Title Page

A PHASE 1, OPEN-LABEL, SINGLE DOSE STUDY TO INVESTIGATE THE PHARMACOKINETICS, SAFETY AND TOLERABILITY OF ZAVEGEPANT INTRANASAL ADMINISTRATION IN HEALTHY CHINESE ADULT PARTICIPANTS

Study Intervention Number:	PF-07930207
Study Intervention Name:	Zavegepant
US IND Number:	Not applicable
EudraCT/EU CT Number:	Not applicable
ClinicalTrials.gov ID:	Not available
Pediatric Investigational Plan Number:	Not applicable
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Phase:	1

Brief Title: A Phase 1 Study to Investigate the Pharmacokinetics of Zavegepant Following Single Intranasal Administration in Healthy Chinese Adult Participants

Document History

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, Open-Label, Single Dose Study to Investigate the Pharmacokinetics, Safety and Tolerability of Zavegepant Intranasal Administration in Healthy Chinese Adult Participants

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Regulatory Agency Identification Number(s):

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

Rationale: The purpose of the study is to evaluate the PK, safety, and tolerability of zavegepant following intranasal administration of 10 mg single dose in healthy Chinese adult participants. Results from this study will be used to support zavegepant 10 mg IN China registration for the acute treatment of migraine.

Objectives and Endpoints:

Objectives	Endpoints
Primary:	**Primary:**
• To characterize the systemic exposure of zavegepant following IN administration of 10 mg single dose in healthy Chinese adult participants.	• Zavegepant plasma PK parameters: C_{max}, AUC_{last}, and AUC_{inf}, as data permits
Secondary:	**Secondary:**
• To assess the safety and tolerability of zavegepant following IN administration of 10 mg single dose in healthy Chinese adult participants. • To characterize the plasma PK profile of zavegepant following IN administration of 10 mg single dose in healthy Chinese adult participants.	• AEs, clinical safety laboratory tests, vital signs (BP and PR), physical examinations, and 12-lead ECGs. • Additional zavegepant plasma PK parameters: T_{max}, $t_{½}$, CL/F and Vz/F, as data permits

Overall Design:

This is a Phase 1, open-label, single dose study to characterize the PK, safety and tolerability of zavegepant in healthy Chinese adults following a single intranasal dose of 10 mg. Approximately 12 eligible participants, ages of 18 to 55 years (inclusive), will be enrolled in the study.

Screening evaluation will occur within 28 days prior to the study intervention administration (Day 1). Participants will be admitted to the CRU the day before Day 1 and will be kept under safety monitoring for 2 days at the CRU. Participants will receive 10 mg single dose of IN zavegepant on Day 1. The PK of zavegepant will be characterized following Day 1 dosing. A telephone follow-up will be made 28-35 days after the single dose.

This study will be conducted in a single center in China.

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

Number of Participants:

Approximately 12 participants will be enrolled in the study.

Note: "Enrolled" means a participant's, or their legally authorized representative's, agreement to participate in a clinical study following completion of the informed consent process and assignment to study intervention. A participant will be considered enrolled if the informed consent is not withdrawn prior to participating in any study activity. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Study Population:

Key inclusion and exclusion criteria are listed below:

Inclusion Criteria

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

1. Male or female Chinese participants, between the ages of 18 and 55 years, inclusive, at the time of signing the ICD.

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

2. Male and female Chinese participants who are overtly healthy as determined by medical evaluation

3. BMI of 18.0 to 30.0 kg/m^2; and a total body weight ≥50.0 kg (110 lb) for males and ≥45.0 kg (99 lb) for females.

4. Non-smoker (no use of tobacco or nicotine products within 3 months prior to screening).

5. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

Exclusion Criteria

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

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

2. Clinically significant history of nasal conditions that may affect the administration or absorption of the nasal product.

3. Other medical or psychiatric condition that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.

4. Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, nasal inspection, vital signs, 12-lead ECG, or clinical laboratory determinations beyond what is consistent with the target population.

5. Positive result for COVID-19 at the time of Screening and admission.

6. Refer to Section 6.9 Prior and Concomitant Therapy. Use of medication other than topical products without significant systemic absorption.

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

8. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest.

9. Standard 12-lead ECG that demonstrates clinically relevant abnormalities that may affect participant safety or interpretation of study results.

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

    - AST **or** ALT level > ULN;
    - Total bilirubin level > ULN;
    - ANC **or** ALC level > ULN.

Study Arms and Duration:

Study Intervention	
Intervention Name	Zavegepant (PF-07930207)
Unit Dose Strength(s)	10 mg
Route of Administration	Intranasal
Use	Experimental
IMP or NIMP/AxMP	IMP

Study staff will administer the IN spray in one nostril to each participant.

Statistical Methods:

There is no statistical hypothesis for this study, therefore, the study sample size is not based on statistical decision rule. The sample size has been chosen based on the need to minimize exposure to humans of a new chemical entity and to fulfill the NMPA requirement of adequate PK data to support zavegepant China registration. A sufficient number of participants will be screened to achieve 12 participants enrolled to study intervention.

Ethical Considerations:

Zavegepant is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate pharmacokinetic, safety, and tolerability data in healthy Chinese adults. Data from this study provide the basis for the clinical development of zavegepant as a potential new pharmacological agent for the acute treatment of migraine in China.

All study intervention risks are communicated through the IB. Based on the totality of available clinical and nonclinical data, and taking into account the measures to monitor and minimize risk to study participants, the overall benefit/risk profile supports the clinical investigation of zavegepant 10 mg single IN administration in healthy Chinese adults.

1.2. Schema

Not applicable.

1.3. Schedule of Activities

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

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

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 7.	**Screen**	**Inpatient stay at CRU**			**Tele F/U**	**Early Discont**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 28-35**		• All screening should be done ≤28 days before the first dose. • Follow-up may occur via telephone contact and must occur 28-35 days after administration of the final dose of study intervention.
Informed consent	X						• Informed consent should be obtained prior to undergoing any study-specific procedures. • See Section 10.1.3 for additional information.
CRU confinement		X	X				
Demography	X						
Medical/medication history	X	X					• Medication history will be updated at each visit
Inclusion/exclusion criteria	X	X					• See Section 5.1 and Section 5.2.
Review alcohol/caffeine/tobacco	X	X					
PE (including height and body weight at screening only)	X	X				X	• A complete PE may be done at screening or Day -1; otherwise, brief PE envisioned for findings during previous PE or new/open AEs, at the investigator discretion. See Section 8.3.1.

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 7.	**Screen**	**Inpatient stay at CRU**			**Tele F/U**	**Early Discont**	**Notes**
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 28-35**		• All screening should be done ≤28 days before the first dose. • Follow-up may occur via telephone contact and must occur 28-35 days after administration of the final dose of study intervention.
Nasal inspection	X	X	X	X		X	• The nasal passages and turbinates will be visually inspected with a nasal speculum and light at screening and Day -1 (to exclude participants with mucosal erythema, congestion, septal defects etc), prior to dosing, and 24 hours (±30 min) post-dose to detect evidence of nasal inflammation or edema. In addition, participants will be queried regarding new nasal symptoms and AEs, which will be recorded as appropriate until resolution.
Vital signs (BP and PR)	X		X	X		X	• Supine BP and PR will be performed at screening, within 1 hour prior to dosing, and approximately 2 hours (±10 min) post-dose. See Section 8.3.3 for details.
12-Lead ECG	X		X	X		X	• Supine ECGs will be performed at screening, within 1 hour prior to dosing, and approximately 24 hours (±30 min) post-dose. See Section 8.3.4 for details.
Safety laboratory	X	X		X		X	• Screening, Day -1, and 24 hours (±30 min) post-dose. See Appendix 2 for safety laboratory tests in the study.
Pregnancy test (WOCBP only)	X	X		X		X	• A serum pregnancy test is required at screening. Following screening serum or urine β-hCG for female participants of childbearing potential. See Section 8.3.7 for details.
Contraception check	X	X			X	X	
FSH	X						• For confirmation of postmenopausal status only. See Section 10.4.3 for the definition of postmenopausal.
Alcohol test, urine cotinine, and urine drug testing	X	X					
HIV, HBsAg, HCVAb, Syphilis test	X						

Table 1. Study Schedule of Assessment

Visit Identifier Abbreviations used in this table may be found in Appendix 7.	Screen	Inpatient stay at CRU			Tele F/U	Early Discont	Notes
Days Relative to Day 1	**Day -28 to Day -2**	**Day -1**	**Day 1**	**Day 2**	**Day 28-35**		• All screening should be done ≤28 days before the first dose. • Follow-up may occur via telephone contact and must occur 28-35 days after administration of the final dose of study intervention.
COVID-19 test(s)	X						• The timing and methods of COVID-19 test(s) should follow the requirements from local regulations or the investigator (CRU).
Study intervention administration			X				
PK blood sampling			X	X		X	• See Table 2 for details.
CRU discharge				X			• Discharge from CRU after completing protocol required activities on the day.
Serious and nonserious AE monitoring	X	→	→	X	X	X	• See Section 8.4.3 for follow-up AE and SAE assessments.

Table 2. PK Sampling Timepoints

Visit Identifier																	**Notes**
Study Day	**Day 1**															**Day 2**	Hour 0 = predose sample collection; The pre-dose blood draw will be taken within 1 hour before dosing. See Section 8.5 for details of PK sample collection.
Minutes/Hours Before/After Dose	**0 min**	**5 min**	**10 min**	**20 min**	**30 min**	**40 min**	**50 min**	**1 hr**	**1.5 hr**	**2 hr**	**3 hr**	**4 hr**	**8 hr**	**12 hr**	**16 hr**	**24 hr**	
Study intervention administration	X																
PK blood sampling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

2. INTRODUCTION

Migraine is a common and debilitating neurological disorder that affects approximately 15% of the adult population. It 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. Approximately half of migraine patients experience nausea or vomiting at the time of migraine onset and patients with migraine are also known to have gastroparesis, which can slow absorption of oral medications.

Zavegepant (BHV-3500; formerly BMS-742413 or vazegepant) is a selective, high-affinity, small molecule CGRP receptor antagonist in development for the treatment of migraine. Zavegepant 10 mg intranasal has been developed for the acute treatment of migraine. It offers a novel IN CGRP receptor antagonist therapy for the acute treatment of migraine with the potential to address important unmet medical needs and optimize speed of efficacy onset and an alternate route of administration for patients who suffer from prominent nausea and vomiting at the time of migraine onset. Intranasal zavegepant provides ultrarapid onset, durable efficacy without the risk of MOH, and without contraindications or warnings regarding use by patients with CV disease.

A regional Phase 3 Study (C5301008) is being proposed to evaluate the efficacy and safety of zavegepant 10 mg versus placebo in the acute treatment of migraine in Asian (including Chinese) adults.

2.1. Study Rationale

The purpose of the study is to evaluate the PK, safety, and tolerability of zavegepant following intranasal administration of 10 mg single dose in healthy Chinese adult participants. Results from this study will be used to support zavegepant 10 mg IN China registration for the acute treatment of migraine.

2.2. Background

The pharmacology, safety pharmacology, PK, metabolism, toxicology and clinical dose-ranging efficacy and safety of zavegepant IN administration had been comprehensively studied. A summary of relevant, currently available data is provided in this protocol. Additional details and further information for this compound could be found in the current IB.

2.2.1. Nonclinical Overview

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

2.2.2. Clinical Overview

2.2.2.1. Safety overview

In clinical studies, approximately 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 (eg, dysgeusia, throat irritation, nasal congestion, nasal discomfort), as well as nausea and back pain, and the majority have been of mild to moderate intensity.

2.2.2.2. Clinical Pharmacology Overview

The clinical pharmacology of IN zavegepant has been well characterized in a comprehensive program based on 10 Phase 1 studies. These studies were conducted in approximately 746 participants including normal healthy participants (N=699), participants in specific populations (eg, moderate hepatic impairment; N=8), and participants with migraine (N=39). The objective of the clinical pharmacology program was to describe the PK of IN zavegepant and identify factors that may affect clinical pharmacology.

Zavegepant is rapidly absorbed (T_{max}: 0.54 hr) following a single zavegepant 10 mg IN dose. The effective half-life of zavegepant 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 to 40 mg. No evidence of meaningful accumulation was observed across a dose range of 5 to 20 mg zavegepant IN.

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. Co-administration of 200 mg QD itraconazole with a single dose of IN zavegepant 10 mg had no impact on the $AUC_{0\text{-}inf}$ of IN zavegepant; zavegepant geometric mean C_{max} was slightly lowered by approximately 12% but was not deemed to be clinically relevant.

The absolute bioavailability of zavegepant was estimated to be 5.12% after a 10 mg IN dose. Zavegepant is 89.8% bound (10.2% free) to human plasma proteins and does not preferentially distribute into red blood cells. The human IV 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 compared to 11.7% recovered in the urine. Exposure to zavegepant accounted for approximately 90% of circulating plasma total radioactivity based on $AUC_{0\text{-}inf}$, indicating minimal uncharacterized

circulating components in the plasma, which is consistent with the metabolite profiling results showing zavegepant comprises 94.85% of the radioprofile in plasma.

The intrinsic factor of hepatic impairment was explored in a dedicated study. In addition, the effects of the intrinsic factors such as sex, age, weight, BMI, race, ethnicity, renal and hepatic function were defined through PPK modeling. No meaningful impact on zavegepant exposures were identified with these covariates with the exception of moderate hepatic impairment which showed an approximately 2-fold increase in zavegepant exposure in both the dedicated study and from the PPK model. It is recommended that zavegepant dose frequency be adjusted in moderate hepatic impairment subjects to no more than once every 48 hours. No change in zavegepant dose frequency is recommended in subjects with mild hepatic impairment. The impact of severe hepatic impairment has not been studied and therefore administration of zavegepant in subjects with severe hepatic impairment is not recommended.

Based on the human ADME study, the contribution of renal clearance to zavegepant elimination is minimal (<12%); additionally, zavegepant has a low metabolic clearance and is only moderately (<90%) bound to plasma proteins. Also, based on the PPK analysis, renal impairment did not reveal a significant difference in the PK of zavegepant in subjects with CrCl ranging from 52 to >90 mL/min. Therefore, changes in renal function are not expected to affect the exposure of zavegepant. IN zavegepant may be administered in patients with renal impairment without dose adjustment.

2.3. Benefit/Risk Assessment

Zavegepant is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate pharmacokinetic, safety, and tolerability data in healthy Chinese adults. Data from this study provide the basis for the clinical development of zavegepant as a potential new pharmacological agent for the acute treatment of migraine in China.

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(s)]		
Not applicable	Not applicable	Not applicable
Study Procedures		
The study intervention will be administered intranasally via a liquid spray device.	The intranasal administration could be affected by some human and operational factors, such as the way of handling the devices and the way of inhalation and exhalation. These may lead to higher variabilities in PK data.	Enhance site training and participants education in terms of the study intervention administration. For all the study participants, the study intervention administration should be performed by no more than 3 study staff to minimize the variabilities in device handling.
Relatively intensive PK sampling and narrow time window within 1 hour post dose.	Risk of PK sample collection outside the required time window might be higher.	Enhance site communication and site feasibility estimation. Actual PK sampling times will be used in the derivation of PK parameters.
Other		
The COVID-19 pandemic may pose risks to study participation.	Participants may have increased risk of SARS-CoV-2 infection by undergoing a study procedure at a study facility.	Inclusion of COVID-19 specific assessments in the Schedule of Activities as required by local regulations or the investigator (CRU). Short CRU confinement: 3 days (2 nights).

2.3.2. Benefit Assessment

Zavegepant is not expected to provide any clinical benefit to healthy participants. This study is designed primarily to generate pharmacokinetic, safety, and tolerability data in healthy Chinese adults. Data from this study provide the basis for the clinical development of zavegepant as a potential new pharmacological agent for the acute treatment of migraine in China.

2.3.3. Overall Benefit/Risk Conclusion

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

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary:	**Primary:**
• To characterize the systemic exposure of zavegepant following IN administration of 10 mg single dose in healthy Chinese adult participants.	• Zavegepant plasma PK parameters: C_{max}, AUC_{last}, and AUC_{inf}, as data permits
Secondary:	**Secondary:**
• To assess the safety and tolerability of zavegepant following IN administration of 10 mg single dose in healthy Chinese adult participants. • To characterize the plasma PK profile of zavegepant following IN administration of 10 mg single dose in healthy Chinese adult participants.	• AEs, clinical safety laboratory tests, vital signs (BP and PR), physical examinations, and 12-lead ECGs. • Additional zavegepant plasma PK parameters: T_{max}, $t_{½}$, CL/F and Vz/F, as data permits

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1, open-label, single dose study to characterize the PK, safety and tolerability of zavegepant in healthy Chinese adults following a single intranasal dose of 10 mg. Approximately 12 eligible participants, ages of 18 to 55 years (inclusive), will be enrolled in the study.

Screening evaluation will occur within 28 days prior to the study intervention administration (Day 1). Participants will be admitted to the CRU the day before Day 1 and will be kept under safety monitoring for 2 days at the CRU. Participants will receive 10 mg single dose of IN zavegepant on Day 1. The PK of zavegepant will be characterized following Day 1 dosing. A telephone follow-up will be made 28-35 days after the single dose.

This study will be conducted in a single center in China.

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

4.2. Scientific Rationale for Study Design

Zavegepant is being developed for the acute treatment of migraine via the IN route.

The clinical pharmacology of IN zavegepant has been well characterized in a comprehensive program based on 10 Phase 1 studies oversea. There should be no expected significant PK difference between different races based on the totality of oversea data. This study is the first China standalone Phase 1 study with zavegepant in healthy Chinese population.

The objectives of this Phase 1 is to characterize the PK, safety and tolerability of zavegepant in healthy Chinese adults. Results from this study will be used to support the ethnic difference/similarity analysis between Chinese and non-Chinese, and to support zavegepant China registration.

The effect of sex was evaluated in the PPK analysis of zavegepant. After adjusting for the effects of body weight, females were found to have no meaningful change (<20%) in clearance or volume of distribution as compared to males when administered zavegepant 10 mg, IN. No special labeling guidance with respect to dosage and administration is needed for sex. Therefore, male and/or female Chinese participants will be enrolled in this study.

Although no evidence of embryolethality and teratogenicity were found in animal embryofetal development studies in rats and rabbits with zavegepant, women of childbearing potential (WOCBP) are recommended to use effective methods of contraception before and during exposure to zavegepant in order to prevent pregnancy. No data are available on the potential in vivo transfer of zavegepant or its metabolites into human breast milk. Therefore, non-pregnant, non-lactating females will be included in the study and any female of childbearing potential will be included if they use appropriate methods of contraception (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.[1]

4.3. Justification for Dose

The intranasal dose of 10 mg has been carried forward as the therapeutic dose for acute treatment of migraine based on the clinically significant efficacy and acceptable safety profile observed with zavegepant. A regional Phase 3 Study (C5301008) is being proposed to

evaluate the efficacy and safety of zavegepant 10 mg versus placebo in the acute treatment of migraine in Asian (including Chinese) adults. Results from these studies (C5301009 and C5301008) will be used to support Zavegepant 10 mg IN China registration for the acute treatment of migraine.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

A participant is considered to have completed the study if they have completed all visits of the study, including the last scheduled procedure shown in the SoA. Follow-up visits in addition to those in the SoA may be scheduled at investigator discretion, including to monitor open AE, or based on emerging data.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. A prescreening tool may be utilized for study recruitment purposes, it will include collection of information that reflects the enrollment of population including, where permitted under local regulations, age, sex, and ethnicity. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

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

5.1. Inclusion Criteria

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

Age and Sex:

1. Male or female Chinese participants, between the ages of 18 and 55 years, inclusive, at the time of signing the ICD.

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

    - Chinese participants are defined as individuals currently residing in mainland China who were born in China and have both parents of Chinese descent.

Other Inclusion Criteria:

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

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

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

3. BMI of 18.0 to 30.0 kg/m^2; and a total body weight ≥50.0 kg (110 lb) for males and ≥45.0 kg (99 lb) for females.

4. Non-smoker (no use of tobacco or nicotine products within 3 months prior to screening).

5. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions:

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

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

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

2. Significant history of seizure disorder other than a single childhood febrile seizure (eg, epilepsy).

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

4. History of gallstone or cholecystectomy.

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

Prior/Concomitant Therapy:

6. Refer to Section 6.9 Prior and Concomitant Therapy. Use of medication other than topical products without significant systemic absorption

   - Prescription medication within 14 days or 5 half-lives (whichever is longer) prior to the first dosing (hormonal contraception allowed);
   - Over-the-counter products and natural health products (including acetaminophen-containing products, all intranasal spray medications/saline, herbal remedies such as Butterbur root or extracts, homeopathic and traditional medicines, probiotics, food supplements such as vitamins, minerals, amino acids, essential fatty acids, and protein supplements used in sports) within 7 days or 5 half-lives (whichever is longer) prior to the first dosing, with the exception of the occasional use of ibuprofen;
   - A depot injection or an implant of any drug within 6 months prior to the first dosing;
   - Small molecule CGRP receptor antagonists within 1 month prior to dosing;
   - Biologic CGRP receptor antagonist within 6 months prior to dosing;
   - Oxymetazoline (or other nasal spray decongestants) from at least 14 days prior to the first dosing;
   - Receipt of any vaccination, including COVID-19 vaccine, within 14 days prior to first dosing.

Prior/Concurrent Clinical Study Experience:

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

Diagnostic Assessments:

8. Any clinically significant abnormal laboratory test results or positive test found during medical screening.

9. Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, nasal inspection, vital signs, 12-lead ECG, or clinical laboratory determinations beyond what is consistent with the target population.

10. Screening supine BP ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), following at least 5 minutes of supine rest. If BP is ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic), the BP should be repeated 2 more times and the average of the 3 BP values should be used to determine the participant's eligibility.

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

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

    - AST **or** ALT level > ULN; Only abnormal values between 1-1.5 × ULN may be repeated once for confirmation to below ULN.

    - Total bilirubin level > ULN; participants with a history of Gilbert's syndrome may have direct bilirubin measured and would be eligible for this study provided the direct bilirubin level is ≤ ULN.

    - ANC **or** ALC level > ULN.

13. Positive urine drug screen, alcohol breath test, or urine cotinine test at screening or baseline.

14. Positive pregnancy test at screening or baseline (Day -1).

15. Positive result for COVID-19 at the time of Screening and admission.

Other Exclusion Criteria:

16. History of significant alcohol abuse within 6 months prior to screening or regular use of alcohol within 6 months prior to the screening visit (more than fourteen units of alcohol per week [1 unit = 150 mL of wine, 360 mL of beer, or 45 mL of 40% alcohol]).

17. History of significant drug abuse within 6 months prior to screening or use of soft drugs (such as marijuana) within 3 months prior to the screening visit or hard drugs

(such as cocaine, PCP, crack, opioid derivatives including heroin, and amphetamine derivatives) within 1 year prior to screening.

18. History of anaphylaxis reaction, a documented hypersensitivity reaction, or a clinically important reaction to any drug.

19. Donation of plasma within 30 days prior to dosing. Donation or loss of blood (excluding volume drawn at screening) of approximately 400 mL or more within 60 days prior to dosing.

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

21. Inability to be venipunctured and/or tolerate catheter venous access.

22. Habitual use of snuff tobacco.

23. Any reason which, in the opinion of the PI, would prevent the participant from participating in the study.

24. History of sensitivity to heparin or heparin-induced thrombocytopenia.

25. Unwilling or unable to comply with the criteria in the Lifestyle Considerations section of this protocol.

26. 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.

5.3. Lifestyle Considerations

The following guidelines are provided:

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 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.

5.3.2. Meals and Dietary Restrictions

- Participants must abstain from all food and drink (except water) at least 4 hours prior to any safety laboratory evaluations.
- Participants will refrain from consuming red wine, grapefruit, or grapefruit-related citrus fruits (eg, Seville oranges, pomelos, fruit juices) from 7 days prior to the first dose of study intervention until collection of the final PK blood sample.
- Food or beverages containing xanthine derivatives or xanthine-related compounds or energy drinks from 48 hours prior to dosing until after the last PK blood sample collection .

5.3.3. Caffeine, Alcohol, and Tobacco

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

5.3.4. Activity

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

5.4. Screen Failures

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

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

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.

6.1. Study Intervention(s) Administered

Zavegepant (PF-07930207) is formulated as 10 mg for intranasal single dose administration. The study intervention will be provided in single use unidose nasal spray devices fully prepared and ready for administration.

Study Intervention	
Intervention Name	Zavegepant (PF-07930207)
Arm Name	Single Arm
Type	Drug
Dose Formulation	Nasal spray
Unit Dose Strength(s)	10 mg
Dosage Level(s)	Single dose
Route of Administration	Intranasal
Use	Experimental
IMP or NIMP/AxMP	IMP
Sourcing	Provided centrally by the sponsor Refer to the IP manual.
Packaging and Labeling	Study intervention will be provided in unidose nasal spray. Each spray will be labeled as required per country requirement.
Current/Former Name(s) or Alias(es)	Zavegepant (PF-07930207)

6.1.1. Administration

Following an overnight fast of at least 10 hours, participants will receive study intervention at approximately 0800 hours (plus or minus 2 hours). Investigator site personal will administer study intervention according to the IPM.

Study staff will administer the IN spray in one nostril to each participant. After the dose is administered, participants will be asked to remain seated upright for approximately 10 minutes in order to avoid any study intervention leakage. Participants must not blow their nose for 2 hours after dosing and will be requested to gently sniff up any nasal drip. Participants must inform the staff if they sneeze or if the product drips out of their nose.

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

Under no circumstance may a participant be administered a supplementary dose of study medication.

6.2. Preparation, Handling, Storage, and Accountability

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

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

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

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

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

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

7. The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability,

reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.

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

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

Zavegepant will be handled and prepared according to the IPM that will be provided to the site. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

All spray devices will be presented as single-use devices.

6.3. Assignment to Study Intervention

This is an open-label study. No randomization or blinding mechanisms will be used. The investigator's knowledge of the treatment should not influence the decision to enroll a particular participant or affect the order in which participants are enrolled.

The investigator will assign participant numbers to the participants as they are screened for the study. Pfizer will provide an allocation schedule to the investigator. The participant will receive the study intervention in compliance with the SoA and the protocol instruction.

6.4. Blinding

This is an open-label study.

6.5. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of the dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.6. Dose Modification

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

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

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

6.8. Treatment of Overdose

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

There is no specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the study medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up.
3. Document the quantity of the excess dose as well as the onset time of the overdose in the CRF.
4. Overdose is reportable to Pfizer Safety **only when associated with an SAE.**
5. Obtain a blood sample for PK analysis within 2 hours from the last dose of study intervention if requested by the study medical monitor (determined on a case-by-case basis).

6.9. Prior and Concomitant Therapy

Use of prescription or nonprescription drugs and dietary and herbal supplements for the timeframes specified below and throughout the study are prohibited. Limited use of nonprescription medications that are not believed to affect participant safety or the PK profile of the study intervention may be permitted on a case-by-case basis following approval by the sponsor.

Main study restrictions include:

- Biologic CGRP receptor antagonist within 6 months prior to the first dosing until after the last PK blood sample collection of the study;
- A depot injection or an implant of any drug within 6 months prior to the first dosing until after the last PK blood sample collection of the study;
- Small molecule CGRP receptor antagonists within 1 month prior to the first dosing until after the last PK blood sample collection of the study;
- Oxymetazoline (or other nasal spray decongestants) from at least 14 days prior to the first dosing until after the last PK blood sample collection of the study;
- Prescription medication within 14 days or 5 half-lives (whichever is longer) prior to the first dosing until after the last PK blood sample collection of the study (hormonal contraception allowed);
- OTC products (including acetaminophen-containing products, all intranasal spray medications/saline) within 7 days or 5 half-lives (whichever is longer) prior to the first dosing until after the last PK blood sample collection of the study, with the exception of the occasional use of ibuprofen;
- Natural health products (including herbal remedies such as Butterbur root or extracts, homeopathic and traditional medicines, probiotics, food supplements such as vitamins, minerals, amino acids, essential fatty acids, and protein supplements used in sports) within 7 days or 5 half-lives (whichever is longer) prior to the first dosing until after the last PK blood sample collection of the study;
- Receipt of any vaccination, including COVID-19 vaccine, within 14 days prior to first dosing.

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

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

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

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:

- Refused further study procedures;
- Lost to follow-up;
- Safety reason;
- Death;
- Study terminated by sponsor.

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

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

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

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

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

7.2.1. Withdrawal of Consent

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

7.3. Lost to Follow-up

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

The following actions must be taken before a participant is deemed lost to follow-up :

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

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

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

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Administrative Procedures

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

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

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

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

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

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that make it unfeasible to perform the

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

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

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

The total blood sampling volume for individual participants for PK assessment in this study is approximately 48 mL. The other blood sampling for safety or other assessments should be collected according to the SoA, and the actual volume will depend on the clinical practice in the CRU. The total blood sampling volume for individual participants in this study will be described in the informed consent. The actual collection times and volumes 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 Concomitant Therapy sections of the protocol.

8.2. Efficacy Assessments

Not Applicable.

8.3. Safety Assessments

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

8.3.1. Physical Examinations

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

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

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

Height and weight will also be measured and recorded as per the SoA. For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat

surface. Participants must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

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 with a nasal speculum and light at screening and Day -1 (to exclude participants with mucosal erythema, congestion, septal defects etc), prior to dosing, and 24 hours (±30 min) post-dose to detect evidence of nasal inflammation or edema. In addition, participants will be queried regarding new nasal symptoms and AEs, which will be recorded as appropriate until resolution.

8.3.3. Vital Signs

8.3.3.1. Blood Pressure and Pulse Rate

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

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

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

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

8.3.4. Electrocardiograms

Standard 12-lead ECGs 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 (eg, 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 5 minutes in a supine position.

To ensure safety of the participants, a qualified individual at the investigator site will make comparisons to baseline measurements. Additional ECG monitoring will occur if a) a postdose QTcF interval is increased by ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG. If either of these conditions occurs, then 2 additional ECGs will be collected approximately 2 to 4 minutes apart to confirm the original measurement. If the QTcF values from these repeated ECGs remain above the threshold value, then a single ECG must be repeated at least hourly until QTc values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement.

If a) a postdose QTcF interval remains ≥60 ms from the baseline **and** is >450 ms; or b) an absolute QT value is ≥500 ms for any scheduled ECG for greater than 4 hours (or sooner, at the discretion of the investigator); or c) QTcF value 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).

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 6.

8.3.5. Clinical Safety Laboratory Assessments

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

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

All laboratory tests with values considered clinically significant and abnormal during participation in the study or within 2 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.

8.3.6. COVID-19 Specific Assessments

Participants will be tested for COVID-19 infection prior to being admitted to the clinic for confinement or site visit in compliance with the requirements from local regulations or the investigator. Additional testing for COVID-19 (eg, chest radiograph) may be required by local regulations or by the investigator.

8.3.7. 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.

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

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

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

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

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

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

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

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant provides informed consent, which is obtained before undergoing any study-related procedure and/or receiving study

intervention), through and including a minimum of 28 calendar days, except as indicated below, after the last administration of the study intervention.

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

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

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

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

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

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

8.4.2. Method of Detecting AEs and SAEs

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

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

8.4.3. Follow-Up of AEs and SAEs

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

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

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

8.4.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

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

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

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

8.4.5.1. Exposure During Pregnancy

An EDP occurs if:

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

Not applicable.

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

Not applicable.

8.4.8. Adverse Events of Special Interest

Not applicable.

8.4.8.1. Lack of Efficacy

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

8.4.9. Medical Device Deficiencies

Not applicable.

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.

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

Blood samples of approximately 3 mL, to provide approximately 1.2 mL plasma, will be collected for measurement of plasma concentrations of zavegepant as specified in the SoA. Instructions for the collection and handling of biological samples will be provided in the laboratory manual or by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

The actual times may change, but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing. Collection of samples up to and including 10 hours after dose administration that are obtained within 10% of the nominal time relative to dosing (eg, within 6 minutes of a 60 minute sample) will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF. Collection of samples more than 10 hours after dose administration that are obtained ≤1 hour away from the nominal time relative to dosing will not be captured as a protocol deviation, as long as the exact time of the collection is noted on the source document and the CRF.

Samples will be used to evaluate the PK of zavegepant. Samples collected for analyses of zavegepant plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study, or for metabolite identification and/or evaluation of the bioanalytical method.

Genetic analyses will not be performed on these plasma samples . Participant confidentiality will be maintained.

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

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

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

8.6. Genetics

8.6.1. Specified Genetics

Specified genetic analyses are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not included in this study.

8.9. Health Economics

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

9. STATISTICAL CONSIDERATIONS

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

9.1. Statistical Hypotheses

There is no statistical hypothesis for this study.

9.2. Analysis Sets

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

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

9.3. Statistical Analyses

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

9.3.1. General Considerations

No formal statistical tests will be performed. Descriptive summaries will be provided for all endpoints.

9.3.2. Pharmacokinetic Analysis

9.3.2.1. Derivation of PK parameters

Zavegepant plasma PK parameters will be derived from the concentration-time profile using noncompartmental methods as detailed in Table 3. Actual PK sampling times will be used in the derivation of PK parameters. In the case that actual PK sampling times are not available, nominal PK sampling time will be used in the derivation of PK parameters.

Table 3. Plasma PK Parameters for Protocol C5301009

Parameter	Definition	Method of Determination
C_{max}	Maximum plasma concentration	Observed directly from data
AUC_{last}	Area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{inf}[a]	Area under the plasma concentration-time profile from time 0 extrapolated to infinite time	$AUC_{last} + (C_{last}/k_{el})$, where C_{last} is the predicted plasma concentration at the last quantifiable time point estimated from the log-linear regression analysis
T_{max}	Time for C_{max}	Observed directly from data
$t_{½}$[a]	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log-linear concentration-time curve
CL/F[a]	Apparent clearance	$Dose/AUC_{inf}$
V_z/F[a]	Apparent volume of distribution	$Dose/(AUC_{inf} \times k_{el})$

a. If data permit.

9.3.2.2. Statistical Methods for Pharmacokinetic Data

The plasma concentration of zavegepant will be listed and descriptively summarized by nominal sampling time. Individual participant and summary profiles (mean and median plots) of the plasma concentration-time data will be plotted using actual and nominal sampling times respectively.

The plasma PK parameters of zavegepant will be listed and summarized descriptively, as data permit. For AUC_{last}, AUC_{inf}, and C_{max}, box and whisker plots for individual participant parameters overlaid with geometric means will be plotted. The PK parameter analysis set will be used.

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

9.3.3. Safety Analyses

All safety analyses will be performed on the safety population.

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

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

9.3.3.1. Electrocardiogram Analyses

Changes from baseline for the ECG parameters HR, QTcF , PR interval, and QRS complex will be summarized by time. The frequency of uncorrected QT values above 500 ms will be tabulated.

The number (%) of participants with maximum postdose QTcF values and maximum increases from baseline in the following categories will be tabulated:

Safety QTcF Assessment

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

9.4. Interim Analyses

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

9.5. Sample Size Determination

There is no statistical hypothesis for this study, therefore, the study sample size is not based on statistical decision rule. The sample size has been chosen based on the need to minimize exposure to humans of a new chemical entity and to fulfill the NMPA requirement of adequate PK data to support zavegepant China registration. A sufficient number of participants will be screened to achieve 12 participants enrolled to study intervention.

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 theirright 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.

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/or the site 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 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 StoD System.

To facilitate access to their investigator and the sponsor's MQI for study-related medical questions or problems from nonstudy 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.

Table 4. Protocol-Required Safety Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hemoglobin Hematocrit RBC count Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN (urea) and creatinine Glucose (fasting) Calcium Sodium Potassium Chloride Total CO_2 (bicarbonate) AST, ALT Total bilirubin Alkaline phosphatase Uric acid Albumin Total protein	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Microscopy[a]	COVID-19 test[e] <u>At screening and/or Day-1:</u> • FSH[b] • Alcohol test • Urine cotinine • Urine drug screening[c] • Pregnancy test (β-hCG)[d] • HBsAg • HCVAb • HIV • Syphilis test (TPPA)

a. Only if UTI is suspected or urine blood, protein, nitrites or leukocyte esterase is positive.
b. For confirmation of postmenopausal status only.
c. The minimum requirement for drug screening includes cocaine, THC, opiates/opioids, benzodiazepines, and amphetamines (others are site and study specific).
d. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/EC. Serum or urine β-hCG for female participants of childbearing potential.
e. The timing and methods of COVID-19 test(s) should follow the requirements from local regulations or investigator (CRU).

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 Meeting 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 non-pathogenic

The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a participant exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

g. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as significant medical events that may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording AEs on the CRF and for reporting SAEs 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/SAEs associated with EDP or EDB **Note:** Instances of EDP or EDB not associated with an AE or SAE are not captured in the CRF	All instances of EDP are reported (whether or not there is an associated SAE)* All instances of EDB are reported (whether or not there is an associated SAE)**
Environmental or occupational exposure to the product under study to a nonparticipant (not involving EDP or EDB)	None. Exposure to a study non-participant is not collected on the CRF	The exposure (whether or not there is an associated AE or SAE) must be reported***

* **EDP** (with or without an associated 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.

- 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. Premenarchal.
2. 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.

3. Postmenopausal female.

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition:

  - A high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years old and not using hormonal contraception or HRT.

  - A female on HRT and whose menopausal status is in doubt will be required to use one of the highly effective nonestrogen hormonal contraception methods if she wishes to continue her HRT during the study. Otherwise, she must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.4. Contraception Methods

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

The following contraceptive methods are appropriate for this study:

<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

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 blood 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: 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.

10.7. Appendix 7: Abbreviations

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

Abbreviation	Term
Abs	absolute
ADL	activity/activities of daily living
ADME	Absorption Distribution Metabolism Excretion
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{inf}	area under the plasma concentration-time profile from time 0 extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time profile from time 0 to the time of the last quantifiable concentration (C_{last})
AV	atrioventricular
AxMP	auxiliary medicinal product
β-hCG	β-human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
bpm	beats per minute
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CGRP	calcitonin gene-related peptide
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CL/F	apparent clearance
C_{last}	the last quantifiable concentration
C_{max}	maximum observed concentration
CO_2	carbon dioxide (bicarbonate)
COVID-19	coronavirus disease 2019
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CRU	clinical research unit
CSR	Clinical Study Report
CT	calcitonin
CTIS	Clinical Trial Information System
CV	cardiovascular
CYP	cytochrome P450
DCT	data collection tool

Abbreviation	Term
DILI	drug-induced liver injury
EC	ethics committee
ECC	emergency contact card
ECG	electrocardiogram or electrocardiography
eCRF	electronic case report form
EDB	exposure during breastfeeding
E-DMC	External Data Monitoring Committee
EDP	exposure during pregnancy
eSAE	electronic serious adverse event
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)
FSH	follicle-stimulating hormone
F/U	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C antibody
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICD	Informed Consent Document
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IMP	investigational medicinal product
IN	intranasal
IND	Investigational New Drug
INR	international normalized ratio
IP	investigational product
IPAL	Investigational Product Accountability Log
IPM	investigational product manual
IRB	Institutional Review Board
IV	intravenous
LBBB	left bundle branch block
LFT	liver function test
MOH	medication-overuse headache
MQI	medically qualified individual
NIMP	non-investigational medicinal product
NMPA	National Medical Products Administration
NOAEL	no observed adverse effect level
OTC	over-the-counter

Abbreviation	Term
PCP	phencyclidine
PE	physical examination
PI	Primary Investigator
PK	pharmacokinetic(s)
PPK	Population Pharmacokinetic
PSSA	Pfizer's Serious Adverse Event Submission Assistant
PVC	premature ventricular contraction/complex
QD	once daily
QTc	corrected QT interval
QTcF	QTc corrected using Fridericia's formula
RBC	red blood cell
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SoA	schedule of activities
SOP	standard operating procedure
SRSD	Single Reference Safety Document
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{½}$	terminal half-life
T bili	total bilirubin
THC	tetrahydrocannabinol
ULN	upper limit of normal
T_{max}	time for C_{max}
TPPA	Treponema pallidum particle agglutination
US	United States
UTI	urinary tract infection
V_z/F	apparent volume of distribution
WBC	white blood cell
WOCBP	woman/women of childbearing potential

11. REFERENCES

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