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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

Statistical Analysis Plan Date: 18Mar2020

NON-CLINICAL AND TRANSLATIONAL SCIENCES

CLINICAL PHARMACOLOGY

A Pharmacokinetic Data Analysis Plan (DAP) for Study 3110-108-002 Entitled "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"

Document Number	3110-108-002 DAP
Project Name and Number:	Ubrogepant (AGN-241688, MK-1602)
Protocol Number:	3110-108-002
Phase:	1
Clinic Start Date:	26 September 2019
Study Clinical Pharmacologist:	[redacted]
Sponsor:	Allergan plc
Version:	Final
Date:	18 March 2020

1 Table of Contents

2 List of Abbreviations

AUC_{0-t}	area under the plasma concentration versus time curve, from time 0 to time t, time of last measurable concentration
$AUC_{0-\infty}$	area under the plasma concentration versus time curve, from time 0 to infinity
BLQ	below limit of quantitation
CDISC	Clinical Data Interchange Standards Consortium
CI	confidence interval
C_{last}	last measurable concentration
CL/F	apparent total body clearance of drug from plasma after extravascular administration
C_{max}	maximum plasma drug concentration
CRF	case report form
CSF	cerebrospinal fluid
CSR	clinical study report
DAP	data analysis plan
ECG	electrocardiogram
EOD	end of dosing
λ_z	terminal phase rate constant
ln	natural logarithm
PK	pharmacokinetic
PKS	Phoenix Knowledgebase Server
sFTP	secure file transfer protocol
$T_{½}$	apparent terminal-phase half-life
T_{max}	time of maximum plasma drug concentration
V_z/F	apparent volume of distribution during the terminal phase after extravascular administration

3 Introduction

The data analyses outlined in this document are to support clinical study 3110-108-002. In this study, measurements will be made for ubrogepant and CGRP concentrations in plasma [redacted]. This data analysis plan (DAP) outlines how data analyses of these measurements will be conducted. Additional analysis may be conducted, if necessary. Safety analyses are described separately in the Statistical Analysis Plan.

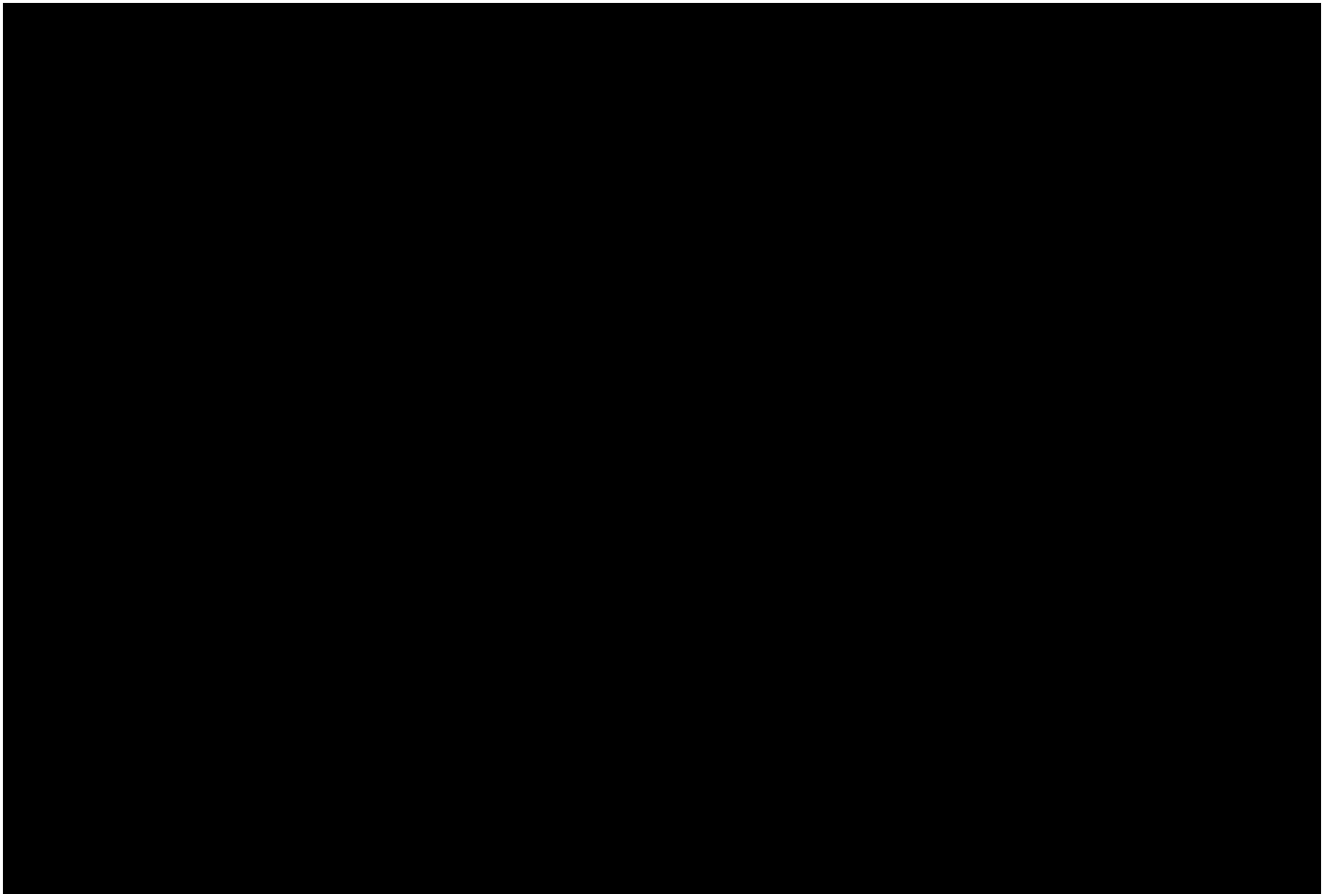
4 Objectives

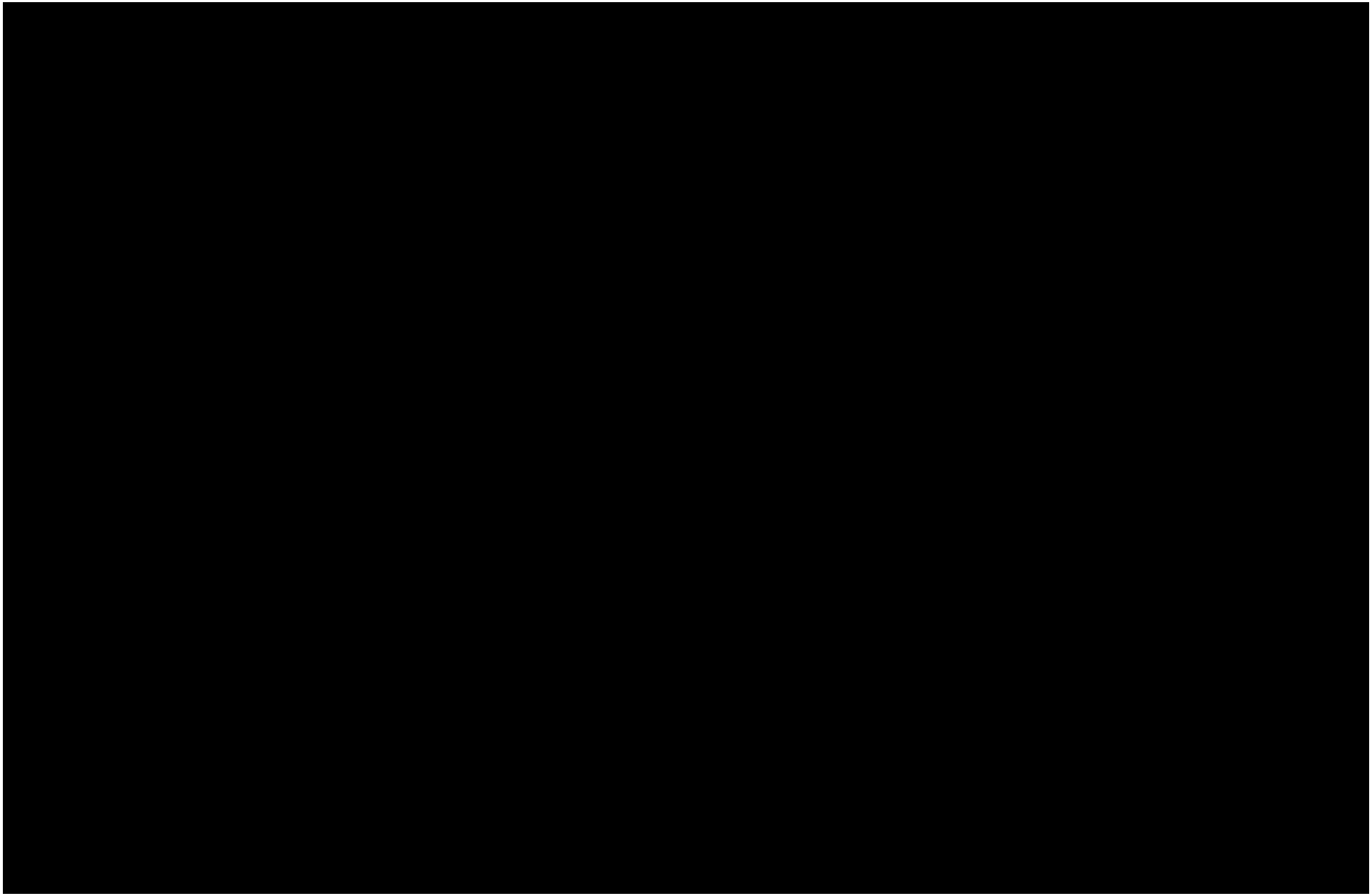
The primary objective of this study is to evaluate the effect of single dose erenumab or galcanezumab on the PK of ubrogepant in participants with migraine. The secondary objectives of the study are to evaluate secondary pharmacokinetic (PK) parameters of ubrogepant following administration of ubrogepant and erenumab, or ubrogepant and galcanezumab, and when ubrogepant is administered alone as well as 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. [redacted]

5 Methods

5.1 Study Design

This study is 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.





5.2 Analysis Populations

The analysis populations will consist of participants as defined below:

- The safety population includes all participants who receive/take ≥ 1 administration of study intervention
- The PK1 population includes all participants who have evaluable plasma PK parameters of ubrogepant for both ubrogepant alone and ubrogepant in combination with erenumab or galcanezumab

[redacted]

- The PK3 population includes all participants who have at least 1 CGRP concentration measurement in plasma

5.3 Sample Size Considerations

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] is considered reasonable to achieve the objectives of the study.

5.4 Software

Pharmacokinetic analysis, summarization of concentration-time data and PK parameter values, and statistical analysis of PK parameter values will be performed using Phoenix® WinNonlin® (Version 8.0 or newer). Tabulations will be exported into Word 2016 (or newer) for formatting. Plotting of concentration-time profiles and scatter graphs (if applicable) will be performed using Phoenix WinNonlin (Version 8.0 or newer), Excel 2016 (or newer) or SigmaPlot 14 (or newer).

5.5 Methodology of Measurements

5.5.1 Pharmacokinetic Methodology

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. In Part A and Part B, PK blood samples to determine ubrogepant plasma concentrations will be collected at 0 hour (predose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12,

14, and 24 hours postdose on Days 1 and 12. These samples will also be used for the determination of CGRP concentrations.

A total of 52 venous blood samples (26 in Part A and 26 in Part B) per participant will be collected for PK and biomarker analysis. Within 30 minutes from the time of the blood draw, blood samples must be centrifuged at no less than 2500*g* for 10 minutes at approximately 4°C. After centrifugation, the plasma samples will be harvested and transferred into 2 prechilled, coded polypropylene tube(s). The samples will then be flash-frozen in a dry ice and alcohol bath (with isopropyl alcohol, ethanol, isopropanol, acetone, or methanol) and stored at approximately –20°C or colder.

Total blood volume collected per participant for PK samples is 104 mL (26 blood samples, 4 mL each) in Part A and Part B, respectively.

[redacted]

Plasma concentrations of ubrogepant will be determined using a validated liquid chromatography-tandem mass spectrometry method [redacted]

5.5.2 Biomarker Methodology

In Part A and Part B, PK blood samples to determine ubrogepant plasma concentrations will be collected at 0 hour (predose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 14, and 24 hours postdose on Days 1 and 12. These samples will also be used for the determination of biomarker (CGRP) concentrations. [redacted]. Plasma and [redacted] of CGRP will be determined using a qualified ELISA assay.

5.6 Data Handling and Storage

A source data file from [redacted] will be transferred to Data Management via secure File Transfer Protocol (sFTP). Data Management will use the data for reconciliation against case report form (CRF) data and general cleaning.

Data Management shall provide the data file to Statistical Programming who will add the data to the [redacted] software for the calculation of PK parameters. Once the [redacted] is created, Statistical Programming will notify the Allergan Clinical Pharmacology representative via email and transfer it to the relevant group via a shared study-specific repository, in the [redacted].

Pharmacokinetic analysis and statistical analysis of pharmacokinetic data will be performed using [redacted] or other appropriate software.

Unless otherwise specified in subsequent sections, these general data handling instructions will be followed:

- All measured data will be used in analysis initially unless it may be excluded in accordance to regulatory guidances. Measured data not used and the reasons for its exclusion from the final analysis will be documented in the clinical study report (CSR).
- The actual sampling times will be used in the calculations of PK parameter values, nominal sample times will be used in the calculation of descriptive statistics.
- All postdose time points for which no sample is collected will be treated as missing. No value will be imputed for these missing values.
- Concentration data below the lower limit of quantitation (BLQ) will be defaulted to 0.00.

A data file (‘.xpt’ or ‘.xls’ format) containing PK parameter values will be generated by the Clinical Pharmacology representative and added to the shared study-specific repository for retrieval by Statistical Programming and for archival. If necessary, a document defining the content and CDISC parameter names will also be provided. Other files necessary to reproduce the analysis of PK parameter values, e.g., the WinNonlin Project file, will be archived in PKS or another appropriate study-specific repository.

6 Data Analysis

6.1 Pharmacokinetics

The following pharmacokinetic parameters for ubrogepant determined from plasma concentration data for each part of the study will be calculated using noncompartmental analysis:

AUC_{0-t}	Area under the plasma concentration-time curve from time 0 to t hours post-dose, calculated by the linear-log trapezoidal rule
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from time 0 to infinity, as calculated by Phoenix WinNonlin ($AUC_{0-\infty}$). $AUC_{0-\infty}$ values will be calculated and reported for all participants, however values will only be included in the summary statistics and statistical analysis if the % extrapolated area (AUC%) is ≤ 20%.
AUC%	Percent of AUC extrapolated from the last measurable concentration to infinity: [AUC% = (($(AUC_{0-\infty} - AUC_{0-t})/AUC_{0-\infty}$) *100)]
C_{max}	Maximal observed plasma concentration
CL/F	Apparent oral clearance is the oral dose divided by $AUC_{0-\infty}$
λ_z	Apparent terminal-phase rate constant, determined by performing a regression analysis on the terminal linear phase of semi-logarithmic plots of individual 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 $r^2 > 0.80$. The values included in the regression analyses will be determined by WinNonlin and will be reviewed and revised as necessary by the Clinical Pharmacologist.
T_{max}	Time corresponding to maximal plasma concentration
$T_{½}$	Apparent terminal-phase half-life, calculated as $0.693/\lambda_z$
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration

If the extrapolated AUC is > 20%, the $AUC_{0-\infty}$, CL/F, and V_z/F values will be listed by participant but excluded from descriptive statistics.

The PK parameter values will be reported up to at least 2 decimal places. [redacted]

6.2 Biomarkers

The percent change from baseline in plasma CGRP levels will be calculated using Excel 2016 (or newer) and will be presented by study intervention and nominal timepoint for each part of the study for the PK3 population. [redacted].

7 Data Summarization and Statistical Analysis

7.1 Data Summarization

PK1 Population

Descriptive statistics (arithmetic mean, standard deviation, relative standard deviation, maximum, minimum) will be reported for the plasma concentrations of ubrogepant at each nominal time point for all participants in the PK1 Population by study part and by study intervention. Descriptive statistics (arithmetic mean, standard deviation, relative standard deviation, maximum, median, minimum) will be calculated for ubrogepant PK parameters for each study part by study intervention for all participants in the PK1 Population. Additionally, the geometric mean will be reported for ubrogepant C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, CL/F, and V_z/F parameters.

[redacted]

[redacted]

PK3 Population

For each part of the study, individual values and descriptive statistics will be reported for the plasma CGRP concentrations at each nominal time point for all participants in the PK3 population. Changes at postdose from baseline by study intervention will be reported for the plasma CGRP concentrations at each nominal time point by study part for all participants in the PK3 population.

7.2 Statistical Analysis

Plasma 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 in each part of the study for the PK1 population. Statistical analysis will be based on log-transformed values for the C_{max} and AUC parameters of ubrogepant. For each study part, the 2-sided 90% CI 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 (Test, Day 12) versus ubrogepant alone (Reference, 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%.

[redacted]

8 Presentation of Final Results

Presentation of data will be performed using the software described in Section 5.4.

- Ratios, coefficient of variation, and confidence intervals will be presented as percentages.
- Percentages will be presented to 2 decimal places.
- Descriptive statistics presented in summary tables in the study report will be presented to a number of decimal places (at least 2) that is consistent with the data from which the statistics were derived.
- Participants will be identified in the listings using their participant number.

All data used, and results will be presented in data tables and listings.

9 Changes to Analysis Plan

None

10 References

None

Electronic Signatures