Clinical Trial Protocol

	Document Number:	**c36371216-05**
EudraCT No.	2021-005270-26	
BI Trial No.	0352-2159	
BI Investigational Medicinal Product	NA	
Title	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	
Lay Title	A study to test different ways to measure the effect of atomoxetine on impulsive behavior in young adults with Attention Deficit Hyperactivity Disorder (ADHD)	
Clinical Phase	NA	
Clinical Trial Leader	[redacted] Phone: [redacted]	
Coordinating Investigator	[redacted] Phone: [redacted]	
Current Version and Date	**Version: 4.0** **28 Feb 2024**	
Original Protocol Date	**25 October 2021**	**Page 1 of 67**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original Protocol date	25 Oct 2021
Revision date	28 Feb 2024
BI trial number	0352-2159
Title of trial	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
Coordinating Investigator	[redacted]
Trial site(s)	Multicenter trial in approximately 5 clinical sites across Germany
Clinical phase	Not applicable
Trial rationale	To investigate the effects of impulsivity-reducing ADHD medication atomoxetine on impulsivity as measured by behavioral laboratory tasks in ADHD patients.
Trial objective(s)	Translational study to identify the best-suited impulsivity measures for use in 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.
Trial endpoints	Primary endpoints: Change from baseline after single dose and at steady state for: • Change from baseline in total score of Barratt Impulsiveness Questionnaire v.11 (BIS-11) after single dose (at day 1) • Change from baseline in total score of Barratt Impulsiveness Questionnaire v.11 (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) Secondary endpoints: • Percentage of patients with (S)AEs [redacted]
Trial design	Randomized, placebo-controlled, double-blind, parallel group trial.
Total number of patients randomised	80*
Number of patients per treatment group	40 per treatment arm * Additional subjects may be entered to allow the sample size of 80 evaluable subjects who completed the study per protocol. Thus, the actual number of subjects entered may exceed 80, but will not exceed 96.
Diagnosis	Adult Attention Deficit Hyperactivity Disorder (ADHD)

Main inclusion and exclusion criteria	Male and female subjects, age of 18-45 years; Diagnosis of ADHD according to DSM-5, currently undergoing diagnostic assessment and/or treatment for ADHD (registered with psychiatrist/ clinic/study site); Able and willing to discontinue the use of any psychotropic medications for treatment of ADHD symptoms, as well as of all relevant co-medication for comorbid conditions during the study; Subjects have a moderate symptom of ADHD with combined score of 4 or higher in Clinical Global Impression-ADHD-Severity (CGI-ADHD-S) at Screening; Hyperactivity/Impulsivity subscale of the ADHD check-list min 8 (at least moderate for impulsivity);
Test product(s)	Atomoxetine
dose	40 mg
mode of administration	Oral with 240 mL of water after an overnight fast of at least 10 h
Comparator product(s)	Placebo
dose	Not applicable
mode of administration	Oral with 240 mL of water after an overnight fast of at least 10 h
Duration of treatment	14 days with once daily doses
Statistical methods	For the single behavioral measures (primary endpoints), analysis of covariance (ANCOVA) will be used to compare means between groups. This will be done after single-dose and at steady state. Descriptive statistics will be calculated for all endpoints.

FLOW CHART

Visit	Day	Planned Time [h:min]	time (actual day) [h:min] (*Assumed dosing time is 8:00am, but the actual dosing time may differ for a particular subject*)	Physical examination	Behavioral test battery[2]	Questionnaires[3]	Laboratory/ Urinalysis	PK sampling	C-SSRS	CGI-ADHD-S	ECG, vital signs[6] (BP, PR)	Adverse events / Con. med
1	-28 to -16(14)		**Screening[1]**	X			X		X	X	X	▲ | X | ▼
2	-16 to -14		**Baseline**		X	X	X[7]					
3	1	-0:30	Predose	X			X	X	X		X[9]	
		0:00	8:00 **Drug administration**									
		1:00	Breakfast									
		2:00	10:00		X	X		X[10]				
		3:00	11:00					X[11]				
		4:00	12:00 Lunch	X[13]							X[9]	
			Training/Dispence Medication[4] Discharge from trial site									X
	2	24:00	8:00 Drug intake									▲
	3	48:00	8:00 Drug intake									X ▼
	4	72:00	8:00 Drug intake						X			X[8]
	5	96:00	8:00 Drug intake									▲
	6	120:00	8:00 Drug intake									X ▼
	7	144:00	8:00 Drug intake									X[8]
	8	168:00	8:00 Drug administration	X			X[7]	X[12]	X		X	X
			Training/Dispense Medication[4] Breakfast Discharge from trial site									▲ X ▼
	9	192:00	8:00 Drug intake									
	10	216:00	8:00 Drug administration						X			X[8]
	11	240:00	8:00 Drug intake									▲ X
	12	264:00	8:00 Drug intake									▼
	13	288:00	8:00 Drug intake									X[8]

FLOW CHART (cont.)

Visit	Day	Planned Time [h:min]	time (actual day) [h:min] *(Assumed dosing time is 8:00am, but the actual dosing time may differ for a particular subject)*	Physical examination	[redacted]	Questionnaires[3]	Laboratory/Urinalysis	PK sampling	C-SSRS	ECG, vital signs[6] (BP, PR)	Adverse events / Con. med
4	14		Pre-dose	X			X	X	X	X	X
		312:00	8:00 Drug administration								▲
		313:00	9:00 Breakfast								
		314:00	10:00		X	X		X[10]			X
		315:00	11:00					X[11]			
		316:00	12:00 Lunch Discharge from the site	X[13]						X[9]	▼
5	19-28	EOS[5]	EOS	X			X		X	X	X

1. Screening to be performed within 28 days before drug administration; including subjects information (may be done the day before), informed consent, demographics including determination of the body weight, smoking and alcohol history, relevant medical history, concomitant medication, physical examination and review of vital signs/ECG/laboratory including pharmacogenomic, drug and virus screening, visual acuity test, C-SSRS, CGI-ADHD-S, and review of inclusion/exclusion criteria.
   Patients may be familiarized with the behavioural test battery during the visit for screening.
2. [redacted]
3. Questionnaires will consist of BIS-11 and S-UPPS-P.
4. Subjects will be trained in the taking of the medication and the compliance app before receiving the dosages for the next timeframe. This will be performed once on day 1 (subjects will receive dosage for up to day 7) and once on day 8, when the dosage will be increased (subjects will receive dosage up to day 14).
5. End-of-study-examination (e.o.s.) to be performed at least 4 days after last drug administration. Including physical examination, vital signs/ECG/laboratory(except drug-screen); concomitant medication, C-SSRS, review of adverse events
6. All blood pressure measurements, as well as pulse rate will be measured after 5 minutes of rest in the supine position.
7. Urine Drug Test only
8. Telephone contact
9. Vital signs only
10. Shortly before starting the tests
11. Shortly after the tests/scales completion
12. Pre-dose
13. Formal assessment and confirmation of the patients fitness by investigator or designee

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ABBREVIATIONS AND DEFINITIONS

AE	Adverse Event
ADHD	Attention Deficit Hyperactivity Disorder
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BI	Boehringer Ingelheim
BIS	Barrett Impulsiveness Scale
CA	Competent Authority
CI	Confidence Interval
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organisation
C-SSRS	Columbia Suicidal Severity Rating Scale
CTP	Clinical Trial Protocol
CYP	Cytochrome P450
[redacted]	
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
EC	Ethics Committee
ECG	Electrocardiogram
(e)COA	(electronic) Clinical Outcome Assessment
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EoS	End of Study (corresponds with End of Trial)
EoT	End of Treatment
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FOT	Fully outsourced trial
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice

HA	Health Authority
IB	Investigator's Brochure
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
[redacted]	
INN	International Non-Proprietary Name
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
LPLT	Last patient last treatment
MedDRA	Medical Dictionary for Drug Regulatory Activities
p.o.	per os (oral)
PK	Pharmacokinetics
RA	Regulatory Authority
SAE	Serious Adverse Event
SC	Steering Committee
SOP	Standard Operating Procedure
[redacted]	
S-UPPS-P	Short Urgency, Perseverance, Premeditation, and Sensation Seeking-Positive Urgency Impulsive Behavior Scale
SUSAR	Suspected Unexpected Serious Adverse Reactions
t_{max}	Timepoint of maximum plasma concentration
TMF	Trial Master File
WHO	World Health Organisation
WOCBP	Woman of childbearing potential

1. INTRODUCTION

Impulsivity, a neurocognitive endophenotype present in a broad range of psychiatric disorders, and defined as the tendency towards rash decisions without adequate forethought, often resulting in mistimed and premature actions [R20-4114].
Impulsivity can be broadly divided into motor and decisional subtypes reviewed below. Motor impulsivity includes waiting impulsivity or premature anticipatory responding prior to a cue predicting reward and response inhibition or stopping inhibition of a prepotent response. Decisional impulsivity includes delay and probabilistic discounting of reward and reflection impulsivity - the tendency to make rapid decisions without adequate accumulation and consideration of the available evidence [R21-2496].
While there is relative consensus about the clinical significance of impulsivity, there has been less consensus regarding measurement of impulsivity. There have been two main broad ways to measure impulsivity in humans: questionnaires and behavioural laboratory measures [P15-02354]. Of the questionnaires, the Barratt Impulsiveness Scale (BIS) has been widely used, showing increased impulsivity in many different clinical populations [R06-1093; R15-1437]. The advantage of questionnaire measures of impulsivity is their ease of use and sensitivity across different patient populations.
S-UPPS-P Impulsive Behavior Scale is a 20-item self-report that assesses five subscales (urgency, premeditation, perseverance, sensation seeking, and positive urgency) that are used to measure five distinct dimensions of impulse behavior in adolescents and adults (ages 12 and older) [R19-3281]. It is designed to measure impulsivity across dimensions of the Four Factor Model of personality: Premeditation (lack of), Urgency, Sensation Seeking, Perseverance (lack of).
For the behavioral laboratory measures of impulsivity different assessments have been developed based on different behavioral definitions of impulsivity[R21-2496].

There is considerable evidence that disorders clinically associated with impulsivity show impairment on a variety of questionnaire and behavioral measures of impulsivity [R15-0969; R15-0953; R15-0954; R15-0957]. 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.

1.1 MEDICAL BACKGROUND

Although there have been several studies showing that medications can reduce impulsivity in clinical groups [R15-3365; R15-3366], there has not been consistency in the impulsivity assessment battery across these studies. These studies are critical if impulsivity measures are to be used as outcome measures in clinical trials. This trial will take the first step in producing data on the reliability of the tests and scales in ADHD patients, with impulsivity as a core characteristic of the disorder. In addition, this study will produce information on the population variability and effect size after treatment for the different behavioral laboratory tasks in ADHD patients.

1.2 DRUG PROFILE

Atomoxetine is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD). The efficacy of Atomoxetine was established in several clinical trials and is approved for medical use since 2002 in the USA and 2006 in Germany for children, and since 2013 for adults. It has been shown to significantly reduce inattentive and hyperactive symptoms, and it has little known abuse potential. Atomoxetine's use can be abruptly stopped without significant discontinuation effects.
The initial therapeutic effects of atomoxetine usually take 2–4 weeks to become apparent.
The maximum recommended total daily dose in children and adolescents over 70 kg and adults is 100 mg.

Mode of action
Atomoxetine is a highly selective norepinephrine reuptake inhibitor.

Key pharmacokinetic characteristics

Orally administered atomoxetine is rapidly and completely absorbed. First-pass metabolism by the liver is dependent on CYP2D6 activity, resulting in an absolute bioavailability of 63% for extensive metabolizers and 94% for poor metabolizers. Maximum plasma concentration is reached in 1–2 hours. The half-life of atomoxetine varies widely between individuals, with an average range of 4.5 to 19 hours. As atomoxetine is metabolized by CYP2D6, exposure may be increased 10-fold in CYP2D6 poor metabolizers. If taken with food, the maximum plasma concentration decreases by 10-40% and delays the t_{max} by 1 hour. Drugs affecting gastric pH have no effect on oral bioavailability. Atomoxetine is excreted primarily as 4-hydroxyatomoxetine-O-glucuronide, mainly in the urine.

Drug interactions
Atomoxetine is a substrate for CYP2D6. Concurrent treatment with a CYP2D6 inhibitor such as bupropion, fluoxetine, or paroxetine has been shown to increase plasma atomoxetine by

100% or more, as well as increase *N*-desmethylatomoxetine levels and decrease plasma 4-hydroxyatomoxetine levels by a similar degree.
Atomoxetine has been found to directly inhibit hERG potassium currents with an IC_{50} of 6.3 µM, which has the potential to cause arrhythmia. QT prolongation has been reported with atomoxetine at therapeutic doses and in overdose; it is suggested that atomoxetine not be used with other medications that may prolong the QT interval (Appendix 10.2), concomitantly with CYP2D6 inhibitors (Appendix 10.1) and caution to be used in poor metabolizers.
Other notable drug interactions include:

- Antihypertensive agents, due to atomoxetine acting as an indirect sympathomimetic
- Indirect-acting sympathomimetics, such as pseudoephedrine, norepinephrine reuptake inhibitors, or MAOIs
- Direct-acting sympathomimetics, such as phenylephrine or other α_1 adrenoceptor agonists, including pressors such as dobutamine or isoprenaline and β_2 adrenoceptor agonists
- Highly plasma protein-bound drugs: atomoxetine has the potential to displace these drugs from plasma proteins which may potentiate their adverse or toxic effects. *In vitro*, atomoxetine does not affect the plasma protein binding of aspirin, desipramine, diazepam, paroxetine, phenytoin, or warfarin

Residual Effect Period
The Residual Effect Period (REP) of Atomoxetine is 4 days and is projected based on 5* longest $t_{1/2}$ of 19h. This is the period after the last dose with measurable drug levels and pharmacodynamic effects still likely to be present.

Clinical Data
Commonly reported side effects of atomoxetine include constipation, insomnia, decreased appetite, and xerostomia. Other side effects include dermatitis, dysmenorrhea, erectile dysfunction, dizziness, dyspepsia, ejaculatory disorder, urinary hesitancy, ejaculation failure, and diaphoresis.
For a more detailed description of the Atomoxetine profile, please refer to the Summary of Product Characteristics (SmPC) [R21-3079]. For more uncommon adverse effect and risks mitigation

1.3 RATIONALE FOR PERFORMING THE TRIAL

The overall goal of this project is to investigate the effects of impulsivity-reducing ADHD medication atomoxetine on impulsivity as measured by questionaires and behavioural laboratory tasks in ADHD patients.
This study is needed to establish appropriate protocols for impulsivity tasks, if impulsivity measures are to be used as outcome measures in future clinical studies that will eventually lead to approval of new medications for the treatment of impulsivity, potentially across different diagnostic disorders.

1.4 BENEFIT - RISK ASSESSMENT

The overall safety profile of Atomoxetine is outlined in the current Summary of Product Characteristics (SmPC) [R21-3079].

1.4.1 Benefits

Participation in this clinical trial is without any therapeutic benefit for patients taking part in this trial. Their participation, however, is of major importance to investigate pharmacological modulation of impulsivity by atomoxetine after single dose and at steady-state, to define the best-suited waiting impulsivity task to be used in future therapeutic trials. Subjects are exposed to risks of study procedures and risks related to the exposure to the trial medication.

Potential benefits:

Subjects will undergo a free, thorough psychiatric screening consisting of questionnaires and other behavioral measures of impulsivity as noted in the flow chart. Any clinically relevant diagnoses discovered during this screening will be discussed with subjects and they will be referred for treatment for these abnormalities. Additionally, if the study medication proves to be safe and effective, it can be considered by investigator for the patients treatment after the study.

1.4.2 Risks

Procedure-related risks

The use of an indwelling venous catheter or venepuncture for e.g. blood sampling may result in mild bruising and, in rare cases, in transient inflammation of the wall of the vein, or nerve injury, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period.

The total volume of blood withdrawn per patient during the entire study will not exceed 300 mL. This is less than the volume of a normal blood donation (500 mL). No health-related risk to patients is expected from withdrawal of this volume of blood.

Drug-related risks and safety measures

Participants will be closely monitored during the trial participation (including safety laboratory, AE monitoring, physical and neurological examinations) to ensure that worsening of pre-existing conditions or any newly occurring events are detected and any necessary actions taken according to stopping criteria (see section 3.3.4).

Suicide related behaviour (suicide attempts and suicidal ideation) has been reported in patients treated with atomoxetine.
Risk mitigation:
In the interest of ensuring participant safety, trial participants will be proactively screened and monitored for SIB.

Atomoxetine can affect heart rate and blood pressure. Most patients taking atomoxetine experience a modest increase in heart rate (mean <10 bpm) and/or increase in blood pressure (mean <5 mm Hg).
Risk mitigation:

- Subjects with relevant findings in BP, PR or ECG at Screening, cardiovascular disorders, history of relevant hypertension or orthostatic hypotension, fainting spells or blackouts, use of drugs that might prolong the QT/QTc interval, marked (Section 3.3.3), or subjects with additional risk factors for Torsade de Pointes arrhythmia (Section 3.3.3) are excluded from trial participation.
- Heart rate and blood pressure be measured and recorded before treatment is started and, during treatment, after dose adjustment to detect possible clinically important increases.

Very rarely, spontaneous reports of liver injury, manifested by elevated hepatic enzymes and bilirubin with jaundice, have been reported.
Risk mitigation:

- Liver enzymes (ALT, AST) will be measured before, during and after dosing.
- Atomoxetine will be discontinued in patients with jaundice or laboratory evidence of liver injury.

Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, mania or agitation in patients without a prior history of psychotic illness or mania can be caused by atomoxetine at usual doses. Additionally, there have been rare reports of anxiety and depression or depressed mood, very rare reports of tics, aggressive behaviour, hostility, or emotional lability.
Risk mitigation:

- Patients will be closely monitored for the appearance of any psychiatric symptoms.
- Atomoxetine will be discontinued.

Seizures are a potential risk with atomoxetine.
Risk mitigation:

- Patients with a history of seizure will be excluded from study participation.
- Atomoxetine will be discontinued in any patient developing a seizure.

Although uncommon, allergic reactions, including anaphylactic reactions, rash, angioneurotic oedema, and urticaria, have been reported in patients taking atomoxetine.
Risk mitigation:

- Patients will be in-house at the trial site under close medical observation 4 hours after first drug administration.
- Patients with a history of severe allergic reactions or known allergy to atomoxetine will be excluded from the trial participation.

Atomoxetine has a minor influence on the ability to drive and use machines. Atomoxetine has been associated with increased rates of fatigue, somnolence, and dizziness relative to placebo in paediatric and adult patients.
Risk mitigation:

- Patients will be advised to use caution when driving a car or operating hazardous machinery until they are reasonably certain that their performance is not affected by atomoxetine.

For atomoxetine clinical data on exposed pregnancies and breastfeeding are limited.
Risk mitigation:

- Pregnant and lactating females will be excluded from the trial participation.
- Females of childbearing potential must also agree to use an acceptable method of contraception during the study participation up to until EOT.
- Exclusionary pregnancy testing will be performed at screening, and regularly during the study.

1.4.3 Discussion

The nature of the target, the mechanism of action and safety profile of Atomoxetine are well known and understood.

In the context of the unmet medical need and anticipated benefit of development of the reliable test battery to measure impulsivity, the benefit risk evaluation of the compound, based upon the available clinical information, is favourable.

Considering the medical need for the development of a better tolerated and more effective treatments for psychiatric patients, the expected benefit outweighs the potential risks.
The impulsivity tool set developed in this trial could be implemented in the future trials for patients screening and to enable early decision making. Furthermore, these tests may enable to select the patients most suitable for inclusion in early patient clinical studies and could also be included as secondary endpoints in phase II-III clinical studies.

2. TRIAL OBJECTIVES AND ENDPOINTS

The overall goal of this study to establish appropriate protocols for impulsivity tasks.

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main 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.

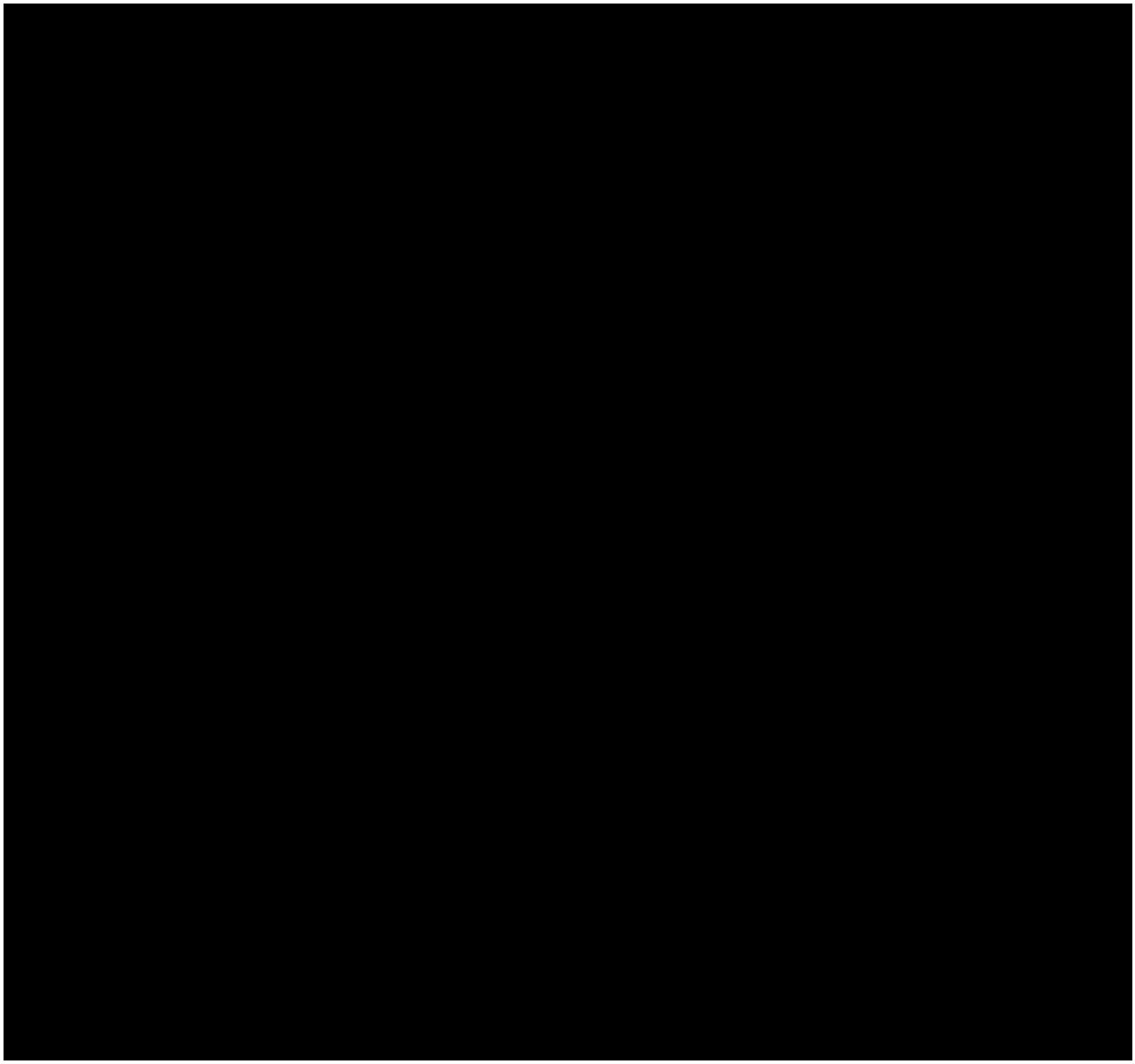
- The primary objectives are to investigate the effect of atomoxetine on impulsivity after single dose and at steady state measured by the total score of BIS-11 and S-UPPS-P Impulsive Behavior Scale.
- The secondary objective is to evaluate the safety of atomoxetine.

2.1.2 Primary endpoint(s)

- Change from baseline in total score of Barratt Impulsiveness Questionnaire v.11 (BIS-11) after single dose (at day 1)
- Change from baseline in total score of Barratt Impulsiveness Questionnaire v.11 (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)

2.1.3 Secondary endpoint(s)

Percentage of patients with (S)AEs.



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is a multi-center, randomized, double-blind, placebo controlled parallel-group trial in patients with ADHD. A targeted total of approx. 96 patients with ADHD meeting the entry criteria are planned to be randomized into this trial.
Patients will be enrolled into the trial once consent has been signed. Patients suitable after screening will undergo base-line 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. 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.

An overview of all relevant trial activities is provided in the Flow Chart. For visit schedules and details of trial procedures at selected visits, refer to Sections 6.1 and 6.2, respectively.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

This is an exploratory, randomized, double-blind, parallel arm, multiple dose, active comparator trial of Atomoxetine (impulsivity-reducing ADHD medication) and Placebo, with a 3 weeks screening period, 2-week treatment period and a 4-days follow-up, in patients with moderate ADHD.

Patients will be randomized according to a 1:1 ratio to either Atomoxetine or Placebo in a blinded fashion.
The effects on impulsivity in behavioral laboratory tasks will be collected and assessed at baseline, on day 1 after single dose, and day 14 at steady state in addition, safety measures will be collected until end of trial. Collectively, this information will help to establish appropriate protocols for impulsivity tasks and facilitate the design of the future clinical programs.

3.3 SELECTION OF TRIAL POPULATION

Impulsivity is a primary symptom of ADHD, therefore subjects with moderate symptoms of ADHD will be included in this trial.
The total of approximately 96 patients (80 evaluable patients with 40 patients per arm) are planned to be randomized into the study. It is planned that approximately 5 trial centers will be participating in this trial to ensure sufficient number of patients are randomized. It is expected that approximately 15-20 patients will be randomized at each trial center. If enrolment is delayed, additional sites may be recruited. To avoid differential cultural influence on study results, the study will be conducted in 1 country only. It is expected that a significant proportion of study participants, especially the younger ones, will not be regularly receiving any of the prohibited medication, prior to the onset of the trial. Investigators will be prompted to preferentially include patients who are not in receipt of regular pharmacological treatment for ADHD (thus require no discontinuation). Patients who are on treatment for ADHD should have successfully sustained medication-free periods in their medical history, without experiencing any significant deterioration based on medical records.
Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all sites at the same time once a sufficient number of patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial. Patients already in screening at this time will be allowed to continue to randomisation if eligible.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the Investigator Site File (ISF) irrespective of whether they have been treated with investigational drug or not.
If retrospectively it is found that a patient has been randomized in error (=did not meet all inclusion criteria or met one or more exclusion criteria), the sponsor or delegate should be contacted immediately. Based on an individual benefit-risk assessment a decision will be made whether continued trial participation is possible or not.

3.3.1 Main diagnosis for trial entry

Patients with a stable clinical presentation must have moderate symptoms of ADHD with combined score of 4 or higher in Clinical Global Impression-ADHD-Severity (CGI-ADHD-S) and Hyperactivity/Impulsivity subscale min 8.
Please refer to section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

1. Male and female subjects, 18-45 years of age at the time of consent meeting diagnostic criteria of ADHD per DSM-5 at screening visit and currently undergoing diagnostic assessment and/or treatment for ADHD
2. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.

3. A diagnosis of the moderate symptoms of ADHD confirmed with combined score of 4 or higher in Clinical Global Impression-ADHD-Severity (CGI-ADHD-S) at Screening; Hyperactivity/Impulsivity subscale min 8 (at least moderate for impulsivity measure with ADHD checklist)
4. Able and willing to discontinue the use of any psychotropic medications for treatment of ADHD symptoms, as well as of all relevant co-medication for comorbid conditions during the study (for reference see section 4.2.2.1 and Appendix 10.2)

5. Women of childbearing potential (WOCBP)[1] must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria and instructions on the duration of their use is provided in the patient information.

3.3.3 Exclusion criteria

1. Per DSM-5, had ever met diagnostic criteria for schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar disorder, delusional disorder or MDD with psychotic features at the time of screening.
2. Diagnosis of any mental disorder (according to DSM-5) that was primary focus of treatment within 6 months prior to Screening or at Baseline (as per clinical discretion of the investigator). *
3. Any psychiatric disorder, including the ones mentioned under #1, that in the opinion of the investigator would compromise participants' safety and/or validity of the data.
4. Current or recent (in the 6 months prior to screening) suicidal ideation or behaviour of type 4 or 5 in the C-SSRS.
5. Any finding in the medical examination (including BP, PR, temperature, or ECG) deviating from normal and assessed as clinically relevant by the investigator.
6. Repeated measurement of systolic blood pressure outside the range of 90 to 145 mmHg, diastolic blood pressure outside the range of 45 to 90 mmHg, or pulse rate outside the range of 45 to 95 bpm.
7. A marked baseline prolongation of QT/QTc interval (such as QTc intervals that are repeatedly greater than 450 ms in males or repeatedly greater than 470 ms in females) or any other relevant ECG finding at screening.
8. A history of additional risk factors for *Torsade de Pointes* (such as heart failure, hypokalaemia, or family history of Long QT Syndrome).
9. Any laboratory value outside the reference range that the investigator considers to be of clinical relevance.
10. Any evidence of a concomitant disease assessed as clinically relevant by the investigator (gastrointestinal, hepatic, renal, respiratory, cardiovascular, metabolic, immunological, or hormonal disorders).
11. Diseases of the central nervous system (including but not limited to any kind of seizures, stroke, brain tumor or any other major neurological or developmental illness.

12. Major surgery (major according to the investigator's assessment) performed within 8 weeks prior to randomisation or planned within 2 months after screening.
13. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin or in situ carcinoma of uterine cervix.
14. History of relevant orthostatic hypotension, fainting spells, or blackouts
15. History of relevant allergy or hypersensitivity (including allergy to the trial medication or its excipients) or known contraindications to atomoxetine.
16. Patients who must or wish to continue the intake of restricted medications (see section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial.
17. Patients not expected to comply with the protocol requirements or not expected to complete the trial as scheduled (e.g. chronic alcohol or drug abuse or any other condition that, in the investigator's opinion, makes the patient an unreliable trial participant).
18. Known pharmacogenetic CYP2D6 status (poor metabolizers).
19. Drug abuse or positive drug screening.
20. Previous enrolment in this trial, or currently enrolled in another drug trial, or less than 30 days since ending another drug trial or receiving other investigational treatment(s).
21. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
22. History or evidence of narrow angle glaucoma.
23. History or evidence of pheochromocytoma.
24. Chronic or relevant acute infections.

1. A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilisation.
* The following are not excluded: Substance Induced Mood Disorder, Major Depressive Disorder in remission, Generalized Anxiety Disorder in remission, Post-Traumatic Stress Disorder in remission, recreational/occasional substance use as long as willing to stop for duration of the study, Borderline Personality Disorder.

3.3.4 Discontinuation of patients from treatment or assessments

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see sections 3.3.4.1 and 3.3.4.2 below.
However, if the patients agree, they should stay in the trial. Even if continued trial treatment is not possible, they should attend further trial visit to ensure their safety.
Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.
The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and CRF. If applicable, consider the requirements for Adverse Event collection reporting (please see section 5.2.6.2).

3.3.4.1 Discontinuation of trial treatment

Ideally, the patient should attend the End of Trial visit. Should the patient not agree, at least phone contact should occur at the scheduled visit time point to collect the most relevant information: vital status (please see section 5.2.6.2.1), outcome events, adverse events, or last contact date in case of lost to follow-up.

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment. The patient will be asked to explain the reasons but has the right to refuse to answer.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of the investigator, the safety of the patient cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future.
- The patient needs to take concomitant medication that interferes with the safety of the investigational medicinal product or other trial treatment (refer to sections 4.2.2.1).
- The patient can no longer receive trial treatment for medical reasons such as surgery, adverse events, other diseases, or pregnancy.The patient shows disease progression/worsening that precludes further participation in the trial per investigator's clinical judgement. The participant develops suicidal ideation of type 4 or 5 in the C-SSRS (i.e., active suicidal thought with intent but without specific plan, active suicidal thought with plan and intent) or suicidal behavior (i.e. actual attempt, interrupted attempt, aborted attempt or preparatory acts or behavior).If new efficacy / safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, discontinue the trial treatment for all patients or take any other appropriate action to guarantee the safety of the trial patients.

Even if the trial treatment is discontinued, the patients remain in the trial and, given their agreement, will undergo the procedures for early treatment discontinuation and follow-up as outlined in the Flow Chart and section 6.2.3.

3.3.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision.

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

- Failure to meet expected enrolment goals overall or at a particular trial site.

- New efficacy or safety information invalidating the earlier positive benefit-risk-assessment, please see section 3.3.4.1.

Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

Further treatment and follow up of patients affected will occur as described in section 3.3.4.1. The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The trial medication will be provided by Boehringer Ingelheim or a designated CRO.

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1:1 Test product 1

Substance:	Atomoxetin [redacted] ®
Pharmaceutical formulation:	Capsules
Source:	[redacted]
Unit strength:	40 mg
Posology:	80 mg on Day 1 (after randomization); 2-0-0 40 mg QD from Day 2 to day 7 inclusive; 1-0-0 80 mg QD from Day 8 to day 14 inclusive; 2-0-0
Mode of administration:	Per os

Table 4.1.1: 2 Test Product 2

Substance:	Placebo to Atomoxetin tablets available on the market
Pharmaceutical formulation:	Film-coated tablet
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	NA
Posology:	2 tablets QD on Day 1 (after randomization); 2-0-0 1 tablet QD from Day 2 to day 7 inclusive; 1-0-0 2 tablets QD from Day 8 to day 14 inclusive; 2-0-0
Mode of administration:	Per os

Any unused product or waste material will be disposed of in accordance with local requirements.

4.1.2 Selection of doses in the trial and dose modifications

Atomoxetine is approved for treatment of ADHD. The doses of Atomoxetine selected for this trial generally follow the approved posology of Atomoxetine for the treatment of ADHD (initiated at a total daily dose of 40 mg for a minimum of 7 days prior to upward dose titration according to clinical response and tolerability up to 80 mg daily).
The higher first dose is necessary to investigate whether a single dose of atomoxetine reduces impulsivity in behavioral laboratory tasks and deemed clinically acceptable under close medical surveillance.

4.1.3 Method of assigning patients to treatment groups

After the assessment of all in- and exclusion criteria, each eligible patient will be randomised to a treatment group according to a randomisation plan in a 1:1 ratio at Day1/visit 3 via Interactive Response Technology (IRT). Note that the medication number is different from the patient number (the latter is generated during screening via the IRT System).

4.1.4 Drug assignment and administration of doses for each patient

The medication assignment will be provided through IRT. The assigned medication numbers must be entered in the eCRF, and the corresponding medication kits must be given to the patient. At Visit 3, after randomization, patients will receive their first medication kit.
Administration of trial medication will be performed after subjects have fasted overnight; fasting is to start no later than 10 h before the scheduled dosing.
The first dose of trial medication will be taken at the study site under supervision of the dedicated site staff. Subjects will be kept under close medical surveillance until 4 h after the first drug administration.
On days 1 and 8, patients will receive medication kits containing supplies for a total of 7 treatment days (7 treatment days plus 1 day reserve to cover for possible damage). Patients will be instructed to take the study medication orally with water and without food. Return of the used/unused medication kits will occur at Visit 3 (day 8) and Visit 4 (day 14). Patients should be instructed not to take their trial medication in the morning of visits on days 8 and 14, as patients will be dosed at the site after pre-dose PK sampling.

Table 4.1.4: 1 Dosage and treatment schedule

Treatment	Substance	Unit strength	Dosage	Total dose
T (Test)	Atomoxetine	40 mg	80 mg doses on day 1 40 mg doses on Days 2 to Day 7 (6 days) 80 mg doses on Days 8 to Day 14 (7 days)	800 mg
R (Reference)	Placebo	NA	2 tablets on day 1 1 tablet on Days 2 to Day 7 (6 days) 2 tablets on Days 8 to Day 14 (7 days)	NA

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This is a double-blind trial, therefore patients, Investigators (outcome assessors) and everyone involved in trial conduct (except the trial personnel involved in the dispensing the trial medication–third-party blinding) will remain blinded with regard to the randomized treatment assignments until after the final database lock, in order to limit the occurrence of any bias which the knowledge of treatment may have.

Taking into account that Atomoxetine and Placebo differ in their presentations, medications will be packaged to the identical blisters, and the secondary packaging (boxes containing blisters) will be identical for both Atomoxetine and Placebo, allowing the blinding of the site staff. The appearance of both presentations used in the study matches the medication available on the market, therefore the patient's blindness to the treatment will be granted. Blinding of treatments to the site will be maintained by using a third-party blinding, where the study drug will be dispensed/administered to the patients on days 1, 8 and 14 by persons who are independent of the other clinical trial procedures and not involved in other aspects of the study. Details on the medication handling at the site will be provided in the Pharmacy manual and filed in ISF.

All trial data will be handled open label. This means that trial functions of the sponsor and responsible global vendor are unblinded (including CTL/PM, data managers, statisticians, bioanalysts, pharmacokineticists, pharmacometricians).

This is acceptable because they are neither in contact with subjects nor with site staff.

Access to the randomisation schedule will be controlled and documented by a signed confidentiality statement, which will be stored in the TMF.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's Pharmacovigilance group to access the randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives for processing in the PV database system and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.
For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.
If the storage conditions are found to be outside the specified range, the Clinical Research Associate CRA (as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered by the sponsor or delegate when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the RA / ethics committee,
- Availability of a signed and dated clinical trial contract between the sponsor or delegate and the investigational site,
- Approval / notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics. Patients should be instructed to return unused investigational drug.

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, IRT will track whether IMP is destroyed or returned to distribution vendor, and will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use- by') dates, and the unique code numbers assigned to the investigational medicinal product and trial patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products received from the sponsor. At the time of return to the appointed CRO / or destruction on site , the investigator or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no specific rescue drugs foreseen for the treatment of AEs. There are no special emergency procedures to be followed.
Atomoxetine is relatively non-toxic in overdose. Single-drug overdoses involving over 1500 mg of atomoxetine have not resulted in death. The recommended treatment for atomoxetine overdose includes use of activated charcoal to prevent further absorption of the drug.
In case of AEs in need of treatment, the investigator can authorize an appropriate therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all medical evaluation results have returned to an acceptable level.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study or must refer them for appropriate ongoing care according to local guidelines and daily practice, respectively.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Following medications are prohibited during the treatment period:

- All psychotropic medications, concomitant use of CYP2D6 inhibitors, sympathomimetics, Monoamine Oxidase Inhibitors (MAOI) should not be taken for two weeks before, during and 2 weeks after treatment with Atomoxetine, and at least 5 half-lives before base-line visit;

- Antihypertensive Drugs, Pressor Agents (e.g., dopamine, dobutamine), beta 2 agonists or other drugs that increase/decrease blood pressure should be used cautiously because of possible effects on blood pressure and heart rate;
- Use of alternative or traditional medicines (e.g. Chinese traditional medicine, herbal medication, St. John's Wort, Ayurveda medications, etc.).

Occasional (single dose) concomitant use of benzodiazepines and non-benzodiazepine hypnotics are allowed during study at a dose equivalent to ≤ 1.0 mg of lorazepam per day, for the management of AEs (e.g. anxiety and/or insomnia). Such drugs should be stopped immediately after the AE is resolved and should be avoided within approx. 48 hours before planned impulsivity testing.
Stable therapy with SSRI might be continued with caution as judged by investigator (except for Paroxetine and Fluoxetine which are inhibitors of CYP2D6). If patient receiving current treatment with SSRI, the dose must have been stable for a minimum of 2 months prior to screening and when possible maintained at a lower range.
In case of AEs, any treatment deemed necessary per the clinical judgment of investigator for the management of AEs considering patient safety is allowed.
Investigators are encouraged to adhere to the restrictions listed in the Appendix 10.2 or contact the sponsor or sponsor's medical representative.

4.2.2.2 Restrictions on diet and lifestyle

In general, patients should keep their usual habits throughout the study for diet and exercise, as well as nicotine, alcohol, and caffeine intake. These habits should be within acceptable daily amounts, at the discretion of the investigator, and should not be drastically changed throughout the study.
It is recommended that patients exercise caution when driving or operating machinery until they are reasonably certain that the study medication does not adversely affect their ability to engage in such activities.
Patients have to fast prior to trial visits.
Alcoholic beverages, grapefruits, Seville oranges (sour or bitter oranges) and their juices, and dietary supplements and products containing St. John's wort (*Hypericum perforatum*) are not permitted from 7 days before the first administration of trial medication until the last drug administration.

Methylxanthine-containing drinks or foods (such as energy drinks, or chocolate) are not allowed from 4 h before until after each impulsivity assessment. Usual intake of coffee, tea and/or cola can be maintained throughout the trial excluding excessive use.

4.2.2.3 Contraception requirements

For female patients of child-bearing potential, adequate contraception is to be maintained throughout the course of the trial.

Women of childbearing potential (WOCBP - for the definition please refer to section 3.3.2) must use two methods of contraception, which include one highly effective method of birth control per ICH M3 (R2) that result in a low failure rate of less than 1%, plus one barrier method. Contraception must be used during the treatment and follow-up period. Acceptable forms of contraception are: One of the following highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1%:

- Use of hormonal methods of contraception associated with inhibition of ovulation
  a. combined (estrogen and progestogen containing) hormonal contraception:
     - oral
     - intravaginal
     - transdermal
  b. progestogen-only hormonal contraception:
     - oral
     - injectable
     - Implantable
- Placement of intrauterine device (IUD) or intrauterine hormone releasing system (IUS)
- Bilateral tubal occlusion or ligation
- Vasectomy (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate and provided that male partner is the sole sexual partner of the WOCBP trial participant).

plus, one of these barrier methods:

- Male or female condom with or without spermicide
- Cap, diaphragm, or sponge with spermicide
- patients must abstain from male-female sex (this is defined as being in line with the preferred and usual lifestyle of the patient).

Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods; declaration of abstinence for the duration of exposure to study drug; and withdrawal are not acceptable.

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medication including empty package material with them when attending visits.

Based on tablet / capsule counts, treatment compliance will be calculated as shown in the formula below. Compliance will be verified by the CRA authorised by the sponsor or delegate.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of tablet / capsule actually taken} \times 100}{\text{Number of tablet / capsule which should have been taken as directed by the investigator}}$$

If the number of doses taken is not between 80-120%, site staff will explain to the patient the importance of treatment compliance.
Additionally, as an exploratory approach, daily intake of the study drugs will be monitored using a smartphone app. Please see section 5.6.1 for further details.

5. ASSESSMENTS

The status of ADHD will be assessed during screening by using the Clinical Global Impression-ADHD-Severity (CGI-ADHD-S). To investigate the impulsivity the outcomes of the behavioral laboratory tasks will be utilized.

5.1 ASSESSMENT OF EFFICACY

S-UPPS-P Impulsive Behavior Scale Urgency, Perseverance, Premeditation, and Sensation Seeking – Positive Urgency

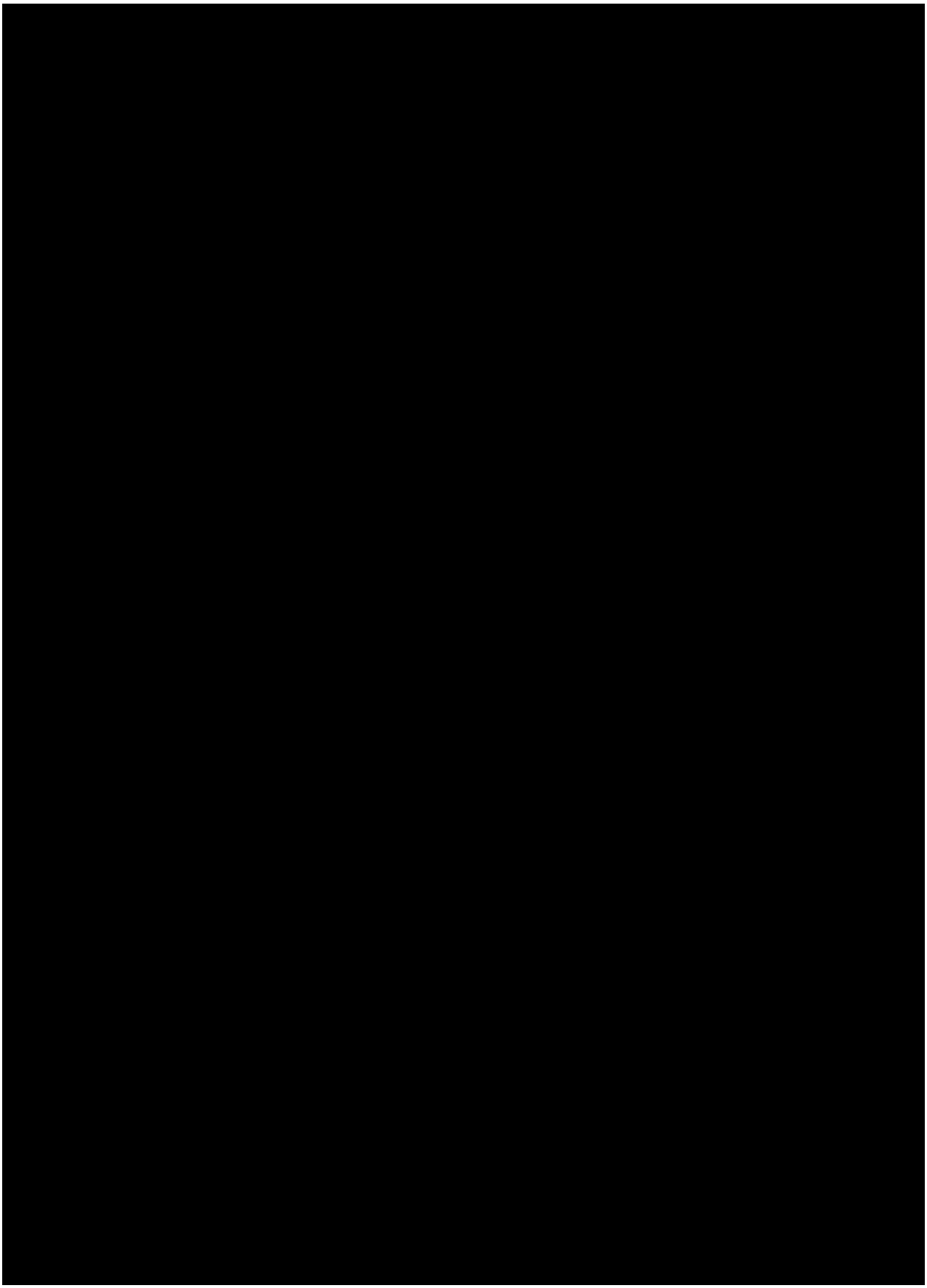
The S-UPPS-P is a shortened version of the original UPPS-P (Urgency, Perseverance, Premeditation, and Sensation Seeking – Positive Urgency) impulsive behavior scale that has been developed and validated as a reliable alternative to the full version (R19-3281).
The S-UPPS-P is comprised of 20 items, 4 items specifically selected from each of the 5 pathways. The first pathway, Urgency, assesses an individual's tendency to give in to strong impulses, specifically when accompanied by negative emotions such as depression, anxiety, or anger. The next pathway, (lack of) Perseverance, assesses an individual's ability to persist in completing jobs or obligations despite boredom and/or fatigue. The third pathway, (lack of) Premeditation, assesses an individual's ability to think through the potential consequences of his or her behavior before acting. The fourth pathway, Sensation Seeking, measures an individual's preference for excitement and stimulation. And the final pathway, Positive Urgency, assesses an individual's tendency to give in to strong impulses, when accompanied by positive emotions such as excitement or good mood.
Each item on the S-UPPS-P is rated on a 4-point scale ranging from 1 (Strongly Agree) to 4 (Strongly Disagree).
The S-UPPS-P Impulsive Behavior Scale ranges from 20 to 80 with a higher score indicating an increased impulsive behavior.

The S-UPPS-P is to be completed by the patient and should take approximately 8-10 minutes to complete. The S-UPPS-P will be captured using the rater station/tablet provided by the vendor.

Barratt Impulsiveness Questionnaire v.11 (BIS-11) [R06-1093]

BIS-11 is a widely used self-report measure of impulsiveness. It includes 30 items that are scored to yield six first-order factors (attention, motor, self-control, cognitive complexity, perseverance, and cognitive instability impulsiveness) and three second-order factors (attentional, motor, and non-planning impulsiveness).
The total BIS-11 score ranges from 30 to 120 with a higher score indicating an increased impulsive behavior.

BIS-11 is to be completed by the patient and should take approximately 20 minutes to complete. The BIS-11 will be captured using the rater station/tablet provided by the vendor.



[redacted]

5.2 ASSESSMENT OF SAFETY

5.2.1 Physical examination

A complete physical examination will be performed at screening and end of trial visit. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin. Abbreviated physical examination including evaluation of the neurological status will be performed on all other timepoints as indicated in the flowchart.
Measurement of height and body weight will be performed at screening only.
The results must be included in the source documents available at the site.
Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and / or treated as medically appropriate.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the flowchart, prior to blood sampling.
This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. The results must be included in the source documents available at the site. Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and / or treated as medically appropriate.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in the table 5.2.3.1. For the sampling time points please see the flowchart.
All analyses will be performed by a local laboratory, the respective reference ranges will be provided in the ISF.
Patients have to be fasted at least 6 hours for the blood sampling for the safety laboratory.
Pregnancy testing will be performed using serum at Screening and local at the site using urine at all applicable visits thereafter.

The local laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to section 5.2.6).

Table 5.2.3:1 Safety laboratory tests

Category	**Test name**
Haematology	Hct Hb RBC count / erythrocytes White blood cells / leukocytes Platelet count / thrombocytes
Diff. Automatic	Neutrophils (relative count) Lymphocytes (relative count)
Diff. Manual (if Diff Automatic is abnormal)	Neutrophils, bands (stabs) Neutrophils, polymorphonuclear Lymphocytes
Enzymes	AST (GOT) ALT (GPT) Creatine Kinase CK-MB, **only if CK is elevated** Gamma-Glutamyl Transferase (GGT)
Electrolytes	Calcium Sodium Potassium
Substrates	Glucose Creatinine Bilirubin total Bilirubin direct **(if total is elevated)** Bilirubin indirect **(if total is elevated)** Cholesterol, total TSH (at screening only)
Urine Pregnancy test (only for female patients of childbearing potential) at randomization and continued as indicated in the Flow Chart (including EoT)	Human Chorionic Gonadotropin in the urine
Serum Pregnancy test (only for female patients of childbearing potential) at screening and if urine pregnancy test is positive)	Human Serum Chorionic Gonadotropin
Urinalysis (dipstick) at screening only	Urine Protein Urine Glucose Urine RBC / erythrocytes

Table 5.2.3:2 Exclusionary laboratory tests

Functional lab group	Test name
Drug screening (urine) as indicated in the Flow chart	Amphetamine/MDA[1] Barbiturates Benzodiazepine Cannabis Cocaine Methadone Methamphetamine/MDMA/Ecstasy Opiates Phencyclidine Tricyclic antidepressants
Screening for infections (only at screening)[2]	HBsAg (qualitative) Hepatitis C antibodies (qualitative) HIV-1, and HIV-2 antibody (qualitative, where mandated by local authorities at the discretion of the investigator where clinically indicated)

[1] Subjects with a valid prescription for amphetamines for the treatment of ADHD, or occasional use of Marijuana will not be excluded, and can be retested.

[2] Additional testing for infectious diseases can be added as required

5.2.4 Electrocardiogram

The 12-lead ECGs must be administered by a qualified technologist and results will be recorded as scheduled in the flowchart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance. ECGs may be repeated for quality reasons and a repeated recording used for analysis.
Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.
Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and / or treated as medically appropriate.

5.2.5 Other safety parameters

5.2.5.1 Assessment of suicidality

Suicidal risk will be assessed by the C-SSRS. The C-SSRS is a semi-structured, investigator rated interview, developed by clinical experts in cooperation with the FDA, assessing both suicidal behavior and suicidal ideation. It does not give a global score but provides some categorical and some severity information specifically for behavior and ideation. The C-SSRS is completed by the interviewer.
The C-SSRS has been widely used in large multi-national clinical trials. The C-SSRS will be administered first at screening (Visit 1) (using the 'Baseline / Screening' version) with the aim to exclude subjects with active moderate or severe symptomatology within a specified time prior to screening.

After screening (Visit 1) the assessment 'since last visit' will be performed on days 1, 4, 8, 10, 14 and EOT ('Since Last Visit version'). The investigator is to review/consider the C-SSRS results for plausibility and clinical relevance. If the positive report is confirmed, appropriate actions for the subject's safety have to be initiated.
All C-SSRS reports of suicidal ideation type 4 or 5 and all reports of suicidal behavior must be reported as separate SAEs by the investigator.
For 'Self-injurious behavior, no suicidal intent' (Type 11) standard AE / SAE reporting rules are to be applied.
For each C-SSRS report of suicidal ideation type 1, 2 or 3 after start of the trial, the investigator is to decide based on clinical judgment whether it represents an AE as defined in the protocol, and if it is considered an AE then it must be reported accordingly.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

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 BI SAE form (if applicable):
- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination, and laboratory test results, 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.

Regarding AEs in the context of suicidal risk assessment by C-SSRS, section 5.2.5.1 should be adhered.

5.2.6.1.2 Serious adverse event

A serious adverse event (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 medial 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.

5.2.6.1.3 AEs considered "Always Serious"

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined above.
The latest list of "Always Serious AEs" can be found in the eDC system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described in section 5.2.6.2.
Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in section 5.2.6.2, subsections "AE Collection" and "**AE reporting to sponsor and timelines".**

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see section 5.2.6.2.2.
No AESIs have been defined for this trial.

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) that is / are easily tolerated.
Moderate:	Sufficient discomfort to cause interference with usual activity.
Severe:	Incapacitating or causing inability to work or to perform usual activities.

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine the relationship between the adverse event and the BI investigational compound, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the trial drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the trial drug concerned).
- Continuation of the event despite the withdrawal of the medication, considering the pharmacological properties of the compound (e.g. after 5 half-lives).
  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- There is an alternative explanation, e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned.
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.
The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of trial (= the End of Study (EoS) visit):
  all AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of trial:
  the investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer and trial drug related SAEs and trial drug related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see section 5.2.6.2.2), but not on the CRF.

5.2.6.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form to the sponsor's unique entry point immediately hours of becoming aware of the event, the country specific process will be specified in the ISF. The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

5.2.6.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.
The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Studies (Part B).
The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and / or AESI, only the Pregnancy Monitoring Form for Clinical Studies and not the SAE form is to be completed. If there is an SAE and / or AESI associated with the pregnancy an SAE form must be completed in addition.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

A total of up to 7 PK samples will be collected per patient, at Visit 3 and Visits 4. Please refer to Flowchart for time schedule for PK blood sampling.
Collection of plasma samples at specified timepoints may be used to determine drug plasma concentrations for confirmation of adequate exposure.

5.3.2 Methods of sample collection

Details about sample collection, preparation, required tubes, labelling of tubes, storage and shipment (frequency and addresses) will be provided in the laboratory manual.

Plasma samples will be stored frozen at about -20°C or below at the participating sites. The samples will be shipped on dry ice.
The analysis will be performed under the responsibility of Drug Metabolism and Pharmacokinetics, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany at a suitable contract research organization. As described in section 4.1.5.1, the bioanalyst will be unblinded during sample analysis.
Plasma samples will be discarded at latest 6 months after the final clinical trial report has been signed.

[redacted]

5.3.4 Pharmacokinetic - pharmacodynamic relationship

Evaluation of a PK/PD relationship is not planed; however, some additional exploratory investigations may be undertaken if considered reasonable.

5.4 ASSESSMENT OF BIOMARKER(S)

5.4.1 Drug interaction biomarkers

Not applicable

5.4.2 Pharmacodynamics, safety, and patient selection biomarkers

This section refers to exploratory biomarkers. Established biomarkers of efficacy and safety are described and discussed in sections 5.1 and 5.2.

5.5 BIOBANKING

Not applicable

5.6 OTHER ASSESSMENTS

5.6.1 Medication adherence and reminder system

In addition to the regular calculation of treatment compliance as described in section 4.3, this study will employ an additional medication adherence monitoring for all subjects in the study

using a smartphone app. Patients will download the app onto their own mobile device. The built-in reminders and a communication system allow real-time intervention in case of drug interruptions. These measures will not supersede or replace the physician and/or prescribed medication protocol of the patients. Use of this platform does not present risk to the patients, but rather encourages adherence to the predefined medication intake per protocol . Use of the platform will be required for all subjects in the study.

5.6.2 Pharmacogenomic evaluation

Pharmacogenomic investigations explore the role of genetic variations in determining an individual's response to drugs. Therefore, one mandatory blood sample for pharmacogenomic testing will be taken from each subject. All participants will be prospectively genotyped for CYP2D6 in order to predict their CYP2D6 poor metabolizer status, and the results will be available before inclusion into the study.
One blood sample of at approx. 3 mL will be taken from an arm vein into a blood EDTA tube during the screening visit. Directly after blood collection, gently invert the blood EDTA tube at least 8 times and then store the blood sample at a temperature of approximately -20°C or below until shiping on the dry ice.

DNA will be extracted and used for genotyping of CYP2D6. This data will not be part of the CTR.

All remaining samples will be destroyed after the end of the trial.

5.7 APPROPRIATENESS OF MEASUREMENTS

All safety measurements performed during this trial are standard measurements and will be performed to monitor safety aspects in an appropriate way. All efficacy measurements performed during this trial are standard or exploratory measurements and will be performed to assess the treatment response on impulsiveness in an appropriate way.
In addition, measurement of the atomoxetine concentration may support efficacy and safety analysis.
Therefore, the appropriateness of all measurements applied in this trial is given.

6. INVESTIGATIONAL PLAN

In the event of force majeure or other disruptive circumstances (e.g. pandemic, war) the investigational plan as per this clinical trial protocol may not be feasible at a site. With the consent of the patient, sponsor and investigator may agree on alternative, back-up or rescue methodology which may include but will not be limited to virtual patient visits and assessments, home healthcare nurse visits, and direct-to-patient shipments of trial treatment. Such alternative measures may be described in a specific Trial Continuity Plan, and will also be mentioned in the patient information leaflet

6.1 VISIT SCHEDULE

All patients must adhere to the visit schedule as specified in the Flow Chart. Each visit date is to be counted from Day 1. If any visit has to be rescheduled, the sponsor should be informed, and the subsequent visits should follow the original visit date schedule. Additional visits for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures to be performed at each visit are listed in the Flow Chart. Additional details regarding visit procedures are provided below.
The following requirements for the conduct of the rating scales assessments need to be followed:

- The Suicidality assessments should preferentially be done by the same rater for a given patient throughout the study period.
- During the assessments, patients are allowed to take short breaks as needed, in the judgement of the rater/investigator
- The site staff must be properly trained and training documentation has to be filed in the ISF; it is the responsibility of the Principal Investigator at the site to ensure proper training of all members of the site staff involved in the neuropsychological assessments

6.2.1 Screening and run-in periods

Informed Consent for trial participation
All patients must sign an Informed Consent consistent with ICH-GCP guidelines prior to any study specific procedures. Please refer to section 8.1 for details.
Screening Period
The Screening period, i.e. the phase before the first administration of the trial drug, starts at Visit 1. The Screening period may be as long as 28 days but should be kept as short as possible.

- IRT All patients who are screened must be registered with IRT. If the screening results in a screen failure, patient must be recorded as screen failure in IRT as soon as

possible and within the 28-day screening period. Details of IRT procedures can be found in the IRT Manual filed in the ISF.

- During the screening visit, demographics information will be collected. This includes: age on the day of informed consent (in years), Sex (male, female in order to describe the subject`s sex at birth), and social status (years of education and employment status). For women: of childbearing potential yes / no in order to characterize the patient population and as a basis for contraception requirements, as well as the date of the last menstrual cycle should be documented at each visit.

- The medical examination will include height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests including pharmacogenomics sampling, drug screen, and a physical examination including abbreviated neurological exam.

Run-in Period

If intake of any of the restricted medications was identified, investigator will evaluate whether discontinuation of this treatment is justified and would not jeopardize the patient's safety. If discontinuation of restricted medication is possible, the patient will be advised to stop the intake of the prohibited drugs immediately (ad minimum 2 weeks prior to the planned base-line visit).
This decision and date of discontinuation must be documented in the patient notes.

Baseline Conditions

Approximately 2 weeks before planned randomisation visit on day 1, patients preliminary confirmed to be eligible for study participation will undergo base-line evaluation Visit 2 (day -14 to -16).
The following will be performed/collected:

- Urine drug screen
- S-UPPS-P
- BIS-11

[redacted]

6.2.2 Treatment period(s)

Visit 3 (day 1)

Once patients have completed screening, have met all the inclusion criteria and none of the exclusion criteria, randomization can occur through a registration call using the IRT system. Upon randomization via the IRT, medication kit will be dispensed. After all Day 1 safety assessments (including clinical laboratory, C-SSRS, urine drug screen and pregnancy test for WOCBP) and pre-dose PK sampling are completed, the first dose should be taken at the clinic under supervision of the site personal responsible for drug administration only.

Patients will be kept under close medical surveillance for at least 4 h following the first drug administration.

Approx. 2 hours after the drug intake, PK sample will be taken shortly before starting the tesks, and the impulsivity assessments will be performed under supervision of the dedicated site staff:

- S-UPPS-P
- BIS-11

[redacted]

Shortly after completing all assesments, PK sample will be taken Thereafter, the standard lunch will be served, and the subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or [redacted] designee. The patient will be instructed to contact the site if they are experiencing any AEs between site visits. Trial drug kit for the next 7 days until day 8 will be dispensed for home administration.

Day 8

Patients should not take trial medication before coming to the clinic on day 8. Patients will be dosed at the clinic after pre-dose PK blood samples are taken.

Following safety assessments will be performed - physical examination (including abbreviated neurological exam), ECG, vital signs, drug screen, assessment of C-SSRS, AEs and concomitant therapy.
Medication compliance will be checked, and the next dose will be taken at the clinic under supervision of the site personal responsible for drug administration only. Thereafter, trial drug kit for next 7 days (until day 14) will be dispensed for home administration. The patient will be instructed to contact the site if they are experiencing any AEs between site visits.

Patients will be contacted by the investigator or designee on days 4, 7, 10 and 13 after administration of the trial medication to collect the information on subject's wellbeing. In addition, a C-SSRS will be performed on days 4 and 10, and subjects will be reminded about the upcoming visit on days 7 and 13.

Visit 4 (day 14)

Patients should not take trial medication before coming to the clinic. Patients will be dosed at the clinic after pre-dose PK blood samples are taken.

Following safety assessments will be performed - physical exam (including abbreviated neurological exam), ECG, vital signs, safety lab (including drug screen, and pregnancy test for WOCBP), assessment of C-SSRS, AEs and concomitant therapy. Thereafter, last dose will be administered.

Approx. 2 hours after the drug intake, PK sample will be drown shortly before starting the tesks the impulsivity assessments will be performed under supervision of the dedicated site staff:

- S-UPPS-P
- BIS-11

Thereafter, PK sample will be taken, the standard lunch will be served, and the subjects will then be allowed to leave the trial site after formal assessment and confirmation of their fitness by the investigator or [redacted] designee.

6.2.3 Follow-up period and trial completion

EoS - Visit 5 (day 19 to 28)

All Subjects completed the treatment (or who discontinue treatment before the end of the planned treatment period) should undergo the EoTrial Visit.

Following safety assessments will be performed: C-SSRS, physical exam, ECG, vital signs, safety lab (including urine pregnancy test for WOCBP), assessment of AEs and concomitant therapy.

If needed in the opinion of the investigator, after the EoS (End of Trial) visit additional visits may be scheduled for continued safety monitoring.

Abnormal assessments or lab values judged clinically relevant by the investigator will be monitored until they returned to a medically acceptable level.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The main objectives of this trial are stated in Section 2.1.
To investigate whether atomoxetine reduces impulsivity in ADHD patients after single dose and after repeated dosing at steady state ANCOVAs will be applied. Furthermore, for measurements taken at multiple time points a mixed model for repeated measurements (MMRM) can be applied to each primary endpoint if deemed necessary.

7.1 NULL AND ALTERNATIVE HYPOTHESES

It is not planned to test any statistical hypotheses in a confirmatory sense. All statistical analyses are exploratory even if they use confirmatory methods.

7.2 PLANNED ANALYSES

7.2.1 General considerations

Continuous variables are characterized by their distributional summary statistics. Ordinal, counts, and categorical variables are summarized by counts and frequencies. For variables measured for more than once during the course of the study, descriptive statistics are provided at each time point. In addition, if they are continuous, changes from baseline are calculated by subtracting baseline values from post-baseline values. Summary plots such as histograms, barplots, or boxplots are produced as visual aids for understanding the distributions of these variables.

Analysis sets:
Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The TS includes 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 (TS1): The TS1 includes 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. For the rationale please see section 7.2.2.
- Treated set (TS14): 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). The TS14 will be used for the primary analysis at day 14. For the rationale please see section 7.2.2.
- Per Protocol set (PPS): The per protocol set includes all subjects of the TS which have no important protocol deviations (ref. to DV Domain). The PPS will be used for sensitivity analysis of efficacy.
- If needed, further analysis sets might be defined in the TSAP.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (iPD) categories will be specified in the Domain Deviation (DV). Protocol deviations will be identified no later than in the Report Planning Meeting, and the iPD categories will be updated as needed.

7.2.2 Handling of Intercurrent Events

The expected intercurrent events of interest in this trial are:

- Treatment discontinuation
- Use of rescue therapy
- Use of concomitant therapy
- Death

Intercurrent events (and their handling) that are not listed will be decided by blinded review based on the general principle outlined and will be documented in the TSAP.

The primary strategy is trying to estimate the effect of treatment under good compliance but regardless of concomitant and/or rescue therapies. The strategies for handling intercurrent

events in this trial are as follows:

Treatment discontinuation is handled with a While-on-Treatment strategy: A patient needs to receive at least 90% of the planned treatments to enable the measurement of the treatment effect under good compliance. For details compare the definition of analyses sets (TS1 and TS14) above.

Use of concomitant and rescue therapies will be handled with a treatment policy strategy. Only if there is a high amount of concomitant and/or rescue therapies an additional strategy resulting in supplementary analyses will be performed.

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 will be used.

Each analysis will reference the strategy for handling intercurrent events that it will be estimating. The estimand is thereby defined by this section together with section 7.2.3. Table 7.2.2: 1 provides an overview of the handling of intercurrent events within the primary strategy.

Table 7.2.2: 1 Handling of intercurrent events as per ICH E9(R1)

Intercurrent Event	Strategy for handling of intercurrent events
Treatment Discontinuation	While-on-Treatment
Use of concomitant therapy	Treatment Policy
Use of rescue therapy	Treatment Policy
Death	Composite

7.2.3 Primary objective analyses

To investigate whether atomoxetine reduces impulsivity in Barratt Impulsiveness Questionnaire v.11 (BIS-11) and/or S-UPPS-P Impulsive Behavior Scale in ADHD patients after single dose and after repeated dosing at steady state, an ANCOVA, will be used. For the analyses at day 1 the TS1 will be used and for the analyses at day 14 the TS14 will be used for the primary analysis. Furthermore the strategy 1 for handling intercurrent events will be used for all primary analyses. The primary analyses will be performed on the final database lock at the end of the trial milestone (compare section 8.6).

7.2.4 Secondary objective analyses

Please see Section 7.2.6.

7.2.6 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the REP, a period of 4 days the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the REP. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) at database lock.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

7.2.7 Other Analyses

Concerning the analysis of PK plasma samples, please see section 5.3.1.
Concerning PK/PD relationship investigations, please see section 5.3.4.

7.2.8 Interim Analyses

No formal interim analysis will be performed. Instead, an overview of the different analysis time points is given below.
A first preliminary analysis might take place after approximately 60% of patients have completed treatment (first preliminary analysis time point) and will include all efficacy data listed in section 5.1.

Another preliminary, exploratory analysis of the primary and further efficacy endpoints may be performed based on all evaluable data after last subject out (and prior to final data base lock).

The cut-off date will be the date on which the last patient completes visit 4 and will be the same for all patients. A database snapshot will be taken with regard to this cut-off date; it will include all efficacy data listed in the section 5.1 available in the database up to the cut-off date and will be used for performing the analysis. Only cumulative results will be presented, i.e., patient level and safety data will be excluded. Details regarding statistical analysis will be outlined in the TSAP. As described in section 4.1.5 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. But 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.

Team members (CRAs, medical monitor) involved in the conduct of the trial as well as the site personnel and patients will remain blinded until the final database lock. The primary analysis is performed on the final database lock. The CTR will be written based on this final database lock. The final database lock will take place when the end of trial milestones is achieved.

7.3 HANDLING OF MISSING DATA

In general, missing data will not be imputed.

Safety
It is not planned to impute missing values for safety parameters.

PK
It is not planned to impute missing values for PK.

Other endpoints
Missing data for each impulsivitiy tool will be handled according to each manual, e.g. missing responses in questionnaires or missing repetitions in motoric assessments, if described in the tool's handbook. Deviations from the handbooks are to be avoided and need to be justified in the TSAP. Entire missing endpoints will generally be handled as missing without imputation. Details on missing data handling will be specified in the TSAP.

7.4 RANDOMISATION

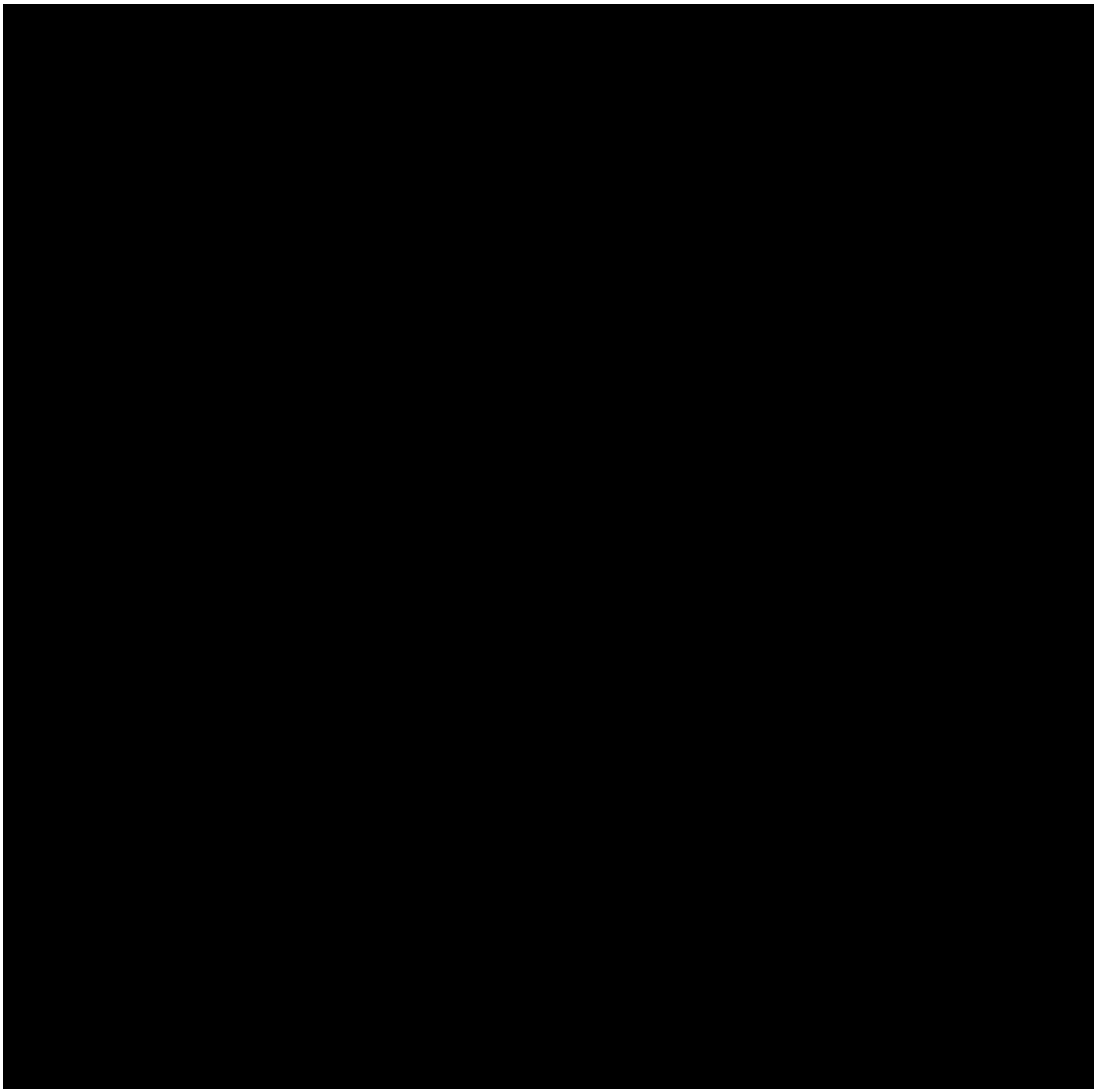
BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented.

7.5 DETERMINATION OF SAMPLE SIZE

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.

As an example, we provide the Power computation for the endpoint [redacted]

[redacted]



8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC / EU regulation 536/2014 and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as "protocol deviation".
Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

The investigator will inform the sponsor or delegate immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

The certificate of insurance cover is made available to the investigator and the patients and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.
Prior to patient participation in the trial, written informed consent must be obtained from each patient according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient.
The patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator or [redacted]delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.
The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, for fully outsourced trials, documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.
Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.
A quality assurance audit / inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. See section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to section 4.1.8.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).
Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.
The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.
If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.
For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations)

- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation
- Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion / exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The investigator / institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents / data, including progress notes, copies of laboratory and medical test results, which must always be available for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor or delegate will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site(s):
The trial site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).
Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.
To ensure confidentiality of records and personal data, only pseudonymised data will be transferred to the sponsor by using a patient identification number instead of the patient's name. The code is only available at the site and must not be forwarded to the sponsor. In case patient's records will be forwarded e.g. for SAE processing or adjudication committees, personal data that can identify the patient will be redacted by the site prior to forwarding. Access to the patient files and clinical data is strictly limited: personalised treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

A potential data security breach will be assessed regarding the implications for rights and privacy of the affected person(s). Immediate actions as well as corrective and preventive actions will be implemented. Respective regulatory authorities, IRBs / IECs and patients will be informed as appropriate.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, biobanking and future use of biological samples and clinical data, in particular

- Sample and data usage have to be in accordance with the separate biobanking informed consent
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay / equipment validation depending on the intended use of the biomarker data
- Samples and / or data may be transferred to third parties and other countries as specified in the biobanking ICF

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.
The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").

The first preliminary analysis time point is defined as the date when approximately 60% of patients have completed treatment. This milestone is optional and might not be performed.The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.
Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.
Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.
The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.
A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.
The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).
A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.
Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.
The trial will be managed by a FOT vendor based on a contract which specifies the delegated responsibilities and duties. BI has appointed a Clinical Trial Leader, responsible for coordinating all required activities, in order to:

- oversee and manage the trial in accordance with applicable regulations and SOPs,
- direct the clinical trial team and oversee the FOT vendor in the preparation, conduct, and reporting of the trial,
- ensure appropriate training.

In the participating country the trial will be performed by a Contract Research Organisation (CRO) based on a contract. The CRO will perform project management, clinical field monitoring, medical monitoring, and reporting.
Data Management and Statistical Evaluation will be done by CRO according to BI and CRO SOPs.
Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI and CRO SOPs. A list of responsible persons and relevant local information can be found in the ISF.
A local laboratories, and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Laboratory Manual, available in the ISF.

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10. APPENDICES

10.1 LIST OF THE RESTRICTED CONCOMITANT MEDICATION

CYP2D6 Inhibitors

- Amiodarone (Cordarone)
- Bupropion (Wellbutrin)
- Chlorpheniramine (Chlor-Trimeton)
- Chloroquine (Aralen)
- Chlorpromazine (Thorazine)
- Cinacalcet (Sensipar)
- Diphenhydramine (Benadryl)
- Duloxetine (Cymbalta)
- Fluoxetine (Prozac)
- Halofantrine (Halfan)
- Haloperidol (Haldol)
- Imatinib (Gleevec)
- Paroxetine (Paxil)
- Perphenazine (Trilafon)
- Propafenone (Rythmol)

- Propoxyphene (Darvon)
- Quinacrine (Atabrine)
- Quinidine (Quinidex, etc)
- Quinine
- Terbinafine (Lamisil)

Marketed MAOIs

Nonselective MAO-A/MAO-B inhibitors

- Hydrazine (antidepressant)
- Isocarboxazid (Marplan)
- Hydracarbazine
- Phenelzine (Nardil)
- Non-hydrazines
- Tranylcypromine (Parnate, Jatrosom)

Selective MAO-A inhibitors

- Bifemelane (Alnert, Celeport)
- Moclobemide (Aurorix, Manerix)
- Pirlindole (Pirazidol)

Selective MAO-B inhibitors

- Rasagiline (Azilect)
- Selegiline (Deprenyl, Eldepryl, Emsam, Zelapar)
- Safinamide (Xadago)
- Linezolid is an antibiotic drug with weak, reversible MAO-inhibiting activity.
- Methylene blue, the antidote indicated for drug-induced methemoglobinemia, among a plethora of other off-label uses, is a highly potent, reversible MAO inhibitor.

10.2 LIST OF THE DRUGS THAT MAY CAUSE QT PROLONGATION

Antiarrhythmic agents

Class IA

Because of the predominance of the potassium blocking activity, TdP is seen more frequently with therapeutic levels of quinidine. Sodium blocking activity is dominant with subtherapeutic levels, which does not lead to QT prolongation and TdP.

- Disopyramide
- Procainamide
- Propafenone
- Quinidine

Class III

Class III antiarrhythmic drugs are potassium channel blockers that cause QT prolongation and are associated with TdP.

- Amiodarone
- Ibutilide
- Sotalol

Psychotropic medications[

Psychotropic medications have been shown to lengthen the QT interval and induce TdP, especially when given intravenously or in higher concentrations.

Typical antipsychotics

- Chlorpromazine
- Haloperidol
- Thioridazine
- Atypical antipsychotics
- Quetiapine
- Risperidone

Mild QT prolongation can be caused by risperidone but there are no specific drug warnings associated with this.

- Ziprasidone

SSRIs

An EKG is recommended before patients are prescribed SSRI agents citalopram and escitalopram if the prescribed dose is above 40 mg or 20 mg per day, respectively.

SNRIs

- Venlafaxine
- Tricyclic antidepressants
- Amitriptyline
- Desipramine
- Doxepin
- Imipramine

Antibiotics

- Macrolides
- Azithromycin
- Clarithromycin
- Erythromycin
- Fluoroquinolones
- Ciprofloxacin
- Levofloxacin
- Moxifloxacin

Other agents

- Chloroquine
- Cisapride
- Foscarnet
- Hydroxychloroquine
- Ketoconazole
- Methadone
- Octreotide
- Tacrolimus
- Tamoxifen

β2 agonists

Short-acting β2 agonists (SABAs)

- bitolterol—Tornalate
- fenoterol—Berotec
- isoprenaline (INN) or isoproterenol (USAN)—Isuprel
- levosalbutamol (INN) or levalbuterol (USAN)—Xopenex
- orciprenaline (INN) or metaproterenol (USAN)—Alupent
- pirbuterol—Maxair
- procaterol
- ritodrine—Yutopar
- salbutamol (INN) or albuterol (USAN)—Ventolin
- terbutaline—Bricanyl
- albuterol—Ventolin/ Proventil

Long-acting β2 agonists (LABAs)

- arformoterol—Brovana
- bambuterol—Bambec, Oxeol
- clenbuterol—Dilaterol, Spiropent
- formoterol—Foradil, Oxis, Perforomist
- salmeterol—Serevent

Ultra-long-acting β2 agonists

- abediterol
- carmoterol
- indacaterol—Arcapta Neohaler (U.S.), Onbrez Breezhaler (EU)
- olodaterol—Striverdi Respimat
- vilanterol

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		17 Feb 2022
EudraCT number **EU number**		2021-005270-26
BI Trial number		0352-2159
BI Investigational Medicinal Product(s)		NA
Title of protocol		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

To be implemented only after approval of the IRB / IEC / Competent Authorities	X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval	☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only	☐

Section to be changed		Section 2.1.1, Section 2.2.1 .
Description of change		The following text has been added: 2.1.1: • 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. 2.2.1: 

		[redacted]
Rationale for change		Study objectives were specified as recommended by the RA.
Section to be changed		Synopsis, Section 3.3, 3.3.1
Description of change		Patient population was specified, and patients with severe symptoms of ADHD excluded from the study participation.
Rationale for change		Recommendation of RA has been addressed.
Section to be changed		Flow chart, Section 5.2.5.1.
Description of change		Suicidality assessments during the telephone contacts were added.
Rationale for change		To intensify the safety monitoring as recommended by RA.
Section to be changed		Section 5.6
Description of change		Section 5.6.2 Pharmacogenomic assessment has been added.
Rationale for change		As recommended by RA, prospective PG analysis has been added to exclude CYP2D6 poor metabolizes.
Section to be changed		Section 6.2.1, 6.2.2
Description of change		Pharmacogenomic sampling and clarification of the activities to be performed during the telephone contacts were added.
Rationale for change		Clarification of the CTP procedures.

11.2 GLOBAL AMENDMENT 2

Date of amendment		16 Mar 2022
EudraCT number **EU number**		2021-005270-26
BI Trial number		0352-2159
BI Investigational Medicinal Product(s)		NA
Title of protocol		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
To be implemented only after approval of the IRB / IEC / Competent Authorities		☐
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		X
Section to be changed		Section 8.1
Description of change		The following text has been deleted: • "Or the patient`s legally representative"
Rationale for change		The possibility of including patients incapable of giving consent personally has been deleted, as recommended by the RA.

11.3 GLOBAL AMENDMENT 3

Date of amendment		28 Feb 2024
EudraCT number **EU number**		2021-005270-26
BI Trial number		0352-2159
BI Investigational Medicinal Product(s)		NA
Title of protocol		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

To be implemented only after approval of the IRB / IEC / Competent Authorities	X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval	☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only	☐

Section to be changed		Flow Chart
Description of change		Foot note 13, “Formal assessment and confirmation of patients fitness by the investigator or [redacted] designee”, was added. Drug test at EoT excluded as per section 6.2.3.
Rationale for change		To correct the incostistency between the section 6.2.2 and flow-chart.
Section to be changed		Study synopsis, Section 3.3.2
Description of change		Inclusion criterium 1, age ot study participants was increased to 45.
Rationale for change		The possibility of including patients up to 45 years old.
Section to be changed		Section 4.2.2.1
Description of change		The timeframe of 5 halflives related to the baseline visit for prohibited medication was added.
Rationale for change		The minimum period for abstaining from prohibited psychothropic medication in relation to the base-line impulsivity testing is specified.

APPROVAL / SIGNATURE PAGE

Document Number: c36371216 **Technical Version Number:5.0**

Document Name: clinical-trial-protocol-version-04

Title: 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

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	28 Feb 2024 14:59 CET
Author-Trial Statistician		28 Feb 2024 16:20 CET
Approval-Clinical Program [redacted]		28 Feb 2024 22:03 CET
Verification-Paper Signature Completion		07 Mar 2024 13:45 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed