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Protocol Title: INTERCEPT (Initiating Early Control of Migraine Pain and Associated Symptoms): A Randomized, Double-blind, Single-dose, Placebo-controlled Study to Assess the Efficacy and Safety of AXS-07 (meloxicam and rizatriptan) for the Acute Treatment of Migraine in Adults.

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Certain information within this protocol has been redacted to protect either personally identifiable information (PII) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information.
- Other information as needed to protect the confidentiality of Axsome Therapeutics, personal information, or to otherwise protect the integrity of the clinical study.

INTERCEPT (Initiating Early Control of Migraine Pain and Associated Symptoms): A Randomized, Double-blind, Single-dose, Placebo-controlled Study to Assess the Efficacy and Safety of AXS-07 (meloxicam and rizatriptan) for the Acute Treatment of Migraine in Adults.

Statistical Analysis Plan (SAP)

Sponsor
Axsome Therapeutics, Inc.
[redacted]

Version 1.00 12 March 2020

SPONSOR APPROVAL

The undersigned have reviewed the format and content of this prospective statistical analysis plan (SAP) and have approved it for use to analyze the AXS-07-303 data.

TABLE OF CONTENTS

1.0 DOCUMENT HISTORY

Version	Date	Changes made since previous version
1.00	12 Mar 2020	Final

2.0 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ADR	adverse drug reaction
CFR	Code of Federal Regulations
CRA	clinical research associate
CRO	clinical research organization
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	investigator's brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	institutional review board
ITT	intent-to-treat
IWRS	interactive web response system
MBS	most bothersome symptom
PGI-C	Patient Global Impression of Change
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
UADR	unexpected adverse drug reaction
UAE	unexpected adverse event
US	United States
WHO	World Health Organization

3.0 INTRODUCTION

[redacted]

The purpose of this document is to provide details on study populations and on how the variables will be derived, how missing data will be handled, as well as details on statistical methodologies to be used to analyze the safety and efficacy data from the study.

The document may evolve over time, for example, to reflect the requirements of protocol amendments or regulatory requests. However, the final SAP must be finalized, approved by the Sponsor, and placed on file before the database is locked and treatment codes are unblinded. The approved plan will be used to carry out all analyses for the clinical study report. Deviations, if any, from the approved plan will be noted in the clinical study report.

4.0 STUDY DESCRIPTION

4.1 STUDY OBJECTIVES

Primary Objective
The primary objective of the study is to evaluate the efficacy of AXS-07 as measured by the following two co-primary efficacy variables:

1. Percentage of subjects with headache pain freedom at Hour 2; and
2. Percentage of subjects with absence of the most bothersome symptom (MBS; nausea, photophobia, or phonophobia) at Hour 2.

These two co-primary efficacy variables will be used to establish the superiority of AXS-07 over placebo.

Key Secondary Objectives:
To assess the effect of AXS-07 on time to headache pain freedom and functional disability.

Secondary Objectives:
Secondary objectives include assessment of the effect of AXS-07 on:

- Percentage of subjects with headache pain freedom over time
- Time to sustained headache freedom through Hour 24
- Percentage of subjects able to perform normal activity over time
- Patient Global Impression of Change (PGI-C) scores at Hour 2
- Percentage of subjects MBS free over time
- Percentage of subjects with headache pain freedom between Hours 2 and 24 (24-hour sustained pain-free)
- Percentage of subjects with headache pain freedom between Hours 2 and 48 (48-hour sustained pain-free)
- [redacted]
- Percentage of subjects using rescue medication
- Time to rescue medication use
- Treatment response based on presence of allodynia, BMI, pain intensity, presence of depression, and use of preventive medication

4.2 STUDY TREATMENTS

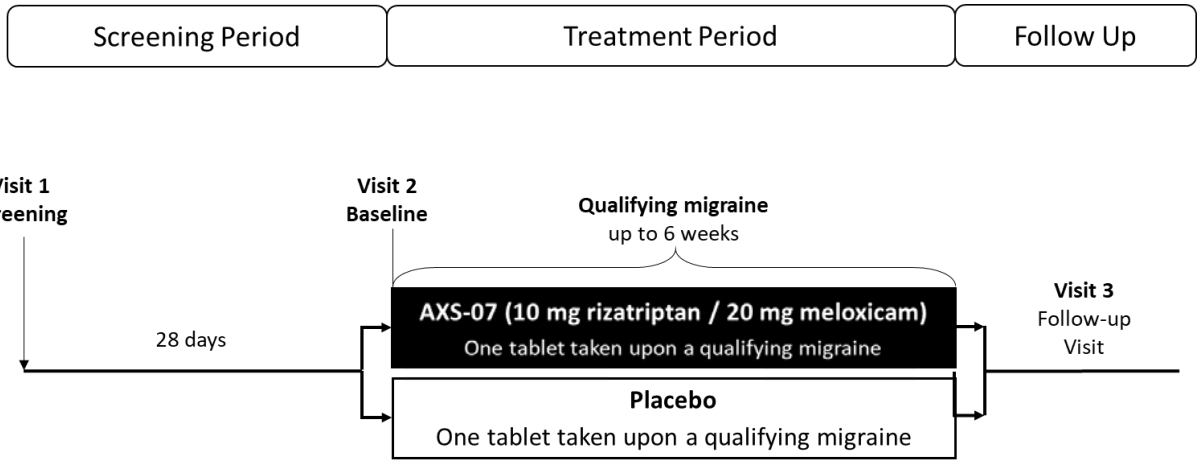
The following study medications will be provided:

- **AXS-07**: a fixed-dose combination tablet consisting of 20 mg meloxicam and 10 mg rizatriptan in the form of a single layer tablet for oral administration.
- **Placebo**: a single layer tablet with no active ingredient for oral administration that matches the appearance of AXS-07.

4.3 STUDY DESIGN

The study is a Phase 3, multicenter, randomized, double-blind, single-dose, placebo-controlled trial to evaluate the efficacy and safety of AXS-07 in subjects with migraine attacks. The co-primary efficacy endpoints are the 1) percentage of subjects with headache pain freedom at Hour 2, with headache pain freedom defined as a reduction in headache severity to no pain, and 2) absence of the MBS (nausea, photophobia, or phonophobia) at Hour 2, with the MBS defined at the onset of migraine, prior to drug administration. The key secondary endpoints are the time to headache pain freedom and the ability to perform normal activity at Hour 2.

In order to qualify as a migraine which can be treated with study drug, the migraine must be of mild (1) pain intensity when reporting the baseline headache characteristics. The design of the study is illustrated below.



Details of the study design, including the schedule of all assessments, can be found in the protocol.

4.4 RANDOMIZATION AND BLINDING

Subjects who successfully complete the Screening visit (Visit 1) will enter into a 28-day Screening Period during which they will record the details (baseline characteristics, headache pain intensity, associated migraine symptoms, and treatments used) of all migraines during this time. The subject must report at least 1 and no more than 8 migraines during the 28-day period in order to continue to be eligible. Subjects who continue to meet all eligibility criteria, will be randomly assigned at Visit 2 (randomization) to receive AXS-07 or placebo at 1:1 ratio, dispensed for at-home treatment of a single migraine attack of mild pain intensity. Subjects will have 6 weeks to treat a qualifying migraine.

5.0 ANALYSIS POPULATIONS

5.1 SAFETY POPULATION

The safety population will include all subjects who have taken study medication. Analyses based on this population will group subjects according to the treatment they actually received regardless of the treatment they were randomized to receive. All safety analyses will use the safety population.

5.2 INTENT-TO-TREAT (ITT) POPULATION

The ITT population is the primary analysis population and will include data from all subjects who are randomized and have a qualifying migraine episode.

5.3 PER PROTOCOL POPULATION

The Per Protocol population will include all ITT subjects without major protocol violations. The criteria for major protocol violation will be determined and documented prior to database lock. Subjects with major protocol violations will be flagged in data listings.

6.0 GENERAL CONVENTIONS

Unless otherwise stated, all analyses will be performed [redacted] and all hypothesis tests will be conducted at a two-sided significance level of 0.05. P-values will be presented with 3 decimals and p-values that are less than 0.001 will be presented as <0.001.

Continuous data will be summarized using descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Frequencies and percentages will be used to summarize categorical (discrete) data. Presentations of categorical data will generally suppress percentages for items where the count is zero in order to draw attention to the nonzero counts. In general, mean, standard deviation, median, minimum, maximum, and percentages will be presented with one decimal.

Unless otherwise stated, confidence intervals, when presented, will be constructed at the two-sided 95% level. For binomial variables, the 95% confidence intervals will be constructed using the normal approximation without continuity correction.

Data listings will present all data collected on CRFs by study drug, center, and subject number. Unless otherwise stated, data will be presented by treatment and subject within treatment.

6.1 DEFINITION OF BASELINE

Unless otherwise stated, the last observed measurement on the date of randomization will be considered the baseline measurement. If multiple observations are made during baseline, the baseline will be defined as the average of the observations obtained during the baseline phase.

[redacted]

6.3 CHANGES TO PLANNED ANALYSES

Draft versions of the SAP will be numbered sequentially as Version 0.0i. The final approved version will be numbered as Version 1.00. Revisions after the "Final" version will be numbered as Version 1.0x. The Clinical Study Report will document any changes made after the final version approved before unblinding.

7.0 DESCRIPTION OF THE STUDY POPULATIONS

All tables, figures, and listings must include a population descriptor (e.g., ITT or Safety) in the titles.

7.1 DISPOSITION

Subject disposition summaries will be presented by treatment arm and will include the number of subjects randomized, the number and percentage of randomized subjects in the safety and ITT populations, as well as the number and percentage of subjects who complete the study. The summaries will also include the reasons for early discontinuation from the study.

Disposition summaries will be presented for safety and intent-to-treat populations separately.

7.2 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

A summary of demographics and baseline characteristics will be presented by treatment arm and overall for the ITT and Safety populations. The demographic characteristics will, at the minimum, consist of age, sex, ethnicity, and race using descriptive statistics.

Age will be calculated based on the following conditional algorithm:

- Has the patient had his/her birthday this year?
    - Yes, then AGE = (year of informed consent) – (year of birth).
    - No, then AGE = (year of informed consent) – (year of birth) – 1.

Clinical baseline characteristics summarized will include, at minimum, BMI, frequency of migraines, and prior migraine medication use.

7.3 MEDICAL HISTORY

A medical history listing will be presented.

8.0 PRIOR AND CONCOMITANT MEDICATIONS

All medications recorded on the CRFs will be coded using the WHO DRUG Dictionary Enhanced March 2019. Prior and concomitant medications will be summarized by treatment arm in the safety population by anatomical therapeutic chemical (ATC) Class Level 4 and WHO Drug base substance preferred name.

Prior medications are defined as medications with stop dates occurring before the date of first administration of any study treatment component. Concomitant medications are defined as medications with start dates occurring on or after the date of first administration of any study treatment component and no more than 30 days after the last study visit. Medications with start and stop dates that bracket the date of first administration of any study treatment component will be summarized as both prior and concomitant medications.

Medications that were clearly stopped prior to the date of first administration of any study treatment component will be included in the prior medications table, and medications that were clearly started on or after the date of first administration of any study treatment component will be included in the concomitant medications table. All other medications will be included in both the prior and concomitant medications tables.

Prior and concomitant medications will be summarized for the safety population.

9.0 EFFICACY ANALYSES

9.1 PRIMARY EFFICACY VARIABLES

The primary objective of the study is to evaluate the efficacy of AXS-07 as measured by the following two co-primary efficacy variables:

1. Percentage of subjects with headache pain freedom at Hour 2; and
2. Percentage of subjects with absence of the most bothersome symptom (MBS; nausea, photophobia, or phonophobia) at Hour 2.

These two co-primary efficacy variables will be used to establish the superiority of AXS-07 over placebo.

9.1.1 DERIVATIONS OF CO-PRIMARY EFFICACY VARIABLES

To qualify as a responder for headache pain freedom at Hour 2, the pain intensity score at Hour 2 must be equal to 0 (none) and to qualify as a responder for absence of the most bothersome symptom (MBS) at Hour 2, the MBS scale at Hour 2 must be equal to “Absent”.

9.1.2 PRIMARY ANALYSES

Percentage of responders for each of the co-primary efficacy variables will be presented. Between treatment group comparisons will be performed via chi-square tests. The differences and the two-sided 95% confidence intervals of the differences as well as the p-values of the differences will be presented.

In the primary analysis, subjects who take rescue medication before Hour 2 or who do not have an Hour 2 value will be treated as non-responders. [redacted]

9.2 KEY SECONDARY EFFICACY OUTCOME

The key secondary efficacy variables are time to headache pain freedom and the ability to perform normal activity (functional disability = none) at Hour 2.

Time to headache pain freedom is the time in minutes from the dosing of the study medication to the time when pain freedom (pain intensity score equals to 0) is first obtained. This time to event variable will be analyzed via a log-rank model with treatment effects. The time-to-event "survival" curve will be presented using the Kaplan-Meier method. Median time-to-event and the 95% confidence interval of the median times will be presented, if estimable. In these time-to-event analyses, subjects who do not have the event during the entire study will be censored at Hour 24.

Functional disability (0-none, 1-mild, 2-moderate, 3-severe) will be analyzed as a responder variable, defined as the percent of subjects reporting "none" on the functional disability scale, as a change from the baseline variable. The percent of subjects reporting none on the functional disability scale will be analyzed using the same methods used to analyze the co-primary efficacy variables.

Change from baseline in functional disability will be analyzed using Mixed Model Repeated Measures (MMRM) methods. All post-baseline observations will be utilized; missing values will remain as missing, i.e. no attempt will be made to impute missing values, and only observed values will be used in the data analysis. The model will include treatment, timepoints, treatment by timepoints interaction as fixed effects, and baseline as the covariate. The covariance structure will be assumed to be unstructured. If the estimates do not converge, SAS default covariance structure (Variance Components) will be assumed. [redacted]

[redacted]

9.3 OTHER SECONDARY EFFICACY OUTCOMES

Below is the list of efficacy variables to be analyzed:

Pain Related

- Percentage of subjects with headache pain freedom over time
- Average pain intensity over time
- Percentage of subjects with headache pain freedom between Hours 2 and 24 (24-hour sustained pain-free)
- Percentage of subjects with headache pain freedom between Hours 2 and 48 (48-hour sustained pain-free)
- Percentage of subjects with freedom from pain progression or worsening (defined as pain intensity of 0 or 1) at Hour 2
- Percentage of subjects with sustained freedom from pain progression or worsening (defined as pain intensity of 0 or 1) between Hours 2 and 24 (24-hour sustained progression free)
- Percentage of subjects with sustained freedom from pain progression or worsening (defined as pain intensity of 0 or 1) between Hours 2 and 48 (48-hour sustained progression free)
- Percentage of subjects with sustained headache pain freedom between Hours 1.5 and 24
- Percentage of subjects with sustained headache pain freedom between Hours 1 and 24
- [redacted]
- Time to sustained headache freedom through Hour 24
- Time to sustained headache freedom through Hour 48
- Time to headache pain worsening, defined as when the severity of migraine pain is greater than mild
- Percentage of patients with headache pain worsening (defined as pain intensity of 2 or 3) over time

Functional Disability

- Change from baseline in functional disability to Hour 2
- Change from baseline in functional disability over time
- Percentage of subjects able to perform normal activity (functional disability = none) at Hour 2
- Percentage of subjects able to perform normal activity (functional disability = none) at Hour 1.5
- Percentage of subjects able to perform normal activity (functional disability = none) at Hour 1
- Percentage of subjects able to perform normal activity (functional disability = none) over time
- Sustained ability to function at a normal level (functional disability = none) from Hours 2 to 24
- Sustained ability to function at a normal level (functional disability = none) from Hours 2 to 48
- Time to being able to perform normal activity (functional disability = none)

Most Bothersome Symptoms

- Percentage of subjects with absence of MBS over time
- Percentage of subjects with sustained freedom from MBS from Hour 2 to Hour 24
- Percentage of subjects with sustained freedom from MBS from Hour 2 to Hour 48
- Percentage of subjects with absence of photophobia at Hour 2 in the subset of subjects that reported the presence of photophobia at headache baseline
- Percentage of subjects with absence of phonophobia at Hour 2 in the subset of subjects that reported the presence of phonophobia at headache baseline
- Percentage of subjects with absence of nausea at Hour 2 in the subset of subjects that reported the presence of nausea at headache baseline
- Percentage of subjects with absence of photophobia over time in the subset of subjects that reported the presence of photophobia at headache baseline
- Percentage of subjects with absence of phonophobia over time in the subset of subjects that reported the presence of phonophobia at headache baseline
- Percentage of subjects with absence of nausea over time the subset of subjects that reported the presence of nausea at headache baseline

Rescue Medication Use

- Percentage of subjects using rescue medication within 24 hours after administration of study medication
- Percentage of subjects using rescue medication within 48 hours after administration of study medication
- Time to rescue medication use

Other Secondary Endpoints

- Patient Global Impression of Change (PGI-C) scores at Hour 2
- PGI-C scores over time
- Treatment response based on presence of allodynia, BMI, pain intensity, presence of depression, and use of preventive medication

The variables related to percentages

The variables related to percentages will be analyzed via the same methodology used to analyze the co-primary efficacy variables described above. For variables related to sustained response, to qualify as a responder, the subjects must be a responder within that defined time window.

Responders on the 24-hour sustained pain freedom endpoint are defined as:

1. All reported pain intensity between Hours 2 and 24 must be 0;
2. Pain intensity at Hours 2 and 24 must be 0;
3. Pain intensity must be available for at least Hour 12 or 16; and
4. No rescue medication use through Hour 24.

Responders on the 48-hour sustained pain freedom endpoint are defined as:

1. All reported pain intensity between Hours 2 and 48 must be 0;
2. Pain intensity at Hours 2 and 48 must be 0;
3. Pain intensity must be available for at least Hour 12 or 16; and
4. No rescue medication use through Hour 48.

The variables related to change from baseline
The variables related to change from baseline will be analyzed using Mixed Model Repeated Measures (MMRM) methods described above.

The variables related to time to event
Variables related to time to event will be analyzed via a log-rank model with treatment effects. The time-to-event "survival" curve will be presented using the Kaplan-Meier method. Median time-to-event and the 95% confidence interval of the median times will be presented, if estimable. In these time-to-event analyses, subjects who do not have the event during the entire study will be censored at Hour 24.

In the analyses for time to sustained headache pain freedom and time to headache pain freedom, subjects who take rescue medication will be considered censored at Hour 24.

Patient Global Impression of Change (PGI-C) scores at Hour 2
Patient Global Impression of Change (PGI-C) scores at Hour 2 will be analyzed via the Cochran-Mantel-Haenszel (CMH) test for mean score difference using score=ridit option. Frequency of the categories will also be presented.

9.4 MISSING VALUE HANDLING PROCEDURES

Unless otherwise stated, missing values will not be imputed.

[redacted]

[redacted]

9.7 INTERIM ANALYSES

No interim analysis will be performed.

[redacted]

9.9 POWER AND SAMPLE SIZE JUSTIFICATION

In this study, approximately 150 subjects will be randomized to the AXS-07 and placebo groups. Approximately 150 subjects per arm will provide 90% power to detect a treatment difference at a two-sided significance level of 0.05, assuming that the responder rate for pain freedom at Hour 2 is ≤15% for the placebo control and ≥ 29%.

10.0 SUMMARIES OF MEASURES OF SAFETY

Safety analyses will be performed for the safety population. Safety evaluations will be based on the incidence, severity, relatedness, and type of adverse events, as well as on clinically significant changes in the subject's physical examination, and vital signs. Safety variables will be tabulated and presented by study drug actually received.

Because there is no pre-specified safety outcome defined in terms of AEs or vital signs, any formal comparisons between the treatment arms with respect to specific safety parameters will be post-hoc.

10.1 EXTENT OF EXPOSURE

Summary statistics of exposure to study drug will be tabulated by treatment group, and by cumulative dose received.

10.2 ADVERSE EVENTS

Each AE and SAE term recorded on the case report forms (CRFs) by primary system organ class (SOC) will be mapped to a preferred term using the MedDRA dictionary. The investigator will assess AE severity and relationship to the study treatment.

A treatment emergent adverse event (TEAE) is defined as any AE with an onset date on or after the date of dosing, or any ongoing event on the date of first dose that worsens in severity after the date of randomization. Only non-serious TEAEs with an onset date prior to the date of the last dose and serious TEAEs with an onset date prior to the date of the final visit + 30 days will be tabulated in summary tables. However, all AEs recorded will be listed. For the purpose of calculating treatment emergence and inclusion in summary tables, incomplete onset dates will be imputed as detailed in Appendix A.

AEs will be summarized by the number and percentage of subjects in each primary SOC and preferred term. Patients will be counted only once for each primary SOC and each preferred term. Summary tables of AEs by primary SOC, preferred term and severity will be provided. If a subject has more than one AE coded to the same preferred term, the subject will be counted only once for that preferred term by using the event with the highest severity. Similarly, if a subject has more than one AE within a primary SOC category, the subject will be counted only once in that SOC category by using the event with the highest severity. AEs by primary SOC, preferred term and relationship to study drug will be provided as well. If a subject has more than one AE coded to the same preferred term, the subject will be counted only once for that preferred term by using the most related event. Similarly, if a subject has more than one AE within a primary SOC category, the subject will be counted only once in that primary SOC category by using the most related event. In addition, serious adverse events (SAE) by primary SOC and preferred term will be provided. Deaths and SAEs will be summarized similarly to AEs. All adverse event tables will also include the total number of events, counting multiple events per patient.

In the AE summary, preferred terms within each SOC will appear in alphabetical order as well as in decreasing order of total incidence.

Frequencies for deaths and hospitalizations will also be summarized by treatment group and overall.

Other safety analyses will be performed as appropriate

10.3 VITAL SIGNS

Vital signs will consist of blood pressure (systolic and diastolic blood pressure, mm Hg), pulse rate (beats per minute), and respiratory rate (breaths/min), collected while sitting, following a rest period of at least 5 minutes. Vital sign values and change from baseline in the vital signs will be summarized for each treatment group.

10.4 PHYSICAL EXAM

Physical Exam data for each subject will also be presented in a listing.

11.0 IDENTIFICATION AND SUMMARY OF PROTOCOL DEVIATIONS

Major protocol deviations from entry criteria and treatment compliance will be summarized as far as they can be extracted from numeric or coded study data.

12.0 DATA QUALITY ASSURANCE

Accurate and reliable data collection will be ensured by verification and cross check of the CRFs against the investigator's records by the study monitor (source document verification) and by the maintenance of a drug–dispensing log by the investigator. Collected data will be entered into a computer database and subject to electronic and manual quality assurance procedures.

13.0 REFERENCES

None

14.0 APPENDICES

14.1 APPENDIX A - IMPUTATION ALGORITHM FOR PARTIAL AND MISSING DATES

This section describes missing date imputation methods.

For Adverse Events

If onset date is completely missing, onset date is set to date of randomization.
If (year is present and month and day are missing) or (year and day are present and month is missing):

- If year = year of randomization, then set month and day to month and day of randomization
- If year < year of randomization, then set month and day to December 31.
- If year > year of randomization, then set month and day to January 1.

If month and year are present and day is missing:

- If year = year of randomization and
    - If month = month of randomization then set day to day of first dose
    - If month < month of first dose then set day to last day of month
    - If month > month of first dose then set day to first day of month
- If year < year of randomization then set day to last day of month
- If year > year of randomization then set day to first day of month

For all other cases, set onset date to date of randomization.

For Concomitant Medications

Start Date: If start date is completely missing and end date is not prior to randomization, then the medication will be classified as concomitant. If start date is completely missing and end date is prior to randomization, then the medication will be classified as prior.

If (year is present and month and day are missing) or (year and day are present and month is missing) then set month and day to January 1. If year and month are present and day is missing then set day to first day of month.

End Date: If end date is completely missing then the medication will be classified as concomitant.
If (year is present and month and day are missing) or (year and day are present and month is missing) then set month and day to December 31. If year and month are present and day is missing then set day to last day of the month.

Note: that if both start and end dates are missing then the medication will be classified as concomitant.