NCT04179474

Study ID: 3110-108-002

Title: A Phase 1b, Two-Part, Open-Label, Fixed-Sequence, Safety, Tolerability and Drug-Drug Interaction Study Between Single Dose Erenumab or Galcanezumab and Multiple Dose Ubrogepant in Participants with Migraine

Protocol Date: 14Aug2019

Title Page

Protocol Title: A Phase 1b, Two-Part, Open-Label, Fixed-Sequence, Safety, Tolerability and Drug-Drug Interaction Study Between Single Dose Erenumab or Galcanezumab and Multiple Dose Ubrogepant in Participants with Migraine

Protocol Number: 3110-108-002

Product: Ubrogepant (AGN-241688, MK-1602)

Brief Protocol Title: Drug-Drug Interaction Study of Ubrogepant with Erenumab or Galcanezumab

Study Phase: 1b

Sponsor Name and Legal Registered Address:

Allergan Pharmaceuticals International Limited, Clonshaugh Industrial Estate, Coolock, Dublin 17, Ireland

US Agent: Allergan Sales, LLC, 2525 Dupont Dr, Irvine, California 92612, USA

Regulatory Agency Identifying Number(s): IND #113924

SAE Reporting Fax Number/Email:

Business Unit	Email	Phone	Fax
Allergan	[redacted]	[redacted]	[redacted]

Approval Date: 14 August 2019

Sponsor Signatories:

[redacted]	**Date**
[redacted]	**Date**

The signatures of the sponsor signatories are collected on the protocol approval page.

Table of Contents

[redacted]

List of Tables

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 1b, Two-Part, Open-Label, Fixed-Sequence, Safety, Tolerability and Drug-Drug Interaction Study Between Single Dose Erenumab or Galcanezumab and Multiple Dose Ubrogepant in Participants with Migraine

Protocol Number: 3110-108-002

Brief Title: Drug-Drug Interaction Study of Ubrogepant with Erenumab or Galcanezumab

Study Phase: 1b

Study Rationale:

Ubrogepant is a novel, oral calcitonin gene-related peptide (CGRP) receptor antagonist, currently seeking approval for the acute treatment of migraine. Migraine patients with episodic or chronic migraine are likely to be taking Aimovig® (erenumab) or Emgality® (galcanezumab) subcutaneously (SC) for the prevention of migraines. There is a high likelihood that physicians could prescribe ubrogepant for the acute treatment of breakthrough migraines in patients already taking migraine preventives. Ubrogepant is extensively metabolized in the liver by cytochrome P450 (CYP)3A4, while erenumab and galcanezumab are not metabolized by CYP enzymes. Although a significant metabolic interaction is not expected when ubrogepant and erenumab or ubrogepant and galcanezumab are co-administered, this study will evaluate the potential for a pharmacokinetic (PK) interaction and provide safety and tolerability information when ubrogepant and erenumab or ubrogepant and galcanezumab are co-administered.

Objectives and Endpoints:

Objectives	Endpoints
Primary	**Primary**
To evaluate the effect of single dose erenumab or galcanezumab on the PK of multiple dose ubrogepant in participants with migraine	Area under the plasma concentration versus time curve from time 0 to time t (AUC_{0-t}) and from time 0 to infinity ($AUC_{0-\infty}$), and maximum plasma drug concentration (C_{max}) of ubrogepant when ubrogepant and erenumab or ubrogepant and galcanezumab are administered together and when ubrogepant is administered alone

Objectives	Endpoints
Secondary	**Secondary**
To evaluate secondary PK parameters of ubrogepant following administration of ubrogepant and erenumab or ubrogepant and galcanezumab and when ubrogepant is administered alone	Time of maximum plasma drug concentration (T_{max}), terminal elimination rate constant (λ_z), terminal elimination half-life ($T_{½}$), apparent total body clearance of drug from plasma after extravascular administration (CL/F), and apparent volume of distribution during the terminal phase after extravascular administration (V_z/F) of ubrogepant when ubrogepant and erenumab or ubrogepant and galcanezumab are co-administered and when ubrogepant is administered alone
To evaluate the safety and tolerability profiles when ubrogepant and erenumab or ubrogepant and galcanezumab are administered in combination and when administered alone in participants with a history of 2 or more migraine attacks per month	Changes from baseline in vital signs, clinical laboratory measurements, physical examinations, and electrocardiograms (ECGs) Incidence of adverse events (AEs) including severity and causality of AEs, as well as AEs leading to discontinuation
[redacted]	[redacted]

Overall Study Design:

This study will be a Phase 1b, 2-part, multi-center, open-label, fixed-sequence drug interaction study in 40 male and female participants who have been diagnosed with migraine for at least 1 year and are aged 18 through 50 years. In Part 1, 20 participants will receive a single oral dose of 100 mg ubrogepant alone (Study Intervention A) on Day 1, a single SC injection of 140 mg erenumab alone (Study Intervention B) on Day 8, followed by once daily oral doses of 100 mg ubrogepant on Days 12 through 15 (Study Intervention D) under fasted conditions. Similarly, in Part 2, a separate cohort of 20 participants will receive a single oral dose of 100 mg ubrogepant alone (Study intervention A) on Day 1, 2 consecutive SC injections of 120 mg galcanezumab alone (Study intervention C) on Day 8, followed by once daily oral doses of 100 mg ubrogepant on Days 12 through 15 (Study Intervention D) under fasted conditions.

If all doses are well tolerated, the duration of participation in the study will be 46 ± 3 days (Day –1 through the safety Follow-up visit on Day 45), not including the Screening Visit.

- Duration:
  - Screening: Up to 21 days (Day -21 to Day -1)
  - Intervention Period: Up to a total of 17 days (Day -1 to Day 16)
  - Follow-up period: 30 (±3) days after the last dose
- PK and Biomarker Sampling

  In Part 1 and Part 2, PK and biomarker blood samples for the analysis of ubrogepant and CGRP concentrations will be collected at 0 hour (predose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 14, and 24 hours postdose on Days 1 and 12.

  [redacted]

- Safety Measurements

  The safety and tolerability profiles when ubrogepant and erenumab or ubrogepant and galcanezumab are co-administered and when each study intervention is administered alone in participants with migraine will be evaluated by clinical assessment of AEs, physical examinations, safety 12-lead ECGs, standard laboratory safety tests (hematology, serum chemistry, and urinalysis), and by measurements of vital signs at specified time points after each study intervention.

Number of Participants:

A total of 40 participants will be enrolled in the study; 20 participants in Part 1 and a separate cohort of 20 participants in Part 2. Part 1 and Part 2 will enroll in parallel. [redacted] Participants who prematurely discontinue from the study may be replaced at the discretion of the sponsor.

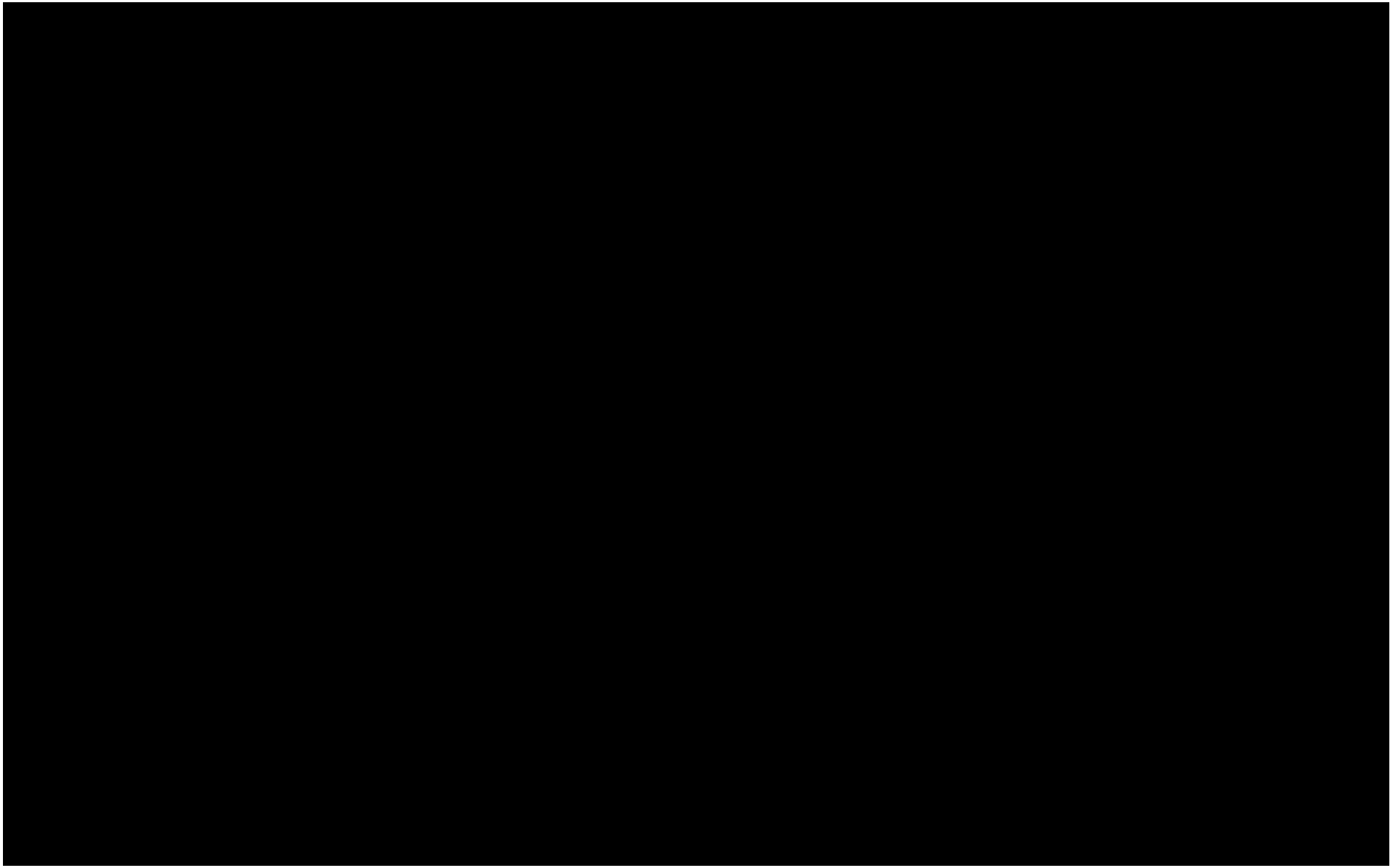
Number of Sites: Up to 3 sites in the United States

Intervention Groups and Study Duration:

Study Intervention A:	Single oral 100-mg dose of ubrogepant tablet on Day 1
Study Intervention B:	Single subcutaneous injection of 140-mg erenumab on Day 8
Study Intervention C:	Two consecutive subcutaneous injections of 120-mg galcanezumab on Day 8
Study Intervention D:	Repeated once daily oral doses of 100-mg ubrogepant on Days 12, 13, 14, and 15

If all doses are well tolerated, the duration of participation in the study will be 46 ± 3 days (Day –1 through the safety Follow-up Visit on Day 45), not including the Screening Visit.

Data Monitoring Committee: No



[redacted]

2. Introduction

Migraine affects 18% of women and 6% of men in the United States with a peak prevalence occurring between the ages of 25 to 55 years. Approximately one third of those with migraine have 3 or more migraines per month, and over half report severe impairment or the need for bed rest during an attack (Lipton et al, 2007). In the United States, work loss due to migraine is estimated to cost ~ $13 billion annually (Hu et al, 1999). Prevalence is similar in Europe, with migraine affecting 17.6% of women and 8% of men (Stovner and Andree, 2010). The Global Burden of Disease Study 2010 (Vos et al, 2012) estimated the global prevalence of migraine to be 14.7%, making it the third most common disease in the world in both males and females. Migraine was ranked seventh highest among specific causes of disability globally (Steiner 2013).

Calcitonin gene-related peptide (CGRP) is a neuropeptide implicated in the pathophysiology of migraine. CGRP levels in the cranial venous outflow (ie, external jugular vein) are increased during a migraine attack (Goadsby and Edvinsson, 1993) and exogenously administered CGRP has been shown to trigger migraine-like headache in migraineurs. The majority (80 to 90%) of trigeminal Aδ fibers that innervate the dura contain CGRP, suggesting that these fibers may be involved in sterile neurogenic inflammation and migraine pain transmission. Furthermore, the CGRP receptor is present on human meningeal and cerebral blood vessels. These observations suggest that activation of the trigeminovascular system, with release of CGRP, may play a key role in migraine pathogenesis and that inhibition of CGRP function may yield a novel therapeutic approach to treating migraine.

This study will evaluate the safety, tolerability, and PK of ubrogepant, a CGRP antagonist, when administered to participants with migraine receiving erenumab or galcanezumab.

2.1. Study Rationale

Ubrogepant is a novel, oral CGRP receptor antagonist, currently seeking approval for the acute treatment of migraine. Migraine patients with episodic or chronic migraine are likely to be taking Aimovig (erenumab) or Emgality (galcanezumab) subcutaneously (SC) for the prevention of migraines. There is a high likelihood that physicians could prescribe ubrogepant for the acute treatment of breakthrough migraines in patients already taking migraine preventives. Ubrogepant is extensively metabolized in the liver by cytochrome P450 (CYP)3A4, while erenumab and galcanezumab are not metabolized by CYP enzymes. Although a significant metabolic interaction is not expected when ubrogepant and erenumab or ubrogepant and galcanezumab are co-administered, this study will evaluate the potential for a PK interaction and provide safety and tolerability information when ubrogepant and erenumab or ubrogepant and galcanezumab are co-administered.

2.2. Background

Ubrogepant

Ubrogepant, a novel oral CGRP receptor antagonist, that is chemically distinct from both telcagepant and MK-3207, is being developed for the acute treatment of migraine. Current standard of care for the acute treatment of migraines includes triptans, NSAIDs, and ergots. Ubrogepant has completed Phase 3 evaluation for the acute treatment of migraine.

Preclinical and clinical studies conducted to date for ubrogepant have shown no evidence of hepatotoxicity. The toxicity studies conducted to date have demonstrated considerable safety margins over the projected efficacious clinical exposure. For the highest anticipated dose used in clinical studies of 100 mg with potential redosing in the same day (AUC 4.4 µM•hr for a total dose of 200 mg), the safety margins are 3.5- and 74-fold over the rat NOAEL and monkey NOEL exposures, respectively. The nonclinical toxicity profile of ubrogepant via the oral route of administration supports the continuation of dosing via the oral route in appropriately designed clinical trials. The findings from the developmental toxicology studies in rats and rabbits and a fertility study in rats support inclusion of women of childbearing potential (WOCBP) in clinical trials in compliance with the study protocol and applicable regulatory guidelines.

In Phase 1 studies, single doses of 1 to 400 mg ubrogepant and multiple doses of ubrogepant up to 400 mg once daily (QD) for 10 consecutive days and 150 mg QD for 28 consecutive days have been evaluated. Ubrogepant was generally safe and well tolerated in these studies. In the multiple dose safety and tolerability studies evaluating hepatic effects of 150 mg QD for 28 days and high frequency, intermittent dosing of 100 mg (2 days ubrogepant followed by 2 days placebo) for 56 days, no signs of drug-induced liver injury (DILI) were observed based on a systematic measurement of serum ALT and aspartate aminotransferase (AST). The most frequently reported clinical AEs in these Phase 1 studies include nasopharyngitis, headache, and nausea. Adverse events have generally been transient and mild to moderate in intensity. Dose-proportional PK was noted in the dose range of 1 to 400 mg. Ubrogepant is rapidly absorbed with maximum plasma concentrations achieved in 0.5-1.5 hours. Ubrogepant is metabolized to an inactive metabolite almost exclusively by CYP3A4 with subsequent glucuronidation. Ubrogepant has a short terminal elimination half-life ($T_{½}$) of 5 to 7 hours with no accumulation after QD repeated dosing.

A Phase 2b clinical study was conducted, which compared 1-, 10-, 25-, 50-, and 100-mg doses of ubrogepant to placebo in the acute treatment of migraine. Overall, all the ubrogepant doses tested were well tolerated and the adverse event profile of all ubrogepant doses did not differ significantly from placebo. For the primary efficacy endpoint of pain freedom at 2 hours, ubrogepant doses of 1 and 10 mg did not differ from placebo, but doses of 25, 50, and 100 mg were better than placebo. For the primary efficacy endpoint of pain relief at 2 hours none of the ubrogepant doses differed from placebo, probably due to a high placebo response rate.

Further efficacy and safety of ubrogepant were established in 2 randomized, double-blind, placebo-controlled, single-attack, Phase 3 studies (UBR-MD-01 and UBR-MD-02). The results from these studies demonstrated that both ubrogepant 50 mg and 100 mg are superior to placebo in the acute treatment of migraine based on the coprimary efficacy endpoints (pain freedom and

absence of the most bothersome migraine-associated symptom at 2 hours after the initial dose of investigational product). Study UBR-MD-02 demonstrated that ubrogepant 25 mg was superior to placebo for the coprimary endpoint pain freedom at 2 hours after the initial dose; however, statistical significance was not achieved for the coprimary endpoint absence of the most bothersome migraine-associated symptom at 2 hours after the initial dose. The efficacy in each study was supported by the prospectively defined secondary and additional endpoints. A long-term safety extension study, UBR-MD-04, was conducted and supported the safety of ubrogepant evidenced in the 2 pivotal studies.

Additional information and a detailed description of the chemistry, pharmacology, toxicology, efficacy, and safety of ubrogepant can be found in the ubrogepant Investigator's Brochure, (Edition 6, 2019). Rationale for dose selection is described in Section 4.3.

Erenumab

Erenumab-aooe (Aimovig®) is a human immunoglobulin G2 (IgG2) monoclonal antibody (MAB) that has high affinity binding to the CGRP receptor and antagonizes CGRP receptor function. Erenumab is indicated for the preventive treatment of migraine in adults. Erenumab is produced using recombinant DNA technology in Chinese hamster ovary (CHO) cells. It is composed of 2 heavy chains, each containing 456 amino acids, and 2 light chains of the lambda subclass, each containing 216 amino acids, with an approximate molecular weight of 150 kDa.

Erenumab exhibits non-linear kinetics as a result of binding to the CGRP receptor. Less than 2-fold accumulation was observed in trough serum concentrations (C_{min}) for episodic and chronic migraine patients following SC administration of 70 mg once monthly and 140 mg once monthly doses. Serum trough concentrations approached steady state by 3 months of dosing. The effective half-life of erenumab is 28 days. Median peak serum concentrations were attained in approximately 6 days, and estimated absolute bioavailability was 82%. Two elimination phases were observed for erenumab. At low concentrations, the elimination is predominantly through saturable binding to target (CGRP receptor), while at higher concentrations the elimination of erenumab is largely through a non-specific, non-saturable proteolytic pathway. Erenumab is not metabolized by CYP enzymes; therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of CYP enzymes are unlikely.

Additional information for erenumab can be found in the Aimovig® USPI.

Galcanezumab

Galcanezumab-gnlm (Emgality®) is a humanized immunoglobulin G4 (IgG4) MAB that binds to CGRP ligand and blocks its binding to the receptor. Galcanezumab is produced in CHO cells by recombinant DNA technology. Galcanezumab is composed of 2 identical immunoglobulin kappa light chains and 2 identical immunoglobulin gamma heavy chains and has an overall molecular weight of approximately 147 kDa.

Galcanezumab exhibits linear PK and exposure increases proportionally with doses between 1 and 600 mg. A loading dose of 240 mg achieved the serum galcanezumab steady-state concentration after the first dose. The time to maximum concentration is 5 days, and the elimination half-life is 27 days. Following a SC injection of galcanezumab, the time to maximum

concentration was about 5 days. Galcanezumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG. Galcanezumab is not metabolized by CYP enzymes; therefore, interactions with concomitant medications that are substrates, inducers, or inhibitors of CYP enzymes are unlikely.

Additional information for galcanezumab can be found in the Emgality® USPI.

2.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably expected adverse events of ubrogepant may be found in the ubrogepant Investigator's Brochure. Based on the observed nonclinical and clinical safety profile of ubrogepant, evaluation of ubrogepant in large Phase 3 trials was supported and these trials are currently completed with a potentially favorable risk/benefit. Since ubrogepant is an investigational product currently being considered for approval by the US FDA, the benefit/risk assessment of the product has not yet been completed by the FDA.

3. Objectives and Endpoints

Objectives	Endpoints
Primary To evaluate the effect of single dose erenumab or galcanezumab on the PK of multiple dose ubrogepant in participants with migraine	**Primary** Area under the plasma concentration versus time curve from time 0 to time t (AUC_{0-t}) and from time 0 to infinity ($AUC_{0-\infty}$), and maximum plasma drug concentration (C_{max}) of ubrogepant when ubrogepant and erenumab or ubrogepant and galcanezumab are administered together and when ubrogepant is administered alone
Secondary To evaluate secondary PK parameters of ubrogepant following administration of ubrogepant and erenumab or ubrogepant and galcanezumab and when ubrogepant is administered alone	**Secondary** Time of maximum plasma drug concentration (T_{max}), terminal elimination rate constant (λ_z), terminal elimination half-life ($T_{½}$), apparent total body clearance of drug from plasma after extravascular administration (CL/F), and apparent volume of distribution during the terminal phase after extravascular administration (V_z/F) of ubrogepant when ubrogepant and erenumab or ubrogepant and galcanezumab are co-administered and when ubrogepant is administered alone
To evaluate the safety and tolerability profiles when ubrogepant and erenumab or ubrogepant and galcanezumab are administered in combination and when administered alone in participants with a history of 2 or more migraine attacks per month	Changes from baseline in vital signs, clinical laboratory measurements, physical examinations, and ECGs Incidence of AEs including severity and causality of AEs, as well as AEs leading to discontinuation
[redacted]	[redacted]

4. Study Design

4.1. Overall Design

This study will be a Phase 1b, 2-part, multi-center, open-label, fixed-sequence drug interaction study in 40 male and female participants who have been diagnosed with migraine for at least 1 year and are aged 18 through 50 years. In Part 1, 20 participants will receive a single oral dose of 100 mg ubrogepant alone (Study Intervention A) on Day 1, a single SC injection of 140 mg erenumab alone (Study Intervention B) on Day 8, followed by once daily oral doses of 100 mg ubrogepant on Days 12 through 15 (Study Intervention D) under fasted conditions. Similarly, in Part 2, a separate cohort of 20 participants will receive a single oral dose of 100 mg ubrogepant alone (Study intervention A) on Day 1, 2 consecutive SC injections of 120 mg galcanezumab alone (Study intervention C) on Day 8, followed by once daily oral doses of 100 mg ubrogepant on Days 12 through 15 (Study Intervention D) under fasted conditions.

If all doses are well tolerated, the duration of participation in the study will be 46 ± 3 days (Day –1 through the safety Follow-up Visit on Day 45), not including the Screening Visit.

- Duration:
  - Screening: Up to 21 days (Day -21 to Day -1)
  - Intervention Period: Up to a total of 17 days (Day -1 to Day 16)
  - Follow-up period: 30 (±3) days after the last dose

- PK and Biomarker Sampling

  In Part 1 and Part 2, PK blood samples for the analysis of ubrogepant and CGRP concentrations will be collected at 0 hour (predose), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 14, and 24 hours postdose on Days 1 and 12.

  [redacted]

- Safety Measurements

  The safety and tolerability profiles when ubrogepant and erenumab or ubrogepant and galcanezumab are co-administered and when each study intervention is administered alone in participants with migraine will be evaluated by clinical assessment of AEs, physical examinations, safety 12-lead ECGs, standard laboratory safety tests (hematology, serum chemistry, and urinalysis), and by measurements of vital signs at specified time points after each study intervention.

- Number of Participants

  A total of 40 participants at up to 3 sites in the United States will be enrolled in the study; 20 participants in Part 1 and a separate cohort of 20 participants in Part 2. Part 1 and Part 2 will enroll in parallel.[redacted]

[redacted]. Participants who prematurely discontinue from the study may be replaced at the discretion of the sponsor.

4.2. Scientific Rationale for Study Design

The multi-center, open-label, fixed-sequence design is considered adequate to assess the potential effect on the safety and PK of ubrogepant when ubrogepant and erenumab or ubrogepant and galcanezumab are co-administered. Considering the long half lives of erenumab and galcanezumab (about 28 days), the fixed-sequence design allows for the evaluation of the effect of erenumab/galcanezumab on the PK of ubrogepant. The washout period of 7 days between Study Intervention A and Study Intervention B (Part 1) or Study Intervention C (Part 2) is adequate given ubrogepant's short $T_{½}$ of 5-7 hours. [redacted] Multiple dose administration of ubrogepant following erenumab or galcanezumab administration will help to assess the safety/tolerability of the combinations in a potential real world setting of administering ubrogepant to acutely treat an acute migraine attack in participants who are already on a preventive medication, either erenumab or galcanezumab.

4.3. Justification for Dose

- The ubrogepant dose of 100 mg (administered as one 100 mg tablet) is the highest clinical dose of ubrogepant for which approval is being sought.
- A multiple-dose once daily administration of ubrogepant will provide a dosing regimen similar to the potential real-world use of ubrogepant in combination with migraine preventive MABs and is considered adequate to satisfy the objectives of the study.
- 140 mg erenumab and 240 mg galcanezumab are the highest approved doses of the CGRP receptor MAB (erenumab) and CGRP ligand MAB (galcanezumab), respectively.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit (Follow-up) of the last participant in the study on Day 45 (± 3 days), or at early termination.

A participant is considered to have completed the study if he/she has not been terminated early and has completed all phases of the study through the last visit (Follow-up) on Day 45 ± 3 (30 [± 3] days after the last dose of study intervention).

5. Study Population

Study participants will be individuals with at least a 1-year history of migraine with or without aura, consistent with a migraine diagnosis according to the International Classification of Headache Disorders, 3rd edition, (ICHD-3, 2018).

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:

1.	**Age**
1.01	Participant must be 18 to 50 years of age inclusive, at the time of signing the informed consent.
2.	**Type of Participant and Migraine Characteristics**
2.01	At least a 1-year history of migraine with or without aura consistent with a diagnosis according to the International Classification of Headache Disorders, 3rd edition, (ICHD-3, 2018)
2.02	By history, the participant's migraines typically last between 4 and 72 hours if untreated or treated unsuccessfully and migraine episodes are separated by at least 48 hours of headache pain freedom
2.03	History of at least 2 migraine attacks per month in the 2 months prior to Screening
2.04	Have a sitting pulse rate ≥ 45 beats per minute (bpm) and ≤ 100 bpm during the vital sign assessment at the Screening Visit. Clinical site may perform a maximum of 2 repeats of vital sign measurements if the initial measurement is out of range.
2.05	Negative test results for benzoylecgonine (cocaine), methadone, barbiturates, amphetamines, benzodiazepines, cannabinoids, opiates, and phencyclidine at the Screening Visit and Day -1; unless explained by concomitant medication use (eg, opioids prescribed for migraine pain)
[redacted]	[redacted]
[redacted]	[redacted]

4.	**Sex**
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
	[redacted]
5.02	Female participants willing to minimize the risk of inducing pregnancy for the duration of the clinical study and follow-up period
	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

5.2. Exclusion Criteria

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

1.	**Medical Conditions and History**
1.01	Difficulty distinguishing migraine headache from tension-type or other headaches
1.02	Has a history of migraine aura with diplopia or impairment of level of consciousness, hemiplegic migraine, or retinal migraine as defined by ICHD-3
1.03	Has a current diagnosis of new persistent daily headache, trigeminal autonomic cephalgia (eg, cluster headache), or painful cranial neuropathy as defined by ICHD-3
1.04	Required hospital treatment of a migraine attack 3 or more times in the 6 months prior to Screening
1.05	Has a chronic non-headache pain condition requiring daily pain medication (with the exception of pregabalin)
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
3.02	Participation in any other clinical investigation using an experimental drug within 30 days prior to study intervention administration
3.03	Participation in a blood or plasma donation program within 60 or 30 days,

	respectively, prior to study intervention administration
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

1. Water can be allowed as desired except for 1 hour before and after oral study intervention administration. Participants will be required to undergo a 10-hour overnight fast prior to dosing on Days 1, 12, 13, 14, and 15 and will maintain a fasted condition for an additional 4 hours following oral dose administration on these days. The oral study intervention will be administered with 240 mL of water. Following each dose administration, participants will continue their fast and remain seated upright and awake for 4 hours.
2. Participants will be served meals at appropriate times on admission days. On dosing days with study intervention administration (Days 1, 8, 12, 13, 14, and 15); no breakfast will be provided, but a standard lunch, dinner, and snack will be provided at approximately 4 hours postdose, 10 hours postdose, and 13 hours postdose, respectively. On all other days of confinement, breakfast, lunch, dinner, and snack will be served at approximately 0800, 1200, 1800, and 2100 hours, respectively.
3. Seville oranges, beverages or food containing quinine (bitter lemon, tonic water), poppy seeds, or taken dietary supplements or other foods or beverages that may affect various drug-metabolizing enzymes and transporters (eg, grapefruit, grapefruit juice, grapefruit-containing beverages), vegetables from the mustard green family (eg, kale, broccoli, watercress, collard greens, kohlrabi, brussel sprouts, mustard), or charbroiled meats must not be consumed within 14 days prior to dosing and throughout the duration of the study.
4. A copy of the menu with the total nutritional content (fat, protein, carbohydrates, and calories) of each component of each meal and snack will be made available to the sponsor at the start of the study. Participants will be instructed to consume the entire contents of each meal and snack, if possible. Study center personnel will document the percentage or the amount of consumed food for each participant.
5. While admitted in the study center, participants will be provided with standardized low-fat (< 20 g) meals.
6. Participants must refrain from implementing drastic changes in their diet or start a new diet during the study.

5.3.2. Caffeine, Alcohol, and Tobacco

1. Participants will abstain from ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) for at least 2 hours before dosing and at least 4 hours after dosing.
2. Alcohol intake should be limited to no more than 1 drink per day throughout the study. A drink is defined as a 12-ounce can/bottle of beer, a 4-ounce glass of wine, or 1 ounce of liquor.

3. Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are in the clinical unit.

5.3.3. Activity

Maintaining a consistent lifestyle when participating in a clinical trial is vital. Participants will abstain from strenuous exercise or starting an intense exercise regimen for at least 7 days before blood collection for clinical laboratory tests on Day 1 and throughout the duration of the study, including the follow-up period. Participants may participate in light recreational activities during the study conduct (eg, watching television, reading).

5.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failures) may be rescreened unless the reason for screen failure was a positive urine drug screen. A participant who is rescreened will be assigned a new identification number and must sign the informed consent at the time of re-screening.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Study Intervention A:	Single oral 100-mg dose of ubrogepant tablet on Day 1
Study Intervention B:	Single SC injection of 140-mg erenumab on Day 8
Study Intervention C:	Two consecutive SC injections of 120-mg galcanezumab on Day 8
Study Intervention D:	Repeated once daily oral doses of 100-mg ubrogepant on Days 12, 13, 14, and 15

Migraine participants will be randomized to either Part 1 or 2 and will receive study interventions in a fixed sequence. Parts 1 and 2 could be conducted in parallel. In Part 1, 20 participants will receive a single oral dose of 100 mg ubrogepant alone (Study Intervention A) on Day 1, a single SC injection of 140 mg erenumab alone (Study Intervention B) on Day 8, followed by once daily oral doses of 100 mg ubrogepant on Days 12 through 15 (Study Intervention D) under fasted conditions. Similarly, in Part 2, a separate cohort of 20 participants will receive a single oral dose of 100 mg ubrogepant alone (Study Intervention A) on Day 1, 2 consecutive SC injection of 120 mg galcanezumab alone (Study Intervention C) on Day 8, followed by once daily oral doses of 100 mg ubrogepant on Days 12 through 15 (Study Intervention D) under fasted conditions. There will be a 7-day washout period between the administration of Study Intervention A and Study Intervention B (Part 1) or Study Intervention A and Study Intervention C (Part 2) and an 11-day washout period between ubrogepant doses.

Table 6-1 Study Interventions

Study Intervention Name	Ubrogepant (Intervention A)	Ubrogepant (Intervention D)	Aimovig (Erenumab) (Intervention B)	Emgality (galcanezumab) (Intervention C)
Dose Formulation	Tablet	Tablet	Solution for injection	Solution for injection
Identity of Formulation	100 mg ubrogepant	100 mg ubrogepant	140 mg/mL erenumab aooe	120 mg/mL galcanezumab gnlm
Device Configuration	NA	NA	Single-dose prefilled SureClick autoinjector [redacted] or single-dose prefilled syringe [redacted]	Single-dose prefilled pen [redacted] or single-dose prefilled syringe [redacted]
Route of Administration	Oral	Oral	Subcutaneous injection	Subcutaneous injection
Dosing Instructions	1 tablet to be administered with 240 mL of water, under fasted conditions on Day 1	1 tablet to be administered with 240 mL of water, under fasted conditions on Days 12, 13, 14, and 15	Single subcutaneous injection of 140-mg erenumab in the abdomen, thigh, or upper arm on Day 8	Two consecutive subcutaneous injections of 120-mg galcanezumab in the abdomen, thigh, back of the upper arm, or buttocks on Day 8
Packaging and Labeling	Study intervention will be provided in bottles, each containing 35 tablets. Each bottle will be labeled as required per country requirement.	Study intervention will be provided in bottles, each containing 35 tablets. Each bottle will be labeled as required per country requirement.	Study intervention will be provided as either single-dose prefilled SureClick autoinjector or single-dose prefilled syringe. Each autoinjector/pre-filled syringe will be labeled as required per country requirement.	Study intervention will be provided as either single-dose prefilled pen or single-dose prefilled syringe. Each pre-filled pen/pre-filled syringe will be labeled as required per country requirement.
Manufacturer	Allergan plc, Clonshaugh, Ireland	Allergan plc, Clonshaugh, Ireland	Amgen Inc, Thousand Oaks, CA	Eli Lilly and Company, Indianapolis, IN

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention 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 or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. All unused study intervention and empty kits and bottles must be returned to the sponsor at the termination of the study. Unit counts will be performed when the study intervention is returned, and all study intervention must be accounted for. Used syringes and pens should be discarded at the site.

6.3. Measures to Minimize Bias: Randomization and Blinding

Participants will be randomized to 1 of 2 parts: Part 1 or Part 2. Participants randomized to Part 1 will receive Study Intervention A on Day 1, Study Intervention B on Day 8, and Study Intervention D once daily on Days 12 through 15. Participants randomized to Part 2 will receive Study Intervention A on Day 1, Study Intervention C on Day 8, and Study Intervention D once daily on Days 12 through 15.

This is an open-label study; no blinding of assigned study intervention will occur.

6.4. Study Intervention Compliance

Participants will receive all doses under the direct supervision of study center personnel. Each participant's mouth and hands will be checked to ensure that the oral study interventions A and

D have been taken. Subcutaneous injections for study interventions B and C will be administered by site staff. Study intervention compliance will be assumed to be 100% when oral and subcutaneous dosing has been recorded in the eCRF.

Dosing should occur at the same time each dosing day for a participant; differences in dosing times > 60 minutes will be noted as protocol deviations, and the reason for deviation must be recorded in the source documents and eCRFs.

Galcanezumab injections should be administered consecutively with no more than 5 minutes between injections. A difference in injection times > 5 minutes will be noted as protocol deviations, and the reason for deviation must be recorded in the source documents and eCRFs.

The study center will keep an accurate drug disposition record that specifies the amount of study intervention administered to each participant and the date of administration.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter, prescription medicines, vitamins, herbal supplements, and/or cannabis or other specific categories of interest) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Indication
- Dates of administration including start and end dates
- Dosage information including dose and frequency

At screening, upon admission to and discharge from the study center, EOD, and the Follow-up Visit, study center staff will question each participant specifically on the use of concomitant medications. Study center staff must notify the sponsor immediately if a participant consumes any concomitant medications not permitted by the protocol. Participants who admit to using prohibited concomitant medications may be discontinued from the study at the discretion of the investigator or the sponsor.

6.5.1. Prohibited Interventions and Washout Before the Study

Participants must discontinue any of the medications listed in the table below for the specified period prior to Day -1. These medications are prohibited for the duration of the study. Other stable medications being used at screening may be continued. A medication will be considered stable if the dose and frequency remain unchanged for at least 14 days prior to screening.

The investigator or sponsor reserves the right to exclude a participant from participation in the study if a medication taken 14 or more days before the study start may interfere with the study outcome (eg, a drug with prolonged half-life).

Any hormonal product taken within 30 days or any other medication taken within 14 days before the first dose of study intervention will be recorded in the eCRF as a prior medication.

The decision to administer a prohibited medication/intervention during the study period is done with the safety of the study participant as the primary consideration. When possible, the sponsor should be notified before the prohibited medication/intervention is administered.

6.5.2. Permitted Interventions

Therapy considered necessary for the participant's welfare may be given at the discretion of the investigator. If the permissibility of a specific concomitant medication or prior medication/intervention is in question, please contact the sponsor. All concomitant/prior medication use must be reviewed by the investigator in consultation with the sponsor prior to enrollment.

The following medications are allowed during the study, but are prohibited within 48 hours prior to taking oral study intervention:

- any triptan
- any ergot derivative
- any opioid
- any NSAID
- any other form of analgesic (including acetaminophen and Excedrin®)
- any antiemetic agent
- any proton pump inhibitor

The following medications are allowed during the study, but are prohibited within 24 hours prior to taking oral study intervention:

- any antacid
- any H2 blocker

Aspirin up to 325 mg/day is allowed for cardiac prophylaxis. Daily use of gabapentin/pregabalin is allowed.

Selective serotonin reuptake inhibitors (SSRI) or serotonin norepinephrine reuptake inhibitors (SNRI) will be permitted provided that treatment is stable at Screening and continues without change in dose throughout the study. SSRIs and SNRIs may not be started during the study.

For medications taken for migraine, all past and current medications will be recorded in the eCRF. Any medication taken during the study between the date of the first dose of study intervention and the date of the EOD visit will be recorded in the eCRF as a concomitant medication; any medication started after the EOD visit will not be considered a concomitant medication and should not be captured in the eCRF.

6.5.3. Rescue Medicine

The study site will supply rescue medication that will be obtained locally. Rescue medication includes medications for the acute treatment of migraine. The following rescue medications may be used: triptans, ergotamines, NSAIDs, acetaminophen or combination analgesics (ie Excedrin®), opioids, or other medications that are not explicitly prohibited and may be taken during the study. In the Screening period, rescue medication can be taken if headache of any severity develops.

Although the use of rescue medications is allowable at any time during the study, the use of rescue medications should be delayed, if possible, for at least 2 hours following the administration of study intervention. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.5.4. Prohibited Interventions During the Study

Interventions that are prohibited during the entire study, including the duration of the Follow-up Visit, are described in Table 6-2.

6.6. Dose Modification

No dose modification is allowed through the duration of the study

6.7. Intervention after the End of the Study

There will be no study intervention administered after the end of the study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

A premature discontinuation will occur if a participant who signs the ICF and receives study intervention ceases participation in the study, regardless of circumstances, before the completion of the protocol-defined study procedures.

Notification of early participant discontinuation from the study and the reason for discontinuation will be made to the sponsor and will be clearly documented on the appropriate case report form.

Reasons for discontinuation from the study treatment and/or the study may include the following commonly used or other acceptable terms:

Commonly Used Terms	Other Acceptable Terms
Adverse event	Death
Lost to follow-up	Technical problems
Non-compliance with study drug	
Other	
Physician decision	
Pregnancy	
Protocol deviation	
Site terminated by sponsor	
Study terminated by sponsor	
Withdrawal by subject	

7.1. Discontinuation of Study Intervention

Criteria for discontinuation of the participant from study intervention are described above. Participants who discontinue study intervention must be discontinued from the study and should undergo EOD evaluations at early termination.

Discontinuation of study intervention due to any clinically significant findings in clinical laboratory determinations, vital sign or ECG measurements should be considered by the investigator if the investigator believes that it is in best interest of the participant. Any new clinically relevant finding should be reported as an AE.

Discontinuation of study intervention for abnormal liver function should be considered by the investigator when a participant meets one of the conditions outlined in Section 8.3.6 or if the investigator believes that it is in best interest of the participant.

See the SoA in Section 1.2 for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- See the SoA (Section 1.2) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

7.3. Lost to Follow Up

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

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and 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 will be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- 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.
- A detailed listing of study assessments by day is presented in Appendix 8.
- Study center staff will admit participants into a nonsmoking environment on Days -1, and 7. Participants will remain in the study center until 24 hours following study intervention administration on Day 1 and on Days 7 through 16 for a total of 11 overnight stays (2 overnight stays on Days -1 and 1; and 9 overnight stays on Days 7 through 15). Participants will be released from the study center on Day 2 after the 24-hour postdose PK blood draw and on Day 16 after completion of the 96-hour or EOD assessments. Participants will be administered doses of Study Intervention B or Study Intervention C on Day 8, and ubrogepant doses (Study Intervention A and D) on Days 1 and 12 through 15 at the study center.

[redacted]

- The amount of blood collected from each participant over the duration of the study will be approximately 194 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Efficacy Assessments

No applicable.

8.2. Safety Assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Physical examinations should be completed by a professionally trained physician or health professional listed on Form FDA 1572 and licensed to perform physical examinations.

8.2.2. Vital Signs

Vital signs will be assessed as follows:

- Screening: Blood pressure (BP), pulse rate, respiratory rate, height, weight, and temperature
- Interim: BP and pulse rate

- EOD: BP, pulse rate, respiratory rate, weight, and temperature
- Blood pressure and pulse measurements will be assessed in a sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Study center staff will assess vital signs at the nominal times (relative to the dosing time) or within 30 minutes prior to the nominal times (see Section 1.2, SoA, for additional details on assessment timepoints). Assessments performed outside this window will be noted as protocol deviations, and the reason for deviation must be documented in the source documents. Predose vital signs must be assessed within 120 minutes prior to the dosing time.
- For interim and EOD assessments, participants who have a sitting systolic BP ≥ 160 mm Hg or ≤ 90 mm Hg or who have a sitting diastolic BP ≥ 100 mm Hg or ≤ 45 mm Hg will undergo at least 2 BP reassessments within 15 minutes of the original. Participants who have a pulse rate > 100 bpm or < 45 bpm will undergo at least 2 pulse rate reassessments within 15 minutes of the original. If the second repeat of BP and/or pulse rate continues to be out of range, the investigator or subinvestigator must assess its clinical significance. Participants should be discontinued from the study if interim BP or pulse rate values are deemed clinically significant. If this occurs at screening, participants will be excluded from the study.

8.2.3. Electrocardiograms

- A standard 12-lead ECG will be performed in the supine position at the nominal times (relative to the dosing times) or within 45 minutes prior to the nominal times as outlined in the SoA (see Section 1.2). Assessments performed outside this window will be noted as protocol deviations, and the reason for deviation must be documented in the source documents. Predose ECGs must be performed within 120 minutes prior to the dosing time.
- The paper speed will be a standard 25 mm/sec; the ECG tracing will be kept at the study center. Measurements will be recorded for the following parameters in lead II or lead III: heart rate, PR interval, QRS duration, QT interval, QTcB, and QTcF. All ECGs will be clinically interpreted by the investigator or subinvestigator.
- For interim and EOD ECGs, participants who have an abnormal QT result (QTcF ≥ 450 msec for male participants or ≥ 470 msec for female participants or uncorrected QT ≥ 500 msec) will undergo at least 2 ECG reassessments within 15 minutes of the original. If the second repeat of ECG results continues to be out of range, the investigator or subinvestigator must assess its clinical significance. Participants should be discontinued from the study if interim ECG results are deemed clinically significant.

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.

- At screening, the investigator or subinvestigator will assess the clinical significance of any values outside the reference ranges provided by the laboratory, and participants with abnormalities judged to be clinically significant will be excluded from the study.
- 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 eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory 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 during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical safety physician.
    - 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.
    - All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the SoA.
- Urine dipstick kits may be used to conduct drugs-of-abuse screens and pregnancy tests at the study center at screening and on admission days.
- Study center local laboratories may be used to conduct drugs-of-abuse screens and pregnancy tests on admission days. Local laboratories may also be used to conduct safety or eligibility tests that require quick results (which the central laboratory is unable to provide) only if the test sample is split and sent to the central laboratory in addition to the local laboratory. Prior to using a local laboratory, the study center must ensure that the laboratory is listed on the Form FDA 1572 and that copies of the laboratory certificates and reference ranges are provided to the sponsor.

8.2.5. Suicidal Risk Monitoring

Not applicable.

8.3. Adverse Events and Serious Adverse Events

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

AEs will be reported by the participant.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and any other study-specific terms as relevant and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention and/or study (see Section 7).

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

All AEs, including SAEs, from the signing of the ICF until the Follow-up Visit/30 days after the last dose of study intervention will be collected at the timepoints specified in the SoA (Section 1.2), and as observed or reported spontaneously by study participants.

Medical occurrences that begin before the start of study intervention, but after obtaining informed consent will be recorded in the AE section of the eCRF and will be considered pretreatment AEs.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

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.

8.3.2. Method of Detecting AEs and SAEs

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.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs/SAEs and AEs of special interest (as defined in Section 8.3.6) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

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 or designee 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 health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.

New or updated information will be recorded in the originally completed eCRF.

The investigator will submit any updated SAE data to sponsor or designee within 24 hours of receipt of the information.

8.3.4. 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 towards 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, and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the investigator's brochure or state other documents and will notify the IRB, if appropriate according to local requirements.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

8.3.5. Pregnancy

- Details of all pregnancies in female participants, and if indicated, female partners of male participants will be collected from the signing of the ICF and until 33 days for female and 93 days for male participants.
- If a pregnancy is reported, the investigator should inform the sponsor or designee within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 7.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are considered SAEs.

8.3.6. AEs of Special Interest

AEs of special interest (AESI) that warrant ongoing monitoring and rapid communication by the investigator to the sponsor are potential Hy's Law cases and ALT/AST elevations, and are outlined below.

8.3.6.1. Potential Hy's Law Cases

Criteria for potential Hy's Law cases are as follows:

- ALT or AST ≥ 3 × upper limit of normal (ULN) AND
- Total bilirubin ≥ 2 × ULN AND
- Alkaline phosphatase < 2 × ULN

Study site personnel must report every participant who meets these potential criteria. Typically, all 3 analytes will be obtained from the same sample, but they may come from multiple samples

taken within a 24-hour period. This requirement applies from the time the participant signs the ICF for the study until 30 days after the final protocol-defined study procedure or the last known dose of study intervention (if the final visit does not occur).

Investigators must inform the sponsor when the above criteria have been met. A possible Hy's law case must be faxed to the sponsor on an AE of Special Interest Form as soon as possible (within 24 hours of learning of the possible Hy's law case) to the SAE/Pregnancy fax number, even if no AE has occurred. The eCRF for potential Hy's law cases must be completed within 7 calendar days. Every effort to determine the cause of the liver enzyme abnormalities must be made, and close monitoring should be initiated in conjunction with the medical safety physician and in accordance with the FDA Guidance for Industry, Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009. The participant should return to the study site and be evaluated as soon as possible, preferably within 48 hours from the time the investigator becomes aware of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

8.3.6.2. ALT or AST Elevations

A treatment-emergent ALT or AST ≥ 3 × ULN is considered an AESI. Any participant with this laboratory result after the study intervention was taken must have repeat testing within 48 to 72 hours to confirm the abnormality. For this repeat testing, the following labs must be drawn: hematology and chemistry panels, international normalized ratio (INR), serum acetaminophen level, urine drugs of abuse screen, and blood alcohol level. An extra blood serology sample must be collected and sent to the central laboratory for further diagnostic testing at a later date, if needed. In addition, the investigator will perform a complete history and examination to evaluate the participant for possible liver disease.

All AESIs must be reported to Allergan within 24 hours of the time the investigator becomes aware of the event using the abnormal liver function reporting form and the AE eCRF. All new elements of history, physical examination, diagnostic testing results, and other relevant medical reports are to be reported for each AESI.

If an ALT or AST elevation ≥ 3 × the ULN is confirmed, close medical follow-up is required: For these participants, the following laboratory tests may be performed following consultation with the medical personnel at Allergan: anti-hepatitis A IgM, hepatitis B surface antigen, anti-hepatitis B core IgM, hepatitis C antibody, hepatitis C quantitative ribonucleic acid by polymerase chain reaction, anti-hepatitis E IgM, anti-hepatitis E IgG, Cytomegalovirus IgM antibody, and Epstein-Barr Virus IgM antibody. The participant must be followed clinically, and further medical evaluation (for other causes of acute hepatic injury) should be done per the judgment of the investigator and in conjunction with medical personnel at Allergan. In general, the chemistry panel should be repeated 1 to 2 times per week to follow the course of ALT/AST elevation.

Study interventions must be discontinued if any of the following criteria are met:

- ALT or AST ≥ 3 × ULN and the participant is symptomatic with the appearance of fatigue, nausea, vomiting, right upper quadrant pain, or tenderness, fever, rash, or eosinophilia (> 5%)
- ALT or AST ≥ 3 × ULN and total bilirubin > 2 × ULN
- ALT or AST ≥ 3 × ULN and INR > 1.5
- ALT or AST ≥ 5 × ULN for more than 2 weeks
- ALT or AST ≥ 8 × ULN

The participant may be rechallenged with study intervention only after consultation with the Allergan Medical Monitor. For participants who are not rechallenged with study intervention, they should be discontinued from the study and complete an EOD Visit and Follow up Visit. Participants should receive appropriate follow-up as per standard of care.

The investigator must contact the Allergan Medical Monitor to discuss all cases of confirmed ALT/AST elevation ≥ 3 × ULN. All ALT/AST elevations must be followed until ALT and AST return to < 1.5 × ULN and there is full clinical resolution.

8.3.7. Medication Errors

Medication error refers to any unintended error in the dosing and/or administration of the study intervention as per instructions in the protocol. Medication errors generally fall into 4 categories as follows:

- Wrong study drug/device
- Wrong dose (including dosing regimen, strength, form, concentration, amount)
- Wrong route of administration, including wrong site of administration (eg, wrong eye)
- Wrong participant (ie, not administered to the intended participant)

Medication errors include occurrences of overdose and underdose of the study intervention.

Overdose: Unintentional administration of a quantity of the study intervention given per administration or per day that is above the maximum recommended dose according to the reference safety information or protocol for the study intervention or comparator as applicable. This also takes into account cumulative effects due to overdose.

Underdose: Unintentional administration of a quantity of the study intervention given per administration or per day that is under the minimum recommended dose according to the reference safety information or protocol.

8.4. Treatment of Overdose

Ubrogepant: Single or multiple doses of up to 400 mg of ubrogepant once daily have been administered to participants in completed Phase 1 studies. Ubrogepant was found to be safe and well tolerated at the doses studied. There has been no evidence of clinically significant safety

findings in routine clinical laboratory tests, ECGs, or vital signs, and no observed drug-related liver enzyme elevations at the highest doses studied.

For this study, any dose of ubrogepant greater than 400 mg within a 24-hour time period will be considered an overdose.

Single doses of up to 210 mg of Aimovig have been studied in participants; any doses higher than 210 mg will be considered as an overdose.

Single doses of up to 600 mg of Emgality have been studied in participants; any doses higher than 600 mg will be considered as an overdose.

At present, specific information regarding treatment of overdose for ubrogepant is unavailable. In case of an acute overdose, it is recommended that the stomach be emptied and oral gavage with activated charcoal be used to help reduce absorption of ubrogepant.

The sponsor does not recommend specific intervention for an overdose.

In the event of an overdose, the investigator should:

1. Contact the medical safety physician immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities until study intervention can no longer be detected systemically (at least 2 days).
3. Obtain a plasma sample for PK analysis (within 1 day from the date of the last dose of oral study intervention and within 5 days of SC injected study intervention) if requested by the medical safety physician (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical safety physician based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

8.5.1. Blood PK Sampling Procedure

Starting on Days 1 and 12, PK blood samples to determine ubrogepant plasma concentrations will be collected at 0 hour (predose) and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 14, and 24 hours postdose. These samples may also be used to determine CGRP concentrations.

PK blood samples should be drawn at the nominal times specified above, relative to the dosing time, and the actual time of the blood draw must be recorded in the source documents and eCRFs. Samples taken more than ± 5 minutes from the nominal time will be noted as protocol deviations, and the reason for deviation must be recorded in the source documents and eCRFs. Predose samples must be drawn within 30 minutes of the dosing time.

Study center staff will record the atomic clock times of all blood draws for each participant and will label Vacutainer and polypropylene tubes with a coded label that corresponds to the

participant number and blood draw time. The study center will supply the coded labels. The study center will be responsible for Vacutainer, polypropylene tubes, and all other supplies.

Any changes in the timing or addition of timepoints 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 will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

A qualified phlebotomist will collect each participant's blood via an indwelling catheter or venipuncture from either arm into prechilled 4-mL Vacutainer tubes containing K_2EDTA as an anticoagulant (Appendix 9).

Blood Volume Collected per Participant

- Total: approximately 194 mL
- PK and biomarker blood samples: 104 mL (26 blood samples, 4 mL each)
- Screening and end-of-study clinical laboratory analysis: 90 mL

Within 30 minutes from the time of the blood draw, blood samples must be centrifuged at no less than 2500g for 10 minutes at approximately 4°C. After centrifugation, the plasma samples will be harvested and transferred into 2 prechilled, coded polypropylene tubes. The samples will then be flash-frozen in a dry ice and alcohol bath (with isopropyl alcohol, ethanol, isopropanol, or methanol) and stored at approximately -20°C.

Study center staff will send plasma samples to the BA laboratory for bioanalysis as directed by the Allergan study team (see Appendix 9 for shipping instructions). Before shipment and on the day of shipment, the sponsor and BA laboratory will be notified by email as to the time and method of shipment.

[redacted]

8.5.3. Plasma PK [redacted] Bioanalysis

Concentrations of ubrogepant in plasma [redacted] es will be determined using validated and qualified liquid chromatography-tandem mass spectrometry methods, respectively.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers and Other Assessments

Measurement of CGRP concentrations in plasma [redacted] will be attempted from the PK samples at the timepoints specified in Sections 8.5.1 and 8.5.2. These samples will be collected, processed, and shipped as described in Sections 8.5.1 and 8.5.2 above.

Biomarker blood samples should be drawn at the nominal times specified above, relative to the dosing time, and the actual time of the blood draw must be recorded in the source documents and eCRFs. Samples taken more than ± 5 minutes from the nominal time will be noted as protocol deviations, and the reason for deviation must be recorded in the source documents and eCRFs. Predose samples must be drawn within 30 minutes of the dosing time.

[redacted]

[redacted]

8.9. Health Economics/Medical Resource Utilization and Health Economics

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

9. Statistical Considerations

9.1. Statistical Hypotheses

Not applicable.

9.2. Sample Size Determination

This is a study to evaluate the safety, tolerability and PK of ubrogepant when co-administered with CGRP MABs. Although the sample size is not based on a statistical calculation, inclusion of 40 participants (20 participants in each part [redacted] s considered reasonable to achieve the objectives of the study.

9.3. Populations for Analyses

The analysis populations will consist of participants as defined below:

Table 9-1 Analysis Populations

Population	Definition
Pharmacokinetic (PK1)	All participants who have evaluable PK parameters of ubrogepant for both ubrogepant alone and ubrogepant in combination with erenumab or galcanezumab
[redacted]	[redacted]
Safety	All participants who received ≥ 1 administration of study intervention

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock and will describe the participant populations to be included in the analyses and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of PK and safety data.

9.4.1. Pharmacokinetic Analyses

The principal parameters describing the PK of ubrogepant will be derived from plasma concentrations using noncompartmental analysis with the software program [redacted] Plasma concentrations below the limit of quantification will be treated as zero for all PK calculations. The actual sampling times will be used in the calculations of PK parameters in this study.

9.4.1.1. Pharmacokinetic Parameters

The following PK parameters for ubrogepant will be calculated based on standard [redacted] equations: area under the plasma concentration versus time curve from time 0 to time t (AUC_{0-t}) and from time 0 to infinity ($AUC_{0-\infty}$), maximum plasma drug concentration

(C_{max}), time of maximum plasma drug concentration (T_{max}), terminal elimination rate constant (λ_z), terminal elimination half-life ($T_{½}$), apparent total body clearance of drug from plasma after extravascular administration (CL/F), and apparent volume of distribution during the terminal phase after extravascular administration (V_z/F).

The AUC_{0-t} will be calculated by using the linear-log trapezoidal rule.

Estimates of $T_{½}$ will be calculated based on λ_z. The λ_z will be determined by performing a regression analysis on the terminal linear phase of semilogarithmic plots of individual ubrogepant concentration-time data using a minimum of three concentration-time points in the elimination phase excluding C_{max}. λ_z will be considered to be valid if $r^2 > 0.8$.

9.4.1.2. Statistical Analyses of Pharmacokinetic Data

Details of the statistical analyses of ubrogepant PK data (concentrations and parameters) will be described in the PK analysis plan finalized before database lock.

Descriptive statistics will be provided for all PK parameters of ubrogepant for participants in the Pharmacokinetic PK1 population by study part and by study intervention. PK parameters (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) for ubrogepant will be compared using a linear mixed-effects model with study intervention as fixed effect and participant as a random effect.

Statistical analysis will be based on log-transformed values for the C_{max} and AUC parameters of ubrogepant. The 2-sided 90% CI for each study part will be constructed for the ratio of least squares geometric means of C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ of ubrogepant in combination with CGRP MAB on Day 12 versus ubrogepant alone on Day 1. No effect of co-administration with CGRP MABs on the PK of ubrogepant will be concluded if the 90% CIs for the ratios of ubrogepant PK parameters for test study intervention versus reference study intervention are within the limits of 80% to 125%.

Descriptive statistics will be reported for the plasma concentrations of ubrogepant by study part at each nominal time point for all participants in the Pharmacokinetic PK1 population. [redacted]

9.4.2. Safety Analyses

The safety analysis will be performed using the safety population and will be fully defined in the SAP. The safety parameters will include AEs, clinical laboratory parameters, vital signs, and ECG parameters. Safety analyses will be reported for each study part separately.

9.4.2.1. Adverse Events

An AE will be considered a TEAE if the AE began or worsened (increased in severity or became serious) on or after the date (and time, if known) of the first dose of study intervention. However, an AE that occurs more than 30 days after the last dose of study intervention will not be counted as a TEAE.

An AE will be considered a TESAE if it is a TEAE that additionally meets any SAE criterion.

The number and percentage of participants with TEAEs in each study intervention group will be tabulated by system organ class and preferred term and by system organ class, preferred term, and severity. The number and percentage of participants with study intervention-related TEAEs in each study intervention group will be tabulated by system organ class and preferred term.

If more than 1 AE is coded to the same preferred term for the same participant, the participant will be counted only once for that preferred term using the most severe and most related occurrence for the summarizations by severity and by relationship to study intervention.

Summary tables will be provided for participants with TESAEs and participants with TEAEs leading to discontinuation if 5 or more participants reported such events. Listings of all AEs, SAEs, and AEs leading to discontinuation by participant will be presented.

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

An AE will be assigned to the study intervention when it occurred on or after the first dose of the study intervention or the subsequent washout period in which the AE occurred, before the first dose of the next study intervention. An AE will be assigned to the last study intervention of the study intervention sequence if it occurred on or after the first dose of the last study intervention administration.

9.4.2.2. Clinical Laboratory Assessments

Descriptive statistics for clinical laboratory values (in SI units) at baseline, EOD, Follow-up visit, and changes from baseline at each assessment will be presented overall for each clinical laboratory parameter in each part of the study.

Descriptive statistics for interim clinical laboratory values at predose, postdose, and changes from predose at postdose will be presented by study intervention in each part of the study.

The criteria for potentially clinically significant (PCS) laboratory values will be detailed in the SAP. The number and percentage of participants who have PCS postbaseline clinical laboratory values will be tabulated overall for EOD assessment and Safety Follow-up visit and by study intervention for interim assessments. The percentages will be calculated relative to the number of participants who have available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants mentioned prior with at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided for the safety population.

9.4.2.3. Vital Signs

Descriptive statistics for vital signs (systolic and diastolic BP, pulse rate, weight, respiration rate, and temperature) at baseline (screening), EOD, and changes from baseline at EOD will be presented overall in each study part.

Descriptive statistics for interim vital signs (systolic and diastolic BP, pulse rate) at predose, postdose, and changes from predose at postdose will be presented by study intervention in each part of the study.

Vital signs values will be considered to be PCS if they meet both the observed-value criteria and the change-from-baseline-value criteria that will be detailed in the SAP. The number and percentage of participants who have PCS postbaseline vital sign values will be tabulated overall for EOD and by study intervention for interim assessment. The percentages will be calculated relative to the number of participants who have available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants mentioned prior with at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided for the safety population.

9.4.2.4. Electrocardiograms

Descriptive statistics for ECG parameters (heart rate, PR interval, QRS duration, QT interval, and QTc) at baseline, EOD, and changes from baseline at EOD will be presented overall in each study part.

Descriptive statistics for interim ECG parameters at predose, postdose, and changes from predose at postdose will be presented by study intervention in each part of the study.

The criteria for PCS ECG values will be detailed in the SAP. The number and percentage of participants who have PCS postbaseline ECG values will be tabulated overall for EOD and by study intervention for interim assessments. The percentages will be calculated relative to the number of participants who have available non-PCS baseline values and at least 1 postbaseline assessment. The numerator will be the total number of participants mentioned prior with at least 1 PCS postbaseline value. A supportive listing of participants with PCS postbaseline values will be provided for the safety population.

9.5. Interim Analyses

No interim analysis is planned for this study.

9.5.1. Data Monitoring Committee

Not applicable.

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 CIOMS International Ethical Guidelines
    - Applicable ICH GCP guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, 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 annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
    - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
    - Providing oversight of the overall conduct of the study at the site and adherence to requirements of applicable local regulations, for example 21 CFR, ICH guidelines, the IRB, and European regulation 536/2014 for clinical studies (if applicable)

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 his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

- 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, HIPAA requirements, where applicable, and the IRB or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

- Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
- The participant must be informed that his/her 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 his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

10.1.5. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRFs 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.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.

- Study monitors will perform ongoing source data verification 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, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator as stated in the clinical trial agreement. 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.

10.1.6. 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's site.
- Data entered in the eCRF that are transcribed 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.

10.1.7. Study and Site Closure

The sponsor or 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. 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, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If a study is prematurely terminated or suspended due to safety issues, the sponsor shall inform all investigators and the regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB is also to be informed promptly and provide the reason(s) for the termination or suspension by the sponsor or by the investigator, as specified by the applicable regulatory requirements. If a premature termination or suspension occurs, the sponsor shall remain responsible for providing resources to fulfill the protocol obligations and existing agreements for follow-up of participants enrolled in the study, and each investigator or authorized designee shall promptly inform enrolled participants, if applicable.

10.1.8. Publication Policy

- Allergan as the sponsor has proprietary interest in this study. Authorship will be established prior to the writing of the manuscript.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.9. Compliance with Protocol

The investigator is responsible for compliance with the protocol at the investigational site. A representative of the sponsor will make frequent contact with the investigator and his/her research staff and will conduct regular monitoring visits at the site to review participant and study intervention accountability records for compliance with the protocol. Protocol deviations will be discussed with the investigator upon identification. Significant protocol deviations will be reported to the IRB according to the IRB's reporting requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 10-1 will be performed by the central laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 10-1 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet count RBC count Hemoglobin Hematocrit	RBC indices: MCV MCH MCHC	WBC count with differential (absolute): Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical Chemistry[a]	BUN Creatinine Glucose (fasting)	Potassium Sodium Calcium	AST ALT Alkaline phosphatase	Total, direct, and indirect bilirubin Total protein Cholesterol, chloride, albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, by dipstick • Microscopic examination (if blood or protein is abnormal)			
Other Screening Tests	• Drugs of abuse[b]: Benzoylecgonine (cocaine), methadone, barbiturates, amphetamines, benzodiazepines, cannabinoids, opiates, and phencyclidine • Serum human chorionic gonadotropin (β-hCG) pregnancy test at screening and serum or urine test on admission days[b] • Serology: anti-HIV type 1 and type 2 antibody, hepatitis B surface antigen (HbsAg), and anti-hepatitis C virus • Coagulation: prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR) • Postmenopausal females: FSH to confirm postmenopausal state.			

[a] Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are provided in Section 8.3.6. All events of ALT ≥ 3 × upper limit of normal (ULN) and bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT ≥ 3 × ULN and international normalized ratio (INR) >1.5, if INR is measured, which may indicate severe liver injury (possible Hy's law- Section 8.3.6.1), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

[b] Urine dipstick kits may be used to conduct drugs-of-abuse screens and pregnancy tests at the study center on admission days.

Investigators must document their review of each laboratory safety report.

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

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. • 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. **Adverse Event of Special Interest (AESI)** An AESI (serious or nonserious) is one of scientific and medical concern specific to the sponsor's study intervention or program, which warrants ongoing monitoring and rapid communication by the investigator to the sponsor. Such an event might warrant further investigation in order to characterize and understand it. The following AESIs have been identified for the study intervention(s) in this protocol: potential Hy's law cases (see Section 8.3.6.1) and AST or ALT elevations (see Section 8.3.6.2). Serious AESIs should be reported to the sponsor within 24 hours. The AESI form, along with a targeted questionnaire, if applicable, should be used for reporting the AESI, even if a serious outcome may not apply.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease); for example:
  - The test result is associated with accompanying symptoms, and/or
  - The test result requires additional diagnostic testing or medical/surgical intervention, and/or
  - The test result 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, and/or
  - The test result is considered to be an AE by the investigator or sponsor.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in 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. Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE. • 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 pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

Definition of SAE

SAEs must meet both the AE criteria described above and the seriousness criteria listed below.

An SAE is defined as any untoward medical occurrence that, at any dose:
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 detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or intervention 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 intervention of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent 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), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but 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 intervention 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.

Recording and Follow-up of AEs and/or SAEs

AE and SAE Recording
• When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE or SAE information in the participant's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form of the eCRF. • It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the sponsor or designee AE or SAE eCRF page. • There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. 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 the sponsor or designee. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

MILD	A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
MODERATE	A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
SEVERE	A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

An event is defined as *serious* when it meets at least one 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.
- 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.
- The investigator will use clinical judgment to determine the relationship.
- 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 his/her assessment.
- For each AE or SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE or SAE and has 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 sponsor or designee. 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 or designee.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• See Section 8.3.3.

Reporting of SAEs

SAE Reporting within 24 hours
• Email is the preferred method to transmit SAE information. The email address is IR-Clinical-SAE@allergan.com. • Facsimile transmission of the SAE information is also acceptable. The fax number is +1-714-796-9504 (backup number is +1-714-246-5295). • In rare circumstances and in the absence of facsimile equipment, notification by telephone (see the study contact list) is acceptable with a copy of the SAE 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 SAE form within the designated reporting time frames. • Contacts for SAE reporting can be found on the protocol title page.

10.4. Appendix 4: Abbreviations

Abbreviation	Definition
λ_z	terminal elimination rate constant
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
aPTT	activated partial thromboplastin time
AUC	area under the curve
$AUC_{0-\infty}$	area under the plasma concentration-vs-time curve from time 0 to infinity
AUC_{0-t}	area under the plasma concentration-vs-time curve from time 0 to time t
BA	bioanalytical
BMI	body mass index
BP	blood pressure
BUN	blood urea nitrogen
CGRP	calcitonin gene-related peptide
CHO	Chinese hamster ovary
CDISC	Clinical Data Interchange Standards Consortium
CIOMS	Declaration of Helsinki and Council for International Organizations of Medical Sciences
CL	clearance
CL/F	apparent total body clearance of drug from plasma after extravascular administration
C_{max}	maximum plasma drug concentration
C_{min}	trough serum concentrations
CRF	case report form
[redacted]	[redacted]
CYP3A4	cytochrome P450
DILI	drug-induced liver injury
CRO	contract research organization
CSR	clinical study report
ECG	electrocardiogram
eCRF	electronic case report form
EOD	end of dosing
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GC-MS	gas chromatography-mass spectrometry
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin

Abbreviation	Definition
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council on Harmonisation
ICHD	International Classification of Headache Disorders
ID	identification
IgG	immunoglobin
IgG2	immunoglobulin G2
IgG4	immunoglobulin G4
IgM	immunoglobulin M
INR	international normalized ratio
IRB	institutional review board
IV	intravenous
MAB	monoclonal antibodies
MCV	mean corpuscular volume
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
NOAEL	no observable adverse effect level
NOEL	no observable effect level
NSAID	nonsteroidal anti-inflammatory drug
PCS	potentially clinically significant
PT	prothrombin time
PK	pharmacokinetic
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
RBC	red blood cell
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SNRI	serotonin norepinephrine reuptake inhibitors
SoA	schedule of activities
SUSAR	suspected unexpected serious adverse reaction
SSRI	selective serotonin reuptake inhibitors
$T_{½}$	terminal elimination half-life
T_{max}	time of maximum plasma drug concentration
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event

Abbreviation	Definition
ULN	upper limit of normal
USPI	United States package insert
V_z/F	apparent volume of distribution during the terminal phase after extravascular administration
WBC	white blood cell
WOCBP	woman of childbearing potential

10.5. Appendix 5: Standard Discontinuation Criteria

This table provides participant discontinuation criteria for this protocol. CDISC terminology is used, and thus *subject* or *patient* is used instead of *participant* (as used elsewhere in this protocol). These terms are interchangeable.

CDISC Submission Value	CDISC Definition
Adverse event	Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. For further information, see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (modified from ICH E2A) Synonyms: side effect, adverse experience. See also serious adverse event, serious adverse experience. (CDISC glossary)
Death	The absence of life or state of being dead (NCI)
Lost to follow-up	The loss or lack of continuation of a subject to follow-up
Non-compliance with study drug	An indication that a subject has not agreed with or followed the instructions related to the study medication (NCI)
Other	Different than the one(s) previously specified or mentioned (NCI)
Physician decision	A position, opinion, or judgment reached after consideration by a physician with reference to subject (NCI)
Pregnancy	Pregnancy is the state or condition of having a developing embryo or fetus in the body (uterus), after union of an ovum and spermatozoon, during the period from conception to birth. (NCI)
Protocol deviation	An event or decision that stands in contrast to the guidelines set out by the protocol (NCI)
Site terminated by sponsor	An indication that a clinical study was stopped at a particular site by its sponsor (NCI)
Study terminated by sponsor	An indication that a clinical study was stopped by its sponsor (NCI)
Technical problems	A problem with some technical aspect of a clinical study, usually related to an instrument (NCI)
Withdrawal by subject	An indication that a study participant has removed itself from the study (NCI)

10.6. Appendix 6: Study Tabular Summary

This table is intended for use in posting study information to registries (eg, ClinicalTrials.gov).

Parameter Group	Parameter	Value
Trial information	Trial Title	A Phase 1b, Two-Part, Open-Label, Fixed-Sequence, Safety, Tolerability and Drug-Drug Interaction Study Between Single Dose Erenumab or Galcanezumab and Multiple Dose Ubrogepant in Participants with Migraine
	Clinical Study Sponsor	Allergan Pharmaceuticals International Limited, Clonshaugh Industrial Estate, Coolock, Dublin 17, Ireland US Agent: Allergan Sales, LLC, 2525 Dupont Ave, Irvine, California 92612, USA
	Trial Phase Classification	Phase 1b
	Trial Indication	NA
	Trial Indication Type	NA
	Trial Type	Drug-Drug interaction
	Trial Length	45 ± 3 days
	Planned Country of Investigational Sites	United States
	Planned Number of Subjects	40
	FDA-regulated Device Study	No
	FDA-regulated Drug Study	IND #113924
	Pediatric Study	No
Subject information	Diagnosis Group	Participants with migraine for at least 1 year
	Healthy Subject Indicator	No
	Planned Minimum Age of Subjects	18
	Planned Maximum Age of Subjects	50
	Sex of Participants	Both male and female
	Stable Disease Minimum Duration	1 year

Parameter Group	Parameter	Value
Treatments	Investigational Therapy or Treatment	Ubrogepant
	Intervention Type	Drug interaction
	Pharmacological Class of Investigational Therapy	CGRP receptor antagonist
	Dose per Administration	Study Intervention A: Single oral 100-mg dose of ubrogepant tablet on Day 1 Study Intervention B: Single SC injection of 140-mg erenumab on Day 8 Study Intervention C: Two consecutive SC injections of 120-mg galcanezumab on Day 8 Study Intervention D: Repeated once daily oral doses of 100-mg ubrogepant on Days 12, 13, 14, and 15
	Dose Units	mg
	Dosing Frequency	Single and daily
	Route of Administration	Oral (ubrogepant)
	Current Therapy or Treatment	Erenumab and galcanezumab
	Added on to Existing Treatments	No
	Control Type	active
	Comparative Treatment Name	Erenumab or galcanezumab, single dose; subcutaneous administration
Trial design	Study Type	Interventional
	Intervention Model	Parallel
	Planned Number of Arms	2 arms per study part, 2 study parts
	Trial Is Randomized	Yes
	Randomization Quotient	Randomization by study intervention in each part (erenumab in Part 1, galcanezumab in Part 2)
	Trial Blinding Schema	Open-label
	Stratification Factor	None
	Adaptive Design	No
	Study Stop Rules	None

10.7. Appendix 7: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Childbearing Potential (WOCBP)

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

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

     Note: Supporting documentation from the physician who performed the surgery is needed.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Contraception Guidance:

Male Participants

Nonvasectomized male participants with female partners of childbearing potential are eligible to participate if they agree to the following during the protocol-defined timeframe in Section 5.1 (during the intervention period and for at least 93 days after the last dose of study intervention):

- Agree to use a male condom with spermicide when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant

In addition, nonvasectomized male participants must refrain from donating sperm during the intervention period and for at least 93 days after the last dose of study intervention.

Nonvasectomized male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during intervention period and for at least 93 days after the last dose of study intervention.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to use an acceptable method of contraception consistently and correctly during the study intervention period and for at least 33 days after the last dose of study intervention.

Acceptable birth control methods include:

- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide
- Nonhormonal intrauterine device
- Hormonal contraceptives
- Bilateral tubal ligation
- Bilateral tubal occlusion (eg, Essure®)

A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable, birth control methods.

Pregnancy Testing:

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test at screening and also a negative urine or serum test on Day -1.
- Additional pregnancy testing should be performed during the study intervention period on Day 7.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information:

Male Participants with Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

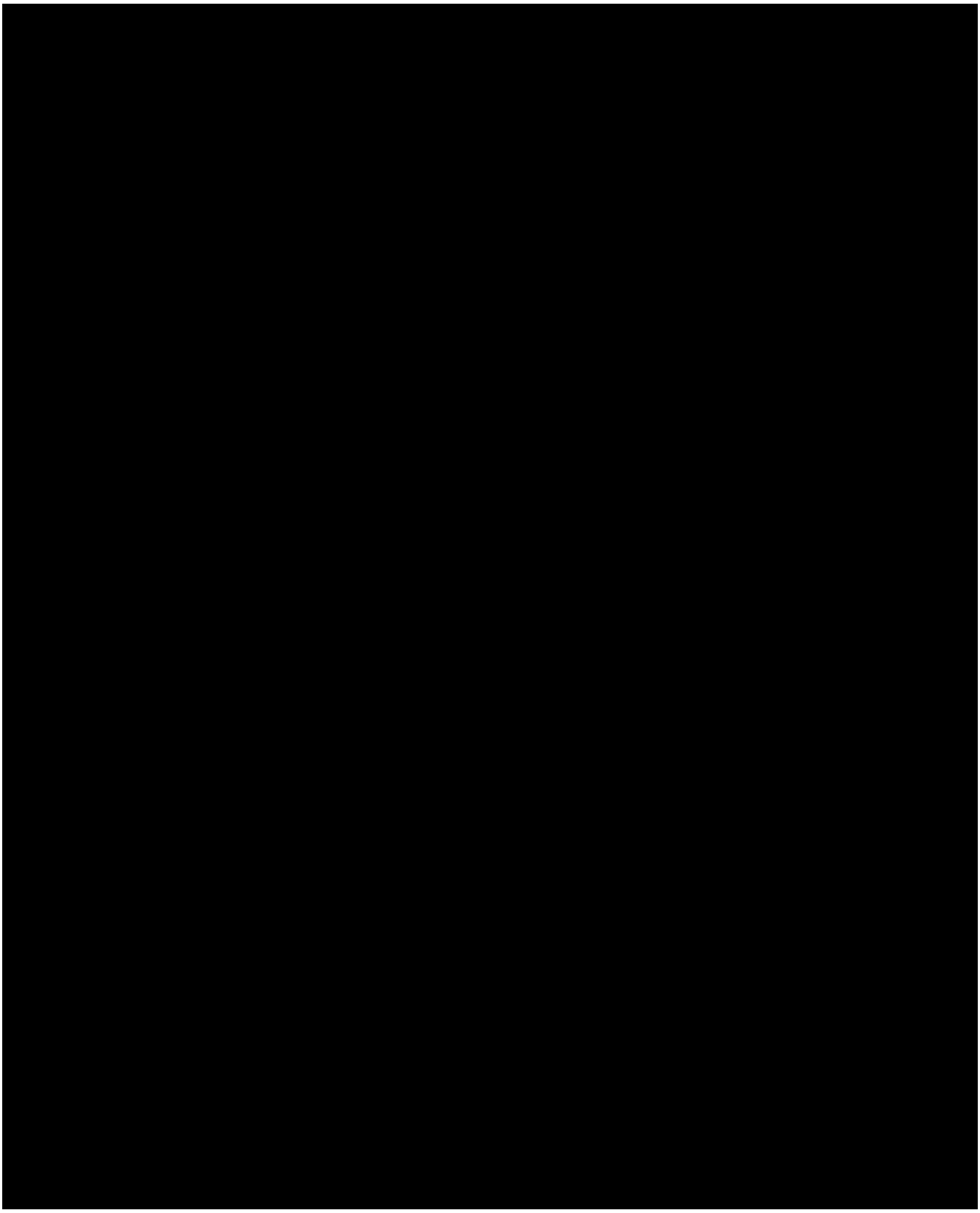
Female Participants Who Become Pregnant

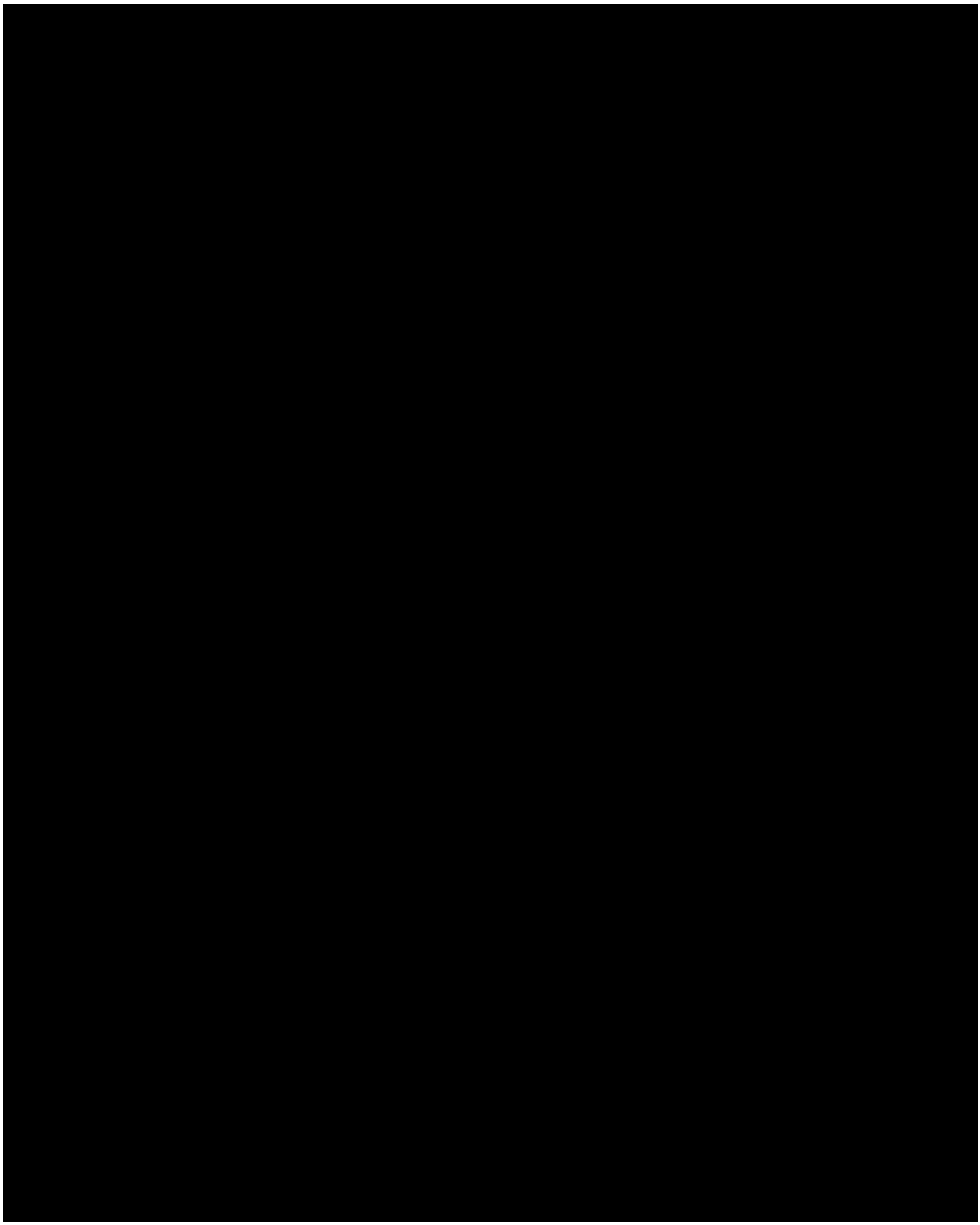
- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) or genetic abnormalities (whether leading to an elective abortion or not) are always considered to be SAEs and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

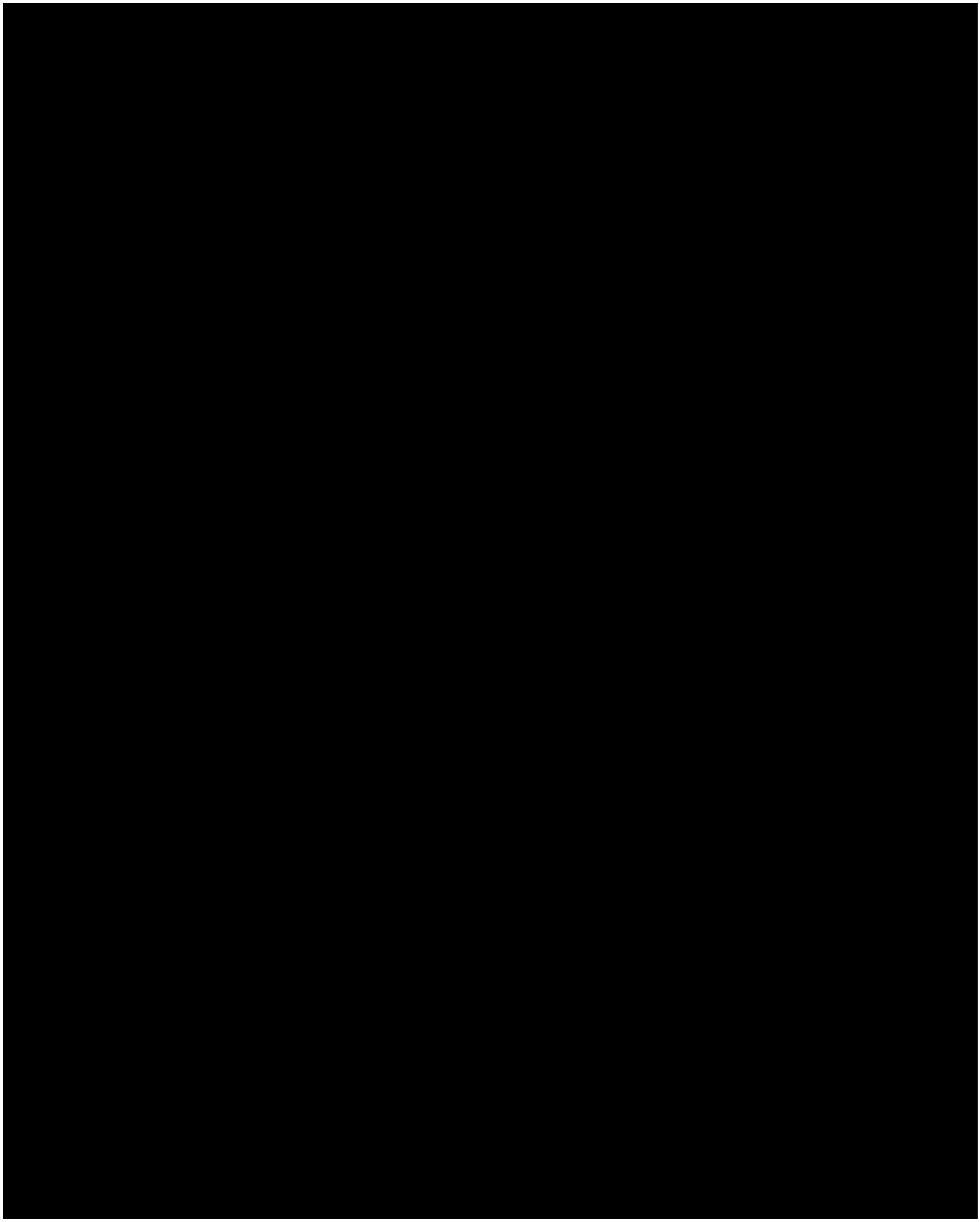
10.8. Appendix 8: Study Schedule Supplement

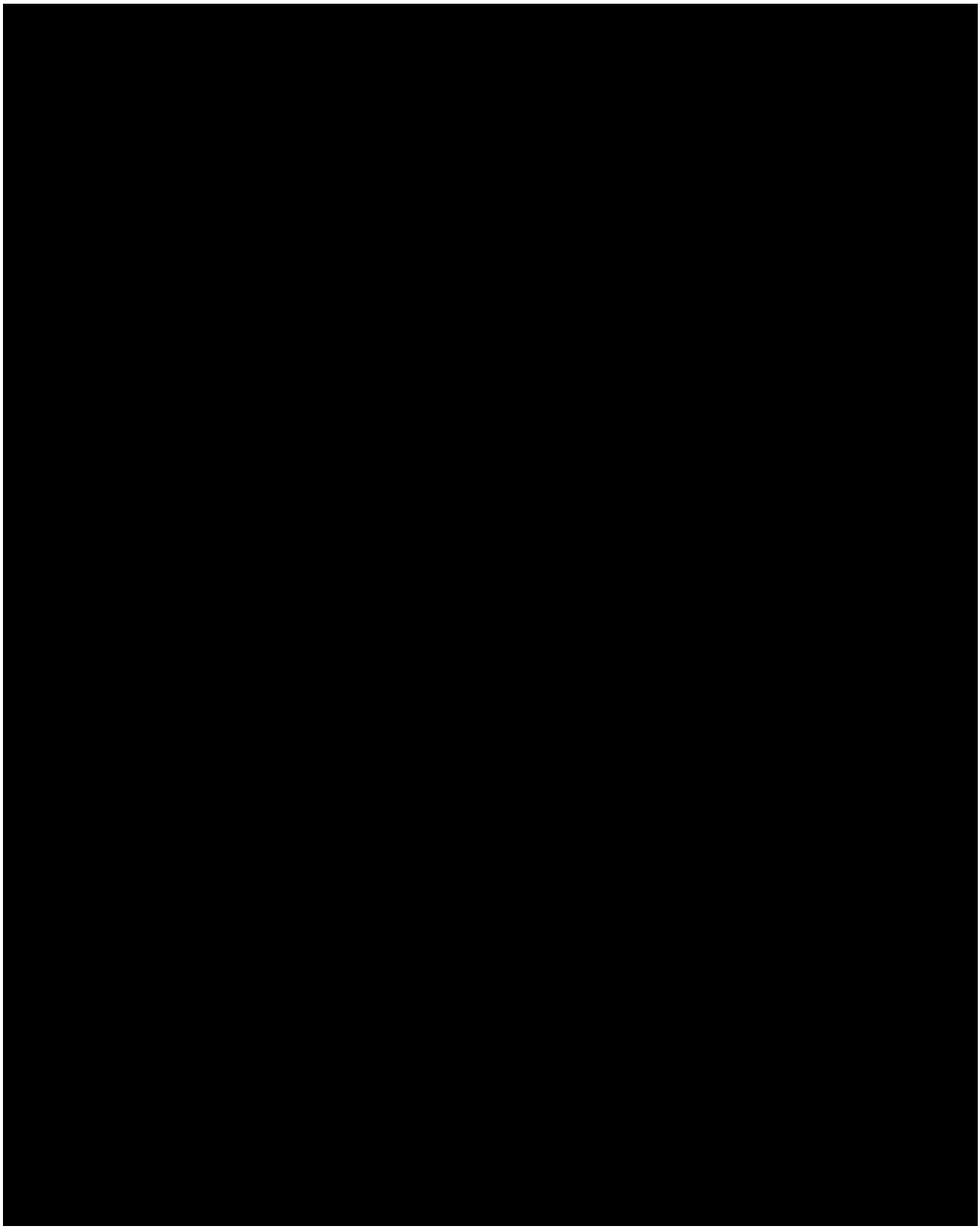
Study procedures are shown in the following sections for participants after enrollment in the study. When procedure times coincide, assess the ECG first, measure vital signs, draw PK and biomarker blood samples at the scheduled time, collect the PK [redacted] sample, and then serve the meal, unless otherwise specified. With the exception of the fasting requirements prior to study intervention dosing, meal times are approximate and may be adjusted by the study center as needed, with documentation provided to the sponsor before the start of the study.

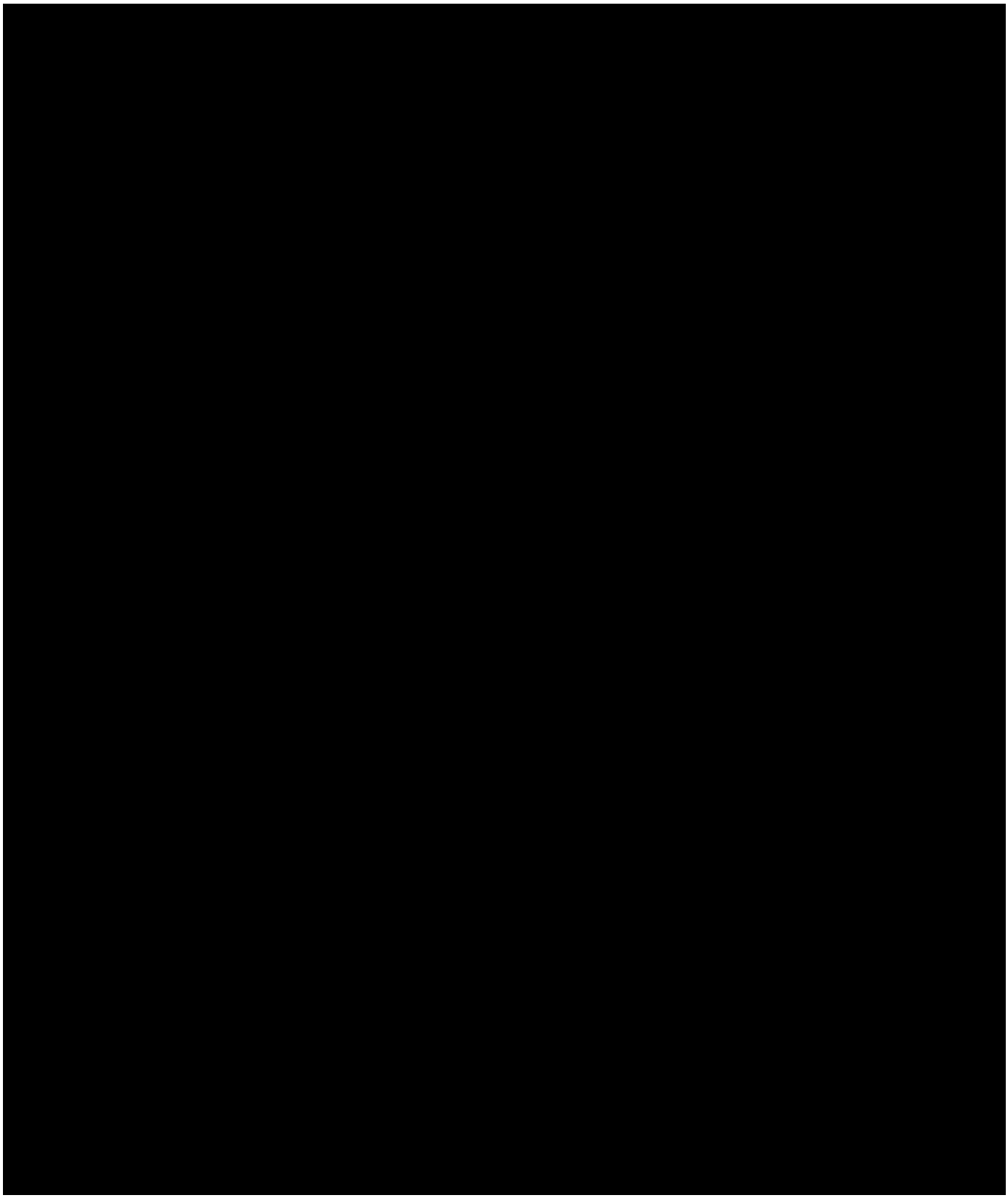
[redacted]

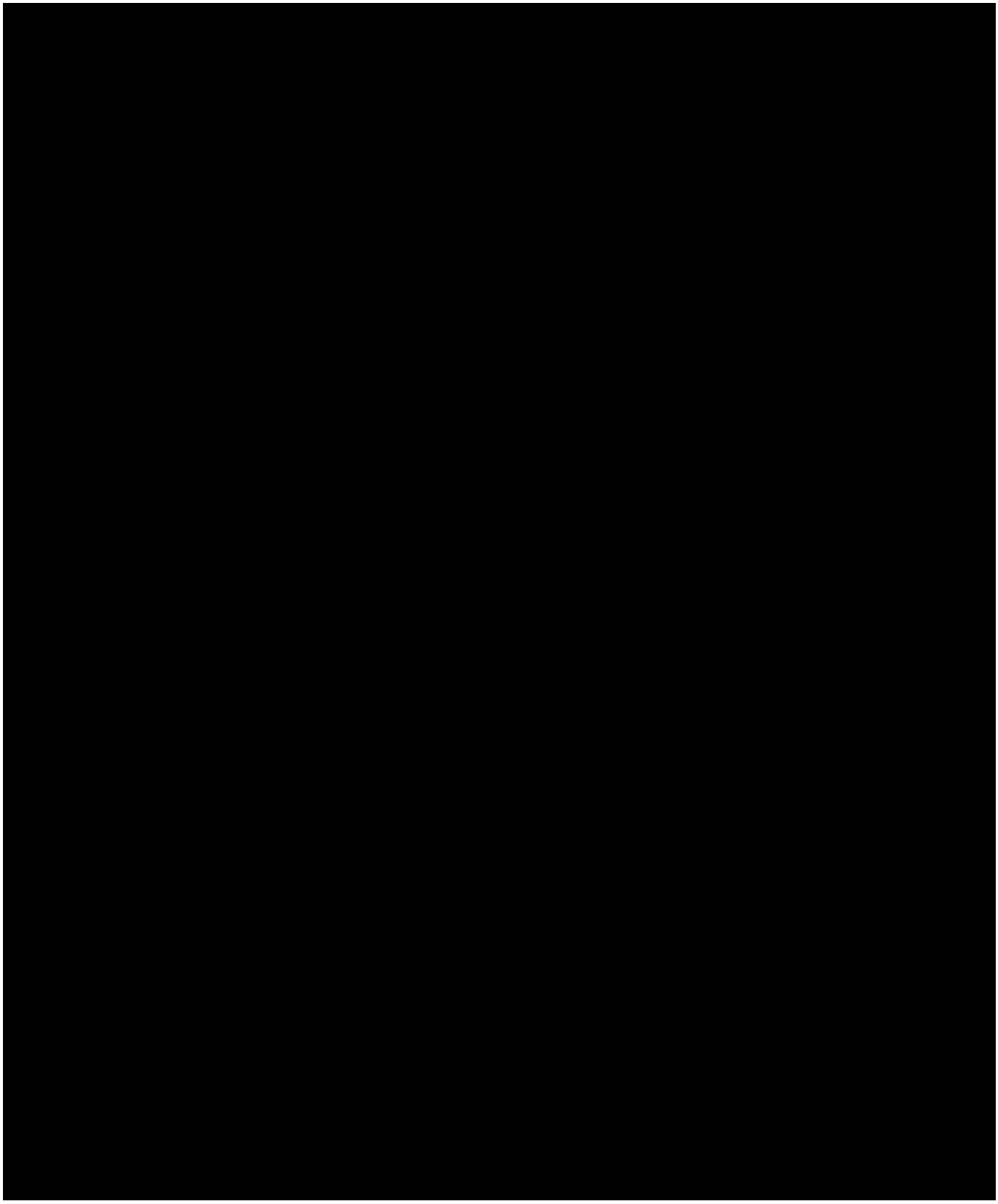












11. References

Aimovig® USPI. https://www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/aimovig/aimovig_pi_hcp_english.ashx. Accessed 03Jun2019.

Emgality® USPI. https://pi.lilly.com/us/emgality-uspi.pdf. Accessed 03Jun2019.

Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M. et al.Years lived with disability (YLD) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2163–2196.

Goadsby PJ and Edvinsson L. The Trigeminovascular System and Migraine: Studies Characterizing Cerebrovascular and Neuropeptide Changes Seen in Humans and Cats. Ann Neurol. 1993;33:48-56.

Hu XH, Markson LE, Lipton RB, Stewart WF, Berger ML. Burden of migraine in the United States. Arch Intern Med. 1999;159:813-818.

International Classification of Headache Disorders, 3rd edition. Cephalalgia. International Headache Society. 2018;38(1):1-211.

Lipton RB, Bigal ME, Diamond M, Fretag F, Reed ML, and Steward WF. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007;68:343-349.

Steiner TJ, Stover LJ, and Birbeck GL. Migraine: the seventh disabler. J Headache Pain. 2013:14:1.

Stovner LJ and Andree C. Prevalence of headache in Europe: a review for the Eurolight project. J Headache Pain. 2010;11:289–299.

US Food and Drug Administration. Guidance for industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009. available at http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm174090.pdf. Accessed 01 February 2018.