NCT02549196

Study ID: CPC-001-12

Title: A phase II, dose titration study of CPC-201 in Patients with Dementia of Alzheimer's Type

Statistical Analysis Plan Date: 02 Aug 2017

STATISTICAL ANALYSIS PLAN
FOR PROTOCOL CPC-001-12

Sponsor: CHASE PHARMACEUTICALS	Chase Pharmaceuticals Corporation a subsidiary of Allergan plc, 2525 Dupont Drive, Irvine, California 92612, USA
Protocol Number:	CPC-001-12
Protocol Title:	A Phase II, Dose Titration Study Of CPC-201 In Patients With Dementia Of Alzheimer's Type
Protocol Date / Version:	July 22, 2016/Version 3

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Plan Version:	SAP – Final Version 1.0
Plan Date:	02 August 2017

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Prepared by:	[redacted]
SAP Version:	SAP – Final Version 1.0
SAP Date:	02 August 2017

I have read and approve the Statistical Analysis Plan specified above and agree on its content:

[redacted]

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ABBREVIATIONS, ACRONYMS, AND DEFINITIONS

Abbreviation	Definition
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's Disease Assessment Scale – Cognitive subscale
AE	adverse event
ASA	American Statistical Association
CFR	Code of Federal Regulations
CNS	central nervous system
CRF	case report form
C-SSRS	Columbia Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
DSM IV	Diagnostic and Statistical Manual of Mental Disorders (4th edition)
DSMB	data safety monitoring board
ECG	electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	heart rate
ICF	informed consent form
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental Status Exam
MTD	maximum tolerated dose
NIA-ADA	National Institute on Aging-Alzheimer's Association
PK	pharmacokinetics
PP	per-protocol
PT	Preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SOC	System Organ Class
SOP	standard operating procedure
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the planned analyses and reporting for the clinical trial protocol CPC-001-12, sponsored by Chase Pharmaceutical Corporation. The reader of this SAP is encouraged to review the complete protocol, as this plan contains only a limited overview of protocol information. The main objective of the plan is to provide details pertaining to statistical methodology, data conventions, and processes used for the analysis of data from this trial.

The format and content of this SAP are structured to provide sufficient detail to meet the requirements specified by the International Conference on Harmonization (ICH) E9: Guidance on Statistical Principles in Clinical Trials. All analyses planned and presented in this SAP will follow the ethical guidelines published by the American Statistical Association (ASA).

The following documents were reviewed in preparation of this Statistical Analysis Plan:

- Version 3.0, protocol, July 22, 2016
- Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics (2010)
- ASA Ethical Guidelines for Statistical Practice (2016)
- The Royal Statistical Society: Code of Conduct (2014)
- ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3, 1996)
- ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9, 1998)

2. PROTOCOL DESIGN

2.1 Design Overview

This is a Phase II, ascending dose study of CPC-201 in patients with dementia of Alzheimer's type to determine the optimal dose titration schedule. The study involves a step wise cohort design in two different patient populations: Group 1 will consist of patients who have been treated with donepezil 5 or 10 mg/day (given once daily) for at least 4 weeks just prior to Day1. Group 2 will consist of patients who have never been treated with donepezil before (donepezil naïve) or who have not received any other

AChEI for the past 6 months.

Original Plan

Donepezil dose will be increased at weekly intervals, in accordance with the schedules given below, to its first intolerable dose (FID) or maximum allowed dose (MAD) 60 mg/day together with solifenacin 15 mg/day. If a patient does not tolerate a donepezil dose higher than 40mg/day with solifenacin 15 mg/day, the solifenacin dose can be increased to 20mg/day per the Investigator's decision.

Cohort 1	1st week: 20mg donepezil + 15mg solifenacin 2nd week: 30mg donepezil + 15mg solifenacin 3rd week: 40mg donepezil + 15mg solifenacin 4th week: 50mg donepezil + 15mg (or 20mg) solifenacin 5th week: 60mg donepezil + 15mg (or 20mg) solifenacin
Cohort 2*	1st week: 20mg donepezil + 15mg solifenacin 2nd week: 40mg donepezil + 15mg solifenacin 3rd week: 60mg donepezil + 15mg (or 20mg) solifenacin
Cohort 3*	1st week: 20mg donepezil + 15mg solifenacin 2nd week: 60mg donepezil + 15mg (or 20mg) solifenacin

*: The dose titration schedule of Cohort 2 and 3 may be altered based on Cohort 1 result.

Patients reaching their FID or having completed one week treatment with MAD, have two options.

Option 1: Patient will be allowed to immediately enter a long term extension at their maximum tolerated dose (MTD) or MAD.

Option 2: Patients may choose not to enter the long term extension, in which case the Investigator will decide whether the patient should discontinue high dose of donepezil without down-titration, or whether donepezil should be downtitrated to their own standard of donepezil dose. Whatever the decision, the patient will be treated at least an additional 7 days with solifenacin 15 mg/day.

First Amendment

After 8 subjects in Cohort 1 and 1 subject in Cohort 2 were enrolled, the protocol was amended to add Cohort 1b and to limit to enroll only Group 1.

Patients currently treated with donepezil (Group 1) will receive solifenacin 15 mg/day

during a two week run in period; donepezil treatment will continue at 10mg/day. Once on 15 mg/day of solifenacin for two weeks (based upon the investigator judgment), the donepezil dose will be increased at weekly or bi-weekly intervals, in accordance with the schedules given below, to its first intolerable dose (FID) or maximum allowed dose (MAD) of 60mg/day

Cohort 1b	1st-2nd week: 10mg donepezil + 15mg solifenacin 3rd week: 20mg donepezil + 15mg solifenacin 4th week: 30mg donepezil + 15mg solifenacin 5th week: 40mg donepezil + 15mg solifenacin 6th week: 50mg donepezil + 15mg (or 20mg) solifenacin 7th week: 60mg donepezil + 15mg (or 20mg) solifenacin

Second Amendment

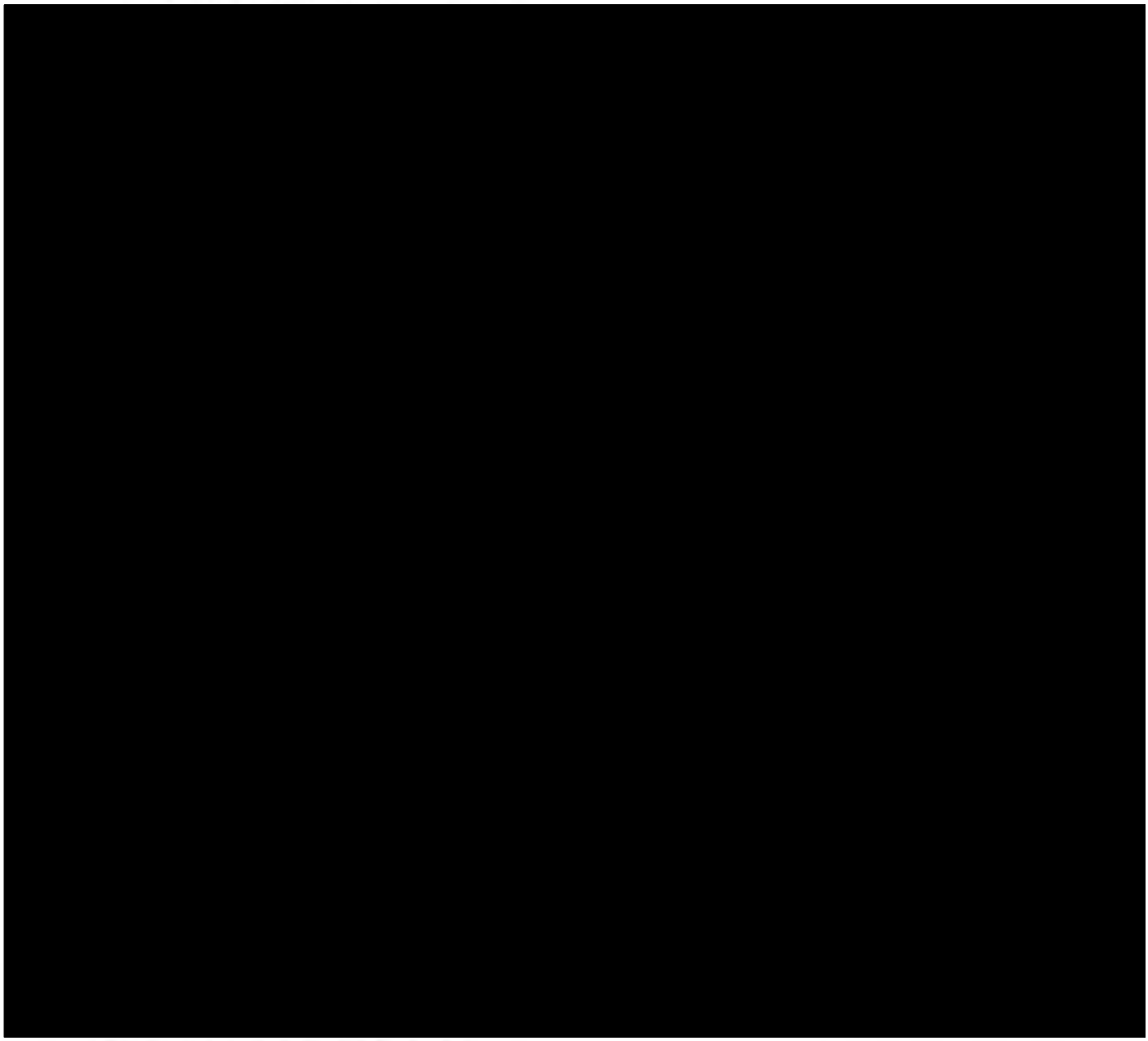
After 6 subjects were enrolled in Cohort 1b, the protocol was amended to add Cohort 3c.

All subjects entering the study in cohort 3 will start with a dose regimen of 10mg donepezil + 15mg solifenacin and will continue to increase the donepezil dose by 5mg increments every 7 days (or up to 14 days per PI discretion) up to 40mg or the MTD.

Cohort 3c	1st week: 10mg donepezil + 15mg solifenacin 2nd week: 15mg donepezil + 15mg solifenacin 3rd week: 20mg donepezil + 15mg solifenacin 4th week: 25mg donepezil + 15mg solifenacin 5th week: 30mg donepezil + 15mg solifenacin 6th week: 35mg donepezil + 15mg solifenacin 7th week: 40mg donepezil + 15mg solifenacin

All the schedule of assessments for this study are presented in the protocol and also in the Appendix 1 of this SAP.

2.2 Clinical Trial Treatments



2.2.2 Randomization and Blinding

This is a single-blind dose escalating open label study. The subject, caregiver, and site personnel who assess MMSE and ADAS-Cog are blinded.

2.3 Protocol Objective(s)

2.3.1 Primary Objective

To determine the optimal initial dose and subsequent dose titration schedule (rate and increment) for CPC-201.

2.3.2 Secondary Objectives

To evaluate the safety and tolerability of CPC-201 as a function of dose and initial rate of dose titration.

2.4 Study Outcome Measures

2.4.1 Primary Outcome Measure

The primary outcome for this study is optimal initial dose and subsequent dose titration schedule (rate and increment) for CPC-201.

- The FID of each patient
- The MTD of each patient

2.4.2 Secondary Outcome Measures

2.4.2.1 Safety Assessments

Safety will also be evaluated on:

- Dose limiting side effects
- AEs and SAEs (type, severity, and frequency),
- vital signs (systolic and diastolic blood pressure; radial artery pulse rate; body weight),
- 12-lead ECG,
- Safety lab,
- Physical examination, and
- Suicidality modified C-SSRS.

[redacted]

[redacted]

- [redacted]
- [redacted]

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- [redacted]

3. SAMPLE SIZE DETERMINATION

No formal sample size calculation has been made. Based on experience from previous similar studies, a total 4-6 evaluable subject per group per cohort is considered sufficient.

4. INTERIM ANALYSIS/DSMB

No Interim Analysis (IA) was planned to be conducted.

5. HYPOTHESIS TO BE TESTED

There is no formal hypothesis testing for this study. The study is not powered to reliably yield statistically significant conclusions.

6. ANALYSIS POPULATIONS

6.1 Safety Population

The Safety population is defined as all subjects those who received at least one dose of any study drug. This population will be used for analysis of safety parameters.

6.2 MTD (Maximum Tolerable Dose) Evaluable population

The MTD evaluable population is defined as all subjects who completed the donepezil dose titration. This population will be used for summary of the primary study outcome.

7. DATA CONVENTION AND RELATED DEFINITIONS

7.1 Baseline Definition

For all parameters, baseline will be defined as the last available value before the first treatment.

7.2 Duplicate Data

For unplanned duplicate data within protocol-specified visit duration, the last measured value will be used for the analysis. If it is not possible to identify the "last measured value" the average of the duplicate values will be used.

No data will be excluded. All collected data will be listed.

7.3 Handling of Missing Data

All data will be used as observed, and no imputations will be made for any missing data point. All summaries will be based on observed data only.

7.4 Multicenter Clinical Trials

This is a multi-center clinical trial.

7.5 Multiple Comparisons and Multiplicity

Not applicable for this study.

7.6 Covariates and Prognostic Factors

Not applicable for this study.

7.7 Stratification Factors

Not applicable for this study.

7.8 Standard Calculations

7.8.1 Age

Age will be calculated as the number of completed years between the date of informed consent and the subject's birth date.

Age (years) = integer of[(date of informed consent – date of birth)/ 365.25+ 0.5]

7.8.2 Body Mass Index (BMI)

BMI will be calculated using height (in cm) and weight (in kg) according to the formula noted below.

BMI (kg/m^2) = weight (kg) / [[height (cm)/100]^2]

7.8.3 Change from Baseline

Change will be calculated using according to the formula noted below.

Change= Post Baseline Data – Baseline Data

7.8.4 QTcF

QTcF will be calculated using according to the formula noted below.

$$QTcF = QT/RR^{1/3}$$
$$(RR=60/VR)$$

8. STATISTICAL METHODS

All data from this clinical trial will be provided in data listings, study drug, clinical trial center, subject, and time point (if applicable).

Data summary will be according to the variable type:

- Continuous data summaries will include:
  - Number of observations, mean, standard deviation, median, and minimum and maximum values.
- Categorical data summaries will include:
  - Frequency counts and percentages.

8.1 Summarizing and Tabulating the Collected Data

8.1.1 Subject Disposition and Withdrawals

There will be a detailed accounting of all subjects who sign an informed consent to participate in this study. The following will be summarized:

- The number of subjects who are enrolled
- The number of subjects who completed the Dose Titration
- The number of subjects who discontinued prior to completion of the dose titration
  - Reasons for discontinuation will also be summarized descriptively
- The number of subjects who completed the long term extension (Optional)
- The number of subjects who discontinued during the long term extension
  - Reasons for discontinuation will also be summarized descriptively

In addition, there will also be a listing of all discontinued subjects, which will provide the specific reason for discontinuation.

8.1.2 Demographics and Other Baseline Characteristics

Individual subject demographic and baseline characteristics including baseline disease status based on MMSE data (i.e., Mild: 21-30, Moderate: 10-20 and Severe: <10) will be summarized and also presented in subject data listings. Medical history data will be listed for safety population subjects.

8.1.3 Prior and Concomitant Medications

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

All prior and concomitant medications recorded in the case report form will be using the most recent version of WHO Drug dictionary. Descriptive summaries will be prepared using the coded term. All prior and concomitant medications recorded in the case report form will be listed.

Medications entered as donepezil and memantine are captured in the Alzheimer's disease history and will not be included in the summary and listings of prior and concomitant medications.

8.1.4 Study Drug Administration

All available study drug administration data will be listed and/or summarized.

8.2 Analysis Primary Outcome Measure

The primary outcome measure for the study is the optimal initial dose and subsequent dose titration schedule of donepezil when given with solifenacin (15 mg/day or 20 mg/day).

Time to reach FID (First Intolerable Dose) for each patient will be presented as a subject specific listing. The proportion of subjects at the different MTD levels and those who were able to tolerate the highest dose of donepezil (i.e., 40 mg/day) and the MTD will be summarized descriptively. In addition, descriptive summary (i.e., n, mean, SD) of the highest dose reached will be presented.

The dose limiting side effect will be listed.

8.3 Analysis of Secondary Outcome Measures

8.3.1 Analysis of Safety and Tolerability Data

The Safety population will be used for all analyses of safety and tolerability. All Safety and tolerability parameters will be analyzed as a function of dose and dose titration schedule and be presented descriptively and as data listings.

8.3.1.1 Adverse Events

Adverse events will be classified by system organ class (SOC) and preferred term (PT) according to the most recent version of MedDRA dictionary.

TEAE are defined as events with an onset on or after administration of the first dose of study drug. TEAEs will be summarized, System Organ Class, and preferred term. The following TEAE summaries will be provided:

- Top line summary table including
    - all treatment emergent Adverse Events (TEAEs), treatment related TEAE and treatment unrelated TEAE,
    - Serious treatment emergent Adverse Events (STEAEs), treatment related STEAE and treatment unrelated STEAE
    - Deaths
- Overall (*i.e.,* regardless of severity or relationship to treatment)
- By cohort (i.e., 1, 2, 1b, 3c)
- By study phase (i.e., titration and long term extension)
- By severity grade (mild, moderate, severe)
- By relationship to study drug (definitely, probably, possibly, not related)

Unless otherwise specified, at each level of subject summarization, a subject will be counted only once. If there is more than one occurrence of an event, the event of the worst severity or the worst-case relationship category will be summarized.

Serious Adverse Events (SAEs) will also be summarized by relationship.

8.3.1.2 Laboratory Tests (Safety laboratory test and urinalysis)

For the continuous laboratory parameters, descriptive statistics will be presented. Additionally, parameters will be categorized as low, normal or high according to laboratory range specifications. The number and percentage of subjects will be presented by dosing cohort.

All available results of the clinical laboratory evaluations will be listed and summarized. Laboratory evaluations include hematology, serum chemistry and urinalysis.

Summary statistics of raw data and change from baseline values for each laboratory parameter will be presented and time point. Data will be summarized as appropriate to the variable type.

- For continuous data, summaries will include the number of observations, mean, standard deviation, median, and minimum and maximum values.
- For categorical data, frequency counts and percentages will be used.

For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded.

8.3.1.3 Vital Signs and weight

Summary statistics of raw data and change from baseline values will be presented by time point during each study period for each vital sign parameter (including Blood Pressure, Heart Rate, Respiration Rate, Temperature, and Body weight).

Summaries will include the number of observations, mean, standard deviation, median, and minimum and maximum values. For change from baseline summaries, subjects with an undefined change from baseline, because of missing data, will be excluded.

8.3.1.4 Electrocardiogram (ECGs)

The ECG parameters include ventricular rate (beats per minute), PR interval (msec), QRS interval (msec), and QT interval (msec). All the evaluations from the site measurement will be presented. In addition ECG parameters RR and QTcF will be calculated per the formula in Section 7.8.4 and will be summarized.

Descriptive statistics of raw data and change from baseline values for each ECG measurement will be presented. For change from baseline summaries, subjects with an undefined change from baseline, because of missing baseline data, will be excluded.

8.3.1.4.1 Individual Subject Changes (Shift Tables)

Individual subject changes will be identified through shift tables. Shift tables will be presented for the investigator ECG interpretation (i.e., Normal, Abnormal (not clinically significant) and Abnormal (clinically significant)) with counts and percentages of subjects for shift (change) from baseline, using the normal ranges.

8.3.1.4.2 Clinically Significant Abnormalities

A by-subject listing of treatment-emergent clinically significant ECGs will be prepared.

8.3.1.5 Physical Examination

All physical examination findings will be listed.

8.3.1.6 Assessment of Suicidality

Suicidality will also be assessed using the modified Columbia Suicide Severity Rating Scale (C-SSRS). All the results from this scale will be listed and summarized.

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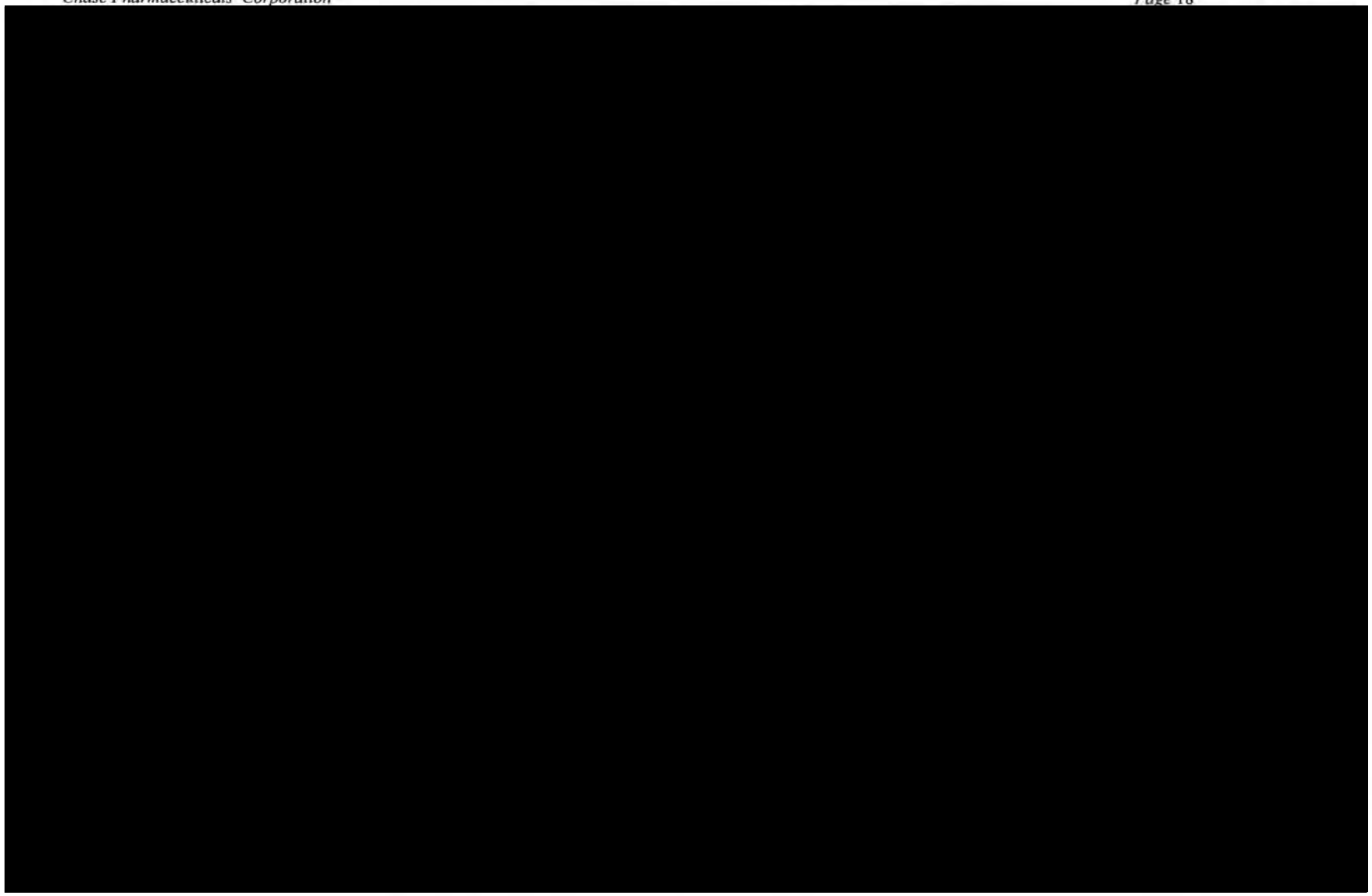

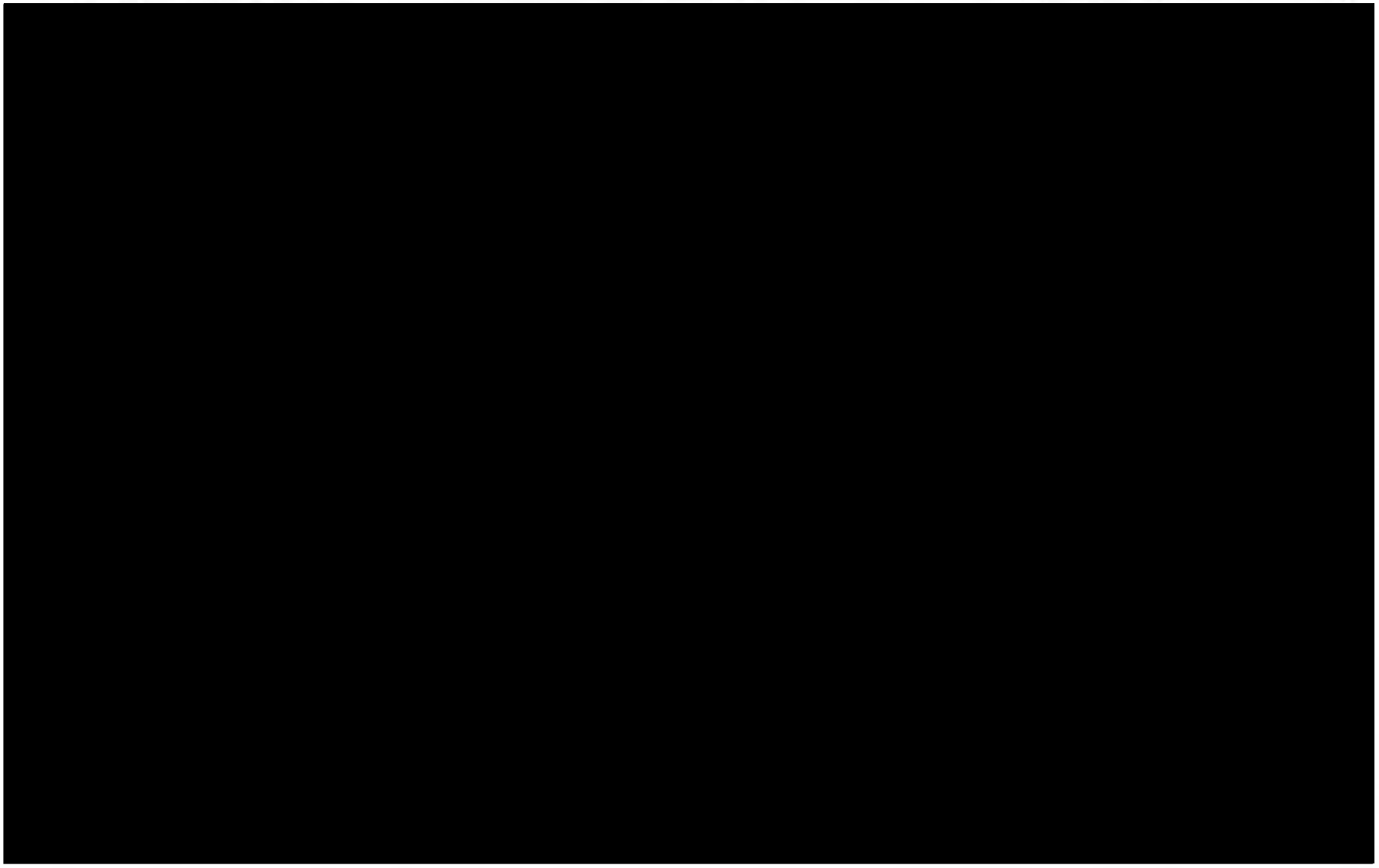

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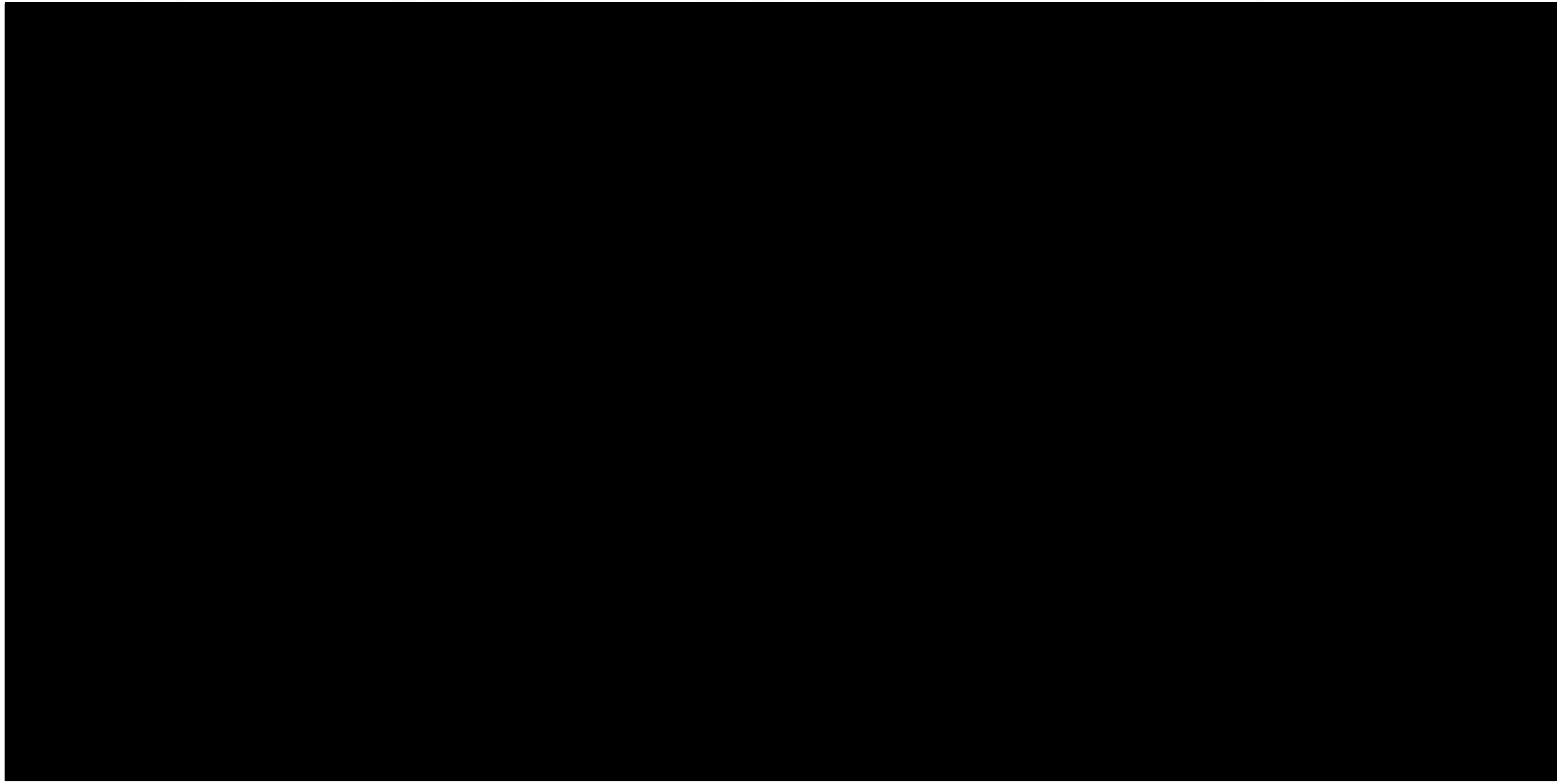

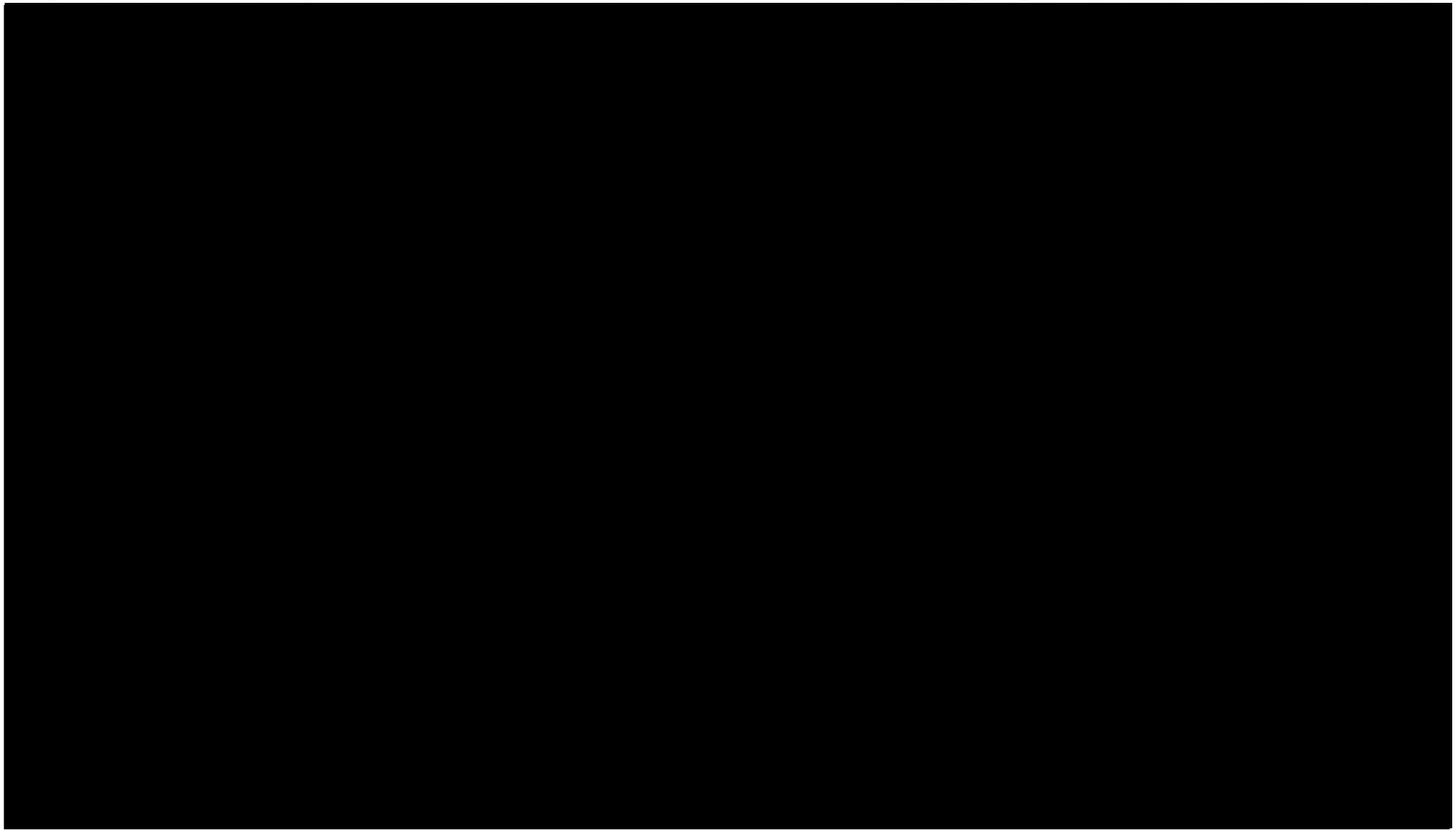

10. APPENDIX 2

10.1 Planned By-Subject Listings

DISPOSITION/WITHDRAWALS (LISTINGS 16.2.1.X)

ELIGIBILITY AND PROTOCOL DEVIATIONS (LISTINGS 16.2.2.X)

EXCLUDED SUBJECTS (LISTINGS 16.2.3.X)

DEMOGRAPHICS, POPULATION, AND BASELINE CHARACTERISTICS (LISTINGS 16.2.4.X)

DRUG COMPLIANCE (LISTINGS 16.2.5.X)

EFFICACY RESPONSE DATA (LISTINGS 16.2.6.X)

ADVERSE EVENT DATA (LISTINGS 16.2.7.X)

SAFETY DATA (LISTINGS 16.2.8.1.X)

OTHER SAFETY DATA (LISTINGS 16.2.8.2.X)

OTHER LISTINGS (LISTINGS 16.2.8.3.X)

10.2 Planned Summary Tables

POPULATION DISPOSITION AND PROTOCOL DEVIATIONS
POPULATION DEMOGRAPHICS AND BASELINE CHARACTERISTICS
CONCOMITANT MEDICATION USAGE
SAFETY SUMMARIES
- ADVERSE EVENT SUMMARIES
- SERIOUS ADVERSE EVENTS
- LABORATORY
- VITAL SIGNS AND PE
- OTHER SAFETY

EFFICACY SUMMARIES

11. REFERENCES

1. ASA. (2016) Ethical Guidelines for Statistical Practice. Prepared by the Committee on Professional Ethics, April, 2016.
2. The Royal Statistical Society: Code of Conduct (2014).
3. E8 General Considerations for Clinical Trials, ICH Guidance, Federal Register, 1997.
4. Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics (2010).
5. Guideline for Industry: Structure and Content of Clinical Study Reports (ICH E3), July 1996.
6. ICH Guidance on the Statistical Principles for Clinical Trials (ICH E9, 1998).