NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Concept Elicitation Qualitative Study: Migraine Patient Experiences with Zavegepant
Protocol number	C5301035
Protocol version identifier	V1.0
Date	20 February 2025
EU Post Authorization Study (PAS) register number	1000000442
Active substance	N02CD08 (Zavegepant)
Medicinal product	Zavzpret™
Research question and objectives	The study aims to address the following research question: what are the patients´ perceptions and experiences regarding the use of zavegepant as an acute treatment for migraine in the real-world setting in the United States (US)? The study has the following objectives: 1. Understand the patient experience with taking zavegepant for acute treatment of migraine 2. Understand the experienced benefits/risks of zavegepant use, including but not limited to poor usability 3. Explore how patients balance the experienced benefits/risks of zavegepant 4. Understand how patients weigh potential risks, including but not limited to poor usability,

	associated with medications to acutely treat migraine attacks
Country	United States
Author	Redacted Redacted Redacted

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AEM	Adverse event monitoring
CGRP	Calcitonin Gene-related Peptide
CRF	Case Report Forms
DCT	Data collection tool
DSU	Drug Safety Unit
EDP	Exposure during pregnancy
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practices
HCP	Healthcare Provider
HMA	Heads of Medicines Agencies
ID	Identification
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
NI	Non-Interventional
NIS	Non-Interventional Study
Redacted	[redacted]
PASS	Post-Authorization Safety Study
RWD	Real-World Data
STAR	Sense-Think-Act-Relate
US	United States
YRR	Your Reporting Responsibilities

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, Degree(s)	Job Title	Affiliation	Address
Redacted	Redacted	Redacted	Redacted
Redacted	Redacted	Pfizer Inc.	Redacted

Additional Investigators of the protocol

Name, Degree(s)	Job Title	Affiliation	Address
Redacted	Redacted	Redacted	Redacted
Redacted	Redacted	Redacted	Redacted
Redacted	Redacted	Redacted	Redacted
Redacted	Redacted	Redacted	Redacted
Redacted	Redacted	Redacted	Redacted

4. ABSTRACT

Title: Concept Elicitation Qualitative Study: Migraine Patient Experiences with Zavegepant

Version

1.0 20 February 2025

Main Author

Redacted

Rationale and background: Migraine is a highly prevalent neurological condition and one of the most common and disabling disorders. Characterized by recurrent episodes of intense, debilitating headaches often accompanied by nausea, sensitivity to light and sound, and sometimes aura, migraine presents a substantial burden to patients and healthcare systems. Zavegepant (Zavzpret^{TM}), a novel calcitonin gene-related peptide (CGRP) receptor antagonist, was approved by the FDA in March 2023 for the acute treatment of migraine. This research aims to evaluate the overall patient experience with zavegepant, including but not limited to taste disorders, and how these experiences influence their decisions about migraine treatment.

Research question and objectives: the study aims to address the following research question: what are the patients´ perceptions and experiences regarding the use of zavegepant as an acute treatment for migraine in the real-world setting in the United States (US)? Thus, the following objectives will be assessed: (1) understand the patient experience with taking zavegepant for acute treatment of migraine; (2) understand the experienced benefits/risks of zavegepant use, including but not limited to poor usability; (3) explore how patients balance the experienced benefits/risks of zavegepant; (4) understand how patients weigh potential risks, including but not limited to poor usability, associated with medications to acutely treat migraine attacks.

Study design: this is a cross-sectional, non-interventional study, involving one-on-one interviews with eligible respondents.

Population: Participants aged 18 years old or older, who have used zavegepant at least once in the past 3 months, who reside in the US, who do not indicate or exhibit speaking or hearing difficulties, or do not lack sufficient understanding of English, and who provide informed consent will be invited to participate in the study. Up to 20 participants will be recruited, including a mix of individuals with positive, neutral, and negative experiences with the medication, as well as varying frequencies of use. A screener question will be used to assess participants' overall experience (positive, neutral, or negative) with the medication. To ensure balanced representation, there will be a minimum of 3 participants in each experience group recruited. A semi-structured interview guide will be used to collect qualitative data from participants.

Variables: During the qualitative interviews, the following variables will be collected: demographic characteristics, zavegepant usage pattern, migraine history, overall experience with zavegepant.

Study size: Research shows that 15 interviews are enough to ensure that all relevant concepts have been exhausted in the interview process. Once 15 interviews are completed, the information saturation will be assessed (whether any new key concepts are still being identified by the last interview). If no new key concepts are emerging, the data collection will be concluded. However, if new concepts continue to arise, an additional 5 participants will be recruited to further explore these insights.

Data analysis: A content and thematic analysis of the interview data will be performed. The verbatim transcripts will be uploaded to a qualitative data analysis program, such as MAXQDA 24, which enables the assignment of codes to emerging themes and helps facilitate organization of the data. An outcomes researcher will review the first two transcripts and develop an initial coding system, specifying key themes, and sub-themes. The draft code system and respective transcripts will be reviewed by a second outcomes researcher and revisions will be made as appropriate. Concepts that emerge during content analysis will be analyzed for concept saturation, or the exercise of confirming that no new key concepts have been identified by the final point of data collection.

Milestones:

Milestone	**Planned date**
Start of data collection	15 March 2025
End of data collection	20 May 2025
Registration in the HMA-EMA Catalogues of RWD Studies	09 March 2025
Final study report	15 December 2025

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Start of data collection	15 March 2025
End of data collection	20 May 2025
Registration in the HMA-EMA Catalogues of RWD Studies	09 March 2025
Final study report	15 December 2025

7. RATIONALE AND BACKGROUND

Migraine is a highly prevalent neurological condition that affects over 148 million people worldwide, making it one of the most common and disabling disorders. In the United States alone, over 40 million individuals suffer from migraines [1]. Characterized by recurrent episodes of intense, debilitating headaches often accompanied by nausea, sensitivity to light and sound, and sometimes aura, migraine presents a substantial burden to patients and healthcare systems [2].

Zavegepant (Zavzpret™), a novel calcitonin gene-related peptide (CGRP) receptor antagonist, was approved by the FDA in March 2023 for the acute treatment of migraine. Clinical trials have demonstrated its efficacy in providing headache and symptom relief, with a statistically significant percentage of patients achieving freedom from headaches and most bothersome symptoms. Despite mild adverse effects, such as taste disorders and nausea, Zavzpret's overall safety and tolerability profile remains acceptable [3].

In placebo-controlled, double-blind trials, taste disorders were experienced by 18% of patients [4,5]. In contrast, this side effect was reported in 39% of participants in an open-label, long-term safety trial [6]. Although dysgeusia is generally considered mild to moderate in severity, healthcare professionals (HCPs) have noted an increasing awareness over its possible impact on patient experience. Anecdotal reports suggest that some patients may consider this side effect significant enough to influence their decision to continue treatment, and the question remains as to whether these adverse events, including but not limited to taste disorders, are considered acceptable trade-offs between efficacy and safety.

Given the potential for side effects, such as dysgeusia, to affect uptake and overall satisfaction with treatment, it is crucial to gain a deeper understanding of patient experiences with zavegepant. Currently, there is limited information available from the patient perspective on how they balance the benefits/risks of zavegepant, including but not limited to poor usability, and also in comparison with other acute migraine medications. This research aims to evaluate the overall patient experience with zavegepant, including but not limited to taste disorders, and how these experiences influence patient's choice of the most appropriate migraine treatment.

This noninterventional study is designated as a PASS and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

The study aims to address the following research question: what are the patients´ perceptions and experiences regarding the use of zavegepant as an acute treatment for migraine in the real-world setting in the United States (US)?
The study has the following objectives:

1. Understand the patient experience with taking zavegepant for acute treatment of migraine

2. Understand the experienced benefits/risks of zavegepant use, including but not limited to poor usability

3. Explore how patients balance the experienced benefits/risks of zavegepant

4. Understand how patients weigh potential risks, including but not limited to poor usability, associated with medications to acutely treat migraine attacks

For the purpose of study outcomes assessment, risks associated with zavegepant include, but is not limited to, side effects, poor usability, limited access to the medication, or any undesirable or negative aspect of the medication that makes it less acceptable to use.

9. RESEARCH METHODS

9.1. Study Design

This is a cross-sectional qualitative study involving one-on-one interviews with US respondents who have used zavegepant at least once in the past 3 months. This qualitative study will involve conducting a 60-minute one-on-one, semi-structured interviews via online conferencing/telephone. This methodology allows the collection of patient perception and real-world experiences regarding the use of zavegepant for migraine treatment and will provide an in-depth understanding of patient experience unmet treatment needs. In-depth interviews provide detailed and specific data wherein patients articulate their thoughts, making qualitative interviews the most appropriate method of inquiry [7].

Interviews will be conducted by a moderator from Redacted a global market research firm specializing in qualitative research. After providing their consent, the moderator will ask participants questions following a semi-structured interview guide to explore participants' experiences with migraine, zavegepant treatment and experiences. The discussion guide was developed based on the STAR (Sense-Think-Act-Relate) framework, which has been used in previous study [9]. All interviews will be audio recorded for transcription and qualitative analysis. Participants will be informed in advance that all information will be anonymized

9.2. Setting

Up to 20 participants will be recruited, including a mix of individuals with positive, neutral, and negative experiences with the medication, as well as varying frequencies of use. Before providing their informed consent to participate in the study, participants will complete a screener to determine their eligibility and assess their overall experience (positive, neutral, or negative) with the medication. To ensure balanced representation, there will be a minimum of 3 participants in each experience group recruited. To minimize recall bias, the study will initially include only patients who have used Zavegepant at least once in the past 3 months. If recruitment challenges arise, patients who used Zavegepant within the past 4 to 6 months will be identified and considered for rescreening. Research shows that 15 interviews is enough to ensure that all relevant concepts have been exhausted in the interview process [9]. Once the 15 interviews are completed, the information saturation will be assessed (whether any new key

concepts are still being identified by the last interview). If no new key concepts are emerging, the data collection will be concluded. However, if new concepts continue to arise, an additional 5 participants will be recruited to further explore these insights. Concepts that emerge during content analysis will be analyzed for concept saturation, or the exercise of confirming that no new key concepts have been identified by the final point of data collection. Content analysis is well-suited to inform the assessment of saturation as it helps to quantify who said what and will be utilized to confirm study objectives have been met. Additionally, meeting saturation of concepts will help establish the validity and quality of the research.

Participants will be identified, recruited, and will have their interview scheduled by Redacted an Redacted subcontractor that has access to different patient panels from where potential participants will be selected. Redacted will recruit respondents from known migraine patients who have previously opted in to participating in research. If needed, Redacted will reach out to known prescribers of zavegepant in the United States to identify patients. These prescribers will reach out to patients and provide information to contact Redacted in order to be recruited, if they are interested. Redacted may also work with migraine patient advocacy groups to recruit patients. This multi-pronged recruitment strategy will help ensure the study population is representative by capturing diverse patient perspectives and experiences. Respondents who participate in the qualitative interviews will receive $125 in compensation for their time and valuable input.

In cases of provider referral, providers' offices will not collect information about the patient. If a potential participant is interested in the study, the provider will provide the contact information to the recruiter.

The recruitment and data collection are expected to take place over a period of 10 weeks.

9.2.1. Inclusion Criteria

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Aged 18 years old or older
2. Have used zavegepant at least once in the past 3 months
3. Reside in US
4. Evidence of a personally signed (or acknowledged if obtained electronically or online) and dated informed consent document indicating that the participant has been informed of all pertinent aspects of the study.

9.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Indicates or exhibits speaking or hearing difficulties, or lacks sufficient understanding of English, which would make a telephone conversation challenging

9.3. Variables

Participants will complete a single one-on-one interview session. A semi-structured interview guide will be used to collect qualitative data from participants. The following sections provide a description of the instrument that will be administered as part of the study:

Table 1. Variables description

Group	Role	Data source	Variables	Operational definition
Demographic	Baseline characteristics	Screener	Age	In years
			Gender	Single choice: Male/Female/No-binary/A gender not listed/Prefer not to answer
			US state of residence	Single choice: US states list
			Community type	Single choice: Major metropolitan area, population > 500,000/ Urban area, population between 100,000 and 500,000/ Suburb of a large city, population > 100,000/ Small city, population between 30,000 and 100,000/ Rural or small town, population < 30,000
			Race	Single choice: African American_Black/ Asian/ American Indian_Alaska Native/ Native Hawaiian or Other Pacific Islander/ White or Caucasian/ Other/ Prefer not to answer
			Hispanic or Latin/a origin	Single choice: Yes, Hispanic or Latino/a origin/ No, not Hispanic or Latino/a origin/ Prefer not to answer
			Health conditions	Multiple choice: Cluster headache/ Concussion/ Lupus/ Migraine/ Multiple sclerosis/ Osteoporosis/ Sleep apnea/ Thyroid disease/ Vascular disease/ Cardiovascular disease/ No, none of the above

Table 1. Variables description

Group	Role	Data source	Variables	Operational definition
			Prescribed medication currently in use or used in the past 6 months for the acute treatment of migraine	Multiple choice: Amerge® (naratriptan)/ FROVA® (frovatriptan)/ IMITREX®, Sumavel® DosePro®, Zembrace® (sumatriptan)/ Nurtec® ODT (rimegepant)/ Relpax® (eletriptan)/ Reyvow® (lasmiditan)/ UBRELVY® (ubrogepant)/ Tosymra® (sumatriptan nasal spray)/ Trudhesa® (dihydroergotamine mesylate)/ ZAVZPRET™ (zavegepant)/ ZOMIG® (zolmitriptan) - oral tablet, ODT, or nasal spray/ None of the above
			Last time taking Zavzpret™	Single choice: 30 days ago or less/ 31-60 days ago/ 61-90 days ago/ More than 3 months ago but in the last 6 months/ More than 6 months ago/ I don´t recall
			First time taking Zavzpret™	Month-Year (range July-2023 to current date)
			Frequency of use	Total times used; single choice: Once/ 2-4 times/5-9 times/ 10-19 times/ 20 times or more
			Headache days per month in the past 3 months	Average of days
			Overall experience with Zavzpret™	Single choice: Positive/ Neutral/ Negative
Introduction	Baseline characteristics	One-on-one interview	Who do you live with?	As informed by the participant
			What do you like to do in your free time?	As informed by the participant
			Are you employed?	As informed by the participant
			How long have you experienced migraine?	As informed by the participant

Table 1. Variables description

Group	Role	Data source	Variables	Operational definition
Migraine background	Baseline characteristics	One-on-one interview	How often do you have migraine attacks?	As informed by the participant
			How severe your migraine attacks are?	As informed by the participant
			What symptoms do you experience with your migraine attacks?	As informed by the participant. Prompt questions: - light, noise sensitivity, nausea, vomiting or other symptoms? - most bothersome symptom? - what extent symptoms differ based on severity of the attack? - how long do the symptoms lasts?
			How do you handle a migraine attack?	As informed by the participant. Prompt questions: - what circumstances drive the decision to use a prescription medication to treat headache pain? - how many prescription medications are available to take to stop a migraine attack? - how do you choose which medication to use?
			Is there a time that you considered using a prescription medication for migraine attacks, but decided not to?	As informed by the participant. Prompt questions: - what factors influence this decision? - have there ever been effects from the medication that prevent you from wanting to take a prescription medication for migraine attacks?

Table 1. Variables description

Group	Role	Data source	Variables	Operational definition
Learning about zavegepant	Outcome	One-on-one interview	How did you originally hear about Zavzpret™?	As informed by the participant
			What factors led you to first use Zavzpret™?	As informed by the participant.
			How was Zavzpret™ described to you when you originally heard about it?	As informed by the participant. Prompt questions: - What instructions did your provider provide regarding taking Zavzpret™? - how to determine when to take Zavzpret™?
			Before you took Zavzpret™ for the first time, what did you expect from taking it?	As informed by the participant. Prompt questions: - Did you have expectations about how it would feel?
			What, if any, questions, and/or concerns did you have?	As informed by the participant.
Experience taking zavegepant	Outcome	One-on-one interview	How long have you been using Zavzpret™?	As informed by the participant. Prompt question: - How many times have you used [did you use] it?
			How often do you use Zavzpret™?	As informed by the participant. Prompt question: - What percentage of migraine attacks do you use it for?
			Which character best represents the impact of Zavzpret™ on your life?	Images will be available for participant selection
			When do you choose to use Zavzpret™?	As informed by the participant.
			What are your goals with taking Zavzpret™?	As informed by the participant. Prompt question: - To what extent are these met in reality?

Table 1. Variables description

Group	Role	Data source	Variables	Operational definition
				- Are your goals for Zavzpret™ different than goals for other acute medications for migraine?
			What are your overall impressions of Zavzpret™?	As informed by the participant. Prompt question: - What about your perceptions of taking Zavzpret™ as a nasal spray?
			Are there things that you like about Zavzpret™?	As informed by the participant. Prompt question: - How important are these relative to other medications for acute attacks?
			Are there things you do not like about Zavzpret™?	As informed by the participant. Prompt questions: - How important are these relative to other medications for acute attacks? - To what extent do these drawbacks impact your willingness to use the treatment?
			How easy or difficult has it been for you to continue to take Zavzpret™?	As informed by the participant.
			How easy or difficult has it been for you to get Zavzpret™?	As informed by the participant. Prompt question: - [If reporting only access issues]: Have you encountered any other difficulties, beyond insurance or copays?
			Has there ever been a time where you were reluctant to take Zavzpret™?	As informed by the participant. Prompt question: - for what reason?
			Do you think you will use Zavzpret™ again?	As informed by the participant. Prompt question: - Why or why not?

Table 1. Variables description

Group	Role	Data source	Variables	Operational definition
			Where would you rank Zavzpret™ in terms of your 'go to' treatment relative to your other available prescription acute migraine medications?	As informed by the participant. Prompt question: - Please tell me how you arrive at this ranking.
			How would you describe the impacts of taking Zavzpret™?	As informed by the participant. Prompt question: - Have you experienced any unwanted effects from Zavzpret™?
			How would you describe the taste?	As informed by the participant. Prompt questions: - How long does this taste last after taking Zavzpret™? - How would you rate the severity of the taste on a scale from "1 – not at all severe" to "10-extremely severe"?
			What do you do, if anything, to manage the taste?	As informed by the participant. Prompt questions: - Did you ever take anything to help minimize the effect of the taste? What?
			To what extent is the taste a drawback of the treatment?	As informed by the participant. Prompt question: - Has this taste ever impacted your use of Zavzpret™?
			How does this taste impact your quality of life, if at all?	As informed by the participant. Prompt questions: - How if at all does this taste impact you emotionally? - How would you rate the impact of the taste on your quality of life on a scale from "1 – no impact" to "10-extreme impact"?

Table 1. Variables description

Group	Role	Data source	Variables	Operational definition
Conclusion	Outcome	On-on-one interview	Overall, how satisfied are you with Zavzpret™ on a scale from 1 to 10?	Scale 1-10. Prompt question: - How did you choose that number?
			Assign a number of points that indicate how impactful the feature is in taking or not taking Zavzpret™: Freedom from pain: _____ How quickly it works for headache pain relief: _____ Return to normal function: _____ Duration of effectiveness: _____ Nasal spray as mode of administration: _____ Nasal discomfort from using spray: _____ Taste of the medicine: _____	The numbers across features should sum to 100
			Is there anything that we have not discussed that you think would be important for me to know?	As informed by the participant.
			Adverse event reporting (if applicable)	As informed by the participant.

9.4. Data Sources

The one-on-one interviews will be conducted via online conferencing/telephone. The moderator will contact the participant at the time of the scheduled interview. The moderator will review the purpose of the call, review the key components of the informed consent form previously reviewed and endorsed by the participant during the screening process, and obtain verbal consent to be recorded.

9.4.1. Other Sources of Data

Not Applicable.

9.5. Study Size

The qualitative interviews will be conducted via online conferencing/telephone with up to 20 adults who have used zavegepant in the past 3 months. After the first 3 interviews, interim review will be conducted, and the discussion guide may be refined to enhance its effectiveness in capturing key insights. Once the initial 15 interviews are completed, if necessary, up to 5 additional participants will be recruited and evaluated, increasing the total enrollment number to 20. In qualitative research, sample size is determined based on concept saturation. The FDA defines saturation as "the point when no new relevant or important information emerges and collecting additional data will not likely add to the understanding of how participants perceive the concept of interest." [10,11].

Concept saturation is typically established between nine and seventeen interviews, particularly in studies where the study population is homogenous and study objectives are clearly defined [9].

9.6. Data Management

The enrollment and interview materials and recordings will be saved on a secure Redacted network drive only accessible to Redacted staff members. All data collected in this study will be treated confidentially in accordance with all appropriate legislation. Only staff from Redacted, responsible for data collection, will know the identity of the (potential) participants. Study staff will be instructed to maintain complete confidentiality of all collected data. Interview transcripts will have any identifying information removed and will be kept on secure servers. No identifying information (e.g., names, addresses, or other distinguishing information) will be collected in the interviews.

Each participant will be identified by a unique identification (ID) number. The database which stores the recordings allows for direct exportation into the qualitative analysis software (MAXQDA 24). Because each participant will be identified by a unique ID number, the working data files will be anonymized and will not contain any identifying information apart from the ID number. Unless otherwise agreed between Pfizer and Redacted or prohibited by local laws or regulations, Redacted will deliver deidentified or pseudonymized transcripts to Pfizer at the conclusion of the study.

9.6.1. Case Report Forms (CRFs)/Data Collection Tools (DCTs)/Electronic Data Record

As used in this protocol, the term DCT should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A completed DCT is required for each included participant. The completed original DCTs are the sole property of Pfizer and should not be made available in any form to third parties,

except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. Redacted shall ensure that the DCTs are securely stored at the Redacted servers in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

Redacted has ultimate responsibility for the collection and reporting of all data entered on the DCTs as required and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The DCT serves as the source document. Any corrections to entries made in the DCTs must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, Redacted agrees to keep all study-related records. The records should be retained by Redacted according to local regulations or as specified in the vendor contract, whichever is longer. Redacted must ensure that the records continue to be stored securely for so long as they are retained.

If Redacted becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless Redacted and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Records must be retained for longer than 15 years if required by applicable local regulations.

Redacted must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data Analysis

The coding process, including the development of codes and categories, will be collaborative with members of the Redacted team and Pfizer. Members of the research team will engage in reflexivity, the process of examining one's own beliefs and judgements, as well as how these beliefs and judgements impact how they think and interpret data [12]. A preliminary round of coding and review will establish key categories of interest. The data collected will align with the structure of the discussion guide, exploring respondents' migraine experiences and history, symptom management, treatment decisions, introduction to zavegepant, its usage and impact, as well as access, side effects, and other barriers to treatment. MAXQDA v24 will be used to code and facilitate organization of the data. To begin, a primary coder will systematically read the transcripts, form understandings, and establish a preliminary coding

system using two to three transcripts. This first code system will outline key concepts and categories that arise from the data, particularly those related to answering the primary objectives of this study. The code system will be developed using both inductive and deductive approaches. A priori codes will emerge from concepts outlined in the interview guide: migraine experiences and history, symptom management, treatment decisions, introduction to zavegepant, zavegepant usage and impact, side effects and other barriers to treatment. To ensure that the study also captures the spontaneous and unexpected areas of patient experience, codes will also arise based on how patients describe their lived experience. As these are based on patient response in the interview, these cannot be prespecified. The draft code system and respective transcripts will be reviewed by the study team. Codes will be adapted and refined as needed. Codes will be adapted and refined as needed, meaning that codes may be added, eliminated, or merged depending on the needs of the project and feedback from the team. At this point, the draft codebook will be shared with Pfizer for review and approval. After the initial code frame is established, the coder will review and code the remainder of the transcripts using the revised codebook. Results from the second round of coding will be reviewed and discussed by the study team, who will meet intermittently to make refinements to the code system.

Concepts that emerge during content analysis will be analyzed for concept saturation, or the exercise of confirming that no new key concepts have been identified by the final point of data collection. The study team will also assess saturation with the goal of identifying code saturation in core codes [9]. The study team should be able to establish code saturation (no new information emerged and codes were repeated) by the end of data analysis, demonstrating the range of concepts [13]. Meeting saturation of concepts will help establish the validity and quality of the research.

While qualitative research does not primarily rely on numerical counts, the analysis will quantify commonly mentioned concepts to provide additional insight into participant responses. Upon completion of coding and finalization of the codebook, relevant numerical counts will be extracted from MAXQDA to indicate the number of participants mentioning a particular concept.

9.8. Quality Control

Data collection will be conducted according to the study procedures outlined in this protocol. Participants will be assured of the confidential nature of the interviews. Participants will also be informed at the beginning of the interview that they may choose to terminate the interview at any time if they feel uncomfortable or wish to withdraw from the study. If a participant expresses discomfort or requests to stop, the interviewer will immediately cease the interview without further questioning. Interviewers will review all forms for completeness prior to concluding the study visit.

To ensure the quality and accuracy of data, a rigorous quality control process will be implemented throughout the qualitative study. The research team will actively monitor data collection by listening to live interviews and/or reviewing each transcripts to track emerging

themes and identify inconsistencies. Regular meetings with the client will be held to discuss findings, including expected and unexpected concepts, ensuring that insights remain relevant and aligned with study objectives.

All interviews will be audio recorded for transcription and qualitative analysis. The research team will use MAXQDA, a software that stores data for the researcher to systematically code and analyze transcripts. Triangulation and reflexivity are key aspect of rigor in qualitative research, and as such, the research team will collaboratively review the data at least twice (after three interviews have been coded and at the end of the coding process). These meetings will not only refine the codebook and verify alignment with study objectives, but also will allow the researchers to reflexively discuss their own positions and how this influences the interpretation of the data. This approach follows an iterative approach to ensure rigor and trustworthiness.

Upon completion of coding and finalization of the codebook, relevant numerical counts will be extracted from MAXQDA to indicate the number of participants mentioning a particular concept. Given the semi-structured nature of interviews, not all participants will answer the same questions in the same way, and response variations will be considered when interpreting findings. Concept saturation will also be assessed to confirm that key themes have been sufficiently captured.

At every step of data processing, results will be cross checked by Redacted team members who independently verify that the data have been handled appropriately and accurately. Any inconsistencies identified during this process are corrected before any further analysis is completed. Additionally, all findings will undergo a final review by both Redacted and Pfizer to ensure that data is correctly represented, qualitative insights are clearly communicated, and study conclusions are both meaningful and valid. While qualitative research emphasizes the richness of participant experiences over numerical precision, our systematic approach ensures that emerging concepts are accurately identified and reliably reported.

9.9. Limitations of the Research Methods

It is possible that participants who volunteer for qualitative research interviews may be more educated and/or more vocal than those who do not. This selection bias is intrinsic to the type of study and therefore the results presented will be limited in terms of generalizability [14]. Although the study may not represent the perception of the general population, given the limited sample, the aim is to provide further insights and a more depth of understanding regarding the use of zavegepant.

To minimize bias associated with level of independence, interviews will be conducted via telephone so as to not require close proximity for the interviews.

Responses may be influenced by recall and self-presentation biases which could introduce additional error. However, self-reported data collection is a standard approach, and any potential problems with recall bias are anticipated to be constant across participants and time points. Additionally, diagnoses and other self-reported clinical variables cannot be

independently confirmed. Given the cross-sectional nature of the study, statements of causality cannot be made from the study results, and temporal relationships between study variables cannot be rigorously assessed. Although the discussion guide was developed based on the STAR (Sense-Think-Act-Relate) framework, the tool has not been validated and therefore, its reliability and validity in assessing patient´s perspectives of zavegepant use may be limited.

9.10. Other Aspects

Not Applicable

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant personal data. - Such measures will include omitting participant names or other directly identifiable data in any transcripts, recordings, reports, publications, or other disclosures, except where required by applicable laws.

Participant personal data will be stored at Redacted servers in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. Redacted 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, Redacted shall 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 natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, any participant names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, participant-specific code. Redacted will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of participants' personal data consistent with the vendor contract and applicable privacy laws.

10.2. Patient Consent

The informed consent documents and any participant recruitment materials must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process and any participant recruitment materials must be reviewed and approved by Pfizer, approved or receive exemption status by the IRB before use, and available for inspection. The party

responsible for data collection must ensure that each study participant is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the participant's personal data. The party responsible for data collection further must ensure that each study participant is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

Participants will review and acknowledge an online consent during the screening process. At the start of the interview, the moderator will again review key components of the informed consent form. If participants agree to be interviewed, they will provide a verbal consent at that time.

10.3. Patient Withdrawal

Respondents may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the sponsor for safety, behavioral, or administrative reasons.

If the participant withdraws from the study, and also withdraws consent for disclosure of future information, no additional data should be collected, and the respondent will not be compensated for participation. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

10.4. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of Redacted to have prospective approval of the study protocol, protocol amendments, materials describing the consent process (e.g., statement regarding agreement to participate), and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained by Redacted. Copies of IRB/IEC approvals should be forwarded to Pfizer.

10.5. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in:

- Guidelines for Good Pharmacoepidemiology Practices (GPP). Public Policy Committee, International Society of Pharmacoepidemiology. Pharmacoepidemiology and Drug Safety 2015; 25:2-10. https://onlinelibrary.wiley.com/doi/full/10.1002/pds.3891

- Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) http://www.ispor.org/workpaper/practices_index.asp

- European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological

Standards in Pharmacoepidemiology
http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml

- Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ ucm071696.pdf

- FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance s/UCM243537.pdf

- FDA Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims
http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

REQUIREMENTS

This study does not involve treating healthcare professionals (HCP) collecting data on individual patients, and the data collection tool used in this study does not intend to identify product safety information. However, the data collection tool will be completed by participants by online conferencing/telephone, and a participant could volunteer product safety information to the telephone interviewer. Any safety information that is volunteered, for example by the patient him/herself, health care professional, lay person, during the course of this research must be reported as described below.

The following must be reported on the "Non-Interventional Study (NIS) Adverse Event Monitoring (AEM) Report Form for Protocols without Stipulated Active Collection of Adverse Events" hereinafter referred to as the NIS AEM Report Form: safety events (serious and non-serious adverse events, when associated with the use of a Pfizer product), and scenarios involving exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, occupational exposure and off-label use **(all reportable, regardless of whether associated with a safety event)**, when associated with the use of a Pfizer product.

Exposure during pregnancy (EDP) reports are reportable using the NIS AEM Report Form and the EDP Supplemental Form, irrespective of the presence of an associated safety event.

EDP are not reportable for the following scenarios: None.

If the mother or the fetus experiences a safety event during administration of such drugs, the safety event must be reported without the event EDP reported.

For EDP, in studies exclusively of pregnant people, data on the exposure to the Pfizer product during pregnancy, are not reportable. However, if the mother or the fetus experiences any adverse events (either serious or non-serious), the event must be reported without the event EDP.

If a study participant volunteers any of the above product safety information, study staff Redacted must complete the NIS AEM Report Form and submit it to the Pfizer Drug Safety Unit (DSU) within 24 hours of becoming aware of the safety event. Included in the completion of the NIS AEM Report Form is the study participant's contact information, if contact information is available or is provided by the study participant and consent allows this; complete contact information should be obtained so that, once the NIS AEM Report Form is sent to Pfizer, the NIS AEM Report Form can be assessed and processed according to Pfizer's standard operating procedures, including requests for follow-up to the study participant.

Study staff Redacted who will fill in with appropriate research activities, eg, administer the data collection tool by telephone, interact with study participants, address any query from participants about the study must complete the following Pfizer training:

- *"Your Reporting Responsibilities (YRR) with Supplemental Topics."*

This training must be completed by study staff Redacted prior to the start of data collection. The training includes a "Confirmation of Training Statement" (for signature by the trainee) as a record of completion, which must be kept in a retrievable format. The study vendor will also provide copies of all signed training statements to Pfizer.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Following the conclusion of respondent recruitment, Redacted will provide Pfizer with a final report of the study findings. The results of the study are intended to be published in the scientific literature or presented at a scientific congress.

For all publications relating to the study, Pfizer will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if Redacted is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, Redacted will inform Pfizer immediately of any urgent safety measures taken to protect the study participants against any immediate hazard, and of any serious breaches of this NI protocol that Redacted becomes aware of.

13. REFERENCES

1. Law, H., Chung, M., Nissan, G., Janis, H., & Amirlak, B. (2020, April 23). Hospital Burden of Migraine in United States Adults: A 15-year National Inpatient Sample Analysis. Plast Reconstr Surg Glob Open, 8(4), e2790. doi:10.1097/GOX.0000000000002790

2. Pescador Ruschel, M., & De Jesus, O. (2024). Migraine Headache. StatPearls. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK560787/

3. Ahmed, U., Saleem, M., Osman, M., & Shamat, S. (2023, December 13). Novel FDA-approved zavegepant drug for treating migraine. Ann Med Surg (Lond), 86(2), 923-925. doi:10.1097/MS9.0000000000001620

4. Croop R, Madonia J, Stock DA, Thiry A, Forshaw M, Murphy A, Coric V, Lipton RB. Zavegepant nasal spray for the acute treatment of migraine: A Phase 2/3 double-blind, randomized, placebo-controlled, dose-ranging trial. Headache 2022 Oct;62(9):1153-1163. doi: 10.1111/head.14389

5. Lipton RB, Croop R, Stock DA, Madonia J, Forshaw M, Lovegren M, Mosher L, Coric V, Goadsby PJ. Safety, tolerability, and efficacy of zavegepant 10 mg nasal spray for the acute treatment of migraine in the USA: a phase 3, double-blind, randomised, placebo-controlled multicentre trial. Lancet Neurol. 2023 Mar; 22(3):209-217. doi: 10.1016/S1474-4422(22)00517-8.

6. Mullin K, Croop R, Mosher L, Fullerton T, Madonia J, Lipton RB. Long-term safety of zavegepant nasal spray for the acute treatment of migraine: A phase 2/3 open-label study. Cephalalgia. 2024 Aug; 44(8): 1-9. doi: 10.1177/03331024241259456.

7. Lamont, M., & Swidler, A. (2014). Methodological Pluralism and the Possibilities and Limits of Interviewing. Qualitative Sociology, 37(2), 153–171. https://doi.org/10.1007/s11133-014- 9274-z

8. Dwyer Orr L, Sadik K, Beusterien K, Loomer S, King-Concialdi K, Krupsky K, Brighton E, Kirksey L, Florez N. Drivers and barriers to health-seeking behaviors and interactions: a qualitative study of Black patients with lung cancer and with peripheral artery disease. Curr Med Res Opin. 2025 Jan 16:1-9. doi: 10.1080/03007995.2024.2444420.

9. Hennink, M., & Kaiser, B. N. (2022). Sample sizes for saturation in qualitative research: A systematic review of empirical tests. Social Science & Medicine, 292, 114523.

10. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Devices and Radiological Health. 2009.

11. Fusch, P. I., & Ness, L. R. (2015). Are We There Yet? Data Saturation in Qualitative Research. The Qualitative Report, 20(9), 1408-1416. doi.org/10.46743/2160-3715/2015.2281.

12. Olmos-Vega, F. M., Stalmeijer, R. E., Varpio, L., & Kahlke, R. (2022). A practical guide to reflexivity in qualitative research: AMEE Guide No. 149. Medical Teacher, 45(3), 241–251. https://doi.org/10.1080/0142159X.2022.2057287

13. Hennink, MM; Kaiser, BN; Macroni, VC. Code Saturation Versus Meaning Saturation: How Many Interviews Are Enough? Qual Health Res. 2017 Mar;27(4):591-608. doi:10.1177/1049732316665344

14. Collier D, Mahoney J. Insights and Pitfalls: Selection Bias in Qualitative Research. *World Politics*. 1996;49(1):56-91. doi:10.1353/wp.1996.0023

14. LIST OF TABLES

15. LIST OF FIGURES

None.

16. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Document reference number/version	Date	Title
1	Version 1.0	03 February 2025	Screener questionnaire
2	Version 1.0	20 February 2025	Discussion guide

17. ANNEX 2. ADDITIONAL INFORMATION

Not Applicable

Document Approval Record

Document Name:	C5301035_NIS protocol_Migraine Patient Experiences with Zavegepant_V1.0_20FEB2025
Document Title:	C5301035_NIS protocol_Migraine Patient Experiences with Zavegepant_V1.0_20FEB2025

Signed By:	Date(GMT)	Signing Capacity
Redacted	18-Mar-2025 00:07:02	Redacted
Redacted	20-Mar-2025 16:26:14	Redacted