Title Page

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ZAVEGEPANT INTRANASAL (IN) FOR THE ACUTE TREATMENT OF MIGRAINE IN ASIAN ADULTS

Study Intervention Number:	PF-07930207
Study Intervention Name:	Zavegepant
US IND Number:	134120
EudraCT Number:	NA
ClinicalTrials.gov ID:	Not Available
Pediatric Investigational Plan Number:	NA
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Brief Title:

A Phase 3 Study to Evaluate the Efficacy and Safety of Zavegepant for the Acute Treatment of Migraine in Asian Adults

Document History

Document	Version Date
Original protocol	22 February 2023

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Zavegepant Intranasal (IN) for the Acute Treatment of Migraine in Asian Adults

Brief Title: A Phase 3 Study to Evaluate the Efficacy and Safety of Zavegepant for the Acute Treatment of Migraine in Asian Adults

Regulatory Agency Identification Number(s):

US IND Number:	134120
EudraCT Number:	NA
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Rationale:

Zavegepant is being developed for the acute treatment of migraine via the intranasal route. The purpose of the study is to evaluate the efficacy and safety of zavegepant 10 mg versus placebo in the acute treatment of migraine (with or without aura) in Asian adults by measuring freedom from pain and freedom from MBS (selected from nausea, photophobia or phonophobia just prior to treatment of the migraine) at 2 hours postdose. Information regarding time to onset of action, sustainability of pain freedom, and freedom from functional disability will also be obtained.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To compare the efficacy of zavegepant with placebo in the acute treatment of migraine.	The following co-primary endpoints will be tested: • Percentage of participants with a pain intensity of none (pain freedom) at 2 hours postdose.	Co-primary estimands: • The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none at 2 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 2 hours postdose will be regarded as a failure.
	• Percentage of participants with an MBS reported before dosing that is absent at 2 hours postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with an MBS reported before dosing that is absent at 2 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 2 hours postdose will be regarded as a failure.
Secondary:	**Secondary:**	**Secondary:**
Key Secondary Objectives:	**Key Secondary Endpoints:**	**Key Secondary Estimands:**
• To compare zavegepant with placebo for measures of early pain relief.	• Percentage of participants with a pain intensity of none or mild at 15 minutes postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none or mild at 15 minutes postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 15 minutes postdose will be regarded as a failure.
	• Percentage of participants with a pain intensity of none or mild at 30 minutes postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none or mild at 30 minutes postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 30 minutes postdose will be regarded as a failure.
	• Percentage of participants with a pain intensity of none or mild at 2 hours postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none or mild at 2 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 2 hours postdose will be regarded as a failure.

Objectives	Endpoints	Estimands
• To compare zavegepant with placebo for return to normal function.	• Percentage of participants with a functional disability level of normal at 2 hours postdose, evaluated for participants with functional disability at the time of dosing.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a functional disability level of normal at 2 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention and had functional disability at the time of dosing. Intercurrent event of taking rescue medication at or before 2 hours postdose will be regarded as a failure.
• To compare zavegepant with placebo for measures of sustained pain relief.	• Percentage of participants with a pain intensity of none or mild at all time points from 2 to 24 hours postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none or mild at all time points from 2 to 24 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 24 hours postdose will be regarded as a failure.
	• Percentage of participants with a pain intensity of none or mild at all time points from 2 to 48 hours postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none or mild at all time points from 2 to 48 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 48 hours postdose will be regarded as a failure.
• To compare zavegepant with placebo for measures of early return to normal function.	• Percentage of participants with a functional disability level of normal at 30 minutes postdose, evaluated for participants with functional disability at the time of dosing.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a functional disability level of normal at 30 minutes postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention and had functional disability at the time of dosing. Intercurrent event of taking rescue medication at or before 30 minutes postdose will be regarded as a failure.
	• Percentage of participants with a functional disability level of normal at 60 minutes postdose, evaluated for participants with functional disability at the time of dosing.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a functional disability level of normal at 60 minutes postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention and had functional disability at the time of dosing. Intercurrent event of taking rescue medication at or before 60 minutes postdose will be regarded as a failure.
Other Secondary Objectives:	**Other Secondary Endpoints:**	**Other Secondary Estimands:**
• To compare zavegepant with placebo for freedom from individual non-headache associated symptoms of migraine.	• Percentage of participants with **phonophobia** absent at 2 hours postdose, evaluated for participants with phonophobia present at the time of dosing.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with phonophobia absent at 2 hours postdose among all randomized participants with migraine headache of moderate or

Objectives	Endpoints	Estimands
		severe intensity who took study intervention and had phonophobia at the time of dosing. Intercurrent event of taking rescue medication at or before 2 hours postdose will be regarded as a failure.
	• Percentage of participants with **photophobia** absent at 2 hours postdose, evaluated for participants with photophobia present at the time of dosing.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with photophobia absent at 2 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention and had photophobia at the time of dosing. Intercurrent event of taking rescue medication at or before 2 hours postdose will be regarded as a failure.
	• Percentage of participants with **nausea** absent at 2 hours postdose, evaluated for participants with nausea present at the time of dosing.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with nausea absent at 2 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention and had nausea at the time of dosing. Intercurrent event of taking rescue medication at or before 2 hours postdose will be regarded as a failure.
• To compare zavegepant with placebo for additional measures of sustained efficacy.	• Percentage of participants with a pain intensity of none at all time points from 2 to 24 hours postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none at all time points from 2 to 24 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 24 hours postdose will be regarded as a failure.
	• Percentage of participants with a pain intensity of none at all time points from 2 to 48 hours postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none at all time points from 2 to 48 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 48 hours postdose will be regarded as a failure.
	• Percentage of participants with pain relapse (any pain intensity above 'none') at any time point after 2 hours postdose, evaluated for participants with pain freedom at 2 hours postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of mild, moderate, or severe at any time point after 2 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention and had pain freedom at 2 hours postdose. Intercurrent event of taking rescue medication at or before 48 hours postdose will be regarded as a failure.
• To compare zavegepant with placebo for rescue medication use.	• Percentage of participants taking rescue medication within 24 hours postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants taking rescue medication within 24 hours postdose among all randomized participants with migraine headache of moderate or

Objectives	Endpoints	Estimands
		severe intensity who took study intervention. No relevant intercurrent event is considered since taking rescue medication is the analysis objective.
• To further compare zavegepant with placebo for early pain relief.	• Percentage of participants with a pain intensity of none or mild at 60 minutes postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none or mild at 60 minutes postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 60 minutes postdose will be regarded as a failure.
• To further compare zavegepant with placebo for early return to normal function.	• Percentage of participants with a functional disability level of normal at 15 minutes postdose, evaluated for participants with functional disability at the time of dosing.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a functional disability level of normal at 15 minutes postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention and had functional disability at the time of dosing. Intercurrent event of taking rescue medication at or before 15 minutes postdose will be regarded as a failure.
• To evaluate the safety and tolerability of zavegepant in the acute treatment of migraine.	• Number and percentage of participants with AEs of moderate or severe intensity, SAEs, local irritation AEs, and grade 3 or 4 laboratory test abnormalities.	• Not applicable.

Overall Design:

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter, single-attack, outpatient evaluation of the efficacy and safety of zavegepant versus placebo for the acute treatment of migraine in Asian adults.

The total duration of study participation will be up to approximately 16 weeks. This includes a 3-28 day Screening Phase, a Treatment Phase that can last up to 45 days or until the participant has a migraine headache that reaches moderate or severe pain intensity, followed by an EOT Visit 7 (+2) days after the administration of study intervention, and a Follow-Up Visit 28-35 days after the administration of study intervention for safety monitoring. The study intervention will be zavegepant 10 mg or matching placebo. The study will randomize approximately 1400 participants in a 1:1 ratio between the 2 treatment groups (zavegepant or placebo). Randomization will be stratified by the use of stable prophylactic migraine medications through randomization (yes or no) and country/region.

After randomization, the participants will be dispensed a single dose of double-blind study intervention. The participants will be instructed to take study intervention as an outpatient, if they have a migraine headache of moderate or severe pain intensity, and only after they have reported their pre-dosing migraine characteristics in the eCOA handheld device. After

participants confirm taking study intervention in the eCOA handheld device, they will report the following efficacy data in the eCOA handheld device at 15, 30, 45, 60 and 90 minutes postdose, and 2, 3, 4, 6, 8, 24 and 48 hours postdose: headache pain intensity using a 4-point numeric rating scale (none, mild, moderate, severe); the status (present or absent) and intensity (mild, moderate, or severe) of migraine associated symptoms (nausea, photophobia, phonophobia), and their current MBS before taking study intervention; functional disability level using a 4-point numeric rating scale (normal, mildly impaired, severely impaired, requires bedrest). Participants will also complete the PGIC ratings at 30 minutes, 60 minutes, 2 hours and 24 hours postdose in the eCOA handheld device.

The participants will return to the study site for the EOT Visit within 7 (+2) days of taking study intervention for review of the eCOA handheld device, assessment of study intervention compliance, and monitoring of safety and tolerability as indicated in the SoA. Every effort should be made to conduct the EOT Visit within the specified window of 7 (+2) days after the administration of study intervention. If a participant has NOT treated a migraine attack with study intervention within 45 days after randomization, they are still required to complete all EOT Visit procedures. All participants must return used and unused study intervention and eCOA handheld device to the study center.

A Follow-Up Visit will occur 28-35 days after treatment for safety follow-up of AEs and/or abnormal laboratory tests. Participants may be contacted via telephone. Every effort should be made to conduct the Follow-Up Visit within 28-35 days after treatment. If a participant has NOT treated a migraine attack with study intervention within 45 days after randomization, they are not required to complete the Follow-Up Visit.

Number of Participants:

Approximately 1400 participants will be randomized to the zavegepant or placebo treatment group in a 1:1 ratio (approximately 700 per group).

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. Asian (based on country of participation and ethnicity status) participants aged 18 years or older at screening.

2. Participants with minimum 1 year history of migraine (with or without aura) prior to the Screening Visit, consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd Edition, including the following:

    - Migraine attacks present for more than 1 year with the age of onset prior to 50 years of age.

- Migraine attacks, on average, lasting about 4 - 72 hours if untreated.
- Not more than 8 attacks of moderate or severe pain intensity per month within last 3 months.
- Participants must be able to distinguish migraine attacks from tension/cluster headaches.
- At least 2 consistent migraine headache attacks of moderate or severe intensity in each of the 3 months prior to the Screening Visit and throughout the Screening Phase (participant self-report).
- Less than 15 days with headaches (migraine or non-migraine) per month in each of the 3 months prior to the Screening Visit and throughout the Screening Phase (participant self-report).
- Participants on prophylactic migraine medication are permitted to remain on therapy if they have been on a stable dose for at least 3 months prior to Screening Visit, and if the dose is not expected to change through the EOT Visit.
- Participants with contraindications for use of triptans may be included provided they meet all other study entry criteria.

Exclusion Criteria

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

1. History of retinal migraine, basilar migraine or hemiplegic migraine.
2. History or current evidence of uncontrolled, unstable or recently diagnosed cardiovascular or cardiometabolic disease including:
    - Diagnosis of ischemic heart disease, coronary artery vasospasm, and cerebral ischemia during the 6 months prior to Screening Visit.
    - Events of MI, ACS, PCI, cardiac surgery, stroke or TIA during the 6 months prior to Screening Visit.
    - ECG findings at the Screening Visit including:
        - QTcF interval >470 msec.
        - Left Bundle Branch Block.
        - Right Bundle Branch Block with a QRS duration ≥150 msec.
        - Intraventricular Conduction Defect with a QRS duration ≥150 msec.

- Uncontrolled hypertension (high blood pressure); a single blood pressure measurement of greater than 150 mmHg systolic or 100 mmHg diastolic after 10 minutes of rest at the Screening Visit is exclusionary.

- Uncontrolled diabetes, defined as HbA1c ≥7.5% at the Screening Visit.

3. Major depressive disorder, anxiety disorder, or other significant psychiatric disorder including:

   - Major depressive episode within the last 12 months, major depressive disorder or any anxiety disorder requiring more than 1 medication for each disorder. Medications to treat major depressive disorder or an anxiety disorder must have been at a stable dose for at least 3 months prior to the Screening Visit provided the medication is not otherwise prohibited.

   - Current diagnosis of major depressive disorder requiring treatment with atypical antipsychotics.

   - Schizophrenia, bipolar disorder, or borderline personality disorder.

   - Response of "yes" to Question 4 or 5 for suicidal ideation, **or** on any suicidal behavioral question on the C-SSRS for the period of 1 year prior to Screening Visit and during the study, **or** participants present a serious risk of suicide in the opinion of the investigator.

4. Acute or chronic pain syndromes (such as fibromyalgia, chronic pelvic pain, CRPS). Other pain syndromes (including trigeminal neuralgia), psychiatric conditions, dementia, or significant neurological disorders (other than migraine) that, in the investigator's opinion, interfere with study assessments.

5. Conditions that may affect the administration or absorption of the nasal product:

   - History of nasal surgery in the 6 months preceding the Screening Visit.

   - Evidence at Screening Visit of significant nasal conditions (eg, severe septum deviation, nasal deformity or blockage, inflammation, perforation, mucosal erosion or ulceration, polyposis, nasal trauma) as evaluated by the investigator or medically qualified delegate.

   - Presence of piercings in the nose that, in the opinion of the investigator, would be likely to interfere with positioning of the unidose nasal spray device and successful completion of the dosing procedure.

6. Current use of any prohibited concomitant medication(s) or participants unwilling/unable to use a permitted concomitant medication(s).

7. History of use of ergotamine medications or triptans on greater than/equal to 10 days per month on a regular basis for greater than/equal to 3 months. **Or** history of non-narcotic analgesic intake on greater than/equal to 15 days per month for greater than/equal to 3 months (eg, acetaminophen, NSAIDs, gabapentin) ***for other pain indications***.

8. **ANY** of the following findings at the Screening Visit and laboratory tests as assessed by the study-specific laboratory:

   - Class 2 or Class 3 obesity, defined as body mass index ≥35 kg/m^2.
   - eGFR <30 mL/min using the recommended CKD-EPI equations.
   - Total bilirubin >1.5 × ULN (may be repeated once, with fractionation, for confirmation during the Screening Phase, and direct bilirubin >1.5 × ULN is exclusionary if Gilbert's syndrome is suspected).
   - AST (SGOT) or ALT (SGPT) >1.5 × ULN (may be repeated once for confirmation during the Screening Phase).
   - Neutrophil count ≤1000/μL (or equivalent).

Study Arms and Duration:

Participants will receive a single dose of zavegepant or placebo in this study. The total duration of study participation will be up to approximately 16 weeks.

Study Intervention(s)		
Intervention Name	Zavegepant (PF-07930207)	Placebo
Arm Name (group of participants receiving a specific treatment or no treatment)	Zavegepant (PF-07930207)	Placebo
Unit Dose Strength(s)	10 mg per 0.1 mL	0 mg per 0.1 mL
Route of Administration	Intranasal	Intranasal
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP

Study Arm(s)		
Arm Title	Zavegepant (PF-07930207)	Placebo
Arm Type	Experimental	Placebo
Arm Description	Participants will receive a single dose zavegepant (PF-07930207) 10 mg	Participants will receive a single dose placebo

Statistical Methods:

It is anticipated that about 90% of the 700 randomized participants will have a headache in the allotted time period, resulting in approximately 630 participants evaluable for efficacy in each treatment group. A target sample size of 1260 evaluable participants will provide approximately 95.7% power for the co-primary endpoint of pain freedom at 2 hours postdose, approximately 87.5% power for the co-primary endpoint of MBS freedom at 2 hours postdose, and approximately 84% power to detect a difference between treatment groups for both co-primary endpoints jointly.

Descriptive statistics for all efficacy and safety endpoints at appropriate time points will be provided by treatment group. Continuous variables will be summarized by standard descriptive statistics (n, mean, standard deviation, median, minimum and maximum), and categorical variables will be summarized with the number and percentage of participants in each category (with the corresponding sample size).

In treatment comparisons of binary endpoints, for individual treatment group, CIs based on normal approximation will be generated; for the treatment difference, a CMH test stratified by country/region will be used, and CIs will be based on a normal approximation.

The frequencies of the following postdose safety endpoints will be presented by treatment group: AEs by intensity; SAEs; AEs related to study intervention; local irritation AEs; laboratory test abnormalities by toxicity grade; and liver function test elevations.

Ethical Considerations:

The results of previous studies of zavegepant support the investigation for the acute treatment of migraine, and there is a favorable benefit-risk profile to support the rationale for this study. Taking into account the measures to minimize risk to participants, the potential risks associated with zavegepant are justified by the anticipated benefits that may be afforded to participants for the acute treatment of migraine.

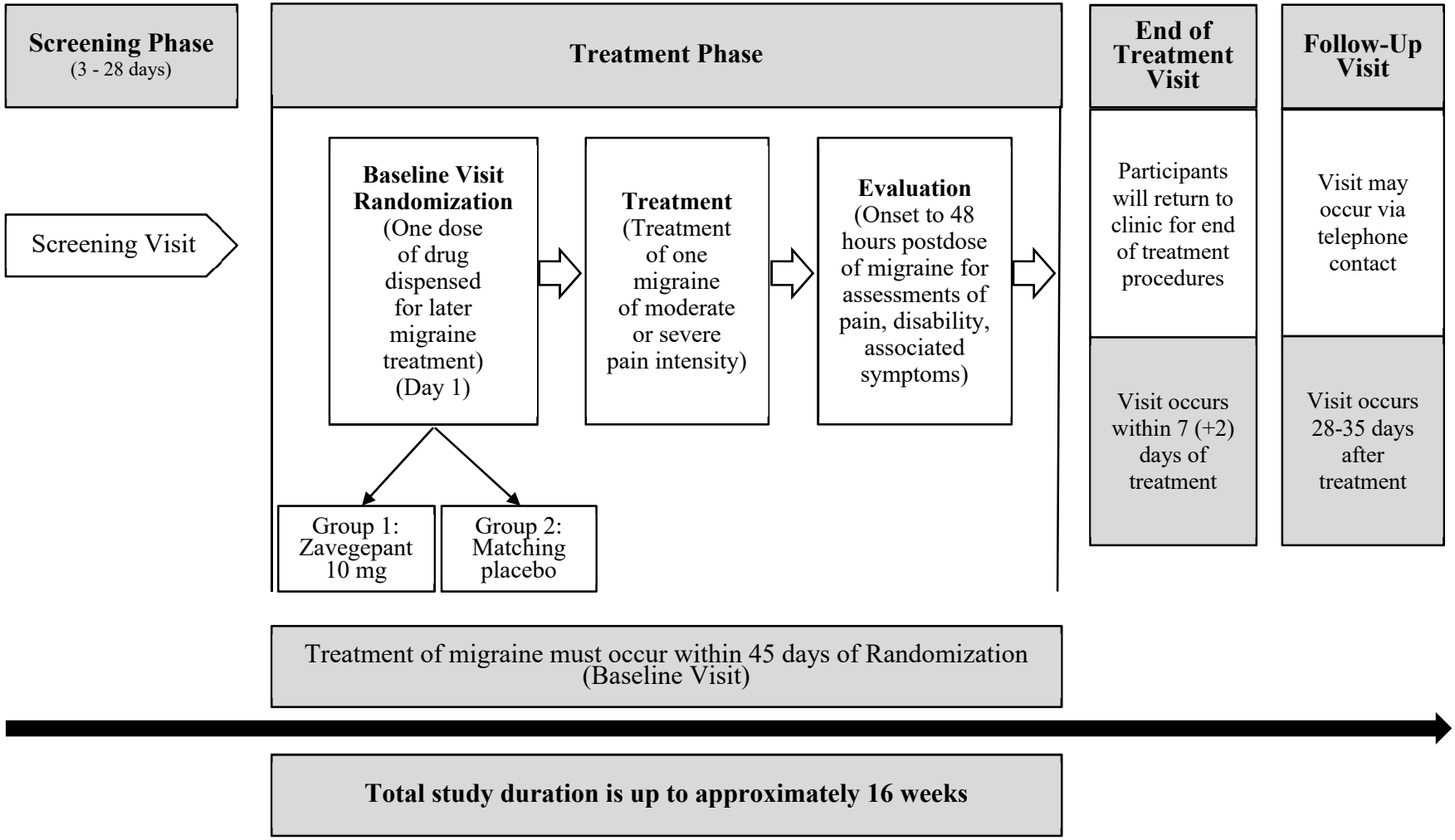
- Participants may experience improvements during the study and will benefit from more intense monitoring and more frequent assessments compared to usual standard of care. Participants may benefit from contributing to the understanding of the potential efficacy for the acute treatment of migraine, such as freedom from pain, freedom from MBS, and freedom from functional disability.

- Based on the experience with zavegepant, the potential risks for zavegepant are primarily associated with IN administration (ie, dysgeusia, throat irritation, nasal congestion, nasal discomfort), and the majority of AEs have been of mild to moderate intensity.

- Participants randomized to placebo arm may not experience the potential efficacy. Rescue medication or prescribed standard of care medication is permitted during this study.

- Participants will be expected to commit time and may experience some discomfort while undergoing study assessments. In addition, participants of childbearing potential must agree to use appropriate contraception methods.

1.2. Schema



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 8.	Screen	Treatment Phase			EOT	F/U	Early Discont	Notes
	3-28 days	Day 1 Baseline Visit (Randomization)	Migraine Headache of Moderate or Severe Intensity Before Study Intervention Administration	Post Study Intervention Administration: 15, 30, 45, 60 and 90 minutes, 2, 3, 4, 6, 8, 24 and 48 hours	Within 7 (+2) days of treatment	28-35 days after treatment		• Baseline Visit may only occur after all screening procedures are completed and the participant meets all inclusion/exclusion criteria. • Every effort should be made to conduct the EOT Visit within the specified window of 7 (+2) days after administration of study intervention. If a participant has NOT treated a migraine attack with study intervention within 45 days after randomization, they are still required to complete the EOT Visit. • Follow-Up Visit may occur via telephone contact and must occur 28 to 35 days after administration of study intervention. • See Section 4.1 for additional information.
Informed consent	X							Informed consent should be obtained prior to undergoing any study-specific procedures. After informed consent is signed, participants will be enrolled in the IRT system. See Section 10.1.3 for additional information.
Inclusion/exclusion criteria	X	X						See Section 5.1 and 5.2 for additional information.
Demographics	X							
Randomization		X						At randomization, the participant will be randomized in the IRT and randomization number is assigned. Randomization will be stratified by the use of stable prophylactic migraine medications through randomization (yes or no) and country/region.
Medical History and Physical Examinations								
Medical history	X	X						
Migraine history assessment (signs/ symptoms/ prior treatment/ frequency/ intensity)	X	X						See Section 5.1 for additional information.
Physical examination	X				X		X	Height will only be captured at the Screening Visit.

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Nasal inspection	X	X			X		X	The nasal passages and turbinates will be visually inspected with a nasal speculum or otoscope at the Screening, Baseline and EOT Visits to detect evidence of nasal inflammation or edema. See Section 8.3.2 for additional information.
Vital signs	X	X			X		X	See Section 8.3.3 for additional information.
12-Lead ECG	X				X		X	See Section 8.3.4 for additional information.
Contraception check	X	X			X	X	X	See Section 5.3.1 and Appendix 4 for additional information.
Laboratory Assessments								See Section 8.3.5 and Appendix 2 for additional information.
Hematology	X				X		X	
Blood chemistry (inc. eGFR)	X				X		X	
Urinalysis	X				X		X	
Urine drug screen for drugs of abuse	X				X		X	
Liver Function Tests (LFTs)	X				X		X	
FSH, if applicable, to determine WOCBP status	X							
HbA1c	X							
Pregnancy test (only for WOCBP)	X (Serum)	X (Urine)			X (Serum)		X (Serum)	A serum pregnancy test will be collected at the Screening and EOT Visits. Confirmatory urine pregnancy test will be completed on site at Baseline Visit and any subsequent visits for confirmation at the investigator's discretion.
Study Intervention and Other Treatments								See Section 6 for additional information.
Dispense study intervention		X						Participants should be instructed that the dose should be administered once the migraine attack reaches moderate or severe pain and after the participant has completed all the required migraine assessments in the handheld. The handheld will prompt the participant when they should administer study intervention.

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 8.	Screen	Treatment Phase			EOT	F/U	Early Discont	Notes
	3-28 days	Day 1 Baseline Visit (Randomization)	Migraine Headache of Moderate or Severe Intensity Before Study Intervention Administration	Post Study Intervention Administration: 15, 30, 45, 60 and 90 minutes, 2, 3, 4, 6, 8, 24 and 48 hours	Within 7 (+2) days of treatment	28-35 days after treatment		• Baseline Visit may only occur after all screening procedures are completed and the participant meets all inclusion/exclusion criteria. • Every effort should be made to conduct the EOT Visit within the specified window of 7 (+2) days after administration of study intervention. If a participant has NOT treated a migraine attack with study intervention within 45 days after randomization, they are still required to complete the EOT Visit. • Follow-Up Visit may occur via telephone contact and must occur 28 to 35 days after administration of study intervention. • See Section 4.1 for additional information.
Study intervention administration			X					Participants will use their assigned eCOA handheld device before study intervention administration to answer questions upon experiencing a migraine headache of moderate or severe pain intensity. The participant will administer study intervention if the following criteria are met: 1) the headache remains moderate or severe; 2) the participant has completed all the required migraine assessment questions in the handheld, including their current MBS, and 3) the participant has not already taken prohibited medications. See Section 6.1 for additional information.
Prior/concomitant treatment(s)	X	X	X	X	X	X	X	Participants should keep track of their concomitant medications on the paper diary provided. The paper diaries should be kept as source documents. See Section 6.9 for additional information of prohibited concomitant medications and rescue medication.
Assessments								See Section 8 for additional information.
Assessments of migraine pain, migraine symptoms (phonophobia, photophobia, and nausea) and functional disability			X	X				See Section 8.2 for additional information.
Patient Global Impression of Change (PGIC) ratings				X				PGIC ratings will be assessed by participants at 30 minutes, 60 minutes, 2 hours and 24 hours postdose and will be captured in the eCOA handheld device. See Section 8.2.5 for additional information.
Serious and nonserious AE monitoring	X	X	X	X	X	X	X	See Section 8.4 for additional information.
Columbia-Suicide Severity Rating Scale (C-SSRS)	X	X			X		X	C-SSRS will be clinician administered on site with a paper form. The source document will be provided by Pfizer. The assessment period for completing the scale is 1 year prior to the Screening Visit and during the study. See Sections 5.2 and 8.3.7 for additional information.

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Study Supplies								See Sections 4.1 and 6.9 for additional information.
Paper diary assigned to participant	X	X						Concomitant medication paper diary will be provided to participants at the Screening Visit. Rescue medication paper diary will be provided to participants at the Baseline Visit.
Paper diary returned/ reviewed		X			X		X	Concomitant medication paper diary should be returned to site at Baseline and EOT Visits for review and EDC entry. Rescue medication paper diary should be returned to site at EOT Visit for review and EDC entry.
eCOA handheld device assigned to participant		X						
Patient education: study intervention administration with instruction for use document		X						The study personnel **MUST** train the participant on the proper use of unidose nasal spray device using instructions to be provided to each participant. This study intervention is to be taken when a migraine attack reaches moderate or severe pain intensity on the numeric rating scale (NRS) as indicated in the handheld.
Patient education: eCOA handheld device participant online training/ training device		X						The study personnel **MUST** instruct and train the participant on the proper use of the handheld to **ENSURE** proper understanding and use of the tool, **PRIOR to** the participant leaving the office.
Enter use of study intervention in eCOA handheld device			X					
eCOA handheld device returned/ reviewed					X		X	Site staff review and confirm all data points are transferred from the handheld and reset handheld for future participant use, **PRIOR to** the participant leaving the clinic.

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 8.	Screen	Treatment Phase			EOT	F/U	Early Discont	Notes
	3-28 days	Day 1 Baseline Visit (Randomization)	Migraine Headache of Moderate or Severe Intensity Before Study Intervention Administration	Post Study Intervention Administration: 15, 30, 45, 60 and 90 minutes, 2, 3, 4, 6, 8, 24 and 48 hours	Within 7 (+2) days of treatment	28-35 days after treatment		• Baseline Visit may only occur after all screening procedures are completed and the participant meets all inclusion/exclusion criteria. • Every effort should be made to conduct the EOT Visit within the specified window of 7 (+2) days after administration of study intervention. If a participant has NOT treated a migraine attack with study intervention within 45 days after randomization, they are still required to complete the EOT Visit. • Follow-Up Visit may occur via telephone contact and must occur 28 to 35 days after administration of study intervention. • See Section 4.1 for additional information.
Return used and unused study intervention to site for reconciliation					X		X	

2. INTRODUCTION

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

Zavegepant (PF-07930207) is a selective, high affinity, small molecule CGRP receptor antagonist in development for the treatment of migraine. Zavegepant is being developed for the acute treatment of migraine via the intranasal route.

2.1. Study Rationale

The purpose of the study is to evaluate the efficacy and safety of zavegepant 10 mg versus placebo in the acute treatment of migraine (with or without aura) in Asian adults by measuring freedom from pain and freedom from MBS (selected from nausea, photophobia or phonophobia just prior to treatment of the migraine) at 2 hours postdose. Information regarding time to onset of action, sustainability of pain freedom, and freedom from functional disability will also be obtained.

2.2. Background

Migraine is a common and debilitating neurological disorder that affects approximately 15% of the adult population, listed as the second leading cause of years lived with disability worldwide.[7] The 1-year prevalence of migraine (IHS criteria) among adults in China, Korea and Japan ranged from 6.0% to 14.3%. Peak prevalence ranged from 11% to 20% for women and 3% to 8% for men (30- to 49-year-olds). Migraine was significantly associated with high levels of disability and negative effects on quality of life. Studies suggested low levels of disease awareness/diagnosis within these three countries. Of individuals with migraine from China, 52.9% to 68.6% had consulted a physician previously, 37.2% to 52.7% diagnosed with headache had not been diagnosed with migraine previously, and 13.5% to 18% had been diagnosed with migraine previously. Of individuals with migraine from Japan, 59.4% to 71.8% had never consulted a physician previously, 1.3% to 7.3% regularly consulted physicians for their headache, and only 11.6% of individuals with migraine were aware that they had migraine. Findings from one population-based study of South Korea showed that only 24.4% of individuals with migraine had consulted a physician for headache, 64.3% were taking medication for their headache and, of these, most (92.8%) were using OTC medication. In addition, studies suggested high over-the-counter medication use and low prescription medication use in these countries. The significant levels of humanistic burden among the available studies suggest that there are substantial unmet needs for migraine with

regard to appropriate diagnosis, and better management of and therapies for treatment of migraine across East Asia.[8]

Migraine is characterized by moderate to severe episodic unilateral pulsating headaches that last for 4 to 72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia.[9] Triptans are the mainstay treatment of migraine attacks with varying results including incomplete and inconsistent relief at 2 hours, and the recurrence of migraine within 24-48 hours after treatment. Nevertheless, the use of triptans is limited in patients with certain comorbidities. They are contraindicated in patients with cardiovascular events (ie, myocardial infarction), conditions (ie, angina) and procedures (ie, carotid endarterectomy) due to vasoconstrictive properties.

Zavegepant is a new approach to the treatment of migraine, which avoids the cardiovascular effects produced by active vasoconstriction associated with the current standard triptan therapy (non-selective 5-HT1B/1D agonists). In addition, zavegepant administered IN could be especially advantageous for patients who cannot tolerate an oral medication due to vomiting or severe nausea.

2.2.1. Nonclinical Overview

2.2.1.1. Nonclinical Pharmacology, Pharmacokinetics and Safety

A series of in vitro and in vivo PK and metabolism studies were conducted with zavegepant in rats, dogs, rabbits, mice and monkeys. Safety studies were also performed in rat and monkey to determine tolerability, potential for local irritation, and to assess systemic toxicity.

Refer to the IB for more details on the nonclinical pharmacology, pharmacokinetics and toxicology of zavegepant.

2.2.2. Clinical Overview

As of 03 Oct 2022, an estimated 3354 participants have been administered zavegepant (IN, oral, or radiolabeled IV) across the clinical development program, including: 700 healthy participants and special populations; 2622 participants with migraine; 29 participants with COVID-19; and 3 participants with asthma.

2.2.2.1. Clinical Pharmacology

Based on the completed clinical studies of IN zavegepant, the following observations were made regarding the zavegepant PK properties. Zavegepant is rapidly absorbed (T_{max}: 0.54 hr) following a single zavegepant 10 mg IN dose. The effective half-life of zavegepant, which is considered more clinically relevant than 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 the 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 administration.

The results of a 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. Zavegepant may be co-administered with a triptan without dose frequency modification. Lack of a clinically significant effect on the exposures of EE and LNG following co-administration of zavegepant 20 mg IN and an 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 39% increase in the C_{max} and an approximate two-fold increase in zavegepant AUC was observed in participants with moderate hepatic impairment.

Zavegepant was metabolized by recombinant CYP3A4 and to a lesser extent by recombinant CYP2D6 as shown with in vitro assays, although the overall rate of hepatic metabolism of zavegepant was very low. The human ADME study demonstrated that the primary route of elimination of zavegepant is through biliary elimination, with 84.9% of the total radioactivity recovered in feces following a [^{14}C]-zavegepant IV dose, and the contribution of renal clearance to zavegepant elimination is minimal (<12%).

Co-administration of itraconazole (strong CYP3A4 inhibitor and P-gp inhibitor) with IN zavegepant showed no clinically relevant changes in the exposure of zavegepant suggesting strong CYP3A and P-gp inhibitors may be co-administered with IN zavegepant without dose adjustment. 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, co-administration 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 and C_{max} by approximately 2-fold in presence of rifampin suggesting that drugs that inhibit both the OATP1B3 and NTCP transporters could increase the exposure of zavegepant. Therefore, zavegepant dose frequency should be adjusted during co-administration with inhibitors of both OATP1B3 and NTCP transporters to no more than once every 48 hours. 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 $AUC_{[0\text{-inf}]}$ 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.

Refer to the IB for more details on the clinical pharmacology of zavegepant.

2.2.2.2. Clinical Efficacy

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 (BHV3500-201), zavegepant doses of 10 mg and 20 mg via IN administration demonstrated statistically significant efficacy on both co-primary endpoints of freedom from pain at 2 hours postdose

and freedom from MBS at 2 hours postdose, with little meaningful differences between doses observed. Therefore, the 10 mg dose was selected for further development of intranasal zavegepant for the acute treatment of migraine.

A confirmatory Phase 3 study of zavegepant 10 mg IN administration for the acute treatment of migraine (BHV3500-301) demonstrated statistically significant efficacy for both co-primary endpoints of freedom from pain at 2 hours postdose and freedom from MBS at 2 hours postdose, as well as for 13 of the 17 secondary endpoints tested. These alpha-protected secondary endpoints included measures of ultrarapid onset (eg, pain relief at 15 minutes postdose) and durability of response (eg, sustained pain relief from 2 to 48 hours postdose).

Refer to the IB for more details on the clinical efficacy of zavegepant.

2.2.2.3. Clinical Safety

In clinical studies, approximately 2700 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 1185 adult participants with migraine (BHV3500-201). 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).

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). The most frequently occurring adverse events in clinical studies to date have been associated primarily with intranasal administration (ie, dysgeusia, throat irritation, nasal congestion, nasal discomfort), as well as nausea and back pain, and the majority have been of mild to moderate intensity.

BHV3500-106 was a Phase 1, daily dosing, open-label, safety study of oral zavegepant 100 mg QD in healthy participants. The dose selected for this daily dosing study was based on achieving exposures of zavegepant similar to that for the 10 mg once daily dose administered by the intranasal route. In this study, oral zavegepant 100 mg once daily for up to 8 weeks in healthy participants was well tolerated and demonstrated a favorable safety profile. Through demonstration of clinically relevant sustained systemic exposure after oral administration of zavegepant, the results of this study support the safety conclusions and the overall benefit-risk assessment for the intranasal route of administration.

Refer to the IB for more details on the clinical safety of zavegepant.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of zavegepant may be found in the IB, which is the SRSD for this study.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: Zavegepant		
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). Nasal inspection will be conducted on Screening Visit, Baseline Visit and EOT Visit per the SoA. AEs and clinical laboratory results will be monitored on an ongoing basis.
Use of a placebo arm.	Participants randomized to placebo arm may not experience freedom from pain and freedom from MBS efficacy, as well as freedom from functional disability.	Rescue medication or prescribed standard of care medication is permitted during this study as specified in Section 6.9.2.

2.3.2. Benefit Assessment

The participants may experience improvements during the study and will benefit from more intense monitoring and more frequent assessments compared to usual standard of care. Based on the results of BHV3500-201 and BHV3500-301, participants may benefit from contributing to the understanding of the potential efficacy of zavegepant for the acute treatment of migraine, such as freedom from pain, freedom from MBS, and freedom from functional disability specifically in the Asian population in which little clinical evidence has been collected to date.

Administration of zavegepant was well tolerated at 5 mg, 10 mg, and 20 mg as a single IN spray in adult participants with migraine (BHV3500-201). Zavegepant 10 mg IN was well tolerated in a completed long-term safety study (up to 8 doses per month) in adult participants with migraine for up to 52 weeks (BHV3500-202) and in the completed study of the acute treatment of migraine (BHV3500-301). The most frequently occurring adverse events in clinical studies to date have been primarily associated with IN administration (ie, dysgeusia, throat irritation, nasal congestion, nasal discomfort), and the majority have been of mild to moderate intensity.

Clinical benefit of zavegepant superior to placebo will be further assessed for the acute treatment of migraine in Asian adults in this study, and participants may benefit from the potential efficacy.

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures to minimize risk to study participants, the overall benefit-risk profile of zavegepant is favorable. The potential risks identified in association with zavegepant are justified by the anticipated benefits that may be afforded to participants for the acute treatment of migraine.

3. OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives	Endpoints	Estimands
Primary:	**Primary:**	**Primary:**
• To compare the efficacy of zavegepant with placebo in the acute treatment of migraine.	The following co-primary endpoints will be tested: • Percentage of participants with a pain intensity of none (pain freedom) at 2 hours postdose.	Co-primary estimands: • The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none at 2 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 2 hours postdose will be regarded as a failure.
	• Percentage of participants with an MBS reported before dosing that is absent at 2 hours postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with an MBS reported before dosing that is absent at 2 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 2 hours postdose will be regarded as a failure.
Secondary:	**Secondary:**	**Secondary:**
Key Secondary Objectives:	**Key Secondary Endpoints:**	**Key Secondary Estimands:**
• To compare zavegepant with placebo for measures of early pain relief.	• Percentage of participants with a pain intensity of none or mild at 15 minutes postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none or mild at 15 minutes postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 15 minutes postdose will be regarded as a failure.
	• Percentage of participants with a pain intensity of none or mild at 30 minutes postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none or mild at 30 minutes postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 30 minutes postdose will be regarded as a failure.
	• Percentage of participants with a pain intensity of none or mild at 2 hours postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none or mild at 2 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 2 hours postdose will be regarded as a failure.

Objectives	Endpoints	Estimands
• To compare zavegepant with placebo for return to normal function.	• Percentage of participants with a functional disability level of normal at 2 hours postdose, evaluated for participants with functional disability at the time of dosing.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a functional disability level of normal at 2 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention and had functional disability at the time of dosing. Intercurrent event of taking rescue medication at or before 2 hours postdose will be regarded as a failure.
• To compare zavegepant with placebo for measures of sustained pain relief.	• Percentage of participants with a pain intensity of none or mild at all time points from 2 to 24 hours postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none or mild at all time points from 2 to 24 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 24 hours postdose will be regarded as a failure.
	• Percentage of participants with a pain intensity of none or mild at all time points from 2 to 48 hours postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none or mild at all time points from 2 to 48 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 48 hours postdose will be regarded as a failure.
• To compare zavegepant with placebo for measures of early return to normal function.	• Percentage of participants with a functional disability level of normal at 30 minutes postdose, evaluated for participants with functional disability at the time of dosing.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a functional disability level of normal at 30 minutes postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention and had functional disability at the time of dosing. Intercurrent event of taking rescue medication at or before 30 minutes postdose will be regarded as a failure.
	• Percentage of participants with a functional disability level of normal at 60 minutes postdose, evaluated for participants with functional disability at the time of dosing.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a functional disability level of normal at 60 minutes postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention and had functional disability at the time of dosing. Intercurrent event of taking rescue medication at or before 60 minutes postdose will be regarded as a failure.
Other Secondary Objectives:	**Other Secondary Endpoints:**	**Other Secondary Estimands:**
• To compare zavegepant with placebo for freedom from individual non-headache associated symptoms of migraine.	• Percentage of participants with **phonophobia** absent at 2 hours postdose, evaluated for participants with phonophobia present at the time of dosing.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with phonophobia absent at 2 hours postdose among all randomized participants with migraine headache of moderate or severe

Objectives	Endpoints	Estimands
		intensity who took study intervention and had phonophobia at the time of dosing. Intercurrent event of taking rescue medication at or before 2 hours postdose will be regarded as a failure.
	• Percentage of participants with **photophobia** absent at 2 hours postdose, evaluated for participants with photophobia present at the time of dosing.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with photophobia absent at 2 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention and had photophobia at the time of dosing. Intercurrent event of taking rescue medication at or before 2 hours postdose will be regarded as a failure.
	• Percentage of participants with **nausea** absent at 2 hours postdose, evaluated for participants with nausea present at the time of dosing.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with nausea absent at 2 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention and had nausea at the time of dosing. Intercurrent event of taking rescue medication at or before 2 hours postdose will be regarded as a failure.
• To compare zavegepant with placebo for additional measures of sustained efficacy.	• Percentage of participants with a pain intensity of none at all time points from 2 to 24 hours postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none at all time points from 2 to 24 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 24 hours postdose will be regarded as a failure.
	• Percentage of participants with a pain intensity of none at all time points from 2 to 48 hours postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none at all time points from 2 to 48 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 48 hours postdose will be regarded as a failure.
	• Percentage of participants with pain relapse (any pain intensity above 'none') at any time point after 2 hours postdose, evaluated for participants with pain freedom at 2 hours postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of mild, moderate, or severe at any time point after 2 hours postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention and had pain freedom at 2 hours postdose. Intercurrent event of taking rescue medication at or before 48 hours postdose will be regarded as a failure.
• To compare zavegepant with placebo for rescue medication use.	• Percentage of participants taking rescue medication within 24 hours postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants taking rescue medication within 24 hours postdose among all randomized participants with migraine headache of moderate or

Objectives	Endpoints	Estimands
		severe intensity who took study intervention. No relevant intercurrent event is considered since taking rescue medication is the analysis objective.
• To further compare zavegepant with placebo for early pain relief.	• Percentage of participants with a pain intensity of none or mild at 60 minutes postdose.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a pain intensity of none or mild at 60 minutes postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention. Intercurrent event of taking rescue medication at or before 60 minutes postdose will be regarded as a failure.
• To further compare zavegepant with placebo for early return to normal function.	• Percentage of participants with a functional disability level of normal at 15 minutes postdose, evaluated for participants with functional disability at the time of dosing.	• The estimand is the treatment effect of zavegepant relative to placebo in terms of the difference in percentage of participants with a functional disability level of normal at 15 minutes postdose among all randomized participants with migraine headache of moderate or severe intensity who took study intervention and had functional disability at the time of dosing. Intercurrent event of taking rescue medication at or before 15 minutes postdose will be regarded as a failure.
• To evaluate the safety and tolerability of zavegepant in the acute treatment of migraine.	• Number and percentage of participants with AEs of moderate or severe intensity, SAEs, local irritation AEs, and grade 3 or 4 laboratory test abnormalities.	• Not applicable.
Tertiary/Exploratory:	**Tertiary/Exploratory:**	**Tertiary/Exploratory:**
• To evaluate the time course of zavegepant efficacy vs placebo.	• Percentage of responders at each of the assessed time points (15, 30, 45, 60, 90 minutes; 2, 3, 4, 6, 8, 24, and 48 hours) for each of the primary and secondary endpoints described above that assess a specific time point.	• As described above for each primary and secondary endpoint, using the applicable time point.
• To estimate zavegepant relative to placebo for the PGIC ratings.	• Percentage of participants with the overall status improvement at 30 minutes, 60 minutes, 2 hours and 24 hours postdose, and the total score of PGIC.	• Not applicable.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter, single-attack, outpatient evaluation of the efficacy and safety of zavegepant versus placebo for the acute treatment of migraine in Asian adults. The study intervention is formulated as zavegepant 10 mg IN or matching placebo. The study intervention will be administered using an unidose nasal spray device containing a single dose of zavegepant or matching placebo. The

participants will be instructed to take their study intervention, as an outpatient, if they have a migraine headache which reaches moderate or severe pain intensity.

The total duration of study participation will be up to approximately 16 weeks. This includes a 3-28 day Screening Phase, a Treatment Phase that can last up to 45 days or until the participant has a migraine headache that reaches moderate or severe pain intensity, followed by an EOT Visit 7 (+2) days after the administration of study intervention and a Follow-Up Visit 28-35 days after the administration of study intervention for safety monitoring.

Approximately 1750 participants will be screened to randomize approximately 1400 participants in a 1:1 ratio between the 2 treatment groups (zavegepant or placebo). Before any study procedures are performed, participants must sign informed consent. After informed consent is signed, participants will be enrolled in the IRT system. The participant's migraine history and medical history will be collected at the Screening Visit. Participants will also undergo all screening procedures as indicated in the SoA. Screening Visit must be completed in person.

Within 3-28 days from the Screening Visit, participants will return to the site for the Baseline (Randomization) Visit. Participants who meet all eligibility criteria may be randomized at the Baseline Visit. After randomization is completed in the IRT, study intervention will be dispensed to participants to take home for a single attack of moderate or severe pain intensity occurring up to 45 days after the Baseline (Randomization) Visit. The participants will be provided with an eCOA handheld device. The eCOA handheld device may also be referred to as a handheld or an eDiary. Once a participant experiences a migraine headache of moderate to severe intensity, they should record this in the handheld. The handheld will instruct the participant to take study intervention after the initial assessments are completed in the device. The participant will complete assessments for 48 hours after taking study intervention to record efficacy and other quality of life measures, refer to Section 8.2 Efficacy Assessments for additional information. The study personnel **MUST** instruct and train the participant on the proper use of the handheld to **ENSURE** proper understanding and use of the tool, **PRIOR to** the participant leaving the office at Baseline Visit. Baseline Visit must be completed in person. **Participants in this study may be randomized only once. Under NO circumstances may a participant be re-randomized**.

Participants should be encouraged to treat their **FIRST** qualifying migraine attack (moderate or severe pain intensity) that occurs during the Treatment Phase. If participants are unable to treat their first qualifying migraine, refer to Section 6.9.2 Rescue Medication for a list of medications that are allowed during the course of this study.

Participants will return to the site for EOT Visit (after assessments in the handheld are completed) within 7 (+2) days after administration of study intervention. The "+2" day window is included for scheduling purposes only. Every effort should be made to conduct the EOT Visit within the specified window of 7 (+2) days after administration of study intervention. At the EOT Visit, medication compliance and monitoring of safety assessments will be performed as indicated in the SoA. If a participant has NOT treated a migraine attack with study intervention within 45 days after randomization, they are still required to complete

all EOT Visit procedures. All participants must return used and unused study intervention and their handheld device to site. Certain provisions may be implemented, in order to minimize potential hazards to the participants due to COVID-19 **ONLY** at the EOT Visit. These provisions may allow alternatives to in-person study visits and include but are not limited to the following: conducting remote study visits via phone/telemedicine video, focusing on safety assessments during remote visits, performing safety labs via local labs or professional in-home phlebotomy vendors, and shipping of study intervention if needed. Any potential issues should be discussed with sponsor and will be addressed on an individualized basis. Components of the EOT Visit may be conducted under the provisions mentioned above (remote via phone/telemedicine, local labs, etc.), and the window visit may be extended by 5 days due to COVID-19 **ONLY** if circumstances warrant in order to minimize any potential risks to participant safety. Refer to Section 8.3.4.1 and 8.3.5.1 for additional information.

Follow-Up Visit will occur 28-35 days after treatment for safety follow-up of AEs and/or abnormal laboratory tests. Participants may be contacted via telephone. Every effort should be made to conduct the Follow-Up Visit within 28-35 days after treatment. If a participant has NOT treated a migraine attack with study intervention within 45 days after randomization, they are not required to complete the Follow-Up Visit.

4.2. Scientific Rationale for Study Design

The efficacy of zavegepant in the acute treatment of migraine has been demonstrated in BHV3500-201, pivotal, Phase 2/3, double-blind, randomized, placebo-controlled, dose-ranging study of zavegepant 5 mg, 10 mg and 20 mg. This was confirmed in BHV3500-301, a pivotal, Phase 3, double-blind, randomized, placebo-controlled, efficacy and safety study of zavegepant 10 mg. In both trials, zavegepant was administered via intranasal route.

The design of this study will be similar to the pivotal study BHV3500-301. The data from this study will allow characterization of the relative efficacy and safety of zavegepant 10 mg IN versus placebo in the acute treatment of migraine in Asian adults by measuring freedom from pain and freedom from MBS (selected from nausea, photophobia or phonophobia just prior to treatment of the migraine) at 2 hours postdose. Information regarding time to onset of action, sustainability of pain freedom, and freedom from functional disability will also be obtained.

The study intervention is formulated as zavegepant 10 mg IN or matching placebo. The study intervention will be administered using an unidose nasal spray device containing a single dose of zavegepant or matching placebo. The participants will be instructed to take their study intervention, as an outpatient, if they have a migraine headache which reaches moderate or severe pain intensity.

4.2.1. Diversity of Study Population

This study is designed to enroll participants from Asia, to ensure the study population is representative of the Asian patient population that will use zavegepant in clinical practice.

4.2.2. Choice of Contraception/Barrier Requirements

Both women of childbearing potential, as well as those who are of non-childbearing potential, may be enrolled given the availability of EFD nonclinical toxicity studies with zavegepant. Contraception method is required and measures will be taken to limit the risk of pregnancy in the female population of childbearing potential enrolled (See Appendix 4).

The potential risk of exposure to zavegepant in a sexual partner of a male participant in this study via ejaculate is low, and therefore no contraception (condom) use in male participants is warranted. The calculated safety margin is ≥100-fold between the estimated partner exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies. The safety margin of 100-fold is based on applying a 10-fold safety factor for interspecies extrapolation and a 10-fold safety factor for susceptible populations.[10]

4.3. Justification for Dose

As of 03 Oct 2022, a total of 9 zavegepant IN clinical studies have been completed, including 6 Phase 1 studies, a Phase 2/3 study (BHV3500-201), a Phase 2/3 long-term safety study (BHV3500-202), and a Phase 3 study (BHV3500-301). In the IN clinical studies conducted to date, zavegepant has been administered as a spray using a single dose device that delivers 0.1 mL. Zavegepant has been investigated in the dose range from 0.1 mg to 40 mg IN.

BHV3500-201 was a pivotal, Phase 2/3, double-blind, randomized, placebo-controlled, dose-ranging (5 mg, 10 mg, or 20 mg) study of zavegepant IN for the acute treatment of migraine. The primary objective was to evaluate the efficacy of zavegepant compared with placebo in the acute treatment of migraine as measured by the co-primary endpoints of freedom from pain, and freedom from MBS associated with migraine at 2 hours postdose, while identifying an optimal dose for evaluation in the Phase 3 clinical development program.

In this study, a total of 1673 participants were randomized to receive zavegepant (5 mg, 10 mg, or 20 mg) or matching placebo. The randomization was stratified by the use of prophylactic migraine medication (yes or no). A total of 1588 participants were treated with zavegepant IN 5 mg (388 participants), 10 mg (394 participants), 20 mg (403 participants), or matching placebo (403 participants). Overall, 1578 participants completed the study. The 10 mg and 20 mg doses achieved statistical superiority to placebo on both co-primary endpoints of freedom from pain and freedom from MBS at 2 hours postdose. Rapid onset of pain relief was seen as early as 15 minutes with return to normal function at 30 minutes. The benefits of zavegepant were durable and sustained without rescue medication through 48 hours postdose. There were minimal differences in therapeutic response between the 10 mg and 20 mg doses across the co-primary and most secondary endpoints.

Based on the data from this pivotal study, a durable efficacy profile for zavegepant was established. This efficacy profile, together with a favorable safety profile led to the selection of the zavegepant 10 mg IN dose as the lowest fully efficacious dose to support Phase 3 clinical studies.

BHV3500-301 was a Phase 3, double-blind, randomized, placebo-controlled, multi-center, outpatient evaluation of the efficacy and safety of a single IN dose of zavegepant as compared to placebo in the acute treatment of migraine. A total of 1282 participants were treated (zavegepant 10 mg IN: 629; placebo: 653) in this study. Zavegepant 10 mg via IN administration demonstrated statistically significant efficacy on both co-primary endpoints of freedom from pain and freedom from MBS at 2 hours postdose. This study confirmed that zavegepant, administered as a single 10-mg dose IN spray, was well tolerated in adult participants with migraine headache of moderate or severe pain intensity, and demonstrated an acceptable safety profile.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit (Follow-Up Visit) of the last participant in the study.

A participant is considered to have completed the study if they have completed all periods of the study, including the Follow-Up 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. Asian (based on country of participation and ethnicity status) participants aged 18 years or older at screening.

    - Refer to Appendix 4 for reproductive criteria for male (Section 10.4.1) and female (Section 10.4.2) participants including requirement for pregnancy testing (Section 8.3.6).

Disease Characteristics:

2. Participants with minimum 1 year history of migraine (with or without aura) prior to the Screening Visit, consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd Edition,[9] including the following:

    - Migraine attacks present for more than 1 year with the age of onset prior to 50 years of age.
    - Migraine attacks, on average, lasting about 4 - 72 hours if untreated.
    - Not more than 8 attacks of moderate or severe pain intensity per month within last 3 months.
    - Participants must be able to distinguish migraine attacks from tension/cluster headaches.
    - At least 2 consistent migraine headache attacks of moderate or severe intensity in each of the 3 months prior to the Screening Visit and throughout the Screening Phase (participant self-report).
    - Less than 15 days with headaches (migraine or non-migraine) per month in each of the 3 months prior to the Screening Visit and throughout the Screening Phase (participant self-report).
    - Participants on prophylactic migraine medication are permitted to remain on therapy if they have been on a stable dose for at least 3 months prior to Screening Visit, and if the dose is not expected to change through the EOT Visit.
    - Participants with contraindications for use of triptans may be included provided they meet all other study entry criteria.

5.2. Exclusion Criteria

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

Medical Conditions:

1. History of retinal migraine, basilar migraine or hemiplegic migraine.
2. History or current evidence of uncontrolled, unstable or recently diagnosed cardiovascular or cardiometabolic disease including:

    - Diagnosis of ischemic heart disease, coronary artery vasospasm, and cerebral ischemia during the 6 months prior to Screening Visit.
    - Events of MI, ACS, PCI, cardiac surgery, stroke or TIA during the 6 months prior to Screening Visit.

- ECG findings at the Screening Visit including:
  - QTcF interval >470 msec.
  - Left Bundle Branch Block.
  - Right Bundle Branch Block with a QRS duration ≥150 msec.
  - Intraventricular Conduction Defect with a QRS duration ≥150 msec.
- Uncontrolled hypertension (high blood pressure); a single blood pressure measurement of greater than 150 mmHg systolic or 100 mmHg diastolic after 10 minutes of rest at the Screening Visit is exclusionary.
- Uncontrolled diabetes, defined as HbA1c ≥7.5% at the Screening Visit.

3. Major depressive disorder, anxiety disorder, or other significant psychiatric disorder including:
   - Major depressive episode within the last 12 months, major depressive disorder or any anxiety disorder requiring more than 1 medication for each disorder. Medications to treat major depressive disorder or an anxiety disorder must have been at a stable dose for at least 3 months prior to the Screening Visit provided the medication is not otherwise prohibited.
   - Current diagnosis of major depressive disorder requiring treatment with atypical antipsychotics.
   - Schizophrenia, bipolar disorder, or borderline personality disorder.
   - Response of "yes" to Question 4 or 5 for suicidal ideation, **or** on any suicidal behavioral question on the C-SSRS for the period of 1 year prior to Screening Visit and during the study, **or** participants present a serious risk of suicide in the opinion of the investigator (see Section 8.3.7).
4. Acute or chronic pain syndromes (such as fibromyalgia, chronic pelvic pain, CRPS). Other pain syndromes (including trigeminal neuralgia), psychiatric conditions, dementia, or significant neurological disorders (other than migraine) that, in the investigator's opinion, interfere with study assessments.
5. Conditions that may affect the administration or absorption of the nasal product:
   - History of nasal surgery in the 6 months preceding the Screening Visit.
   - Evidence at Screening Visit of significant nasal conditions (eg, severe septum deviation, nasal deformity or blockage, inflammation, perforation, mucosal

erosion or ulceration, polyposis, nasal trauma) as evaluated by the investigator or medically qualified delegate.

- Presence of piercings in the nose that, in the opinion of the investigator, would be likely to interfere with positioning of the unidose nasal spray device and successful completion of the dosing procedure.

6. History of, treatment for, or evidence of, alcohol or drug abuse within the past 12 months or participants who have met DSM-V criteria[11] for any significant substance use disorder within the past 12 months from the date of the Screening Visit, **or** a positive drug screen for drugs of abuse that in the investigator's judgment is medically significant, in that it would impact the safety of the participant or the interpretation of the study results. In addition:

   - Detectable levels of cocaine, amphetamine, and PCP in the drug screen are exclusionary. Participants who are positive for amphetamines, and who are on a prescribed amphetamine medication for an approved indication (ie, ADHD) will be allowed into the study at the investigator's discretion. This determination by the investigator must be well documented in the participant's source medical records. The stimulant dose must be stable from 3 months prior to the Baseline Visit and through the EOT Visit.

   - Detectable levels of marijuana in the drug screen are not exclusionary, if in the investigator's documented opinion the participant does not meet DSM-V criteria[11] for substance use disorder, and the positive test does not signal a clinical condition that would impact the safety of the participant or interpretation of the study results.

7. Hematologic or solid malignancy diagnosis within 5 years prior to the Screening Visit. Participants with a history of localized basal cell or squamous cell skin cancer are eligible for the study if they are cancer-free prior to the Screening Visit in this study.

8. Other social, medical (including drug or other allergy), or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

Prior/Concomitant Therapy:

9. Current use of any prohibited concomitant medication(s) or participants unwilling/unable to use a permitted concomitant medication(s). Refer to Section 6.9 Prior and Concomitant Therapy.

10. History of use of ergotamine medications or triptans on greater than/equal to 10 days per month on a regular basis for greater than/equal to 3 months. **Or** history of non-narcotic analgesic intake on greater than/equal to 15 days per month for greater

than/equal to 3 months (eg, acetaminophen, NSAIDs, gabapentin) ***for other pain indications***.

Prior/Concurrent Clinical Study Experience:

11. Participation in clinical trial with non-biological investigational agents or interventional treatments (last study visit occurring) within the 30 days prior to Baseline Visit. Participation in clinical trial with biological investigational agents (last study visit occurring) within 90 days prior to Baseline Visit. Participation in any other investigational clinical trial while participating in this clinical trial.

12. Previous participation in any zavegepant study within the last 2 years.

Diagnostic Assessments:

13. **ANY** of the following findings at the Screening Visit and laboratory tests as assessed by the study-specific laboratory:

    - Class 2 or Class 3 obesity, defined as body mass index ≥35 kg/m^2.
    - eGFR <30 mL/min using the recommended CKD-EPI equations in Section 10.6.2.
    - Total bilirubin >1.5 × ULN (may be repeated once, with fractionation, for confirmation during the Screening Phase, and direct bilirubin >1.5 × ULN is exclusionary if Gilbert's syndrome is suspected).
    - AST (SGOT) or ALT (SGPT) >1.5 × ULN (may be repeated once for confirmation during the Screening Phase).
    - Neutrophil count ≤1000/μL (or equivalent).

Other Exclusion Criteria:

14. 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.

15. Unwilling or unable to comply with all scheduled visits, treatment plan, laboratory tests, and other study procedures, including the inability to perform self-report diary for the duration of participation in the study in the investigators opinion.

5.3. Lifestyle Considerations

5.3.1. Contraception

In female participants of child-bearing potential, 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. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use acceptable 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.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently enrolled in the study. If the participant does not meet all eligibility criteria, the participant will be considered a Screen Failure. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any SAE.

Participants in this study may be screened only once. Rescreening is not permitted.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all prespecified investigational, 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 (PF-07930207) 10 mg or matching placebo.

6.1. Study Intervention(s) Administered

Zavegepant (PF-07930207), is formulated as 10 mg for intranasal single dose administration using an unidose nasal spray device. Zavegepant and matching placebo are identical in appearance.

Study Intervention(s)		
Intervention Name	Zavegepant (PF-07930207)	Placebo
Arm Name (group of participants receiving a specific treatment or no treatment)	Zavegepant (PF-07930207)	Placebo
Type	Drug	Drug
Dose Formulation	Nasal spray	Nasal spray
Unit Dose Strength(s)	10 mg per 0.1 mL	0 mg per 0.1 mL
Dosage Level(s)	Single dose	Single dose
Route of Administration	Intranasal	Intranasal
Use	Experimental	Placebo
IMP or NIMP/AxMP	IMP	IMP
Sourcing	Provided centrally by the sponsor Refer to the IPM.	Provided centrally by the sponsor Refer to the IPM.
Packaging and Labeling	Study intervention will be provided in unidose nasal spray. Each nasal spray will be labeled as required per country requirement. Products will be provided with blinded labels.	Study intervention will be provided in unidose nasal spray. Each nasal spray will be labeled as required per country requirement. Products will be provided with blinded labels.
Current/Former Name(s) or Alias(es)	Zavegepant (PF-07930207)	NA

Study Arm(s)		
Arm Title	Zavegepant (PF-07930207)	Placebo
Arm Type	Experimental	Placebo
Arm Description	Participants will receive a single dose zavegepant (PF-07930207) 10 mg	Participants will receive a single dose placebo
Associated Intervention Labels	Zavegepant (PF-07930207)	Placebo

For some special cases, study intervention may be shipped by courier to study participants if permitted by local regulations and in accordance with storage and transportation requirements for the study intervention. Pfizer does not permit the shipment of study intervention by mail. The tracking record of shipments, including temperature monitoring data, and the chain of custody of study intervention must be kept in the participant's source documents/medical records.

6.1.1. Administration

Study intervention (unidose nasal spray containing zavegepant or matching placebo) will be packaged in a labeled carton. There are no dose adjustments in this study and participants will receive study intervention sufficient to treat 1 migraine headache of moderate or severe intensity within 45 days of randomization (Baseline Visit).

Participants will be dispensed the study intervention and **MUST** be trained on the proper use of unidose nasal spray device using instructions provided at randomization (Baseline Visit). The participant will be instructed to take their study intervention, as an outpatient, if they have a migraine headache which reaches moderate or severe intensity.

Participants will take the unidose nasal spray from the carton at the time of moderate or severe migraine headache onset ***ONLY after answering all the questions required including their current pain intensity and migraine associated symptoms (status and intensity), and identified their current MBS (selected from phonophobia, photophobia or nausea) in the handheld***. The handheld will instruct the participant to take study intervention after the initial assessments are completed in the device.

Participants will administer a single spray of the medication from the device. Participants **MUST** inform the study staff if they sneeze, if the device malfunctions or if the device does not dispense a complete spray as soon as possible.

All occurrences of dose misadministration should be communicated to Pfizer, refer to Section 8.4.10 Medication Errors for additional information.

Under no circumstance may a participant be assigned a second dose of study intervention.

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 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 IPM.

5. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label. Site staff will instruct participants on the proper storage requirements for take-home study intervention.

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. All study intervention that is taken home by the participant, both used and unused, must be returned to the investigator by the participant. **Returned study intervention must not be redispensed to the participants.**

8. Further guidance and information for the final disposition of unused study interventions are provided in the IPM. 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 as described in the IPM.

6.2.1. Preparation and Dispensing

A qualified staff member will dispense the study intervention using unique container numbers via an IRT system in the labelled carton provided, in quantities appropriate according to the SoA. A second staff member will verify the dispensing. The participant should be instructed to maintain the product in the carton provided throughout the course of dosing and return the carton to the site at the next study visit.

6.3. Assignment to Study Intervention

Allocation of participants to treatment groups will proceed through the use of an IRT system. The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a randomization number corresponding to the assigned treatment group, and DU or container number(s) when study intervention is being supplied via the IRT system. The IRT system will provide a confirmation report containing the participant number, randomization number, and DU or container number assigned. The confirmation report must be stored in the site's files.

Randomization will occur in the IRT. Randomization will be stratified by the use of stable prophylactic migraine medications through randomization (yes or no) and country/region.

Study intervention will be dispensed at the Baseline Visit as indicated in the SoA.

The study-specific IRT reference manual and IPM will provide the contact information and further details on the use of the IRT system.

6.4. Blinding

This is a double-blind study with administration of zavegepant 10 mg or matching placebo.

6.4.1. Blinding of Participants

Participants will be blinded to their assigned study intervention.

6.4.2. Blinding of Site Personnel

Investigators and other site staff will be blinded to participants' assigned study intervention.

6.4.3. Blinding of the Sponsor

Sponsor staff will be blinded to participants' assigned study intervention, except for sponsor staff involved in the assignment or distribution of study intervention.

6.4.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the study medical monitor prior to unblinding a participant's treatment assignment unless this could delay further management of the participant. If a participant's treatment assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IPM will provide the contact information and further details on the use of the IRT system.

6.5. Study Intervention Compliance

Responsible study personnel will dispense the study intervention at randomization (Baseline Visit). When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at the EOT visit. Compliance will be documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

A record of the number of study intervention dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention date, including date for intervention delays, will also be recorded in the CRF.

Participants have to be counselled on the importance of taking the study intervention as directed when a migraine occurs and reaches moderate or severe pain intensity. If the participant does not have a qualifying migraine or take their study intervention within 45 days of the Baseline Visit, they should return to the clinic for their EOT Visit and return their study intervention.

6.6. Dose Modification

The study intervention will be administered using an unidose nasal spray device containing a single dose of zavegepant or matching placebo. Dose modification is not permitted in this 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. It is expected that participants will be treated as required with standard-of-care treatments, as advised by their usual care physician.

6.8. Treatment of Overdose

This is a single and fixed dose study. There is no clinical experience with overdose of zavegepant. Treatment of overdose with zavegepant should consist of general supportive measures.

There is no specific treatment for an overdose with zavegepant.

In the event of an overdose, the investigator/treating physician 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 at least until the next scheduled follow-up.

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.**

6.9. Prior and Concomitant Therapy

Participants in this study will be allowed to be on certain concomitant medications that have been prescribed. Attempts should be made not to alter the doses and regimens of the concomitant medications after randomization and for the duration of participation in this study, except in circumstances where a change in dose is deemed medically necessary. Any changes must be captured in the CRF.

Hormonal contraceptives that meet the requirements of this study are allowed to be used in participants who are WOCBP (see Appendix 4).

Low dose aspirin (ie, 100 mg or less) for documented cardiovascular prophylaxis is allowed.

All concomitant medications 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 medications at each visit.

A concomitant medication paper diary will be provided to participants at the Screening Visit. Use of any concomitant medication will be recorded by the participant on a paper diary and returned to the site at the Baseline and EOT Visits.

Medications taken before the administration of study intervention will be documented as a prior therapy. Medications taken after the administration of study intervention will be documented as concomitant therapy.

6.9.1. Prohibited Concomitant Medications

The medications listed below are prohibited during the study, ie, starting at the Screening Visit and through the EOT Visit, unless otherwise specified. Site are encouraged to contact the sponsor should there be questions as to whether a medication is permitted or prohibited.

1. St. John's Wort taken 14 days prior to randomization and through the EOT Visit.
2. Herbal products including TCMs for the treatment of headache taken 14 days prior to randomization and through the EOT Visit.
3. Barbiturate-containing products (ie, Fioricet, Fiorinal, butalbital, phenobarbital) taken 14 days prior to randomization and through the EOT Visit.
4. Modafinil taken 14 days prior to randomization and through the EOT Visit.
5. Butterbur root or extracts taken 14 days prior to randomization and through the EOT Visit.
6. Narcotics, such as opioids (eg, morphine, codeine, oxycodone and hydrocodone) taken 2 days prior to randomization and through the EOT Visit.

7. Acetaminophen or acetaminophen containing products taken 2 days prior to randomization (acetaminophen up to 1000 mg/day is allowed as rescue medication. Refer to Section 6.9.2). During the Screening Phase (3-28 days), use of acetaminophen or acetaminophen containing products at daily dosing levels of greater than 1000 mg/day is also prohibited.

8. Marijuana and all forms of ingested or inhaled CBD and THC-containing products.

9. Muscle relaxants (baclofen is allowed as rescue medication, Refer to Section 6.9.2 Rescue Medication).

10. Acute or chronic treatment with OTC or prescription nasal sprays. Participants must stop all OTC/prescription nasal sprays 14 days prior to the Screening Visit and through the EOT Visit.

11. OTC or prescription topical nasal steroids, oxymetazoline, topical nasal antihistamines, topical nasal anticholinergics, and topical nasal mast cell stabilizers used within 14 days prior to the Screening Visit and through the EOT Visit.

12. New prophylactic migraine medication is not permitted to add unless the dose level has been kept stable for at least 3 months prior to the Screening Visit and through the EOT Visit.

13. CGRP antagonist biologics (ie, galcanezumab, erenumab, fremanezumab, and eptinezumab-jjmr) must be discontinued 6 months prior to the Screening Visit and are prohibited through the EOT Visit.

14. Oral gepants taken 14 days prior to the Screening Visit and through the EOT Visit (ie, rimegepant, ubrogepant and atogepant).

15. Lasmiditan taken 14 days prior to randomization and through the EOT Visit.

16. Atypical antipsychotics such as aripiprazole, olanzapine, quetiapine, ziprasidone, risperidone or valproic acid/valproate.

17. Lamotrogine.

18. Use of Cefaly® or any other device for migraine treatment within 12 weeks of the Screening Visit and through the EOT Visit.

19. Acupuncture for the treatment of headache used from the Screening Visit and through 48 hours postdose of study intervention administration.

6.9.2. Rescue Medication

The study site will not supply rescue medication that will be obtained locally by participants. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

In all circumstances, the participant will always continue to complete the handheld entries through the 48-hour assessment after taking the study intervention. A Rescue Medication paper diary will be provided to participants at the Baseline Visit. Participants will record any rescue medication taken on the Rescue Medication paper diary and return to the site at the EOT Visit.

After administration of study intervention, **ALL** other headache medication is prohibited during the first 2 hours postdose of study intervention administration. A participant who does not experience relief of their migraine headache at the end of 2 hours after administration of study intervention ***(and after the 2-hour assessments have been completed on the handheld device)***, will be permitted to use ONLY the following rescue medication: ***aspirin, ibuprofen, acetaminophen up to 1000 mg/day (this includes Excedrin Migraine), naproxen (or any other type of NSAID), antiemetics (ie, metoclopramide or promethazine), or baclofen. These are the only medications allowed for rescue treatment after 2 hours postdose of study intervention***.

If the migraine is relieved by study intervention at 2 hours postdose but then returns to a moderate or severe pain intensity level between 2 and 48 hours postdose, the participant will be permitted to take the same rescue therapy as outlined above.

During the 45 days of the Treatment Phase, if the participant has a nonqualifying migraine (attack with mild pain) or a migraine that they do not treat with study intervention, the participant is permitted to use only the following medications: ***aspirin, ibuprofen, naproxen (or any other type of NSAID), antiemetics (ie, metoclopramide or promethazine), or baclofen***.

After completing all assessments in their handheld (through 48 hours postdose and before returning to the clinical site for EOT Visit), if participants experience a migraine, they are allowed to take their prescribed standard of care medication per local practice (including triptans if not contraindicated and acetaminophen up to 1000 mg/day, this includes Excedrin Migraine or other similar combination products), provided the medication is not otherwise prohibited.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Since this is a single-dose study, this section is not applicable.

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:

- Criteria for a potential Hy's law case are met – refer to Section 10.5;
- Intent to become pregnant or pregnancy confirmed via β-hCG testing;

- Safety or tolerability concern arises, in particular if not responsive to symptomatic management, double-blind study intervention may be stopped in an individual participant at the discretion of the investigator.

- See Section 8.3.7 for guidance on study discontinuation based on results from the C-SSRS.

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.

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 return to the clinic for 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.

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.

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 individual participants in this study is up to approximately 35 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 Lifestyle Considerations and Prior and Concomitant Therapy sections of the protocol.

8.1.1. Telehealth Visits

The Follow-Up Visit may occur via telephone contact and must occur 28 to 35 days after administration of study intervention.

Telehealth visits may be used to assess participant safety and collect data points. Telehealth includes the exchange of healthcare information and services via telecommunication technologies (eg, audio, video, videoconferencing software) remotely, allowing the participant and the investigator to communicate on aspects of clinical care, including medical advice, reminders, education, and safety monitoring. The following assessments must be performed during a telehealth visit (see the SoA):

- Review and record study intervention(s), including compliance and missed doses.
- Review and record any AEs and SAEs since the last contact. Refer to Section 8.4.
- Review and record any new concomitant medications or changes in concomitant medications since the last contact.
- Review and record contraceptive method and results of pregnancy testing. Confirm that the participant is adhering to the contraception method(s) required in the protocol. Refer to Appendix 4.

Study participants must be reminded to promptly notify site staff about any change in their health status.

8.2. Efficacy Assessments

8.2.1. Pain

Participants will record the headache pain intensity using a 4-point numeric rating scale (none, mild, moderate, severe) before and after taking study intervention in the handheld at time points of 15, 30, 45, 60, and 90 minutes and 2, 3, 4, 6, 8, 24 and 48 hours postdose as indicated in the SoA.

8.2.2. Nausea, Phonophobia and Photophobia

Participants will record the status (present or absent) and intensity (mild, moderate, or severe) of migraine associated symptoms (photophobia, phonophobia, nausea) in the handheld at the same time points as headache pain intensity as indicated in the SoA.

Participants will also record their current MBS (selected from nausea, phonophobia or photophobia) in the handheld before taking study intervention.

8.2.3. Rescue Medication

Participants must **NOT** take rescue medication until 2 hours postdose with study intervention. Participants will record their use of rescue medication in a paper diary. Refer to Section 6.9.2 Rescue Medication.

8.2.4. Functional Disability

Participants will record their functional disability level using the Functional Disability scale, a 4-point numeric rating scale (normal, mildly impaired, severely impaired, requires bedrest) in the handheld at the same time points as headache pain intensity as indicated in the SoA.

8.2.5. Patient Global Impression of Change (PGIC)

PGIC ratings are increasingly being used as a "gold standard" for determining clinically important change. Participants will record their overall status change in the eCOA handheld device at 30 minutes, 60 minutes, 2 hours and 24 hours postdose using the 7-point numeric rating scale (very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse) in the handheld as indicated in the SoA.[12]

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

Physical examinations will be performed by a medically qualified or appropriately delegated site staff. Participants will undergo a complete physical examination at the Screening Visit and at the scheduled visits as indicated in the SoA.

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded. Height will only be captured at the Screening Visit.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

Physical examination findings collected during the study will be considered source data 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 by the investigator or medically qualified delegate with a nasal speculum or otoscope at the Screening, Baseline and EOT Visits (refer to the SoA) to detect evidence of significant nasal conditions that may affect the

administration or absorption of the nasal product (ie, severe septum deviation, nasal deformity or blockage, inflammation, perforation, mucosal erosion or ulceration, polyposis, nasal trauma). Nasal findings will be recorded as appropriate and followed until resolution.

8.3.3. Vital Signs

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.

8.3.3.1. Blood Pressure and Pulse Rate

Sitting BP and PR measurements will be assessed with an automated device. Manual techniques will be used only if an automated device is not available. When done manually, PR will be measured in the brachial/radial artery for at least 30 seconds.

BP and PR measurements should be preceded by at least 10 minutes of rest with the participant in a sitting position, in a quiet setting without distractions. The same arm (preferably the dominant arm) will be used throughout the study. Participants should be instructed not to speak during measurements.

Vital signs will be taken before collection for laboratory tests and consist of a single measurement of PR and single BP measurement.

Additional collections of BP and PR will be permitted, as necessary, to ensure appropriate collection of safety data.

8.3.4. Electrocardiograms

A central ECG service will be utilized for all ECGs and based on the central read, the investigator will determine if any abnormalities are of clinical significance.

Standard 12-lead ECGs utilizing limb leads (with a 10-second rhythm strip) should be collected at times specified in the SoA section of this protocol using an ECG machine that automatically calculates the HR and measures PR interval, QT interval, QTcF, and QRS complex. Alternative lead placement methodology using torso leads (ie, Mason-Likar) should not be used given the potential risk of discrepancies with ECGs acquired using standard limb lead placement. All scheduled ECGs should be performed after the participant has rested quietly for at least 10 minutes in a supine position.

If a) a postdose QTcF interval remains ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QTcF value is ≥500 ms for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF values get progressively longer, the participant should undergo continuous ECG monitoring. A cardiologist should be consulted if QTcF values do not return to less than the criteria listed above after 8 hours of monitoring (or sooner, at the discretion of the investigator).

ECG data will be submitted to a central laboratory for measurement. The final ECG report from the central laboratory should be maintained in the participant's source documentation and be the final interpretation of the ECG recording. Any clinically significant changes from the baseline ECG at the Screening Visit may potentially be AEs (Appendix 7) and should be evaluated further, as clinically warranted.

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 7.

8.3.4.1. Alternative Facilities for Electrocardiograms

The participant may visit an alternative facility to have the ECGs performed due to COVID-19 **ONLY** for safety monitoring at the EOT Visit. Any potential issues should be discussed with sponsor and will be addressed on an individualized basis. Qualified study site personnel must order, receive, and review results. ECGs can also be performed at home through home health vendors or through remote device collection.

8.3.5. Clinical Safety Laboratory Assessments

A central laboratory vendor will be utilized for this study and a laboratory manual will be provided to each site.

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 to 35 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 5 for suggested actions and follow-up assessments in the event of potential DILI.

See Appendix 6 for instructions for laboratory testing to monitor kidney function and reporting laboratory test abnormalities.

8.3.5.1. Alternative Facilities for Clinical Safety Laboratory Assessment

Protocol-specified safety laboratory evaluations may be conducted at a local laboratory due to COVID-19 **ONLY** for safety monitoring at the EOT Visit, during a mobile visit, or at home if permitted by local regulations. The local laboratory may be a standalone institution or within a hospital. Any potential issues should be discussed with sponsor and will be addressed on an individualized basis.

If a local laboratory is used, qualified study site personnel must order, receive, and review results. Site staff must collect the local laboratory reference ranges and certifications/ accreditations for filing at the site. Laboratory test results are to be provided to the site staff as soon as possible. The local laboratory reports should be filed in the participant's source documents/medical records. Relevant data from the local laboratory report should be recorded on the CRF.

8.3.6. Pregnancy Testing

A 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 the participant's receiving 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. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded if the serum pregnancy result is positive.

Pregnancy tests will be conducted as indicated in the SoA. If applicable, a FSH test will be obtained at Screening Visit to confirm WOCBP status.

8.3.6.1. At-Home Pregnancy Testing

Home pregnancy test will be provided to WOCBP after completion of Baseline Visit. WOCBP who suspect that they have become or may have become pregnant despite using proper birth control methods, should use the home pregnancy test provided at Baseline Visit at any time during the study. A home urine pregnancy testing kit with a sensitivity of at least 25 mIU/mL may be used by the participant to perform the test at home, if compliant with local regulatory requirements. The pregnancy test outcome, if performed at home, should be documented in the participant's source documents/medical records and relevant data recorded on the CRF. Confirm that the participant is adhering to the contraception method(s)

required in the protocol. If the pregnancy test is positive, participants should not take study intervention and should immediately contact the investigator.

8.3.7. Suicidal Ideation and Behavior Risk Monitoring

8.3.7.1. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a an interview-based rating scale to systematically assess suicidal ideation and suicidal behavior.[13,14] The C-SSRS "Screening version" will be used at the Screening Visit and the "Since Last Visit version" will be used at subsequent visits specified in the SoA in this study.

The C-SSRS Assessment is intended to help establish a person's immediate risk of suicide. The C-SSRS is a clinician administered scale that should be administered by a certified rater. This scale will be collected on site with a paper form. The C-SSRS should be reviewed by the investigator or designee before the participant is allowed to leave the site.

Any "Yes" responses must be immediately evaluated by the investigator. If the investigator determines that a participant is at risk of suicide, self-harm, appropriate measures to ensure the participant's safety and obtain mental health evaluation must be implemented. In such circumstances, the participant will not be permitted in the study (refer to Section 5.2) or must immediately be discontinued from the study. The event should be recorded as either an AE or SAE as determined by the investigator and reported within 24 hours to the sponsor.

8.3.7.1.1. Rater Qualifications

For certain specific rating assessments, only qualified raters will be allowed to evaluate and/or rate participants in this study. The minimum qualifications a rater must meet for each study rating assessment will be outlined in the training materials provided to each participating site. The level of experience with the target population (or equivalent), specific scale experience (or equivalent), and certification required (if applicable) will be listed and used to determine whether a rater is approved for a given assessment. The rater must become certified to perform selected study assessments before they can participate in the conduct of the study. For specifically defined assessments, rater training and standardization exercises may be conducted, and written documentation will be provided by the site for each rater's certification. In return, each site will be provided written documentation outlining each rater's certification for specific study assessments. Recertification may be required at periodic intervals during the study. The raters who administer specific study assessments will be documented in a centralized location and all site staff who administer ratings will be verified in the site study documentation during the conduct of the study.

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 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 CT SAE Report Form.

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 CT SAE Report Form.

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 CT SAE Report Form 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.

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 inhalation or skin contact.
    - A male family member or healthcare provider who has been exposed to the study intervention by 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 on the CT SAE Report Form and an EDP Supplemental Form, 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 CT SAE Report Form and EDP Supplemental Form. 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 CT SAE Report Form 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 EDP Supplemental Form. 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 preprocedure 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 live-born 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 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 CT SAE Report Form. 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 CT SAE Report Form 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 CT SAE Report Form, 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 CT SAE Report Form must be maintained in the investigator site file.

8.4.6. Cardiovascular and Death Events

This part is not applicable in this study.

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

This part is not applicable in this study.

8.4.8. Adverse Events of Special Interest

The following AEs of special interest will be assessed: hepatic-related AEs, potential drug abuse AEs, cardiovascular AEs, suicidality AEs, and local irritation AEs. The mapping of preferred terms to each of these AE categories will be based on Zavegepant Core SAP and subject to changes due to a new MedDRA version or clinical review.

AESIs are examined as part of routine safety data review procedures throughout the clinical trial and as part of signal detection processes. Should an aggregate analysis indicate that these prespecified events occur more frequently than expected, eg, based on epidemiological data, literature, or other data, then this will be submitted and reported in accordance with Pfizer's safety reporting requirements. Aggregate analyses of safety data will be performed on a regular basis per internal SOPs.

All AESIs must be reported as an AE or SAE following the procedures described in Sections 8.4.1 through 8.4.4. An AESI is to be recorded as an AE or SAE on the CRF. In addition, an AESI that is also an SAE must be reported using the CT SAE Report Form.

8.4.8.1. Lack of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE**.

8.4.9. Medical Device Deficiencies

Medical Device Deficiencies are not applicable in this study.

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 CT SAE Report Form 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;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;

- The administration of study intervention that has undergone temperature excursion from the specified storage range, ***unless*** it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, 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 CT SAE Report Form **only when associated with an SAE.**

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Genetics

Genetic analyses are not evaluated in this study.

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

The treatment comparison being made in this study is zavegepant 10 mg versus placebo. The null and alternative hypotheses are shown below. The test will be 2-sided.

The null hypothesis (H_0) is that the difference in the stratified response rate between treatment groups is zero.

The alternative hypothesis (H_1) is that the difference in the stratified response rate between treatment groups is not zero.

9.1.1. Estimands

9.1.1.1. Primary Estimand/Co-primary Estimands

The co-primary estimands are defined by the following attributes:

- Population: all randomized participants with migraine headache of moderate or severe intensity who took study intervention.
- Endpoints: percentage of participants with pain intensity of none at 2 hours postdose and separately, the percentage of participants with an MBS reported on study before dosing that is absent at 2 hours postdose. The MBS before dosing is reported as nausea, phonophobia, or photophobia. Symptom status is reported postdose as present or absent for each symptom (nausea, phonophobia, and photophobia).
- Treatment condition: zavegepant and placebo.
- Intercurrent event: taking rescue medication at or before 2 hours postdose will be regarded as a failure.
- Population-level summary: difference in percentages between treatment groups.

9.1.1.2. Secondary Estimands

The secondary efficacy estimands using the same strategy as the co-primary estimands are defined by the following attributes:

- Population: all randomized participants with migraine headache of moderate or severe intensity who took study intervention.
    - For the objective of evaluating return to normal function, phonophobia freedom, photophobia freedom, and nausea freedom at 2 hours postdose, the population will be participants defined above who had functional disability (mildly impaired, severely impaired, or requires bedrest), phonophobia present, photophobia present, and nausea present, respectively, at the time of dosing.
    - For the objective of evaluating pain relapse, the population will be participants defined above who had pain freedom at 2 hours postdose.

- Endpoints:
    - percentage of participants with a pain intensity of none or mild at 15 minutes, 30 minutes, 60 minutes, 2 hours postdose, at all time points from 2 to 24 hours postdose, at all time points from 2 to 48 hours postdose, respectively.
    - percentages of participants with a functional disability level of normal at 15 minutes, 30 minutes, 60 minutes and 2 hours postdose, respectively.
    - percentage of participants with phonophobia absent, with photophobia absent at 2 hours postdose, respectively.
    - percentage of participants with a pain intensity of none at all time points from 2 to 24 hours postdose, at all timepoints from 2 to 48 hours postdose, respectively.
    - percentage of participants with nausea absent at 2 hours postdose.
    - percentage of participants with a pain intensity of mild, moderate, or severe at any time point from 2 to 48 hours postdose.
- Treatment condition: zavegepant and placebo.
- Intercurrent event: taking rescue medication at or before the corresponding assessed time points as specified in the endpoints postdose will be regarded as a failure.
- Population-level summary: difference in percentage of participants achieving the specific outcome at time points of interest between treatment groups.

The secondary efficacy estimand for objective of rescue medication use is defined by the following attributes:

- Population: all randomized participants with migraine headache of moderate or severe intensity who took study intervention.
- Endpoint: percentage of participants taking rescue medication within 24 hours postdose.
- Treatment condition: zavegepant and placebo.
- No relevant intercurrent event is considered since taking rescue medication is the analysis objective.
- Population-level summary: difference in percentages between treatment groups.

9.1.2. Multiplicity Adjustment

Type I error is controlled by a hierarchical gate-keeping procedure. First, the family of 2 co-primary endpoints is tested. In particular, zavegepant is tested for superiority against placebo at a 2-sided alpha=0.05 level for both co-primary endpoints. If the tests of both co-

primary endpoints are significant (ie, both p-values are ≤0.05), then the key secondary endpoints are tested hierarchically at the 2-sided alpha=0.05 level in the order shown in Section 3. Thus, a key secondary endpoint is tested only if the preceding key secondary endpoint in the hierarchy is determined to be significant (ie, p-value ≤0.05). If a test in the hierarchy is not significant, then any further tests on endpoints in the sequence will have p-values presented only for descriptive purposes, and no conclusions are drawn from those results.

For other secondary endpoints and exploratory endpoints, no attempt is made to adjust for multiplicity. Any other secondary endpoints and exploratory endpoints for which p-values are produced are evaluated at an unadjusted, 2-sided alpha=0.05 level and presented only for descriptive purposes.

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 after screening. 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.
FAS	All participants in the enrolled analysis set who are randomly assigned to study intervention (zavegepant or placebo).
EAS	All participants in the full analysis set who satisfy the following criteria: • Randomized only once • Have a migraine of moderate or severe pain intensity at the time of dosing • Take study intervention (zavegepant or placebo) • Have postdose efficacy data (ie, non-missing pain intensity, phonophobia status, photophobia status, nausea status, or functional disability level with

Participant Analysis Set	Description
	finding date/time after the study intervention date/time).
Safety analysis set	All participants in the enrolled analysis set who take study intervention (zavegepant or placebo).

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

Descriptive statistics for all efficacy and safety endpoints at appropriate time points will be provided by treatment group. Continuous variables will be summarized by standard descriptive statistics (n, mean, standard deviation, median, minimum and maximum), and categorical variables will be summarized by the number and percentage in each category (with the corresponding sample size).

In treatment comparisons of binary endpoints, a stratified CMH test will be used, and CIs will be based on a normal approximation to the binomial distribution.

9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

9.3.2.1. Main Analytical Approach

Zavegepant will be tested for superiority against placebo at an alpha=0.05 level for both co-primary endpoints using the EAS. For each endpoint, treatment groups will be compared using a CMH test for the difference in percentages of participants achieving the endpoint response criteria (zavegepant-placebo) stratified by country/region. The stratified difference in percentages between treatment groups will be presented with p-value and a 95% CI based on normal approximation. For individual treatment group, the percentage of participants achieving the endpoint response criteria will be presented with a 95% CI based on normal approximation.

Participants with missing data at 2 hours postdose or taking rescue medication at or before 2 hours postdose will be classified as failures.

9.3.2.2. Sensitivity Analyses

Sensitivity analyses for co-primary endpoints include the following:

- Multiple imputation: The main analysis is repeated using a multiple imputation approach to impute missing data for a co-primary endpoint at 2 hours postdose.

Appropriate covariates may be included. First, intercurrent events of taking rescue medication at or before 2 hours postdose will be regarded as a failure. Next, missing response status (responder versus failure) in the 2-hour postdose analysis window is imputed for participants who are not missing any of the covariates (participants missing any of the covariates are considered failures). The same statistics as the main analysis are presented. The imputation details and analysis window will be described in the SAP.

- Varying response rate imputation: The main analysis is repeated by imputing missing data for a primary endpoint at 2 hours postdose in each treatment group with varying response rates over the range of 0%, 10%, 20% and 30%. First, intercurrent events of taking rescue medication at or before 2 hours postdose will be regarded as a failure. Next, missing response status (responder versus failure) in the 2-hour postdose analysis window is imputed. The imputation details and analysis window will be described in the SAP.

9.3.2.3. Subgroup Analyses

Subgroup analyses will be performed for the co-primary endpoints and will be described in the SAP.

9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

The EAS will be used for the analysis of the secondary endpoints. For endpoints based on a single time point, such as phonophobia freedom at 2 hours postdose, participants with missing data at a single time point will also be classified as failures. For endpoints based on multiple time points, such as sustained pain relief from 2 to 48 hours postdose, participants with missing data at (a) 2, 24, or 48 hours postdose, or (b) more than 1 time point from 3 to 8 hours postdose will also be classified as failures.

9.3.4. Tertiary/Exploratory Endpoint(s) Analysis

For each efficacy endpoint, response over time will be tabulated for the EAS by treatment group as the number and percentage of participants who achieve the endpoint response criteria at each time point from 15 minutes through 48 hours postdose. Endpoints will include pain freedom, MBS freedom, pain relief, return to normal function, photophobia freedom, phonophobia freedom, and nausea freedom.

9.3.5. Safety Analyses

The frequencies of the following postdose safety endpoints will be tabulated by treatment group for the safety analysis set: AEs by intensity; SAEs; AEs related to study intervention; local irritation AEs; laboratory test abnormalities by toxicity grade; and liver function test elevations.

The investigators will determine the intensity of AEs and the relationship of AEs to study intervention. The investigators' terms will be coded using the latest version of the MedDRA available at the start of the study. AEs will be presented by system organ class and preferred term.

Laboratory test results will be graded according to numeric laboratory test criteria in CTCAE if available; otherwise, results will be graded according to numeric laboratory test criteria in DAIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.

Deaths will be listed without regard to onset for the enrolled analysis set.

9.3.5.1. Electrocardiogram Analyses

Values and changes from baseline for the ECG parameters HR, QTcF, PR interval, and QRS complex will be summarized descriptively by treatment group and time point (ie, baseline and EOT).

The number and percentage of participants with maximum postdose QTcF values and maximum increases from baseline in the categories below will be tabulated by treatment group. The number and percentage of participants with uncorrected QT values >500 ms will also be presented

Safety QTcF Assessment

Degree of Prolongation	Mild (ms)	Moderate (ms)	Severe (ms)
Absolute value	>450 to 480	>480 to 500	>500
Increase from baseline		>30 to 60	>60

9.3.6. Other Analyses

Not applicable.

9.4. Interim Analyses

No interim analysis will be conducted for this study.

9.5. Sample Size Determination

It is anticipated that about 90% of the 700 participants randomized to each treatment group will have a headache in the allotted time period, resulting in approximately 630 participants evaluable for efficacy in each treatment group.

The sample size calculation is based on pooled efficacy results from the Phase 2/3 BHV3500-201 and Phase 3 study BHV3500-301. The response rates for zavegepant 10 mg and for the placebo group in pooled analysis were 23.2% and 15.1%, respectively, for pain freedom at 2 hours postdose, and 40.5% and 32.1%, respectively, for MBS freedom at 2 hours postdose.

A target sample size of 1260 evaluable participants (630 per group) will provide approximately 95.7% power for the co-primary endpoint of pain freedom at 2 hours postdose, approximately 87.5% power for the co-primary endpoint of MBS freedom at 2 hours postdose, and approximately 84% power to detect a difference between treatment groups for both endpoints jointly, using a 2-sided alpha of 0.05.

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.

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 standard operating procedures 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 24 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.

QTLs are predefined parameters that are monitored during the study. Important deviations from the QTLs and any remedial actions taken will be summarized in the CSR.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data 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 and monitoring 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.

Definition of what constitutes source data and its origin can be found in the Source Document Locator, which is maintained by the sponsor.

Description of the use of the computerized system is documented in the Data Management Plan, which is maintained by the sponsor.

The investigator must maintain accurate documentation (source data) 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. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

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 or designee/CRO 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.

10.1.10. Publication Policy

For multicenter trials, the primary publication will be a joint publication developed by the investigator and Pfizer reporting the primary endpoint(s) of the study covering all study sites. 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.

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, subject to the other requirements described in this section.

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.

10.1.11. 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 supporting study documentation/study portal or other electronic system.

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, (c) site emergency phone number active 24 hours/day, 7 days per week, and (d) Pfizer Call Center number.

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. The Pfizer Call Center number is to be used when the investigator and site staff are unavailable. The Pfizer Call Center number is not for use by the participant directly; if a participant calls that number directly, they will be directed back to the investigator site.

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.

If possible, participants should be fasting for a minimum of 8 hours prior to all blood draws. However, if a participant is not fasting at a given visit, the blood draw should still be performed, and the non-fasting status should be documented.

Table 2. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Local Dipstick Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN (urea) and creatinine eGFR using CKD-EPI equations Glucose (fasting) Calcium Sodium Potassium Chloride AST, ALT Total bilirubin Direct bilirubin Indirect bilirubin CK Alkaline phosphatase LDH (lactate dehydrogenase)	Protein (qual) Blood (qual) Nitrites Leukocyte esterase Microscopy[a]	• Urine drug screening[b] • Pregnancy test (β-hCG)[c] At Screening Visit only: • FSH[d] • HbA1c
	For suspected DILI [e] AST/ALT T bili, direct and indirect bili Total bile acids, GGT Total protein, albumin Alkaline phosphatase CK PT, INR Acetaminophen/paracetamol or protein adduct levels Hepatitis serology		

a. Only if UTI is suspected or urine blood, protein, nitrites, or leukocyte esterase is positive.
b. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, PCP, barbiturates, benzodiazepines, and amphetamines (others are site and study specific).
c. Serum or urine β-hCG for female participants of childbearing potential as indicated in the SoA.
d. For confirmation of postmenopausal status only.
e. Additional tests may be needed for Hy's Law. See Appendix 5 for detailed information. Participants may have to return to the study site to provide additional blood samples for these laboratory tests.

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 laboratory 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.

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 nonpathogenic

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 on the CT SAE Report Form 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 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 for reporting of SAE information.

Safety Event	**Recorded on the CRF**	**Reported on the CT SAE Report Form 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 or 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 nonparticipant 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 AE or SAE): any pregnancy information is reported to Pfizer Safety using the CT SAE Report Form and EDP Supplemental Form; if the EDP is associated with an SAE, then the SAE is reported to Pfizer Safety using the CT SAE Report Form.
** **EDB** is reported to Pfizer Safety using the CT SAE Report Form, 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 CT SAE Report Form.

- 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.

- 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.

- 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 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 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. • If the electronic system is unavailable, then the site will use the paper SAE DCT (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 the preferred method to transmit this information to Pfizer Safety. • 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

No contraception methods are required for male participants in this study, as the calculated safety margin is ≥100 fold between the estimated maternal exposure due to seminal transfer and the NOAEL for serious manifestations of developmental toxicity in nonclinical studies.

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 definitions below in Section 10.4.3).

  OR

- Is a WOCBP and agrees to use an acceptable contraceptive method during the intervention period (for a minimum of 28 days after the last dose of study intervention). 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 in adolescents or athletes) 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 of age 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:

<u>Highly Effective Methods That Have Low User Dependency</u>

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;
    - Intravaginal;
    - Transdermal.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
    - Oral;
    - Injectable.

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.

Other Effective Methods

9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
10. Male or female condom, with or without spermicide.
11. Cervical cap, diaphragm, or sponge with spermicide.
12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-Up Assessments and Study Intervention Rechallenge Guidelines

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, total bile acids, 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, 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.

10.6. Appendix 6: Kidney Safety Monitoring Guidelines

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

Standard kidney safety monitoring requires assessment of baseline and postbaseline serum creatinine (Scr measurement to eGFR [Scr-based eGFR] or [eCrCl]). Baseline and postbaseline Scys makes it feasible to distinguish AKI from other causes of Scr increase. If Scr increase is confirmed after baseline, then reflex measurement of Scys is indicated to estimate the combined Scr-Scys eGFR calculation (for adults only).

Regardless of whether kidney function monitoring tests are required as a routine safety monitoring procedure in the study, if the investigator or sponsor deems it necessary to further assess kidney safety and quantify kidney function, then these test results should be managed and followed per standard of care.

10.6.2. Age-Specific Kidney Function Calculation Recommendations

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

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

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10.6.3. Adverse Event Grading for Kidney Safety Laboratory Abnormalities

AE grading for decline in kidney function (ie, eGFR or eCrCl) will be according to KDIGO criteria.

10.7. Appendix 7: 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) or 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 seconds' 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.
• 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 periods of asystole ≥3.0 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 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 enumerated list of major events of potential clinical concern 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 to be reported as AEs/SAEs.

10.8. Appendix 8: Abbreviations

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

Abbreviation	Term
5-HT1B/1D	5-hydroxytryptamine receptor 1B/1D
Abs	absolute
ACS	Acute Coronary Syndrome
ADHD	attention deficit hyperactivity disorder
ADL	activity/activities of daily living
ADME	absorption, distribution, metabolism and excretion
AE	adverse event
AESI	adverse event of special interest
AKI	acute kidney injury
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{[0\text{-}inf]}$	area under the concentration-time curve from time 0 to infinity
AV	atrioventricular
AxMP	auxiliary medicinal product
β-hCG	β-human chorionic gonadotropin
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CBD	cannabidiol
CFR	Code of Federal Regulations
CGRP	calcitonin gene-related peptide
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CKD-EPI	chronic kidney disease epidemiology
C_{max}	maximum observed concentration
CMH	Cochran–Mantel–Haenszel
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CRPS	complex regional pain syndrome
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
CTIS	Clinical Trial Information System
CYP	cytochrome P450
DAIDS	Division of Acquired Immunodeficiency Syndrome

Abbreviation	Term
DCT	data collection tool
DDI	drug-drug interaction
DILI	drug-induced liver injury
Discont	discontinuation
DSM-V	The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DU	dispensable unit
EAS	efficacy analysis set
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCOA	electronic clinical outcome assessment
eCrCl	estimated creatinine clearance
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDC	Electronic Data Capture
E-DMC	External Data Monitoring Committee
EFD	embryo-fetal development
EDP	exposure during pregnancy
EE	ethinyl estradiol
eGFR	estimated glomerular filtration rate
EOT	end of treatment
eSAE	electronic serious adverse event
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FAS	full analysis set
FSH	follicle-stimulating hormone
F/U	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HbA1c	hemoglobin A1c
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
IHS	International Headache Society
IMP	investigational medicinal product
IN	intranasal

Abbreviation	Term
IND	Investigational New Drug
INR	international normalized ratio
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
KDIGO	Kidney Disease: Improving Global Outcomes
LBBB	left bundle branch block
LDH	lactate dehydrogenase
LFT	liver function test
LNG	levonorgestrel
MBS	most bothersome symptom
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MQI	medically qualified individual
NA	not applicable
NIMP	noninvestigational medicinal product
NOAEL	no observed adverse effect level
NRS	numeric rating scale
NSAIDs	non-steroidal anti-inflammatory drugs
NTCP	sodium taurocholate cotransporting polypeptide
OATP	organic anion transporting polypeptide
OTC	Over-the-Counter
PCI	Percutaneous Coronary Intervention
PCP	phencyclidine
PGIC	Patient Global Impression of Change
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PR	pulse rate
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PT	prothrombin time
PVC	premature ventricular contraction
QD	once daily
QRS	time from ECG Q wave to the end of the S wave corresponding to ventricle depolarization
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
QTL	quality tolerance limit
qual	qualitative
RBC	red blood cell
SAE	serious adverse event

Abbreviation	Term
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
Scr	serum creatinine
Scys	serum cystatin C
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SmPC	Summary of Product Characteristics
SoA	schedule of activities
SOP	standard operating procedure
SRSD	Single Reference Safety Document
ST-T	ST-segment and T-wave
SUSAR	Suspected Unexpected Serious Adverse Reaction
T bili	total bilirubin
TCM	Traditional Chinese Medicine
THC	tetrahydrocannabinol
TIA	transient ischemic attack
T_{max}	time to reach maximum concentration
ULN	upper limit of normal
US	United States
UTI	urinary tract infection
WBC	white blood cell
WOCBP	woman/women of childbearing potential

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