[redacted]

Boehringer Ingelheim

2021-005270-26

Double-blind, randomized, parallel group, placebo controlled clinical trial to evaluate the effects of atomoxetine on impulsivity in behavioral laboratory tasks in adult ADHD patients

Statistical Analysis Plan

Version: Final 2.0, 05-Feb-2024

[redacted]

BI trial number: 0352-2159

SPONSOR SIGNATURE PAGE

Approved by: _____ _____

[redacted]

Date

Approved by: _____ _____

[redacted]

Date

Approved by: _____ _____

[redacted]

Date

[redacted] SIGNATURE PAGE

Signatures below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	[redacted] Project Role: [redacted]

TABLE OF CONTENTS

REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	Date of last signature	Initial version
1.1	Not applicable	Clarification of derivations of psychometric outcomes. Correction of ANCOVA variable transformation instructions for [redacted]. Derivation clarification for [redacted]. Added clarification of duration conversion for year, month, week. Minor corrections in text consistency.
2.0	Date of last signature	

LIST OF ABBREVIATIONS

Abbreviation / Acronym	Definition / Expansion
[redacted]	
ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BIS	Barrett Impulsiveness Scale
BLQ	Below Limit of Quantification
CDISC	Clinical Data Interchange Standards Consortium
CRF	Case Report Form
C-SSRS	Columbia Suicidal Severity Rating Scale
CV	Coefficient of Variation
[redacted]	
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ES	Enrolled Set
ICC	Intraclass Correlation Coefficient
LLOQ	Lower Limit of Quantification
ln	Natural Logarithm
LSmean	Least-squares mean
ms	milliseconds
MedDRA	Medical Dictionary for Regulatory Activities
NOS	No Sample
PK	Pharmacokinetics
PK-PPS	Pharmacokinetic Per Protocol Set
PPS	Per Protocol Set
PT	MedDRA Preferred Term
[redacted]	
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	MedDRA System Organ Class

Abbreviation / Acronym	Definition / Expansion
[redacted]	
S-UPPS-P	Short Urgency, Perseverance, Premeditation, and Sensation Seeking-Positive Urgency Impulsive Behavior Scale
TEAE	Treatment-emergent Adverse Event
TS	Treated Set
TS1	Treated Set 1
TS14	Treated Set 14
WHODD	World Health Organisation Drug Dictionary

1 INTRODUCTION

This is a study to test different ways to measure the effect of atomoxetine on impulsive behavior in young adults with Attention Deficit Hyperactivity Disorder (ADHD).

There is considerable evidence that disorders clinically associated with impulsivity show impairment on a variety of questionnaire and behavioral measures of impulsivity. The key questions that will be addressed in this study include: (1) Do ADHD patients, with impulsivity as a core characteristic of the disorder, have a distinct behavioral profile based on questionnaire and behavioral laboratory measures before and after treatment with atomoxetine? (2) Are there specific measures that are reliable and sensitive measures of impulsivity which might be used across diagnoses? The answers to these questions are of importance in the selection of outcome measures for treatment and Phase I/II assessments of potential pharmacotherapies for different disorders.

The analyses described in this Statistical Analysis Plan (SAP) are based upon the following study documents:

- Trial Protocol, Version 3.0 (March 16, 2022)
- electronic Case Report Form (eCRF), Version 2.0 (March 09, 2022)

The study will be analyzed as described in the above-mentioned version of the trial protocol unless explicitly specified otherwise.

The content of this SAP is compatible with the International Council for Harmonisation E9 Guidance documents.

2 STUDY OBJECTIVES

The main objective of this trial is to identify the best-suited impulsivity measures for use in the future clinical trials, to investigate pharmacological modulation of impulsivity by atomoxetine after single dose and at steady-state, and to assess effect sizes and population variability.

- The primary objectives are to investigate the effect of atomoxetine on impulsivity after single dose and at steady state measured by the total score of BIS-11 and S-UPPS-P Impulsive Behavior Scale.
- The secondary objective is to evaluate the safety of atomoxetine.

[redacted]

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is an exploratory Phase I, multi-center, randomized, double-blind, placebo controlled parallel group trial in patients with ADHD. A targeted total of approximately 96 patients with ADHD meeting the entry criteria are planned to be randomized into this trial. The study drug is atomoxetine, an impulsivity-reducing ADHD medication.

Patients will be enrolled into the trial once consent has been signed. Patients suitable after screening will undergo baseline impulsivity assessments at Visit 2 and will be randomized to the 2-week double-blind treatment period (placebo or Atomoxetine in 1:1 ratio) at Visit 3 Day 1.

After the completion of the 2-week double-blind treatment period or following early discontinuation of trial medication at any point, patients will complete the last planned safety visit (End of Trial visit) 4 days after the last drug intake.

3.2 Trial Endpoints

3.2.1 Primary Endpoints

- Change from baseline in total score of BIS-11 after single dose (at Day 1)
- Change from baseline in total score of BIS-11 at steady state (at Day 14)
- Change from baseline in total score of S-UPPS-P Impulsive Behavior Scale after single dose (at Day 1)
- Change from baseline in total score of S-UPPS-P Impulsive Behavior Scale at steady state (at Day 14)

3.2.2 Secondary Endpoint

- Percentage of patients with (S)AEs:
    - Percentage of patients with treatment-emergent AEs*
    - Percentage of patients with treatment-emergent SAEs*

* This is a clarification of the protocol-defined endpoint.

[redacted]

[redacted]

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All datasets, tables, figures and patient data listings will be independently checked for consistency, integrity, in accordance with standard [redacted] procedures.

4.2 General Presentation Considerations

The below-mentioned general principles will be followed throughout the study:

- Continuous data will be summarized in terms of the mean, standard deviation (SD), median, lower and upper quartiles, minimum, maximum and number of observations, unless otherwise stated. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. Derived statistics like mean, median, SD will be reported to one more decimal place than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic. Descriptive statistics will only be presented if $n \geq 3$. If no participants have data at a given time point, $n = 0$ will be presented. If $n < 3$, only the n, minimum and maximum will be presented, the other descriptive statistics will be left blank.
- Categorical data will be summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages. Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Unless otherwise stated, percentages will be calculated using n (the number of observations with non-missing values) as the denominator. If applicable, the category 'missing' will be added as needed as a separate category.
- Variables measured more than once will be summarized for each time point.
- Change from baseline will be calculated as the visit value of interest minus the baseline value.
  Percentage change from baseline will be calculated as the change from baseline value divided by the baseline value (i.e. [post-baseline value – baseline value] / baseline value × 100).
- Summary tables, in general, will be presented by treatment arm as follows:

Atomoxetine	Placebo	Total
N = xx	N = xx	N = xx

  - "Total" column will be optional.
- All variables shown in summaries will also be included in patient data listings.

- Patient data listing will be presented and sorted by treatment arm, unique subject identifier and relevant visits or dates, if applicable.
- Dates will be formatted according to the International Standards Organization (ISO) 8601 standard. If time is part of a datum, then it will be added as YYYY-MM-DDThh:mm (e.g., 2022-02-12T14:31 being February 12th, 2022, 2:31 p.m.).
- Rounding for all variables will occur only as the last step of a derivation, immediately prior to presentation in listings and tables. No intermediate rounding will be actively performed on derived variables.
- Every table, listing and figure will be produced with
    - Client name and study ID
    - An electronic date stamp to document when it was produced
    - The name of the program used for creation
- Further formatting and presentation standards can be specified in the Tables, Listings and Figure mock shell document.

4.2.1 Baseline and End of Study

Baseline

For efficacy endpoints, the assessment closest to Day -14 (planned day of Visit 2) will be considered the baseline assessment. However, no assessment after Day -7 will be used as baseline.

For safety endpoints, the last valid non-missing assessment prior to the first dose of study drug will be considered the baseline assessment.
For assessments on the day of first intake:

- Where time is not captured but a nominal pre-treatment indicator is available, the nominal pre-treatment indicator will serve as sufficient evidence that the assessment occurred prior to first dose.
- Where neither time nor a nominal pre-treatment indicator are captured, the assessment will be considered prior to the first dose if such procedures are required by the protocol to be conducted before the first dose.

End of Study

'End of Study' will be defined as the last available post-treatment assessment.

4.2.2 Study Day

A 'Study Day' will be calculated relative to the date of Visit 3 (Day 1). For assessments after and on Day 1:

Study Day = Assessment Date – Day 1 Date + 1.

Pre-Visit 3 assessments will be calculated resulting in a negative Study Day:

Study Day = Assessment Date – Day 1 Date.

4.2.3 Duration Conversion

Whenever durations are converted into different time units,

- A year will consist of 365.25 days.
- A month will consist of 365.25/12 days.
- A week will consist of 7 days.

4.3 Software

All report outputs will be produced using SAS® version 9.4 or a later version in a secure and validated environment.

All report outputs (tables, listings, figures and statistical appendices) will be provided to the Sponsor

- in RTF format as individual files and
- in PDF format as combined files (specified in the mock TFL shell document).

The outputs will be categorized by type (tables, listings, figures and statistical appendices) and numbered logically and according to the Sponsor's numbering standards. A mock shell document will be created to define details of outputs.

4.3.1 Handling of Missing Data

All missing or partial data will be presented in the participant data listing as they are recorded on the CRF.

When appropriate, the following rules will be implemented so as not to exclude patients from statistical analyses due to missing or incomplete data:

4.3.1.1 Efficacy Variables

Statistical methods for missing data in efficacy variables are described in Section 4.10**Error! Reference source not found.**.

4.3.1.2 Safety Variables

Missing safety data will generally not be imputed.
However, safety assessment values of the form of "<x" (i.e. below the lower limit of quantification) or ">x" (i.e. above the upper limit of quantification) will be imputed as "x" in the calculation of summary statistics but displayed as "<x" or ">x" in the listings.
Additionally, AE that have missing causality will be assumed to be related to study drug.
Missing severity of an AE will be assumed to be severe. Occurrence of this is unlikely, as severity and causality are mandatory fields in the eCRF.

4.3.1.3 Dates for AEs

The imputation of missing / incomplete AE onset date/time is performed according to the following steps:

Step 1: For each missing / incomplete AE onset date, an interval (INT_START, INT_END) is defined. The true unknown analysis start date of the AE is assumed to be within this interval.

Scenario of AE onset date	INT_START	INT_END
Completely missing AE onset date	Min(AE end date, Date of informed consent)	Min(AE end date, Date of last visit)
Only year of AE onset date is non-missing	Min(AE end date, 01 JAN of the reported year)	Min(AE end date, 31 DEC of the reported year)
Only year and month of AE onset date are non-missing	Min(AE end date, 01 of the reported month)	Min(AE end date, Last date of the reported month)

Note: Completely missing AE end date will not be considered in this derivation step. Partially missing AE end date (i.e. year and month are non-missing or only year is non-missing) will be temporarily assigned the largest possible date in the observed year or month and year in this derivation step.

Step 2: Derive an imputed AE onset date based on the interval from step 1

Scenarios	On-Study AE / Not On-Study AE	Imputed AE onset date
1. Date of baseline is within the interval [INT_START, INT_END]	On-study	Date of baseline
2. Date of baseline is before INT_START	On-study	INT_START from step 1
3. Date of baseline is after INT_END or missing	Not on-study	INT_END from step 1

Step 3: The AE onset date / time imputation flag(s) are set according to the level of imputation performed and the standard CDISC rules for imputation or the legacy data imputation rules.

4.3.1.4 Dates for Medications

In case of (partially) missing start and end dates of concomitant medications and non-drug therapies, the dates will be imputed so that the extent of exposure to the concomitant medication/non-drug therapy is maximal:

- Missing start day will be imputed as the first day of the month.

- Missing end day will be imputed as the last day of the month.
- Missing start month will be imputed as the first month of the year (January).
- Missing end month will be imputed as the last month of the year (December).

4.4 Study Patients

4.4.1 Disposition of Patients

Disposition of patients will be based on the ES.

The number and percentage of patients enrolled, screened, dosed, completed or prematurely discontinued the study including primary reason for discontinuation will be presented by treatment group and total. Percentages will be based on the number of patients in the ES.

A by-patient listing of disposition will be presented including date of informed consent, date/time of first and last study drug, study completion status and date of completion/premature discontinuation with primary reason for discontinuation.

In case of interim analyses, the status will include ongoing for patients enrolled, but not completed or discontinued.

Reasons for screen failure will be listed for patients failing screening.

4.4.2 Protocol Deviations

Important protocol deviations (IPDs) are defined as those deviations from the protocol likely to have an impact on the perceived efficacy of study drug. The impact of IPDs on efficacy results will be investigated by assessing the robustness of the study results and conclusions to the choice of analysis set, both including and excluding data potentially affected by IPDs.

This evaluation of importance will be completed before database lock and resulting residence of patients in each analysis set confirmed and approved by the Sponsor. The final confirmation is planned to be performed within the Data Review Meeting minutes signed prior to database lock. During study conduct, regular protocol deviation reviews will be performed, which allow assigning an action for analysis “Exclude from Per Protocol Set (PPS) Analysis”, which will be used to identify IPDs.

The major/minor protocol deviations and default action to be taken regarding the exclusion of subjects or affected data from specific analyses are defined in the project-specific Protocol Deviation Specification, but can differ from the classification as IPD.

Any major protocol deviations as well as all IPDs (if different) will be listed and the number and percentage of patients with IPDs summarized by type of deviation based on the Treated Set.

4.5 Analysis Sets

Enrolled Set (ES)	All patients who signed informed consent. The ES will be used for patient disposition information.
Entered Subjects	All subjects of the ES who have a pre-treatment assessment of any impulsivity test or questionnaire (This includes subjects who are not treated).
Treated Set (TS)	All subjects who were treated with at least one dose of study drug (i.e. placebo or atomoxetine). The TS will be used for safety analysis.
Treated Set 1 (TS1)	All subjects who were treated at Day 1 with one dose of study drug (i.e. placebo or atomoxetine). The TS1 will be used for the primary analysis at Day 1.
Treated Set 14 (TS14)	All subjects in the TS who were treated according to protocol for at least 90% (not more than one missed dose) of the planned doses of study drug (i.e. placebo or atomoxetine). The TS14 will be used for the primary analysis at Day 14. Please see Section 4.9.2 for definition of treatment compliance.
Per Protocol Set (PPS)	All subjects of the TS which have no IPDs. The PPS will be used for sensitivity analysis of efficacy.
Pharmacokinetic Per Protocol Set (PK-PPS)	The PK-PPS includes all subjects from the TS who provide at least one PK value that was not excluded due to a protocol deviation relevant to the evaluation of PK.

A summary of the number and percentage of patients in each analysis set will be presented for the ES, with denominators based on the number of patients who were enrolled.

A by-patient listing of analysis set details will be presented for all enrolled patients, including the patient identifier, site and indication of inclusion into/exclusion from each analysis set.

Upon database release, protocol deviation and analysis set outputs will be produced and will be sent to Boehringer Ingelheim for review. An analysis population classification meeting will be arranged to discuss the outputs and to decide which subjects and/or subject data will be excluded from certain analyses (especially for the set PK-PPS but not limited to this set). Decisions made regarding the exclusion of subjects and/or subject data from analyses will be documented and approved by Boehringer Ingelheim.

If a subject is allocated the incorrect study drug as per the study randomisation list, subjects will be analyzed ‘as treated’ i.e. by actual treatment group for all outputs as follows. Identification of such cases will be confirmed and documented in the Data Review Meeting minutes.

- TS1: Subjects will be counted towards the treatment arm as treated regardless of their randomisation.

- TS14: In the rare case of partial mistreatment (both atomoxetine and placebo), the patient will be part of TS14 only if either more than 90% of the received doses are atomoxetine or more than 90% of the received doses are placebo. Percentages less than 90% will lead to exclusion from TS14 (as the compliance is less than 90%).
- TS: In the rare case of partial mistreatment (both atomoxetine and placebo), the patient will be analyzed as belonging to the atomoxetine arm for all safety analyses.

4.6 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be listed by patient and summarized descriptively by treatment group and total using the TS. This includes aget screening, sex, ethnicity, race, highest level of education at screening, and status of employment at screening. Birth year will only be listed.

If the subject has consumed alcohol in the past 3 months (Yes/No) and if the subject consumed tobacco (current/previous/never) will be summarized by counts and percentage relative to the number of subjects in the TS.

Detailed alcohol and smoking history information will only be listed.

4.7 Medical History and Concomitant Illnesses

Medical history and concomitant illnesses, i.e. medical conditions with an onset date earlier than the screening visit date and end date either before screening visit (medical history) or still ongoing at time of screening (concomitant illness).

These medical conditions are collected via the eCRF and then coded using MedDRA version 24.1 or higher.

All related medical history will be listed including description of the disease/procedure, MedDRA SOC, PT, start date and stop date (or ongoing, if applicable). Number of subjects with a history or concomitant illness will be counted by SOC and PT and by treatment group. Percentages will be based on the number of subjects in the TS.

4.8 Prior and Concomitant Medications

Medication taken before and during the study are collected in the eCRF and coded according to ATC classification of the WHODD January 2022 or later.

Medication start and stop dates will be compared to the date of Visit 2 to allow medications to be classified as either Prior only, both Prior and Concomitant, or Concomitant only. Medications captured that start after the treatment completion/withdrawal date will be listed but will not be classified or summarized.

- Medications that start and stop prior to the date of Visit 2 will be classified as Prior only.

- If a medication starts before the date of Visit 2 and stops on or after the date of Visit 2, then the medication will be classified as both Prior and Concomitant.
- Medications will be classified as Concomitant only if they have a start date on or after the date of Visit 2, but not after the last dose of study drug.

If medication start and/or stop dates are missing or partial, the dates will be compared as far as possible with the date of first dose of study drug. Medications will be assumed to be Concomitant only, unless there is clear evidence (through comparison of partial dates) to suggest that the medication started prior to Visit 2. If there is clear evidence to suggest that the medication started prior to Visit 2, the medication will be assumed to be both Prior and Concomitant, unless there is clear evidence to suggest that the medication stopped prior to Visit 2. If there is clear evidence to suggest that the medication stopped prior to Visit 2, the medication will be assumed to be Prior only.

The duration of the medication will be calculated as:

$$\text{Duration} = (\text{end date}) - (\text{start date}) + 1$$

The TS will be used for listing and summary of prior and concomitant medication. The patient data listing and summary table will include the anatomical main group (level 1), the therapeutic subgroup (level 2), preferred name and reported term. Counts and percentages of subjects taking medication for each of these levels will be based on the number of subjects in the TS.

4.9 Treatment Exposure / Compliance

4.9.1 Treatment Exposure

The study drug administration dates and times for site treatment visits will be listed for each participant for the planned administration visits together with administered number of capsules as documented in the study drug administration eCRF.

Additionally, daily intake of the study drug is monitored using a smartphone app serving as a reminder to the subjects for intake of the medication. Each pill intake is planned to be captured with date and time.

A subject level listing will be created for the TS to present both eCRF and e-diary information of study drug intake. This listing will include the number of pills administered at treatment visits (eCRF), date and time of each intake documented in the e-diary, total number of pills taken per subject as well as the number of actual days of study drug intakes, the number of planned days of study drug intakes and the treatment compliance percentage (per Section 4.9.2).

The total number of pills taken per subject as well as the treatment compliance percentage will be summarized by treatment group for the TS.

4.9.2 Compliance

The study drug is to be taken once daily in either 80 mg or 40 mg doses. Subject compliance to study drug will be evaluated as percentage of missed dosing days determined by e-diary data for

drug intake monitoring at home. The number of planned days of study drug intake is 14 days for all patients. Partial intake of study drug (e.g. 40 mg instead of 80 mg) will be counted as compliant.

$$Treatment\ compliance\ (\%) = \frac{number\ of\ actual\ days\ of\ study\ drug\ intakes}{number\ of\ planned\ days\ of\ study\ drug\ intakes} * 100$$

4.10 Endpoint Evaluation

4.10.1 Analysis and Data Conventions

Analyses on the primary, secondary, and further exploratory endpoints will be conducted in an exploratory way and therefore no formal statistical hypothesis testing is planned in this study and no formal sample size calculations (see Section 4.12) were performed.

4.10.1.1 Multi-center Studies

All sites (i.e. investigational sites) will be combined together for the purposes of the analysis.

4.10.1.2 Handling of Dropouts or Missing Data

Dropouts will be defined as patients who prematurely discontinue from the study and study drug at the same time for any reason. This also includes patients who are lost to follow-up.

Handling of missing data due to dropout is described in Sections 4.10.1.6 and 4.10.3 for efficacy variables, no action for missing data due to dropouts is taken for other variables. Patients who dropped out will not be excluded from any summaries, except where clearly stated.

4.10.1.3 Multiple Comparisons/Multiplicity

Given that

- No formal hypothesis testing is planned and
- The study has an exploratory nature

No adjustments for multiplicity and methods for controlling the Type I error are required.

4.10.1.4 Interim Analyses

No formal interim analysis will be performed and therefore no methods for controlling the Type I error are required. No formal interim clinical trial report is planned.

The following preliminary, exploratory, and non-decisional analyses may be performed:

- A first preliminary exploratory analysis of the primary and further efficacy endpoints might be performed when approximately 60% of patients will have completed treatment (i.e. Visit 4 - Day 14 – end of treatment) and will include all efficacy data. The cut-off date will be the date on which the 48th patient (i.e. 60% of 80 evaluable patients) completes Visit 4.
- A second preliminary exploratory analysis of the primary and further efficacy endpoints may be performed when the last patient will complete treatment (i.e. Visit 4 - Day 14 –

end of treatment) and will include all efficacy data. The cut-off date will be the date on which the last patient completes Visit 4.

- Preliminary exploratory analysis of PK concentrations of atomoxetine may be performed based on all evaluable data prior to data base lock. This may be necessary e.g. to confirm treatment compliance and appropriateness of measurements for primary analysis and/or, if required, to inform other investigations in development. In contrast to the final PK calculations, the preliminary, exploratory analysis may be based on planned sampling times rather than on actual times, regardless of whether actual times were within the time windows or not. Therefore, minor deviations of preliminary and final results may occur. No formal preliminary PK report will be written. This analysis of PK data may be standalone or combined with one of the other analyses.

The cut-off dates will be the same for all patients. A database snapshot will be taken with regard to these cut-off dates, including all efficacy data available in the database up to the cut-off date, and will be used for analysis purpose. Only cumulative results will be presented, i.e. patient level and safety data will be excluded. Investigators (outcome assessors) and everyone involved in trial conduct (except the trial personnel involved in the administering the trial medication–third-party blinding) will remain blinded and will not have access to the unblinded snapshot data. Trial functions of the sponsor and responsible global vendor are unblinded (including CTL/PM, data managers, statisticians, bioanalysts, pharmacokineticists, pharmacometricians) and will conduct all interim analyses.

[redacted]

4.10.1.6 Vomiting and Nausea

Cases of vomiting and nausea can occur following intake of atomoxetine. Vomiting and nausea events will be captured as AEs and the sites / patients will be encouraged to report start and end times of these events to identify impact on study drug as well as impulsivity testing. Such AEs will be summarized separately (please refer to Section 4.11.1).

If the start time of the AE of vomiting or nausea is missing, it will be assumed not to have affected treatment or impulsivity assessment.

On Day 1 and Day 14, occurrence of vomiting post-dose, but before PK sampling will lead to exclusion of any following PK sample from summary statistics (see Section 4.10.5) for the PK concentrations of that day. E.g., if vomiting occurs on Day 14 post-dose, but before the first sampling time on Day 14, both Day 14 samples (pre- and post-impulsivity testing) will be excluded from PK summaries. Such events will be reviewed during AE review and the preliminary and/or interim analysis or at the Data Review Meeting prior to database lock.

It is expected that vomiting and nausea can have influence on the conduct of impulsivity assessments. For the primary analysis, occurrence of these events will not lead to exclusion from the analysis and this event is handled by the treatment policy strategy.

[redacted]

4.10.2 Primary Endpoints

4.10.2.1 Change from Baseline in Total Score of Barratt Impulsiveness Questionnaire v.11 After Single Dose (at Day 1)

All analyses described below for the primary efficacy variables will be analyzed on the TS1 by randomized treatment arm, regardless of any changes to dose interval.

The estimand is specified through the following definitions of population, variable, treatment condition, ICE, and population-level summary:

Population: Defined by the inclusion/exclusion criteria.

Variable: Absolute change from baseline to Day 1 in total score of BIS-11 questionnaire.

The Barratt Impulsiveness Scale is a questionnaire designed to assess the personality/behavioral construct of impulsiveness. It is composed of 30 items/questions describing common impulsive or non-impulsive (for reverse scored items) behaviors and preferences. Items are scored on a 4-point scale from "1" for the least impulsive choice to "4" for most impulsive choice (i.e. Rarely/Never = 1; Occasionally = 2; Often = 3; Almost Always/Always = 4). The total score is given by the sum of the scores of the single items, thus ranging from 30 (minimum score – most favorable score) to 120 (maximum score – least favorable score).

Treatment condition: Atomoxetine arm vs. placebo arm.

Intercurrent events (ICE): Premature discontinuation from treatment: While-on-treatment strategy. Only assessments prior to the occurrence of the intercurrent event will be considered.

Use of concomitant/rescue therapy: Treatment policy strategy. The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs.

Vomiting or nausea: Treatment policy strategy. The estimate is accepted to include occurrences of this intercurrent event: the value

for the variable of interest is used regardless of whether or not the intercurrent event occurs.

Death: Composite strategy. It is not expected that there will be any death during the study but if any death occurs it will be handled with a composite strategy where the worst possible outcome (i.e. maximum score of 120) will be used in the analysis.

Population-level summary: Difference in mean change from baseline to Day 1 in total score of BIS-11 between Atomoxetine arm and placebo arm.
Negative differences favor the atomoxetine arm.

4.10.2.2 Change from Baseline in Total Score of Barratt Impulsiveness Questionnaire v.11 at Steady State (at Day 14)

All analyses described below for the primary efficacy variables will be analyzed on the TS14 by randomized treatment arm, regardless of any changes to dose interval.

The estimand is specified through the following definitions of population, variable, treatment condition, intercurrent events, and population-level summary:

Population: Defined by the inclusion/exclusion criteria.

Variable: Absolute change from baseline to Day 14 in total score of BIS-11 questionnaire.
See above for details on BIS-11 questionnaire and total score.

Treatment condition: Atomoxetine arm vs. placebo arm.

Intercurrent events (ICE): Premature discontinuation from treatment: While-on-treatment strategy. Only assessments prior to the occurrence of the intercurrent event will be considered.

Use of concomitant/rescue therapy: Treatment policy strategy. The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs.
Vomiting or nausea: Treatment policy strategy. The estimate is accepted to include occurrences of this intercurrent event: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs.

Death: Composite strategy. It is not expected that there will be any death during the study but if any death occurs it will be handled with a composite strategy where the worst possible outcome (i.e. maximum score of 120) will be used in the analysis.

Population-level summary: Difference in mean change from baseline to Day 14 in total score of BIS-11 between Atomoxetine arm and placebo arm.
Negative differences favor the atomoxetine arm.

4.10.2.3 Change from Baseline in Total Score of S-UPPS-P Impulsive Behavior Scale After Single Dose (at Day 1)

All analyses described below for the primary efficacy variables will be analyzed on the TS1 by randomized treatment arm, regardless of any changes to dose interval.

The estimand is specified through the following definitions of population, variable, treatment condition, intercurrent events, and population-level summary:

Population: Defined by the inclusion/exclusion criteria.

Variable: Absolute change from baseline to Day 1 in total score of S-UPPS-P Impulsive Behavior Scale questionnaire.

The S-UPPS-P Impulsive Behavior Scale is a questionnaire designed to assess impulsivity as a multi-faceted and multi-dimensional construct, comprising five impulsive personality traits. It is composed of 20 items/questions describing impulsive or non-impulsive (for reverse scored items) behavior. Items are scored on a 4-point scale from "1" for the least impulsive choice to "4" for most impulsive choice (i.e. Agree Strongly = 1; Agree Some = 2; Disagree Some = 3; Disagree Strongly = 4). The total score is given by the sum of the scores of the single items, thus ranging from 20 (minimum score – most favorable score) to 80 (maximum score – least favorable score).

Treatment condition: Atomoxetine arm vs. placebo arm.

Intercurrent events (ICE): Premature discontinuation from treatment: While-on-treatment strategy. Only assessments prior to the occurrence of the intercurrent event will be considered.

Use of concomitant/rescue therapy: Treatment policy strategy. The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs.

Vomiting or nausea: Treatment policy strategy. The estimate is accepted to include occurrences of this intercurrent event: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs.

Death: Composite strategy. It is not expected that there will be any death during the study but if any death occurs it will be handled with a composite strategy where the worst possible outcome (i.e. maximum score of 80) will be used in the analysis.

Population-level summary: Difference in mean change from baseline to Day 1 in total score of S-UPPS-P Impulsive Behavior Scale between atomoxetine arm and placebo arm.
Negative differences favor the atomoxetine arm.

4.10.2.4 Change from Baseline in Total Score of S-UPPS-P Impulsive Behavior Scale at steady state (at Day 14)

All analyses described below for the primary efficacy variables will be analyzed on the TS14 by randomized treatment arm, regardless of any changes to dose interval.

The estimand is specified through the following definitions of population, variable, treatment condition, intercurrent events, and population-level summary:

Population: Defined by the inclusion/exclusion criteria.

Variable: Absolute change from baseline to Day 14 in total score of S-UPPS-P Impulsive Behavior Scale questionnaire.

See above for details on S-UPPS-P questionnaire and total score.

Treatment condition: Atomoxetine arm vs. placebo arm.

Intercurrent events (ICE): Premature discontinuation from treatment: While-on-treatment strategy. Only assessments prior to the occurrence of the intercurrent event will be considered.

Use of concomitant/rescue therapy: Treatment policy strategy. The occurrence of the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs.

Vomiting or nausea: Treatment policy strategy. The estimate is accepted to include occurrences of this intercurrent event: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs.

Death: Composite strategy. It is not expected that there will be any death during the study but if any death occurs it will be handled with a composite strategy where the worst possible outcome (i.e. maximum score of 80) will be used in the analysis.

Population-level summary: Difference in mean change from baseline to Day 14 in total score of S-UPPS-P Impulsive Behavior Scale between atomoxetine arm and placebo arm.
Negative differences favor the atomoxetine arm.

4.10.2.5 Main Analysis

For the analysis of the primary efficacy variables, an ANCOVA will be used, with the questionnaire score at baseline as a covariate and the treatment arm as fixed factor.

The above-mentioned ICEs except for death are expected. Occurrences of missing data will generally be assumed at random and therefore missingness handled by case-exclusion for each ANCOVA, meaning only pairs of available baseline and post-baseline assessments will be analyzed. The case of missingness due to treatment-related AE will be investigated in Sensitivity Analysis 2.

Only in case of death missing data will be imputed using the composite strategy using the worst possible outcome (i.e. maximum score of 120 for the BIS-11 questionnaire and 80 for the S-UPPS-P Impulsive Behavior Scale questionnaire) for patients who die in between baseline assessment and Day 14 assessment.

In the example of the change from baseline in total score of BIS-11 at steady state (at Day 14), the observation at Day 14 of patient i receiving treatment t can be written as follows:

$$Y_{it} = \beta_0 + \mu_t + x_i\beta_{base} + \epsilon_{it}$$

with

- Y_{it} being the change from baseline to Day 14 for the ith patient,
- β_0 being the intercept,
- μ_t being the treatment effect,
- x_i being the baseline BIS-11 questionnaire score of patient i,
- β_{base} the fixed effect of the baseline BIS-11 questionnaire score,
- ϵ_{it} the residual error with $\epsilon_{it} \sim N(0, \sigma_t^2)$ being the residual error for treatment arm t.

In terms of the model parameters, the estimate of the population-level summary of the estimand (i.e. the treatment effect at Day 14) can then be expressed as

$$\widehat{diff}_{treat} = \hat{\mu}_t^{(Atomoxetine)} - \hat{\mu}_t^{(Placebo)}.$$

Summary tables will include number of patients, LSmean)change, (unadjusted) mean change and SD and baseline means of each treatment group and the estimate of the treatment difference expressed as LSmean difference including the corresponding two-sided 95% confidence interval. Each ANCOVA will be accompanied by a residual plot showing the predicted value versus the

standardized residual. SAS html outputs for each ANCOVA procedure will be stored as statistical output appendix.

[redacted]

4.10.3 Secondary Endpoints

Please refer to Section 4.11.1 Adverse Events.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.10.5 Pharmacokinetics

4.10.5.1 Pharmacokinetic Concentrations

All collected pharmacokinetic concentrations of atomoxetine will be listed for each participant and by treatment (at least the Placebo samples for the timepoints Visit 3, Planned Time 2:00 hours and Visit 4, 314:00 hours will be measured) in the TS. Listings will include actual sampling times relative to dose administration, the subject's inclusion in the PK-PPS and concentrations' inclusion/exclusion from the analysis with the reason for exclusion. Plasma concentrations below the LLOQ will be presented as BLQ in the listings.

Plasma concentration data of a patient will be included in the PK analyses (i.e. descriptive summaries), if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (in a Data Review Meeting prior to database lock) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Only concentrations within the validated concentration range will be used. Handling of pharmacokinetic concentrations will be done according to BI standards. Exclusion of a patient's data will be documented in the Clinical Trial Report and excluded data listed together with the reason for exclusion.

Reasons for data exclusions considered include, but are not limited to:

- Vomiting occurs on Day 1 or 14 post-dose, but prior to or during a PK sampling and will be finally confirmed during AE review (see Section 4.10.1.6)
- PK samples are collected more than 30 minutes before the nominal time of 2:00 hours after study drug administration (start time of impulsivity testing), and / or more than 30 minutes after the nominal time of 3:00 hours after study drug administration (end of impulsivity testing) after study drug administration on Day 1 and 14 and will be confirmed during PK data review
- No study drug intake on Day 1 or 14

Plasma concentrations of atomoxetine will be summarized by treatment group, visit and nominal timepoint. The following descriptive statistics will be presented for plasma concentrations obtained at each nominal time point: n, arithmetic mean, SD, arithmetic coefficient of variation (CV%), geometric mean, geometric CV%, geometric SD, median, minimum, maximum and percentiles 10, 25 (1^{st} quartile), 75 (3^{rd} quartile) and 90.

The geometric mean / SD will be calculated as the exponential value of the arithmetic mean / SD of natural logarithm transformed concentrations. The geometric CV% will be calculated as $gCV\% = SQRT(e^{s^2}-1)*100$; where s is the standard deviation of the log-transformed values.

The following rules will be followed with regards to the number of decimal places and presentation of data in the tables and listings of concentration data:

- Source data shall be used in all derived PK concentrations without prior rounding.
- Statistics resulting from computations (mean, SD, geometric mean, geometric SD, median and percentiles) will be tabulated to one more digit compared to the source data, but with a maximum of four significant digits.
- Minimum and maximum values will be tabulated to the same precision as the source data, but with a maximum of four significant digits.
- Geometric coefficient of variation (CV) % and coefficient of variation (CV%) will be presented to one decimal place.

[redacted]

4.10.5.2 Handling of Values Below the Limit of Quantification

Concentrations identified as Below the Limit of Quantification (BLQ) will be substituted by LLOQ/2 for calculations.

All concentrations BLQ will be labeled as such in the concentration data listings. Missing samples will be reported as no sample ("NOS") and excluded from analysis. Summary statistics

will only be calculated if the number of available, non-BLQ values is ≥ 3. If this number is < 3, only the n, minimum and maximum will be presented.

4.10.5.3 Pharmacokinetic Parameters

No pharmacokinetic parameters will be calculated. Only plasma concentrations and descriptive statistics of plasma concentrations will be reported.

4.11 Safety Evaluation

All safety listings, summaries and analyses will be based upon the TS as defined in Section 4.5.

4.11.1 Adverse Events

- An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

  An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether considered related or not.

  The following should also be recorded as an AE in the CRF and Boehringer Ingelheim SAE form (if applicable):

  - Worsening of the underlying disease or of other pre-existing conditions.
  - Changes in vital signs (body temperature, systolic and diastolic blood pressure, and pulse rate), ECG, physical examination (QTc interval and interpretation, clinically relevant abnormal findings), assessment of suicidality via C-SSRS and laboratory test results (hematology, chemistry, enzymes, electrolytes, substrates, pregnancy test, urinalysis [at screening]), if they are judged clinically relevant by the investigator.
  - If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.
- A TEAE is defined as an AE that begins or that worsens in severity after at least one dose of the study drug has been administered. Only AEs with start date until 4 days after the last dose of study drug are considered as TEAEs.
- An SAE is defined as any AE, which fulfils at least one of the following criteria:
  - results in death,
  - is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
  - requires inpatient hospitalisation or prolongation of existing hospitalisation

  - results in persistent or significant disability or incapacity,
  - is a congenital anomaly / birth defect,
  - is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

- Adverse events will be coded using theMedDRA Version 24.1 or higher.
- Listings and tables showing AEs will be based on the TS.
- Where dates are missing or partially missing, AEs will be assumed to be treatment-emergent, unless there is clear evidence (through comparison of partial dates) to suggest that the AE started prior to the first dose of study drug.
- Adverse event summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC, in the study drug treatment group, and then alphabetically for SOC, and PT within SOC.
- For each subject and each AE, the worst severity recorded will be attributed and used in the by-severity summaries. Similarly, the worst causality (most related to treatment) will be attributed and used in the by-causality summaries. If severity or causality is missing, the worst case will be assumed.

AE information will be listed per subject including the MedDRA SOC, PT and reported term. The listing will include at least age, sex, race of the patient and start/end date/time, relationship to study drug per the investigator's opinion, severity, seriousness, outcome, duration, leading to dropout, action taken of the event.

The following descriptive summaries will be produced for TEAEs with percentages based on the number of subjects in the TS:

- A summary of the number and percentage of subjects reporting a TEAE by seriousness, relationship to study drug, maximum severity, death and leading to discontinuation for each treatment group
- A summary of the number and percentage of subjects reporting a TEAE by treatment group, SOC and PT including the number of events.
- A summary of the number and percentage of subjects reporting an SAE by treatment group, SOC and PT including the number of events.

- A summary of the number and percentage of subjects reporting a TEAE resulting from the C-SSRS assessment 'since last visit' (per the investigator's clinical judgement) by treatment group, seriousness, SOC and PT including the number of events.
- A summary of the number and percentage of subjects reporting treatment-emergent vomiting or nausea by treatment group, SOC and PT including the number of events.
- A summary of the number and percentage of subjects reporting a TEAE that exceed a frequency of 5 percent within any treatment arm by treatment group, SOC and PT including the number of events (i.e. only those events with a PT that occurs in more than 5% of patients of the TS).

4.11.2 Clinical Laboratory Evaluation

All safety laboratory analyses will be performed by local laboratories, the respective reference ranges will be used by the investigator to assess abnormality, which will be captured in the CRF as an overall assessment:

- Normal
- Abnormal – Clinically Significant
- Abnormal – Not Clinically Significant

with specification of the laboratory assessment in case of clinically significant abnormality.

Laboratory values will not be received for analysis.

The assessments will be listed in parameter groups:

- Urinalysis
- Viral Serology
- Hematology
- Chemistry

and are scheduled to be collected for:

- Visit 1
- Visit 2 (only drug test)
- Visit 3, Day 1 (pre-dose)
- Visit 3, Day 8 (only drug test)
- Visit 4
- Visit 5

The overall assessment and each specified clinically significant abnormal parameter will be listed for each patient and visit/timepoint by treatment group including age, sex and any additional details recorded on the eCRF for abnormal clinically significant.

4.11.3 Vital Signs, Physical Findings, ECG and Menstrual Cycle Information

The following **vital signs** parameters will be listed and summarized based on the TS.

- Temperature
- Pulse rate (beats/min)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)

will be assessed at

- Visit 1
- Visit 3 (Day 1 pre-dose and 4h post-dose)
- Visit 3 (Day 8)
- Visit 4 (pre-dose and 4h post-dose)
- Visit 5

The overall assessment and each specified clinically significant abnormal parameter will be listed for each patient and visit/timepoint by treatment group including age, sex and any additional details recorded on the eCRF for abnormal clinically significant.

Physical examination will be performed at

- Visit 1
- Visit 3 (Day 1 pre-dose)
- Visit 3 (Day 8)
- Visit 4 (pre-dose)
- Visit 5

Physical exam findings are recorded per the eCRF as weight and height, as well as overall interpretation of body systems:

1. Normal
2. Abnormal – Clinically Significant
3. Abnormal – Not Clinically Significant

and specified only if Abnormal – Clinically Significant.

A by-patient listing of physical exam results will be presented, including the patient identifier, visit, study day of finding, indication of whether exam was performed and reason examination not performed (if applicable), specified body system, physical exam result, additional details recorded on the eCRF for abnormal clinically significant, height and weight.

Standard safety **12-lead ECG**s will be performed at

- Visit 1
- Visit 3 (Day 8)
- Visit 4
- Visit 5

The following ECG parameters will be recorded:

- QTc-interval (msec)

The ECG will be evaluated by the Investigator as

- Normal
- Abnormal – Clinically Significant
- Abnormal – Not Clinically Significant

All ECG parameters will be listed by patient and captured time point.

Menstrual cycle information (provision of information and date of last menstrual period) will be captured at each site visit. This information will be presented in a by-patient listing for all female patients.

4.11.4 Safety Monitoring (Independent Data Monitoring Committee, Data Monitoring Committee, Data and Safety Monitoring Board)

Not applicable.

4.12 Determination of Sample Size

No formal testing of hypotheses has been planned for this study. Therefore, no formal sample size calculations were performed.

It is planned to enter a total of 80 evaluable subjects in the trial, because this sample size is considered sufficient to achieve the aims of this exploratory trial with regards to the primary and secondary endpoints, but also concerning the sufficiency of the sample size of further endpoints of particular interest.

For more details, please refer to the Clinical Trial Protocol Section 7.5.

4.13 Changes and Clarifications in the Conduct of the Study or Planned Analysis

Clarification

According to CTP Section 7.2.1, the TS14 analysis set is defined as “The TS14 includes all subjects who were treated according to protocol for at least 90% (not more than one missed dose) of the planned doses of study drug (i.e. placebo or atomoxetine).”, while Section 4.3 defines

treatment compliance percentage via number of tablets, the treatment compliance used for analysis of TS14 is according to SAP Section 4.9.2 based of days of study drug intake, not the number of tablets, which is used to monitor study conduct.

Changes

Not applicable.

5 REFERENCES

[1] Mazur, JE. An adjusting procedure for studying delayed reinforcement. In: Mazur, JE.; Nevin, JA.; Rachlin, H., editors. Quantitative analysis of behavior: vol 5. the effects of delay and intervening events on reinforcement value. Hillsdale: Erlbaum; 1987. p. 55-73.

[2] McGraw, Kenneth & Wong, S.P. (1996). Forming Inferences About Some Intraclass Correlation Coefficients. Psychological Methods. 1. 30-46. 10.1037/1082-989X.1.1.30.

6 APPENDICES

Not applicable.

[redacted]

Approval Signatures

Document Name: Statistical Analysis Plan 08 Feb 2024 0352-2159

Document Number: VV-TMF-2021429

[redacted] **Version Number:**

System Version Number: 2 .0

Document Approvals	
Reason for signing: Approved	Name: [redacted] Role: Sponsor Date of signature: 06-Feb-2024 10:25:01 GMT+0000
Reason for signing: Approved	Name: [redacted] Role: Sponsor Date of signature: 06-Feb-2024 11:18:35 GMT+0000
Reason for signing: Approved	Name: [redacted] Role: Biostatistics Date of signature: 08-Feb-2024 10:48:37 GMT+0000
Reason for signing: Approved	Name: [redacted] Role: Sponsor Date of signature: 08-Feb-2024 15:59:02 GMT+0000