CLINICAL STUDY PROTOCOL

Sponsor Study Reference:	SOMCT03	**NCT number**: NCT05475483
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EudraCT number:	2021-003453-28	
Study title:	Phase IIb, randomized, double-blind, placebo-controlled study in parallel groups assessing the efficacy and safety of two doses of SOM3355 in patients suffering from Huntington's Disease with choreic movements.	
Drug name:	SOM3355 (bevantolol hydrochloride)	
Indication:	Huntington's disease	
Drug development phase:	Phase IIb	
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Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Sponsor representative, the Investigator Team, Regulatory Authorities, and members of the Research Ethics Committee and Institutional Research Board.

Regulatory statement

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements.

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LIST OF ABREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AUC	Area under the plasma concentration curve
BARS	Barnes Akathisia Rating Scale
BDI	Beck Depression Inventory
BID	Twice daily
BP	Blood Pressure
bpm	Beats per minute
CAG	Cytosine-Adenine-Guanine
CGI	Clinical Global Impression
C_{max}	Maximum observed plasma concentration
CRA	Clinical Research Associate
CRO	Contract Research Organization
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	Clinical Trial
DBP	Diastolic Blood Pressure
deuTBZ	Deutetrabenazine
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
ESS	Epworth Sleepiness Scale
FA	Functional Assessment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HD	Huntington's Disease
HPLC	High Performance Liquid Chromatography
HR	Heart Rate
HTT	Huntingtin gene
Htt	Huntingtin protein
IB	Investigator’s Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonization

Abbreviation	Definition
IMP	Investigational Medicinal Product
IWRS	Interactive Web Response System
MAO	Monoamine Oxidase
MoCA	Montreal Cognitive Assessment
PBA-s	Problem Behavior Assessment-short form
PD	Pharmacodynamics
PGI	Patient Global Impression
PI	Principal Investigator
PK	Pharmacokinetics
PoC	Proof of Concept
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SmPC	Summary of Product Characteristics
SOM3355	Bevantolol hydrochloride (racemate)
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBZ	Tetrabenazine
TEAE	Treatment Emergent Adverse Event
TFC	Total Functional Capacity
T_{max}	Time corresponding to occurrence of C_{max}
TMC	Total Maximal Chorea
TMS	Total Motor Score
UHDRS®	Unified Huntington's Disease Rating Scale
US	United States
VMAT2	Vesicular monoamine transporter type 2

1. PROTOCOL SUMMARY

1.1. SYNOPSIS

Title	Phase IIb, randomized, double-blind, placebo-controlled study in parallel groups assessing the efficacy and safety of two doses of SOM3355 in patients suffering from Huntington's Disease with choreic movements.
Phase	Phase IIb.
Indication	Treatment of Huntington's Disease (HD) patients with choreic movements.
Rationale	Huntington's disease (HD) is an inherited progressive neurodegenerative disease. Chorea, an involuntary jerky movement that is purposeless and abrupt, is one of the most prominent symptoms in HD. No effective disease-modifying therapies exist for HD, and treatment is symptomatic relief. Chorea is treated by tetrabenazine (TBZ), approved in Europe and the United States (US), and the long-acting derivative deutetrabenazine (deuTBZ), approved in the US only. Both drugs are vesicular monoamine transporter type 2 (VMAT2) inhibitors depleting monoamines in presynaptic neurons. It is thought that the consequent modulation of dopamine signaling across neural synapses reduces the dyskinetic movements, such as chorea. The labels of both compounds carry a black-box warning by the Food and Drug Administration (FDA) and special warnings by the European Medicines Agency (EMA) since they can increase the risk of depression and suicidality in HD patients. SOM Biotech, using a computational virtual screening approach (SOM^{AI}PRO) combined with *in vitro* screening methods, aimed to discover new potential treatments for HD that might offer clinical benefits over the current marketed HD treatments. Potential candidates were identified to be repositioned as VMAT2 inhibitors. One candidate named SOM3355 was bevantolol hydrochloride, developed and commercialized as an antihypertensive drug in Japan, China, and South Korea. *In vitro*, SOM3355 provided functional inhibition of the VMAT2 with similar potency to that of TBZ but different binding properties that may provide less risk of severe side effects. Relying on its VMAT2 inhibition activity, and the good tolerability shown in previous trials at doses from 100 to 600 mg/day administered once or twice daily (OD or BID), SOM Biotech is now developing SOM3355 for the treatment of the dyskinetic movement disorders related to HD.

	A first proof-of-concept (PoC) Phase IIa trial was conducted in 32 HD patients to test the efficacy and safety of SOM3355 100 and 200 mg BID doses compared to placebo. This provided confirmation of the expected effects of SOM3355 on the chorea symptoms measured by the Total Maximal Chorea (TMC) score, which significantly improved while patients were receiving 200 mg BID SOM3355 in comparison to placebo. SOM3355 was well-tolerated, with no concern about depression or suicidality risk, and the most frequent treatment emergent adverse events, all mild or moderate, being bradycardia, hypotension, insomnia, and falls, which were expected and explained by the known effects of the drug. Following the results of the first PoC and the PK-PD assessment indicating that higher doses may be more efficacious, this Phase IIb study will be conducted.
Objectives	The primary objective of the study is to assess the efficacy of two doses of SOM3355 (400 mg/day and 600 mg/day taken twice daily [BID] over at least 8 weeks at maintenance dose) compared to placebo to reduce chorea in HD patients measured by the change in TMC score (primary efficacy endpoint). Secondary objectives of the study are: To evaluate the safety and tolerability of two doses of SOM3355 (400 mg/day and 600 mg/day taken) compared with placebo in HD patients, with particular attention to depression and suicidality and to the cardiovascular hemodynamic parameters. And to evaluate the efficacy of the two doses of SOM3355 (400 mg/day and 600 mg/day taken BID) compared with placebo on: the change of Clinical Global Impression (CGI-C), the change of Patient Global Impression (PGI-C), the percentage of responders based on the improvement ≥2 in TMC score, the percentage of change of TMC score. A pharmacokinetic (PK) sub-study in a subset of 24 patients will allow to determine the PK profile of the two doses of SOM3355 (200 mg and 300 mg given twice per day) at steady state and to model PK-PD assessments of hemodynamic and cardiac parameters.
Study design	This is an international, multicenter, double-blind, randomized, placebo-controlled, parallel-group Phase IIb study assessing two doses of SOM3355 (400 or 600 mg/day), taken as 200 mg BID or 300 mg BID, in patients presenting choreic symptoms related to HD.

	Patients who meet all of the eligibility criteria will be randomized at the inclusion visit (Visit 1) to one of 3 treatment arms to receive either SOM3355 400 mg/day, SOM3355 600 mg/day, or placebo, all given BID. Dosing will start with an up titration in the first 3 weeks and will be maintained at a fixed dose for 7 weeks. After 10 weeks, patients will down titrate to 1 capsule a day of study drug for 1 week, followed by 1 capsule a day of placebo to assess the effect of drug interruption. Ambulatory patients will be recruited by reference centers for HD in collaboration with patient advocacy groups and the European HD network. A sub-study will characterize the PK profile of the 2 doses (400 mg/day or 600 mg/day) given twice daily for at least one week in a subset of patients (n = 24) who consent to be hospitalized for 24 hours for blood sampling and cardiac and hemodynamic assessments.
Sample size	A total of 129 patients (43 in each arm, accounting for a drop-out rate of 10%) will be randomized (1:1:1).
Inclusion criteria	Eligibility criteria to participate in this study are: 1. Males or females ≥21 years old. 2. Patients with a diagnosis of Huntington's Disease determined by a movement disorders expert and confirmed by a number of HTT gene cytosine-adenosine-guanine (CAG) repeats ≥36. 3. UHDRS® Total maximal chorea (TMC) score ≥10. 4. UHDRS® Total Functional Capacity (TFC) ≥7 (corresponding to mildly to moderately impaired patients). 5. Able to walk independently or with minimal assistance. 6. Females of child-bearing potential must use a medically accepted effective method of birth control, agree to continue this method for the duration of the study and for at least 1 month following the last dose of study drug, and be negative to serum pregnancy test performed at the screening visit (Refer to section 5.4 for complete advice on contraception requirements of this study). Female patients should not be breast-feeding. 7. In the opinion of the Investigator, the patient must have adequate support to comply with the entire study requirements as described in this protocol (e.g. transportation to and from the trial site, self-rating scales, drug compliance, scheduled visits, etc.).

	8. Able and willing to provide written informed consent prior to any study-related procedure being performed at the screening visit.
Exclusion criteria	Patients are excluded from the study if any of the following criteria apply: 1. Onset of HD symptoms prior to age of 21 years, corresponding to juvenile forms of HD. 2. HD patients presenting rigid akinesia. 3. Use of other vesicular monoamine transporter type 2 (VMAT2) inhibitors such as tetrabenazine, deutetrabenazine, or valbenazine within 3 months before enrollment, and at any time during the study period; and use of other antichoreic treatment such as any neuroleptic within 2 months or amantadine, memantine, riluzole within 1 month before enrollment and along the study. 4. Patients who experienced severe depression or suicide attempt in the last 5 years. 5. Severe untreated or under-treated psychiatric illness such as active suicidal ideation or behavior (BDI-21 item #9 >0 and active suicidal ideation in C-SSRS) or depression at screening and/or initiation visit (BDI-21 items total score >30); although patients taking authorized antidepressant therapy at a stable dose for at least 2 months and stabilized can be enrolled. 6. Patients with a history of, or current, hypotension (SBP <110 mmHg), bradycardia (HR <50 bpm), or orthostatic hypotension as defined by the European Society of Hypertension (reduction in SBP ≥20 mmHg or in DBP ≥10 mmHg). 7. Patients with hypertension already treated with more than 2 antihypertensive drugs. 8. Other active clinically significant illness, including unstable cardiovascular disease, angina pectoris, congestive heart failure, pulmonary hypertension, peripheral arterial disease, history of pheochromocytoma, asthma, COPD, diabetic ketoacidosis or metabolic acidosis, or neoplastic pathology, which could interfere with the study conduct, or counter-indicate the study treatment, or to place the patient at risk during the trial, or compromise their study participation. 9. Any significant serious abnormality in the electrocardiogram (ECG), e.g. recent myocardial infarction, significant sinus bradycardia (<50 bpm), atrioventricular block (grades I to III with PR >240msec), sinoatrial block, atrial sinus disease or prolonged QTc interval at screening (ECG

	Bazett's corrected QT interval (QT /√ [HR/60] >450 msec for males or >470 msec for females), or a known history of long QTc syndrome. 10. Patients with severe hepatic impairment, or with severe renal impairment, or with any other significant abnormality in the physical examination or clinical laboratory results that, in the Investigator's opinion, would not be compatible with study participation or represent a risk for the patient while in the study. 11. Females who are pregnant or lactating, or who intend to become pregnant during the study period. 12. Patients with allergy under desensitization, with known psoriasis, or a known allergy / hypersensitivity to any ingredients of the trial medication or placebo. 13. History of alcohol or substance abuse in the previous 12 months. 14. Patients participating in any other study, and the use of any investigational therapy, within 1 month prior to entry in this study.
Previous and concomitant medications	Prohibited treatments: VMAT2 inhibitors such as tetrabenazine, deutetrabenazine, or valbenazine are forbidden within 3 months prior to randomization and at any time during the whole study. Neuroleptics indicated to treat chorea such as haloperidol, pimozide, or tiapride, and all other neuroleptics used off label as dopamine D2 receptor blockers to treat chorea are forbidden within 2 months prior to randomization and at any time during the whole study. The following treatments are forbidden within 1 month prior to randomization and during the whole study: • All monoamine oxidase (MAO) inhibitors. • Levodopa and dopa-agonist drugs: apomorphin, ropinirole, pramipexole, rotigotine. • Reserpine. • Glutamate antagonists: amantadine, memantine, riluzole. • Anti-arrhythmic drugs inducing bradycardia: diltiazem, verapamil, amiodarone, digitalis, quinidine, sotalol, disopyramide. • Any other beta blocker antihypertensive medication. • Central antihypertensive treatments: clonidine, methyldopa, rilmenidine.

	Authorized treatments: Patients treated with antihypertensive drugs such as diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or calcium blockers (dihydropyridines only) can continue their treatment at a stable dose during the whole study, with maximum of a dual combination of 2 antihypertensive drugs, and if the patient has stable blood pressure. Patients treated for depression and stabilized with non IMAO (inhibitors of MAO) antidepressants can continue their treatment at stable dose during the whole study. Allowed antidepressants are: • SSRIs (selective serotonin reuptake inhibitors): fluoxetine, paroxetine (see precautions below), citalopram, sertraline. • SNRIs (serotonin-noradrenaline reuptake inhibitors): duloxetine, venlafaxine. • TCAs (tricyclic antidepressants): amitriptyline, clomipramine, imipramine, nortriptyline, lofepramine. Neuroleptics treatment (excluding haloperidol, pimozide, and tiapride), if needed to treat a behavior disorder and prescribed for at least 3 months at a stable dose, can be maintained at a stable dose during the whole study, provided that it is approved on a case-by-case basis by the Steering Committee before enrolment of the patient. Treatments to be used with precautions (because of risk of interactions): • Alpha-blockers. • Local beta-blockers (eye drop) or pilocarpine (eye drop). • Anticholinesterase drugs: donepezil, rivastigmine. • Strong CYP2D6 inhibitors may increase the blood levels of SOM3355 (such as paroxetine fluoxetine, quinidine, bupropion, dacomitinib, tipranavir).
Investigational treatments	The study medication will be provided in capsules of SOM3355 dosed at 200 mg or 300 mg, or matching placebo. SOM3355 capsules will contain 2 or 3 tablets of 100 mg of the commercial form of bevantolol (Calvan® 100 mg tablets). The capsules will be identical in appearance to ensure that neither the patient nor the Investigator or the clinical staff know the exact nature of the study medication. Patients should take 1 capsule in the morning during the first week and then 1 capsule twice per day, one in the morning and one in the evening (every 12 hours) during the following 9 weeks, and then only 1 capsule in the morning during the last 2 weeks. Capsules can be taken with food.

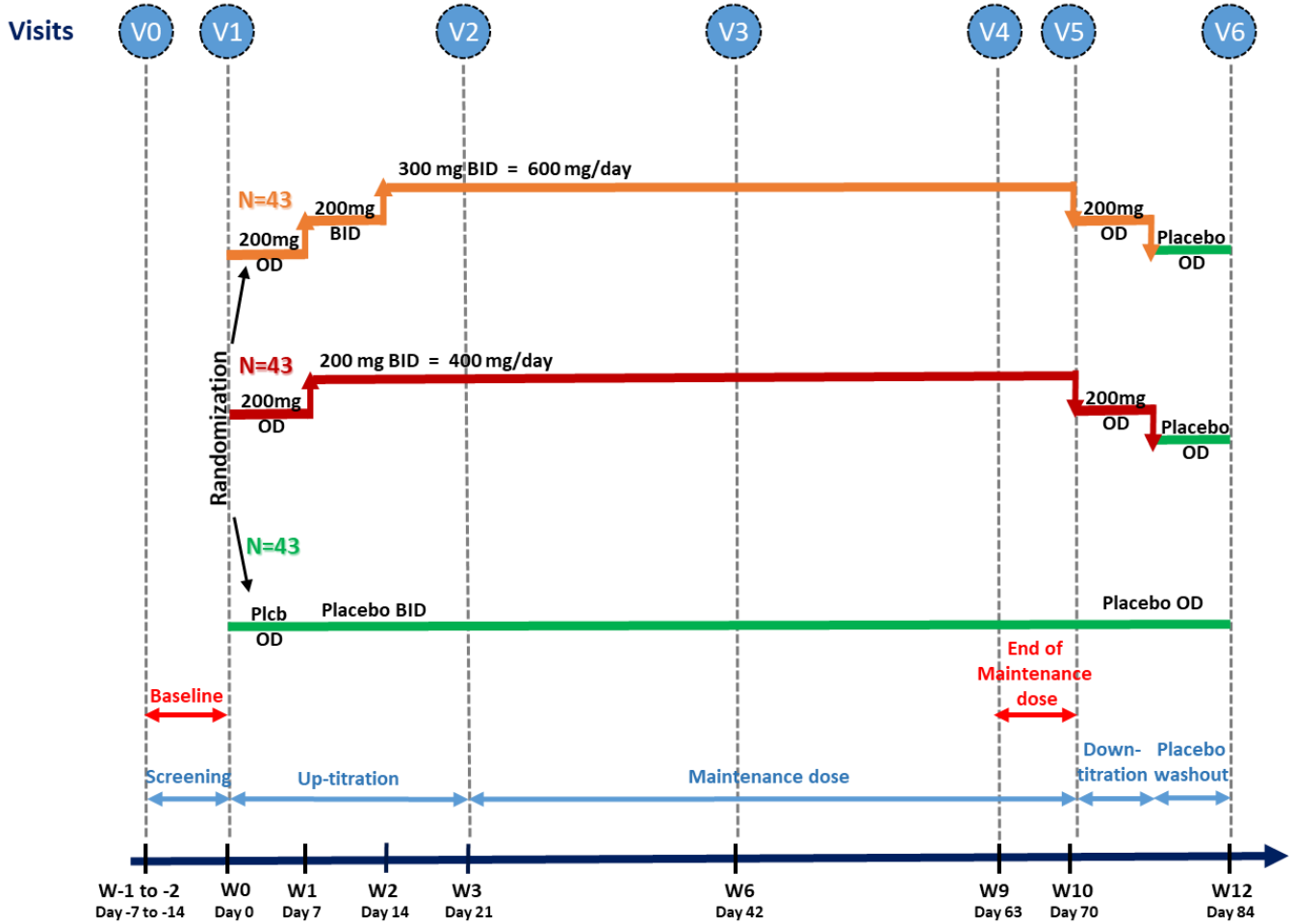
	At the inclusion visit (Day 0), patients will be allocated according to the randomization list to one of the 3 treatment arms, starting with 3 weeks of up-titration, to receive either SOM3355 400 mg/day, SOM3355 600 mg/day, or placebo for up to 10 weeks. This will be followed by 1 week of down titration and 1 week of placebo wash-out period to assess the effect of drug interruption. The total treatment duration of this double-blind study, from the inclusion visit, will be 12 weeks (+ 1 or 2 weeks for screening before inclusion): 11 weeks under the active drug treatment (or placebo), and 1 week under placebo for all patients at the end of the study.
Primary efficacy endpoint	The primary measure of efficacy will be the change in Total Maximal Chorea (TMC) sub-score of the Unified Huntington's Disease Rating Scale (UHDRS®) between baseline and end of maintenance dose (the mean of Visit 4 and Visit 5 minus the mean of Visit 0 and Visit 1). The TMC score is a standardized, reliable chorea assessment based on frequency and severity in 7 body regions.
Secondary efficacy endpoints	Key secondary efficacy endpoint: • Change from baseline in the Clinical Global Impression (CGI-C). Other secondary efficacy endpoints: • Change from baseline in the Patient Global Impression (PGI-C). • TMC-response defined as improvement ≥2 in TMC score between baseline and end of maintenance dose. • Percentage of change in TMC score between baseline and the end of maintenance dose. • Change from baseline in Total Motor Score (TMS) of the UHDRS®. • Change from baseline in Gait sub-score of the UHDRS®. • Change from baseline in Dystonia sub-score of the UHDRS®. • Change from baseline in EQ5D-5L measuring quality of life.
Safety endpoints	Safety assessments will include the following: • Incidence, frequency, and severity of adverse events (AEs) in each treatment group. • Change from baseline in: • Vital signs: blood pressure (BP), including orthostatic BP, and heart rate (HR).

	• ECGs. • Clinical laboratory test results (chemistry, hematology). • Physical examination findings, weight. • Columbia-Suicide Severity Rating Scale (C-SSRS) assessing suicidality. • Beck Depression Inventory (BDI) scale assessing depression. • Epworth Sleepiness Scale (ESS) assessing sleepiness. • Total Functional Capacity (TFC) of the UHDRS® assessing functioning. • Functional Assessment of the UHDRS®. • Barnes Akathisia Rating Scale (BARS) assessing akathisia. • Montreal Cognitive Assessment (MoCA) scale to assess cognitive disturbances. • Problem Behaviors Assessment short form (PBA-s) to assess behavioral symptoms in HD.
PK-PD assessments	**SOM3355 plasma concentration** will be measured at each visit under treatment with SOM3355 (i.e. from Visit 2 to Visit 5) in all patients. Plasma samples will be collected pre-dose (before the dug intake) and 2 hours after the drug intake (corresponding to the expected T_{max}) at Visit 2 and Visit 4, and only pre-dose at Visit 3 and Visit 5. **Prolactin plasma level** will be measured at each visit from Visit 1 to Visit 6 in all patients. Plasma samples will be collected pre-dose (before the dug intake) and 2 hours after the drug intake (at T_{max}) at Visit 2 and Visit 4, and only pre-dose at Visit 1, Visit 3, Visit 5, and Visit 6.
PK sub-study	A PK sub-study will be conducted to characterize the PK profile of repeated doses of SOM3355 at 400 and 600 mg/day. This analysis will be performed by collecting 12-hour PK samples (H0, H0.5, H1, H1.5, H2, H3, H5, H8, and H12) in 8 patients per arm (24 patients in total) that will be hospitalized for 24 hours at Visit 2. In addition, cardiac and hemodynamic parameters will be collected in parallel, with 12-hour cardiac Holter and blood pressure measurements before each PK sample, to allow PK-PD modeling assessments. These patients will be recruited by 3 or 4 sites able to manage the logistics of PK sampling.

Sample size and statistical methodology	Sample size calculation The sample size requires enrollment of a total of 129 patients in the randomized treatment period, allowing for a drop-out rate of 10%. Eligible patients will be randomized in blinded fashion in a 1:1:1 ratio i.e. 43 patients in each arm (SOM3355 400 mg/day, SOM3355 600 mg/day, or placebo). Assuming a treatment difference of -2.5 points in the change from baseline of TMC score compared to placebo and a standard deviation of 3.5, 39 patients per arm are needed to provide at least 80% power that at least 1 dose of SOM3355 will be significantly superior to placebo at the 2-sided 0.025 significance level. This is based on the use of a two-sided t-test for the mean TMC score change. With a dropout rate of approximately 10%, 43 patients per arm have to be enrolled i.e. a total of 129 patients. If the dropout rate is higher than 10%, then an upward adjustment of sample size might be considered. Statistical methods The primary efficacy analyses will be based on the modified intent-to-treat (mITT) Population, which is defined as all randomized patients with at least one dose of the study treatment and one post-baseline assessment of the TMC score. A mixed-effect linear model for repeated measures (MMRM) will be used to compare each active treatment group to placebo for change in TMC score from baseline (defined as the average values from Visit 0 and Visit 1) to the end of maintenance therapy (defined as the average values from Visit 4 and Visit 5), 9-10 weeks after the start of study treatment. The least square mean (LSM) estimate for each treatment group and difference in LSM estimates at end of maintenance dose between active treatments and placebo group with their confidence intervals will be provided. To control the overall type I error at 0.05 for the statistical comparisons of the 2 dose levels vs placebo, a Holm procedure will be used for the primary endpoint. For the secondary endpoints, the significance level is set at two-sided 0.05. An interim analysis for futility is planned when 65 patients enrolled (around 50% of the total patients) have either completed Visit 5 or have discontinued the study early. Safety analyses will be based on the safety population, which is defined as all randomized patients having received at least one dose of study treatment.

Study duration and sites	The total duration of this double-blind study will be 12 weeks + 1 or 2 weeks for screening. The study will be conducted in 16 to 20 investigating sites located in Europe. Each site should be able to recruit at least 6 eligible patients. Proposed countries are Spain, France, Italy, Germany, Poland, UK, and Switzerland.
Study Timelines	The study is planned to start by the end of 2021 (Q4) and last one year.

1.2. STUDY SCHEMA



Total study duration 12 weeks (+1 or 2 weeks for screening) – 11 weeks under SOM3355 active drug

Figure 1: Study Schema

1.3. SCHEDULE OF ACTIVITIES

Table 1: Schedule of Activities by Visit

Visit	V0	V1	V2	V3	V4	V5	V6
	Screening (baseline 1)	Randomization (baseline 2)	End of Up-titration	Maintenance Dose (interim)	Maintenance Dose (end 1)	Maintenance Dose (end 2)	End of study
Day	D-7 to -14	D0	D21 ± 2 days	D42 ± 2 days	D63 ± 2 days	D70± 2 days	D84 ± 2 days
Week	W-1 to -2	W0	W3	W6	W9	W10	W12
Informed consent	X						
Inclusion and exclusion criteria	X	X					
Randomization		X					
Demographics and medical history	X						
Physical and neurological examination	X	X	X	X	X	X	X
Vital signs (HR, BP, …)	X	X	X	X	X	X	X
UHDRS® motor part	X	X	X	X	X	X	X
CGI, PGI		X	X	X	X	X	X
C-SSRS, BDI, ESS	X	X	X	X	X	X	X
UHDRS® (TFC, FA)	X	X*				X	
EQ-5D, BARS, MoCA and PBA-s		X		X***		X	
ECG	X	X**	X		X		X
Blood sample for safety	X			X		X	
Blood sample for prolactin level		X[1]	X[2]	X[1]	X[2]	X[1]	X[1]
Blood sample for PK			X[2]	X[1]	X[2]	X[1]	
Hospitalization for 12-h PK sampling			X****				
Pregnancy test in female	X						X
Adverse events		X	X	X	X	X	X
Co-medications	X	X	X	X	X	X	X
Dispensation of study drug		X	X	X	X	X	
Drug accountability & compliance			X	X	X	X	X

* Only TFC at V1 (inclusion visit)

** ECG triplicated at V1 (inclusion visit)

*** PBA-s only

**** At V2, hospitalization of only 8 patients per arm (24 patients in total) for 12-h PK sampling by 3-4 selected sites + ECG Holter and BP measurement at each sampling time point

[1] Blood sample only at pre-dose

[2] Blood sample at pre-dose and at Tmax (2 hours after drug intake)

2. INTRODUCTION

2.1. BACKGROUND

2.1.1. Huntington's Disease and chorea symptoms

HD is an inherited progressive neurodegenerative disease for which the precise pathological process is far from understood. HD is caused by an expanded repeat sequence of three nucleotides, cytosine-adenine-guanine (CAG) in the Huntingtin gene (*HTT*) on chromosome 4. This results in the production of a mutant huntingtin (mHtt) protein with an abnormally long polyglutamine repeat sequence. As long as the number of CAG repeats in the *HTT* gene is lower than 27, the section is stable (normal range). If the number of repeats is between 27 and 35 (intermediate repeat length), that individual will not develop HD. However, a CAG repeat number of 27 or more is unstable and liable to increase when passed on to the next generation, meaning that those children carry a risk of developing HD. Individuals with a CAG repeat number between 36 and 39 may develop HD, but only late in life, with a less severe phenotype. This is known as the reduced-penetrance repeat length range. When the number of CAG repeats is higher than 39, a person will develop HD within a normal lifespan – most often in mid-adult life. In rare cases, the CAG expansion can be exceptionally long, leading to disease onset in adolescence or childhood (juvenile HD). Patients who develop the disease before the age of 10 often have more than 80 CAG repeats (McColgan et al, 2018; Ross et al, 2009). The mutant Huntingtin (mHtt) protein has a propensity to form abnormal aggregates that impact multiple cellular processes. Furthermore, the multiple functions of the protein are disturbed.

The age of clinical onset in HD is highly variable, with a mean of ~45 years (Ross et al, 2014). Most people with the CAG repeat expansion seem healthy until adulthood; however subtle motor, cognitive and psychiatric deficits can be identified up to 10-15 years before the onset of manifest disease and this is referred to as the premanifest stage of the disease (McColgan et al, 2018). The course of typical adult-onset HD can be divided into premanifest and manifest periods. The premanifest period is subdivided into the pre-symptomatic phase, in which individuals are clinically unaffected, and the prodromal phase, characterized by subtle multimodal features, in which chorea is prominent. The manifest period follows, in which motor and cognitive symptoms become more pronounced. In later stages of manifest HD, incoordination, dystonia, bradykinesia, rigidity, and cognitive impairment are commonly more prominent than chorea (Ross et al, 2014).

Chorea is one of the most prominent symptoms in HD and occurs early in the disease. It is an involuntary jerky movement that is purposeless and abrupt. Chorea predominantly affects the distal extremities and facial muscles in early stages of the disease (Ross et al, 2010). The severity of chorea in patients with HD varies, but abnormal movements usually become gradually more serious and many patients develop very severe chorea that compromises daily living (Vuong et al, 2018). Chorea then spreads to involve more proximal regions of the body, increasing in amplitude and amount until some patients may be affected for the entire time they are awake. Activation of facial and neck muscles can cause head turning, eye closure, and tongue protrusion, whereas involvement of axial muscles can lead to extension and arching of the back. It can cause problems with writing and can also contribute to falling Pharmacological intervention is aimed at symptomatic relief by restoring

the balance of neurotransmitters thought to be involved in the pathogenesis of HD, particularly dopamine.

The central dopaminergic pathways in HD patients are affected with dysfunction of both dopamine release and dopamine receptors. Dopamine is released from pre-synaptic terminals, which activates dopamine receptors. The dopamine is then transported back into the pre-synaptic terminal, where vesicular monoamine transporter type 2 (VMAT2) repackages the dopamine into the vesicles.

Although motor onset is usually the point at which a diagnosis is made, most HD patients experience personality changes, depression, and anxiety before chorea (the hallmark of HD). Psychiatric symptoms are another common manifestation of HD, along with cognitive decline and behavioral difficulties. Data from the European Huntington's Disease Network's Registry suggested that approximately 39.3% of their participants had severe psychiatric problems such as suicidal ideation and attempts, depression, irritability, aggressive behaviors and psychosis (Orth et al, 2010). Moreover, cognitive changes, manifested by loss of recent memory, poor judgment, and impaired concentration and acquisition, occur in nearly all HD patients (Fahn et al, 2011). Chorea, a hallmark characteristic of HD, contributes to balance impairment and falls, which greatly impact quality of life. Falls are one of the strongest predictors of nursing home placement (Wheelock et al, 2003). As further evidence of the central role chorea plays in HD, one study demonstrated a direct connection between chorea and worsened condition. This study used the United Huntington's Disease Rating Scale (UHDRS®), which measures motor function, cognitive function, behavioral abnormalities, and functional capacity, to see which aspects of HD impacted patients the most (Huntington Study Group, 1996). They found that only shifts in the UHDRS® chorea score correlated with changes in complex task performance after 3 years, such as peg insertion, which particularly reflects motor impairment, as well as higher cognitive and executive dysfunction (Andrich et al, 2007).

A drug to improve chorea in HD patients would have great benefit. Based on the widespread effects of chorea in this patient population, such a drug might have the potential to reduce the negative effects of the disease, possibly improving quality of life, patient independence, and survival (Coppen et al, 2017).

2.1.2. Current treatments of chorea

Currently, chorea is treated by tetrabenazine (TBZ) the first approved drug for the treatment of chorea in HD both in Europe and in the United States. The long-acting derivative deutetrabenazine (deuTBZ) is approved in the US only. Both existing drugs are vesicular monoamine transporter type 2 (VMAT2) inhibitors. They deplete monoamines in presynaptic neurons by inhibiting the VMAT2 uptake from the cytoplasm into the synaptic vesicles for storage, resulting in rapid degradation of cytoplasmic dopamine by MAOs. It is thought that the consequent modulation of dopamine signaling across neural synapses reduces the dyskinetic movements, such as chorea. The labels of both compounds carry a black-box warning by the Food and Drug Administration (FDA) and special warnings by the European Medicines Agency (EMA) since they can increase the risk of depression and suicidality in HD patients. Thus, they are contraindicated in patients who are actively suicidal and in patients with inadequately treated depression or severe depression, and patients must be closely monitored for the development of depressive symptoms or suicidal ideation. In addition, their co-administration with

other neuroleptic drugs may increase the possibility of parkinsonism, neuroleptic malignant syndrome and akathisia (Caroff et al, 2020).

A variety of other available agents are used off-label (e.g. amantadine, neuroleptics, etc.) to treat chorea symptoms with lack of high quality evidence (Mestre et al, 2009). The use of neuroleptics for HD chorea is primarily based on years of clinical experience, especially when psychiatric symptoms such as psychosis, depression, or aggressive behavior are present, but the evidence for their use to treat chorea is limited to mostly small open-label studies, case reports, or retrospective chart reviews. In Europe, since a recent revision of its labelling in 2017, haloperidol is the only neuroleptic that has the indication of the "treatment of mild to moderate chorea in HD, when other medicines do not work or have unacceptable side effects". Pimozide and tiapride are also authorized in some European member states for the treatment of abnormal involuntary movements that occur in HD, such as chorea. Atypical neuroleptics (olanzapine, clozapine, risperidone) are more frequently used off label to treat chorea in patients presenting associated psychiatric disorders or aggressive behavior, but again these treatments have not shown strong evidence of their efficacy on chorea and have a less favorable safety profile (agranulocytosis with clozapine, weight increase with risperidone).

2.1.3. SOM3355 selection as VMAT2 inhibitor

SOM Biotech, using a computational virtual screening approach (SOM^{AI}PRO) combined with *in vitro* screening methods, aimed to discover new potential treatments for HD from a database of compounds that already have regulatory approval and that might offer clinical benefits over the current marketed HD treatments. Potential candidates were identified, which could be repositioned as VMAT2 inhibitors. One candidate named SOM3355 was bevantolol hydrochloride, which was originally developed by Warner-Lambert in the '80s and commercialized as an antihypertensive drug by Nippon Chemiphar Co. Ltd in Japan, China, and South Korea. In addition to its known activity as a selective β1-blocker, SOM Biotech has discovered a new activity of bevantolol as a VMAT2 inhibitor.

SOM Biotech is developing SOM3355 (bevantolol hydrochloride) as an inhibitor of VMAT2 for the treatment of dyskinetic movement disorders related to HD.

2.1.4. Summary of Relevant Non-Clinical Studies with SOM3355

Consequent to the virtual screening, *in vitro* validation of the VMAT2 inhibitory properties of SOM3355 was undertaken.

2.1.4.1. In vitro assays and mechanism of action

The pharmacology of SOM3355 (bevantolol hydrochloride) in relation to its desired therapeutic effect of inhibiting VMAT2 was characterized in *in vitro* studies.

In vitro, SOM3355 provided functional inhibition of the VMAT2 with similar potency to that of TBZ, but binding to the TBZ site of the VMAT2 was found approximately 50-fold lower, suggesting that SOM3355 binds to another site on the VMAT2 or in a different mode to TBZ at the TBZ site. Furthermore, unlike TBZ, it was found that SOM3355 also inhibits the VMAT1. The role of VMAT1 in the brain is only now beginning to be unraveled. These differences in the modulation of the VMATs between SOM335 and TBZ may play an important role in the context of the complex involvement of

dopaminergic neural pathways in mediating HD dyskinesia and the prominent psychiatric effects of TBZ.

2.1.4.2. In vivo assays

In male Sprague Dawley rats, SOM3355 does not show the same *in vivo* catalepsy syndrome typical of TBZ even at very high doses. These differences may translate into a better efficacy/safety profile in patients.

2.1.5. Summary of Previous Relevant Non-Clinical Studies with Bevantolol (SOM3355)

Bevantolol was first developed as a selective beta-adrenergic blocking agent in the '80s by Warner-Lambert and a battery of non-clinical studies were conducted, including pharmacology (primary PD, secondary PD, safety pharmacology), PK (absorption, distribution, metabolism and excretion), and toxicity studies including acute and repeat-dose toxicity, genotoxicity, carcinogenicity, and reproductive and developmental toxicity. Extensive non-clinical characterization of bevantolol hydrochloride is available from the legacy file (see Investigator's Brochure §5.1.2).

The *in vitro* and *in vivo* profile of the compound, and how this translates to the clinical situation, have been extensively reviewed (Kaplan et al, 1985; Kaplan et al, 1986; Frishman et al, 1988).

Information on non-clinical PK, and Absorption, Distribution, Metabolism, and Excretion (ADME) is summarized in the Investigator's Brochure §5.2.

2.1.6. Summary of Relevant Clinical Studies

2.1.6.1. First Proof of Concept study in Huntington 's Disease patients (SOM-CT02)

A proof-of-concept (PoC) Phase IIa trial was conducted, with the existing formulation of bevantolol hydrochloride (Calvan®). It was a double-blind, randomized, placebo-controlled crossover study in 32 HD patients, to test the efficacy and safety of SOM3355 100 mg BID and 200 mg BID doses compared to placebo. Patients were randomly assigned to 2 arms of 4 sequential 6-week dose periods, in which they received placebo and SOM3355 at 100 and 200 mg twice daily in a crossover design. The primary endpoint was defined as improvement of at least 2 points in the TMC sub-score of the motor part of the UHDRS® in any active drug period compared with the placebo period. A responder analysis and a mixed model analysis were performed for the primary endpoint. Secondary endpoints were CGI-C and PGI-C, as well as the total functional capacity, functional assessment, total motor score, and gait sub-score of the UHDRS®. Safety was assessed by evaluating adverse events (AEs), with special attention to blood pressure and cardiac function, and the Columbia Suicide Severity Rating Scale, assessing suicidal ideation and behavior. Plasma prolactin levels were also measured during the study.

The responder analysis revealed that more than half of the patients (57.1%) had improvements in the TMC score of at least 2 points in any period with SOM3355 compared with placebo, thus reaching the primary endpoint. Even greater improvements in the TMC score of at least 3, 4, 5, and 6 points compared with placebo were seen with SOM3355 in 28.6%, 25.0%, 17.9%, and 10.7% of the patients, respectively. The mixed-model analysis comparing the different periods showed significant improvement in the TMC score with 200 mg twice daily of SOM3355 compared with placebo

(*P*=0.0224), which was confirmed in ratings of CGI-C and PGI-C. In the other outcome measures of the UHDRS®, no statistical differences were found between SOM3355 and placebo. SOM3355 was well tolerated with only mild or moderate AEs, and with no implications for depression or suicidality risk. The most frequent AEs during SOM3355 administration, all mild or moderate, could be explained by the known effects of the drug such as insomnia, and bradycardia or hypotension that are both related to the β1-blocking effects of bevantolol. Mild elevations in plasma prolactin levels were recorded with SOM3355 (*P*<0.005), probably reflecting the inhibitory effect on the dopamine pathway, consistent with the profile of VMAT2 inhibition. This study confirmed that SOM3355 reduces chorea in patients with HD and has a good safety profile.

2.1.6.2. Previous clinical trials in hypertensive patients (bevantolol)

- **Studies conducted in Caucasian population (by Warner Lambert)**

Initially, bevantolol was developed in Western and Northern Europe by Warner-Lambert in the 1980s as a β1-adrenoreceptor antagonist for the treatment of hypertension and *angina pectoris*. A high number of clinical studies assessing bevantolol were conducted including more than 1400 subjects. Amongst the Phase I studies, there were 8 key Phase I studies that determined the PK profile of bevantolol in healthy volunteers (single and repeated doses, administered intravenously [IV] or orally as solution or tablet), and special PK-PD studies in patients with hypertension (N=32) or *angina pectoris* (N=12), or in patients with renal or pulmonary impairment (N=50) (Latts et al, 1986).

The oral formulation was then tested in 4 controlled trials in patients with *angina pectoris* (N=165) at doses of 150 to 300 mg/day given twice daily for 2 to 12 weeks, and in 4 controlled trials in patients with hypertension (N=772) at doses of 100 to 600 mg/day given either once or twice daily for 6 weeks to 6 months. The majority of the patients (N=715) in these controlled trials were treated for 4 to 8 weeks, 56 received bevantolol for 12 weeks and 132 for 6 months.

In one trial in patients with hypertension, the dosage was up-titrated to 600 mg/day in 47 patients until the end of the 6-week double-blind period, and then continued for further 6 months of double-blind treatment. At the end, the non-responders on hypertension (n=17) were given a further 4/8 weeks of treatment (under review every 2 weeks) with a combination of bevantolol 400 mg/day given in 2 intakes plus hydrochlorothiazide (25 mg twice daily, increased if necessary to 50 mg twice daily after 2 weeks) (Maclean 1988; WL-775-101).

Additionally, under 600 patients were treated for 12 weeks or longer (up to 4 years) at doses up to 600 mg/day in long-term open label extension studies.

Table 2: Overview of the Doses of Bevantolol Used in the Main Published Clinical Trials in Hypertension and Angina Pectoris

Study	Study design	Highest dose/day	Number of patients	Study duration
Angina pectoris				
(Gimeno et al., 1986)	Randomized, Placebo-Controlled, Double-Blind Study on Acute, Short- and Long-Term	300 mg	12	14 months

Study	Study design	Highest dose/day	Number of patients	Study duration
(Salonen al., 1986)	Randomized Double-blind study comparing bevantolol to atenolol	300 mg	40	12 weeks
(Farnham et al., 1986)	Randomized Placebo-Controlled Study	300 mg	107	6 weeks
(Rodrigues et al., 1988)	Randomized Double-blind study comparing bevantolol and atenolol	400 mg	39	8 weeks
Hypertension				
(Okawa,1986)	Randomized Placebo-Controlled double-blind study	400 mg	139	8 weeks
(Jain, 1986)	Randomized Placebo-Controlled double-blind study OD vs BID	400 mg	133	7 weeks
	Open label extension	400 mg	133	Up to 2 years
(Al-Khawaja and Jankovic, 2008)	Single center open-label study OD vs BID +24-hour ambulatory intra-arterial blood pressure (BP) recording	600 mg	17	10 weeks
(MacLean, 1988)	Randomized double-blind controlled trial comparing bevantolol to propranolol	600 mg	266	8 months
	Open-label extension in non-responders Combination bevantolol 200 mg BID + hydrochlorothiazide 25-50 mg BID	400 mg	17	8 weeks
Clinical therapeutics & medicine 8(9): 2147-2191, 1992	Bevantolol vs metoprolol	200 mg	236	12 weeks
(Noshiro, 1995)	bevantolol vs propranolol	200 mg		12 weeks
NC -Study Cl-06	Open-label bevantolol in combination with other types of antihypertensive agent	100 mg	28	8 weeks
Hypertension or *angina pectoris*				
(Bray, 1986)	Safety review of 8 double-blind randomized clinical trials in hypertension or *angina pectoris*	400 mg	579	Up to 4 years
(Takeda) (linked to NC-Study Cl-09)	Effect of bevantolol on renal function in hypertensive patients with or without renal impairment	200 mg	13	14 days
Dilated cardiomyopathy				
(Hara et al., 2002)	Open-label study comparing Bevantolol vs metoprolol	80 mg	41	6 months

The integrated summary of safety in all Caucasian trials conducted by Warner-Lambert relate a total of 937 patients having received bevantolol in controlled trials and 706 patients in uncontrolled trials. The most frequently reported AEs (>5%) were fatigue and headache (see Investigator's Brochure § 6.2.1). Previous clinical experience indicates that bevantolol used in multiple studies at doses up to 600 mg/day was safe and effective in the treatment of Caucasian patients with hypertension or chronic angina.

- **Studies conducted in Asian population (by Nippon Chemiphar)**

Additional studies were performed in the Asian population, in a total of 951 subjects/patients enrolled in trials conducted in Japan by Nippon Chemiphar at doses up to 400 mg/day.

2.1.6.3. Marketing experience in hypertension

Moreover, the drug is marketed since 1997 by Nippon Chemiphar in Japan and South Korea (Calvan®) to treat hypertension. The cumulative number of patients exposed from July 1997 to February 2021 is estimated to be more than 2,5 million patients, without any change to the safety profile as reported in the successive PSURs and PBRER.

2.2. RISK / BENEFIT ASSESSMENT

2.2.1. Known Potential Risks

Bevantolol is a cardio selective β1-blocker that is shown to selectively block the positive chronotropic and inotropic action of isoproterenol and is essentially devoid of intrinsic sympathomimetic activity (ISA). It has a mild chronotropic effect at rest and reduces exercise-induced tachycardia and pressor responses. The β1-blocking effects are almost at the same level as that of metoprolol (β1-selective blocker), while being slightly weaker than the effect of propranolol (β1-nonselective blocker).

The safety profile of SOM3355 (bevantolol) in healthy subjects and patients with cardiovascular diseases is well characterized and demonstrated to be safe and tolerable up to 600 mg/day. Therefore, there is no specific reason to suspect that the administration of this compound in non-hypertensive patients can induce clinically relevant complications and in the first trial conducted in HD patients it was well tolerated at doses up to 400 mg/day (see Investigator's Brochure § 7.2). The most frequent AEs during SOM3355 administration in the first Phase 2a study in HD patients were all mild or moderate, did not induce treatment withdrawal, and could be explained by the known effects of the drug such as insomnia, and also bradycardia and hypotension (which are both related to the β1-blocking effects of bevantolol).

Safety assessments will include monitoring of HR and BP at each visit (measured according to standardized conditions, first in the sitting position and then in the supine and standing positions to detect orthostatic hypotension), and ECG performed at key visits will be assessed with central reading.

Moreover, a wide variety of neuropsychiatric symptoms occur in HD, including, depression, anxiety, irritability, obsessive compulsive behavior and psychosis. Depression is the most common condition

with life time prevalence between 40% and 50% (Du et al, 2013) and suicide rates over five times that found among the general population (Paulsen et al, 2005; Orth et al, 2010, Fahn et al, 2011). Some drugs acting on the dopamine pathway like TBZ have warnings about the risk of aggravation of depression and suicidality. But the differentiation of SOM3355 (bevantolol) in pre-clinical assays with differences in the modulation of the VMATs compared to TBZ may play an important role in the context of the complex involvement of dopaminergic neural pathways in mediating HD prominent psychiatric effects. Therefore, we consider that bevantolol would not induce the same psychiatric effects as they were not reported during the clinical experience of its use in hypertension. However, the risk of depression and suicidality will be carefully assessed along the study with the Beck Depression Inventory scale and the Columbia–Suicide Severity Rating Scale.

The Sponsor is aware that in the current environment, hospitals should preferentially treat subjects with COVID-19 and give priority to trials for the prevention or treatment of COVID-19 infection. This trial will therefore only be initiated at a time when it is ethically and operationally feasible for each of the selected study sites to do so (see Section 8.2). There is currently no known increased risk of contracting COVID-19 as a result of taking the IMP. In addition, study visits will be conducted in such a manner as to ensure patient safety is paramount and to eliminate potential risks of COVID-19 transmission.

2.2.2. Known Potential Benefits

SOM3355 might bring advantages to treat dyskinetic movements related to HD with a better safety profile than similar existing drugs. Currently, the treatment modality for such patients is based on tetrabenazine, a VMAT2 inhibitor which is associated with severe secondary effects, including risk of worsening depression, and suicidal thoughts and behavior in patients with HD. Thus, secondary complications of tetrabenazine treatment nowadays are limiting its clinical benefit in patients suffering from this pathological condition. Such effects were not reported with bevantolol neither during its use to treat hypertension nor in the previous trial in HD. SOM3355 presents a similar VMAT2 inhibitory capacity than the reference compound tetrabenazine but with different binding properties leading to its differentiation in monoamines signaling and also a specific binding to VMAT1 receptors that may explain its different safety profile. The previous Phase IIa study conducted with SOM3355 in HD patients showed that more than half of the patients had an improvement of their chorea symptoms measured by a reduction of at least 2 points in the TMC score with SOM3355 compared to placebo, and some patients had even greater improvements, while no neuropsychiatric symptoms were reported.

2.2.3. Assessment of Potential Risks and Benefits

Patients could benefit from treatment with SOM3355, which is known to reduce chorea symptoms as shown in the previous Phase 2a study, and it will be assessed as the primary endpoint.

SOM3355 is a well-known drug which has proven its good safety profile since more than 25 years of use as hypertensive drug. It has no warning regarding neuropsychiatric side effects and it was also well tolerated in the previous trial in HD patients, with no worsening of depression or suicidality although the sample was very limited.

Safety will be carefully monitored along the trial, particularly the risk of depression and suicidality will be assessed at each visit by the physician through specific scales (Beck Depression Inventory and Columbia-SSRS). Patients with known depression should be treated and stabilized with antidepressant therapy. Patients with severe untreated or under-treated depression at screening, or presenting a risk of suicide (item on suicidality >0 in BDI scale) are excluded from this study, and if the risk of suicide arises during the trial the patient should be immediately withdrawn from the study.

The known effect of bevantolol as beta blocker may induce potential side effects such bradycardia or orthostatic hypotension. Patients with a history of, or current, hypotension or bradycardia (HR <50 bpm) at the screening will be excluded from the study. Hemodynamic parameters (HR and BP) will be carefully monitored during the study as well as the recording of ECG to assess any abnormality. Severe permanent bradycardia will be excluded.

2.3. STUDY RATIONALE

In vitro, SOM3355 provided functional inhibition of the VMAT2 with similar potency to that of TBZ but different binding properties that may provide a change in monoamine signaling improving the chorea symptoms of HD with less risk of severe side effects. Relying on its VMAT2 inhibition activity, and good tolerability at doses from 100 to 600 mg/day administered once or twice daily (OD or BID), SOM Biotech is now developing SOM3355 for the treatment of the dyskinetic movement disorders related to HD.

The first Proof of Concept Phase 2 study (SOMCT02) assessing SOM3355 in HD patients is suggestive of its clinical effect on chorea. PK-PD analysis assessed the relationship between plasma levels of SOM3355 and the absolute reduction of TMC score with a linear model. Dose proportionality was shown and modelling allowed us to predict that plasma concentration values around 3000 ng/ml will induce a mean reduction of TMC score of at least 3.0 points compared to placebo. Assuming the dose proportionality, an increase of the dose to 300 mg BID (600 mg/day) would be required in the next trial to obtain such improvement in TMC score and therefore substantial decrease of chorea symptoms that could be comparable to the TBZ effect.

3. OBJECTIVES AND ENDPOINTS

3.1. OBJECTIVES OF THE STUDY

The primary objective of the study is to assess the efficacy of two doses of SOM3355 (400 mg/day and 600 mg/day taken twice daily [BID] over at least 8 weeks at maintenance dose) compared to placebo to reduce chorea in HD patients, measured by the change in TMC score (primary efficacy endpoint).

Secondary objectives of the study are:

To evaluate the safety and tolerability of two doses of SOM3355 (400 mg/day and 600 mg/day taken BID) compared with placebo in HD patients, with particular attention to depression and suicidality and to the cardiovascular hemodynamic parameters.

And to evaluate the efficacy of the two doses of SOM3355 (400 mg/day and 600 mg/day taken BID) compared with placebo on:

- the change of Clinical Global Impression (CGI-C),
- the change of Patient Global Impression (PGI-C),
- the percentage of responders based on the improvement ≥2 in TMC score,
- the percentage of change of TMC score.

A PK sub-study in a subset of 24 patients will allow to determine the PK profile of the two doses of SOM3355 (200 mg and 300 mg given twice per day) at steady state and to model PK-PD assessments of hemodynamic and cardiac parameters.

3.2. PRIMARY EFFICACY ENDPOINT

The primary measure of efficacy will be the change in TMC sub-score of the UHDRS® between baseline and end of maintenance dose (the mean of Visit 4 and Visit 5 minus the mean of Visit 0 and Visit 1).

The TMC score is a standardized, reliable chorea assessment based on frequency and severity in 7 body regions.

3.3. SECONDARY EFFICACY ENDPOINTS

Key secondary efficacy endpoint:

- Change from baseline in Clinical Global Impression (CGI-C),

Other secondary efficacy endpoints:

- Change from baseline in Patient Global Impression (PGI-C).
- TMC-response defined as improvement ≥2 in TMC score between baseline and end of

maintenance dose.

- Percentage of change in TMC score between baseline and the end of maintenance dose.
- Change from baseline in Total Motor Score (TMS) of the UHDRS®.
- Change from baseline in Gait sub-score of the UHDRS®.
- Change from baseline in Dystonia sub-score of the UHDRS®.
- Change from baseline in EQ5D-5L measuring quality of life.

3.4. SAFETY ENDPOINTS

Safety assessments will include the following:

- Incidence, frequency, and severity of AEs in each treatment group.
- Change from baseline in:
  - Vital signs: BP, including orthostatic BP, and HR.
  - ECGs.
  - Clinical laboratory test results (chemistry, hematology).
  - Physical examination findings, weight.
  - C-SSRS assessing suicidality.
  - BDI scale assessing depression.
  - ESS assessing sleepiness.
  - TFC of the UHDRS® assessing functioning.
  - Functional Assessment of the UHDRS®.
  - BARS assessing akathisia.
  - MoCA scale to assess cognitive disturbances.
  - PBA-s to assess behavioral symptoms in HD.

3.5. PK-PD ASSESSMENTS

SOM3355 plasma concentration will be measured at each visit under treatment with SOM3355 (i.e. Visit 2 to Visit 5) in all patients. Plasma samples will be collected pre-dose (before the dug intake) and 2 hours after the drug intake (corresponding to the expected T_{max}) at Visit 2 and Visit 4, and only pre-dose at all other visits (Visit 3 and Visit 5).

Prolactin plasma level will be measured at each visit from Visit 1 to Visit 6 in all patients. Plasma samples will be collected pre-dose (before the dug intake) and 2 hours after the drug intake (at T_{max}) at Visit 2 and Visit 4, and only pre-dose at all other visits (Visit 1, Visit 3, Visit 5 and Visit 6).

4. STUDY DESIGN

4.1. OVERALL DESIGN

This is an international, multicenter, double-blind, randomized, placebo-controlled, parallel-group Phase IIb study assessing two doses of SOM3355 (400 or 600 mg/day), taken as 200 mg BID or 300 mg BID, in patients presenting choreic symptoms related to HD.

The study will enroll 129 patients with a genetically-proven diagnosis of Huntington's Disease (confirmed by HTT gene CAG repeats ≥36), of mild to moderate severity (TFC score ≥7) with choreic symptoms (TMC score ≥10). The patients will be recruited in investigating sites in various European countries. Ambulatory patients will be recruited by reference centers for HD in collaboration with patient advocacy groups and the EHDN.

Patients who meet all of the eligibility criteria will be randomized at Visit 1 in a 1:1:1 ratio to one of the 3 treatment arms to receive either SOM3355 400 mg/day, SOM3355 600 mg/day, or placebo, all given BID. Dosing will start with an up titration in the first 3 weeks and will then be maintained at a fixed dose for 7 weeks. After 10 weeks, patients will down titrate to 1 capsule a day of study drug for 1 week, followed by 1 capsule a day of placebo to assess the effect of drug interruption.

The overall study duration is 12 weeks plus 1 or 2 weeks for screening.

Screening period (1 or 2 weeks before inclusion, from Visit 0 to Visit 1): patients will undergo an independent evaluation by a qualified healthcare provider to determine their capacity to provide informed consent and their eligibility according to the study selection criteria. After informed consent is obtained, patients who are stable from a medical and psychiatric standpoint will undergo a screening evaluation to confirm their eligibility. The evaluations performed at Visit 0 and Visit 1 will be used as baseline to assess the treatment effect.

Randomization (at Visit 1): patients who fulfil all selection criteria at the end of the screening period will be randomized and will initiate therapy with either SOM3355 or placebo.

Up-Titration period (between Visit 1 and Visit 2): patients will start the active treatment with an up-titration period of 3 weeks. They will be instructed to take one capsule every day in the morning during the first week, and then two capsules, one in the morning and one in the evening every day from the second week.

- Patients allocated to 400 mg/day treatment arm will receive 200 mg once daily (OD) the first week, and then 200 mg BID the second and third week.
- Patients allocated to 600 mg/day treatment arm will receive 200 mg OD the first week, 200 mg BID the second week, and then 300 mg BID the third week.
- Patients allocated to the placebo arm will take matching placebo capsules according to the same pattern, once a day during the first week and twice per day from the second week.

Maintenance dose (from Visit 2 to Visit 5): the dose reached in each arm (200 mg BID or 300 mg BID or placebo) will be maintained for 7 additional weeks. At the end of this maintenance dose period, two evaluations will be performed one week apart, at Visit 4 (end of Week 9) and at Visit 5 (end of Week 10), to assess the treatment effect versus baseline.

End of study with 1-week down-titration and 1-week placebo washout (from Visit 5 to Visit 6): during the last 2 weeks (Week 11 and Week 12), the patients will be instructed to take only 1 capsule in the morning. The two arms receiving the active drug will be dispensed capsules dosed at 200 mg for one week to decrease the dosing to 200 mg/day. During the last week, all the patients will receive capsules of placebo.

Patients will return for a **last visit (Visit 6)** to assess the withdrawal of the drug.

4.2. PK SUB-STUDY

A PK sub-study will be conducted to characterize the PK profile of repeated doses of SOM3355 at 400 and 600 mg/day. This analysis will be performed by collecting 12-hour PK samples (H0, H0.5, H1, H1.5, H2, H3, H5, H8, and H12) in 8 patients per arm (24 patients in total) that will be hospitalized for 24 hours at Visit 2. These patients will be recruited by 3 or 4 sites able to manage the logistics of PK sampling.

PK data from this sub-study will be collected in an independent database and analyzed by an independent un-blind central laboratory before the end of the clinical trial. The results will be given in a blinded manner until the final data lock.

In addition, cardiac and hemodynamic parameters will be collected in parallel, with 12-hour cardiac Holter and blood pressure measurements before each PK sample, to allow PK-PD modeling assessments.

4.3. RATIONALE FOR STUDY DESIGN

This 12-week Phase 2b study is designed to evaluate in parallel groups the efficacy, safety and tolerability of two doses of SOM3355 (400 mg/day or 600 mg/day, taken either as 200 mg or 300 mg BID) compared with placebo in HD patients with chorea. A previous Phase 2a study (SOMCT02) has already tested the effect of 400 mg/day SOM3355 (given as 200 mg BID) compared with placebo in a crossover design on 6-week periods, and it has shown a reduction of choreic symptoms measured by a significant decrease of the TMC score, and a good tolerability at the tested dose. For this Phase 2b trial, the regulatory authorities recommended a dose-finding study testing different fixed doses in parallel compared with placebo, to correctly assess the dose effect and determine the best dose to be tested in Phase 3.

It is deemed prudent to initiate the treatment by escalating the dose with weekly increases (200 mg OD the first week and 200 mg BID the second week to reach 300 mg BID on the third week for the patients allocated to the 600 mg/day treatment arm) for better tolerability and to reduce the risk of hypotension or bradycardia at the start of treatment. Then, the reached dose (400 mg/day or 600 mg/day) will be maintained for 7 additional weeks.

At the end of the maintenance dose, the study drug is down-titrated for one week (at 200 mg/day) to avoid an abrupt interruption of the dose, followed by a 1-week placebo washout period to assess the effect of the interruption of the study drug.

4.4. JUSTIFICATION FOR DOSE

The proposed clinical doses are within the dose range studied in the nonclinical program, and the lowest observed adverse effect level (LOAEL) in dogs corresponds to the calculated human equivalent dose (HED) of 1500 mg (see Investigator's brochure § 5.3.2).

The selected doses of 400 mg/day and 600 mg/day taken BID (i.e. 200 mg BID and 300 mg BID) have already been used in previous clinical trials.

Bevantolol in doses up to 600 mg/day has been studied during the clinical development of the drug for the treatment of hypertension and angina pectoris (Maclean et al, 1988; Al.Khawaja et al, 1986). Notably in a randomized trial comparing bevantolol to propranolol in hypertension, 39 patients received the dose of 200 mg BID and 47 patients received the dose of 300 mg BID for a 6-month double-blind period after a 6-week double blind titration period. These doses were well tolerated during this long term therapy.

The previous Phase 2a study in HD (SOMCT02) studied the effect of 400 mg/day SOM3355 (given as 200 mg BID) compared with placebo in a crossover design given for 6 weeks of dosing. The study showed good tolerability and safety of SOM3355 dosed at 200 mg BID in patients with HD. Moreover, in this study, PK-PD assessments have shown dose linearity of plasma concentrations, consistent with the previous published data (Latts et al, 1986), and the relationship between plasma levels of SOM3355 and the absolute reduction of TMC score analyzed with a linear model allowed us to predict that the dose of 300 mg BID would provide plasma concentration values that may induce a mean reduction of TMC score of at least 3 points compared to placebo and therefore substantial decrease of choreic symptoms that could be comparable to TBZ effect.

4.5. END OF STUDY DEFINITION

A patient is considered to have completed the study if he/she has completed all visits of the study. The end of the study is defined as the date of the last visit of the last patient in the study.

5. STUDY POPULATION

5.1. INCLUSION CRITERIA

Eligibility criteria to participate in this study are:

1. Males or females ≥ 21 years old.
2. Patients with a diagnosis of Huntington's Disease determined by a movement disorders expert and confirmed by a number of HTT gene cytosine-adenosine-guanine (CAG) repeats ≥36.
3. UHDRS® Total maximal chorea (TMC) score ≥10
4. UHDRS® Total Functional Capacity (TFC) ≥7 (corresponding to mildly to moderately impaired patients).
5. Able to walk independently or with minimal assistance.
6. Females of child-bearing potential must use a medically accepted effective method of birth control, agree to continue this method for the duration of the study and for at least 1 month following the last dose of study drug, and be negative to serum pregnancy test performed at the screening visit (Refer to section 5.4 for complete advice on contraception requirements of this study). Female patients should not be breast-feeding.
7. In the opinion of the Investigator, the patient must have adequate support to comply with the entire study requirements as described in this protocol (e.g. transportation to and from the trial site, self-rating scales, drug compliance, scheduled visits, etc.).
8. Able and willing to provide written informed consent prior to any study-related procedure being performed at the screening visit.

5.2. EXCLUSION CRITERIA

Patients are excluded from the study if any of the following criteria apply:

1. Onset of HD symptoms prior to age of 21 years, corresponding to juvenile forms of HD.
2. HD patients presenting rigid akinesia.
3. Use of other vesicular monoamine transporter type 2 (VMAT2) inhibitors such as tetrabenazine, deutetrabenazine, or valbenazine within 3 months before enrollment, and at any time during the study period; and use of other antichoreic treatment such as any neuroleptic within 2 months or amantadine, memantine, riluzole within 1 month before enrollment and along the study.
4. Patients who experienced severe depression or suicide attempt in the last 5 years.
5. Severe untreated or under-treated psychiatric illness such as active suicidal ideation or behavior (BDI-21 item #9 >0 and active suicidal ideation in C-SSRS) or depression at screening or baseline (BDI-21 items total score >30); although patients taking authorized antidepressant therapy at a stable dose for at least 2 months and stabilized can be enrolled.

6. Patients with a history of, or current, hypotension (SBP <110 mmHg) or bradycardia (HR <50 bpm), and patients with known orthostatic hypotension as defined by the European Society of Hypertension (reduction in SBP ≥20 mmHg or in DBP ≥10 mmHg).
7. Patients with hypertension already treated with more than 2 antihypertensive drugs.
8. Other active clinically significant illness, including unstable cardiovascular disease, angina pectoris, congestive heart failure, pulmonary hypertension, peripheral arterial disease, history of pheochromocytoma, asthma, COPD, diabetic ketoacidosis or metabolic acidosis, or neoplastic pathology, which could interfere with the study conduct, or counter-indicate the study treatment, or to place the patient at risk during the trial, or compromise their study participation.
9. Any significant serious abnormality in the electrocardiogram (ECG), e.g. recent myocardial infarction, severe sinus bradycardia (<50 bpm), atrioventricular block (grades I to III, with PR >240 msec), sinoatrial block, atrial sinus disease or prolonged QTc interval at screening (ECG Bazett's corrected QT interval (QT /√ [HR/60] >450 msec for males or >470 msec for females), or a known history of long QTc syndrome.
10. Patients with severe hepatic impairment, or with severe renal impairment, or with any other significant abnormality in the physical examination or clinical laboratory results that, in the Investigator's opinion, would not be compatible with study participation or represent a risk for the patient while in the study.
11. Females who are pregnant or lactating, or who intend to become pregnant during the study period.
12. Patients with allergy under desensitization, with known psoriasis, or a known allergy / hypersensitivity to any ingredients of the trial medication or placebo.
13. History of alcohol or substance abuse in the previous 12 months.
14. Patients participating in any other study, and the use of any investigational therapy, within the 1month prior to entry in this study.

5.3. CONCOMITANT MEDICATIONS

All concomitant treatment should be verified and reported in the electronic Case Report Form (eCRF) at each visit.

5.3.1. Prohibited treatments

VMAT2 inhibitors such as tetrabenazine, deutetrabenazine, or valbenazine are forbidden within 3 months prior to randomization and at any time during the whole study.

Neuroleptics indicated to treat chorea such as haloperidol, pimozide, or tiapride, and all other neuroleptics used off label as dopamine D2 receptor blockers to treat chorea are forbidden within 2 months prior to randomization and at any time during the whole study.

The following treatments are forbidden within 1 month prior to randomization and during the whole study:

- All monoamine oxidase (MAO) inhibitors.
- Levodopa and dopa-agonist drugs: apomorphin, ropinirole, pramipexole, rotigotine.
- Reserpine
- Glutamate antagonists: amantadine, memantine, riluzole.
- Anti-arrhythmic drugs inducing bradycardia: diltiazem, verapamil, amiodarone, digitalis, quinidine, sotalol, disopyramide.
- Any other beta blocker antihypertensive medication.
- Central antihypertensive treatments: clonidine, methyldopa, rilmenidine.

5.3.2. Authorized treatments

Patients treated with antihypertensive drugs such as diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or calcium blockers (dihydropyridines only) can continue their treatment at a stable dose during the whole study, with maximum of a dual combination of 2 antihypertensive drugs, and if the patient has stable blood pressure.

Patients treated for depression and stabilized with non IMAO (inhibitors of MAO) antidepressants can continue their treatment at a stable dose during the whole study. Allowed antidepressants drugs are:

- SSRIs (selective serotonin reuptake inhibitors): fluoxetine, paroxetine (see precautions below), citalopram, sertraline.
- SNRIs (serotonin-noradrenaline reuptake inhibitors): duloxetine, venlafaxine.
- TCAs (tricyclic antidepressants): amitriptyline, clomipramine, imipramine, nortriptyline, lofepramine.

Neuroleptics treatment (excluding haloperidol, pimozide, and tiapride, which all have the indication for the treatment of abnormal involuntary movements that occur in HD, such as chorea, in their labeling), if needed to treat a behavior disorder and prescribed for at least 3 months at a stable dose, can be maintained at a stable dose during the whole study, provided that it is approved on a case-by-case basis by the Steering Committee before enrolment of the patient.

Treatments to be used with precautions (because of risk of interactions):

- Alpha-blockers.
- Local beta-blockers (eye drop) or pilocarpine (eye drop).
- Anticholinesterase drugs: donepezil, rivastigmine.
- Strong CYP2D6 inhibitors may increase the blood levels of SOM3355 (such as paroxetine fluoxetine, quinidine, bupropion, dacomitinib, tipranavir).

5.4. CONTRACEPTION

According to the recommendations related to contraception and pregnancy testing in Clinical Trial Facilitation and Coordination Group (CTFG) guidance, based on Calvan® (bevantolol hydrochloride) Summary of Product Characteristics (SmPC) the risk of teratogenicity or fetotoxicity is considered

as possible" in humans taking bevantolol. In consequence, recommendations related to contraception and pregnancy testing in this clinical trial are as following:

Females of child-bearing potential (i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile) who test negative for pregnancy at screening (pregnancy test) must use a reliable method of birth control during the study and for at least 1 month following the last dose of study drug. A pregnancy test should be also performed at the end of the study (Visit 6).

No contraception measures are needed for male subjects with female partner of childbearing potential.

Highly effective methods of birth control for females include:

- Intrauterine device or intrauterine hormone-releasing system.
- Use of oral, implanted (under the skin), transdermal (patches placed on the skin), or other hormonal methods (shots/injection) of hormonal contraception that stop ovulation. These must have been used for at least 3 months before the Screening Visit.
- Surgery to tie both fallopian tubes - female patients who have had both fallopian tubes tied.

If the patient practices true abstinence because of a lifestyle choice (not just to participate in this study), the Investigator may consider an exemption for contraceptive requirements, however, for females a pregnancy test should be done at screening and at the end of the study.

If a female becomes pregnant while receiving the study drug, she should immediately stop taking the medication and notify the Investigator. The patient should attend a final visit to assess her health status. Then, a follow-up with her family doctor / general practitioner should be performed to obtain information about her pregnancy and the birth of her child, including post-natal examination, which will be used to learn more about the effects of the study drug on pregnancy and an unborn baby.

5.5. SCREEN FAILURES

Screen failures are defined as patients who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

5.6. PATIENT IDENTIFICATION AND RANDOMIZATION

Each country will be assigned a 1-digit country code (i.e., 1, 2, 3...). Each participating investigative study center within a country will be assigned a sequential 2-digit number (e.g., 01, 02, 03...), which will be added to the country code to generate the site code or site ID. Each patient will receive a 2-digit number in sequential order at the screening visit after the consent form is signed (e.g., 01, 02,

03...), which will be added to the site code to obtain the patient code or patient ID. Therefore, the Patient IDs will be like 101-01, 101-02, ..., 102-01, 102-02, ..., 201-01, 201-02, ..., 202-01, 202-02....

Enrolled patients who fail screening or discontinue study participation early, regardless of whether treatment was received or not, will retain their patient ID and a new ID will be assigned to the next enrolled patient.

Patients who fulfil all entry criteria will be randomized to receive either SOM3355 at 400 mg/day or 600 mg/day, or placebo, in a 1:1:1 ratio. Randomization will be site-specific and performed by a central Interactive Web Response System (IWRS).

5.7. PATIENT WITHDRAWAL CRITERIA

In accordance with the Declaration of Helsinki, patients will be free to withdraw from the study at any time if they wish to do so, for any reason specified or unspecified. Such withdrawal should not affect the required and provided medical care.

In addition, the Investigator may interrupt the patient participation from the study at any time if he/she considers it necessary for any reason including:

- Pregnancy.
- Ineligibility (either arising during the study or retrospective having been overlooked at screening).
- Significant protocol deviation.
- Significant non-compliance with treatment regimen or study requirements.
- An AE which requires discontinuation of the study medication or results in inability to continue to comply with study procedures, particularly if the patient presents a **severe depression** (BDI-21 item total score ≥30), or **suicidal ideation or behavior** (BDI-21 Item #9 >0 and active suicidal ideation in C-SSRS), or **severe hypotension** (SPB/DBP <90/60 mmHg), or **orthostatic hypotension** as defined by the ESH, or **sustained un-tolerated bradycardia** (HR <50 bpm).
- Consent withdrawn.
- Lost to follow-up.
- The Investigator or Sponsor determines it is in the best interest of the subject to discontinue the patient's participation in the study.

Patients who discontinue study treatment or active participation in the study will no longer receive study treatment but will be followed for safety. When a patient withdraws from the study, the reason(s) for withdrawal shall be recorded by the Investigator on the relevant page of the eCRF. Whenever possible, all patients who discontinue study treatment or withdraw from the study prematurely will undergo all end-of-treatment assessments. Patients who fail to return for final assessments will be contacted by the site staff. Following a minimum of 2 documented unsuccessful telephone calls, a registered letter will be sent to the patient in a final attempt to ensure protocol compliance.

It is vital to obtain follow-up data on any patient withdrawn because of an AE or SAE. In every case, efforts must be made to undertake protocol-specified, safety, follow-up procedures.

5.8. STUDY DISCONTINUATION

5.8.1. Criteria for terminating the trial

The Sponsor reserves the right to terminate the study but intends only to exercise this right for valid scientific or administrative reasons, and reasons related to protection of patients. In all cases the Ethic Committees (IRB/IEC) and Health Authorities should be informed. Possible reason for the study termination can include but are not limited to:

- The discovery of an unexpected, significant or unacceptable risk to patients enrolled in the study.
- A decision on the part of the Sponsor to suspend or discontinue the development of the investigational product.
- Request of any relevant regulatory agency.

5.8.2. Criteria for terminating the study at site

The Sponsor reserves the right to terminate the study at any given investigational site at any time after the study initiation if:

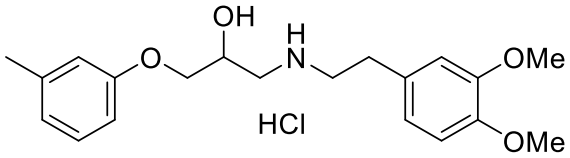
- ICH GCP regulations are not observed.
- Serious and continuous protocol deviations.
- The data generated are of poor quality.
- Changes in personnel or facilities that may adversely affect performance of the study (e.g. low rate of inclusion).

6. INVESTIGATIONAL TREATMENT

6.1. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

SOM3355 is bevantolol hydrochloride, a synthetic drug currently commercialized as a racemic mixture of S-bevantolol (-) and R-bevantolol (+) and used as antihypertensive drug. Bevantolol is approved and has been commercialized in Japan since 1995 as Calvan® by Nippon Chemiphar in the form of 100 mg film-coated tablets.

Bevantolol is a synthetic propanolamine that is 3-aminopropane-1,2-diol in which the hydrogen of the primary hydroxy group is substituted by 3-methylphenyl and one of the hydrogens attached to the nitrogen is substituted by 2-(3,4-dimethoxyphenyl) ethyl.

Chemical Name:	Bevantolol HCl (racemate)
Molecular formula:	$C_{20}H_{27}NO_4 \cdot HCl$
Molecular Weight:	381.897 g/mol
IUPAC Name:	(±)-1-[(3,4-Dimethoxyphenethyl)amino]-3-(m-tolyloxy)-2-propanol hydrochloride
CAS No:	59170-23-9
Chemical Structure:	

(rac)- Bevantolol hydrochloride

In this clinical trial, the investigational medicinal product (IMP) i.e. SOM3355 (bevantolol hydrochloride) will be administered as capsules of 200 mg and 300 mg containing 2 or 3 film-coated 100 mg tablets of Calvan® (the commercial form of bevantolol) or matching capsules of placebo.

The active study drug used in the capsules is the commercial formulation of Calvan® in 100 mg film-coated tablets manufactured by Nippon Chemiphar, imported from Japan and released in Europe by the Contract Manufacturing Organization (CMO) Sharp Clinical Services Ltd, which is responsible for the encapsulation of the tablets and also manufactures the placebo matching capsules.

Description of the 100 mg Calvan® tablets used:

Composition:

- 100 mg of bevantolol hydrochloride per tablet
- Additives: lactose hydrate, microcrystalline cellulose, carmellose, hydroxypropylcellulose, hydrogenated oil, magnesium stearate, hypromellose, macrogol 6000, titanium oxide, and carnauba wax.

- Calvan Tablets 100	Diameter: 8.5mm Thickness: 3.2mm Weight: 169.0mg	NC CE			NCCE

Figure 2: Appearance and Details of Calvan® 100 mg Tablets

According to the SmPC, stability of the tablets are 39 months in blister packs (polyvinylchloride film, aluminum foil) or in sealed brown glass bottles at room temperature and under accelerated test (40°C-75%RH).

Expiration period: 3 years (according to stability test results).

As it is a really stable drug, no special storage conditions are required.

To ensure the blinding, the 100 mg Calvan® tablets will be over-encapsulated in hard gelatin capsules (Swedish orange DBcaps® AAel) in 2 different dosages: 200 mg and 300 mg.

To obtain the different dosages, capsules containing 200 mg (i.e. 2 tablets) and 300 mg (i.e. 3 tablets) of SOM3355, and capsules containing placebo will be prepared by the CMO.

Matching placebo capsules will have the same appearance as the active drug capsules (form, dimension, color, and taste) to ensure that neither the patient, nor the Investigator, nor members of the clinical staff know the identity of the study medication.

6.2. PACKAGING AND LABELLING

The IMP will be packed in HDPE Duma Twist-Off 100 mL bottles containing 14 capsules, which corresponds to 1 week of treatment. Bottles will be labelled in different languages according to country specific directives and regulations and then delivered to the sites' pharmacies.

6.3. MANAGEMENT AND STORAGE

The IMP requested via IWRS will be provided by the CMO to the sites' pharmacies, already packed in bottles and labelled, ready to be supplied to the patients.

The medication product does not require any special storage conditions, so it can be stored at room temperature and no temperature control is needed for shipments and site storage.

The medication will be stored in the sites' pharmacies until the study staff pick them up according to IWRS allocation for dispensation to patients.

All movements of study medication must be documented in an accountability log kept in the pharmacy service. Unused and returned study medication should be kept until the end of the study.

6.4. STUDY DRUG DISPENSING

At each visit, the patient will be dispensed with the sufficient amount of IMP bottles: 1 bottle per week is needed, but additional bottles will be dispensed to secure any potential incident or any delay of the visits, i.e. 1 extra bottle will be added at some visits.

Apart from the IMP bottles, the investigator will give the patient the corresponding page of the Patient Diary, where the patient will register the time and date of all the medication intakes and any incidents.

During the following visit, the patient must return the Diary page completed and the bottles with any leftover medication or full or empty bottles to check treatment compliance and accountability.

6.5. TREATMENT COMPLIANCE AND ACCOUNTABILITY

The Investigator or designated study staff is responsible for monitoring the patient's compliance with study medication during the trial. Compliance will be assessed by capsules count, i.e., evaluation of returned study medication (e.g., amount used/amount expected to be used in the interval between visits) and must be reviewed at every visit by interviewing the patient to determine if he/she is taking study medication as directed.

Compliance will be evaluated by calculating the number of capsules used (capsules dispensed minus capsules returned) divided by the expected number of capsules to be used. A patient will be deemed compliant if the patient has taken ≥80% but ≤120% of the expected tablets of study drug.

When the number of tablets used exceeds the number of expected tablets to be used, the Investigator must clarify the reason for this and in case of over dosage, this must be reported.

6.6. PROCEDURE FOR EMERGENCY INDIVIDUAL UNBLINDING

This study will be conducted in a double blind manner. Neither the patient nor the Investigator will know to which treatment a patient is randomized. The study blind should not be broken except in a medical emergency (where knowledge of the study drug received would affect the treatment of the emergency) or regulatory requirement (e.g., for SAEs or death [in Germany]). At that point, the Investigator may connect to the IWRS and have access to the treatment group for a specific patient.

The unblinding of a patient's treatment must be documented in the source documentation and in the patient's eCRF together with date and time, and the reason of unblinding and signed by investigator.

If possible, such emergencies should be discussed with the trial Medical Manager prior to disclosure of the treatment allocation. Should the code be broken, the Sponsor must be notified immediately.

7. STUDY ASSESSEMENTS

7.1. UNIFIED HUNTINGTON'S DISEASE RATING SCALE (UHDRS®)

The standard clinical assessment tool in HD is the **Unified Huntington's Disease Rating Scale (UHDRS®)**, developed by the Huntington Study Group to monitor disease progression in individual patients, and used in research and clinical practice to determine the efficacy of experimental therapies for the treatment of HD. It assesses 4 domains of clinical performance and capacity in HD: motor function, cognitive function, behavioral abnormalities, and functional capacity. The UHDRS® has undergone extensive reliability and validity testing and has demonstrated to be sensitive to detect longitudinal changes in manifest HD patients. It is used as a major outcome measure in controlled clinical trials (Huntington Study Group, 1996).

The entire UHDRS® is composed of 6 sections (Motor, Cognitive, Behavioral, Functional Assessment, Independence Scale, and Total Functional Capacity).

The motor section is made of 31 items including the assessment of chorea on 7 items (providing the TMC sub-score), dystonia, bradykinesia/rigidity, gait/balance and oculomotor function, and will be rated at each visit for efficacy assessment.

The functional domain comprises 3 sections, namely the total functional capacity (TFC), the functional assessment scale (FA), and the independence scale (IS).

In this study, **UHDRS® motor part will be used to assess efficacy outcomes at each visit**, and TFC and FA scales will be performed at baseline and at the end of the maintenance dose of study drug for safety assessment. The cognitive component and the behavioral assessment won't be used, and are replaced by other recommended scales for HD (Mestre et al, 2018).

At the inclusion, patients will be selected according to their functional status assessed by the TFC scoring the severity of HD and their functioning to exclude severe patients with TFC <7, and the severity of chorea symptoms assessed by the total chorea score that should be ≥10 at the inclusion.

The main efficacy assessment is focused on the choreic movements measured with TMC score included in the motor part of the UHDRS® as primary endpoint. Other sub-scores of the motor part of UHDRS® will also be considered such as TMS assessing overall motor function and the Gait sub-score and Dystonia sub-score.

7.2. EFFICACY ASSESSMENTS

7.2.1. Total Maximal Chorea score (TMC) of the UHDRS®

The TMC score is part of the motor assessment of the UHDRS® consist of the sum of the seven body regions used to assess chorea including the face, oral-buccal-lingual region, trunk and each limb independently. Each territory is scored from 0 (normal findings) to 4 indicating severe abnormalities (0=absent, 1=slight/intermittent, 2=mild, 3=moderate/ common, 4=marked prolonged). The minimum TMC score is 0 (absent) and the maximal score is 28. A decrease in score indicates improvement in chorea.

This scale, which specifically targets a single motor feature in HD (chorea) and has been validated for this purpose, is more adequate in assessing for a specific symptomatic treatment indication.

TMC score will be assessed at each visit.

7.2.2. Total Motor Score (TMS) of the UHDRS®

The motor part of UHDRS® assessing the Total Motor Score is made of 31 items including chorea (TMC sub-score), dystonia, gait/balance, bradykinesia/rigidity, and oculomotor function. The items are rated from 0 to 4, with 0 indicating normal findings and 4 indicating severe abnormalities. The range of the **Total Motor Score (TMS)** is 0 to 124, with higher scores indicating more severe motor impairment.

TMS score will be assessed at each visit.

Sub-scores of gait and dystonia will also be analyzed as individual outcomes.

7.2.3. Clinical Global Impression (CGI) Scale

The CGI is a 7-point Likert Scale that asks the clinicians to rate, considering their total experience with this type of patients, the level of illness due to chorea at baseline on the illness severity ranging from normal (1) to extremely ill (7) (CGI-Severity), and after initiating therapy the overall global improvement (CGI-Change), since the initiation of study drug dosing, ranging from very much worse (7) to very much improved (1), to assess overall response to therapy by the clinician.

CGI-S will be assessed at the inclusion (Visit 1 at Day 0), and CGI-C at each following visit.

7.2.4. Patient Global Impression (PGI) Scale

The PGI is a 7-point Likert Scale that asks the patients to assess their HD symptoms at specific visits: at baseline (PGI-Severity) on the illness severity ranging from normal (1) to extremely ill (7), and after initiating therapy (PGI-Change), ranging from very much worse (7) to very much improved (1), to assess overall response to therapy. In general, patient-rated global measures of change have face validity and have been shown to correlate with disability for a number of chronic conditions.

PGI-S will be assessed at the inclusion (Visit 1 at Day 0), and PGI-C at each following visit.

7.2.5. EQ-5D-5L

EQ-5D-5L measuring quality of life is a validated self-report questionnaire developed by EuroQol Group. This scale is widely used in clinical trials, population studies and real-world clinical settings – and have proven to be valid, reliable and responsive in numerous conditions and populations. The EQ-5D-5L is used worldwide and has been translated into most major languages through a closely monitored translation process.

Aspects of life quality are assessed by measuring 5-item dimension as following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each dimension scored according to five response levels (no problems, slight problems, moderate problems, severe problems, and unable

to/extreme problems) coded from 1 to 5. The respondent is asked to indicate his/her health state by checking the box next to the most appropriate statement in each of the 5 dimensions.

In addition, the patients will use a visual analogue scale (VAS) to assess their own health state on a vertical scale where the extreme endpoints are labelled *'The best health you can imagine'* scoring 100 and *'The worst health you can imagine'* scoring 0. This information can be used as a quantitative measure of the patient's perception of their overall health.

EQ-5D-5L will be rated at the inclusion (Visit 1 at Day 0) and at the end of maintenance dose (Visit 5 at end of Week 10).

7.3. SAFETY ASSESSMENTS

7.3.1. Laboratory Assessments

Safety Laboratory tests (hematology, biochemistry) listed in Table 3 below will be performed *at the screening visit (Visit 0), at the interim visit (Visit 3 at the end of Week 6), and at the end of maintenance dose (Visit 5 at end of Week 10)*. Blood samples for hematology and biochemistry should be obtained prior to study medication dosing. In total, approximately 10 mL blood should be drawn.

Safety laboratory samples will be analyzed via local laboratories. Safety laboratory tests are to be reviewed by the Investigator.

Abnormalities (e.g. AEs) will be defined as laboratory test results that are outside the reference range as defined by the normal range for laboratory test and clinically significant according to the Investigator's assessment.

Table 3: Laboratory Parameters

Hematology		
Red blood cell count	Mean corpuscular hemoglobin	Reticulocytes
Hematocrit	Mean corpuscular volume	White blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Hemoglobin	Platelet count	
Serum chemistry		
Alanine aminotransferase	Aspartate aminotransferase	Alkaline phosphatase
Albumin	C-reactive protein	Calcium
Total Protein	Creatine kinase (CPK)	Phosphate
Bicarbonate	Creatinine	Chloride
Bilirubin, direct and total	Urea	Potassium
Gamma glutamyl transpeptidase	Glucose	Sodium
Other		
Pregnancy test in women of childbearing potential		

7.3.2. Physical Examination

Physical examination will be performed *at each visit*. Any significant change in each system class should be recorded.

7.3.3. Vital signs (Heart rate and Blood Pressure)

Blood pressure and heart rate must be measured in clinic *at the beginning of each visit* (before ECGs and/or blood sample collection) according to the European Society of Hypertension guidelines (Stergiou et al. 2021 ESH guidelines). Standardization for blood pressure measurements is necessary to obtain consistency of the collected data. Vital signs should be measured at each visit in the same conditions, with a validated and calibrated electronic device and using an adequate cuff for the arm circumference of the patient. The electronic device to be used for blood pressure measurement must be listed among the validated devices in the: https://www.stridebp.org website.

Four sequential measures should be performed as follows:

First heart rate and blood pressure measurements should be taken after the patient has rested quietly in a comfortable sitting position for at least 5 minutes, his/her back and arm supported with the middle of the upper arm at heart level, legs uncrossed, and feet flat on the floor.

Orthostatic blood pressure and pulse will be assessed in the supine and standing positions according to the ESH guidelines. The patient should be in supine position for at least 5 minutes before the supine blood pressure and pulse are measured.

The patient will then move to the standing position. Standing blood pressure and pulse will be obtained after the patient has been in the standing position for 1 minute and 3 minutes. Register each measurement with the correct position/time. Ask the patient if he/she is experiencing any symptoms of light-headedness or dizziness.

A drop in BP of ≥20 mm Hg, or in diastolic BP of ≥10 mm Hg, or experiencing light-headedness or dizziness is considered abnormal.

All measurements will be recorded on the vital signs eCRF. Abnormal test results may be repeated at the discretion of the Investigator and must be reported on the corresponding eCRF.

7.3.4. Electrocardiograms (ECGs)

ECG will be performed according to the AHA/ACC recommendations for the standardization and interpretation of the ECG. All ECGs will be performed after at least 5 minutes' rest in a supine or semi-supine position. 12-lead ECGs to assess safety will be recorded *at Screening Visit, inclusion visit (Visit 1), Visit 2, Visit 4, and Visit 6.*

All ECG will be transferred by telemetry to the ECG central reading lab (Banook cardiabase) and ECG parameters (PR, QRS, QT, and QTcF) will be registered in the database and analyzed by a cardiologist. A report will be sent to the site within 48 hours after the visit. One paper version will be edited for the source document that can be examined by the Investigator during the visit.

At the inclusion, the ECG will be triplicated i.e. 3 successive records at 5 minutes of intervals and the average of all parameters will be calculated for baseline reference. This allows to have good quality for the reference ECG. Then the measurements of the 3 ECGs are averaged in a report.

7.3.5. Columbia Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a questionnaire developed by multiple institutions, including Columbia University with NIMH support, used to assess suicide risk in trials of central nervous system active compounds. It is a semi-structured clinical interview that assesses suicidal ideation severity, suicidal ideation intensity, and suicidal behavior (Posner et al, 2011).

The C-SSRS is an interview performed by trained study personnel that should be done at baseline and at each visit during the study as outlined in the Schedule of activities to assess the status of the patient regarding suicide ideation and the risk of suicide attempt. The "Baseline/Screening" C-SSRS form provided at Screening collects the history of suicide attempts, while for subsequent visits the C-SSRS form termed "Since the Last Visit" should be used.

C-SSRS will be assessed at each visit.

7.3.6. Beck Depression Inventory (BDI)

The BDI scale is currently one of the most widely used instruments in both research and clinical practice for assessing depression, with good reliability and validity, which can be used to document changes brought by therapy. Created by Dr. Aaron T. Beck in 1961, and revised in 1996 (BDI-II) for more consistency with the revised DSMIV, it is a 21-question multiple-choice self-report inventory. The questionnaire is composed of items relating to symptoms of depression such as hopelessness and irritability, cognitions such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss, and lack of interest in sex (Wang , 2013).

Each item has four possible degree of severity rated from 0 to 3, and the patient is asked to choose the one that is closest to how he/she feels. The 21 items are summed linearly to create a score which ranges from 0 to 63. It can be administered as an interview by the clinician or as a self-report instrument.

The suicide item #9 includes the following:

0. "I don't have any thoughts of killing myself."
1. "I have thoughts of killing myself, but I would not carry them out."
2. "I would like to kill myself."
3. "I would kill myself if I had the chance."

Total Score Levels of depression (Beck et al, 1988):

0 to 9: **No depression** or minimal depression
10 to 18: **Mild** to moderate depression
19 to 29: **Moderate** to severe depression
30 to 63: **Severe** depression

BDI will be assessed at each visit.

A total score of BDI-21 items ≥30 or item 9 >0 results in an exclusion of the patient from further participation in the study.

7.3.7. Epworth Sleepiness Scale (ESS)

The ESS is a self-administered questionnaire comprised of eight questions that provides a measure of a patient's general level of daytime sleepiness (Johns, 1991). The ESS asks respondents to rate, on a 4-point Likert scale (0 – 3), their usual chances of dozing off or falling asleep in different situations or activities that most people engage in as part of their daily lives. The total ESS score is the sum of 8 item scores and can range between 0 and 24 with a higher score indicating a higher level of daytime sleepiness. Most people can complete the ESS without assistance in 2 or 3 minutes.

ESS will be assessed at each visit.

7.3.8. Total Functional Capacity (TFC) of the UHDRS®

The UHDRS®-TFC scale is a tool used by clinicians to assess the stage of HD and the level of functional capacity in patients on five items: patients' ability to work, manage finances, run a house, take care of themselves, and live at home independently. The TFC score ranges from 0 (worse) to 13.

TFC will be assessed at screening (Visit 0), at the inclusion (Visit 1), and at the end of maintenance dose (Visit 5 at end of Week 10).

7.3.9. Functional Assessment (FA) of the UHDRS®

The UHDRS®-FA scale includes 25 yes/no questions about common daily tasks (range 0 – 25).

FA will be assessed at screening and at the end of the maintenance dose (Visit 5 at end of Week 10).

7.3.10. Barnes Akathisia Rating Scale (BARS)

The BARS (Barnes 1989) is administered by healthcare providers to assess the severity of drug-induced akathisia and is scored as follows: Objective Akathisia, Subjective Awareness of Restlessness and Subjective Distress Related to Restlessness are rated on a 4-point scale from 0 – 3 and are summed yielding a total score ranging from 0 to 9. Then Global Clinical Assessment of Akathisia uses a 5-point scale ranging from 0 – 4.

BARS will be assessed at inclusion and at end of the maintenance dose (Visit 5 at end of Week 10).

7.3.11. Montreal Cognitive Assessment (MoCA) scale

The MoCA scale is a brief screening instrument recommended for the detection of mild cognitive impairment that is sensitive to executive dysfunction in a variety of neurological conditions (Mestre et al, 2018). When used in HD, it was more sensitive to detect mild to moderate cognitive impairment (Mickes et al, 2010; Videnovic et al 2010; Gluhm et al, 2013).

The items of the MoCA examine attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation.

The attention/executive function items include Trail Making Test B, digit span, target detection, verbal fluency, abstraction, and serial seven subtraction. The visuospatial items include clock drawing and cube copying. The language items include object naming and sentence repetition. The memory items include recall of five previously presented words. The orientation items include six orientation-based questions.

MoCA will be assessed at inclusion and at end of the maintenance dose (Visit 5 at end of Week 10).

7.3.12. Problem Behavior Assessment short form (PBA-s)

The PBA short form is the recommended outcome measure for behavioral symptoms in HD (Carlozzi et al, 2014). It is a semi-structured interview containing 11 items, each designed to measure the severity and frequency of behavioral neuropsychiatric symptoms that are frequent in HD: depression, suicidal ideation, anxiety, irritability, aggressive behavior, apathy, obsessive-compulsive symptoms, perseverative thinking, paranoid thinking, hallucinations, and disorientation.

Severity and frequency during the previous 4 weeks are rated separately for each symptom on a 5 point (0–4) scale.

PBA-s will be assessed at inclusion, at the interim visit (Visit 3 at the end of Week 6), and at the end of the maintenance dose (Visit 5 at the end of Week 10).

7.4. SAFETY REPORTING

7.4.1. Definitions

7.4.1.1. Adverse Event (AE)

The term **Adverse Event** covers any sign, symptom, syndrome, or illness which appears or worsens in a patient during the observation period in the clinical study, and which may impair the patient's well-being.

The term also covers laboratory findings or results of other diagnostic procedures which are considered to be clinically relevant (e.g. requiring unscheduled diagnostic procedures or treatment measures, or result in withdrawal from the study).

An AE may be:

- A new illness.
- The worsening of a sign, or symptom of the condition under treatment, or of a concomitant illness. Associated symptoms of Huntington's Disease (such as akathisia or dystonia) should not be considered as AEs except if they increase in terms of intensity and/or frequency.
- A known effect of the study medication (as listed in the SmPC).
- A combination of two or more of these factors.

No causal relationship with the study medication or with the clinical study itself is implied by the use of the term "Adverse Event."

7.4.1.2. Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

A serious AE or drug reaction or any untoward medical occurrence that, at any dose, has one or more of the following attributes:

- **Results in death.**
- **Is life-threatening,** which means that the patient is at immediate risk of death at the time of the SAE; it does not refer to a SAE that hypothetically might have caused death if it was more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization.** Hospitalization is defined as inpatient care that covers more than one calendar day.
- **Results in persistent or significant disability/incapacity**, which means that there is a substantial disruption of a person's ability to carry out normal life functions.
- **Is a congenital anomaly/birth defect.**
- **Is medically important,** defined as an event that may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above, or result in urgent investigation. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in patient hospitalization.

7.4.1.3. Treatment-Emergent Adverse Event (TEAE)

A treatment-emergent adverse event (TEAE) is defined as any event not present prior to the initiation of the study treatment, or any event already present which worsens either in intensity, or frequency following the exposure to the study treatment.

7.4.1.4. Suspected Adverse Reaction

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

7.4.1.5. Adverse Reaction

An adverse reaction means an AE that is caused by a drug. Adverse reactions are a subset of all suspected adverse reactions that conclude the drug caused the event.

7.4.1.6. Unexpected Adverse Event or Suspected Adverse Reaction

An adverse reaction or suspected adverse reaction is considered "unexpected" if the nature or severity of it is not consistent with the applicable product information (e.g. Investigator Brochure Reference Safety Information or Summary of Product Characteristics, as applicable).

7.4.2. Procedures for recording, analyzing and reporting AEs

7.4.2.1. Monitoring and recording of AEs

At each visit, occurrence of AEs will be assessed by verbally asking the patients if they have had any problems or symptoms since their last visit.

For each AE, regardless of the suspected causal relationship to study drug, the Investigator has to report on the AE page(s) of the eCRF the relevant information of the AE including the nature, the anteriority (emergent or not), the timing of event occurrence and resolution, the frequency (intermittent or continuous), the severity (mild, moderate, severe), the relationship with the study drug, and actions taken to treat the adverse experience. The Investigator has also to pursue and obtain adequate information in order to determine the outcome of the AE and also to assess the seriousness, i.e. whether it meets the criteria for classification as a SAE requiring immediate notification to the Sponsor.

Whenever possible, a unifying diagnosis should be recorded in the eCRF as the AE rather than individual signs or symptoms. Similarly, the unifying diagnosis should be recorded as the AE rather than the abnormal laboratory result (i.e. “anemia” instead of “low hemoglobin”). If the AE is a worsening of a past medical condition, the AE should clearly indicate that the past medical condition has worsened using words such as “worsening,” “aggravated,” or “exacerbation.”

AEs will be coded according to the Medical Dictionary for Regulatory Activity (MedDRA current version). AEs will be individually listed per patient number, presenting System Organ Class (SOC), preferred term, emergence, description, date and time of onset, date and time of last study drug administration before AE, duration, time from onset since last study drug administration, frequency, severity and seriousness, relationship to study drug, the required action taken (corrective treatment, hospitalization), and outcome if any.

All AEs (including SAEs) must be followed until satisfactory resolution or stabilization.

Any AE and any measure taken and follow-up result must be recorded in the patient's eCRF, as well as in the patient’s source document. Follow-up laboratory results should be filed with the patient’s source documentation.

7.4.2.2. Analysis and classification of AEs

Assessment of Severity

An assessment of the relative severity (or intensity) of an adverse experience is based on the Investigator’s clinical judgment by using the following scale. The **maximum** severity encountered during the evaluation period should be checked. The assessment of severity should be independent of the assessment of the seriousness of the AE.

- **Mild:** No significant interference with the patient’s usual activities, easily tolerated.
- **Moderate:** moderate interference with the patient’s usual activities.
- **Severe:** major interference with the patient’s usual activities, considered as unacceptable by the physician, or required specific treatment or required discontinuation from the study.

Assessment of Causality

The Investigator will make clinical judgement to determine whether or not, in their opinion, there is a reasonable possibility that the drug caused the adverse event

- **Related/likely:** Clearly related to the investigational agent/procedure, i.e. an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that can be confirmed by improvement on stopping and reappearance of the event after rechallenge and that could not be reasonably explained by the known characteristics of the patient's clinical state.
- **Possibly related/Possible:** Follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.
- **Not related/Unlikely:** Clearly and incontrovertibly due only to extraneous causes, and does not meet criteria listed under possible (possibly related) or likely (related).

Assessment of Outcome

For all AEs the outcome should be documented at the latest at the last visit according to the following criteria:

- **Ongoing.**
- **Recovered**: the patient has fully recovered with no observable residual effects.
- **Recovered with sequelae:** the AE has resulted in a permanent impairment.
- **Unknown:** the outcome of the AE is not known because the patient did not return for follow-up (lost to follow-up).
- **Death** if the patient died due to the AE.

If an AE is still ongoing at the last visit the patient must be followed-up until the outcome can be documented without using the "ongoing" assessment.

In case of sequelae a description of sequelae must be provided in the eCRF. When reporting a death, the Investigator should supply any additional requested information such as autopsy reports (if available) and final medical reports.

In order to ensure the safety of the patients, the Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until the patient has recovered, or until death. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team as it may be asked by the Sponsor.

Assessment of Seriousness

"Seriousness" is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. "Seriousness" (not severity) serves as a guide for defining regulatory reporting obligations for Serious Adverse Events (SAE).

7.4.3. Reporting Serious Adverse Events (SAEs)

All SAEs occurring during study participation must be reported **immediately (within 24 hours)** to the Sponsor representative (or designee), and then to the governing IRB/IEC as required by the IRB/IEC, local regulations, and the governing health authorities.

Prompt notification of SAEs by the Investigator to the appropriate Sponsor contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other patients are met. Any Unexpected SAE which is attributed to investigational product (SUSAR) requires immediate notification to the regulatory agencies. The full report will be sent to the regulatory agencies within the regulatory timelines. The Sponsor should also expedite the safety reporting to all concerned investigator/institutions, to IEC/IRB and regulatory agencies according to the local regulatory timelines.

7.4.3.1. Notification of the SAE and Transmission of the SAE Report

Once an investigator becomes aware that an SAE has occurred, he/she must report the information to the Sponsor (or designee) **within 24 hours.** The SAE form will always be completed as thoroughly as possible with all available details of the event, signed by the Investigator and forwarded to the Sponsor (or designee) within the designated time frames. If the Investigator does not have all information regarding an SAE, he should not wait to receive additional information before notifying the event and completing the form. The form will be updated when additional information is received. Whenever possible, the Investigator will provide an assessment of causality at the time of the initial report as described above.

After the initial report, the SAE should be promptly followed by a detailed writing report including all data allowing to document the event and notably the anonymous copies (with patient study number) from hospitalization's report and any additional examination(s) performed.

For reported death, the Investigator should provide any additional requested information such as autopsy reports if available and terminal medical reports.

7.4.3.2. SAE waived from expedited regulatory reporting to regulatory authorities

For the purpose of the study the following events will not be designated as a SAE:

- hospital admission as a part of the normal planned treatment or monitoring of the studied indication and not associated with any deterioration in condition,
- hospitalization planned before inclusion in the study,
- admission for diagnostic evaluation of an AE,
- overnight hospitalization due to social or travel reasons.

7.4.4. Procedures for Reporting Pregnancy Exposure and Birth Events

The Investigator must promptly report all pregnancies to the Sponsor (or designee). While the pregnancy itself is not considered to be an AE or SAE, any pregnancy complications should be recorded as AEs or SAEs. Any pregnancy should be followed through its conclusion for observation of any congenital anomalies or birth defects which are a SAE.

7.4.5. Data Safety Monitoring Board (DSMB)

According to ICH E6, an independent Data Safety Monitoring Board (DSMB) will be established to assess at intervals the progress of the clinical trial, safety data, and recommend to the Sponsor whether to continue, modify or terminate a trial. The DSMB will have written operating procedures and maintain records of all its meetings, including interim results; these should be available for review when the trial is complete. The independence of the DSMB is intended to control the sharing of important comparative information and to protect the integrity of the clinical trial from adverse impact resulting from access to trial information. The DSMB is a separate entity from an IRB or an IEC, and its composition should include clinicians and clinical trial scientists knowledgeable in the appropriate disciplines including statistics.

A charter will define clearly the roles and responsibilities, the membership (with independent experts in the clinical aspects of the disease and one biostatistician), and organization of the meetings. The procedures should also address the way to keep confidential the data analyzed, the voting rules and the control of dissemination of interim trial results within the Sponsor organization.

7.5. PK-PD ASSESSMENTS

7.5.1. SOM3355 plasma concentration

Blood samples for PK will be obtained in all patients at each visit under active treatment with SOM3355 (or placebo) from Visit 2 to Visit 5 for measurement of **SOM3355 (bevantolol) plasma concentration** at trough (pre-dose), and also 2 hours after dosing at Visit 2 and Visit 4.

Complete information on blood sampling, conditions of plasma preparation and storage, as well as shipment details and central laboratory contact details will be supplied in a separate technical brochure provided by the central laboratory.

Drug quantification will be performed using a validated bioanalytical method based on ultra HPLC coupled to tandem mass spectrometry (UHPLC-MS/MS).

7.5.2. Prolactin plasma level

An increase in prolactin plasma levels was observed with SOM3355 administration in the previous Phase 2a POC study, consistent with that seen with other VMAT2 inhibitors like tetrabenazine. However, the increase was found not to be dose-proportional with SOM3355 levels, showing a mean increase of 1.7- and 1.9-fold at the 100 mg and 200 mg BID doses, respectively (SOMCT02 – PK/PD Report). This may reflect changes in dopaminergic tone in the hypothalamus and/or pituitary gland (Orrillo et al, 2020). Therefore, prolactin plasma levels could be considered as a biomarker of the pharmacodynamic (PD) effect of SOM3355.

Blood samples will be obtained at each visit from Visit 1 to Visit 6 in all patients to measure prolactin plasma concentration, before dosing at each visit and 2 hours after dosing at Visit 2 and Visit 4. Prolactin plasma quantification will be determined by chemiluminescence technique.

Samples will be collected and stored with the PK samples and analyzed by the central laboratory in order to keep the blind during the study.

7.5.3. PK sub-study

A PK sub-study will be conducted to characterize the PK profile of repeated doses of SOM3355 at 400 and 600 mg/day. This analysis will be performed by collecting 12-hour PK samples (H0 before dosing, H0.5, H1, H1.5, H2, H3, H5, H8, H12) in 8 patients per arm (24 patients in total) that will be hospitalized for 24 hours at Visit 2.

These patients will be recruited by 3-4 sites able to manage the logistic of PK sampling. PK sub-study data will be collected in an independent database and analyzed as soon as possible, before the end of the clinical trial. Complete information on blood sampling, conditions of plasma preparation and storage, as well as shipment details for PK sub-study and central laboratory contact details will be supplied in a separate technical brochure provided by the central laboratory.

In addition, cardiac and hemodynamic parameters will be collected in parallel to allow PK-PD modeling assessments. For this, the patients will have cardiac Holter monitor placed on the chest to record ECG during the 12 hours of plasma sampling, allowing to analyze ECG parameters at the same time points than PK samples, and blood pressure will be measured 5 minutes before each PK sample (the patient resting quietly in a comfortable sitting position, his/her back and arm supported with the middle of the upper arm at heart level, legs uncrossed, and feet flat on the floor).

8. CONDUCT OF THE STUDY

For each participant, the total treatment duration, from the inclusion visit, will be 12 weeks (+ 1 or 2 weeks for screening before inclusion) with a total of 7 visits.

The visit schedule and procedure assessments are listed in section 1.3.

This is an outpatient study, except for 24 patients that will be enrolled in the PK sub-study who will be hospitalized for 24 hours at Visit 2. HD patients come to visit their specialist at the hospital on successive time-points. All visits must be performed by investigators and sub-investigators qualified for this study and who are experts in the management of HD patients.

Visits are scheduled as follows:

- V0 - Screening visit: at Day -7 to -14 max (Week -1 to -2 max)
- V1 - Inclusion visit (randomization): at Day 0 (Week 0)
- V2 - End of up-titration: at Day 21 ± 2 Days (Week 3)
- V3 - Interim visit at maintenance dose: at Day 42 ± 2 Days (Week 6)
- V4 - End of maintenance dose #1 at Day 63 ± 2 Days (Week 9)
- V5 - End of maintenance dose #2 at Day 70 ± 2 Days (Week 10)
- V6 - End of study at Day 84 ± 2 Days (Week 12)

If the date of one visit is changed (anticipated or delayed), the next visit should occur according to the original schedule.

8.1. STUDY PROCEDURES AT EACH VISIT

8.1.1. Visit 0 - Screening visit – within 14 days before inclusion

The eligibility of the patients will be assessed during the screening period that starts with the Screening Visit within 1 or 2 weeks before the inclusion. The duration of the screening period is up to 2 weeks and must be long enough to establish inclusion/exclusion criteria from Visit 0 to the inclusion visit (i.e. Visit 1 at Day 0).

At Visit 0, the Investigator must first obtain the patient informed consent as described below, and then check that he/she meets all the inclusion criteria and none of the exclusion criteria.

- ***Obtaining the Patient informed consent***

If a patient is eligible to be enrolled in the study, prior to conduct of any study-specific screening procedures, the Investigator, or designee, will explain to the patient the study procedures, including the risks involved and the fact that its participation is voluntary.

The Investigator should give to the patient the study's IRB/IEC-approved written informed consent form (ICF) and orally present all necessary information to the patient, in order to enable him/her to make an informed and unconstrained decision about participating in the study. An appropriately

signed ICF will be obtained prior to entry into the study for each patient who has made the decision to participate. Information regarding the collection of the patient informed consent should be registered in the source document (date, protocol number, and name of the Investigator or sub-investigator who has informed the patient).

In addition, the following assessments must be performed at Visit 0, and information must be collected and documented in the CRF within the screening period:

- Patient medical history and history of HD diagnosis, with documented genetic diagnosis;
- Patient history of all the treatments must be notified in the source documentation prior to randomization (with regimen, duration, and complications and their treatments);
- Demographics characteristics (age, gender, and ethnic origin);
- Physical and neurological examinations with the presence of chorea symptoms;
- Vital signs (SBP, DBP, orthostatic BP, and heart rate measured according to the standardized method described in section 7.3.3), body height and weight;
- List of current concomitant medications;
- Clinical scores and functional tests: UHDRS®-Motor part (including TMS and TMC, gait and dystonia sub-scores), UHDRS®-Total Functional Capacity, UHDRS®-Functional assessment, and C-SSRS, BDI, and ESS;
- 12-lead ECG (sent for centralized reading by a cardiologist);
- Safety laboratory tests (chemistry, hematology) analyzed by local laboratory (including a pregnancy test if female of childbearing potential).

8.1.2. Visit 1 - Day 0 - Inclusion visit - Randomization

At Visit 1, the Investigator must check that the patient still meets all the inclusion criteria and none of the exclusion criteria. In addition, the following assessments must be performed:

- Physical and neurological examinations;
- Vital signs (SBP and DBP, orthostatic BP, and HR);
- Clinical scores and functional tests: UHDRS®-Motor part, UHDRS®-TFC, EQ-5D-5L, BARS, MoCA scale, PBA-s, C-SSRS, BDI, ESS, CGI-S, and PGI-S;
- 12-lead ECG triplicated as 3 successive records (sent for centralized reading by a cardiologist);
- Blood sample at pre-dose for prolactin level (central lab);
- List of current concomitant medications;
- Recording of AEs;
- Randomization and treatment allocation: if the patient meets the selection criteria, a treatment will be allocated according to the randomization number determined by IWRS;
- Drug dispensation: the patient will receive 4 bottles of study medication and a Patient Diary and will be instructed to take one capsule per day in the morning during the first week, and then during the two following weeks two capsules per day (one in the morning and one in the evening) until the next visit and record the intakes in the Diary. An Extra bottle is dispensed to

be used only if next visit is delayed or Bottle 3 is empty to avoid an interruption of the study treatment. The drug can be taken with food. The first dose will be administered to the patient during the visit. The patient will be instructed to contact the Investigator by phone should an AE occur, and will be asked to bring back the used and unused study medication at the following visit.

- The patient is asked to come at the next visit without taking the morning dose to enable the blood sampling for PK at trough.

8.1.3. Visit 2 - Week 3 - Day 21 - End of up-titration

At Visit 2, the Investigator must perform the following assessments:

- Physical and neurological examinations;
- Vital signs (SBP and DBP, orthostatic BP, and HR);
- Clinical scores and functional tests: UHDRS®-Motor part only (including TMS and TMC, gait and dystonia sub-scores), C-SSRS, BDI, ESS, CGI-C and PGI-C;
- 12-lead ECG (sent for centralized reading by a cardiologist)
- Blood sample at pre-dose and 2 hours after drug intake for PK and prolactin level (central lab);
- List of current concomitant medications;
- Recording of AEs;
- Drug accountability of the returned study medication and review of compliance (the patient is asked whether the investigational treatment was taken as prescribed or any incidents occurred to double-check with the returned Patient Diary);
- Drug dispensation: the patient will receive 4 bottles of study medication and a new Patient Diary and will be instructed to take two capsules per day, one in the morning and one in the evening until the next visit and record the intakes in the Diary. The drug can be taken with food. The first dose will be administered to the patient during the visit. The patient will be instructed to contact the Investigator by phone should an AE occur, and will be asked to bring back the used and unused bottles of study medication at the following visit. An Extra bottle is provided in case of delayed visit to avoid an interruption of the study treatment.
- The patient is asked to come at the next visit without taking the morning dose to enable the blood sampling for PK at trough.

A subset of 24 patients in 3-4 selected investigating sites will be hospitalized for 24 hours for PK sampling. Blood samples should be performed at pre-dose (H0), and 0.5h, 1h, 1.5h, 2h, 3h, 5h, 8h, and 12h post-dose. After the H12 blood sample, the evening intake of the study drug should be given to the patient.

These patients will have cardiac Holter monitor placed on the chest during the 12 hours of plasma sampling to record ECG, and blood pressure should be measured 5 minutes before each PK sample (the patient resting quietly in a comfortable sitting position, his/her back and arm supported with the middle of the upper arm at heart level, legs uncrossed, and feet flat on the floor).

8.1.4. Visit 3 - Week 6 - Day 42 - Interim visit at maintenance dose

At Visit 3, the Investigator must perform the following assessments:

- Physical and neurological examinations;
- Vital signs (SBP and DBP, orthostatic BP, and HR);
- Clinical scores and functional tests: UHDRS®-Motor part only, PBA-s, C-SSRS, BDI, ESS, CGI-C and PGI-C;
- Safety laboratory tests (chemistry, hematology) analyzed by local laboratory
- Blood sample for PK and prolactin level (central lab) at pre-dose only;
- List of current concomitant medications;
- Recording of AEs;
- Drug accountability of the returned study medication and review of compliance (the patient is asked whether the investigational treatment was taken as prescribed or any incidents occurred to double-check with the returned Patient Diary);
- Drug dispensation: the patient will receive 4 bottles of study medication and a new Patient Diary and will be instructed to take two capsules per day, one in the morning and one in the evening until the next visit and record the intakes in the Diary. The drug can be taken with food. The first dose will be administered to the patient during the visit. The patient will be instructed to contact the Investigator by phone should an AE occur, and will be asked to bring back the used and unused bottles of study medication at the following visit. An Extra bottle is provided in case of delayed visit to avoid an interruption of the study treatment;
- The patient is asked to come at the next visit without taking the morning dose to enable the blood sampling for PK at trough.

8.1.5. Visit 4 - Week 9 - Day 63 - 1st assessment at end of maintenance dose

At Visit 4, the Investigator must perform the following assessments:

- Physical and neurological examinations;
- Vital signs (SBP and DBP, orthostatic BP, and HR);
- Clinical scores and functional tests: UHDRS®-Motor part only, C-SSRS, BDI, ESS, CGI-C and PGI-C;
- 12-lead ECG (sent for centralized reading by a cardiologist) at Tmax (2 hours after dosing) just before the blood sample;
- Blood sample for PK and prolactin level (central lab) at pre-dose and 2 hours after dosing;
- List of current concomitant medications;
- Recording of AEs;
- Drug accountability of the returned study medication and review of compliance (the patient is asked whether the investigational treatment was taken as prescribed or any incidents occurred to double-check with the returned Patient Diary);

- Drug dispensation: the patient will receive 2 bottles of study medication and a new Patient Diary and will be instructed to take two capsules per day, one in the morning and one in the evening until the next visit and record the intakes in the Diary. The first dose will be administered to the patient during the visit. The patient will be instructed to contact the Investigator by phone should an AE occur, and will be asked to bring back the used and unused bottles of study medication at the following visit. An Extra bottle is provided in case of delayed visit to avoid an interruption of the study treatment;
- The patient is asked to come at the next visit without taking the morning dose to enable the blood sampling for PK at trough.

8.1.6. Visit 5 - Week 10 - Day 70 - 2nd assessment at end of maintenance dose

At Visit 5, the Investigator must perform the following assessments:

- Physical and neurological examinations;
- Vital signs (SBP and DBP, orthostatic BP, and HR);
- Clinical scores and functional tests: UHDRS®-Motor part, UHDRS®-Total Functional Capacity, UHDRS®-Functional Assessment, EQ-5D-5L, BARS, MoCA scale, PBA-s, C-SSRS, BDI, ESS, CGI-C, and PGI-C;
- Safety laboratory tests (chemistry, hematology) analyzed by local laboratory;
- Blood sample for PK and prolactin level (central lab) at pre-dose;
- List of current concomitant medications;
- Recording of AEs;
- Drug accountability of the returned study medication and review of compliance (the patient is asked whether the investigational treatment was taken as prescribed or any incidents occurred to double-check with the returned Patient Diary);
- Drug dispensation: the patient will receive 2 bottles of study medication - one bottle identified to be used the first week and the other for the second week - and a new Patient Diary and he/she will be instructed to take one capsule per day in the morning for 7 days from the first bottle, and then one capsule per day for 7 days from the second bottle and record the intakes in the Diary. The first dose will be administered to the patient during the visit. The patient will be instructed to contact the Investigator by phone should an AE occur, and will be asked to bring back the used and unused bottles of study medication at the following visit. No Extra bottle will be provided;
- The patient is asked to come at the next visit without taking the morning dose.

8.1.7. Visit 6 - Week 12 - Day 84 - End of study

At Visit 6, the Investigator must perform the following assessments:

- Physical and neurological examinations;
- Vital signs (SBP and DBP, orthostatic BP, and HR);
- Clinical scores and functional tests: UHDRS®-Motor part only, C-SSRS, BDI, ESS, CGI-C and PGI-C;

- 12-lead ECG (sent for centralized reading by a cardiologist);
- Blood sample at pre-dose for prolactin level (Central lab);
- Pregnancy test for female of childbearing potential;
- List of current concomitant medications;
- Recording of AEs;
- Drug accountability of the returned study medication and review of compliance (the patient is asked whether the investigational treatment was taken as prescribed or any incidents occurred to double-check with the returned Patient Diary).

8.2. STUDY CONDUCT DURING A COVID-19 OUTBREAK

The Sponsor acknowledges that hospitals should preferentially treat patients with COVID-19 and prioritize trials for the prevention or treatment of COVID-19 infection. Therefore, this trial will only be initiated when it is ethically and operationally feasible for the selected study sites to do so.

In the event of a further COVID-19 outbreak or further restrictions, the Sponsor in conjunction with the Investigator will review the situation and initiate prepared plans based on the extent of the situation and local conditions. To mitigate for a future impact of the pandemic, the study will be conducted at multiple sites in Europe to increase the possibility of including patients in sites/countries not (or minimally) affected by COVID-19. The Sponsor will adhere to national and local regulations due to the pandemic, and the study or specific sites or countries will halt recruitment and stop treatment of enrolled patients as needed. In any event, the patients' safety will be paramount, and all endeavors will be made to judge whether before a patient is enrolled into the study there is a possibility of all safety assessments being conducted during the patient's entire study period. If the study were to continue, the Sponsor will consider initiating a range of options including, but not limited to:

- *Provision of private transport and protective equipment (at least a mask, gloves and hand sanitizer) to facilitate patient visits to the study site.*
- *Feasibility of gaining remote (telephone or email) informed consent from patients in countries where this is permitted, following the current EMA guidance for management of clinical trials during COVID-19 pandemic.*
- *Initiation and on-going central monitoring of data if study Monitors are not permitted access to study sites.*

Whilst general plans can be prepared in advance, the implementation of each activity will be dependent on local (country, site, patient) circumstances at the time, and the extent of the COVID-19 situation.

In the event that a patient is diagnosed with active COVID-19, the intention is for the patient to continue in the study, and to receive regular phone calls from study staff to monitor safety. The patient should not visit a study site until they have received medical clearance.

All Protocol Deviations as a result of COVID-19, COVID Infections, and any other COVID-19 Impact will be noted as such for future analysis and reporting.

9. STATISTICAL CONSIDERATIONS

9.1. ANALYSIS POPULATIONS

Safety Population: The safety population will include all patients who were administered any study drug. Patients who are assigned a patient number but withdrew prior to dosing will not be included in the safety population. Patients will be included in the treatment group based on the treatment actually received. If relevant, details of their participation and reason for withdrawal will be listed separately in the study report.

Intent-to-Treat (ITT) Population: The ITT Population will include all randomized patients. Patients will be included in the treatment group to which they were randomized, regardless of the treatment that was actually received.

Modified Intent-to-Treat (mITT) Population: The mITT Population will include all patients from the ITT Population who were randomized to treatment, received at least one dose of study drug and had at least one post-baseline assessment of the TMC score. The primary efficacy analysis will be conducted on the mITT Population. Patients will be included in the treatment group to which they were randomized, regardless of the treatment that was actually received.

Per Protocol (PP) Population: The PP Population will include all randomized patients who completed the study without important deviations from the protocol. The decision of the membership in the PP Population will be made during a blinded Data Review Meeting prior to database lock, reviewing all deviations occurred.

9.2. STATISTICAL ASSUMPTIONS

Power calculation is based on results from previous trials that tested VMAT2 inhibitors (TBZ and deuterbenazine) on chorea in HD patients with TMC score as primary endpoint, which showed a standard deviation of 3.5 and 3.9 respectively, and a treatment effect compared to placebo in TMC score of -3.5 and -2.5 respectively.

So we assume a standard deviation of 3.5 and a target difference between active and placebo groups of -2.5 in TMC score in order to ensure a clinically relevant effect of at least -2 in the study.

9.3. SAMPLE SIZE DETERMINATION

The sample size will be a total of **129 patients**. Eligible patients will be randomized in blinded fashion in a **1:1:1 ratio** i.e. **43 patients in each arm** (SOM3355 400 mg/day, SOM3355 600 mg/day, or placebo). Assuming a treatment difference of -2.5 points in the change from baseline of TMC score compared to placebo and a standard deviation of 3.5, 39 patients per arm will provide at least 80% power that at least 1 dose of SOM3355 will be significantly superior to placebo at the 2-sided 0.025

significance level. For the primary endpoint, the overall type I error will be controlled using a Holm procedure. To account for a 10% dropout rate, 43 patients per arm (i.e. a total of 129 patients) will be enrolled.

9.4. STATISTICAL ANALYSES

Details on the statistical analyses described below will be given in a Statistical Analysis Plan (SAP) to be prepared before any analysis or unblinding of data occur.

9.4.1. Primary Efficacy Endpoint

The primary efficacy endpoint for this study is the change in Total Maximal Chorea (TMC) score from baseline (defined for each patient as the average of values at the screening visit (Visit 0) and the inclusion visit (Visit 1)) to the end of maintenance therapy (defined for each patient as the average of values from the end of Week 9 (Visit 4) and the end of Week 10 (Visit 5)).

Primary efficacy analyses will be based on the modified intent-to-treat (mITT) Population.

The estimand of the primary efficacy analysis is defined according to ICH-E9-R1. The estimand reflects a mixed strategy for the inter-current events as presented in the table below.

Table 4: Estimand of the Primary Analysis

Estimand attribute	**Primary definition**		**Rationale (as needed)**
Population	Patients with Huntington's disease with choreic movements		
Endpoint	Change from baseline (Visit 0 and Visit 1) to end of maintenance dose (Visit 4 and Visit 5) in TMC score		
Inter-current events	**Event**	**Strategy**	**Rationale (as needed)**
	Receipt of assigned study treatment	Treatment policy	This strategy applied to align the estimand with the application of the ITT principle.
	Prohibited concomitant treatment during the treatment period	While on treatment	This strategy applied up to the time of the prohibited concomitant treatment.
	Discontinuation from study	Hypothetical policy	This strategy applied for randomized and treated patients using a MMRM approach under MAR assumptions.
Summary measure	Difference in adjusted LS means between active arms and placebo from baseline to end of maintenance visit.		

The primary analysis of the primary efficacy endpoint will be based on a mixed-effect linear model for repeated measures (MMRM) to compare each active treatment group to placebo. The model will include the following factors: treatment group, visit, and treatment-by-visit interaction as fixed effects, and baseline TMC score as covariate. An unstructured (US) variance-covariance matrix will be used to model the within-patient errors. If no reliable results under the US assumption can be obtained, the Toeplitz (TP) covariance structure, followed by the autoregressive (AR1) and Compound Symmetry (CS) covariance structure will be used. The Kenward-Roger method will be used to estimate the denominator degree of freedom.

The least square mean (LSM) estimate for each treatment group and difference in LSM estimates at end of maintenance dose between active treatments and placebo group with their confidence intervals will be provided.

To preserve the family-wise error rate at the 0.05 level when comparing the two doses of SOM3355 versus placebo, statistical testing will be carried out using the Holm procedure. The smallest p-value of the two comparisons will be first compared at the two-sided 0.025 level and if statistically significant, the other p-value will be compared at the two-sided 0.05 level.

Sensitivity analyses on the primary efficacy endpoint will be conducted as follows:

- Primary endpoint will be analyzed using the observed cases (no imputations) using an analysis of covariance (ANCOVA) model.
- Primary endpoint will be analyzed for the ITT Population using a multiple imputation.
- Primary efficacy analysis will be repeated for the PP Population.

9.4.2. Secondary Efficacy Endpoints

The secondary endpoints will be assessed hierarchically in the following order:

- The CGI change between the baseline and the end of maintenance dose
- TMC-response defined as improvement ≥ 2 in TMC score between the baseline and the end of maintenance dose in each group
- The percentage of change in TMC score
- The PGI change between the baseline and the end of maintenance dose
- Total Motor Score (TMS) of the UHDRS®
- Gait sub-score of the UHDRS®
- Dystonia sub-score of the UHDRS®
- EQ-5D-5L measuring quality of life

Secondary efficacy endpoints will be analyzed using the mITT Population.

For continuous efficacy endpoints with longitudinal data, the same MMRM model, as described for the primary endpoint will be performed. For other continuous efficacy endpoint measured at baseline and end of maintenance dose, an ANCOVA model will be used.

Categorical efficacy endpoints will be analyzed using a logistic regression model.

The type I error will be set at 0.05 (two-sided) and the coverage level of confidence intervals to 95% for all secondary efficacy analyses. No multiplicity adjustment will be applied for the statistical inferences of the secondary efficacy endpoints.

9.4.3. Safety Analysis

Safety analyses will be based on the safety population, which is defined as all randomized patients having received at least one dose of study treatment.

Adverse events:

All AEs summaries will be restricted to Treatment Emergent Adverse Events (TEAEs), which are defined as any AEs that occurs or worsens at or after the initiation of IMP. The AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by system organ class (SOC) and preferred term. Each AE summary will be displayed by treatment group.

Number of AEs, frequency and percentage of patients will be reported. For intensity level, the patient will be classified for the highest severity if the patients experienced several AEs.

Onset time of AE from initiation of IMP and AE duration will also be summarized.

Other safety endpoints that will be analyzed:

- Vital signs: blood pressure (BP), including orthostatic BP measurement, and heart rate (HR).
- Electrocardiograms (ECGs).
- Clinical laboratory test results (chemistry, hematology).
- Physical examination findings, weight.
- Columbia-Suicide Severity Rating Scale (C-SSRS).
- Depression Inventory (BDI) scale assessing depression.
- Epworth Sleepiness Scale (ESS) to assess sleepiness.
- Total Functional Capacity (TFC) of the UHDRS®.
- Functional Assessment (FA) of the UHDRS®.
- Barnes Akathisia Rating Scale (BARS).
- Montreal Cognitive assessment (MoCA).
- Problem Behaviors assessment (PBA-s).

9.4.4. PK-PD Analysis

SOM3355 plasma concentration and prolactin level determination will be performed by a central laboratory and analysis of these parameters will be conducted separately and described in a specific Statistical Analysis Plan (SAP).

Prolactin plasma levels and plasma concentrations of SOM3355 obtained from all patients will be listed and summarized using descriptive statistics in tables and graphs, as appropriate.

PK sub-study: 12 hours PK sampling in 24 patients will allow to determine SOM3355 total plasma concentration at 9 time-points from at least 6 patients in each arm receiving active drug, while they

are taking the drug for at least 7 days at the full dose twice per day. PK analysis will be conducted separately and results will be provided in separate reports.

Determination of SOM3355 plasma concentrations will be performed by a central laboratory. PK parameters (AUC, C_{max}, t½, Clearance, etc.) from the individual concentration vs. time profiles will be derived using non-compartmental procedures. The PK analyses of this sub-group will also be described in the specific SAP.

PK-PD analysis will be performed with ECG and BP measurements.

9.5. FUTILITY ANALYSIS

An unblinded interim analysis for futility (non-binding) will take place when at least half of the total number of planned patients ($N = 65$) have completed the study or discontinued early. The analysis will be prepared by a separate team that will communicate the results only to designated recipients, e.g. the Steering Committee and DSMB, to protect the study blind. The primary criterion to assess the futility of the study will be the probability of rejecting the null hypothesis conditional on the accumulated data and the planned sample size. In line with the chosen Holm-Bonferroni multiplicity adjustment, the decision will focus on that hypothesis that yielded the smallest p-value in the interim analysis of the TMC change. A non-binding stop for futility will be recommended if the conditional probability is less than 0.25. Otherwise the study shall be continued without modification unless otherwise recommended by the DSMB.

If a decision is made to stop the trial, then a complete, final analysis will be performed including those patients that were enrolled into the study in the meantime.

10. ETHICS AND LEGAL CONSIDERATIONS

10.1. REGULATION

The trial will be conducted in accordance with the Declaration of Helsinki (and multiple revisions). and in compliance with the protocol, the ICH Guidelines for Good Clinical Practice (ICH E6), the European directives on Clinical Trial Regulation 536/2014 (applicable on 31 January 2022), repealing the Directive 2001/20/CE, and Data Protection General Requirements (2016/680), the General Data Protection Regulation (GDPR 2016/679), and the applicable local country laws/regulations.

10.2. ETHICS COMMITTEE / INSTITUTIONAL REVIEW BOARD APPROVAL

The final study protocol, including the Patient Information and Informed Consent (ICF), will be submitted for approval to the appropriate EC or IRB. Any amendment to these documents will be also submitted to the EC/IRB. In case the protocol amendment changes the scope of the study or increases the risks of the study patients, the Investigator should wait for approval of this amendment by the EC/IRB before implementing the protocol amendment. A copy of the written approval and the approved versions of the documents and a list of the EC/IRB members, their titles and occupations should be forwarded to the responsible study personnel. The written approval should identify the study and document the date of review. All correspondences with the EC/IRB and forward copies of such correspondence should be provided to the Sponsor via the responsible study personnel.

10.3. PATIENT INFORMED CONSENT PROCEDURE

It is the responsibility of the Investigator to give to each patient (or the patient's legally authorized representative) prior to inclusion in the study, full and adequate verbal and written information about the objectives and the procedures of the study, potential risks involved and personal and societal benefits. The patients must be informed about their right to withdraw from the study at any time and for any reason, without sanction, penalty, or loss of benefits to which they are otherwise entitled, and that withdrawal from the study will not jeopardize their future medical care. Before deciding on whether or not to participate, the patient should have sufficient time to think about the study and to discuss the study with a third party if necessary. The Investigators and their staff will be available to answer questions from the patient at any time. Written information (Patient information and ICF) should be given to each patient before enrolment. Furthermore, it is the responsibility of the Investigator to obtain, in accordance with the pertinent local regulations, a signed ICF from each patient (or the patient's legally authorized representative) prior to performing any study-related procedures.

The Patient Information and ICF should be updated or amended whenever new important information that may be relevant to the patient becomes available. Modifications to these documents must be approved by the Sponsor and by the EC/IRB before being implemented.

10.4. PROTOCOL AMENDMENT

With the exception of emergency situations, no changes or deviations in the conduct of this protocol will be permitted. Any change to the study must be documented in a protocol amendment. Such protocol amendments will be made jointly by the Sponsor and the Investigators. Both parties will sign the protocol amendment.

The Investigators will submit the protocol amendment for review by the independent EC/IRB if the change or deviation from the original protocol could increase the risks to the studied patients, or could adversely affect the validity of the investigation, or the rights of the human patients; they have to obtain approval from the independent EC/IRB before such change(s) or deviation are implemented.

If the change(s) or deviation to the original protocol eliminate or reduce the risk to the study patients, the protocol amendment can be implemented before approval has been received from the independent EC/IRB. In such cases, the Investigators will notify the independent EC/IRB within ten working days after implementation and will submit the protocol amendment as soon as possible for information/ favorable opinion from the independent EC/IRB.

If the protocol amendment is of the administrative kind, it will be sent to the EC/IRB for information.

11. QUALITY CONTROL AND QUALITY ASSURANCE

11.1. GOOD CLINICAL PRACTICE (GCP)

The trial will be conducted with respect to the protocol, GCP-ICH and the European directives (EMA), and the local legal requirements.

In conformity with GCP (ICH E6), the Investigator should provide direct access to source data/ documents for trial-related monitoring, audits, IRB/IEC review and regulatory inspection. Any authorized party with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s), to maintain the confidentiality of patient's identities and Sponsor's proprietary information.

11.2. MONITORING

The Sponsor will delegate the monitoring of the study to a Contract Research Organization (CRO). Monitoring will be done by personal visits from a representative of the CRO who will review the case report against source documents and will ensure that the investigation is conducted according to the protocol design, applicable Standard Operating Procedures (SOPs) and regulatory requirements.

The monitor is responsible for checking that the rights and well-being of clinical trial patients are protected and the quality of data is maintained, and ensuring that the investigative site is adhering to the study protocol. Additionally, the monitor ensures that the site is following the legal and ethical requirements as stated in local laws and the principles of GCP.

Source data verification is an essential part of the monitoring process and the Investigator must grant direct access to the original patient's source documents. The Investigator will cooperate with the monitor to ensure that any discrepancies between source data and eCRF are resolved.

11.3. INVESTIGATOR QUALIFICATIONS AND RESPONSIBILITIES

The Investigator should provide a signed and dated copy of his/her current curriculum vitae describing his/her experience, qualifications and training prior to the beginning of the study. He/She should comply with the following conditions:

- Be experienced in neurology, particularly in the management of Huntington's Disease patients and to study procedures/testing facilities adequate for participation in study trial. Notably qualified to assess patients according to UHDRS®.
- Have a sufficient number of HD patients who meet the enrolment goals.
- Have previous clinical research experience with training to Good Clinical Practices.
- Be willing to comply with the study the protocol and to complete all CRFs (eCRF) promptly, and to answer to any query according to the specificities and guidelines provided by the monitor for using the electronic interface.
- Be willing to spend time to complete the administrative work involved in the study.

- Be willing to spend time with the Sponsor monitors (Clinical Research Associates; CRAs) or delegates during the monitoring visits, and to ensure to them direct access to source documents.

The Investigator may appoint such other individuals as he/she may deem appropriate as sub-investigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All sub-investigators shall be appointed and listed in a timely manner. The sub-investigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

11.4. QUALITY CONTROL AND AUDIT

The study may also be subject to a quality assurance audit performed by the Sponsor or its designees, as well as inspection by appropriate regulatory authorities.

The original documents generated in the course of the study will be controlled at each step of the study, both by the Sponsor's representative and the Investigator, in order to guarantee the accuracy of the analyzed data. Auditors should have access to any study records (CRFs, site files, trial master files) and sources (e.g. patients' medical documentation), being understood that these personnel are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information. Investigators accept the possibility to be audited and agree to dedicate necessary time to the proper conduct of the audit at their sites. It will enable to check that the study is being run in conformity to the protocol and to current rules and regulations.

11.5. PROTOCOL DEVIATION

A protocol deviation is any noncompliance with the clinical trial protocol, International Council for Harmonization Good Clinical Practices (ICH-GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the patient, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

The Investigator is responsible for ensuring that the study is conducted in accordance with the protocol. No modifications to the protocol, other than those that are deemed necessary to protect the safety, rights, or welfare of patients by the Investigator are to be made without prior, written approval by the Sponsor. The nature and reasons for the protocol deviation will be recorded where appropriate and indicated. The Sponsor must be notified of all protocol deviations. Significant protocol deviations (e.g. inclusion/exclusion criteria) will be reported to the Sponsor and to the IRB/IEC in accordance with its reporting policy.

12. DATA HANDLING AND RECORD KEEPING

12.1. DATA ENTRY IN THE eCRF

Electronic data capture will be used for the purpose of the study. The eCRF will be developed and validated by the CRO, representative of the Sponsor. The access to the electronic case report form will be provided by the Sponsor to the Investigator. All protocol-required information collected during the study must be entered by the Investigator, or designated representative, in the eCRF.

Details of case report form completion and correction will be explained to the Investigator. If the Investigator authorizes other persons to make entries in the eCRF, the names, positions, signatures, and initials of these persons must be supplied to the Sponsor.

The Investigator, or designated representative, should complete the eCRF pages as soon as possible after information is collected, preferably on the same day that a study patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data. According to the ICH GCP, the monitoring team must check the eCRF entries against the source documents, except for the pre-identified source data directly recorded in the eCRF.

A source data location list will be prepared and updated during the study. This list will be filed in both the trial master file and the Investigator study file.

The completed case report form must be reviewed and signed by the Investigator named in the study protocol. At the end of the study, the Sponsor will retain all case report forms. The Investigator will retain a record of all completed case report forms.

The informed consent form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the eCRFs (e.g. patient's medical file, appointment books, original laboratory records, etc.). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

It is the responsibility of the Investigator to maintain adequate and accurate eCRFs (according to the technology used), designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All eCRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data. Should a correction be made, the corrected information will be entered in the eCRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the eCRF and allow remote monitoring.

The computerized handling of the data by the Sponsor when available in the eCRF may generate queries to which the Investigator is obliged to respond by confirming or modifying the data questioned. The queries with their responses will be managed through the eCRF.

12.2. DATA MANAGEMENT

The data will be entered into a validated FDA 21 CFR part 11 compliant database maintained by the Sponsor or designee. The data management group will be responsible for data processing, in accordance with agreed procedures. The Principal Investigator will electronically sign and date the appropriate eCRF page when instructed to do so by the study CRA. This signature will indicate that the Principal Investigator inspected or reviewed the data in the database, the data queries, and the site notifications, and agrees with the content. The standard procedures for handling and processing eCRF records will be followed per GCP and the Sponsor's (or designee's) SOPs. Complete details of data management will be described in a separate Data Management Plan.

12.3. RECORD RETENTION

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

In order to constitute evidence with respect to product safety or regulatory or legal compliance, the Investigators, investigational sites and Ethics Committees agree to retain study related documents in a location that is secure and to which access can be gained if required. The following documents must be archived: the Investigator's file containing all required GCP documents, including signed Informed Consent forms and patient-related records, and copy of the CRFs. The Investigator and the site should **retain records at least 25 years after the completion or discontinuation of the clinical trial**. If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee. The Investigator must notify the Sponsor prior to destroy any study essential documents following the clinical trial completion or discontinuation.

These documents must be available for inspection by authorized representative of the Sponsor or regulatory authorities. Audits may be performed for quality insurance of data handling.

12.4. DATA PROTECTION

The data collected in this study will only be used for the purpose(s) of the study and to document the evaluation of the benefit/risk ratio, efficacy and safety of the tested product SOM3355.

The patient's personal data, which are included in the Sponsor database, shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

The Sponsor also collects specific data regarding investigator as well as personal data, from any person involved in the study which may be included in the Sponsor's databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

Patient race or ethnicity will be collected in this study. Differences in response to medical products have already been observed in racially and ethnically distinct subgroups of the U.S. population. These differences may be attributable to intrinsic factors (e.g., genetics, metabolism, elimination), extrinsic factors (e.g. diet, environmental exposure, sociocultural issues), or interactions between these factors. Race and ethnicity information will be collected according to the *FDA Guidance for Industry - Collection of Race and Ethnicity Data in Clinical Trials (2005)*, and in accordance of local laws in the different participating countries.

12.5. CONFIDENTIALITY AND PROPERTY RIGHTS

All documents that concern the studied medication and the company's operations belonging to the Sponsor such as patent applications, formulas, manufacturing processes, basic scientific data and analysis bulletins, and any information supplied by the company and not previously published are considered confidential and shall remain the sole property of the Sponsor. The information included in this protocol, along with the Investigator's brochure of the product, the eCRF and the results of the present study are considered as confidential and should not be divulged unless such disclosure is required by law or regulations. The Investigator agrees to use this information only in accomplishing this study and they will not use it for other purposes without written consent from the Sponsor.

In any event, any persons to whom the information is disclosed such as sub-investigators must be informed that the information is confidential and may not be further disclosed by them. The signature of the present protocol by the Investigator is equivalent to a confidentiality agreement.

It is understood by the Investigator that the information from the clinical study will be used by the company in connection with the development of the tested drug and, therefore, may be disclosed as required, to other clinical investigators or to government agencies.

13. FINANCES AND INSURANCE

13.1. FINANCING

The Sponsor will cover the additional costs related to this study. These costs will be defined and agreed upon, before the start of the study. A financial agreement will be made between the parties: institution, investigator and Sponsor, in accordance with each administrative procedure.

13.2. INSURANCE

The Sponsor will contract a specific insurance policy to insure the patients enrolled in the study, in conformity with the national regulations. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy.

14. PUBLICATION POLICY

The Sponsor will be responsible for conducting the statistical analysis and for preparing a Clinical Study Report and must provide a summary of study results to the Investigators.

The Sponsor will publish the results at the end of the study in an international journal on behalf of the study group including all the principle investigators of all sites, after validation and agreement of the manuscript by the publication committee including the Sponsor and the coordinating investigator.

The communication or publication of all or part of the results of this study, including ancillary studies, will be only permitted after written agreement of the Sponsor. Any manuscript or presentation should be submitted at least 30 days before submission to the Sponsor for review and approval. The objective is to ensure consistency between data submitted to regulatory agencies and data appearing in publications and presentations. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights. The Sponsor has the right at any time to publish the results of the study.

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16. APPENDICES

All appendices will be provided in a separate document.

16.1. UHDRS® - MOTOR PART INCLUDING TOTAL MOTOR SCORE (TMS) AND TOTAL MAXIMAL CHOREA (TMC), DYSTONIA AND GAIT SUB-SCORES

16.2. UHDRS® - TOTAL FUNCTIONAL CAPACITY (TFC)

16.3. UHDRS® - FUNCTIONAL ASSESSMENT (FA)

16.4. CLINICAL GLOBAL IMPRESSION (CGI-S AND CGI-C)

16.5. PATIENT GLOBAL IMPRESSION (PGI-S AND PGI-C)

16.6. EQ-5D-5L

16.7. COLUMBIA SUICIDE SEVERITY RATING SCALE (C-SSRS)

16.8. BECK'S DEPRESSION INVENTORY (BDI)

16.9. EPWORTH SLEEPINESS SCALE (ESS)

16.10. BARNES AKATHISIA RATING SCALE (BARS)

16.11. MONTREAL COGNITIVE ASSESSMENT (MOCA)

16.12. PROBLEM BEHAVIOR ASSESSMENT SHORT FORM (PBA-S)

16.13. GUIDANCE OF THE EUROPEAN SOCIETY OF HYPERTENSION FOR BLOOD PRESSURE AND ORTHOSTATIC BP MEASUREMENT