee (Pfizer CRU).

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor's designee (Pfizer CRU).

The investigator must maintain accurate documentation (source record) that supports the information entered in the CRF.

The sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP guidelines, and all applicable regulatory requirements.

10.1.9. Use of Medical Records

There may be instances when copies of medical records for certain cases are requested by Pfizer Safety, where ethically and scientifically justified and permitted by local regulations, to ensure participant safety.

Due to the potential for a participant to be re-identified from their medical records, the following actions must be taken when medical records are sent to the sponsor or sponsor designee:

- The investigator or site staff must redact personal information from the medical record. The personal information includes, but is not limited to, the following: participant names or initials, participant dates (eg, birth date, date of hospital admission/discharge, date of death), participant identification numbers (eg, Social Security number, health insurance number, medical record number, hospital/institution identifier), participant location information (eg, street address, city, country, postal code, IP address), participant contact information (eg, telephone/fax number, email address).

- Each medical record must be transmitted to the sponsor or sponsor designee using systems with technical and organizational security measures to ensure the protection of personal data (eg, Florence is the preferred system if available).

There may be unplanned situations where the sponsor may request medical records (eg, sharing medical records so that the sponsor can provide study-related advice to the investigator). The medical records should be submitted according to the procedure described above.

10.1.10. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or the ICH GCP guidelines;

- Inadequate recruitment of participants by the investigator;

- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.11. Publication Policy

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, participant to the other requirements described in this section.

The investigator agrees to refer to the primary publication in any subsequent publications. Pfizer will not provide any financial compensation for the investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

The investigator will provide Pfizer an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to Pfizer 30 days before submission. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from Pfizer. This allows Pfizer to protect proprietary information and to provide comments, and the investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-intervention or Pfizer-related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and Pfizer will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The investigator will disclose any relationship with Pfizer and any relevant potential conflicts of interest, including any financial or personal relationship with Pfizer, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

10.1.12. Sponsor's Medically Qualified Individual

The contact information for the sponsor's MQI for the study is documented in the study contact list located in the CTMS.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from non-study healthcare professionals, participants are provided with an ECC at the time of informed consent. The ECC contains, at a minimum, (a) protocol and study intervention identifiers, (b) participant's study identification number, and (c) site emergency phone number active 24 hours/day, 7 days per week.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their investigator and site staff, and between the investigator and sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the investigator or site staff related to the care of a participant.

10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the SoA section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Table 4. Protocol-Required Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN Creatinine Cystatin C[a] eGFR, eCrCl[b] Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein For suspected DICI/DIKI: Creatinine (Screat) Cystatin C[a] (Scys) eGFR (Screat only and combined Screat+Scys) eCrCl[b] Urine albumin-to-creatinine-ratio (UACR)	Local dipstick: pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Laboratory: Microscopy and culture[c]	Pregnancy test (β-hCG) Urine drug screening[d] Urine cotinine At screening: • FSH[e] • HBcAb • HBsAb[f] • HBsAg • HCVAb • HIV

a. Cystatin C (Scys): Screening or Baseline Scys is recommended to help differentiate post-baseline DIKI from DICI. Post-baseline, Scys is measured if and only if serum creatinine increase post-baseline is observed (see Section 7.1.1).
b. Screening and Baseline eGFR or eCrCl is measured with Screat-based formula. Age-specific kidney function calculation (see Section 10.7.2) is recommended to assess presence or absence of post-baseline change in kidney function.
c. Only if UTI is suspected and urine dipstick is positive for nitrites or leukocyte esterase or both.
d. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site- and study-specific).
e. For confirmation of postmenopausal status only in females <60 years old and not using hormonal or HRT only.
f. This is a reflex test. HBsAb to be run if HBsAg and/or HBcAb are positive.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition

• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal test results that meet any of the conditions below must be recorded as an AE:
 	
  • Is associated with accompanying symptoms;
 	
  • Requires additional diagnostic testing or medical/surgical intervention;
 	
  • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy.
 	
• Exacerbation of a chronic or intermittent preexisting condition, including an increase in either frequency and/or intensity of the condition.
 	
• New condition detected or diagnosed after study intervention administration, even though it may have been present before the start of the study.
 	
• Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
 	
• Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE or SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of an SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
a. Results in death
b. Is life-threatening The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed below:
d. Results in persistent or significant disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Is a suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.
g. Other situations: • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. • Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording/Reporting and Follow-Up of AEs and/or SAEs During the Active Collection Period

AE and SAE Recording/Reporting
The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs using the CT SAE Report Form *or* via PSSA to Pfizer Safety throughout the active collection period. These requirements are delineated for 3 types of events:

(1) SAEs; (2) nonserious AEs; and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the CT SAE Report Form or the PSSA for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the CT SAE Report Form or the PSSA for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the** CT SAE Report Form or **PSSA to Pfizer Safety Within 24 Hours of Awareness**
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding	All AEs/SAEs associated with EDP or EDB **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study non-participant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated SAE): is reported to Pfizer Safety using the PSSA.

** **EDB** is reported to Pfizer Safety using the PSSA, which would also include details of any SAE that might be associated with the EDB.

*** **Environmental or occupational exposure:** AEs or SAEs associated with occupational exposure are reported to Pfizer Safety using the PSSA.

- When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.

- The investigator will then record all relevant AE or SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the CT SAE Report Form/AE or SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. Refer to Section 10.1.9 for actions that must be taken when medical records are sent to the sponsor or sponsor designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE or SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual ADL.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort, but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual ADL, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship.

Assessment of Causality

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in their assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that they have reviewed the AE or SAE and have provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor**.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as "related to study intervention" for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and PSSA and in accordance with the SAE reporting requirements.

Follow-Up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor, to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or

Follow-Up of AEs and SAEs
investigations, histopathological examinations, or consultation with other healthcare providers. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings, including histopathology. • New or updated information will be recorded in the originally submitted documents. • The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via an Electronic DCT
• The primary mechanism for reporting an SAE to Pfizer Safety will be the electronic DCT (eg, eSAE or PSSA). • If the electronic system is unavailable, then the site will use the paper SAE report form (see next section) to report the event within 24 hours. • The site will enter the SAE data into the electronic DCT (eg, eSAE or PSSA) or paper form (as applicable) as soon as the data become available. • After the study is completed at a given site, the electronic DCT will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic DCT has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to Pfizer Safety by telephone.

SAE Reporting to Pfizer Safety via the CT SAE Report Form
• Facsimile transmission of the CT SAE Report Form is one of the methods to transmit this information to Pfizer Safety. • Facsimile transmission of the CT SAE Report Form is the back-up method to transmit this information to Pfizer Safety in case PSSA is unavailable for more than 24 hours.

SAE Reporting to Pfizer Safety via the CT SAE Report Form
• In circumstances when the facsimile is not working, an alternative method should be used, eg, secured (Transport Layer Security) or password-protected email. If none of these methods can be used, notification by telephone is acceptable with a copy of the CT SAE Report Form sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the investigator to complete and sign the CT SAE Report Form pages within the designated reporting time frames.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention plus an additional 28 days (a spermatogenesis cycle):

- Refrain from donating sperm.

PLUS either**:**

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.

- The male participant should be advised of the benefit for a WOCBP partner using a highly effective method of contraception with a failure rate of <1% per year, as described in Section 10.4.4.

10.4.2. Female Participant Reproductive Inclusion Criteria

The criteria below are part of Inclusion Criterion 1 (Age and Sex; Section 5.1) and specify the reproductive requirements for including female participants. Refer to Section 10.4.4 for a complete list of contraceptive methods permitted in the study.

- A female participant is eligible to participate if she is not pregnant or breastfeeding and at least 1 of the following conditions applies:

- Is not a WOCBP (see definition in Section 10.4.3).

  OR

- Is a WOCBP and agrees to use a highly effective contraceptive method (failure rate of <1% per year) during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate any reproductive safety risk of the study intervention. If a highly effective, user-dependent method is chosen, she agrees to concurrently use an effective barrier method of contraception. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea or oligomenorrhea) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenopausal female with 1 of the following:

    - Documented hysterectomy;
    - Documented bilateral salpingectomy;
    - Documented bilateral oophorectomy.

    For individuals with permanent infertility due to a medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

    Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

2. Postmenopausal female.

    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:
        - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.
        - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

The following contraceptive methods are appropriate for this study:

Highly Effective Methods That Have Low User Dependency

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
    - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.

Highly Effective Methods That Are User Dependent

6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
    - Oral + barrier*
    - Intravaginal + barrier*
    - Transdermal + barrier*
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral + barrier*
    - Injectable + barrier*

Sexual Abstinence

8. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated

in relation to the duration of the study and the preferred and usual lifestyle of the participant

* Acceptable barrier methods to be used concomitantly with options 6 or 7 for the study include any of the following:

- Male or female condom, with or without spermicide;
- Cervical cap, diaphragm or sponge with spermicide;
- A combination of male condom with either cervical cap, diaphragm or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Therefore, where local regulations and IRBs/ECs allow, a blood sample will be collected for DNA analysis.

- The scope of the genetic research may be narrow (eg, 1 or more candidate genes) or broad (eg, the entire genome), as appropriate to the scientific question under investigation.

- The samples may be analyzed as part of a multistudy assessment of genetic factors involved in the response to zavegepant or study interventions of this class to understand treatments for the disease(s) under study or the disease(s) themselves.

- The results of genetic analyses may be reported in the CSR or in a separate study summary, or may be used for internal decision making without being included in a study report.

- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

- The samples will be retained as indicated:

- Retained samples will be stored indefinitely or for another period as per local requirements.

- Participants may withdraw their consent for the storage and/or use of their Retained Research Samples at any time by making a request to the investigator; in this case, any remaining material will be destroyed. Data already generated from the samples will be retained to protect the integrity of existing analyses.

- Samples for genetic research will be labeled with a code. The key between the code and the participant's personally identifying information (eg, name, address) will be held securely at the study site.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-Up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × ULN should be monitored more frequently to determine if they are "adaptors" or are "susceptible."

In the majority of DILI cases, elevations in AST and/or ALT precede T bili elevations (>2 × ULN) by several days or weeks. The increase in T bili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and T bili values will be elevated within the same laboratory sample). In rare instances, by the time T bili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to T bili that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and T bili baseline values within the normal range who subsequently present with AST OR ALT values ≥3 × ULN AND a T bili value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available.

- For participants with baseline AST **OR** ALT **OR** T bili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values AND ≥3 × ULN; or ≥8 × ULN (whichever is smaller).

    - Preexisting values of T bili above the normal range: T bili level increased from baseline value by an amount of ≥1 × ULN **or** if the value reaches ≥3 × ULN (whichever is smaller).

Rises in AST/ALT and T bili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and T bili for suspected Hy's law cases, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, eosinophils (%), and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, total bile acids, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and T bili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

10.7. Appendix 7: Kidney Safety: Monitoring Guidelines

10.7.1. Laboratory Assessment of Change in Kidney Function and Detection of Kidney Injury

Standard kidney safety monitoring requires assessment of baseline and postbaseline Screat measurement to estimate kidney function [Screat-based eGFR] or creatinine clearance [eCrCl]). Obtaining Screening or Baseline Scys and postbaseline reflex Scys (if confirmed Screat increase ≥0.3 mg/dL) makes it feasible to distinguish AKI from DICI. If Screat increase is confirmed after baseline, then reflex measurement of Scys is indicated.

ADULTS: Currently, 2021 CKD-EPI eGFR equations (Screat only-based and combined Screat plus Scys-based) are valid for use in adults only. At baseline Screat and Scys values are needed to calculate 2021 CKD-EPI eGFR by Screat only-based equation (see Table 10.7.2.1.) and by combined Screat plus Scys-based equation. When post-baseline Screat increase ≥0.3 mg/dL is confirmed, then reflex Scys measurement is needed to enable post-baseline comparison of eGFR changes (Screat only-based eGFR and combined Screat plus Scys eGFR).

10.7.2. Age-Specific Kidney Function Calculation Recommendations

10.7.2.1. Adults (18 Years and Above)—2021 CKD-EPI Equations

eGFR (mL/min/1.73m²)[39]

2021 CKD-EPI Screat Only	**Screat** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ⩽ 0.7	NA	$eGFR = 143 \times (Screat/0.7)^{-0.241} \times (0.9938)^{Age}$
Female	if > 0.7	NA	$eGFR = 143 \times (Screat/0.7)^{-1.200} \times (0.9938)^{Age}$
Male	if ⩽ 0.9	NA	$eGFR = 142 \times (Screat/0.9)^{-0.302} \times (0.9938)^{Age}$
Male	if > 0.9	NA	$eGFR = 142 \times (Screat/0.9)^{-1.200} \times (0.9938)^{Age}$
2021 CKD-EPI Screat-Scys Combined	**Screat** *(mg/dL)*	**Scys** *(mg/L)*	**Recommended eGFR Equation**
Female	if ⩽ 0.7	if ⩽ 0.8	$eGFR = 130 \times (Screat/0.7)^{-0.219} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if ⩽ 0.7	if > 0.8	$eGFR = 130 \times (Screat/0.7)^{-0.219} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Female	if > 0.7	if ⩽ 0.8	$eGFR = 130 \times (Screat/0.7)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Female	if > 0.7	if > 0.8	$eGFR = 130 \times (Screat/0.7)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if ⩽ 0.9	if ⩽ 0.8	$eGFR = 135 \times (Screat/0.9)^{-0.144} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if ⩽ 0.9	if > 0.8	$eGFR = 135 \times (Screat/0.9)^{-0.144} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$
Male	if > 0.9	if ⩽ 0.8	$eGFR = 135 \times (Screat/0.9)^{-0.544} \times (Scys/0.8)^{-0.323} \times (0.9961)^{Age}$
Male	if > 0.9	if > 0.8	$eGFR = 135 \times (Screat/0.9)^{-0.544} \times (Scys/0.8)^{-0.778} \times (0.9961)^{Age}$

10.7.3. Kidney Function Calculation Tools

The sponsor has provided the following resources to investigational sites when required to calculate age-specific kidney function at Screening, Baseline, and post-Baseline visits. Site calculations of kidney function can be performed manually, using the age appropriate formulae (see Section 10.7.2) and can use recommended online kidney function calculators to reduce the likelihood of a calculation error.

The United States National Kidney Foundation Online Calculators.

- Adults (18 years and above) - 2021 CKD-EPI Creatinine Online Calculator (eGFR): https://www.kidney.org/professionals/KDOQI/gfr_calculator

Investigational sites are responsible to ensure that the accurate age-specific equation is selected and that the correct units for serum creatinine (mg/dL only), serum cystatin C (mg/L only), total body weight (kg only), and age (years). Investigators are expected to (i) review and confirm correctness of the kidney function calculation results and (ii) evaluate the calculated value within the context of historical information available to them in the participant's medical record. Investigators are responsible for the clinical oversight of the participant eligibility process, kidney function calculation, and dose selection and adjustments per study protocol. Investigators are encouraged to direct questions or uncertainties regarding kidney function and dosing to the Pfizer Clinical Team and Medical Monitor, if needed.

10.7.4. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to Kidney disease: Improving Global Outcomes (KDIGO) criteria.

NON-ONCOLOGY Studies					
KDIGO criteria	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Decreased Kidney Function due to either Acute or Chronic Kidney Injury	eGFR ≥90 mL/min/1.73m² OR eCrCl ≥90 mL/min	eGFR ≥60 to 89 mL/min/1.73m² OR eCrCl ≥60 to 89 mL/min	eGFR 30 to 59 mL/min/1.73m² OR eCrCl 30 to 59 mL/min	eGFR 15 to 29 mL/min/1.73m² OR eCrCl 15 to 29 mL/min	eGFR <15 mL/min/1.73m² OR eCrCl <15 mL/min OR dialysis indicated
Albuminuria	Albuminuria <30 mg/g OR <3 mg/mmol	Albuminuria 30 to 300 mg/g OR 3 to 30 mg/mmol	Albuminuria >300 mg/gm OR <3 mg/mmol		

10.8. Appendix 8: ECG Findings of Potential Clinical Concern

ECG Findings That <u>May</u> Qualify as AEs
• Marked sinus bradycardia (rate <40 bpm) lasting minutes. • New PR interval prolongation >280 ms. • New prolongation of QTcF to >480 ms (absolute). • New prolongation of QTcF by >60 ms from baseline. • New-onset atrial flutter or fibrillation, with controlled ventricular response rate: ie, rate <120 bpm. • New-onset type I second-degree (Wenckebach) AV block of >30-second duration. • Frequent PVCs, triplets, or short intervals (<30 seconds) of consecutive ventricular complexes.
ECG Findings That <u>May</u> Qualify as SAEs

• QTcF prolongation >500 ms.
• Absolute value of QTcF > 450 ms AND QTcF change from baseline >60 ms.
• New ST-T changes suggestive of myocardial ischemia.
• New-onset LBBB (QRS complex>120 ms).
• New-onset right bundle branch block (QRS complex>120 ms).
• Symptomatic bradycardia.
• Asystole
  • In awake, symptom-free participants in sinus rhythm, with documented asystolic pauses ≥3 seconds or any escape rate <40 bpm, or with an escape rhythm that is below the AV node;
  • In awake, symptom-free participants with atrial fibrillation and bradycardia with 1 or more asystolic pauses of at least 5 seconds or longer.
• Atrial flutter or fibrillation, with rapid ventricular response rate: rapid = rate >120 bpm.

- Sustained supraventricular tachycardia (rate >120 bpm) ("sustained" = short duration with relevant symptoms or lasting >1 minute).
- Ventricular rhythms >30 seconds' duration, including idioventricular rhythm (HR <40 bpm), accelerated idioventricular rhythm (HR >40 bpm to <100 bpm), and monomorphic/polymorphic ventricular tachycardia (HR >100 bpm [such as torsades de pointes]).
- Type II second-degree (Mobitz II) AV block.
- Complete (third-degree) heart block.

ECG Findings That Qualify as SAEs

- Change in pattern suggestive of new myocardial infarction.
- Sustained ventricular tachyarrhythmias (>30-seconds duration).
- Second- or third-degree AV block requiring pacemaker placement.
- Asystolic pauses requiring pacemaker placement.
- Atrial flutter or fibrillation with rapid ventricular response requiring cardioversion.
- Ventricular fibrillation/flutter.
- At the discretion of the investigator, any arrhythmia classified as an adverse experience.

The major events of potential clinical concern listed above are recommended as "alerts" or notifications from the core ECG laboratory to the investigator and Pfizer study team, and not to be considered as all-inclusive of what is reported as AEs/SAEs.

10.9. Appendix 9: AEs, ADEs, SAEs, SADEs, USADEs, and Device Deficiencies: Definitions and Procedures for Recording, Evaluating, FollowUp, and Reporting in Medical Device Studies

Definitions of a Medical Device Deficiency

The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and the European MDR 2017/745 for clinical device research (if applicable).

Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study (see Section 6) for the list of sponsor medical devices).

10.9.1. Definition of AE and ADE

AE and ADE Definition
• An AE is defined in Appendix 3 (Section 10.3.1). • An ADE is defined as an AE related to the use of an investigational medical device. This definition includes any AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.9.2. Definition of SAE, SADE, and USADE

SAE Definition
• An SAE is defined in Appendix 3 (Section 10.3.2).
SADE Definition
• An SADE is defined as an ADE that has resulted in any of the consequences characteristic of an SAE. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
USADE Definition

- A USADE (also identified as UADE in US Regulations 21 CFR 813.3) is a SADE that by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis management file.

10.9.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and inadequate information supplied by the manufacturer.

10.9.4. Recording/Reporting and Follow-Up of Medical Device Deficiencies

Device Deficiency Recording
• When a device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostic reports) related to the event. • The investigator will then record all relevant device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice. • If an AE (either serious or nonserious) associated with the device deficiency occurs, then the AE must be entered into the AE section of the CRF. • The investigator will notify the sponsor study team by email within 1 business day of determining that the incident meets the protocol definition of a medical device deficiency. • The sponsor study team will capture the required information on the Medical Device Complaint form along with any associated AE (either serious or nonserious) when applicable and send to the appropriate product quality complaint group. • If the investigator determines that the medical device deficiency may have injured the participant (ie, the medical device deficiency is associated with an AE or SAE), then the investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis will be documented in the participant's medical record and recorded as the AE or SAE rather than the individual signs/symptoms. All relevant details

Device Deficiency Recording

related to the role of the device in regard to the SAE must be included in via PSSA as outlined in Sections 8.4.1.1 and 8.4.1.2.

- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety. Refer to Section 10.1.9 for actions that must be taken when medical records are sent to the sponsor or sponsor designee.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the incident.
- A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency

- If an AE or SAE has occurred in conjunction with a medical device deficiency, the investigator must assess the relationship between each occurrence of the AE or SAE and the medical device deficiency. The investigator will use clinical judgment to determine the relationship.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in their assessment.
- For each device deficiency, the investigator **must** document in the medical notes that they have reviewed the device deficiency and have provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.

Assessment of Causality Occurring in Conjunction With a Medical Device Deficiency
• The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-Up of Medical Device Deficiency
• Follow-up applies to all participants, including those who discontinue study intervention. • The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers. • New or updated information regarding the nature of the device deficiency will be recorded in the originally completed Medical Device Complaint form by the sponsor study team. • New or updated information regarding any SAE that was potentially associated with the medical device deficiency will be submitted to Pfizer Safety via PSSA within 24 hours of receipt of the information, according to the requirements provided in Appendix 3.

10.10. Appendix 10: Prohibited Concomitant Medications That May Result in DDI

The prohibited concomitant medications listed below should not be taken with study intervention for a period of time at least equal to the required washout period listed in the table and throughout the study.

The Pfizer study team is to be notified of any prohibited medications taken during the study. After consulting with the sponsor, the investigator will make a judgment on the ongoing participation of any participant with prohibited medication use during the study.

This list of drugs prohibited for potential DDI concerns with the IMP may be revised during the course of the study with written notification from the sponsor to include or exclude specific drugs or drug categories for various reasons (e.g., emerging DDI results for the IMP, availability of new information in the literature on the DDI potential of other drugs) if the overall benefit/risk assessment is not impacted or if the changes do not significantly impact the safety of participants or the scientific value of the trial.

This is not an all-inclusive list. Site staff should consult with the sponsor or designee with any questions regarding potential DDI.

Drug Category	Drugs	Required Washout Period Requirement
OATP1B3 inhibitors	atazanavir/ritonavir, clarithromycin, cyclosporine, gemfibrozil, lopinavir/ritonavir, rifampin	14 days or 5 half-lives, whichever is longer

Investigators should consult the SRSD for active comparator for information regarding medication prohibited for concomitant use.

Investigators should consult the product label for any other medication used during the study for information regarding medication prohibited for concomitant use.

10.11. Appendix 11: Taste Assessment Questionnaire

1. Questionnaire should be administered to adult participants, preferably by the trained staff. The clinical staff is trained by the CRU clinical coordinator for performing the taste questionnaire and regarding the specific study restrictions.

2. Use colored copy of the questionnaire.

3. Do not alter (reduce or enlarge) the original size of the questionnaire.

4. Please gather the following background information:

Background Information

Study #/Study Site	
Period and Day	
Participant ID (Rand ID)	
Study Intervention	
Collection Date	
Collection Time	
Name of trained staff	
Questionnaire fully completed	Yes/No

Please answer the following questions and provide a mark (✕) on the color bar at 1 (immediately), 5, 10 and 20 minutes after dosing. Please ensure subject has access to these descriptions when completing the questionnaire.

Q1: Overall liking – Please indicate how much you like or dislike the taste of the drug administered.

Q2: Bitterness – Please tell us about the degree of bitterness after drug administration.

Q3: Tongue/mouth burn – Please tell us about the degree of tongue/mouth burn after drug administration.

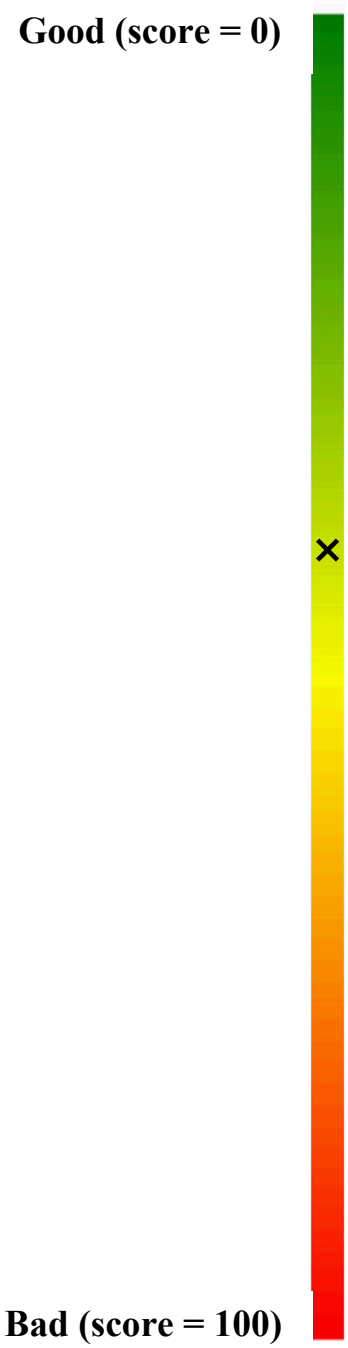
Q4: Throat burn – Please tell us about the degree of throat burn after drug administration.

Q5: Sour taste – Please tell us about the degree of sourness after drug administration.

Q6: Salty taste – Please tell us about the degree of saltiness after drug administration.

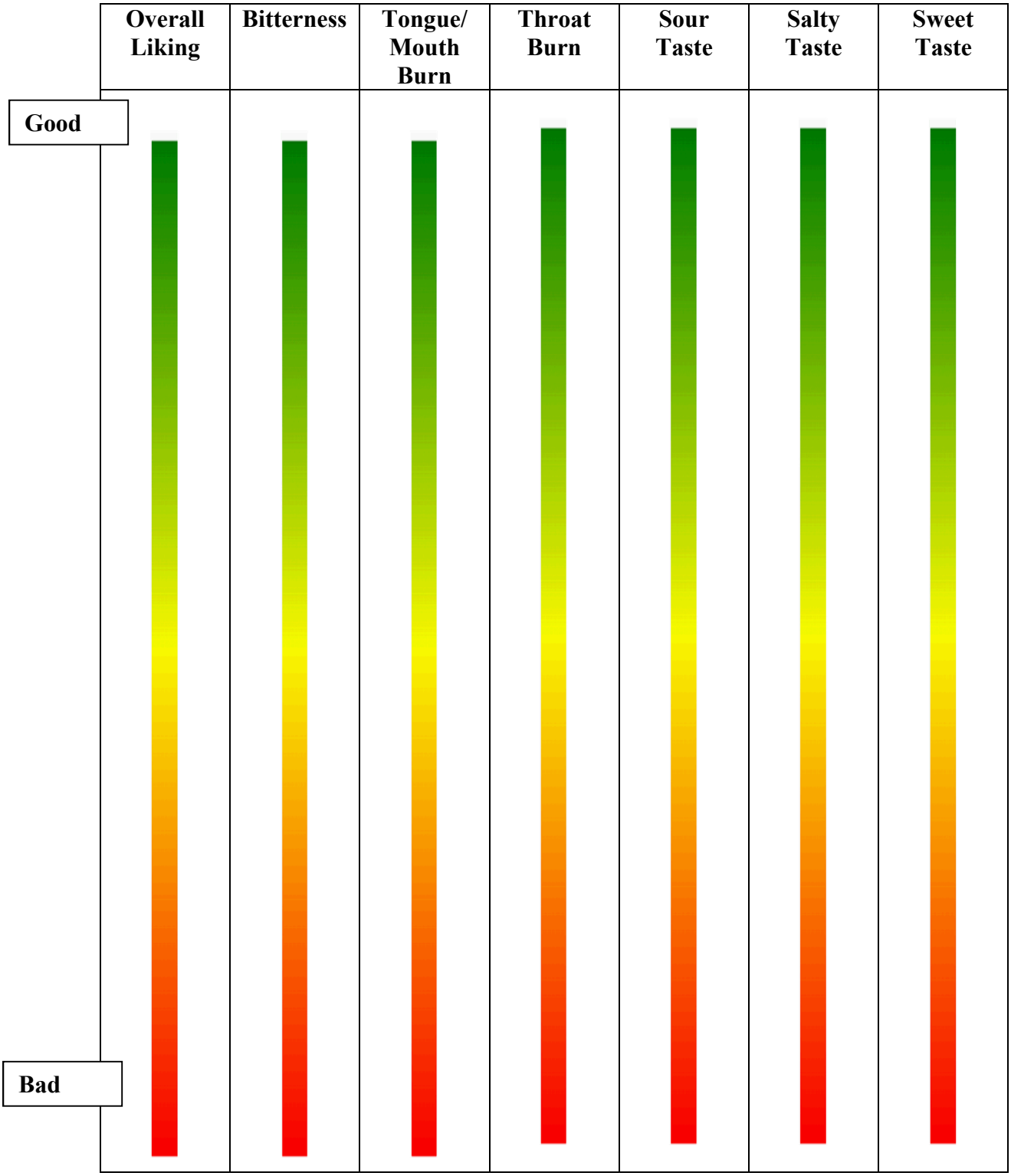
Q7: Sweet taste – Please tell us about the degree of sweetness after drug administration.

Example: How to provide a mark (x) on the color bar



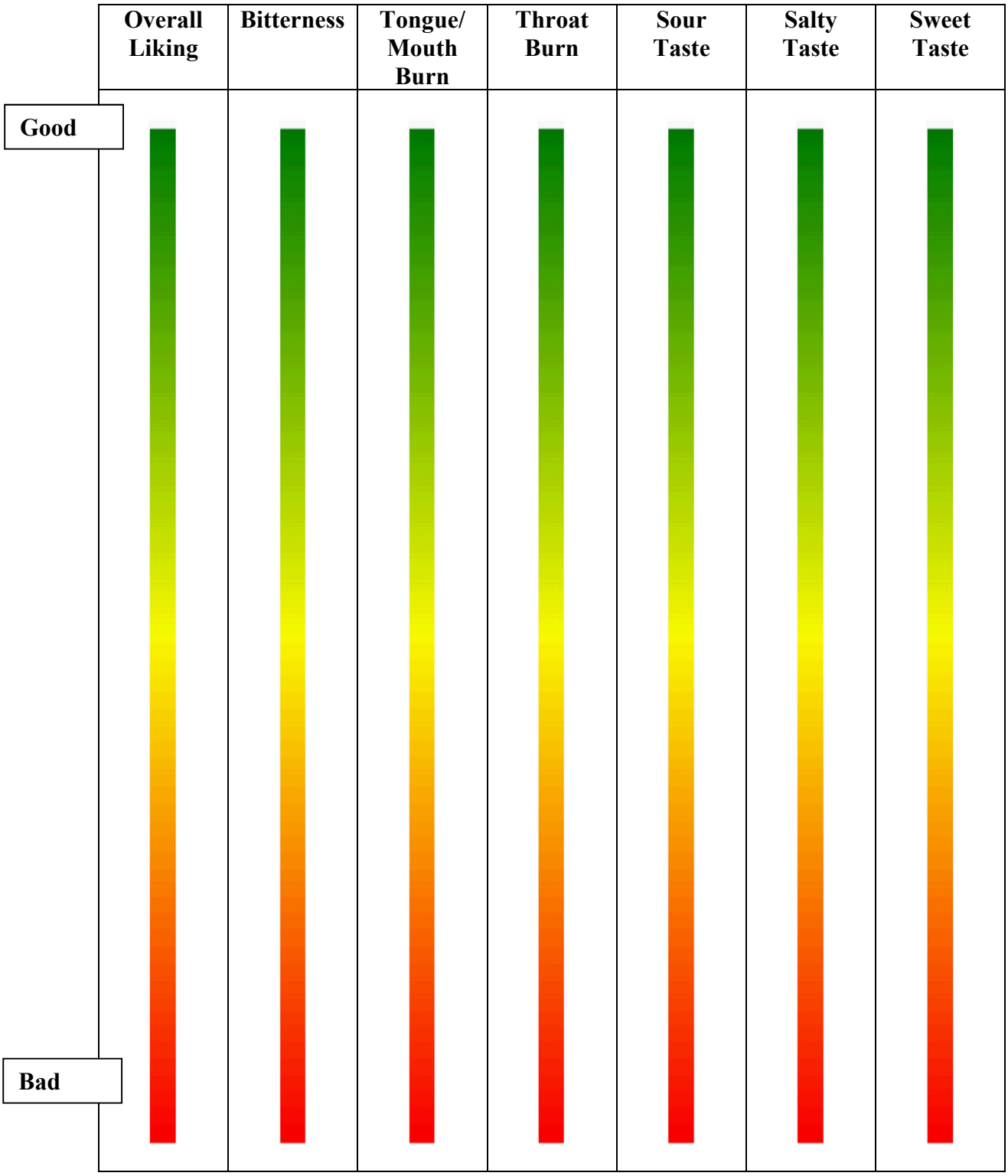
Within 1 minute (immediately) after dosing

Provide a mark (×) <u>on the color bar</u>.



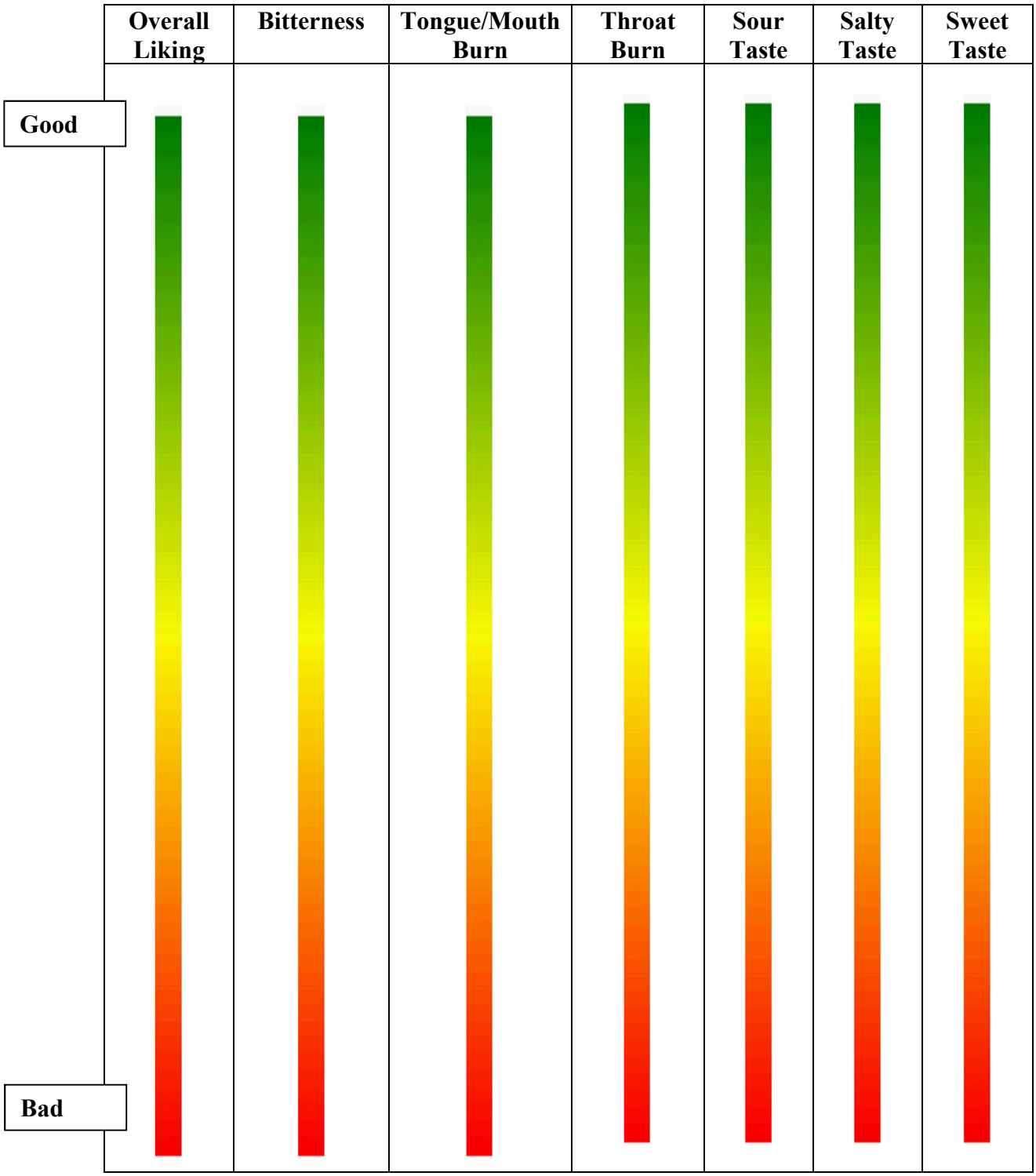
5 minutes after dosing

Provide a mark (×) <u>on the color bar</u>.



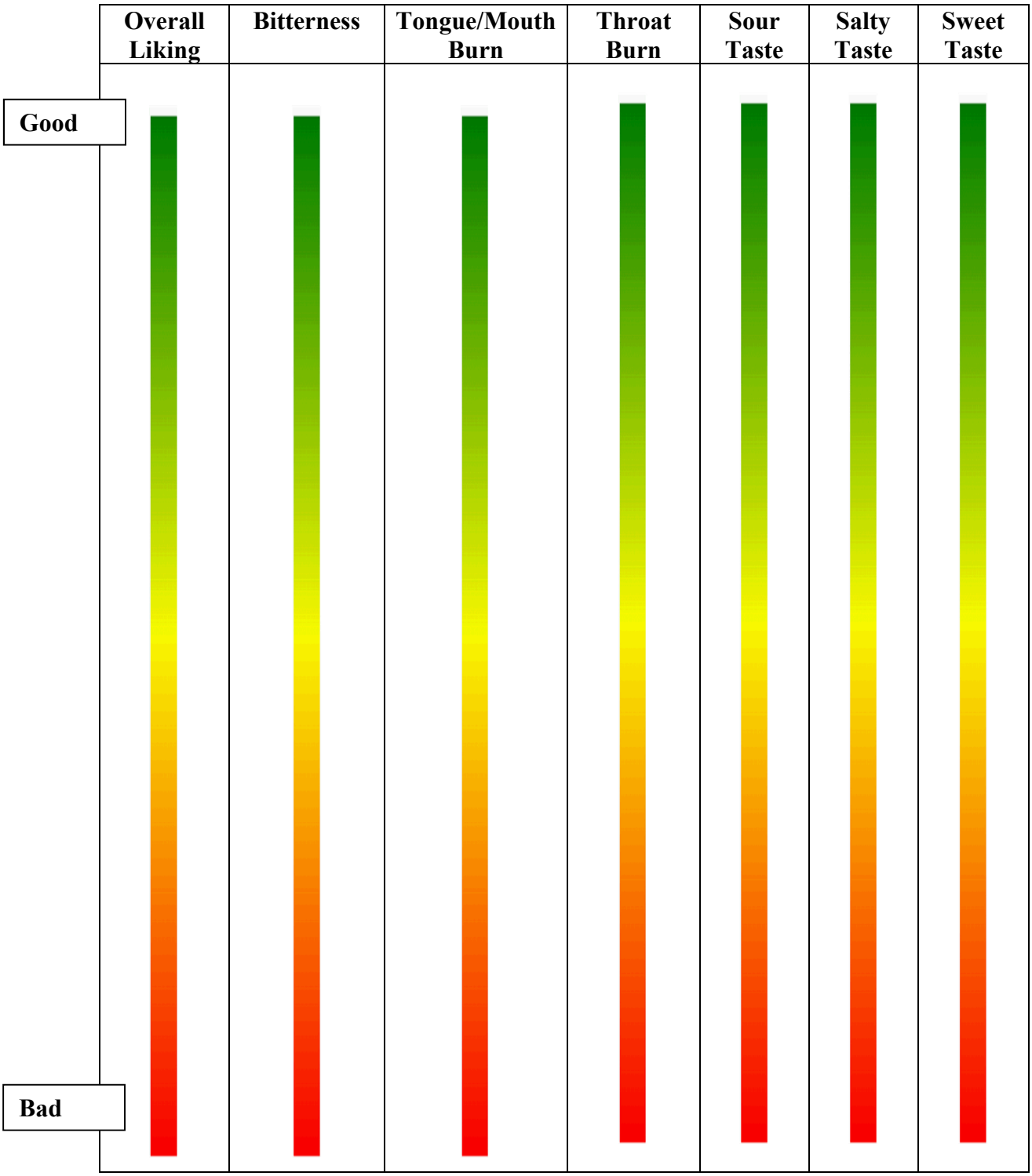
10 minutes after dosing

Provide a mark (×) <u>on the color bar</u>.



20 minutes after dosing

Provide a mark (×) <u>on the color bar.</u>



Additional Feedback – After completing the "20 minute after dosing" taste questions, please provide any additional descriptive feedback in the box below regarding the taste experienced after drug administration.

10.12. Appendix 12: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
A1 to A3	albuminuria (Kidney Disease Improving Global Outcomes [KDIGO] albuminuria severity standardization)
Abs	absolute
ADE	adverse device effect
ADL	activity/activities of daily living
AE	adverse event
AKI	acute kidney injury
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
AUC_{inf}	area under plasma concentration-time profile from time 0 extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time profile from time 0 to the time of last quantifiable concentration (C_{last})
AV	atrioventricular
AxMP	auxiliary medicinal product
β-hCG	β-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
bpm	beats per minute
CFR	Code of Federal Regulations
CGRP	calcitonin gene-related peptide
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
CL/F	apparent clearance
C_{max}	maximum plasma concentration
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
CTIS	Clinical Trial Information System
CTMS	clinical trial management system
CYP	cytochrome P450
DCT	data collection tool
DDI	drug-drug interaction
DICI	drug-induced creatinine increase

Abbreviation	Term
DIKI	drug-induced kidney injury
DILI	drug-induced liver injury
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
EE	ethinyl estradiol
eGFR	estimated glomerular filtration rate
eICD	electronic informed consent document
EOT	end of treatment
eSAE	electronic serious adverse event
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
F/U	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCG	human chorionic gonadotropin
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	informed consent document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IMP	investigational medicinal product
IN	intranasal
IND	Investigational New Drug
INR	international normalized ratio
IP	interventional product
IPAL	Investigational Product Accountability Log
IPM	investigational product manual

Abbreviation	Term
IRB	Institutional Review Board
ISO	International Organization for Standardization
IU/L	international units per liter
IV	intravenous(ly)
KDIGO	Kidney Disease Improving Global Outcomes
k_{el}	elimination constant
LBBB	left bundle branch block
LFT	liver function test
LNG	levonorgestrel
MBS	modified barium swallow
MDR	medical device regulation
MQI	medically qualified individual
NA	not applicable
NIMP	non-investigational medicinal product
NTCP	sodium taurocholate co-transporting polypeptide
OATP	organic anion transporting polypeptide
OTC	over-the-counter
PCRU	Pfizer Clinical Research Unit
PCS	patient-centric sampling
PE	physical examination
P-gp	P-glycoprotein
PI	principal investigator
PK	pharmacokinetic(s)
PO	orally
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction/complex
QD	once daily
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
qual	qualitative
RBC	red blood cell
RNA	ribonucleic acid
SADE	serious adverse device effect
SAE	serious adverse event
SAP	Statistical Analysis Plan
Screat	serum creatinine
Scys	serum cystatin C
SoA	schedule of activities
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	terminal half-life

Abbreviation	Term
T bili	total bilirubin
TEAE(s)	treatment-emergent adverse event(s)
THC	tetrahydrocannabinol
T_{max}	time to C_{max}
UACR	urine albumin-to-creatinine-ratio
UK	United Kingdom
ULN	upper limit of normal
USA	United States of America
USADE	unanticipated serious adverse device effect
US	United States
UTI	urinary tract infection
V_z/F	apparent volume of distribution
WBC	white blood cell
WOCBP	woman/women of childbearing potential

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