NCT02549196

Study ID: CPC-001-12

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

Protocol Amendment 3 Date: 22 July 2016

Investigational Product:	CPC-201 (donepezil plus solifenacin)
Indication:	Treatment of Dementia of Alzheimer Type
Clinical phase:	Phase II, Dose Titration Study
Study code:	CPC-001-12

Dose titration study

A PHASE II, DOSE TITRATION STUDY OF CPC-201 IN PATIENTS WITH DEMENTIA OF ALZHEIMER'S TYPE

Version 3, date: July 22, 2016

Sponsor: Chase Pharmaceuticals Corporation
1825 K Street, NW, Suite 510
Washington, DC 20006

GCP compliance
The study will be performed in compliance with Good Clinical Practices (GCP)
and in accordance with the Declaration of Helsinki

Signature page for the Sponsor

Investigational Product:	CPC-201 (Donepezil plus solifenacin)
Indication:	Treatment of Dementia of Alzheimer Type
Clinical Phase:	Phase II, Dose Titration Study
Study Code:	CPC-001-12
Protocol Version Date:	Version 3 (July 22, 2016)

Reviewed and approved by:

……..

[redacted]

Date: …….

Signature page for the Investigator

This Clinical Trial will be conducted in accordance with the study protocol, the International Conference on Harmonization (ICH), Good Clinical Practices (GCP), the ethical principles outlined in the current valid version of the Declaration of Helsinki and the European as well as other local regulations.

As the Investigator for the Trial, I have read this protocol dated July 22, 2016 and agree to follow this protocol in accordance with all the above-mentioned regulations.

……..

Date: ……....

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LIST OF ABBREVIATIONS

ACh .....Acetylcholine
AChEI .....Acetylcholinesterase Inhibitor
AD.....Alzheimer's disease
ADAS-cog.....Alzheimer's disease Assessment Scale-cognition
ADR.....Adverse Drug Reaction
AE .....Adverse Event
AV.....Atrioventricular
CFS..... ...Cerebrospinal Fluid
CNS.....Central Nervous System
CRF .....Case Report Form
CRO .....Contract Research Organization
C-SSRS. .....Columbia-Suicide Severity Rating Scale
DSM. .....Diagnostic and Statistical Manual of Mental Disorders
E2020. .....Donepezil
ECG.....Electrocardiogram
FDA.....Food and Drug Administration
FID .....First Intolerable Dose
GCP.....Good Clinical Practice
GI .....Gastrointestinal
HR. .....Heart Rate
ICD.....Implantable Cardiac Defibrillator
ICH.....International Conference On Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC .....Independent Ethics Committee
IRB .....Institutional Review Board
KG.....Kilogram
MAD……Maximum Allowed Dose
MEDDRA. .....Medical Dictionary for Regulatory Activities
MG. .....Milligram
ML.....Milliliter
MMSE.....Mini Mental Status Examination
MSEC.....Millisecond
MTD.....Maximum Tolerated Dose
NDA. .....New Drug Application
NG/ML.....Nanogram/Milliliter
NIA-ADA. .....National Institute on Aging – Alzheimer's Disease Association
OAB. .....Overactive Bladder Disorder
OTC.....Over-the-Counter
QTC.....Corrected QT interval
QTCF. .....Corrected QT intervals by Fridericia's formula
PR Interval. .....On ECG, time from onset of P wave to start of QRS Complex
QRS complex. .....On ECG, central part of tracing, Q,R and S waves

QT interval. .....On ECG, interval between start of Q wave and end of the T wave
SOC.....System Organ Class
SOP .....Standard Operating Procedures
SAE.....Serious Adverse Event
SEM. .....Standard Error of Mean
TEAE .....Treatment Emergent Adverse Event
UNL. .....Upper Normal Limit
US .....United States
WHO.....World Health Organization

LIST OF TABLES

PROTOCOL SUMMARY

Name of Sponsor/Company:
Chase Pharmaceuticals Corporation

Name of Investigational Product:
CPC-201: Donepezil plus solifenacin

Name of Active Ingredient:
Donepezil, solifenacin

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

Number of clinical centers:
Multicenter

Objectives:
Primary:

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

Secondary:

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

Methodology:
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.

In this study, 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) of 60mg/day (40 mg/day for Cohort 3c) 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 Cohorts 2 and 3 may be altered based on Cohort 1 result.

Per this amendment, 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
Cohort 2b	1st – 2nd week: 10mg donepezil + 15mg solifenacin 3rd week: 20mg donepezil + 15mg solifenacin 4th week: 40mg donepezil + 15mg solifenacin 5th week: 60mg donepezil + 15mg (or 20mg) solifenacin
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*: The dose titration schedule of Cohorts 2 and 3 may be altered based on Cohort 1 result.

Per this amendment, all patients not treated with an AchEI for at least 6 months (Group 2) will receive 15mg solifenacin and 10mg donepezil for 2 weeks before starting donepezil titration.

Each cohort will include approximately 6 patients donepezil-treated (Group 1) and approximately 6 patients not treated with an AchEI for at least 6 months (Group 2). Within each cohort, Group 2 patients will be enrolled only when at least 3 Group 1 patients have completed dose titration per protocol.

Patients will be enrolled in Cohort 2 only when patients enrolled in Cohort 1 have safely completed titration. Similary, patients will be enrolled in Cohort 3 only when patients enrolled in Cohort 2 have safely completed titration.

Cohorts 1 and 2 were completed prior to this amendment. This amendment is to change the dosing regimen of cohort 3. All subjects entering the study in cohort 3c 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

Patients reaching their FID or having completed one week treatment with donepezil 40mg/day, 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.

Number of patients planned:

To ensure a suitable number of subjects to evaluate the optimal dose titration schedule, approximately 6 patients per population group per cohort will be enrolled.

Diagnosis and main criteria for inclusion:

Males and females suffering from AD

Inclusion Criteria:

1) Signed an Institutional Review Board (IRB) approved informed consent document indicating that they understand the purpose of and procedures required by the study and are willing to participate in the study and comply with all study procedures and restrictions. Informed consent must be obtained from the patient and/or a designated representative prior to initiating screening procedures to evaluate eligibility for the study.
2) Aged 50 – 89 years inclusive.
3) Meeting the diagnosis of probable AD consistent with:
   - Revised National Institute on Aging-Alzheimer's Disease Association (NIA-ADA) criteria and
   - Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria.
4) Mild to severe severity (Mini-Mental Status Exam [MMSE] scores 7 – 24 inclusive).
5) Rosen-Modified Hachinski Ischemia Score of ≤4.
6) Have a suitable caregiver to supervise the at-home administration of study drugs and observe for AEs.
7) Patients will be required to have been treated with donepezil 5 or 10 mg/day (given once daily) for at least 4 weeks just prior to Day1 for Population (group) 1 or;

   Patients have never been treated with donepezil before (donepezil naïve) or who have not received any other AChEI for the past 6 months for Population (group) 2.
8) Patients must be in generally good health as indicated by their medical history and physical examination, vital signs, electrocardiogram (ECG), and standard laboratory tests.

Key exclusion criteria:

The criteria for exclusion of a subject from enrollment in the study are as follows:

1) Women of child bearing potential.
2) History or presence of a seizure disorder.
3) Current unstable peptic ulcer disease, urinary or gastric retention; asthma or obstructive pulmonary disease.
4) History or presence of bladder outflow obstruction, gastrointestinal obstructive disorder or reduced GI motility, or narrow-angle glaucoma.
5) History or presence of gastrointestinal, hepatic, or renal disease, or other condition known to interfere with the absorption, distribution, metabolism or excretion of drugs.
6) Renal and hepatic dysfunction with:
   - Total Bilirubin: >1.5 x UNL

- AST: >2.5 x UNL
- ALT: >2.5 x UNL
- Serum Creatinine: >1.5 x UNL
- Creatinine Clearance: <30 mL/min (calculated by Cockcroft and Gault equation)

7) History or presence of myasthenia.
8) History or family history of Prolonged QT Syndrome.
9) History of unexplained syncope or family history of unexplained syncope or sudden death.
10) Myocardial infarction or hospitalization for congestive heart failure within 6 months.
11) ECG findings of:
    - Complete Left Bundle Branch Block;
    - Ventricular pacing;
    - 2nd degree or 3rd degree AV block;
    - Atrial fibrillation or atrial flutter;
    - HR <45 or >100;
    - PR >220 msec; or
    - QTcF >450 msec in male, >470 msec in female
12) Known hypersensitivity to donepezil, solifenacin or related drugs.
13) History of drug significant allergy.
14) History of substance abuse, known drug addiction, or positive test for drugs of abuse or alcohol.
15) Patients treated with the following medications within 8 weeks of screening
    - Peripherally acting anticholinergics (such as drugs for the treatment of overactive bladder disorder),
    - Psychoactive medications (including antipsychotics, antidepressants, anxiolytics or sedative hypnotics) having significant anticholinergic effects and/or believed to affect cognitive function.

    Other medications are acceptable, at the investigators discretion, if dosage is held stable for at least 4 weeks prior to screening and throughout the study.
16) Patients considered unlikely to co-operate in the study, and/or poor compliance anticipated by the investigator.
17) Patients hospitalized within 4 weeks of screening.
18) Any other clinically relevant acute or chronic diseases which could interfere with patients' safety during the trial, or expose them to undue risk, or which could interfere with study objectives.
19) Patients who have participated in another clinical trial with an investigational drug within previous 30 days.

Investigational product (IP)

Donepezil (Aricept® or generic equivalent): 5 mg, 10 mg tablet
Solifenacin (Vesicare®): 5 mg, 10 mg tablets
Placebo (Similar in size to donepezil 10 mg or solifenacin 5 mg/10 mg tablets

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Duration of treatment:

Screening: 4 weeks

Dosing: up to 7 weeks

Reference therapy, dosage and mode of administration:

None

Statistical Analysis:

Since the objective of this study is to determine the optimal initial dose and subsequent dose titration schedule, the data will be analyzed only by means of descriptive statistics to reveal possible trends that will help guide the design of future, more definitive, clinical trials.

Sample size calculations:

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

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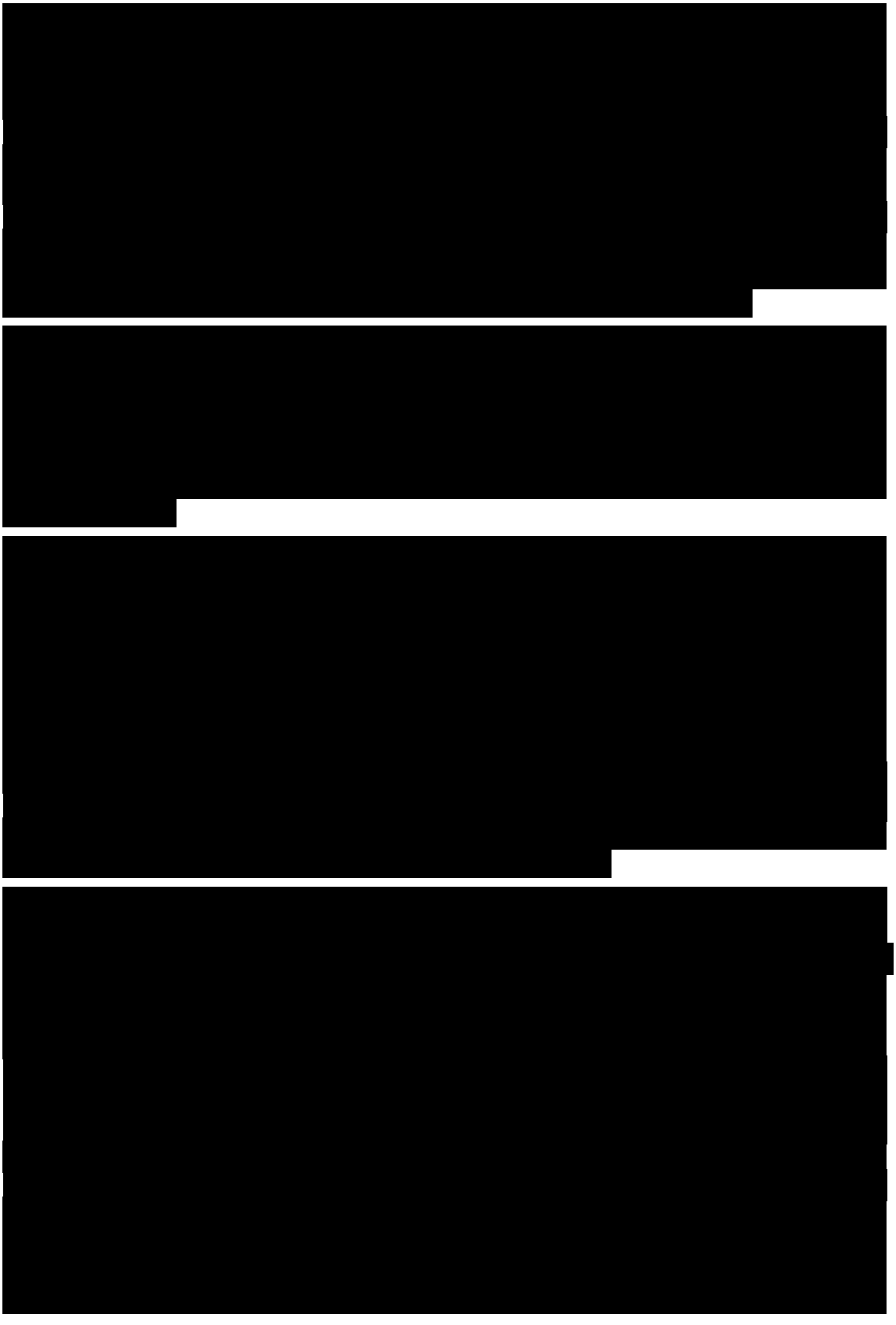

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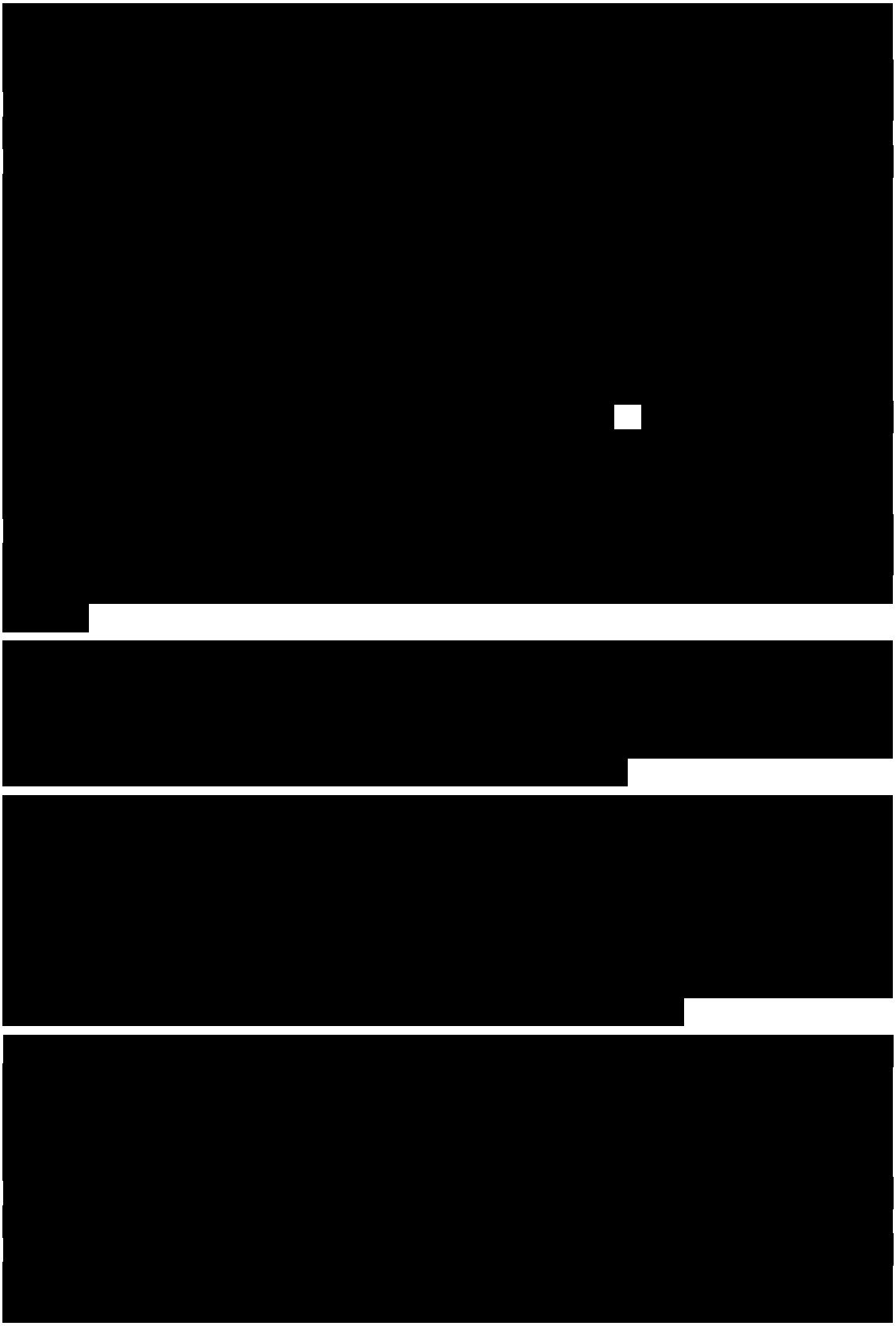

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2 OBJECTIVES

2.1 Primary objective

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

2.2 Secondary objective

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

3 INVESTIGATIONAL PLAN

3.1 Overall Study design

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.

In this study, 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 (40 mg/day for Cohort 3c) 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
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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.

Per this amendment, 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
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Each cohort will include approximately 6 patients donepezil-treated (Group 1) and approximately 6 patients not treated with an AchEI for at least 6 months (Group 2). Within each cohort, Group 2 patients will be enrolled only when at least 3 Group 1 patients have completed dose titration per protocol.

Patients will be enrolled in Cohort 2 only when patients enrolled in Cohort 1 have safely completed titration. Similary, patients will be enrolled in Cohort 3, only when patients enrolled in Cohort 2 have safely completed titration.

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Patients reaching their FID or having completed one week treatment with donepezil 60mg/day (40 mg/day for Cohort 3c), 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.

3.2 Dose Escalation and Stopping rules

For all patients, donepezil dose escalation will be discontinued if they manifest over a 24 hour period after study drug administration the following symptoms judged by the investigator as possibly or probably study-drug related:

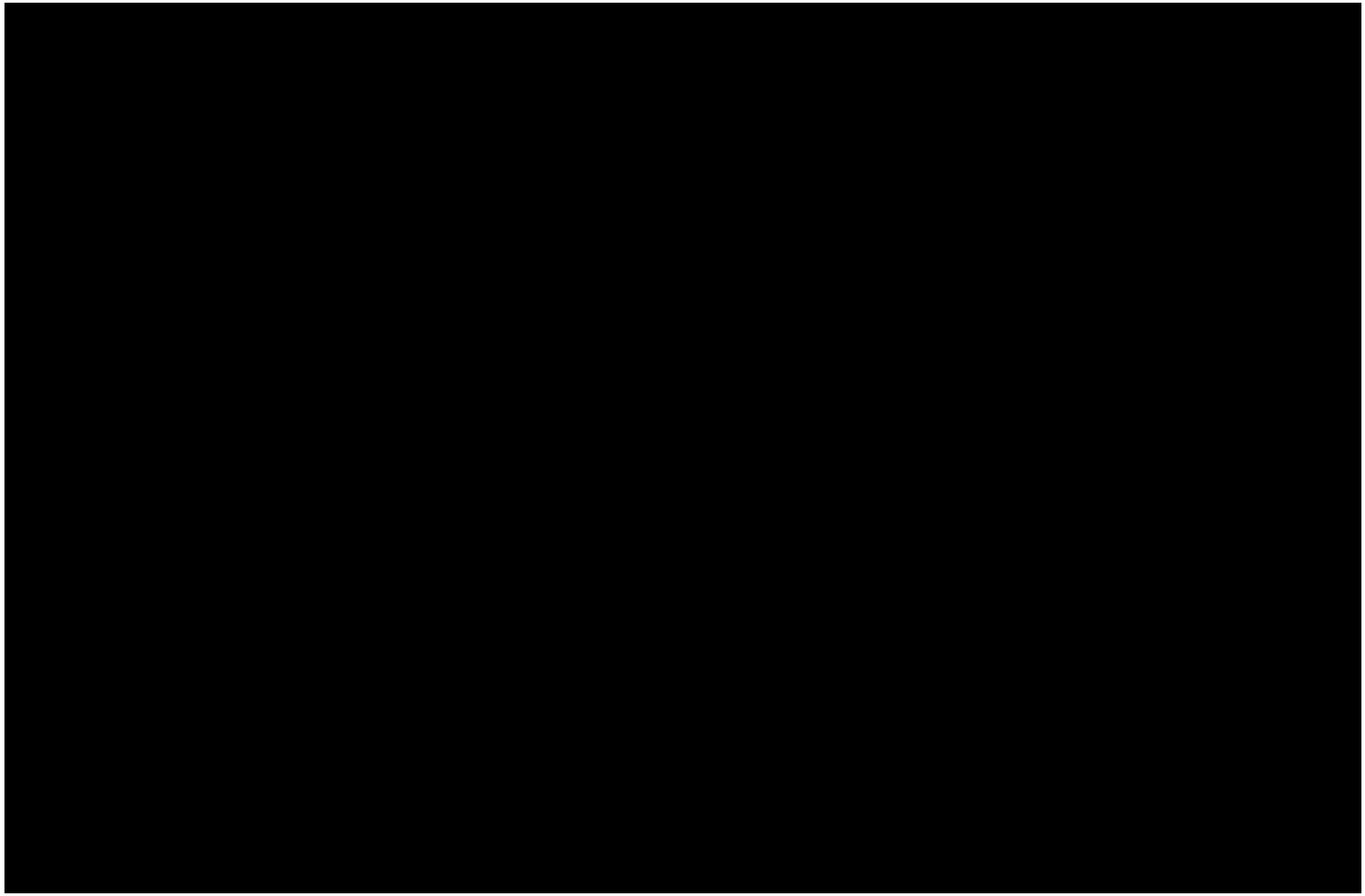
- One (1) episode of vomiting, or
- Two (2) episodes of severe retching (separated by more than one hour on the same day), or
- One (1) episode of severe nausea (Grade 3; defined as nausea interfering with activities of daily living or inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition or hospitalization indicated) and/or severe abdominal discomfort (Grade 3; defined as severely interfering with activities of daily living), or
- Three (3) episodes of moderate nausea (Grade 2; defined as subjectively symptomatic, but not interfering with activities of daily living) and/or moderate abdominal discomfort (Grade 2; defined as interfering with function, but not interfering with activities of daily living) each on the same day, or
- One (1) episode of moderate diarrhea (Grade 2; defined as 4 to 6 stools more than at baseline).
- Any other circumstance that merits an adjustment in study drug dosage in the opinion of the investigator

All those meeting one or more of the foregoing stopping rules will be withdrawn from dose titration and proceed in accordance with either of the two options given above.

3.3 Trial procedures

3.3.1 Schedule of Assessments

The schedule of assessments for the study is provided in Table 1, Table 2 and Table 3.



3.3.2 Study Procedure

For each visit, procedures and assessments are listed in the order in which they should be performed.

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3.5 Discontinuation criteria

3.5.1 Discontinuation of donepezil dose escalation in individual subjects

For all patients, donepezil dose escalation will be discontinued if they manifest over a 24 hour period after study drug administration the following symptoms judged by the investigator as possibly or probably study-drug related:

- One (1) episode of vomiting, or
- Two (2) episodes of severe retching (separated by more than one hour on the same day), or
- One (1) episode of severe nausea (Grade 3; defined as nausea interfering with activities of daily living or inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition or hospitalization indicated) and/or severe abdominal discomfort (Grade 3; defined as severely interfering with activities of daily living), or
- Three (3) episodes of moderate nausea (Grade 2; defined as subjectively symptomatic, but not interfering with activities of daily living) and/or moderate abdominal discomfort (Grade 2; defined as interfering with function, but not interfering with activities of daily living) each on the same day, or
- One (1) episode of moderate diarrhea (Grade 2; defined as 4 to 6 stools more than at baseline).
- Any other circumstance that merits an adjustment in study drug dosage in the opinion of the investigator

3.5.2 Discontinuation of individual subjects from the entire study

During the study, the investigator or the sponsor may decide to discontinue a subject's participation in the study in the following cases:

- A protocol violation occurs;
- A serious or intolerable (other than those listed in the discontinuation of rivastigmine escalation criteria) AE occurs;
- The Sponsor or Investigator terminates the study.
- The subject requests to be discontinued from the study.
- The subject is non-compliant to any part of the study.
- The Investigator feels it is not in the best interest of the subject to continue in the study.

4 SELECTION OF SUBJECTS

4.1 Inclusion criteria

The criteria for inclusion that each subject must meet to be enrolled in the study are as follows:

1. Signed an Institutional Review Board (IRB) approved informed consent document indicating that they understand the purpose of and procedures required by the study and are willing to participate in the study and comply with all study procedures and restrictions. Informed consent must be obtained from the patient and/or a designated representative prior to initiating screening procedures to evaluate eligibility of the study.
2. Aged 50 – 89 years inclusive.
3. Meeting the diagnosis of probable AD consistent with:
   - Revised National Institute on Aging-Alzheimer's Association (NIA-ADA) criteria and
   - Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria.
4. Of mild to severe severity (Mini-Mental Status Exam [MMSE] scores 7 – 24 inclusive).
5. Rosen-Modified Hachinski Ischemia Score of ≤4.
6. Have a suitable caregiver to supervise the at-home administration of study drugs and observe for AEs.
7. Patients will be required to have been treated with donepezil 5 or 10 mg/day (given once daily) for at least 4 weeks just prior to Day1 for Population (group) 1 or;
8. Patients have never been treated with donepezil before (donepezil naïve) or who have not received any other AChEI for the past 6 months for Population (group) 2.
9. Patients must be in generally good health as indicated by their medical history and physical examination, vital signs, electrocardiogram (ECG), and standard laboratory tests.

4.2 Exclusion criteria

The criteria for exclusion of a subject from enrollment in the study are as follows:

1. Women of child bearing potential.
2. History or presence of a seizure disorder.
3. Current unstable peptic ulcer disease, urinary or gastric retention; asthma or obstructive pulmonary disease.
4. History or presence of bladder outflow obstruction, gastrointestinal obstructive disorder or reduced GI motility, or narrow-angle glaucoma.
5. History or presence of gastrointestinal, hepatic, or renal disease, or other condition known to interfere with the absorption, distribution, metabolism or excretion of drugs.
6. Renal and hepatic dysfunction with:
   - Total Bilirubin: >1.5 x UNL
   - AST: >2.5 x UNL

- ALT: >2.5 x UNL
- Serum Creatinine: >1.5 x UNL
- Creatinine Clearance: <30 mL/min

7. History or presence of myasthenia.
8. History or family history of Prolonged QT Syndrome.
9. History of unexplained syncope or family history of unexplained syncope or sudden death.
10. Myocardial infarction or hospitalization for congestive heart failure within 6 months.
11. ECG findings of:
    - Complete Left Bundle Branch Block;
    - Ventricular pacing;
    - 2nd degree or 3rd degree AV block;
    - Atrial fibrillation or atrial flutter;
    - HR <45 or >100;
    - PR >220 msec; or
    - QTcF >450 msec in male, >470 msec in female
12. Known hypersensitivity to donepezil, solifenacin or related drugs.
13. History of drug significant allergy.
14. History of substance abuse, known drug addiction, or positive test for drugs of abuse or alcohol.
15. Patients treated with the following medications within 8 weeks of screening
    - AChEIs (other than donepezil),
    - Peripherally acting anticholinergics (such as drugs for the treatment of overactive bladder disorder),
    - Psychoactive medications (including antipsychotics, antidepressants, anxiolytics or sedative hypnotics) having significant anticholinergic effects and/or believed to affect cognitive function.

    Other medications are acceptable, at the investigators discretion, if dosage is held stable for at least 4 weeks prior to screening and throughout the study.
16. Patients considered unlikely to co-operate in the study, and/or poor compliance anticipated by the investigator.
17. Patients hospitalized within 4 weeks of screening.
18. Any other clinically relevant acute or chronic diseases which could interfere with patients' safety during the trial, or expose them to undue risk, or which could interfere with study objectives.
19. Patients who have participated in another clinical trial with an investigational drug within previous 30 days.

5 STUDY DRUG

5.1 Blinding

This is a single-blind study. The subject, caregiver, and site personnel who assess MMSE and ADAS-Cog are blinded. [redacted]

[redacted]

5.3 Description of Study Drug

[redacted]

[redacted]

Placebo tablet
Placebo tablet is similar in size to donepezil 10 mg or solifenacin 5 mg/10 mg tablets.

5.3.2 Study drug manufacturing and labeling

Donepezil and solifenacin will be purchased by [redacted] from a licensed supplier of these pharmaceuticals.

The placebo tablet will be manufactured, packaged in bottle, labeled by [redacted] Label will include the following information: protocol number, quantity of tablets, required storage conditions, lot number, name and address of the manufacturer and the following cautionary statement: New Drug – Limited by Federal law to investigational use.

5.3.3 Study drug storage, handling and disposal

At the site, all study drugs should be stored at room temperature [redacted] in a secure area accessible only to the designated qualified site personnel. All study drugs must be stored, inventoried and the inventories carefully and accurately documented according to applicable state, federal and local regulations, International Conference on Harmonisation (ICH) Guidelines, Good Clinical Practice (GCP) and study procedures.
The study drug is to be prescribed only by the Investigator or his/her named sub-investigator(s), and is to be used only in accordance with the protocol. The study drug must be distributed only to patients properly enrolled in the study.

The Investigator must keep an accurate accounting of the study drug received from the Sponsor, including the temperature of the storage area, the amount of study drug dispensed to patients, amount of study drug returned to the Investigator by the patients, and the amount returned to the Sponsor upon completion of the study. A detailed inventory must be completed for the study drug.

Unused study drug must be kept in a secure location for accountability and reconciliation by the study monitor. Investigator or designee must provide an explanation for any destroyed or missing study drug or study materials.

Unused study drug may be destroyed on site, per the site's standard operating procedures (SOPs), but only after the Sponsor has granted approval for drug destruction. The monitor must account for all study drugs in a formal reconciliation process prior to study drug destruction. All study drug destroyed on site must be documented. Documentation must be provided to the Sponsor and retained in the Investigator's study files. If a site is unable to destroy study drug appropriately, the site can return unused study drug to the Sponsor or designee upon request. The return of study drug or study drug materials must be documented.

5.4 Concomitant medication

5.4.1 Allowed Mediations

Dosage of allowed concomitant medication should be stabilized for at least 4 weeks prior to screening and should remain constant during the course of the study. Patients on concomitant memantine should be on a stable dose for at least 3 months. With the exception of medications listed in the exclusion criteria (Section 4.2) and in Section 5.4.2 below, concomitant medications will be allowed at the Investigator's discretion.

All concomitant medications and therapies (prescription and OTC) should be recorded in the CRF, with generic name (if known, otherwise brand name), indication, dose, route, frequency, and date(s) of administration. Any change in any of these parameters during the study should be documented.

5.4.2 Prohibited Mediations

Concomitant use of the following drugs is not allowed (such medications must have been discontinued at least 8 weeks prior to screening):

- peripherally acting anticholinergics (such as drugs for the treatment of overactive bladder disorder),
- psychoactive medications (including antipsychotics, antidepressants, anxiolytics or sedative hypnotics) having significant anticholinergic effects and/or believed to affect cognitive function

In addition, the following drugs are prohibited during the study:

- Strong CYP3A4 inhibitors
- Strong CYP3A4 inducers
- Strong CYP2D6 inhibitors

Patients who use prohibited medications during the study listed above may be discontinued from study drug. Medications prescribed after patients have discontinued the study drug will not be considered as prohibited medications.

Note: The discontinuation of a patient due to use of a prohibited medication is dependent upon the Sponsor's decision. The Investigator should contact the Sponsor prior to discontinuing a patient for disallowed medications.

6 ASSESSMENT OF PHARMACOKINETICS

6.1 PK Blood Sampling Schedule and Sample Analysis

The blood samplings will be performed at approximately 15 minutes before and 4 hours (± 15 min) after study drug administration at each visits.

[redacted]

[redacted]

[redacted]

7 SAFETY ASSESSMENTS

7.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical-investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. A TEAE is defined as any AE that occurs after administration of the first dose of study drug. An AE can therefore be an unfavorable and 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. The failure of the anticipated pharmaceutical action of an investigational drug does not constitute a related AE.

AE rating

The condition of the subjects will be closely monitored throughout the study. The investigator will collect the AEs reported spontaneously, observed, or elicited in response to a non-leading question (for example, "How have you been feeling since we last asked you?"). The investigator will record all AEs in the source records and the CRF.

- The intensity/severity of an AE will be rated as follows:

  Mild : Awareness of signs or symptoms, but no disruption of usual activity.
  Moderate : Event sufficient to affect usual activity (disturbing).
  Severe : Inability to work or perform usual activities (unacceptable).

- The causal relationship of an AE to the study drugs will be rated as follows:

  Not related : Temporal relationship of the onset of the event, relative to the administration of the product, is not reasonable or another cause can by itself explain the occurrence of the event
  Unlikely : Is general, this category can be considered applicable to those AEs

related which after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug

Related : AEs incontrovertibly related to the administration of the product.

Of the above definitions, AEs related to study drug are considered adverse reactions, while "unlikely" and "not related" do not represent a causal relationship.

- The action taken with the study drug for an AE will be rated as product withdrawn, not changed, not applicable. AEs requiring therapy will be treated with recognised standards of medical care to protect the health and the well-being of the subject.
- The outcome of an AE will be rated as recovered, recovering, not recovered, recovered with sequellae or fatal. The investigator will follow up any AE until it is resolved or until the medical condition of the subject is stable. All relevant follow-up information will be collected. For AEs that are ongoing at the last visit, the investigator will make thorough efforts to document the outcome.

7.2 Serious Adverse Events (SAE)

An SAE is any untoward medical occurrence that results in death, is life threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. In addition, important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

An AE is life-threatening if the subject is at immediate risk of death from the event as it occurs, i.e. it does not include a reaction that, if it had occurred in a more serious form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not have been considered life-threatening, even though drug-induced hepatitis can be fatal.

An AE is incapacitating or disabling if the experience resulted in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

7.3 Assessment of tolerability

The FID of each patient will be recorded.

7.4 Safety Laboratory Test

Blood samples will be collected as indicated in Table 1-4 for the following clinical laboratory tests:

Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelet count.

Serum chemistry: calcium, sodium, chloride, potassium, blood urea nitrogen, glucose, total bilirubin, alkaline phosphatase, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, creatinine, calculated creatinine clearance, uric acid, phosphorous, total protein, albumin, and globulin.

[redacted]

7.5 Urinalysis

Urine samples will be collected as indicated in Table 1-4 for the following tests: glucose, bilirubin, ketones, specific gravity, blood, pH, protein, urobilinogen, nitrites, and leukocytes and, if necessary, microscopic examination.

7.6 Vital signs and body weight

Vital signs, including blood pressure, heart rate, respiratory rate, and temperature, will be measured after the patient rests in the supine position for at least 5 minutes.

Body weight will be measured as indicated in Table 1-4.

7.7 12-Lead ECGs

A standard 12-lead ECG will be recorded as indicated in Table 1-4. The Investigator will evaluate the ECG results as normal, abnormal, not clinically significant, or abnormal, clinically significant.

If QTcF on an on treatment ECG is ≥500 msec then hold treatment and perform 3 repeat ECGs over 20-60 min; if the mean QTcF of the three ECGs is ≥500 msec, withhold treatment and perform a repeat ECG the following day; if the QTcF has returned to baseline, dosing may resume..

7.8 MMSE

MMSE will be assessed by blinded rater at visits indicated in Table 1-4.

7.9 ADAS-Cog

ADAS-Cog will be assessed by blinded rater at visits indicated in Table 1-4.

7.10 Modified C-SSRS

Modified C-SSRS will be assessed by a qualified and experienced clinician who does not perform psychometric at visits indicated in Table 1-4.

8 PROCEDURES FOR REPORTING TEAES AND SERIOUS ADVERSE EVENTS

8.1 Reporting TEAEs

All TEAEs, regardless of seriousness, severity or presumed relationship to study therapy, must be recorded using medical terminology in the source document and transcribed into the CRF. Whenever possible, the diagnosis should be given when signs and symptoms are due to a common etiology (e.g. cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection" instead of identifying and listing the individual signs and symptoms). The Investigator must record, in the source document and transcribe into the AE page of the CRF, his or her medical assessment of the severity of the event and the relationship of the AE to study drug.

All TEAEs must be followed until they have resolved or until a stable clinical endpoint is reached. All measures required for managing the TEAE and the ultimate outcome of the TEAE must be recorded in the source document and reported in the CRF.

8.2 Reporting Serious Adverse Events

When the Investigator or designee becomes aware that an SAE has occurred, the Sponsor representative must be notified by both telephone and fax, regardless of the relationship (or lack thereof) of the SAE to study drug within 24 hours of the event. All SAEs must be submitted to the Sponsor as a written report, as well as reported verbally. A follow-up report must be submitted to the Sponsor as requested when pertinent information becomes available and if additional information is requested.

The Investigator is responsible for ensuring that the IRB is informed of this information within appropriate IRB established timelines.

ANY SAE OR ADR, INCLUDING ANY OUTCOME OF DEATH DUE TO ANY CAUSE THAT OCCURS DURING THIS STUDY MUST BE REPORTED IMMEDIATELY TO THE SPONSOR REPRESENTATIVE.

This verbal and faxed report must be followed no later than 3 working days by a written report **signed by the Investigator**. The Sponsor is responsible for submitting the report to all applicable regulatory authorities.

9 STATISTICS

Since the objective of this study is to determine the optimal initial dose and subsequent dose titration schedule, the statistics are not applicable.

The data will be analyzed only by means of descriptive statistics to reveal possible trends that will help guide the design of future, more definitive, clinical trials.

9.1 Assessment of Safety and Tolerability and

Safety and tolerability parameters will be analyzed as a function of dose and dose titration schedule.

9.1.1 Assessment of MTD

Descriptive statistics will be presented for the MTD and the FID for each patient in each dose titration schedule.

9.1.2 Adverse Events

Data Listings will present the verbatim-reported event along with the preferred term and SOC, onset and stop dates, severity, relatedness, SAE status, action taken and outcome. For summaries by severity, the most severe event episode will be counted if a subject has more than one event within the same coded term. For summaries of treatment-associated events, the subject will be counted as "associated" for that term if a subject has more than one event within the same coded term or if one event is considered "not associated" and the other "associated".

Unless otherwise indicated, AE summary tables will be presented by study period, treatment group, SOC, and preferred term for each study period.

9.1.3 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 and treatment arm.

9.1.4 ECGs

The overall interpretation of the ECG results will be presented as normal, abnormal (not clinically significant) and abnormal (clinically significant) by time point and study period.

9.1.5 Vital Signs and weight

Descriptive statistics will be presented for each vital sign measurement recorded at each time point during each study period.

9.2 Pharmacokinetics

Blood concentration results of donepezil and solifenacin for each subject will be presented.

9.3 Patient Disposition

Disposition of all subjects will be summarized descriptively.

9.4 Demographics and Baseline Characteristics

Individual subject demographic and baseline characteristics data will be presented in subject data listings. Concomitant medications (all recorded medications) will be listed for enrolled subjects. The listing will be sorted by start date of medication within the standard sort order. The listing will include all collected information.

9.5 Protocol Deviations

All protocol deviations will be listed by subject number.

9.6 Compliance

Dosing information collected on the CRF will be listed for each subject. Compliance will be summarized by presenting the numbers and percentages of subjects receiving each dose of study drug.

10 ACCESS TO SOURCE DATA/DOCUMENTS

Checking of case report forms (CRF's) for completeness and clarity and cross-checking with source documents will be required to monitor the progress of the study. The Monitors are entitled to compare CRF entries with source data and to inform the investigator about errors and omissions. The monitor will request correction / clarification from the investigator using electronic data clarifications that should be answered and closed as quickly as possible. The Investigator will provide direct access to source data/documents for the Sponsor's designated representatives (monitors and auditors) as well as IRB/IEC members and regulatory inspections.

Regulatory authorities and/or the Sponsor's clinical quality assurance personnel may also carry out source data checks and/or on-site audit inspections. These will be carried out giving due consideration to data protection and medical confidentiality. The Investigator is to give the Sponsor whatever support is necessary.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Study Monitoring

The study will be initiated by the Sponsor during an on-site visit after all required study documents have been sent to the Sponsor and approved. A monitor will perform subsequent on-site monitoring visits as frequently as deemed necessary. At these visits, the monitor will compare the data entered onto the CRFs with the hospital or clinic records (source documents) and check for protocol compliance, including a review of records of informed consent, all subject visit dates, all AEs, all concomitant medications,

and key efficacy observations. In addition, drug accountability records will be reviewed and findings from this review will be discussed with the Investigator.

The Sponsor expects that during monitoring visits, the study coordinator, Investigator, CRFs and source documentation will be available and a suitable environment will be provided for review of study-related documents.

11.2 Audits and Inspections

Trial sites, facilities, laboratories and all data (including sources) and documentation must be available for GCP audit by the Sponsor or inspection by competent authorities. Any aspect of the trial may be subject to audit by the Sponsor and/or inspection by regulatory authorities or the IRB. Such audits/inspections may take place at the Sponsor's site(s) or at the trial site including laboratories, pharmacies etc. In case of audit, the monitor will announce this in advance to the Investigator (or representative) and be present at the particular trial site during the audit.

The site staff should assist in all aspects of audit/inspection.

11.3 Data Quality Assurance

The Sponsor and their designated Contract Research Organization (CRO) will implement a system of quality assurance, including all elements described in this protocol. Within this system the CRO SOPs will be implemented to ensure that the clinical trial is conducted in compliance with regulatory requirements and GCP. Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

12 ETHICS AND ADMINISTRATIVE ISSUES

12.1 Ethical conduct of the trial

This protocol was designed and will be conducted, recorded and reported in compliance with the principles of Good Clinical Practice (GCP) regulations and in accordance with the principles outlined in the Declaration of Helsinki. These requirements are stated in federal regulations as well as ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use, "E6 Guideline for Good Clinical Practice". The Sponsor representative will review these obligations with the Investigator prior to the initiation and throughout the course of the study. The Investigator or any of his or her staff should contact the Sponsor representative for any questions or issues regarding compliance with GCP/ICH guidelines.

This study will be conducted in compliance with IRB guidelines and in accordance with applicable regulations regarding clinical safety data management. In addition this study will adhere to all local regulatory requirements and requirements for data protection.
The Investigator should refer to 21 CFR Part 312, Subpart D, ICH Guidelines E6 for clarification of the Investigator's responsibilities for fulfillment of GCP Guidelines for Investigator's qualifications and agreements, adequate resources, medical care of study

subjects, communication with IRB, compliance with the protocol, responsibility for investigational products, randomization procedures, informed consent, records and reporting, premature termination or suspension of a study and final reports.

Before initiating the study, the Investigator/institution must have written and dated approval/favorable opinion from the IRB for the study protocol/amendment(s), written informed consent form, any consent form updates, subject recruitment procedures (e.g. advertisements), and any written information to be provided to subjects, and a statement from the IRB that they comply with GCP requirements. The IRB approval must identify the protocol version as well as the documents reviewed.

12.2 Institutional review board/independent ethics committee (IRB/IEC) and Regulatory Authority

All protocols and protocol amendments must be signed and dated by the Investigator and approved by the IRB prior to implementation. The Investigator must provide an annual report to the IRB on the progress of the study in compliance with 21 CFR Part 56 and the IRB's policies and procedures. The Investigator must provide notification to the IRB of the completion, termination or discontinuation the study. It is required that a yearly review of the protocol by the IRB be documented in a letter from the IRB.

12.3 Subject informed consent

Executed informed consent, and other locally required documents such as those related to Protected Health Information, are required. The consent form must be executed prior to performing any study-related activities that are not part of the subject's routine care. The consent form that is used must be approved by both the reviewing IRB and by the Sponsor representative.

12.4 Subject Data Protection

Each subject must provide written informed consent as well as any authorizations required by local law (e.g. authorizations related to Protected Health Information). The Investigator agrees not to use or disclose Protected Health Information other than as permitted or required by the subject authorization or as required by law.

12.5 Data Monitoring Committee

Not applicable.

12.6 Financial Disclosure

Study personnel on the Form FDA 1572 will complete a financial disclosure form at the beginning of the study. New study personnel added to Form FDA 1572 must also meet these requirements.

12.7 Investigator Obligations

The Investigator should refer to 21 CFR Part 312, Subpart D, ICH Guidelines E6 for clarification of the Investigator's responsibilities to fulfill GCP Guidelines for Investigator's qualifications and agreements, adequate resources, medical care of study

subjects, communication with IRB, compliance with the protocol, responsibility for investigational products, randomization procedures, informed consent, records and reporting, premature termination or suspension of a study and final reports.

The Investigator agrees when signing the protocol to adhere to the instructions and procedures described in it, and thereby, to adhere to the principles of GCP that it conforms to.

12.8 Changes to the Protocol

All protocols and protocol amendments must be signed and dated by the Investigator and approved by the IRB prior to implementation.

12.9 Confidentiality/Publication of the Study

All information supplied to the Investigator by a Sponsor representative and not previously published is considered confidential and remains the sole property of the Sponsor. The Investigator must agree to use this information only to accomplish this study, and must not use it for other purposes without the Sponsor's written consent.
The information developed in this study will be used by the Sponsor in connection with the continued development of this product and thus may be disclosed as required to other clinical Investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the Investigator is obligated to provide the Sponsor with all data obtained in the study.

No publication of any study data, results, other deliverables or records is permitted by the Investigator.

12.10 Discontinuation of entire study

The Sponsor reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance.

In particular cases, the study may be terminated at a single investigational site, if the Sponsor has relevant reasons, e.g., suspicion of a deceit or conduct of the study which is not in accordance to the guidelines for GCP.

If the Sponsor determines such action is needed, the Sponsor will discuss this with the Investigator (including the reasons for taking such action) at that time. When feasible, the Sponsor will provide advance notification to the Investigator of the impending action prior to it taking effect.

The Sponsor will promptly inform all other Investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the Ethics Committee promptly and provide the reason for the suspension or termination.

13 DATA HANDLING AND RECORD KEEPING

13.1 Inspection of Records

Local regulatory agencies may request access to all study records, including source documents, for inspection and copying, in keeping with U.S. regulations. The Investigator should immediately notify the Sponsor of any upcoming regulatory agency inspections. The Sponsor may also perform an audit of the data if deemed necessary.
The Investigator will be responsible for the accuracy of the data entered in the CRFs. The Investigator will permit designated Sponsor representatives and regulatory bodies to have direct access to the source documents to verify data represented in the CRFs.

13.2 Retention of Records

All source documents (e.g. informed consent forms, laboratory reports, progress notes, medical histories, physical and diagnostic findings, diagnosis and pharmacy records, and study drug dispensing/disposition records) that support data in the CRFs of each study subject must be retained in the files of the Investigator for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or at least two years have elapsed since the formal discontinuation of clinical development of the investigational drug. These documents should be retained for a longer period, however, if required by applicable regulatory requirements.

If the Investigator retires, relocates, or for any other reason withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Prior to transfer, the Sponsor representative must be notified in writing of the name and address of the new custodian.

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NCT02549196

Study ID: CPC-001-12

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

Protocol Amendment 2 Date: 04 Jan 2016

Investigational Product:	CPC-201 (donepezil plus solifenacin)
Indication:	Treatment of Dementia of Alzheimer Type
Clinical phase:	Phase II, Dose Titration Study
Study code:	CPC-001-12

Dose titration study

A PHASE II, DOSE TITRATION STUDY OF CPC-201 IN PATIENTS WITH DEMENTIA OF ALZHEIMER'S TYPE

Version 2, date: January 4, 2016

Sponsor: Chase Pharmaceuticals Corporation
1825 K Street, NW, Suite 520
Washington, DC 20006

GCP compliance
The study will be performed in compliance with Good Clinical Practices (GCP)
and in accordance with the Declaration of Helsinki

Signature page for the Sponsor

Investigational Product:	CPC-201 (Donepezil plus solifenacin)
Indication:	Treatment of Dementia of Alzheimer Type
Clinical Phase:	Phase II, Dose Titration Study
Study Code:	CPC-001-12
Protocol Version Date:	Version 2 (January 4, 2016)

Reviewed and approved by:

Signature page for the Investigator

This Clinical Trial will be conducted in accordance with the study protocol, the International Conference on Harmonization (ICH), Good Clinical Practices (GCP), the ethical principles outlined in the current valid version of the Declaration of Helsinki and the European as well as other local regulations.

As the Investigator for the Trial, I have read this protocol dated January 4, 2016 and agree to follow this protocol in accordance with all the above-mentioned regulations.

……..

Date: ……....

Table of contents

LIST OF ABBREVIATIONS

ACh .....Acetylcholine
AChEI .....Acetylcholinesterase Inhibitor
AD.....Alzheimer's disease
ADAS-cog.....Alzheimer's disease Assessment Scale-cognition
ADR.....Adverse Drug Reaction
AE .....Adverse Event
AV.....Atrioventricular
CFS..... ...Cerebrospinal Fluid
CNS.....Central Nervous System
CRF .....Case Report Form
CRO .....Contract Research Organization
C-SSRS. .....Columbia-Suicide Severity Rating Scale
DSM. .....Diagnostic and Statistical Manual of Mental Disorders
E2020. .....Donepezil
ECG.....Electrocardiogram
FDA.....Food and Drug Administration
FID .....First Intolerable Dose
GCP.....Good Clinical Practice
GI .....Gastrointestinal
HR. .....Heart Rate
ICD.....Implantable Cardiac Defibrillator
ICH.....International Conference On Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC .....Independent Ethics Committee
IRB.....Institutional Review Board
KG.....Kilogram
MAD……Maximum Allowed Dose
MEDDRA. .....Medical Dictionary for Regulatory Activities
MG. .....Milligram
ML.....Milliliter
MMSE.....Mini Mental Status Examination
MSEC.....Millisecond
MTD.....Maximum Tolerated Dose
NDA. .....New Drug Application
NG/ML.....Nanogram/Milliliter
NIA-ADA. .....National Institute on Aging – Alzheimer's Disease Association
OAB. .....Overactive Bladder Disorder
OTC.....Over-the-Counter
QTC.....Corrected QT interval
QTCF. .....Corrected QT intervals by Fridericia's formula
PR Interval. .....On ECG, time from onset of P wave to start of QRS Complex
QRS complex. .....On ECG, central part of tracing, Q,R and S waves

QT interval. .....On ECG, interval between start of Q wave and end of the T wave
SOC .....System Organ Class
SOP .....Standard Operating Procedures
SAE .....Serious Adverse Event
SEM. .....Standard Error of Mean
TEAE .....Treatment Emergent Adverse Event
UNL. .....Upper Normal Limit
US .....United States
WHO .....World Health Organization

LIST OF TABLES

PROTOCOL SUMMARY

Name of Sponsor/Company:
Chase Pharmaceuticals Corporation

Name of Investigational Product:
CPC-201: Donepezil plus solifenacin

Name of Active Ingredient:
Donepezil, solifenacin

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

Number of clinical centers:
Multicenter

Objectives:
Primary:

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

Secondary:

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

Methodology:
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.

In this study, 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) of 60mg/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 Cohorts 2 and 3 may be altered based on Cohort 1 result.

Per this amendment, 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
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*: The dose titration schedule of Cohorts 2 and 3 may be altered based on Cohort 1 result.

Per this amendment, all patients not treated with an AchEI for at least 6 months (Group 2) will receive 15mg solifenacin and 10mg donepezil for 2 weeks before starting donepezil titration.

Each cohort will include approximately 6 patients donepezil-treated (Group 1) and approximately 6 patients not treated with an AchEI for at least 6 months (Group 2). Within each cohort, Group 2 patients will be enrolled only when at least 3 Group 1 patients have completed dose titration per protocol.

Patients will be enrolled in Cohort 2 only when patients enrolled in Cohort 1 have safely completed titration. Similary, patients will be enrolled in Cohort 3 only when patients enrolled in Cohort 2 have safely completed titration.

Patients reaching their FID or having completed one week treatment with donepezil 60mg/day, 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.

Number of patients planned:

To ensure a suitable number of subjects to evaluate the optimal dose titration schedule, approximately 6 patients per population group per cohort will be enrolled.

Diagnosis and main criteria for inclusion:

Males and females suffering from AD

Inclusion Criteria:

1) Signed an Institutional Review Board (IRB) approved informed consent document indicating that they understand the purpose of and procedures required by the study and are willing to participate in the study and comply with all study procedures and restrictions. Informed consent must be obtained from the patient and/or a designated representative prior to initiating screening procedures to evaluate eligibility for the study.
2) Aged 50 – 89 years inclusive.
3) Meeting the diagnosis of probable AD consistent with:
   - Revised National Institute on Aging-Alzheimer's Disease Association (NIA-ADA) criteria and
   - Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria.
4) Mild to severe severity (Mini-Mental Status Exam [MMSE] scores 7 – 24 inclusive).
5) Rosen-Modified Hachinski Ischemia Score of ≤4.
6) Have a suitable caregiver to supervise the at-home administration of study drugs and observe for AEs.
7) Patients will be required to have been treated with donepezil 5 or 10 mg/day (given once daily) for at least 4 weeks just prior to Day1 for Population (group) 1 or;

   Patients have never been treated with donepezil before (donepezil naïve) or who have not received any other AChEI for the past 6 months for Population (group) 2.
8) Patients must be in generally good health as indicated by their medical history and physical examination, vital signs, electrocardiogram (ECG), and standard laboratory tests.

Key exclusion criteria:

The criteria for exclusion of a subject from enrollment in the study are as follows:

1) Women of child bearing potential.
2) History or presence of a seizure disorder.
3) Current unstable peptic ulcer disease, urinary or gastric retention; asthma or obstructive pulmonary disease.
4) History or presence of bladder outflow obstruction, gastrointestinal obstructive disorder or reduced GI motility, or narrow-angle glaucoma.
5) History or presence of gastrointestinal, hepatic, or renal disease, or other condition known to interfere with the absorption, distribution, metabolism or excretion of drugs.
6) Renal and hepatic dysfunction with:
   - Total Bilirubin: >1.5 x UNL
   - AST: >2.5 x UNL
   - ALT: >2.5 x UNL
   - Serum Creatinine: >1.5 x UNL
   - Creatinine Clearance: <30 mL/min (calculated by Cockcroft and Gault equation)
7) History or presence of myasthenia.
8) History or family history of Prolonged QT Syndrome.
9) History of unexplained syncope or family history of unexplained syncope or sudden death.
10) Myocardial infarction or hospitalization for congestive heart failure within 6 months.
11) ECG findings of:
   - Complete Left Bundle Branch Block;
   - Ventricular pacing;

- 2nd degree or 3rd degree AV block;
- Atrial fibrillation or atrial flutter;
- HR <45 or >100;
- PR >220 msec; or
- QTcF >450 msec in male, >470 msec in female

12) Known hypersensitivity to donepezil, solifenacin or related drugs.
13) History of drug significant allergy.
14) History of substance abuse, known drug addiction, or positive test for drugs of abuse or alcohol.
15) Patients treated with the following medications within 8 weeks of screening
    - Peripherally acting anticholinergics (such as drugs for the treatment of overactive bladder disorder),
    - Psychoactive medications (including antipsychotics, antidepressants, anxiolytics or sedative hypnotics) having significant anticholinergic effects and/or believed to affect cognitive function.

    Other medications are acceptable, at the investigators discretion, if dosage is held stable for at least 4 weeks prior to screening and throughout the study.
16) Patients considered unlikely to co-operate in the study, and/or poor compliance anticipated by the investigator.
17) Patients hospitalized within 4 weeks of screening.
18) Any other clinically relevant acute or chronic diseases which could interfere with patients' safety during the trial, or expose them to undue risk, or which could interfere with study objectives.
19) Patients who have participated in another clinical trial with an investigational drug within previous 30 days.

Investigational product (IP)

Donepezil (Aricept®): 10 mg tablet (or generic equivalent)
Solifenacin (Vesicare®): 5 mg, 10 mg tablets
Placebo (Similar in size to donepezil 10 mg or solifenacin 5 mg/10 mg tablets

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

Duration of treatment: Screening: 4 weeks Dosing: up to 7 weeks
Reference therapy, dosage and mode of administration: None
Statistical Analysis: Since the objective of this study is to determine the optimal initial dose and subsequent dose titration schedule, the data will be analyzed only by means of descriptive statistics to reveal possible trends that will help guide the design of future, more definitive, clinical trials.
Sample size calculations: No formal sample size calculation has been made. Based on experience from previous similar studies, a total 4-6 evaluable subjects per group per cohort is considered sufficient.

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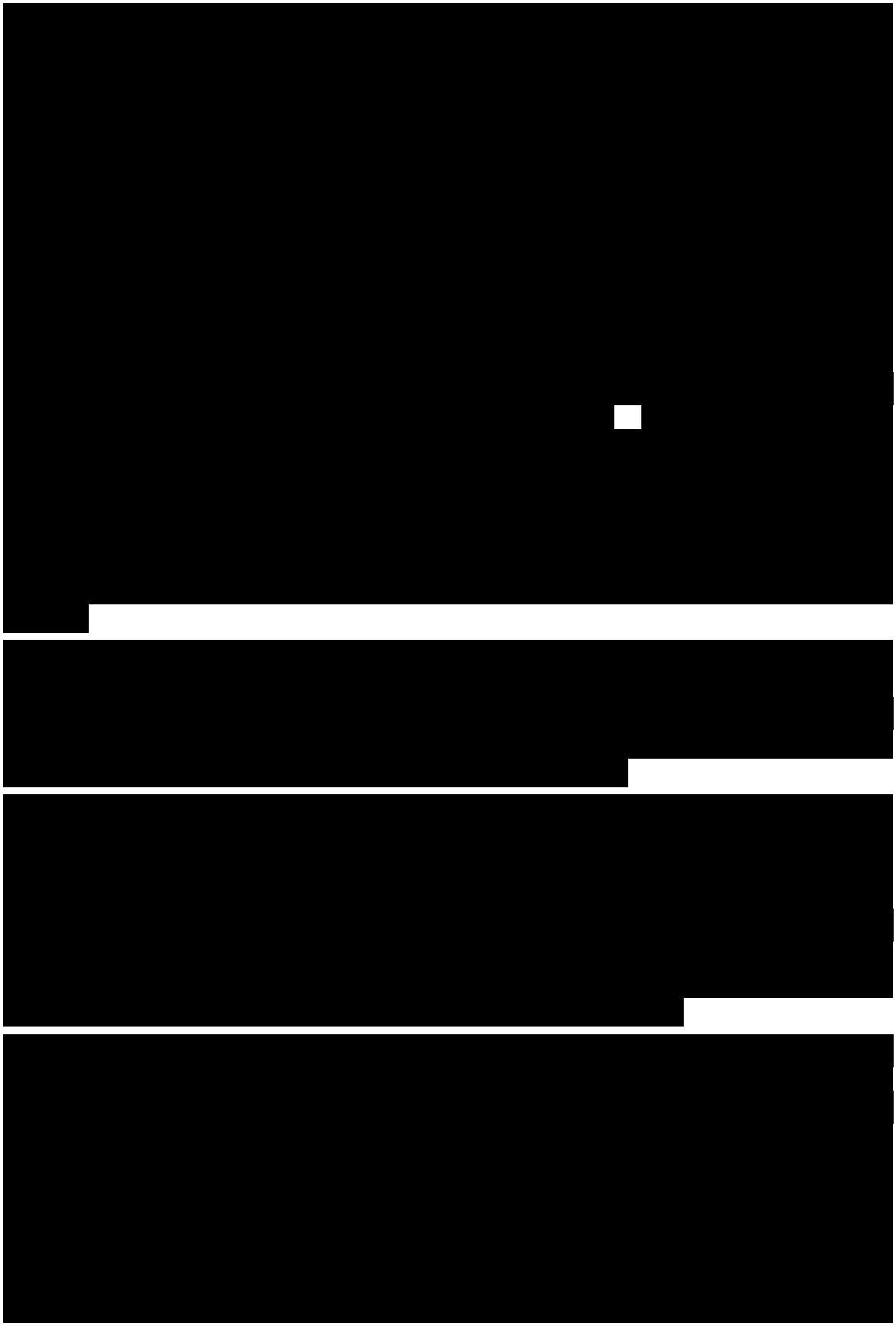

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2 OBJECTIVES

2.1 Primary objective

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

2.2 Secondary objective

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

3 INVESTIGATIONAL PLAN

3.1 Overall Study design

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.

In this study, 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.

Per this amendment, 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
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*: The dose titration schedule of Cohorts 2 and 3 may be altered based on Cohort 1 result.

Per this amendment, all patients not treated with an AchEI for at least 6 months (Group 2) will receive 15mg solifenacin for 2 weeks before starting donepezil.

Each cohort will include approximately 6 patients donepezil-treated (Group 1) and approximately 6 patients not treated with an AchEI for at least 6 months (Group 2). Within each cohort, Group 2 patients will be enrolled only when at least 3 Group 1 patients have completed dose titration per protocol.

Patients will be enrolled in Cohort 2 only when patients enrolled in Cohort 1 have safely completed titration. Similary, patients will be enrolled in Cohort 3, only when patients enrolled in Cohort 2 have safely completed titration.

Patients reaching their FID or having completed one week treatment with donepezil 60mg/day, 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 addtional 7 days with solifenacin 15 mg/day.

3.2 Dose Escalation and Stopping rules

For all patients, donepezil dose escalation will be discontinued if they manifest over a 24 hour period after study drug administration the following symptoms judged by the investigator as possibly or probably study-drug related:

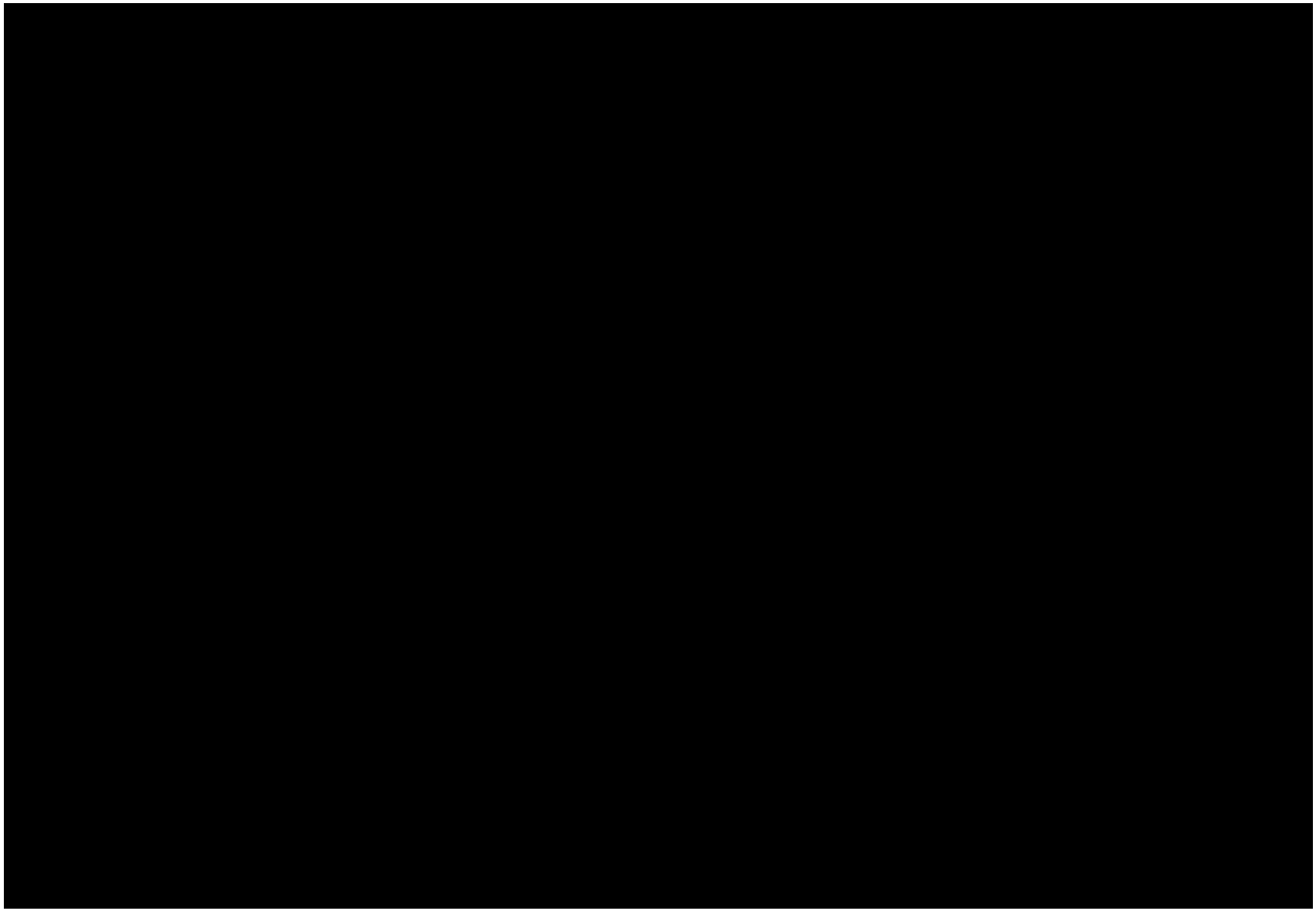
- One (1) episode of vomiting, or
- Two (2) episodes of severe retching (separated by more than one hour on the same day), or
- One (1) episode of severe nausea (Grade 3; defined as nausea interfering with activities of daily living or inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition or hospitalization indicated) and/or severe abdominal discomfort (Grade 3; defined as severely interfering with activities of daily living), or
- Three (3) episodes of moderate nausea (Grade 2; defined as subjectively symptomatic, but not interfering with activities of daily living) and/or moderate abdominal discomfort (Grade 2; defined as interfering with function, but not interfering with activities of daily living) each on the same day, or
- One (1) episode of moderate diarrhea (Grade 2; defined as 4 to 6 stools more than at baseline).
- Any other circumstance that merits an adjustment in study drug dosage in the opinion of the investigator

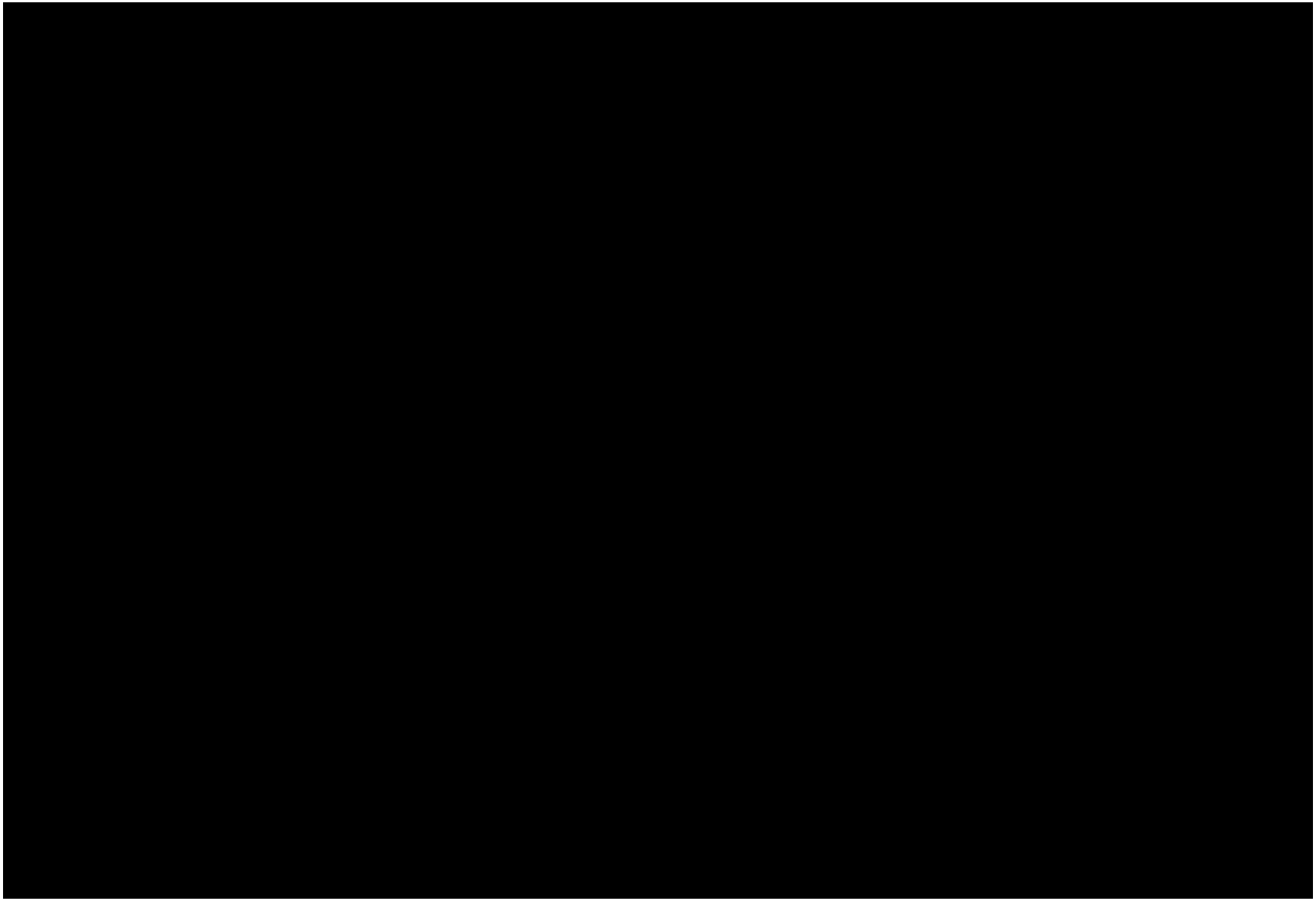
All those meeting one or more of the foregoing stopping rules will be withdrawn from dose titration and proceed in accordance with either of the two options given above.

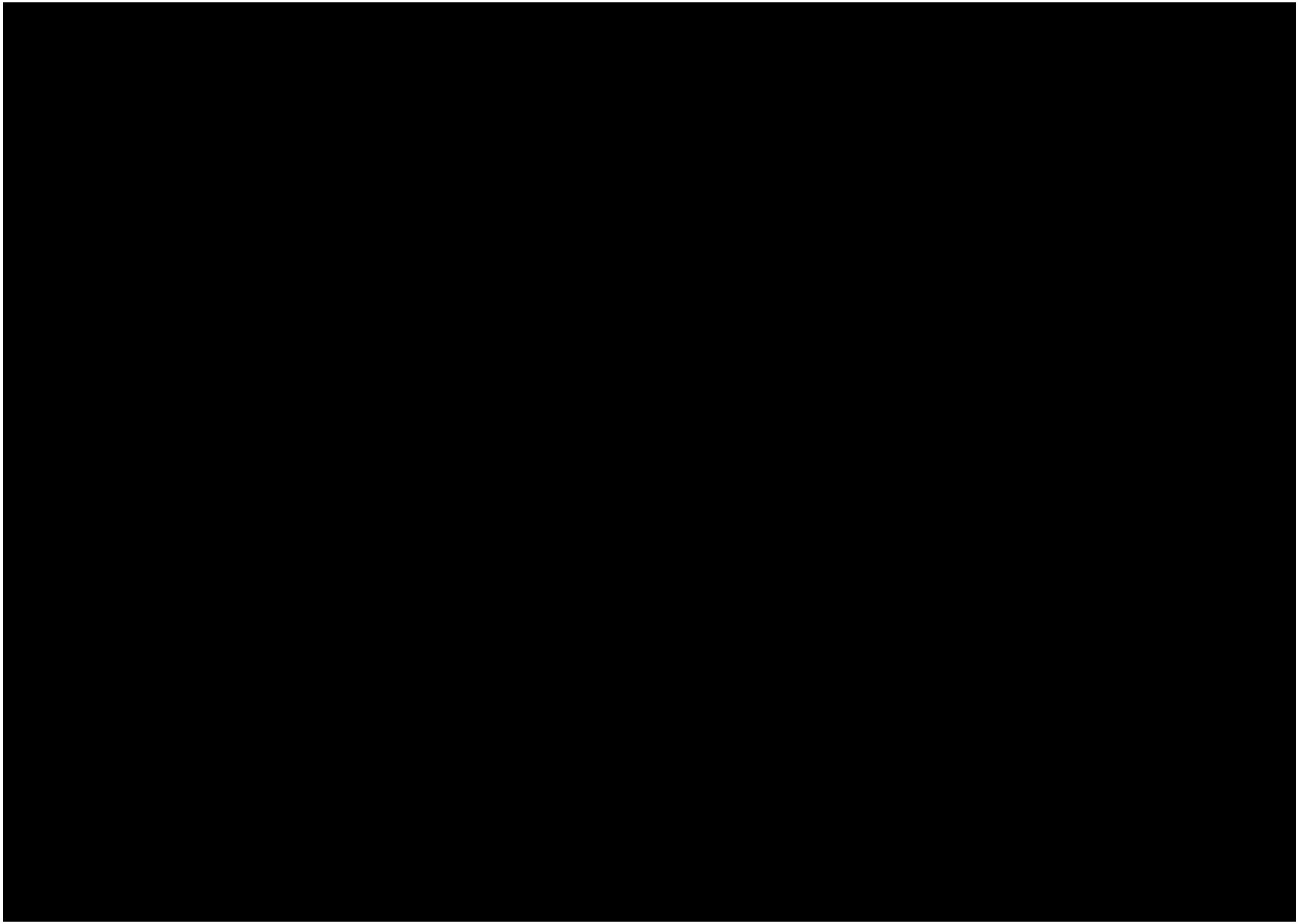
3.3 Trial procedures

3.3.1 Schedule of Assessments

The schedule of assessments for the study is provided in Table 1, Table 2 and Table 3.







3.3.2 Study Procedure

For each visit, procedures and assessments are listed in the order in which they should be performed.

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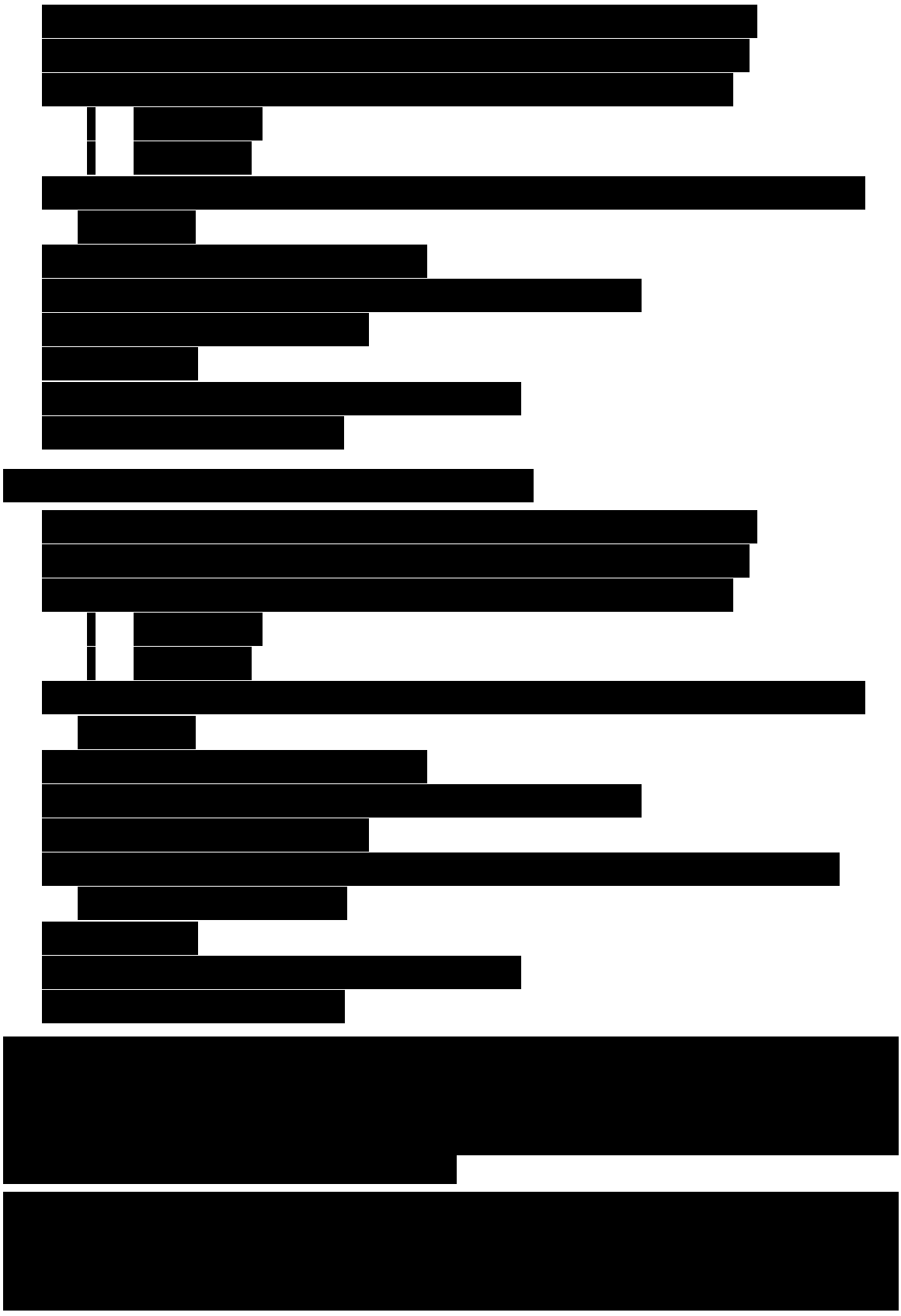

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3.5 Discontinuation criteria

3.5.1 Discontinuation of donepezil dose escalation in individual subjects

For all patients, donepezil dose escalation will be discontinued if they manifest over a 24 hour period after study drug administration the following symptoms judged by the investigator as possibly or probably study-drug related:

- One (1) episode of vomiting, or
- Two (2) episodes of severe retching (separated by more than one hour on the same day), or
- One (1) episode of severe nausea (Grade 3; defined as nausea interfering with activities of daily living or inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition or hospitalization indicated) and/or severe abdominal discomfort (Grade 3; defined as severely interfering with activities of daily living), or
- Three (3) episodes of moderate nausea (Grade 2; defined as subjectively symptomatic, but not interfering with activities of daily living) and/or moderate abdominal discomfort (Grade 2; defined as interfering with function, but not interfering with activities of daily living) each on the same day, or
- One (1) episode of moderate diarrhea (Grade 2; defined as 4 to 6 stools more than at baseline).
- Any other circumstance that merits an adjustment in study drug dosage in the opinion of the investigator

3.5.2 Discontinuation of individual subjects from the entire study

During the study, the investigator or the sponsor may decide to discontinue a subject's participation in the study in the following cases:

- A protocol violation occurs;
- A serious or intolerable (other than those listed in the discontinuation of rivastigmine escalation criteria) AE occurs;
- The Sponsor or Investigator terminates the study.
- The subject requests to be discontinued from the study.
- The subject is non-compliant to any part of the study.
- The Investigator feels it is not in the best interest of the subject to continue in the study.

4 SELECTION OF SUBJECTS

4.1 Inclusion criteria

The criteria for inclusion that each subject must meet to be enrolled in the study are as follows:

1. Signed an Institutional Review Board (IRB) approved informed consent document indicating that they understand the purpose of and procedures required by the study and are willing to participate in the study and comply with all study procedures and restrictions. Informed consent must be obtained from the patient and/or a designated representative prior to initiating screening procedures to evaluate eligibility of the study.
2. Aged 50 – 89 years inclusive.
3. Meeting the diagnosis of probable AD consistent with:
   - Revised National Institute on Aging-Alzheimer's Association (NIA-ADA) criteria and
   - Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria.
4. Of mild to severe severity (Mini-Mental Status Exam [MMSE] scores 7 – 24 inclusive).
5. Rosen-Modified Hachinski Ischemia Score of ≤4.
6. Have a suitable caregiver to supervise the at-home administration of study drugs and observe for AEs.
7. Patients will be required to have been treated with donepezil 5 or 10 mg/day (given once daily) for at least 4 weeks just prior to Day1 for Population (group) 1 or;
8. Patients have never been treated with donepezil before (donepezil naïve) or who have not received any other AChEI for the past 6 months for Population (group) 2.
9. Patients must be in generally good health as indicated by their medical history and physical examination, vital signs, electrocardiogram (ECG), and standard laboratory tests.

4.2 Exclusion criteria

The criteria for exclusion of a subject from enrollment in the study are as follows:

1. Women of child bearing potential.
2. History or presence of a seizure disorder.
3. Current unstable peptic ulcer disease, urinary or gastric retention; asthma or obstructive pulmonary disease.
4. History or presence of bladder outflow obstruction, gastrointestinal obstructive disorder or reduced GI motility, or narrow-angle glaucoma.
5. History or presence of gastrointestinal, hepatic, or renal disease, or other condition known to interfere with the absorption, distribution, metabolism or excretion of drugs.
6. Renal and hepatic dysfunction with:
   - Total Bilirubin: >1.5 x UNL

- AST: >2.5 x UNL
- ALT: >2.5 x UNL
- Serum Creatinine: >1.5 x UNL
- Creatinine Clearance: <30 mL/min

7. History or presence of myasthenia.
8. History or family history of Prolonged QT Syndrome.
9. History of unexplained syncope or family history of unexplained syncope or sudden death.
10. Myocardial infarction or hospitalization for congestive heart failure within 6 months.
11. ECG findings of:
    - Complete Left Bundle Branch Block;
    - Ventricular pacing;
    - 2nd degree or 3rd degree AV block;
    - Atrial fibrillation or atrial flutter;
    - HR <45 or >100;
    - PR >220 msec; or
    - QTcF >450 msec in male, >470 msec in female
12. Known hypersensitivity to donepezil, solifenacin or related drugs.
13. History of drug significant allergy.
14. History of substance abuse, known drug addiction, or positive test for drugs of abuse or alcohol.
15. Patients treated with the following medications within 8 weeks of screening
    - AChEIs (other than donepezil),
    - Peripherally acting anticholinergics (such as drugs for the treatment of overactive bladder disorder),
    - Psychoactive medications (including antipsychotics, antidepressants, anxiolytics or sedative hypnotics) having significant anticholinergic effects and/or believed to affect cognitive function.

    Other medications are acceptable, at the investigators discretion, if dosage is held stable for at least 4 weeks prior to screening and throughout the study.
16. Patients considered unlikely to co-operate in the study, and/or poor compliance anticipated by the investigator.
17. Patients hospitalized within 4 weeks of screening.
18. Any other clinically relevant acute or chronic diseases which could interfere with patients' safety during the trial, or expose them to undue risk, or which could interfere with study objectives.

19. Patients who have participated in another clinical trial with an investigational drug within previous 30 days.

5 STUDY DRUG

5.1 Blinding

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

5.3 Description of Study Drug

Placebo tablet
Placebo tablet is similar in size to donepezil 10 mg or solifenacin 5 mg/10 mg tablets.

5.3.2 Study drug manufacturing and labeling

Donepezil and solifenacin will be purchased by [redacted] from a licensed supplier of these pharmaceuticals.

The placebo tablet will be manufactured, packaged in bottle, labeled by [redacted]. Label will include the following information: protocol number, quantity of tablets, required storage conditions, lot number, name and address of the manufacturer and the following cautionary statement: New Drug – Limited by Federal law to investigational use.

5.3.3 Study drug storage, handling and disposal

At the site, all study drugs should be stored at room temperature [redacted] in a secure area accessible only to the designated qualified site personnel. All study drugs must be stored, inventoried and the inventories carefully and accurately documented according to applicable state, federal and local regulations, International Conference on Harmonisation (ICH) Guidelines, Good Clinical Practice (GCP) and study procedures.
The study drug is to be prescribed only by the Investigator or his/her named sub-investigator(s), and is to be used only in accordance with the protocol. The study drug must be distributed only to patients properly enrolled in the study.

The Investigator must keep an accurate accounting of the study drug received from the Sponsor, including the temperature of the storage area, the amount of study drug dispensed to patients, amount of study drug returned to the Investigator by the patients, and the amount returned to the Sponsor upon completion of the study. A detailed inventory must be completed for the study drug.

Unused study drug must be kept in a secure location for accountability and reconciliation by the study monitor. Investigator or designee must provide an explanation for any destroyed or missing study drug or study materials.

Unused study drug may be destroyed on site, per the site's standard operating procedures (SOPs), but only after the Sponsor has granted approval for drug destruction. The monitor must account for all study drugs in a formal reconciliation process prior to study drug destruction. All study drug destroyed on site must be documented. Documentation must be provided to the Sponsor and retained in the Investigator's study files. If a site is unable to destroy study drug appropriately, the site can return unused study drug to the Sponsor or designee upon request. The return of study drug or study drug materials must be documented.

5.4 Concomitant medication

5.4.1 Allowed Mediations

Dosage of allowed concomitant medication should be stabilized for at least 4 weeks prior to screening and should remain constant during the course of the study. Patients on concomitant memantine should be on a stable dose for at least 3 months. With the exception of medications listed in the exclusion criteria (Section 4.2) and in Section 5.4.2 below, concomitant medications will be allowed at the Investigator's discretion.

All concomitant medications and therapies (prescription and OTC) should be recorded in the CRF, with generic name (if known, otherwise brand name), indication, dose, route, frequency, and date(s) of administration. Any change in any of these parameters during the study should be documented.

5.4.2 Prohibited Mediations

Concomitant use of the following drugs is not allowed (such medications must have been discontinued at least 8 weeks prior to screening):

- peripherally acting anticholinergics (such as drugs for the treatment of overactive bladder disorder),
- psychoactive medications (including antipsychotics, antidepressants, anxiolytics or sedative hypnotics) having significant anticholinergic effects and/or believed to affect cognitive function

In addition, the following drugs are prohibited during the study:

- Strong CYP3A4 inhibitors
- Strong CYP3A4 inducers
- Strong CYP2D6 inhibitors

Patients who use prohibited medications during the study listed above may be discontinued from study drug. Medications prescribed after patients have discontinued the study drug will not be considered as prohibited medications.

Note: The discontinuation of a patient due to use of a prohibited medication is dependent upon the Sponsor's decision. The Investigator should contact the Sponsor prior to discontinuing a patient for disallowed medications.

6 ASSESSMENT OF PHARMACOKINETICS

6.1 PK Blood Sampling Schedule and Sample Analysis

The blood samplings will be performed at approximately 15 minutes before and 4 hours (± 15 min) after study drug administration at each visits.

[redacted]

7 SAFETY ASSESSMENTS

7.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical-investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. A TEAE is defined as any AE that occurs after administration of the first dose of study drug. An AE can therefore be an unfavorable and 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. The failure of the anticipated pharmaceutical action of an investigational drug does not constitute a related AE.

AE rating

The condition of the subjects will be closely monitored throughout the study. The investigator will collect the AEs reported spontaneously, observed, or elicited in response to a non-leading question (for example, "How have you been feeling since we last asked you?"). The investigator will record all AEs in the source records and the CRF.

- The intensity/severity of an AE will be rated as follows:

  Mild : Awareness of signs or symptoms, but no disruption of usual activity.
  Moderate : Event sufficient to affect usual activity (disturbing).
  Severe : Inability to work or perform usual activities (unacceptable).

- The causal relationship of an AE to the study drugs will be rated as follows:

  Not related : Temporal relationship of the onset of the event, relative to the administration of the product, is not reasonable or another cause can by itself explain the occurrence of the event
  Unlikely : Is general, this category can be considered applicable to those AEs

related	which after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug
Related	: AEs incontrovertibly related to the administration of the product.

Of the above definitions, AEs related to study drug are considered adverse reactions, while "unlikely" and "not related" do not represent a causal relationship.

- The action taken with the study drug for an AE will be rated as product withdrawn, not changed, not applicable. AEs requiring therapy will be treated with recognised standards of medical care to protect the health and the well-being of the subject.
- The outcome of an AE will be rated as recovered, recovering, not recovered, recovered with sequellae or fatal. The investigator will follow up any AE until it is resolved or until the medical condition of the subject is stable. All relevant follow-up information will be collected. For AEs that are ongoing at the last visit, the investigator will make thorough efforts to document the outcome.

7.2 Serious Adverse Events (SAE)

An SAE is any untoward medical occurrence that results in death, is life threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. In addition, important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

An AE is life-threatening if the subject is at immediate risk of death from the event as it occurs, i.e. it does not include a reaction that, if it had occurred in a more serious form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not have been considered life-threatening, even though drug-induced hepatitis can be fatal.

An AE is incapacitating or disabling if the experience resulted in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

7.3 Assessment of tolerability

The FID of each patient will be recorded.

7.4 Safety Laboratory Test

Blood samples will be collected as indicated in Table 1-4 for the following clinical laboratory tests:

Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelet count.

Serum chemistry: calcium, sodium, chloride, potassium, blood urea nitrogen, glucose, total bilirubin, alkaline phosphatase, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, creatinine, calculated creatinine clearance, uric acid, phosphorous, total protein, albumin, and globulin.

7.5 Urinalysis

Urine samples will be collected as indicated in Table 1-4 for the following tests: glucose, bilirubin, ketones, specific gravity, blood, pH, protein, urobilinogen, nitrites, and leukocytes and, if necessary, microscopic examination.

7.6 Vital signs and body weight

Vital signs, including blood pressure, heart rate, respiratory rate, and temperature, will be measured after the patient rests in the supine position for at least 5 minutes.

Body weight will be measured as indicated in Table 1-4.

7.7 12-Lead ECGs

A standard 12-lead ECG will be recorded as indicated in Table 1-4. The Investigator will evaluate the ECG results as normal, abnormal, not clinically significant, or abnormal, clinically significant.

If QTcF on an on treatment ECG is ≥500 msec then hold treatment and perform 3 repeat ECGs over 20-60 min; if the mean QTcF of the three ECGs is ≥500 msec, withhold treatment and perform a repeat ECG the following day; if the QTcF has returned to baseline, dosing may resume..

7.8 MMSE

MMSE will be assessed by blinded rater at visits indicated in Table 1-4.

7.9 ADAS-Cog

ADAS-Cog will be assessed by blinded rater at visits indicated in Table 1-4.

7.10 Modified C-SSRS

Modified C-SSRS will be assessed by a qualified and experienced clinician who does not perform psychometric at visits indicated in Table 1-4.

8 PROCEDURES FOR REPORTING TEAES AND SERIOUS ADVERSE EVENTS

8.1 Reporting TEAEs

All TEAEs, regardless of seriousness, severity or presumed relationship to study therapy, must be recorded using medical terminology in the source document and transcribed into the CRF. Whenever possible, the diagnosis should be given when signs and symptoms are due to a common etiology (e.g. cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection" instead of identifying and listing the individual signs and symptoms). The Investigator must record, in the source document and transcribe into the AE page of the CRF, his or her medical assessment of the severity of the event and the relationship of the AE to study drug.

All TEAEs must be followed until they have resolved or until a stable clinical endpoint is reached. All measures required for managing the TEAE and the ultimate outcome of the TEAE must be recorded in the source document and reported in the CRF.

8.2 Reporting Serious Adverse Events

When the Investigator or designee becomes aware that an SAE has occurred, the Sponsor representative must be notified by both telephone and fax, regardless of the relationship (or lack thereof) of the SAE to study drug within 24 hours of the event. All SAEs must be submitted to the Sponsor as a written report, as well as reported verbally. A follow-up report must be submitted to the Sponsor as requested when pertinent information becomes available and if additional information is requested.

The Investigator is responsible for ensuring that the IRB is informed of this information within appropriate IRB established timelines.

ANY SAE OR ADR, INCLUDING ANY OUTCOME OF DEATH DUE TO ANY CAUSE THAT OCCURS DURING THIS STUDY MUST BE REPORTED IMMEDIATELY TO THE SPONSOR REPRESENTATIVE.

This verbal and faxed report must be followed no later than 3 working days by a written report **signed by the Investigator**. The Sponsor is responsible for submitting the report to all applicable regulatory authorities.

9 STATISTICS

Since the objective of this study is to determine the optimal initial dose and subsequent dose titration schedule, the statistics are not applicable.

The data will be analyzed only by means of descriptive statistics to reveal possible trends that will help guide the design of future, more definitive, clinical trials.

9.1 Assessment of Safety and Tolerability and

Safety and tolerability parameters will be analyzed as a function of dose and dose titration schedule.

9.1.1 Assessment of MTD

Descriptive statistics will be presented for the MTD and the FID for each patient in each dose titration schedule.

9.1.2 Adverse Events

Data Listings will present the verbatim-reported event along with the preferred term and SOC, onset and stop dates, severity, relatedness, SAE status, action taken and outcome. For summaries by severity, the most severe event episode will be counted if a subject has more than one event within the same coded term. For summaries of treatment-associated events, the subject will be counted as "associated" for that term if a subject has more than one event within the same coded term or if one event is considered "not associated" and the other "associated".

Unless otherwise indicated, AE summary tables will be presented by study period, treatment group, SOC, and preferred term for each study period.

9.1.3 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 and treatment arm.

9.1.4 ECGs

The overall interpretation of the ECG results will be presented as normal, abnormal (not clinically significant) and abnormal (clinically significant) by time point and study period.

9.1.5 Vital Signs and weight

Descriptive statistics will be presented for each vital sign measurement recorded at each time point during each study period.

9.2 Pharmacokinetics

Blood concentration results of donepezil and solifenacin for each subject will be presented.

9.3 Patient Disposition

Disposition of all subjects will be summarized descriptively.

9.4 Demographics and Baseline Characteristics

Individual subject demographic and baseline characteristics data will be presented in subject data listings. Concomitant medications (all recorded medications) will be listed for enrolled subjects. The listing will be sorted by start date of medication within the standard sort order. The listing will include all collected information.

9.5 Protocol Deviations

All protocol deviations will be listed by subject number.

9.6 Compliance

Dosing information collected on the CRF will be listed for each subject. Compliance will be summarized by presenting the numbers and percentages of subjects receiving each dose of study drug.

10 ACCESS TO SOURCE DATA/DOCUMENTS

Checking of case report forms (CRF's) for completeness and clarity and cross-checking with source documents will be required to monitor the progress of the study. The Monitors are entitled to compare CRF entries with source data and to inform the investigator about errors and omissions. The monitor will request correction / clarification from the investigator using electronic data clarifications that should be answered and closed as quickly as possible. The Investigator will provide direct access to source data/documents for the Sponsor's designated representatives (monitors and auditors) as well as IRB/IEC members and regulatory inspections.

Regulatory authorities and/or the Sponsor's clinical quality assurance personnel may also carry out source data checks and/or on-site audit inspections. These will be carried out giving due consideration to data protection and medical confidentiality. The Investigator is to give the Sponsor whatever support is necessary.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Study Monitoring

The study will be initiated by the Sponsor during an on-site visit after all required study documents have been sent to the Sponsor and approved. A monitor will perform

subsequent on-site monitoring visits as frequently as deemed necessary. At these visits, the monitor will compare the data entered onto the CRFs with the hospital or clinic records (source documents) and check for protocol compliance, including a review of records of informed consent, all subject visit dates, all AEs, all concomitant medications, and key efficacy observations. In addition, drug accountability records will be reviewed and findings from this review will be discussed with the Investigator.

The Sponsor expects that during monitoring visits, the study coordinator, Investigator, CRFs and source documentation will be available and a suitable environment will be provided for review of study-related documents.

11.2 Audits and Inspections

Trial sites, facilities, laboratories and all data (including sources) and documentation must be available for GCP audit by the Sponsor or inspection by competent authorities. Any aspect of the trial may be subject to audit by the Sponsor and/or inspection by regulatory authorities or the IRB. Such audits/inspections may take place at the Sponsor's site(s) or at the trial site including laboratories, pharmacies etc. In case of audit, the monitor will announce this in advance to the Investigator (or representative) and be present at the particular trial site during the audit.

The site staff should assist in all aspects of audit/inspection.

11.3 Data Quality Assurance

The Sponsor and their designated Contract Research Organization (CRO) will implement a system of quality assurance, including all elements described in this protocol. Within this system the CRO SOPs will be implemented to ensure that the clinical trial is conducted in compliance with regulatory requirements and GCP. Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

12 ETHICS AND ADMINISTRATIVE ISSUES

12.1 Ethical conduct of the trial

This protocol was designed and will be conducted, recorded and reported in compliance with the principles of Good Clinical Practice (GCP) regulations and in accordance with the principles outlined in the Declaration of Helsinki. These requirements are stated in federal regulations as well as ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use, "E6 Guideline for Good Clinical Practice". The Sponsor representative will review these obligations with the Investigator prior to the initiation and throughout the course of the study. The Investigator or any of his or her staff should contact the Sponsor representative for any questions or issues regarding compliance with GCP/ICH guidelines.

This study will be conducted in compliance with IRB guidelines and in accordance with applicable regulations regarding clinical safety data management. In addition this study will adhere to all local regulatory requirements and requirements for data protection.
The Investigator should refer to 21 CFR Part 312, Subpart D, ICH Guidelines E6 for clarification of the Investigator's responsibilities for fulfillment of GCP Guidelines for Investigator's qualifications and agreements, adequate resources, medical care of study subjects, communication with IRB, compliance with the protocol, responsibility for investigational products, randomization procedures, informed consent, records and reporting, premature termination or suspension of a study and final reports.

Before initiating the study, the Investigator/institution must have written and dated approval/favorable opinion from the IRB for the study protocol/amendment(s), written informed consent form, any consent form updates, subject recruitment procedures (e.g. advertisements), and any written information to be provided to subjects, and a statement from the IRB that they comply with GCP requirements. The IRB approval must identify the protocol version as well as the documents reviewed.

12.2 Institutional review board/independent ethics committee (IRB/IEC) and Regulatory Authority

All protocols and protocol amendments must be signed and dated by the Investigator and approved by the IRB prior to implementation. The Investigator must provide an annual report to the IRB on the progress of the study in compliance with 21 CFR Part 56 and the IRB's policies and procedures. The Investigator must provide notification to the IRB of the completion, termination or discontinuation the study. It is required that a yearly review of the protocol by the IRB be documented in a letter from the IRB.

12.3 Subject informed consent

Executed informed consent, and other locally required documents such as those related to Protected Health Information, are required. The consent form must be executed prior to performing any study-related activities that are not part of the subject's routine care. The consent form that is used must be approved by both the reviewing IRB and by the Sponsor representative.

12.4 Subject Data Protection

Each subject must provide written informed consent as well as any authorizations required by local law (e.g. authorizations related to Protected Health Information). The Investigator agrees not to use or disclose Protected Health Information other than as permitted or required by the subject authorization or as required by law.

12.5 Data Monitoring Committee

Not applicable.

12.6 Financial Disclosure

Study personnel on the Form FDA 1572 will complete a financial disclosure form at the beginning of the study. New study personnel added to Form FDA 1572 must also meet these requirements.

12.7 Investigator Obligations

The Investigator should refer to 21 CFR Part 312, Subpart D, ICH Guidelines E6 for clarification of the Investigator's responsibilities to fulfill GCP Guidelines for Investigator's qualifications and agreements, adequate resources, medical care of study subjects, communication with IRB, compliance with the protocol, responsibility for investigational products, randomization procedures, informed consent, records and reporting, premature termination or suspension of a study and final reports.

The Investigator agrees when signing the protocol to adhere to the instructions and procedures described in it, and thereby, to adhere to the principles of GCP that it conforms to.

12.8 Changes to the Protocol

All protocols and protocol amendments must be signed and dated by the Investigator and approved by the IRB prior to implementation.

12.9 Confidentiality/Publication of the Study

All information supplied to the Investigator by a Sponsor representative and not previously published is considered confidential and remains the sole property of the Sponsor. The Investigator must agree to use this information only to accomplish this study, and must not use it for other purposes without the Sponsor's written consent.
The information developed in this study will be used by the Sponsor in connection with the continued development of this product and thus may be disclosed as required to other clinical Investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the Investigator is obligated to provide the Sponsor with all data obtained in the study.

No publication of any study data, results, other deliverables or records is permitted by the Investigator.

12.10 Discontinuation of entire study

The Sponsor reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance.

In particular cases, the study may be terminated at a single investigational site, if the Sponsor has relevant reasons, e.g., suspicion of a deceit or conduct of the study which is not in accordance to the guidelines for GCP.

If the Sponsor determines such action is needed, the Sponsor will discuss this with the Investigator (including the reasons for taking such action) at that time. When feasible, the Sponsor will provide advance notification to the Investigator of the impending action prior to it taking effect.

The Sponsor will promptly inform all other Investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the Ethics Committee promptly and provide the reason for the suspension or termination.

13 DATA HANDLING AND RECORD KEEPING

13.1 Inspection of Records

Local regulatory agencies may request access to all study records, including source documents, for inspection and copying, in keeping with U.S. regulations. The Investigator should immediately notify the Sponsor of any upcoming regulatory agency inspections. The Sponsor may also perform an audit of the data if deemed necessary.
The Investigator will be responsible for the accuracy of the data entered in the CRFs. The Investigator will permit designated Sponsor representatives and regulatory bodies to have direct access to the source documents to verify data represented in the CRFs.

13.2 Retention of Records

All source documents (e.g. informed consent forms, laboratory reports, progress notes, medical histories, physical and diagnostic findings, diagnosis and pharmacy records, and study drug dispensing/disposition records) that support data in the CRFs of each study subject must be retained in the files of the Investigator for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or at least two years have elapsed since the formal discontinuation of clinical development of the investigational drug. These documents should be retained for a longer period, however, if required by applicable regulatory requirements.

If the Investigator retires, relocates, or for any other reason withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Prior to transfer, the Sponsor representative must be notified in writing of the name and address of the new custodian.

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NCT02549196

Study ID: CPC-001-12

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

Protocol Date: 10 Sept 2015

Investigational Product:	CPC-201 (donepezil plus solifenacin)
Indication:	Treatment of Dementia of Alzheimer Type
Clinical phase:	Phase II, Dose Titration Study
Study code:	CPC-001-12

Dose titration study

A PHASE II, DOSE TITRATION STUDY OF CPC-201 IN PATIENTS WITH DEMENTIA OF ALZHEIMER'S TYPE

Version 1, date: September 10, 2015

Sponsor: Chase Pharmaceuticals Corporation
1825 K Street, NW, Suite 520
Washington, DC 20006

GCP compliance
The study will be performed in compliance with Good Clinical Practices (GCP)
and in accordance with the Declaration of Helsinki

Signature page for the Sponsor

Investigational Product:	CPC-201 (Donepezil plus solifenacin)
Indication:	Treatment of Dementia of Alzheimer Type
Clinical Phase:	Phase II, Dose Titration Study
Study Code:	CPC-001-12
Protocol Version Date:	Version 1 (September 10, 2015)

Reviewed and approved by:

Signature page for the Investigator

This Clinical Trial will be conducted in accordance with the study protocol, the International Conference on Harmonization (ICH), Good Clinical Practices (GCP), the ethical principles outlined in the current valid version of the Declaration of Helsinki and the European as well as other local regulations.

As the Investigator for the Trial, I have read this protocol dated August 26, 2015 and agree to follow this protocol in accordance with all the above-mentioned regulations.

……..

Date: ……....

Table of contents

LIST OF ABBREVIATIONS

ACh .....Acetylcholine
AChEI .....Acetylcholinesterase Inhibitor
AD.....Alzheimer's disease
ADAS-cog.....Alzheimer's disease Assessment Scale-cognition
ADR.....Adverse Drug Reaction
AE .....Adverse Event
AV.....Atrioventricular
CFS..... ...Cerebrospinal Fluid
CNS.....Central Nervous System
CRF .....Case Report Form
CRO .....Contract Research Organization
C-SSRS. .....Columbia-Suicide Severity Rating Scale
DSM. .....Diagnostic and Statistical Manual of Mental Disorders
E2020. .....Donepezil
ECG.....Electrocardiogram
FDA.....Food and Drug Administration
FID .....First Intolerable Dose
GCP.....Good Clinical Practice
GI .....Gastrointestinal
HR. .....Heart Rate
ICD.....Implantable Cardiac Defibrillator
ICH.....International Conference On Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC .....Independent Ethics Committee
IRB.....Institutional Review Board
KG. .....Kilogram
MAD……Maximum Allowed Dose
MEDDRA. .....Medical Dictionary for Regulatory Activities
MG. .....Milligram
ML.....Milliliter
MMSE. .....Mini Mental Status Examination
MSEC.....Millisecond
MTD.....Maximum Tolerated Dose
NDA. .....New Drug Application
NG/ML. .....Nanogram/Milliliter
NIA-ADA. .....National Institute on Aging – Alzheimer's Disease Association
OAB. .....Overactive Bladder Disorder
OTC.....Over-the-Counter
QTC.....Corrected QT interval
QTCF. .....Corrected QT intervals by Fridericia's formula
PR Interval. .....On ECG, time from onset of P wave to start of QRS Complex
QRS complex. .....On ECG, central part of tracing, Q,R and S waves

QT interval. .....On ECG, interval between start of Q wave and end of the T wave
SOC.....System Organ Class
SOP .....Standard Operating Procedures
SAE.....Serious Adverse Event
SEM. .....Standard Error of Mean
TEAE .....Treatment Emergent Adverse Event
UNL. .....Upper Normal Limit
US .....United States
WHO.....World Health Organization

LIST OF TABLES

PROTOCOL SUMMARY

Name of Sponsor/Company:
Chase Pharmaceuticals Corporation

Name of Investigational Product:
CPC-201: Donepezil plus solifenacin

Name of Active Ingredient:
Donepezil, solifenacin

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

Number of clinical centers:
Multicenter

Objectives:
Primary:

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

Secondary:

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

Methodology:
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.

In this study, 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) of 60mg/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 Cohorts 2 and 3 may be altered based on Cohort 1 result.

Each cohort will include approximately 6 patients donepezil-treated (Group 1) and approximately 6

patients not treated with an AchEI for at least 6 months (Group 2). Within each cohort, Group 2 patients will be enrolled only when at least 3 Group 1 patients have completed dose titration per protocol.

Patients will be enrolled in Cohort 2 only when patients enrolled in Cohort 1 have safely completed titration. Similary, patients will be enrolled in Cohort 3 only when patients enrolled in Cohort 2 have safely completed titration.

Patients reaching their FID or having completed one week treatment with donepezil 60mg/day, 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.

Number of patients planned:

To ensure a suitable number of subjects to evaluate the optimal dose titration schedule, approximately 6 patients per population group per cohort will be enrolled.

Diagnosis and main criteria for inclusion:

Males and females suffering from AD

Inclusion Criteria:

1) Signed an Institutional Review Board (IRB) approved informed consent document indicating that they understand the purpose of and procedures required by the study and are willing to participate in the study and comply with all study procedures and restrictions. Informed consent must be obtained from the patient and/or a designated representative prior to initiating screening procedures to evaluate eligibility for the study.
2) Aged 50 – 89 years inclusive.
3) Meeting the diagnosis of probable AD consistent with:
   - Revised National Institute on Aging-Alzheimer's Disease Association (NIA-ADA) criteria and
   - Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria.
4) Mild to severe severity (Mini-Mental Status Exam [MMSE] scores 7 – 24 inclusive).
5) Rosen-Modified Hachinski Ischemia Score of ≤4.
6) Have a suitable caregiver to supervise the at-home administration of study drugs and observe for AEs.
7) Patients will be required to have been treated with donepezil 5 or 10 mg/day (given once daily) for at least 4 weeks just prior to Day1 for Population (group) 1 or;

   Patients have never been treated with donepezil before (donepezil naïve) or who have not received any other AChEI for the past 6 months for Population (group) 2.
8) Patients must be in generally good health as indicated by their medical history and physical examination, vital signs, electrocardiogram (ECG), and standard laboratory tests.

Key exclusion criteria:

The criteria for exclusion of a subject from enrollment in the study are as follows:

1) Women of child bearing potential.
2) History or presence of a seizure disorder.
3) Current unstable peptic ulcer disease, urinary or gastric retention; asthma or obstructive pulmonary disease.
4) History or presence of bladder outflow obstruction, gastrointestinal obstructive disorder or reduced GI motility, or narrow-angle glaucoma.
5) History or presence of gastrointestinal, hepatic, or renal disease, or other condition known to interfere with the absorption, distribution, metabolism or excretion of drugs.
6) Renal and hepatic dysfunction with:
   - Total Bilirubin: >1.5 x UNL
   - AST: >2.5 x UNL
   - ALT: >2.5 x UNL
   - Serum Creatinine: >1.5 x UNL
   - Creatinine Clearance: <30 mL/min (calculated by Cockcroft and Gault equation)
7) History or presence of myasthenia.
8) History or family history of Prolonged QT Syndrome.
9) History of unexplained syncope or family history of unexplained syncope or sudden death.
10) Myocardial infarction or hospitalization for congestive heart failure within 6 months.
11) ECG findings of:
   - Complete Left Bundle Branch Block;
   - Ventricular pacing;
   - 2nd degree or 3rd degree AV block;
   - Atrial fibrillation or atrial flutter;
   - HR <45 or >100;
   - PR >220 msec; or
   - QTcF >450 msec in male, >470 msec in female
12) Known hypersensitivity to donepezil, solifenacin or related drugs.
13) History of drug significant allergy.
14) History of substance abuse, known drug addiction, or positive test for drugs of abuse or alcohol.
15) Patients treated with the following medications within 8 weeks of screening
   - Peripherally acting anticholinergics (such as drugs for the treatment of overactive bladder disorder),
   - Psychoactive medications (including antipsychotics, antidepressants, anxiolytics or sedative hypnotics) having significant anticholinergic effects and/or believed to affect cognitive function.

   Other medications are acceptable, at the investigators discretion, if dosage is held stable for at least 4 weeks prior to screening and throughout the study.
16) Patients considered unlikely to co-operate in the study, and/or poor compliance anticipated by the investigator.
17) Patients hospitalized within 4 weeks of screening.
18) Any other clinically relevant acute or chronic diseases which could interfere with patients' safety during the trial, or expose them to undue risk, or which could interfere with study objectives.
19) Patients who have participated in another clinical trial with an investigational drug within

previous 30 days.

Investigational product (IP)

Donepezil (Aricept®): 10 mg tablet (or generic equivalent)
Solifenacin (Vesicare®): 5 mg, 10 mg tablets
Placebo (Similar in size to donepezil 10 mg or solifenacin 5 mg/10 mg tablets

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

Duration of treatment:

Screening: 4 weeks

Dosing: up to 5 weeks

Reference therapy, dosage and mode of administration:

None

Statistical Analysis:

Since the objective of this study is to determine the optimal initial dose and subsequent dose titration schedule, the data will be analyzed only by means of descriptive statistics to reveal possible trends that will help guide the design of future, more definitive, clinical trials.

Sample size calculations:

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

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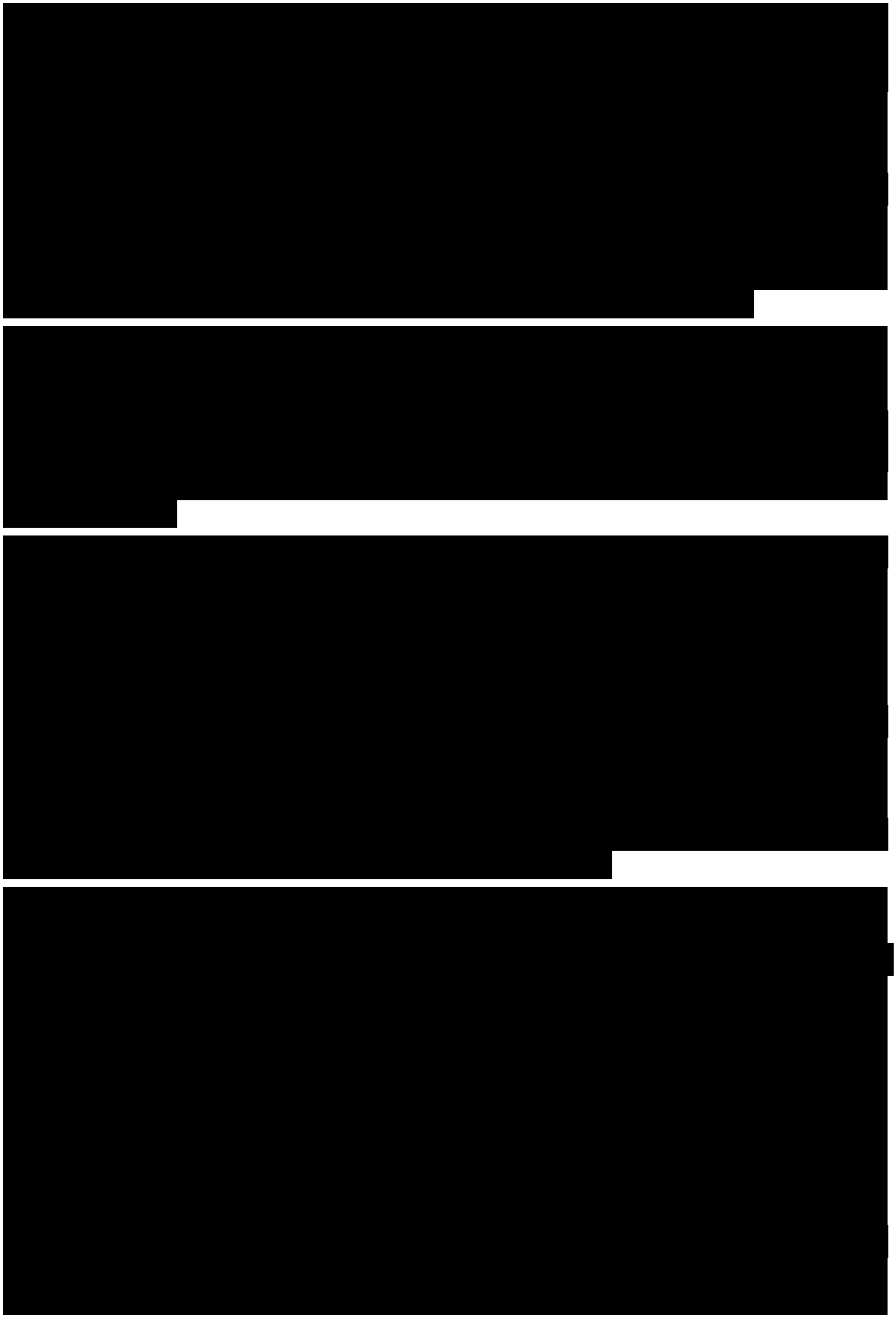

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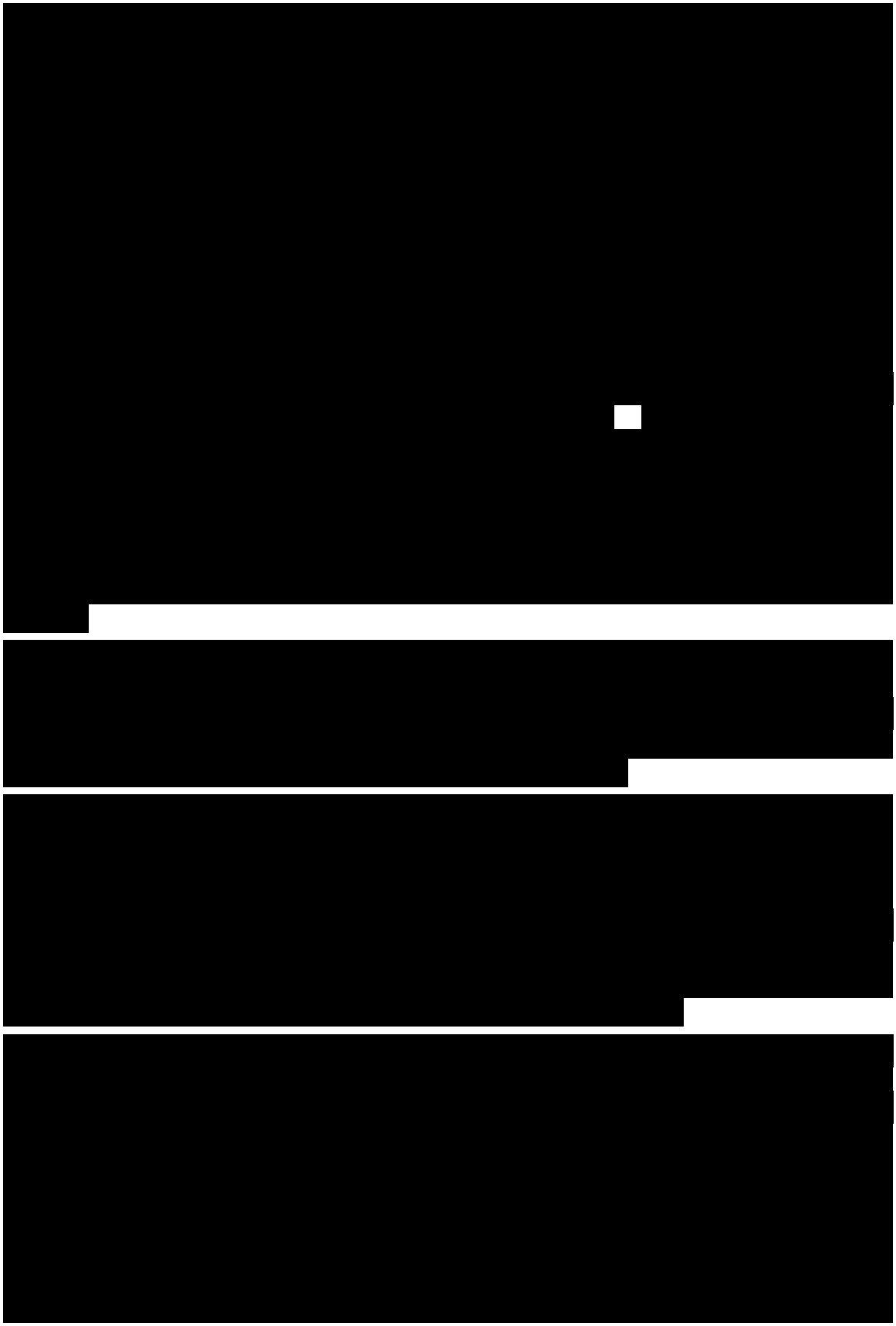

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2 OBJECTIVES

2.1 Primary objective

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

2.2 Secondary objective

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

3 INVESTIGATIONAL PLAN

3.1 Overall Study design

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.

In this study, 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.

Each cohort will include approximately 6 patients donepezil-treated (Group 1) and approximately 6 patients not treated with an AchEI for at least 6 months (Group 2). Within each cohort, Group 2 patients will be enrolled only when at least 3 Group 1 patients have completed dose titration per protocol.

Patients will be enrolled in Cohort 2 only when patients enrolled in Cohort 1 have safely completed titration. Similary, patients will be enrolled in Cohort 3, only when patients enrolled in Cohort 2 have safely completed titration.

Patients reaching their FID or having completed one week treatment with donepezil 60mg/day, 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 addtional 7 days with solifenacin 15 mg/day.

3.2 Dose Escalation and Stopping rules

For all patients, donepezil dose escalation will be discontinued if they manifest over a 24 hour period after study drug administration the following symptoms judged by the investigator as possibly or probably study-drug related:

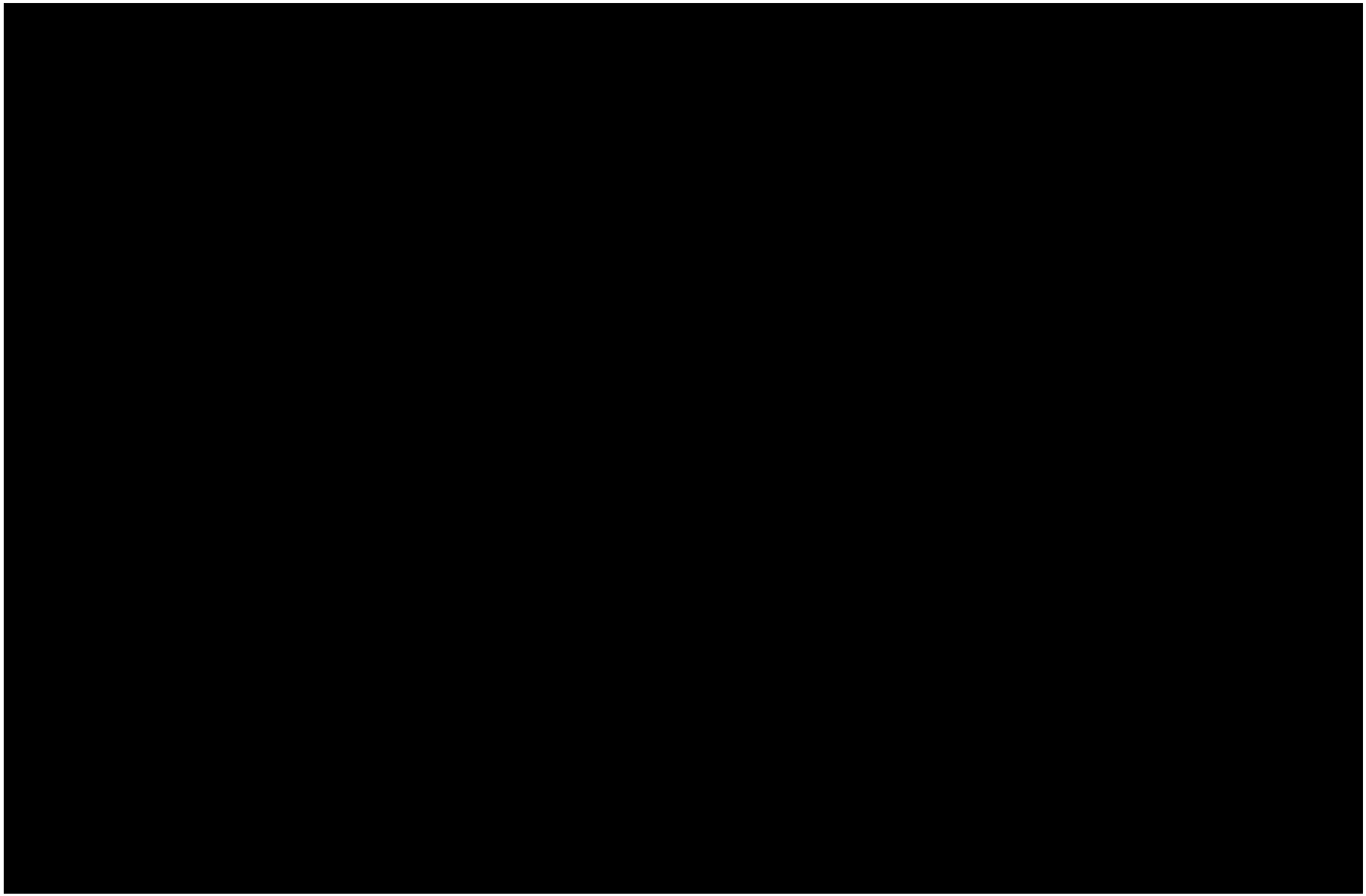
- One (1) episode of vomiting, or
- Two (2) episodes of severe retching (separated by more than one hour on the same day), or
- One (1) episode of severe nausea (Grade 3; defined as nausea interfering with activities of daily living or inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition or hospitalization indicated) and/or severe abdominal discomfort (Grade 3; defined as severely interfering with activities of daily living), or
- Three (3) episodes of moderate nausea (Grade 2; defined as subjectively symptomatic, but not interfering with activities of daily living) and/or moderate abdominal discomfort (Grade 2; defined as interfering with function, but not interfering with activities of daily living) each on the same day, or
- One (1) episode of moderate diarrhea (Grade 2; defined as 4 to 6 stools more than at baseline).
- Any other circumstance that merits an adjustment in study drug dosage in the opinion of the investigator

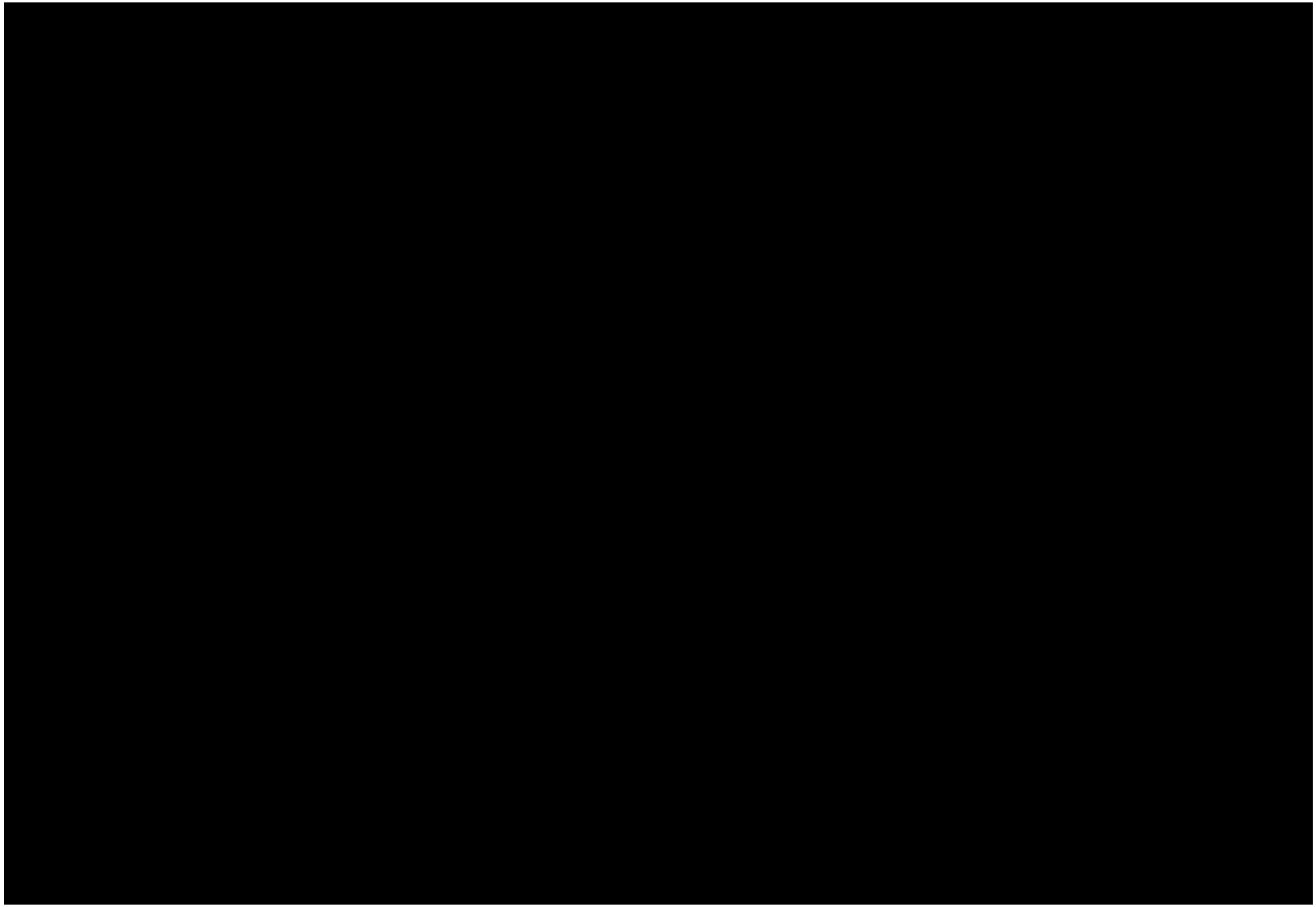
All those meeting one or more of the foregoing stopping rules will be withdrawn from dose titration and proceed in accordance with either of the two options given above.

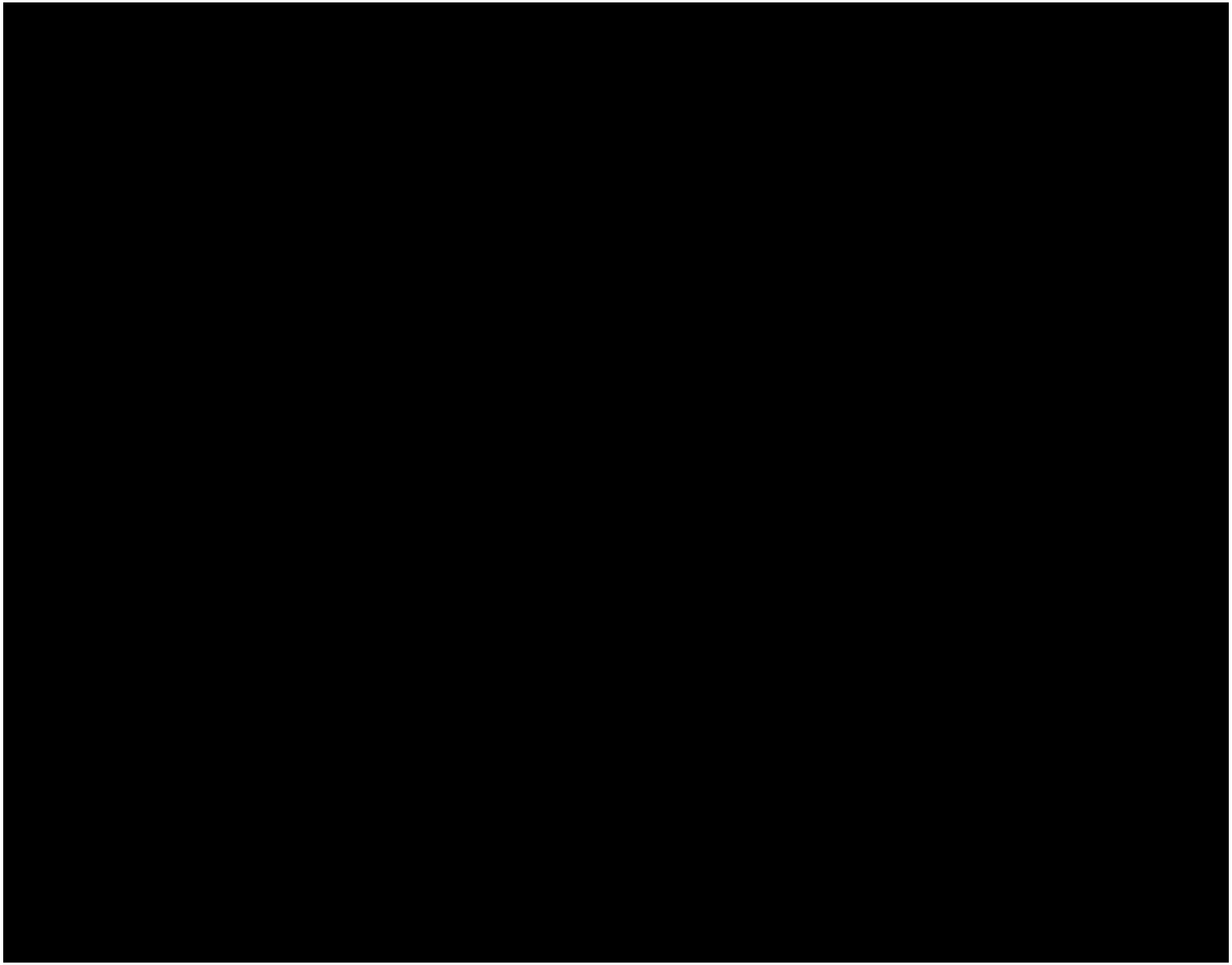
3.3 Trial procedures

3.3.1 Schedule of Assessments

The schedule of assessments for the study is provided in Table 1, Table 2 and Table 3.







3.3.2 Study Procedure

For each visit, procedures and assessments are listed in the order in which they should be performed.

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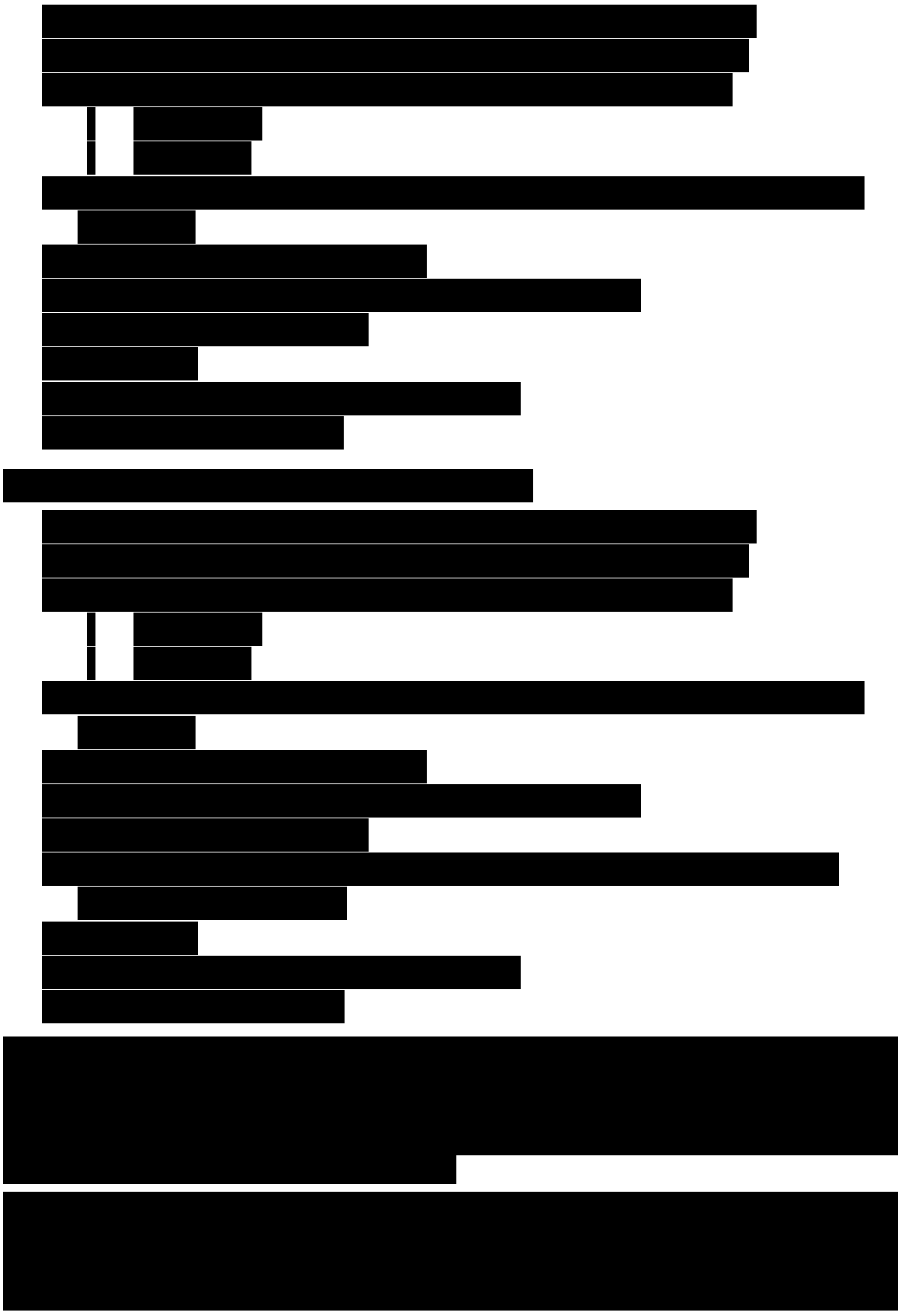

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3.5 Discontinuation criteria

3.5.1 Discontinuation of donepezil dose escalation in individual subjects

For all patients, donepezil dose escalation will be discontinued if they manifest over a 24 hour period after study drug administration the following symptoms judged by the investigator as possibly or probably study-drug related:

- One (1) episode of vomiting, or
- Two (2) episodes of severe retching (separated by more than one hour on the same day), or
- One (1) episode of severe nausea (Grade 3; defined as nausea interfering with activities of daily living or inadequate oral caloric or fluid intake; tube feeding, total parenteral nutrition or hospitalization indicated) and/or severe abdominal discomfort (Grade 3; defined as severely interfering with activities of daily living), or
- Three (3) episodes of moderate nausea (Grade 2; defined as subjectively symptomatic, but not interfering with activities of daily living) and/or moderate abdominal discomfort (Grade 2; defined as interfering with function, but not interfering with activities of daily living) each on the same day, or
- One (1) episode of moderate diarrhea (Grade 2; defined as 4 to 6 stools more than at baseline).
- Any other circumstance that merits an adjustment in study drug dosage in the opinion of the investigator

3.5.2 Discontinuation of individual subjects from the entire study

During the study, the investigator or the sponsor may decide to discontinue a subject's participation in the study in the following cases:

- A protocol violation occurs;
- A serious or intolerable (other than those listed in the discontinuation of rivastigmine escalation criteria) AE occurs;
- The Sponsor or Investigator terminates the study.
- The subject requests to be discontinued from the study.
- The subject is non-compliant to any part of the study.
- The Investigator feels it is not in the best interest of the subject to continue in the study.

4 SELECTION OF SUBJECTS

4.1 Inclusion criteria

The criteria for inclusion that each subject must meet to be enrolled in the study are as follows:

1. Signed an Institutional Review Board (IRB) approved informed consent document indicating that they understand the purpose of and procedures required by the study and are willing to participate in the study and comply with all study procedures and restrictions. Informed consent must be obtained from the patient and/or a designated representative prior to initiating screening procedures to evaluate eligibility of the study.
2. Aged 50 – 89 years inclusive.
3. Meeting the diagnosis of probable AD consistent with:
   - Revised National Institute on Aging-Alzheimer's Association (NIA-ADA) criteria and
   - Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria.
4. Of mild to severe severity (Mini-Mental Status Exam [MMSE] scores 7 – 24 inclusive).
5. Rosen-Modified Hachinski Ischemia Score of ≤4.
6. Have a suitable caregiver to supervise the at-home administration of study drugs and observe for AEs.
7. Patients will be required to have been treated with donepezil 5 or 10 mg/day (given once daily) for at least 4 weeks just prior to Day1 for Population (group) 1 or;
8. Patients have never been treated with donepezil before (donepezil naïve) or who have not received any other AChEI for the past 6 months for Population (group) 2.
9. Patients must be in generally good health as indicated by their medical history and physical examination, vital signs, electrocardiogram (ECG), and standard laboratory tests.

4.2 Exclusion criteria

The criteria for exclusion of a subject from enrollment in the study are as follows:

1. Women of child bearing potential.
2. History or presence of a seizure disorder.
3. Current unstable peptic ulcer disease, urinary or gastric retention; asthma or obstructive pulmonary disease.
4. History or presence of bladder outflow obstruction, gastrointestinal obstructive disorder or reduced GI motility, or narrow-angle glaucoma.
5. History or presence of gastrointestinal, hepatic, or renal disease, or other condition known to interfere with the absorption, distribution, metabolism or excretion of drugs.
6. Renal and hepatic dysfunction with:
   - Total Bilirubin: >1.5 x UNL

- AST: >2.5 x UNL
- ALT: >2.5 x UNL
- Serum Creatinine: >1.5 x UNL
- Creatinine Clearance: <30 mL/min

7. History or presence of myasthenia.
8. History or family history of Prolonged QT Syndrome.
9. History of unexplained syncope or family history of unexplained syncope or sudden death.
10. Myocardial infarction or hospitalization for congestive heart failure within 6 months.
11. ECG findings of:
    - Complete Left Bundle Branch Block;
    - Ventricular pacing;
    - 2nd degree or 3rd degree AV block;
    - Atrial fibrillation or atrial flutter;
    - HR <45 or >100;
    - PR >220 msec; or
    - QTcF >450 msec in male, >470 msec in female
12. Known hypersensitivity to donepezil, solifenacin or related drugs.
13. History of drug significant allergy.
14. History of substance abuse, known drug addiction, or positive test for drugs of abuse or alcohol.
15. Patients treated with the following medications within 8 weeks of screening
    - AChEIs (other than donepezil),
    - Peripherally acting anticholinergics (such as drugs for the treatment of overactive bladder disorder),
    - Psychoactive medications (including antipsychotics, antidepressants, anxiolytics or sedative hypnotics) having significant anticholinergic effects and/or believed to affect cognitive function.

    Other medications are acceptable, at the investigators discretion, if dosage is held stable for at least 4 weeks prior to screening and throughout the study.
16. Patients considered unlikely to co-operate in the study, and/or poor compliance anticipated by the investigator.
17. Patients hospitalized within 4 weeks of screening.
18. Any other clinically relevant acute or chronic diseases which could interfere with patients' safety during the trial, or expose them to undue risk, or which could interfere with study objectives.

19. Patients who have participated in another clinical trial with an investigational drug within previous 30 days.

5 STUDY DRUG

5.1 Blinding

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

5.3 Description of Study Drug

Placebo tablet
Placebo tablet is similar in size to donepezil 10 mg or solifenacin 5 mg/10 mg tablets.

5.3.2 Study drug manufacturing and labeling

Donepezil and solifenacin will be purchased by [redacted] from a licensed supplier of these pharmaceuticals.

The placebo tablet will be manufactured, packaged in bottle, labeled by [redacted] Label will include the following information: protocol number, quantity of tablets, required storage conditions, lot number, name and address of the manufacturer and the following cautionary statement: New Drug – Limited by Federal law to investigational use.

5.3.3 Study drug storage, handling and disposal

At the site, all study drugs should be stored at room temperature[redacted] in a secure area accessible only to the designated qualified site personnel. All study drugs must be stored, inventoried and the inventories carefully and accurately documented according to applicable state, federal and local regulations, International Conference on Harmonisation (ICH) Guidelines, Good Clinical Practice (GCP) and study procedures.
The study drug is to be prescribed only by the Investigator or his/her named sub-investigator(s), and is to be used only in accordance with the protocol. The study drug must be distributed only to patients properly enrolled in the study.

The Investigator must keep an accurate accounting of the study drug received from the Sponsor, including the temperature of the storage area, the amount of study drug dispensed to patients, amount of study drug returned to the Investigator by the patients, and the amount returned to the Sponsor upon completion of the study. A detailed inventory must be completed for the study drug.

Unused study drug must be kept in a secure location for accountability and reconciliation by the study monitor. Investigator or designee must provide an explanation for any destroyed or missing study drug or study materials.

Unused study drug may be destroyed on site, per the site's standard operating procedures (SOPs), but only after the Sponsor has granted approval for drug destruction. The monitor must account for all study drugs in a formal reconciliation process prior to study drug destruction. All study drug destroyed on site must be documented. Documentation must be provided to the Sponsor and retained in the Investigator's study files. If a site is unable to destroy study drug appropriately, the site can return unused study drug to the Sponsor or designee upon request. The return of study drug or study drug materials must be documented.

5.4 Concomitant medication

5.4.1 Allowed Mediations

Dosage of allowed concomitant medication should be stabilized for at least 4 weeks prior to screening and should remain constant during the course of the study. Patients on concomitant memantine should be on a stable dose for at least 3 months. With the exception of medications listed in the exclusion criteria (Section 4.2) and in Section 5.4.2 below, concomitant medications will be allowed at the Investigator's discretion.

All concomitant medications and therapies (prescription and OTC) should be recorded in the CRF, with generic name (if known, otherwise brand name), indication, dose, route, frequency, and date(s) of administration. Any change in any of these parameters during the study should be documented.

5.4.2 Prohibited Mediations

Concomitant use of the following drugs is not allowed (such medications must have been discontinued at least 8 weeks prior to screening):

- peripherally acting anticholinergics (such as drugs for the treatment of overactive bladder disorder),
- psychoactive medications (including antipsychotics, antidepressants, anxiolytics or sedative hypnotics) having significant anticholinergic effects and/or believed to affect cognitive function

In addition, the following drugs are prohibited during the study:

- Strong CYP3A4 inhibitors
- Strong CYP3A4 inducers
- Strong CYP2D6 inhibitors

Patients who use prohibited medications during the study listed above may be discontinued from study drug. Medications prescribed after patients have discontinued the study drug will not be considered as prohibited medications.

Note: The discontinuation of a patient due to use of a prohibited medication is dependent upon the Sponsor's decision. The Investigator should contact the Sponsor prior to discontinuing a patient for disallowed medications.

6 ASSESSMENT OF PHARMACOKINETICS

6.1 PK Blood Sampling Schedule and Sample Analysis

The blood samplings will be performed at approximately 15 minutes before and 4 hours (± 15 min) after study drug administration at each visits.

[redacted]

7 SAFETY ASSESSMENTS

7.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical-investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. A TEAE is defined as any AE that occurs after administration of the first dose of study drug. An AE can therefore be an unfavorable and 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. The failure of the anticipated pharmaceutical action of an investigational drug does not constitute a related AE.

AE rating

The condition of the subjects will be closely monitored throughout the study. The investigator will collect the AEs reported spontaneously, observed, or elicited in response to a non-leading question (for example, "How have you been feeling since we last asked you?"). The investigator will record all AEs in the source records and the CRF.

- The intensity/severity of an AE will be rated as follows:

  Mild : Awareness of signs or symptoms, but no disruption of usual activity.
  Moderate : Event sufficient to affect usual activity (disturbing).
  Severe : Inability to work or perform usual activities (unacceptable).

- The causal relationship of an AE to the study drugs will be rated as follows:

  Not related : Temporal relationship of the onset of the event, relative to the administration of the product, is not reasonable or another cause can by itself explain the occurrence of the event
  Unlikely : Is general, this category can be considered applicable to those AEs

related	which after careful medical consideration at the time they are evaluated, are judged to be unrelated to the study drug
Related	: AEs incontrovertibly related to the administration of the product.

Of the above definitions, AEs related to study drug are considered adverse reactions, while "unlikely" and "not related" do not represent a causal relationship.

- The action taken with the study drug for an AE will be rated as product withdrawn, not changed, not applicable. AEs requiring therapy will be treated with recognised standards of medical care to protect the health and the well-being of the subject.
- The outcome of an AE will be rated as recovered, recovering, not recovered, recovered with sequellae or fatal. The investigator will follow up any AE until it is resolved or until the medical condition of the subject is stable. All relevant follow-up information will be collected. For AEs that are ongoing at the last visit, the investigator will make thorough efforts to document the outcome.

7.2 Serious Adverse Events (SAE)

An SAE is any untoward medical occurrence that results in death, is life threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. In addition, important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

An AE is life-threatening if the subject is at immediate risk of death from the event as it occurs, i.e. it does not include a reaction that, if it had occurred in a more serious form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not have been considered life-threatening, even though drug-induced hepatitis can be fatal.

An AE is incapacitating or disabling if the experience resulted in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.

7.3 Assessment of tolerability

The FID of each patient will be recorded.

7.4 Safety Laboratory Test

Blood samples will be collected as indicated in Table 1-4 for the following clinical laboratory tests:

Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelet count.

Serum chemistry: calcium, sodium, chloride, potassium, blood urea nitrogen, glucose, total bilirubin, alkaline phosphatase, lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, creatinine, calculated creatinine clearance, uric acid, phosphorous, total protein, albumin, and globulin.

[redacted]

7.5 Urinalysis

Urine samples will be collected as indicated in Table 1-4 for the following tests: glucose, bilirubin, ketones, specific gravity, blood, pH, protein, urobilinogen, nitrites, and leukocytes and, if necessary, microscopic examination.

7.6 Vital signs and body weight

Vital signs, including blood pressure, heart rate, respiratory rate, and temperature, will be measured after the patient rests in the supine position for at least 5 minutes.

Body weight will be measured as indicated in Table 1-4.

7.7 12-Lead ECGs

A standard 12-lead ECG will be recorded as indicated in Table 1-4. The Investigator will evaluate the ECG results as normal, abnormal, not clinically significant, or abnormal, clinically significant.

If QTcF on an on treatment ECG is ≥500 msec then hold treatment and perform 3 repeat ECGs over 20-60 min; if the mean QTcF of the three ECGs is ≥500 msec, withhold treatment and perform a repeat ECG the following day; if the QTcF has returned to baseline, dosing may resume..

7.8 MMSE

MMSE will be assessed by blinded rater at visits indicated in Table 1-4.

7.9 ADAS-Cog

ADAS-Cog will be assessed by blinded rater at visits indicated in Table 1-4.

7.10 Modified C-SSRS

Modified C-SSRS will be assessed by a qualified and experienced clinician who does not perform psychometric at visits indicated in Table 1-4.

8 PROCEDURES FOR REPORTING TEAES AND SERIOUS ADVERSE EVENTS

8.1 Reporting TEAEs

All TEAEs, regardless of seriousness, severity or presumed relationship to study therapy, must be recorded using medical terminology in the source document and transcribed into the CRF. Whenever possible, the diagnosis should be given when signs and symptoms are due to a common etiology (e.g. cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection" instead of identifying and listing the individual signs and symptoms). The Investigator must record, in the source document and transcribe into the AE page of the CRF, his or her medical assessment of the severity of the event and the relationship of the AE to study drug.

All TEAEs must be followed until they have resolved or until a stable clinical endpoint is reached. All measures required for managing the TEAE and the ultimate outcome of the TEAE must be recorded in the source document and reported in the CRF.

8.2 Reporting Serious Adverse Events

When the Investigator or designee becomes aware that an SAE has occurred, the Sponsor representative must be notified by both telephone and fax, regardless of the relationship (or lack thereof) of the SAE to study drug within 24 hours of the event. All SAEs must be submitted to the Sponsor as a written report, as well as reported verbally. A follow-up report must be submitted to the Sponsor as requested when pertinent information becomes available and if additional information is requested.

The Investigator is responsible for ensuring that the IRB is informed of this information within appropriate IRB established timelines.

ANY SAE OR ADR, INCLUDING ANY OUTCOME OF DEATH DUE TO ANY CAUSE THAT OCCURS DURING THIS STUDY MUST BE REPORTED IMMEDIATELY TO THE SPONSOR REPRESENTATIVE.

This verbal and faxed report must be followed no later than 3 working days by a written report **signed by the Investigator**. The Sponsor is responsible for submitting the report to all applicable regulatory authorities.

9 STATISTICS

Since the objective of this study is to determine the optimal initial dose and subsequent dose titration schedule, the statistics are not applicable.

The data will be analyzed only by means of descriptive statistics to reveal possible trends that will help guide the design of future, more definitive, clinical trials.

9.1 Assessment of Safety and Tolerability and

Safety and tolerability parameters will be analyzed as a function of dose and dose titration schedule.

9.1.1 Assessment of MTD

Descriptive statistics will be presented for the MTD and the FID for each patient in each dose titration schedule.

9.1.2 Adverse Events

Data Listings will present the verbatim-reported event along with the preferred term and SOC, onset and stop dates, severity, relatedness, SAE status, action taken and outcome. For summaries by severity, the most severe event episode will be counted if a subject has more than one event within the same coded term. For summaries of treatment-associated events, the subject will be counted as "associated" for that term if a subject has more than one event within the same coded term or if one event is considered "not associated" and the other "associated".

Unless otherwise indicated, AE summary tables will be presented by study period, treatment group, SOC, and preferred term for each study period.

9.1.3 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 and treatment arm.

9.1.4 ECGs

The overall interpretation of the ECG results will be presented as normal, abnormal (not clinically significant) and abnormal (clinically significant) by time point and study period.

9.1.5 Vital Signs and weight

Descriptive statistics will be presented for each vital sign measurement recorded at each time point during each study period.

9.2 Pharmacokinetics

Blood concentration results of donepezil and solifenacin for each subject will be presented.

9.3 Patient Disposition

Disposition of all subjects will be summarized descriptively.

9.4 Demographics and Baseline Characteristics

Individual subject demographic and baseline characteristics data will be presented in subject data listings. Concomitant medications (all recorded medications) will be listed for enrolled subjects. The listing will be sorted by start date of medication within the standard sort order. The listing will include all collected information.

9.5 Protocol Deviations

All protocol deviations will be listed by subject number.

9.6 Compliance

Dosing information collected on the CRF will be listed for each subject. Compliance will be summarized by presenting the numbers and percentages of subjects receiving each dose of study drug.

10 ACCESS TO SOURCE DATA/DOCUMENTS

Checking of case report forms (CRF's) for completeness and clarity and cross-checking with source documents will be required to monitor the progress of the study. The Monitors are entitled to compare CRF entries with source data and to inform the investigator about errors and omissions. The monitor will request correction / clarification from the investigator using electronic data clarifications that should be answered and closed as quickly as possible. The Investigator will provide direct access to source data/documents for the Sponsor's designated representatives (monitors and auditors) as well as IRB/IEC members and regulatory inspections.

Regulatory authorities and/or the Sponsor's clinical quality assurance personnel may also carry out source data checks and/or on-site audit inspections. These will be carried out giving due consideration to data protection and medical confidentiality. The Investigator is to give the Sponsor whatever support is necessary.

11 QUALITY CONTROL AND QUALITY ASSURANCE

11.1 Study Monitoring

The study will be initiated by the Sponsor during an on-site visit after all required study documents have been sent to the Sponsor and approved. A monitor will perform

subsequent on-site monitoring visits as frequently as deemed necessary. At these visits, the monitor will compare the data entered onto the CRFs with the hospital or clinic records (source documents) and check for protocol compliance, including a review of records of informed consent, all subject visit dates, all AEs, all concomitant medications, and key efficacy observations. In addition, drug accountability records will be reviewed and findings from this review will be discussed with the Investigator.

The Sponsor expects that during monitoring visits, the study coordinator, Investigator, CRFs and source documentation will be available and a suitable environment will be provided for review of study-related documents.

11.2 Audits and Inspections

Trial sites, facilities, laboratories and all data (including sources) and documentation must be available for GCP audit by the Sponsor or inspection by competent authorities. Any aspect of the trial may be subject to audit by the Sponsor and/or inspection by regulatory authorities or the IRB. Such audits/inspections may take place at the Sponsor's site(s) or at the trial site including laboratories, pharmacies etc. In case of audit, the monitor will announce this in advance to the Investigator (or representative) and be present at the particular trial site during the audit.

The site staff should assist in all aspects of audit/inspection.

11.3 Data Quality Assurance

The Sponsor and their designated Contract Research Organization (CRO) will implement a system of quality assurance, including all elements described in this protocol. Within this system the CRO SOPs will be implemented to ensure that the clinical trial is conducted in compliance with regulatory requirements and GCP. Quality control is applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

12 ETHICS AND ADMINISTRATIVE ISSUES

12.1 Ethical conduct of the trial

This protocol was designed and will be conducted, recorded and reported in compliance with the principles of Good Clinical Practice (GCP) regulations and in accordance with the principles outlined in the Declaration of Helsinki. These requirements are stated in federal regulations as well as ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use, "E6 Guideline for Good Clinical Practice". The Sponsor representative will review these obligations with the Investigator prior to the initiation and throughout the course of the study. The Investigator or any of his or her staff should contact the Sponsor representative for any questions or issues regarding compliance with GCP/ICH guidelines.

This study will be conducted in compliance with IRB guidelines and in accordance with applicable regulations regarding clinical safety data management. In addition this study will adhere to all local regulatory requirements and requirements for data protection.
The Investigator should refer to 21 CFR Part 312, Subpart D, ICH Guidelines E6 for clarification of the Investigator's responsibilities for fulfillment of GCP Guidelines for Investigator's qualifications and agreements, adequate resources, medical care of study subjects, communication with IRB, compliance with the protocol, responsibility for investigational products, randomization procedures, informed consent, records and reporting, premature termination or suspension of a study and final reports.

Before initiating the study, the Investigator/institution must have written and dated approval/favorable opinion from the IRB for the study protocol/amendment(s), written informed consent form, any consent form updates, subject recruitment procedures (e.g. advertisements), and any written information to be provided to subjects, and a statement from the IRB that they comply with GCP requirements. The IRB approval must identify the protocol version as well as the documents reviewed.

12.2 Institutional review board/independent ethics committee (IRB/IEC) and Regulatory Authority

All protocols and protocol amendments must be signed and dated by the Investigator and approved by the IRB prior to implementation. The Investigator must provide an annual report to the IRB on the progress of the study in compliance with 21 CFR Part 56 and the IRB's policies and procedures. The Investigator must provide notification to the IRB of the completion, termination or discontinuation the study. It is required that a yearly review of the protocol by the IRB be documented in a letter from the IRB.

12.3 Subject informed consent

Executed informed consent, and other locally required documents such as those related to Protected Health Information, are required. The consent form must be executed prior to performing any study-related activities that are not part of the subject's routine care. The consent form that is used must be approved by both the reviewing IRB and by the Sponsor representative.

12.4 Subject Data Protection

Each subject must provide written informed consent as well as any authorizations required by local law (e.g. authorizations related to Protected Health Information). The Investigator agrees not to use or disclose Protected Health Information other than as permitted or required by the subject authorization or as required by law.

12.5 Data Monitoring Committee

Not applicable.

12.6 Financial Disclosure

Study personnel on the Form FDA 1572 will complete a financial disclosure form at the beginning of the study. New study personnel added to Form FDA 1572 must also meet these requirements.

12.7 Investigator Obligations

The Investigator should refer to 21 CFR Part 312, Subpart D, ICH Guidelines E6 for clarification of the Investigator's responsibilities to fulfill GCP Guidelines for Investigator's qualifications and agreements, adequate resources, medical care of study subjects, communication with IRB, compliance with the protocol, responsibility for investigational products, randomization procedures, informed consent, records and reporting, premature termination or suspension of a study and final reports.

The Investigator agrees when signing the protocol to adhere to the instructions and procedures described in it, and thereby, to adhere to the principles of GCP that it conforms to.

12.8 Changes to the Protocol

All protocols and protocol amendments must be signed and dated by the Investigator and approved by the IRB prior to implementation.

12.9 Confidentiality/Publication of the Study

All information supplied to the Investigator by a Sponsor representative and not previously published is considered confidential and remains the sole property of the Sponsor. The Investigator must agree to use this information only to accomplish this study, and must not use it for other purposes without the Sponsor's written consent.
The information developed in this study will be used by the Sponsor in connection with the continued development of this product and thus may be disclosed as required to other clinical Investigators or government regulatory agencies. To permit the information derived from the clinical studies to be used, the Investigator is obligated to provide the Sponsor with all data obtained in the study.

No publication of any study data, results, other deliverables or records is permitted by the Investigator.

12.10 Discontinuation of entire study

The Sponsor reserves the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance.

In particular cases, the study may be terminated at a single investigational site, if the Sponsor has relevant reasons, e.g., suspicion of a deceit or conduct of the study which is not in accordance to the guidelines for GCP.

If the Sponsor determines such action is needed, the Sponsor will discuss this with the Investigator (including the reasons for taking such action) at that time. When feasible, the Sponsor will provide advance notification to the Investigator of the impending action prior to it taking effect.

The Sponsor will promptly inform all other Investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the Ethics Committee promptly and provide the reason for the suspension or termination.

13 DATA HANDLING AND RECORD KEEPING

13.1 Inspection of Records

Local regulatory agencies may request access to all study records, including source documents, for inspection and copying, in keeping with U.S. regulations. The Investigator should immediately notify the Sponsor of any upcoming regulatory agency inspections. The Sponsor may also perform an audit of the data if deemed necessary.
The Investigator will be responsible for the accuracy of the data entered in the CRFs. The Investigator will permit designated Sponsor representatives and regulatory bodies to have direct access to the source documents to verify data represented in the CRFs.

13.2 Retention of Records

All source documents (e.g. informed consent forms, laboratory reports, progress notes, medical histories, physical and diagnostic findings, diagnosis and pharmacy records, and study drug dispensing/disposition records) that support data in the CRFs of each study subject must be retained in the files of the Investigator for at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region; or at least two years have elapsed since the formal discontinuation of clinical development of the investigational drug. These documents should be retained for a longer period, however, if required by applicable regulatory requirements.

If the Investigator retires, relocates, or for any other reason withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. Prior to transfer, the Sponsor representative must be notified in writing of the name and address of the new custodian.

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