Clinical Study Protocol	
Compound	NOE-105
Protocol Number	NOE-CFD-201
Version	2.0 Amendment 3 US
Date	25 May 2023

A Double-blind, Placebo-controlled, Phase IIb, Multi-center, Ten-week Prospective Study to Evaluate the Efficacy and Safety of NOE-105 in Adult Male Patients with Childhood Onset Fluency Disorder

Sponsor Name: Noema Pharma AG

Legal Registered Address: Noema Pharma AG, 4051 Basel, Switzerland

Regulatory Agency Identifier Number(s):

Protocol Number: NOE-CFD-201

Version Number: 2.0 Amendment 3 US

Study Intervention: NOE-105
Study Phase: IIb

Short Title: A 10-week efficacy study of NOE-105 in childhood onset fluency disorder (COFD).

Study Physician Name and Contact Information will be provided separately

Principal investigator

[redacted]

PROTOCOL APPROVAL PAGE

Sponsor Signatory:

[redacted]

5/25/2023

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	**Date**
Version 2.0 Amendment 3 US (US only)	25 May 2023
Version 2.0 Amendment 2 US (US only)	01 September 2022
Version 2.0 Amendment 1 US (US only)	13 May 2022
Version 1.0 Amendment 1 Australia (Australia only)	05 May 2022
Version 2.0 and Version 2.0 Addendum 1 (US only)	03 March 2022 and 29 March 2022
Original Protocol (Version 1.0)	30 November 2021

Version 2.0 Amendment 3 US (25 May 2023)

This is a substantial amendment as it contains changes to planned analyses.

Overall Rationale for the Amendment:

The primary rationale for this amendment is to implement health authority requests with regards to the timing of the primary endpoint assessment and the updating of study objectives, and subsequent analysis, to use the estimand framework.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Synopsis	Changes made for consistency with the body of the protocol.	To ensure consistency throughout	Substantial
	Number of evaluable patients removed from table.	Redundant information	Non-substantial
Section 3 Objectives, Endpoints, and Estimands	Title of section changes to include estimands	For consistency with section content	Non-substantial
	Change of timepoint for assessment of the primary endpoint from end point (first visit after administration of the final dose of study medication) to end of 6 weeks.	Health authority request to measure change from randomization over the same duration among patients	Substantial
	Addition of a Supportive Primary Endpoint	To have an additional comparison of interest, as supportive to primary estimand, that considers the full double-blind treatment period of up to 10 weeks	Substantial
	Sub-division of secondary endpoints into ‘KEY Secondary’ and ‘Other Secondary Endpoints’.	To highlight the importance of the secondary end point effect on functional impairment	Substantial
	Change of objective ‘To evaluate the patient’s satisfaction in treatment with NOE105’ from secondary to exploratory.	To highlight that the evaluation of patient’s satisfaction using the MSQ is exploratory/hypothesis generating	Substantial
	Addition of estimand details for primary and secondary objectives.	Health authority request to apply estimand framework to the study objectives	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	Addition of 'suicidality' to safety endpoints.	Previously omitted in error	Substantial
Section 3 Objectives, Endpoints, and Estimands Section 4.2 Scientific Rationale for Study Design Section 8.2.1 Speech Fluency Section 9.1 Statistical Hypotheses Section 9.4.4.1 Primary Estimand (previously Primary Endpoint)	Change of name of assessment of MLGSSS from assessment of severity subset to assessment of total score.	To ensure consistency in terminology	Non-substantial
Section 3 Objectives, Endpoints, and Estimands Section 9.1 Statistical Hypotheses Section 9.4.4.1 Primary Estimand (previously Primary Endpoint)	Change of timepoint for assessment of the primary endpoint from end point (first visit after administration of the final dose of study medication) to end of 6 weeks.	Health authority request to measure change from randomization over the same duration among patients	Substantial
Section 4.1 Overall Design	Description of duration of dosing updated.	To provide additional clarity.	Non-substantial
Section 5.2 Exclusion Criteria	Criteria 3 and 4 renumbered to form sub points of criterion 2.	Correction	Non-substantial
Section 9.2 Sample Size Determination	Changed term from 60 patients should be randomized to 60 patients are planned to be randomized.	To provide flexibility	Non-substantial
	Number of evaluable patients removed.	All randomized patients, including subsequent drop-outs, will be included in the analyses	Non-substantial
Section 9.3 Populations for Analysis	In Table 4: • Description of Full Analysis Set updated • Description of Secondary Full Analysis Set added • Description of Per Protocol analysis set updated	Analysis set definitions have been updated to align with the estimand descriptions	Substantial
Section 9.4 Statistical Analyses	Removed reference to the SAP describing the handling of missing data	Some information on the handling of missing values has now been included in the protocol	Non-Substantial
Section 9.4.2	New text added providing information on overall control of family-wise false-positive rate of 5%	Clarification on how inferential statistics will be performed given	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Inferential Statistics and Significance Testing		that there are multiple secondary endpoints.	
Section 9.4.4.1 Primary Estimand (previously Primary Endpoint)	Details of primary estimand and analysis added.	Health authority request to apply estimand framework to the study objectives	Substantial
Section 9.4.4.2 Supportive Primary Estimand	New section added with description of the analysis of the supportive primary estimand.	Include analysis description of the additional comparison of interest, as supportive to primary estimand, that considers the full double-blind treatment period of up to 10 Weeks	Substantial
Section 9.4.4.3 Secondary Estimand(s) (formerly Secondary Endpoints)	Description of secondary estimands and associated analysis added.	Health authority request to apply estimand framework to the study objectives	Substantial
Section 9.4.5 Safety	Addition of QIDS-16 (previously listed in secondary efficacy endpoint section)	Correction	Substantial

CGI-C, Clinical Global Impression of Change; MLGSSS, Maguire-Leal-Garibaldi Self-rated Stuttering Scale; QIDS-16, Quick inventory of depressive symptomology; SAP, statistical analysis plan.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A double-blind, placebo-controlled, Phase IIb, multi-center, 10-week prospective study to evaluate the efficacy and safety of NOE-105 in adult male patients with childhood onset fluency disorder**.**

Short Title: A 10-week efficacy study of NOE-105 in COFD.

Rationale: The need to develop strategies for the clinical management of COFD and associated disorders is high. The accompanying symptoms and discomforts due to stuttering have a profound impact on the overall functioning and quality of life of the children and adults who stutter and constitute a significant burden to society. The impact of stuttering on social, other aspects of functioning, and quality of life is substantial. It is estimated that deficit in earnings associated with stuttering exceeds US$ 7000 per year in the United States. Persons who stutter also have a higher probability of being unemployed compared with non-stutterers.

There are currently no approved pharmacotherapies for COFD. Antipsychotics are often used off-label and they show efficacy with significant intolerance including motor and metabolic disorders. Therefore, the need for safe and well tolerated therapies for the management of the motor, cognitive, and affective symptoms of the disorder remains high.

NOE-105 is an investigational selective PDE10A inhibitor with a potential therapeutic effect for the treatment of COFD. Inhibition of PDE10A, an enzyme predominantly present in cortico-striatal circuit, triggers inhibition of D2 receptors. The control of dopamine neuronal signaling in the cortico-striatal area, known as “indirect pathway” is expected to enhance speech fluency in patients with DS.

This study in adults with COFD is designed to evaluate the effectiveness of NOE-105 on speech fluency without the severe motor, extrapyramidal, and metabolic side effects.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of NOE105 on speech fluency in adult patients with COFD	• Primary: Change from baseline to end of 6 weeks in the total MLGSSS score • Supportive Primary: Change from baseline to end point in the total MLGSSS score

Key Secondary	
• To evaluate the effect of NOE105 on functional impairment	• Change from baseline to end point in SDS
Other Secondary	
• To evaluate the effect of NOE105 on the change of illness severity as rated by the patient	• PGI-C rating at end point
• To evaluate the effect of NOE105 on the change of illness severity as rated by the clinician	• CGI-C rating at end point
• To evaluate the effect of NOE105 on the severity of illness as rated by patients	• PGI-S rating at end point
• To evaluate the effect of NOE105 on the change in stuttering severity (number of syllables stuttered and duration of hesitance)	• Change from baseline to end point in clinician-rated SSI-4
Safety	
• To evaluate the safety and tolerability of NOE105	• Incidence and severity of AEs, plus assessment of hematology, clinical chemistry, urinalysis, ECG, vital signs, and suicidality.
• To evaluate the effect of NOE-105 on change in mood as rated by the patient	• Change from baseline to end point in QIDS-16

NOTE: End point refers to the first visit following the last dose of study medication.

AE, adverse event; CGI-C, clinical global impression of change; COFD, childhood onset fluency disorder; ECG, electrocardiogram; MLGSSS, Maguire-Leal-Garibaldi Self-rated Stuttering Scale; MSQ, medication satisfaction questionnaire; PGI-C, patient global impression of change; PGI-S, patient global impression of severity; QIDS-16, quick inventory of depressive symptomology; SDS, Sheehan disability scale; SSI-4, stuttering severity instrument -4.

Exploratory endpoints are presented in Section 3.

Overall Design

This is a multicenter, double-blind, parallel arm, placebo-controlled study in male patients with COFD. Following screening to confirm eligibility, patients will commence a blinded placebo run-in period for 7 days. Any participating patient may be randomized 1:1 to NOE-105 or placebo on study days 1, 15, or 29. Patients will complete up to 10 weeks of double-blind treatment (to Study Day 71). Patients will then visit the study site for a follow-up visit within 28 (± 7) days of the date of the last dose of study treatment.

Disclosure Statement: This is a parallel-group efficacy and safety study with 2 arms that are blinded.

Number of Patients:

Enrolled	Estimated 67 patients
Randomly assigned	Estimated 60 patients

Note: "Enrolled" means a patient's agreement to participate in the clinical study following completion of the informed consent process and who are eligible to enter the placebo run-in. Patients who have signed the ICF and are screened for the purpose of determining eligibility for the study, but do not join the placebo run-in phase, are considered "screen failures".

Intervention Groups and Duration:

Following screening to confirm eligibility, on day -7, patients will enter a blinded placebo run-in period for 7 days. Patients may be randomized to NOE-105 or placebo on study days 1, 15, or 29. During the first 3 weeks of treatment following randomization, patients will receive escalating doses of NOE-105 or escalation of placebo until they reach a daily dose of 15 mg or their individual MTD is achieved. Thereafter, patients will be maintained at this dose until they have completed up to 10 weeks of treatment.

Statistical Methods

Continuous variables will be summarized using the following statistics: number of available data, number of missing values, mean, standard deviation, median, Q1, Q3, minimum and maximum values. When relevant, CIs will be computed for the mean.

Categorical variables will be summarized by frequency counts, and percentages for each category. Generally, percentages will be calculated using the number of available data as the denominator (ie, not including missing values).

Between group comparisons will be performed using appropriate two-sided hypothesis tests at the 5% two-sided significance level, except if specified otherwise.

1.2 Schedule of Activities

Table 1 Schedule of Activities

Procedure	**SCREENING**	**PLACEBO RUN-IN**	**TREATMENT Day**											**FOLLOW UP**	**Notes**
	Screening (W-4 to -1) Clinic visit	Run-In (W-1 to 0)	Day 1 (BL)	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	Day 57	Day 64	Day 71 or EoT	28 days after last dose	For patients who are receiving prior medications used to treat stuttering, the screening period will be from W-4 to -2).
Clinic (C) or Remote (R) Visit	C	C	C	C	C	C	C	C	C	C	R	R	C	C	Patients who do not complete the full treatment period will complete an EoT assessment as soon as possible after last dose of study medication.
Time Window (Days)	NA	NA	+ 3	+ 3	+ 3	+ 3	+ 3	+ 3	+ 3	+ 3	+ 3	+ 3	+ 3	± 7	
Informed consent	X														Appendix A 1.2
Eligibility	X														This may include a video interview to confirm a minimum severity of moderate stuttering. Section 5.1 and Section 5.2
Demographics	X														

Procedure	**SCREENING**	**PLACEBO RUN-IN**	**TREATMENT Day**											**FOLLOW UP**	**Notes**
	Screening (W-4 to -1) Clinic visit	Run-In (W-1 to 0)	Day 1 (BL)	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	Day 57	Day 64	Day 71 or EoT	28 days after last dose	For patients who are receiving prior medications used to treat stuttering, the screening period will be from W-4 to -2).
Medical History, including stuttering and psychiatric conditions	X														Section 8.1.1
Physical examination	X												X	X	Section 8.1.1
Randomization			X		X		X								Patients will be randomized to NOE-105 or placebo on Day 1, 15, or 29
MLGSSS		X	X	X	X	X	X	X	X	X	X	X	X		Section 8.2.1
QIDS-16			X										X		Section 8.2.3
SSI-4			X										X		Section 8.2.1
PGI-C			X										X		The baseline assessment will be through a voice recording see Section 8.2.3
PGI-S			X	X	X	X	X	X	X	X	X	X	X		Section 8.2.3
CGI-C													X		The baseline assessment will be made by using

Procedure	**SCREENING**	**PLACEBO RUN-IN**	**TREATMENT Day**											**FOLLOW UP**	**Notes**
	Screening (W-4 to -1) Clinic visit	Run-In (W-1 to 0)	Day 1 (BL)	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	Day 57	Day 64	Day 71 or EoT	28 days after last dose	For patients who are receiving prior medications used to treat stuttering, the screening period will be from W-4 to -2).
															investigator's notes see Section 8.2.3
SDS			X										X		Section 8.2.2
MSQ													X		Section 8.2.4
Vital signs	X		X										X	X	Section 8.1.2
12-lead ECG	X												X	X	Section 8.1.3
Clinical chemistry	X												X	X	Section 8.3.1
Hematology	X												X	X	Section 8.3.1
Urinalysis	X												X	X	Section 8.3.1
Serology	X														Section 8.3.1
Urine drug test	X		As required										X		Section 8.3.1
C-SSRS		X	X	X	X	X	X	X	X	X			X		The baseline assessment will be made at Week -1 Section 8.3.2
Administration of IP		X	X	X	X	X	X	X	X	X	X	X			Section 6.2
Accountability of IP			X	X	X	X	X	X	X	X			X		Section 6.2

Procedure	**SCREENING**	**PLACEBO RUN-IN**	**TREATMENT Day**											**FOLLOW UP**	**Notes**
	Screening (W-4 to -1) Clinic visit	Run-In (W-1 to 0)	Day 1 (BL)	Day 8	Day 15	Day 22	Day 29	Day 36	Day 43	Day 50	Day 57	Day 64	Day 71 or EoT	28 days after last dose	For patients who are receiving prior medications used to treat stuttering, the screening period will be from W-4 to -2).
Adverse Events	X	X													Section 8.4
Concomitant medications	X	X													Section 6.5

BL, baseline; C, clinic (visit); CGI-C, clinical global impression of change; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; EoT, end of treatment; IP, investigational product; MLGSSS, Maguire-Leal-Garibaldi self-rated stuttering scale; MSQ, medication satisfaction questionnaire; PGI-C, patient global impression of change; PGI-S, patient global impression of severity; QIDS-16, quick inventory of depressive symptomology; R, remote (visit); SDS, Sheehan disability scale; SSI-4, stuttering severity index-4; W, week.

2 INTRODUCTION

NOE-105 (formerly known as RO5545954) is a selective, orally active inhibitor of PDE10A, which dose-dependently increases cyclic nucleotides in rat striatum, and triggers inhibition of D2 receptors (Kehler and Nielsen 2011). NOE-105 also produced pro-cognitive effects in several nonclinical assays. In addition, NOE-105 did not increase motor disorders in cynomolgus monkeys and had no impact on glucose tolerance or fasting insulin levels in rats. NOE-105 has the potential to have a more favorable tolerability profile than existing therapies without the induction of metabolic syndrome in patients with COFD.

2.1 Study Rationale

Several data indicate that COFD may be related to a dysfunction in dopaminergic neurotransmission; moreover, it can be relieved by dopaminergic receptor blockers (Murray and Newman 1997, Shaygannejad et al 2013), and PET studies have shown substantial increase in dopamine uptake activity in cortical and subcortical areas (Wu et al 1996). The control of dopamine neuronal signaling in the cortico-striatal area, known as “indirect pathway”, is expected to enhance speech fluency in patients with COFD.

NOE-105 is an investigational selective PDE10A inhibitor with a potential therapeutic effect for the treatment of COFD. Inhibition of PDE10A, an enzyme predominantly present in cortico-striatal circuit, triggers inhibition of D2 receptors.

This study in adults with COFD is designed to evaluate the effectiveness of NOE-105 on speech fluency without the known severe motor, extrapyramidal, and metabolic side effects.

2.2 Background

COFD, otherwise known as stuttering or stammering, is a developmental speech disorder that occurs in 5% of children with spontaneous remission in approximately 70% of cases around the age of 18. Males are affected more than females (ratio 4:1) (Andrews and Dozsa 1977 , Baptista et al 2004 , Chang et al 2008 , Shaygannejad et al 2013). The treatment of stuttering has been described as a controversial and puzzling issue for speech language pathologists (Ingham and Riley 1998), and recent concerns have been expressed about the absence of strict documentation regarding the efficacy of some interventions.

It is generally agreed that stuttering is a speech disorder that has an adverse effect on communication. Communication difficulties are a central component of stuttering (Wu et al 1996). The accompanying symptoms and discomforts due to stuttering have a profound impact on the overall functioning and quality of life of the children and adults who stutter and constitute a significant burden to society. It is estimated that deficit in earnings associated with stuttering exceeds US$ 7000 per year in the US (Gerlach et al 2018). Persons who stutter also have a higher probability of being unemployed compared with non-stutterers.

Haloperidol has been used to treat COFD with some success. However, in many patients, any beneficial effects are accompanied by extrapyramidal side effects (Shireen and Haleem 2011) and drowsiness can also cause discontinuation of treatment (Andrews and Dozsa 1977). A few reports have shown the possible effects of olanzapine to treat stuttering (Lavid et al 1999, Shaygannejad et al 2013, Maguire et al 2004). However, olanzapine also induces obesity and insulin resistant states, which haloperidol does not (Baptista et al 2004, Mathews and Muzina 2007).

There are currently no approved pharmacotherapies for COFD. Antipsychotics are often used off-label and they show efficacy with high rates of AEs. Therefore, the need for safe and well tolerated therapies for the management of the motor, cognitive, and affective symptoms of the disorder remains high.

2.2.1 NOE-105

NOE-105 is a selective, orally active inhibitor of PDE10A, which dose-dependently increases cyclic nucleotides in rat striatum. NOE-105 also produced pro-cognitive effects in several nonclinical assays. In addition, NOE-105 did not increase motor disorders in cynomolgus monkeys and had no impact on glucose tolerance or fasting insulin levels in rats. NOE-105 has the potential to have a more favorable tolerability profile than existing standard of care without the induction of metabolic syndrome in patients with COFD.

PDE10A is part of a superfamily of phosphodiesterases with 11 family members (Lugnier 2006). The role of the phosphodiesterase is to hydrolyze both 3',5'-cyclic adenosine monophosphate (cAMP) and 3',5'- cGMP in neurons. PDE10A mRNA is strongly expressed in the CNS of mammals and is expressed at much lower levels in peripheral tissues, with the exception of the testis. Within the brain, PDE10A is highly expressed in the striatal complex, including the caudate putamen, nucleus accumbens, and olfactory tubercle. The overall pattern of PDE10A protein localization reported in rat brain has been confirmed and extended to include multiple species, including mice, dogs, cynomolgus monkeys, and humans (Andrews and Dozsa 1977; Baptista et al 2004; Chang et al 2008; Andrews and Dozsa 1977

Andrews G, Dozsa M. Haloperidol and the treatment of stuttering. J Fluency Disorders 1977;2:217-24.

Baptista et al 2004
Baptista T, Zárate J, Joober R, Colasante C, Beaulieu S, Páez X, et al. Drug induced weight gain, an impediment to successful pharmacotherapy: Focus on antipsychotics. Curr Drug Targets 2004;5:279–99.

Chang et al 2008
Chang SE, Erickson KI, Ambrose NG, Hasegawa-Johnson MA, Ludlow CL. Brain anatomy differences in childhood stuttering. Neuroimage 2008;39:1333–44.

Coskran et al 2006). At the cellular level, PDE10A is localized in the GABA-containing MSNs, which comprise more than 95% of striatal neurons.

The striatal MSNs function as the principal molecular integrators of cortical glutamatergic and midbrain dopaminergic inputs to basal ganglia to facilitate planning and executing of relevant motor and cognitive patterns, while suppressing unwanted or irrelevant patterns (Graybiel 2000). The MSNs are organized in two neurochemically distinct striatal output pathways, both converging to the thalamus. The direct or striato-nigral pathway is generally considered to promote behavioral activity and is stimulated by dopamine due to MSN expression of dopaminergic D1 receptors, positively coupled to adenylyl cyclase. In contrast, the indirect or striato-pallidal pathway tonically suppresses behavioral output and is inhibited by dopamine due to MSN expression of dopaminergic D2 receptors, negatively coupled to adenylyl cyclase. The high level of expression of PDE10A in the MSNs suggests that inhibition of this enzyme will result in functional changes affecting the circuitry. This hypothesis is confirmed by results of studies in which selective pharmacological inhibition of PDE10A causes a reduction in locomotor activity induced by NMDA-R antagonists (Kehler and Nielsen 2011), an effect which is similar to that of dopamine antagonists that are currently used therapies for the treatment of COFD. These effects on locomotion are believed to be due to the reduction of the D2 signaling or indirect pathway, whereas the effect on the direct pathway, through activation of D1 signaling, is thought to contribute to the modulatory effects on reward-based learning, motivation and cognition of PDE10A inhibitors. Therefore, PDE10A inhibition represents a new approach for the treatment of diseases characterized by a dysregulation of MSNs, such as COFD.

2.2.1.2 NOE-105 Non-clinical Studies

Non-clinical Pharmacology

In vitro, NOE-105 is a potent and selective non-competitive inhibitor of PDE10A with similar efficacy in human, rat, and cynomolgus monkey.

[redacted]

Pharmacokinetics and Metabolism

Multiple-dose pharmacokinetic properties were studied during repeat-dose toxicity studies in rats and cynomolgus monkeys. [redacted].

Relevant drug-drug interactions as a result of inhibition of metabolism or transporters by NOE-105 are not expected. However, increases in NOE-105 exposure as a result of co-administration with CYP3A and CYP2C8 inhibitors or inducers cannot be excluded.

Toxicology and Safety Pharmacology

Oral administration of NOE-105 was well tolerated in rats and cynomolgus monkeys in studies for up to 13 weeks.

[redacted]

[redacted]

2.2.1.3 NOE-105 Clinical Studies

As of 20 October 2020, NOE-105 has been investigated in five completed Phase I clinical studies. Studies BP28373 and BP28845 recruited healthy subjects to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of NOE-105.

[redacted]

- [redacted]

- [redacted]

[redacted]

Clinical Pharmacology

[redacted]

Safety

Healthy subjects

In healthy subjects treated with NOE-105, no deaths or SAEs have been reported as of 20 October 2020.

[redacted]

[redacted]

Patients

In patients with schizophrenia treated with NOE-105, no deaths have been reported as of 20 October 2020. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

NOE-105 was well-tolerated in patients with schizophrenia at doses up to 7.5 mg for 12 days and up to 15 mg when administered using an up-titration regimen.

A detailed description of the clinical data for NOE-105 is provided in the IB.

2.3 Benefit/Risk Assessment

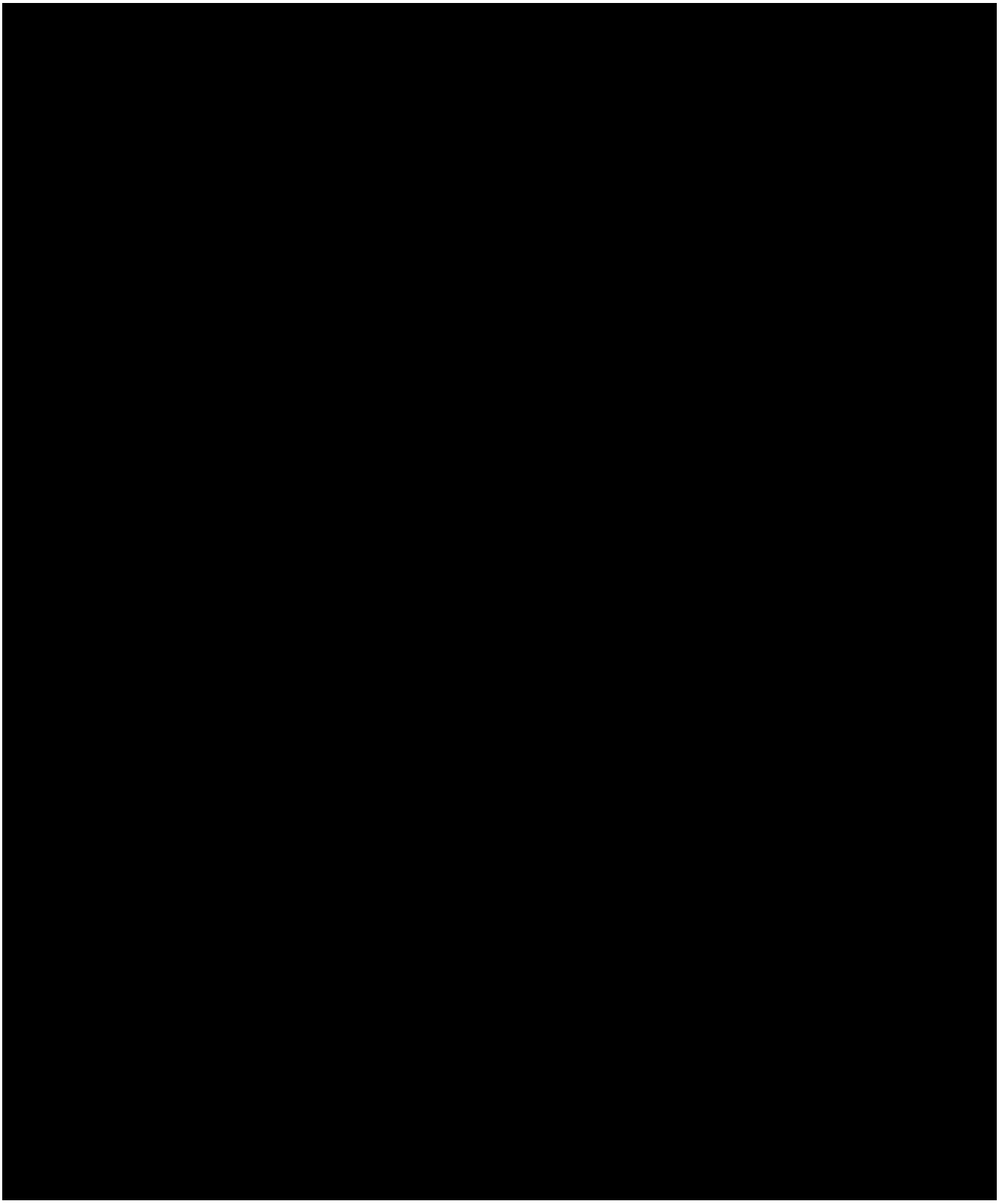
To assess the benefit/risk for participation in this study, preclinical and clinical data for the investigational product have been taken into consideration as well as the risks associated with the study procedures.

More detailed information about the known and expected benefits and potential risks of NOE-105 may be found in the IB.

2.3.1 Risk Assessment

Table 2 Risk Assessment

[redacted]



2.3.2 Benefit Assessment

Patients are expected to have therapeutic benefit from the study medication. Participation in

this study will help to design future therapeutic studies assessing the efficacy, safety, and tolerability of the study medication in the intended final population.

2.3.3 Overall Benefit: Risk Conclusion

Potential risks include the occurrence of acute motor reactions including dystonia, sedation, as well as somnolence or dizziness. These side-effects are reversible and can be treated. Thus, the overall potential long-term benefits to patients outweigh the potential risks to patients participating in this study.

Considering the measures to minimize risk to patients participating in this study, the potential risks identified in association with NOE-105 are justified by the anticipated benefits that may be afforded with NOE-105.

More detailed information about the known and expected benefits, risks and expected AEs with NOE-105 can be found in the IB.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of NOE105 on speech fluency in adult patients with COFD	• Primary: Change from baseline to end of 6 weeks in the total MLGSSS score • Supportive Primary: Change from baseline to end point in the total MLGSSS score
Secondary	
• To evaluate the effect of NOE105 on functional impairment	• Change from baseline to end point in SDS
Other Secondary	
• To evaluate the effect of NOE105 on the change of illness severity as rated by the patient	• PGI-C rating at end point.
• To evaluate the effect of NOE105 on the change of illness severity as rated by the clinician	• CGI-C rating at end point
• To evaluate the effect of NOE105 on the severity of illness as rated by the patient	• PGI-S rating at end point
• To evaluate the effect of NOE105 on the change in stuttering severity (number of syllables stuttered and duration of hesitance)	• Change from baseline to end point in clinician-rated SSI-4
Exploratory	
• To evaluate the patient's satisfaction in treatment with NOE-105	• Rating of the MSQ at end point
Safety	
• To evaluate the safety and tolerability of NOE105	• Incidence and severity of AEs, plus assessment of hematology, clinical chemistry, urinalysis, ECG, vital signs, and suicidality
• To evaluate the effect of NOE-105 on change in mood as rated by the patient	• Change from baseline to end point in QIDS-16

NOTE: End point refers to the first visit following the last dose of study medication.

AE, adverse event; CGI-C, clinical global impression of change; COFD, childhood onset fluency disorder; ECG, electrocardiogram; MLGSSS, Maguire-Leal-Garibaldi Self-rated Stuttering Scale; MSQ, medication satisfaction questionnaire; PGI-C, patient-reported global assessment of change; PGI-S, patient global impression of severity; QIDS-16, quick inventory of depressive symptomology, SDS, Sheehan disability scale; SSI-4, stuttering severity instrument-4.

3.1 Primary Estimand

This study will compare daily dosing of NOE-105 with 3 weeks escalating dose to 15 mg or individual maximum tolerated dose (MTD) versus placebo in adult patients with childhood onset fluency disorder (COFD) for ≥ 2 years (with onset consistent with being developmental in nature before age 8 years).

The primary comparison of interest is the difference between means in the change from baseline to end of Week 6 in speech fluency assessed using the total MLGSSS score. The primary comparison will be made regardless of whether a dose modification or treatment discontinuation occurred due to intolerance or lack of efficacy and regardless of changes in background medication.

The primary estimand is described by the following attributes:

- The treatment of interest is 6 weeks of NOE-105, dosed daily and escalating from 2.5 mg to 15 mg or individual MTD, regardless of any dose modifications or treatment discontinuations due to intolerance or lack of efficacy, which will be compared to daily dosing of placebo.

- The target population is adult male patients with COFD for a minimum of 2 years, with onset consistent with being developmental in nature before 8 years of age.

- The variable of interest is the change from baseline in the total MLGSSS score. The baseline is the last assessment prior to randomization, and the change will be observed at the end of 6 weeks of treatment. [redacted].

- The population-level summary will be the difference in mean change from baseline in the total MLGSSS score for NOE-105 versus placebo.

- There are potential intercurrent events which could affect the experimental measurements required to answer the clinical question. The events and the accompanying strategies for handling these are:

    - Use of concomitant medication will be handled by the treatment policy strategy, where data are collected and analyzed regardless of the occurrence of an intercurrent event, and so will form part of the treatment effect of interest.

- Reduction, interruption, lack of compliance or withdrawal of study treatment due to intolerance or lack of efficacy are included in the treatment intervention of interest and are handled by the treatment policy strategy.

- Withdrawal of study treatment for reasons unrelated to treatment (e.g., personal circumstance such as relocation) will be handled using the hypothetical strategy, that is, assuming treatment had not stopped. Data that are collected after such study treatment discontinuations are disregarded and not included within the analysis.

- Deaths are not expected in this study.

- Post-randomization treatment administration errors will be handled using the hypothetical strategy, that is as if the procedural issue did not occur. Data that are collected after the error are disregarded and not included within the analysis.

3.2 Supportive Primary Estimand

An additional comparison of interest is the difference between means in the change from baseline to end of the treatment period of up to 10 Weeks, regardless of whether a dose modification occurs, and regardless of changes in background medication.

The attributes for this estimand are the same as for the primary estimand except for the below:

- The treatment of interest is up to 10 weeks of NOE-105, dosed daily and escalating from 2.5 mg to 15 mg or individual MTD, regardless of any dose modifications, which will be compared to daily dosing of placebo.

- The variable of interest is the change from baseline in the total MLGSSS score. The baseline is the last assessment prior to randomization, and the change will be observed at the end of treatment whether discontinued early or not.

- Intercurrent events:

    - Withdrawal of study treatment for any reason will be handled using the while on treatment strategy using data that are collected up to and including the first visit after such study treatment discontinuations.

3.3 Secondary Estimands

There are several secondary objectives for which secondary estimands are described. The objectives not referenced below are considered non-confirmatory.

3.3.1 Secondary Estimand 1: Functional Impairment

The comparison of interest is the difference between means in the change from baseline to end of treatment in functional impairment assessed using the SDS. The comparison will be made regardless of whether a dose modification occurs, and regardless of changes in background medication.

The attributes for this estimand are the same as the supportive primary estimand except for the below:

- The variable of interest is the change from baseline in the SDS score. The baseline is the last assessment prior to randomization, and the change will be observed at the end of treatment whether discontinued early or not.

3.3.2 Secondary Estimand 2: Change of Illness Severity as Rated by the Clinician

The comparison of interest is the win odds in the rating of illness severity given by the clinician at end of treatment assessed using the CGI-C. The comparison will be made regardless of whether a dose modification occurs, and regardless of changes in background medication.

The attributes for this estimand are the same as the supportive primary estimand except for the below:

- The variable of interest is the CGI-C rating. The rating will be observed at the end of treatment whether discontinued early or not.
- The population-level summary will be the win odds for NOE-105 versus placebo. That is, the odds of a randomly selected patient in the NOE-105 group having a better outcome than a randomly selected patient in the placebo group.

3.3.3 Secondary Estimand 3: Change of Illness Severity as Rated by the Patient

The comparison of interest is the win odds in the rating of illness severity given by the patient at end of treatment assessed using the PGI-C. The comparison will be made regardless of whether a dose modification occurs, and regardless of changes in background medication.

The attributes for this estimand are the same as the supportive primary estimand except for the below:

- The variable of interest is the PGI-C rating. The rating will be observed at the end of treatment whether discontinued early or not.

- The population-level summary will be the win odds for NOE-105 versus placebo.

3.3.4 Secondary Estimand 4: Illness Severity as Rated by the Patient

The comparison of interest is the win odds in the rating of illness severity given by the patient at end of treatment assessed using the PGI-S. The comparison will be made regardless of whether a dose modification occurs, and regardless of changes in background medication.

The attributes for this estimand are the same as the supportive primary estimand except for the below:

- The variable of interest is the PGI-S rating. The rating will be observed at the end of treatment whether discontinued early or not.

- The population-level summary will be the win odds for NOE-105 versus placebo.

3.3.5 Secondary Estimand 5: Change in Stuttering Severity

The comparison of interest is the difference between means in the change from baseline to end of treatment in stuttering severity assessed using the SSI-4. The comparison will be made regardless of whether a dose modification occurs, and regardless of changes in background medication.

The attributes for this estimand are the same as the supportive primary estimand except for the below:

- The variable of interest is the change from baseline in the SSI-4 score. The baseline is the last assessment prior to randomization, and the change will be observed at the end of treatment whether discontinued early or not.

4 STUDY DESIGN

4.1 Overall Design

This is a multicenter, double-blind, parallel arm, placebo-controlled study in male patients with COFD.

Following screening to confirm eligibility which may include a video interview to confirm a minimal severity of moderate stuttering, on day -7, patients will commence the blinded placebo run-in period for 7 days. Patients will be randomized 1:1 to NOE-105 or placebo on study days 1, 15, or 29. During the first 3 weeks of treatment following randomization, patients will receive escalating doses of NOE-105 or double-blind escalation of placebo until their maximum tolerated dose or 15 mg NOE-105 is reached. Thereafter, patients will be maintained at this dose until they have completed up to 10 weeks of treatment (to study day 71).

Following the double-blind treatment, patients will visit the study site for a follow-up visit 28 (± 7) days after the date of the last dose of study treatment.

As the study has a staggered randomization, which may occur on either Study Day 1, 15 or 29, Study Day 1 may occur up to 4 weeks prior to randomization. All assessments taken post-randomization will be described as 'relative' to randomization day. For example, Relative Day 43 will be the assessment at the end of 6 weeks of treatment, relative to the day of randomization. This could be Study Day 43, but could also be Study Day 58 or 71 depending on the day the patient was randomized.

4.2 Scientific Rationale for Study Design

This study is designed to evaluate the effectiveness of NOE-105 on speech fluency without the known serious motor, extrapyramidal, and metabolic antipsychotic-induced side effects of commonly used treatments for COFD. The use of a parallel group, placebo-controlled design was included to reduce the potential for placebo effect in this population. The primary outcome variable of change from baseline in the patients rated total MLGSSS score was included since this scale is expected to be devoid of the large placebo effect noted using other scales for stuttering, eg, the SSI-3 (Maguire et al 2004).

MLGSSS is a revised version of the SSS scale. SSS was a fully validated scale, used in clinical trials (Maguire et al 2004). Over the years it has become obvious that the SSS can be improved in generalizability and in reduction of overlapping items. In generalizability, SSS had items about phone conversation and impact of authority figure. Feedback from patients and experts indicated that patients tend to avoid phone conversation and select jobs where interaction with an authority figure are not needed. Several items in SSS were found to be overlapping without additive value in assessing stuttering. Therefore, MLGSSS was structured

to address these two problems (Maguire et al 2004). The MLGSSS scale will be validated in this study and applied in future studies with NOE-105 in COFD.

QIDS, including the clinician rated QIDS-C16 and self-report QIDS-SR16 formats, are scales that assess nine criterion symptom domains to diagnose a major depressive episode. There are 16 items in the adult versions of the QIDS-16 measuring the nine criterion symptom domains (sleep, sad mood, appetite/weight, concentration/decision making, self-view, thoughts of death or suicide, general interest, energy level, and restlessness/agitation) that define a major depressive episode. All domains are scored from 0 to 3, with higher scores reflecting greater psychopathology. Total QIDS scores range from 0 to 27 with scores of 5 or lower indicative of no depression, scores from 6 to 10 indicating mild depression, 11 to 15 indicating moderate depression, 16 to 20 reflecting severe depression, and scores greater than 21 indicating very severe depression. QIDS-SR16 has good internal scale consistency and is a sensitive measure of change in depression severity associated with effective treatments.

The primary estimand will be supported by endpoints intended to assess the impact of treatment on functioning, these include the SDS, CGI scale, PGI scale, and the SSI-4 scale. The SDS was originally designed to assess functional impairment associated with anxiety disorder. The SDS is a three-item self-completion scale measuring the impact of symptomatology on work, social, and family functioning. Because of its simplicity, brevity, and high face validity, the SDS has become a widely used outcome measure in clinical trials of a variety of mental health disorders. The CGI scale is a well-established research tool that provides clinician determined summary measure acceptable to all psychiatric disorders and is used in virtually all FDA regulated CNS trials. The PGI is a well-established global index that is used to rate severity and change of different CNS conditions. PGI-S is a single scale question asking the patient to rate their condition on scale 1-7, change of 1 point is considered clinically significant. Finally, the SSI-4 is a reliable stuttering assessment used for both clinical and research purposes. It is an objective assessment of severity and other examinations of stuttering speech.

Patients will be eligible for this study if they have a history of stuttering for ≥ 2 years with onset consistent to developmental in nature before age 8 years. This duration works to support the persistence of the condition. In addition, patients will be required to discontinue any current therapies for COFD for at least 14 days prior to entering the study since variability in background medication could have confounding effects on the outcomes being measured. Further, a 7-day placebo run-in period, plus randomization at one of 3 timepoints will further allow potential placebo-effect to be accounted for. NOE-105 has been shown to have teratogenic effects in rabbits and, therefore, participation in this study will be limited to males.

[redacted]

[redacted]

4.2.1 Participant Input into Design

The protocol and associated procedures were reviewed by patients and a COFD specialist.

4.3 Justification for Dose

For this study, the daily doses of NOE-105 will be between 2.5 mg to 15 mg given continuously and orally (for 6-10 weeks) with food, based on the safety, tolerability, and PK to date.

[redacted]

[redacted] Information on enzyme occupancy is provided in the IB.

4.4 End of Study Definition

A patient is considered to have completed the study if he has completed all phases of the study

including the last visit.

The end of the study is defined as the date of the last visit of the last patient in the study.

4.5 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this clinical study protocol and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) which would prevent the conduct of study related activities at study sites, thereby compromising the study site staff or the patient's ability to conduct the study. The investigator or designee should contact the study Sponsor representative to discuss whether the mitigation plans below should be implemented. The study patients will be required to complete the screening and randomization visits on site prior to having the option to participate in the mitigation plans.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study patients, maintain compliance with GCP, and minimize risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent/assent for the mitigation procedures (note, in the case of verbal consent/assent, the ICF should be signed at the patient's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened patients. The investigator should confirm this with the designated study physician.
- Home or Remote visit: Performed by a site qualified HCP or HCP provided by a TPV.
- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.
- At-home IP administration: Performed by a site qualified HCP or HCP provided by a TPV, or by the patient or the patient's caregiver, if possible. Additional information related to the visit can be obtained via telemedicine.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix E.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known

as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

Age

1 Patient must be 18 to 55 years of age inclusive, at the time of signing the informed consent.

Type of Patient and Disease Characteristics

2 Patients who satisfy DSM-5 criteria for childhood onset fluency disorder and are suitable for pharmacotherapy.

3 Have a history of stuttering for ≥ 2 years with onset consistent to developmental in nature before age 8 years.

4 Patient reported global stuttering experience rated as "moderate" at screening and baseline.

5 Patients must discontinue all medications used to treat stuttering for at least 14 days prior to receiving study treatment. With the exception of antipsychotic therapies (see exclusion criterion #13), other psychotropic drugs will be allowed provided they have been stable for at least 14 days prior to receiving study treatment and are expected to remain stable for the duration of the study.

Weight

6 BMI within the range 19 to 35 kg/m^2 (inclusive).

Sex

7 Male

Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Male patients must use a condom during the treatment period and until the end of relevant systemic exposure in the male patient, plus a further 90-day period. In addition, for a non-pregnant WOCBP partner, contraception should be used as described in Appendix C.

Informed Consent

8 Capable of giving signed informed consent as described in Appendix A which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

9 Able to read and write in English.

5.2 Exclusion Criteria

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

Medical Conditions

1. Stuttering is related to a known neurological cause eg, stroke, etc.
2. Low IQ in the opinion of the investigator.
    a. Note: a previously conducted IQ level assessment can be used by the investigator and does not have to be repeated at screening for study purposes.
    b. Additionally, in the absence of a formal IQ test result, the assessment that the targeted IQ level is reached can be based on the investigator's judgment. The investigator can use proxies to IQ score such as the participant's education level (ie, completion of secondary school education) and/or their employment status.
3. Patients with uncontrolled seizure disorders.
4. A history of severe traumatic brain injury or stroke.
5. Patients who are, in the investigator's opinion, at imminent risk of suicide.
6. Known to have tested positive for human immunodeficiency virus.
7. Known DSM-5 diagnosis of substance abuse or dependence.
8. Unstable medical illness or clinically significant abnormalities on screening tests/exams.
9. Any unstable medical conditions or are currently ill (eg, congenital heart disease, arrhythmia or cancer), which, in the investigator's judgment, will put them at a risk of major AE during this trial, are expected to progress during the study, or will interfere with safety and efficacy assessments.

Prior/Concomitant Therapy

12 Initiation of new behavioral therapies for stuttering within 10 weeks prior to baseline.

13 Use of antipsychotic drug therapy within 14 days prior to receiving treatment until the EoT visit.

Prior/Concurrent Clinical Study Experience

14 Participation in another clinical study with an IP administered in the last 30 days.

15 Patients with a known hypersensitivity to NOE-105 or any of the excipients of the product.

Diagnostic Assessments

16 Positive urine drug screen for cannabinoids, cocaine, or nonprescribed opiates.

Other Exclusions

17 Involvement in the planning and/or conduct of the study (applies to both Noema staff and/or staff at the study site).

18 Judgment by the investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements.

19 Previous randomization in the present study.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Use of any other nutrients known to modulate CYP3A4 activity (eg, grapefruit containing products) within 1 week before the first IP administration until the end of treatment is not permitted.

It is important to remind patients that any use of cannabis or cannabis products may have a direct impact on the study outcome including NOE-105 safety and efficacy.

5.3.2 Caffeine, Alcohol, and Tobacco

Consumption of alcohol from screening until the end of treatment should not exceed an average of 2 units per day (1 unit equates to approximately 330 mL beer, 125 mL wine, or 25 mL of spirits). There are no restrictions on consumption of caffeine or tobacco.

5.3.3 Activity

Patients will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Patients may participate in light recreational activities during studies.

5.4 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently included in the placebo run-in phase. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Only 2 times rescreening is allowed in the study. Rescreened patients should be assigned the same participant number as for the initial screening.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s) or placebo intended to be administered to or medical device(s) utilized by a study patient according to the study protocol.

6.1 Study Intervention(s) Administered

6.1.1 Investigational Products

Arm name	Active	Placebo
Intervention name	NOE-105	Placebo
Type	Drug	Drug
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Route of administration	Oral	Oral
Use	Experimental	Placebo-comparator
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and labelling	Study Intervention will be provided in blister wallets. Each blister wallet will be labelled as required per country requirement	Study Intervention will be provided in blister wallets. Each blister wallet will be labelled as required per country requirement

IMP, Investigational medicinal product; NIMP, Non-investigational medicinal product.

The dose of NOE-105 will be individually up titrated in a blinded fashion. [redacted] Each patient will be maintained at their individual MTD or 15 mg until 10 weeks treatment duration is achieved. [redacted]

6.2 Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only patients enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Study Pharmacy Manual.

All doses of NOE-105 will be taken once daily, orally. All doses will be taken in the morning with food. [redacted] All other dosing can take place at home.

6.3 Measures to Minimize Bias: Randomization and Blinding

At the end of the blinded, placebo run-in period, patients who continue to meet all entry criteria will enter the treatment phase and will be randomized via an IVRS/IWRS to receive one of two treatments (NOE-105 or placebo) on Day 1, Day 15, or Day 29.

Routines for this will be described in the Pharmacy Manual that will be provided to each center.

The randomization code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The investigator documents and reports the action to Noema, without revealing the treatment given to the patient to the Noema staff.

The pharmacovigilance function assigned by the Sponsor retains the right to break the code for SAEs that are unexpected and are suspected to be causally related to an IP and that potentially require expedited reporting to regulatory authorities. Randomization codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

The IVRS/IWRS will be programmed with blind-breaking instructions. In case of an emergency, in which the knowledge of the specific blinded study intervention will affect the immediate management of the patient's condition (eg, antidote available), the investigator has the sole responsibility for determining if unblinding of a patients' intervention assignment is warranted. Patient safety must always be the first consideration in making such a determination. If a patient's intervention assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The investigator documents and reports the action to Noema, without revealing the treatment given to the patient to the Noema staff.

6.4 Study Intervention Compliance

When patients self-administer study intervention(s) at home, compliance with study

intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned capsules, etc during the site visits and documented in the source documents and eCRF. Drug accountability should be recorded in the eCRF.

A record of the number of capsules dispensed to and taken by each patient must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the eCRF.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) that the patient is receiving from the start of screening or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

The Study Physician should be contacted if there are any questions regarding concomitant or prior therapy.

Patients must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the follow-up visit, unless, in the opinion of the investigator and sponsor, the medication will not interfere with the study.

Paracetamol/acetaminophen, at doses of ≤ 2 grams/day, is permitted for use any time during the study. Other concomitant medication may be considered on a case-by-case basis by the investigator in consultation with the Study Physician if required.

6.6 Dose Modification

The investigator will assess the patients and determine the patients' experienced tolerability of the current dose. [redacted]

[redacted]

In making this decision, the investigator will be guided by prior experience with the patient.

[redacted]

6.7 Stopping Criteria

The IDMB will recommend termination of the study if the risk of treatment with NOE-105 exceeds the potential benefit. In general, given that the actual stopping of a study is a complex decision involving several factors, the IDMB will take all the data together and analyze the data collectively, both quantitatively and qualitatively, including performing possible additional analyses and data gathering (eg, epidemiological data for background rates), before recommending that the study be stopped. As such, stopping rules based on inferential statistics will not be applied. The IDMB will be informed of all SAEs and AEs of special interest including dystonia.

6.7.1 Participant Level Stopping Criteria

Patients experiencing any of the following high-risk events should have their treatment with the IP stopped and be discontinued from the study:

- [redacted]
- [redacted]

6.7.2 Study Level Stopping Criteria

The study will be placed on temporary hold (defined as treatment stop for enrolled subjects;

and stop of enrollment of subjects into the study) pending further safety data analysis if the following criteria are met:

- [redacted]

The risk to all patients will be evaluated thoroughly before a decision is taken as to whether to terminate the study prematurely or limit dosing in agreement with the regulatory authorities.

6.8 Intervention After the End of the Study

There will be no further study treatment available following the end of the study. If a patient is withdrawn from study treatment or completes the study, the patient will be treated as determined by the attending physician.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

It may be necessary for a patient to permanently discontinue (definitive discontinuation) study intervention. If study intervention is permanently discontinued, the patient will remain in the study to be evaluated as per the SoA. See the SoA for data to be collected at the time of discontinuation of study intervention (EoT/D71) and patient should also attend follow-up visit for any further evaluations that need to be completed.

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

Discontinued patients may be replaced to ensure 54 evaluable patients (Section 9.2).

7.2 Participant Withdrawal from the Study

A patient may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

A patient who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

At the time of withdrawal from the study, if possible, an EoT visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

The patient will discontinue the study intervention and be withdrawn from the study at that time.

If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, it should be confirmed if he still agrees for existing samples to be used in line with the original consent. If he requests withdrawal of consent for use of samples, destruction of any samples taken and not tested should be carried out in line with what was stated in the informed consent and local regulation. The investigator must document the decision on use of existing samples in the site study records and inform the Global Study Team.

7.3 Lost to Follow up

A patient will be considered lost to follow-up if he repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible and counsel the patient on the importance of maintaining the assigned visit schedule and ascertain whether or not the patient wishes to and/or should continue in the study.
- Before a patient is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.
- Should the patient continue to be unreachable, he will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study are handled as part of Appendix A.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the patient's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The maximum amount of blood collected from each participant over the duration of the study, including any extra assessments that may be required, will not exceed 100 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Medical History, Physical Examination, Electrocardiogram, Weight, and Vital Signs

8.1.1 Medical History and Physical Examinations

A physical examination will be performed and include assessments of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, muscular-skeletal (including spine and extremities) and neurological systems.

Any abnormality identified at screening (prior to signing the ICF) should be recorded on the Medical History eCRF. At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient's notes. New or worsened clinically significant abnormalities should be recorded as AEs on the AE eCRF.

Investigators should pay special attention to clinical signs related to any previous serious illnesses.

Physical examinations will be performed at timepoints as specified in the SoA.

Relevant medical history should be obtained from the patient at screening, including stuttering and psychiatric conditions.

8.1.2 Vital Signs

Vital signs will be performed at timelines as specified in the SoA.

Weight, height (at screening only), temperature, pulse rate, and blood pressure will be assessed.

Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones).

Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse.

8.1.3 Electrocardiograms

An electrocardiogram will be performed at timepoints as specified in the SoA.

Single 12-lead ECG will be obtained as outlined in the SoA (Section 1.2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. All ECGs will be obtaining after the patient has been resting in semi-supine position for at least 10 minutes. For each timepoint, 3 ECG recordings should be taken at about 5 minute intervals. All ECGs will be performed on equipment provided by the Sponsor (or designee) and reviewed by site personnel and a core/central laboratory.

8.2 Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA.

8.2.1 Speech Fluency

Speech fluency will be measured using the MLGSSS, the total MLGSSS score, and the SSI-4.

8.2.2 Overall Functioning

Overall functioning will be assessed using the SDS.

8.2.3 Severity of Patient's Illness

The severity of a patient's illness will be assessed using the PGI-S, PGI-C, CGI-C, and QIDS-16 rating scales.

8.2.4 Acceptability Assessment

The patient's assessment of acceptability will be assessed using the MSQ.

8.3 Safety Assessments

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Clinical Safety Laboratory Assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the visits indicated in the SoA.

Additional safety samples may be collected if clinically indicated at the discretion of the investigator. The date and time of collection will be recorded on the appropriate eCRF.

The clinical chemistry, hematology and urinalysis will be performed at a central laboratory. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The laboratory variables provided in Table 3 will be measured.

Table 3 Laboratory Safety Assessments

<table>
<tr><th>Laboratory Tests</th><th colspan="4">Parameters</th></tr>
<tr><td>Hematology</td><td>Platelet Count
RBC Count
Hemoglobin
Hematocrit</td><td colspan="2">RBC Indices:
MCV
MCH
% Reticulocytes
PT-INR
aPTT at screening only</td><td>WBC count with:
Differential:
Neutrophils
Lymphocytes
Monocytes
Eosinophils
Basophils</td></tr>
<tr><td rowspan="3">Clinical Chemistry</td><td>Urea</td><td>Potassium
Total cholesterol
Triglycerides</td><td>AST/ SGOT</td><td>Total and conjugated bilirubin
GGT</td></tr>
<tr><td>Creatinine</td><td>Sodium
Chloride
Magnesium
Phosphates</td><td>ALT/ SGPT</td><td>Total Protein
Albumin
Creatine phosphokinase</td></tr>
<tr><td>Glucose (fasting)</td><td>Calcium</td><td>Alkaline phosphatase</td><td>Plasma Prolactin</td></tr>
<tr><td>Routine Urinalysis</td><td colspan="4">• Each site should be supplied with a bottle of urinalysis test strips. Urine only sent to central lab for analysis if blood or protein is abnormal and explanation for the positive dipstick result not available.</td></tr>
<tr><td>Other Screening Tests</td><td colspan="4">• Urine drug screen (to include at minimum: amphetamines, methamphetamines, barbiturates, cocaine, opiates, cannabinoids, buprenorphine, methadone and benzodiazepines)
• Serology: HIV-1, HIV-2 and Hepatitis B and Hepatitis C
• All study-required laboratory tests will be performed by a central laboratory</td></tr>
</table>

ALT, alanine aminotransferase; aPTT, activated thromboplastin time; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HIV, human immunodeficiency virus; INR, international normalized ratio; PT, prothrombin time; RBC, red blood cell; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic-pyruvic transaminase; WBC, white blood cell.

The investigator must review the laboratory report, document this review, and record any

clinically significant changes occurring during the study as an AE. The laboratory reports must be filed with the source documents.

Abnormal laboratory findings associated with the underlying disease are not considered clinically significant unless judged by the investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.

All protocol-required laboratory tests must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the source notes.

8.3.2 Other Safety Assessments

NOE-105 is considered to be a CNS-active treatment.

Patients being treated with NOE-105 should be monitored appropriately and observed closely for SIB or any other unusual changes in behavior, especially at the beginning and end of the course of treatment, or at the time of dose changes, either increases or decreases. Patients who experience signs of suicidal ideation or behavior, should undergo a risk assessment. All factors contributing to SIB should be evaluated and consideration should be given to discontinuation of the study treatment.

When informed consent has been given, families and caregivers of patients being treated with NOE-105 should be alerted about the need to monitor patients for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior and to report such symptoms immediately to the study investigator.

Baseline assessment of suicidal ideation and behavior/ treatment emergent suicidal ideation and behavior will be monitored during the study using the C-SSRS.

Planned time points for C-SSRS assessments are provided in the SoA (Section 1.2).

8.4 Adverse Events and Serious Adverse Events

The PI is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

The definitions of an AE or SAE can be found in Appendix B.

AEs will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE.

8.4.1 Adverse Events of Special Interest

[redacted]

8.4.2 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

AEs will be collected from time of signature of the ICF, throughout the treatment period and including the follow-up period.

SAEs will be recorded from the time of signing of the ICF.

If the investigator becomes aware of an SAE with a suspected causal relationship to the IP that occurs after the end of the clinical study in a patient treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

8.4.3 Follow-up of Adverse Events and Serious Adverse Events

Any AEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. Noema retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Adverse event variables

The following variables will be collected for each AE;

- AE (verbatim)
- The date and time when the AE started and stopped
- Maximum intensity, intensity, or changes in intensity
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- Select the appropriate as required: AE caused patient's withdrawal from study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

8.4.4 Causality Collection

The investigator should assess causal relationship between IP and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix B 4.3.

8.4.5 Adverse Events Based on Signs and Symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study site staff: 'Have you had any health problems since you were last asked?' or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.4.6 Adverse Events Based on Examinations and Tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, ECG assessments should therefore only be reported as AEs if they fulfil any of the SAE criteria, are the reason for discontinuation of treatment with the IP or are considered to be clinically relevant as judged by the investigator (which may include but not limited to consideration as to whether treatment or non-planned visits were required or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator should use the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study.

8.4.7 Reporting of Serious Adverse Events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the eCRF.

If any SAE occurs in the course of the study, investigators or other site personnel will inform the appropriate Noema representatives within one day ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Noema representative will work with the investigator to ensure that all the necessary information is provided to the Noema Patient Safety data entry site **within one calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will inform Noema representatives of any follow-up information on a previously reported SAE within one calendar day, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated Noema representative.

If the EDC system is not available, then the investigator or other study site staff reports an SAE to the appropriate Noema representative by telephone.

The Noema representative will advise the investigator/study site staff how to proceed.

For further guidance on the definition of an SAE, see Appendix B 2.

The reference document for definition of expectedness/listedness is the IB for the Noema drug.

8.4.8 Pregnancy

All pregnancies in female partners and outcomes of pregnancy should be reported to Noema except if the pregnancy is discovered before the study patient has received any study intervention.

8.4.9 Medication Error

If a medication error occurs in the course of the study, then the investigator or other site personnel informs the appropriate Noema representatives within **1 day**, ie, immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated Noema representative works with the investigator to ensure that all relevant information is completed within **1** (Initial Fatal/Life-Threatening or follow up Fatal/Life-Threatening) **or 5** (other serious initial and follow up) **calendar days** if there is an SAE associated with the medication error (see Section 8.4.7) and **within 30 days** for all other medication errors.

The definition of a Medication Error can be found in Appendix B 3.

8.5 Overdose

For this study, any dose of NOE-105 greater than 15 mg within a 24 hour time period will be considered an overdose.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE and Accountability modules in the eCRF.
- An overdose without associated symptoms is only reported on the Accountability eCRF.

If an overdose on a Noema study intervention occurs in the course of the study, the investigator or other site personnel inform appropriate Noema representatives immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated Noema representative works with the investigator to ensure that all relevant information is provided to the Noema Patient Safety data entry site **within one or 5 calendar days** for overdoses associated with an SAE (see Section 8.4.7) and **within 30 days** for all other overdoses.

8.6 Human Biological Samples

Instructions for the collection and handling of biological samples will be provided in the study specific laboratory manual. Samples should be stored in a secure storage space with adequate measures to protect confidentiality. For further details on Handling of Human Biological Samples see Appendix D.

8.6.1 Pharmacokinetics

Not applicable.

8.6.2 Immunogenicity Assessments

Not applicable.

8.6.3 Pharmacodynamics

Not applicable.

8.7 Human Biological Sample Biomarkers

Not applicable.

8.7.1 Collection of Optional Biomarker Samples

Not applicable.

8.7.2 Other Study Related Biomarker Research

Not applicable.

8.8 Optional Genomics Initiative Sample

Not applicable.

8.9 Health Economics or Medical Resource Utilization and Health Economics

Not applicable.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

The null hypothesis is that there is no difference in the change from baseline at the end of 6 weeks of treatment in total MLGSSS score (items 1 to 6) between the placebo and NOE-105 groups. The alternative hypothesis is that there is a difference.

9.2 Sample Size Determination

As the primary endpoint for this study is a modified version of the SSS which has not been used before, the sample size estimation is based on the original SSS as it is believed to be a reasonable approximation. Maguire et al (2004) examined the effect of olanzapine vs placebo on stuttering and found an approximately 22% change from baseline at Week 12 in SSS in the active group (SD of 25%) against a change from baseline of less than 1% in the placebo group (Maguire et al 2004).

For the sample size estimation for this study, the common SD is assumed to be the SD observed in the active group (25%) in the historical study. Assuming a treatment effect of 22% change from baseline to end of treatment (in the active group as compared to the placebo), and a two-sided type I error rate of 0.05, a sample size of 54 patients (27 active, 27 placebo) will give over 89% power in this study.

Allowing for a dropout rate of 10% following randomization, a total of 60 patients are planned to be randomized. Additionally, to allow for a 10% drop out rate during the placebo run-in period a total of 67 patients should be enrolled.

Enrolled	Estimated 67 patients
Randomly assigned	Estimated 60 patients

Note: "Enrolled" means a patient's, or their legally acceptable representative's, agreement to participate in the clinical study following completion of the informed consent process and who are eligible to enter run-in. Patients who are screened for the purpose of determining eligibility for the study, but do not join the placebo run-in phase, are considered "screen failures".

9.3 Populations for Analyses

The following populations are defined:

Table 4 Populations for Analysis

Population/Analysis set	Description
Enrolled	All patients who sign the ICF
Randomized	Randomly assigned to study treatment
Full analysis set	Randomized to study treatment when eligible (using eligibility criteria assessments taken prior to randomization), who take at least one dose of study treatment and have at least one MLGSSS available post-randomization.
Secondary full analysis set	Randomized to study treatment whether eligible or ineligible, who take at least one dose of study treatment and have at least one MLGSSS available post-randomization.
Safety analysis set	Randomized to study treatment and take at least one dose of study treatment.
Per protocol analysis set	All patients in the FAS who take all planned doses of study treatment, have MLGSSS available at both baseline and at Week 6 (Relative Day 43) and have no major protocol deviations.

ICF, Informed consent form; MLGSSS, Maguire-Leal-Garibaldi Self-rated Stuttering Scale; FAS, full analysis set.

The primary analysis will be on the Full Analysis Set. Analyses using the Secondary Full Analysis Set and Per Protocol Analysis Set will be secondary. The safety evaluation will be performed on the Safety Analysis Set.
Membership of subjects in each analysis set will be determined at a planned blinded data review meeting (BDRM), prior to any analysis.

9.4 Statistical Analyses

The SAP will be finalized prior to data base lock, and will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses. Any differences to the protocol defined analysis

below will be highlighted within the SAP and also referenced in the final CSR.

Data will be analyzed and reported using SAS® version 9.4 or later.

9.4.1 Descriptive Statistics

Continuous variables will be summarized using the following statistics: number of available data, number of missing values, mean, standard deviation, median, Q1, Q3, minimum and maximum values. When relevant, CIs will be computed for the mean.

Categorical variables will be summarized by frequency counts, and percentages for each category. Generally, percentages will be calculated using the number of available data as the denominator (ie, not including missing values).

9.4.2 Inferential Statistics and Significance Testing

Between group comparisons will be performed using appropriate two-sided hypothesis tests at the 5% two-sided significance level, except if specified otherwise.

An overall, family-wise false-positive rate of 5% for the secondary efficacy endpoints will be maintained, in that no significance of secondary endpoints will be claimed unless the primary statistical analysis is significant at the 5% level.

In addition, the testing of the secondary endpoints will be conducted in a hierarchical fashion, in that once a null hypothesis is not rejected, all subsequent secondary hypothesis tests will be considered to be exploratory. The secondary endpoints in hierarchical order are:

Key Secondary:

1. Change from baseline to end point in SDS

Other Secondaries:

1. CGI-C rating at end point
2. PGI-C rating at end point
3. PGI-S rating at end point
4. Change from baseline to endpoint in clinician-rated SSI-4

For continuous variables the difference in means, the standard error and the 95% two-sided CI will be presented. An ANCOVA model will be used to evaluate the change from baseline, with treatment group and baseline included in the model. Multiple imputation will be used where appropriate for the data and clinical question of interest.

Methods for checking statistical model assumptions and alternative methods of analysis if the assumptions are not fulfilled will be described in the SAP.

Baseline will be the last measurement taken before randomization. For some patients randomization will be on Day 1, while for others this will be on Day 15 or Day 29. For the questionnaires this is likely to be those taken on the day of randomization (pre-randomization) while for safety assessments this is likely to be the measurements taken at screening visit.

9.4.3 General Considerations

9.4.3.1 Participant Accountability

The number of patients screened, receiving at least one dose of placebo in placebo run-in period, randomized, receiving at least one dose of study treatment, having been titrated to the maximum dose, being on randomized treatment for at least 6 weeks, discontinuing study treatment early (along with reasons for early discontinuation), withdrawing from study (along with reasons for withdrawal), and completing the study, and the numbers in each analysis set, will be summarized by treatment group.

9.4.3.2 Protocol Deviations

Patient data will be reviewed for major protocol deviations prior to main analysis database lock at a planned BDRM, and decisions will be documented within the meeting minutes. At this meeting, patients will be reviewed for their inclusion/exclusion from the analysis sets.

9.4.3.3 Demographic and Baseline Characteristics

Descriptive statistics of demographics (eg, age, race and ethnicity) will be presented by treatment group and across all patients. Medical history information will be listed. Other baseline characteristics will be defined in the SAP.

9.4.3.4 Compliance to Study Treatment

Compliance will be summarized by treatment group, based on the number of capsules dispensed and returned.

9.4.4 Efficacy

The primary analysis will examine the NOE-105 group against the placebo group.

9.4.4.1 Primary Estimand

The primary endpoint is the change from baseline to the end of 6 weeks of treatment (Relative Day 43) in the total MLGSSS score, where baseline is defined as the last assessment prior to randomisation (Relative Day 1). The score will be obtained by summing the numerical response to each question at each timepoint. The score and change from baseline (last measurement taken before randomization) in score will be summarized at each timepoint using the Full analysis set.

The main analysis will use an ANCOVA model, with treatment group and baseline score included in the model. and will estimate the change from baseline at the end of 6 weeks of treatment for each treatment group as well as the treatment difference.

The main analysis will address the intercurrent event attribute of the primary estimand, relating to events which will be analysed using the treatment policy strategy, by utilising copy reference multiple imputation to handle missing values.

Two sensitivity analyses will be employed to further assess the handling of missing values. These will include the use of an MMRM model and a jump to reference multiple imputation approach.

Further supplemental analyses may also be included to further support the conclusions of the primary estimand.

9.4.4.2 Supportive Primary Estimand

The supportive primary endpoint is the change from baseline to the end of treatment of up to 10 Weeks in the total MLGSSS score, where baseline is defined as the last assessment prior to randomisation (Relative Day 1). An ANCOVA model will also be used for this estimand with a missing at random multiple imputation apply to sporadically missing data.

9.4.4.3 Secondary Estimand(s)

The scores at baseline (the last measurement taken before randomization) and at end point will be summarized along with the change from baseline at end point for the SDS and the SSI-4. Analysis will be performed, in a similar manner to the primary estimand, where the difference in change from baseline in score between NOE-105 and placebo will also be estimated using an ANCOVA model including treatment and baseline score. Full detail will be provided within the SAP.

The CGI-C, PGI-C, and PGI-S will be summarized by frequency and analyzed using a Wilcoxon Rank Sum test and a win odds ratio will also be presented. The MSQ will be summarized by frequency and percentage of patients providing each response.**Safety**

AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class, preferred term, and treatment group for the number of AEs reported and the number and percentage of patients reporting each AE. A listing of AEs, including onset and resolution dates, severity, relationship to treatment, action taken, and outcome will be provided.

Physical examinations and the C-SSRS questionnaire will be listed.

Other safety endpoints will be summarized by treatment group, as absolute value and change from baseline at each visit; including hematology, biochemistry, urinalysis, ECG, vital signs, and QIDS-16, the details of which will be provided in the SAP.

9.5 Interim Analyses

No interim analysis will be carried out.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, Ethical, and Study Oversight Considerations

A 1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, IB and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study patients.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

A 1.1 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 1.2 Informed Consent/Assent Process

The investigator or his/her representative will explain the nature of the study to the patient or their legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent/assent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The patient record must include a statement that written informed consent/assent was obtained before the patient was enrolled in the study and the date the written consent/assent was obtained. The authorized person obtaining the informed consent/assent must also sign the ICF.

Patients must be re-consented/assented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or their legally authorized representative.

A patient who is rescreened is not required to sign another ICF if the rescreening occurs within 7 days from the previous ICF signature date.

A 1.2.1 Data Protection

Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient who will be required to give consent for their data to be used as described in the informed consent.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

A 1.3 Dissemination of Clinical Study Data

The results of the study will be reported within 1 year from the end of the clinical trial. Irrespective of the outcome, Noema Pharma will submit to the regulatory database a summary of the results of the clinical study within 1 year from the end of the clinical trial. This shall be accompanied by a summary written in a manner that is understandable to laypersons.

A 1.4 Data Quality Assurance

Patient data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). Data recorded electronically by the patient and/or their caregiver will be uploaded into CRF by the site staff at each visit.

The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for at least 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 1.5 Source Documents

The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the study center's patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site for 15 years.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

Study monitors will perform ongoing source data verification (SDV) to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

A 1.6 Study and Site Start and Closure

A 1.6.1 First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of patients.

The first act of recruitment is the first site open and will be the study start date.

A 1.6.2 Study/Site Termination

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further study treatment development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate or no patient recruitment (evaluated after a reasonable amount of time) of patients by the investigator
- Total number of patients included earlier than expected

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the patient and should assure appropriate participant therapy and/or follow-up.

A 1.7 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

B 1 Definition of AE

B 1.1 AE Definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

B 1.2 Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected treatment – treatment interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.
- “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

B 1.3 Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.

- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

B 2 Definition of SAE

An SAE is defined as any serious AE that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the patient has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of treatment dependency or treatment abuse.

B 3 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for a Noema study drug that either causes harm to the patient or has the potential to cause harm to the patient.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the participant received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error eg, medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated eg, tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed eg, kept in the fridge when it should be at room temperature
- Wrong patient received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to patient (excluding IIVRS/IWRS errors)

Examples of events that do not require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS – including those which lead to one of the above listed events that would otherwise have been a medication error
- Patient accidentally missed drug dose(s) eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if a Noema product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

B 4 Recording and Follow-Up of AE and/or SAE

B 4.1 AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the investigator to send photocopies of the patient's medical records to the Sponsor/CRO in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by Sponsor/CRO. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to Sponsor/CRO.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

B 4.2 Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities.

- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

B 4.3 Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. The AE must be characterized as related or unrelated:
  - "Related" conveys that there are facts, evidence, and/or arguments to suggest a causal relationship for the individual case.
  - "Unrelated" is used if there is not a reasonable possibility that the study treatment caused the AE.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the IB.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to the Sponsor/CRO. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor/CRO.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

B 4.4 Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor/CRO to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- If a patient dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor's representative with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.

The investigator will submit any updated SAE data to the Sponsor's representative within 24 hours of receipt of the information.

B 5 Reporting of SAEs

B 5.1 SAE Reporting to the Sponsor/CRO via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor/CRO will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical monitor by telephone.
- Contacts for SAE reporting can be found in the Investigator Study File.

B 5.2 SAE Reporting to Sponsor/CRO via Paper Data Collection Tool

- Facsimile transmission of the SAE paper data collection tool is the back-up method to transmit this information to the Sponsor/CRO.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in Investigator Study File.

Appendix C Contraceptive and Barrier Guidance

C 1 Contraception Guidance

Male patients with female partners of childbearing potential

Male patients with female partners of childbearing potential are eligible to participate if they agree to ONE of the following:

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 5 when having penile-vaginal intercourse with a woman of childbearing potential who is not currently pregnant

In addition, male patients must refrain from donating sperm for the duration of the study and for 90 days after study completion or the last dose of study treatment.

Male patients with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Table 5 Highly Effective Contraception Methods

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency
• Intrauterine device (IUD)
• Bilateral tubal occlusion
• Azoospermic partner (vasectomized or due to a medical cause) *Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.* Note: documentation of azoospermia for a male patient can come from the site personnel's review of the patient's medical records, medical examination, or medical history interview.
Highly Effective Methods[b] That Are User Dependent
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.* • Condom with spermicide *Male condom plus spermicide to be used from Day 1 until 90 days after the end of the study. Note: male condoms are not reliable as a sole contraception method.*

a) Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b) Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception for this study. Male condom and female condom should not be used together (due to risk of failure from friction).

C 2 Collection of Pregnancy Information:

Female partner of male patient:

The investigator will collect pregnancy information on any female partner of a male patient who becomes pregnant while participating in this study.

Information will be recorded on the pregnancy notification form and submitted to the sponsor within 24 hours of learning of a patient's partner's pregnancy. The information will include the anticipated date of birth or termination of the pregnancy at the time of the initial report.

The female partner of the male patient will be followed to determine the outcome of the pregnancy (after obtaining the necessary signed informed consent from the female partner). The investigator will collect follow-up information on the female partner of the male patient and the neonate and the information will be forwarded to the sponsor.

Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

While the investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.

Appendix D Handling of Human Biological Samples

D 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their life cycle.

The Investigator at each site keeps full traceability of collected biological samples from the patients while in storage at the site until shipment or disposal (where appropriate).

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

Noema will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

If required, Noema will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is sooner.

D 2 Withdrawal of Informed Consent/Assent for Donated Biological Samples

If a patient withdraws consent/assent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, Noema is not obliged to destroy the results of this research.

As collection of the biological sample(s) is an integral part of the study, then the patient is withdrawn from further study participation.

The Investigator:

- Ensures patient's withdrawal of informed consent/assent to the use of donated samples is notified immediately to Noema.
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of/destroyed, and the action documented.
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent/assent immediately and that samples are disposed of/destroyed, the action documented, and the signed document returned to the study site.
- Ensures that the patient and Noema are informed about the sample disposal.

Noema ensures the organization(s) holding the samples is/are informed about the withdrawn consent/assent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

D 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) (**https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx**) classifies infectious substances into 3 categories: Category A, Category B or Exempt

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals.

Category A Pathogens are, eg, Ebola, Lassa fever virus. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are, eg, Hepatitis A, C, D, and E viruses. They are assigned the following UN number and proper shipping name

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt – Substances which do not contain infectious substances or substances which are unlikely to cause disease in humans or animals are not subject to these Regulations unless they meet the criteria for inclusion in another class.

- Clinical study samples will fall into Category B or exempt under IATA regulations
- Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content.

Appendix E Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) during which patients may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following notification from the Sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

E 1 Reconsent/Reassent of Study Patients During Study Interruptions

During study interruptions, it may not be possible for the patients to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, remote visits. Reconsent/reassent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Sections E 2 to E 6. Local and regional regulations and/or guidelines regarding reconsent of study patients should be checked and followed. Reconsent/reassent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent/reassent the ICF should be signed at the patient's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent/reassent should be avoided.

E 2 Rescreening of Patients to Reconfirm Study Eligibility

Additional rescreening for screen failures due to study disruption can be performed in previously screened patients. The investigator should confirm this with the designated study physician.

In addition, during study disruption there may be a delay between confirming eligibility of a patient and either enrollment in the study or commencement of dosing with IP. If this delay is outside the screening window specified in Section 1.2, the patient will need to be rescreened to confirm eligibility before commencing study procedures. This will provide another opportunity to rescreen a participant in addition to that detailed in Section 5.4. The procedures detailed in Section 1.2 must be undertaken to confirm eligibility.

E 3 Home or Remote Visit to Replace On-site Visit (where applicable)

A qualified HCP from the study site or TPV service will visit the patient's home or other remote location as per local SOPs, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the clinical study

protocol.

E 4 Telemedicine Visit to Replace On-site Visit (where applicable)

In this appendix, the term telemedicine visit refers to remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the patients will allow AEs, concomitant medication, review compliance of at-home PRO assessments, and healthcare resource utilization to be reported and documented. Scheduled blood sample collection will be performed when the patient can attend a subsequent site visit.

E 5 At-home or Remote Location IP Administration Instructions

If a site visit is not possible, at-home or remote location administration of IP may be performed, within local regulation/guidance. The option of at-home or remote location IP administration ensures patient safety in cases of a pandemic where patients may be at increased risk by traveling to the site/clinic. This will also minimize interruption of IP administration during other study disruptions, eg, site closures due to natural disaster.

A qualified HCP from the study site or TPV service may administer the IP at the patient's home or other remote location according to the CSP, and if allowed by local SOPs, as applicable. All necessary supplies and instructions for administration and documentation of IP administration will be provided. Additional information related to the visit can be obtained via a telemedicine or home visit.

E 6 Data Capture During Telemedicine or Home / Remote Visits

Data collected during telemedicine visits will be collected from the patient by a HCP.

Appendix F Amendment History

Version 2.0 Amendment 2 US (01 September 2022)
This is a substantial amendment as it contains changes to the dose adjustment recommendations in the case of AEs and inclusion/exclusion criteria.

Overall Rationale for the Amendment:
The primary rationale for this amendment is to refine the dose adjustment recommendations in the case of AEs, the addition of an additional screening for drugs of abuse and to update the exclusion criteria to exclude the use of antipsychotic drugs.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Throughout	Correction of minor typographical errors.	Correction of previous minor errors.	Non-substantial
Protocol personnel details	The address and contact details for the principal investigator were removed.	These details were removed as not required and to protect personal information.	Non-substantial
Synopsis Intervention Groups and Duration	The term 'double blind' when describing escalation of placebo was removed.	This term was removed due to being an unnecessary term as it is previously stated that all dosing is blinded. .	Non-substantial
Section 1.2 Schedule of Activities	Time window for visits from Day 1 to Day 71 inclusive amended to + 3 days.	This was amended to ensure that patients are not scheduled for visits too early.	Substantial
	The duration of the screening period was amended to: - Week -4 to Week -1 for patients who are not receiving prior medications used to treat stuttering. - Week -4 to Week -2 for patients who are receiving prior medications used to treat stuttering.	This was amended to allow patients who are not receiving prior medications used to treat stuttering and who have successfully completed all screening procedures to be randomized sooner.	Substantial
	IP administration at Day 71 (EoT) was removed.	This was included previously in error	Substantial
	The note against IP administration stating 'If there is no clinic visit or if the clinic visit is scheduled for later in the day IP can be taken in the morning at home' was removed.	This text was removed as not required since instructions are provided in Section 6.2.	Non-substantial
Section 2.2.1.2 NOE-105 clinical studies	When describing safety data in patients with schizophrenia the following text was added 'As a daily dose of 4 mg risperidone is associated with a high incidence of dystonia, it is unclear whether these events were related to NOE-105 or the underlying risperidone.'	This text was added to provide context around the clinical data.	Non-substantial
Section 3 Objectives and endpoints	The objective 'To evaluate the effect of NOE-105 on change in mood as rated by the patient' was moved from the list of secondary	The assessment of the change in mood was added as a safety measure and had been previously added to the secondary endpoints section in error.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	endpoints to the list of safety endpoints.		
Section 4.3 Justification for dose	The reference to Section 6.6 for details of dose escalation was replaced by Section 6.1.1.	This change was made to correct a previous error.	Non-substantial
Section 5.1 Inclusion criteria	Inclusion criterion number 1 was amended to raise the upper range of the age of patients to 55 years.	The upper age limit was increased to be more reflective of the wider population.	Substantial
	Inclusion criterion number 4 was amended to read 'Patient reported global stuttering experience rated as "moderate" at screening and baseline'.	This was amended to clarify that this criterion is based upon the patient's own judgment.	Non-substantial
	Inclusion criterion number 5 was amended to read "Patients must discontinue all medications used to treat stuttering for at least 14 days prior to **receiving treatment**. **With the exception of antipsychotic therapies (see exclusion criterion number 13),** other psychotropic drugs will be allowed provided they have been stable for at least 14 days prior to receiving treatment and are expected to remain stable for the duration of the study". Bold indicates new text.	This was added to clarify that, whilst other psychotropic drugs are allowed, patients must not continue to use antipsychotic drugs for the duration of the study due to the potential of antipsychotic drugs to interfere with both tolerability and efficacy of NOE105. This is also in line with the newly added exclusion criterion number 20.	Substantial
	Inclusion criterion number 6 was amended to require a BMI of 19 to 35.	The BMI range was widened to be more reflective of the wider population whilst still excluding extreme values.	Substantial
Section 5.2 Exclusion criteria	Exclusion criterion number 13 (Use of antipsychotic drug therapy within 14 days weeks prior to receiving treatment until the EoT visit) was added.	The use of antipsychotic drug therapy has the potential to interfere with both the tolerability and efficacy of NOE-105 and should, therefore, be avoided.	Substantial
	Exclusion criterion 16 (formerly 15) has been amended as follows 'Positive urine drug screen for **cannabinoids,** cocaine, or nonprescribed opiates'. Bold indicates new text.	This addition was made to specify which drugs are excluded since patients who are on stable stimulants due to ADHD or patients on stable benzodiazepines should not be excluded.	Substantial
Section 5.3.1 Dietary Restriction	It was added that 'It is important to remind patients that any use of cannabis or cannabis products may have a direct impact on the study outcome including NOE 105 safety and efficacy'.	The use of cannabis or cannabis products should be avoided as this has the potential to interfere with the safety and efficacy of NOE105.	Substantial
Section 5.3.2 Caffeine, alcohol, and tobacco	It was added that 'There are no restrictions on consumption of caffeine or tobacco'.	This was added to provide clarity.	Non-substantial
Section 6.3 Measures to minimize bias:	This section was amended to state that details of the randomization	This was amended to correct an administrative error.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Randomization and blinding	process are provided in the Pharmacy Manual instead of the IVRS/IWRS user manual.		
Section 6.6 Dose modification	This section was updated to allow investigators the option to resume dosing at the previously well tolerated dose in the case of significant intolerance. Patients who resume dosing at the previously well tolerated dose should remain on that dose until the end of the study.	This was added to allow down-titration for any significant intolerance.	Substantial
Section 7.1 Discontinuation of study intervention	This section was updated to confirm that patients should attend an EoT visit add the full title of that visit.	This change of language was made to provided additional clarity.	Non-substantial
Section 8.1.1 Medical History and Physical Examinations	It was clarified that the cut-off for recording an abnormality as medical history in the eCRF is the signing of the ICF.	To provided further clarity on how to distinguish medical history from an adverse event	Non-substantial
Section 8.3.1 Clinical Safety Laboratory Assessments	Alcohol screening was removed.	Alcohol screening is not required in this study and was previously included in error.	Substantial
Appendix A.1.5 Source documents	Reference to the Study Reference Manual was removed.	This was amended to correct an administrative error.	Non-substantial
Appendix B.5.1 SAE reporting to the sponsor/CRO via an electronic data collection tool.	Reference to the Study Reference Manual was replaced with Investigator Study File.	This was amended to correct an administrative error.	Non-substantial
Appendix B.5.2 SAE reporting to the sponsor/CRO via paper data collection tool.	Reference to the Study Reference Manual was replaced with Investigator Study File.	This was amended to correct an administrative error.	Non-substantial

EoT, end of treatment; IP, investigational product.

Version 2.0 Amendment 1 US (13 May 2022)

This is a substantial amendment as it contains changes that introduce an additional secondary efficacy endpoint (QIDS-16) and will directly affect the study participants.

Overall Rationale for the Amendment:

The primary rationale for this amendment is the addition of an additional secondary endpoint to complement the MLGSSS primary endpoint.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Throughout	Minor typographical and editorial changes were made.	To correct previous typographical errors and to provide clarification.	Non-substantial
	The term “participant” (when used in the context of taking part in the study) was replaced with the term “patient”.	This was made to ensure consistency throughout the document.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	Abbreviated terms and definitions are newly included in the list of abbreviations	New abbreviations included, consistent with the amended text.	Non-substantial
	Cross references were denoted with blue text	This was added to adhere to the Sponsor's new protocol template.	Non-substantial
Synopsis	Changes were made to the synopsis in line with those made in the body of the protocol.	Changes were made to the synopsis to reflect the changes made to the body of the protocol to ensure consistency.	Substantial
Section 1.2 Schedule of Activities	Time windows were updated to read ± rather than +.	This was updated to correct typographical errors.	Non-substantial
	The MLGSSS assessment was added to the placebo run-in.	The addition of the Maguire-Leal-Garibaldi self-rated stuttering scale (MLGSSS) at the run-in visit was made to enable the assessment of placebo effect prior to randomization.	Substantial
	It was added that medical history will include stuttering and psychiatric conditions	This was updated to provide additional clarity.	Non-substantial
	It was updated to state that the end of treatment visit will be completed as soon as possible after the last dose of study medication rather than after completion of study medication	This was updated to provide additional clarity.	Non-substantial
	Assessments of serology clinical laboratory assessments were added to the screening visit in SoA.	Serology at screening added as previously omitted in error from the SoA.	Non-substantial
	Assessment of IP accountability was added at all clinic visits following randomization.	The assessment of drug accountability was added to ensure compliance is monitored.	Non-substantial
	It was added that vital signs, 12-lead ECG, clinical chemistry, hematology, urinalysis, and urine drug screen will be performed at Day 71/EoT.	These assessments had been previously omitted in error.	Substantial
	The note for administration of IP was updated to state that 'If there is no clinic visit or if the clinic visit is scheduled for later in the day IP can be taken in the morning at home'	This was added to provide clarity.	Non-substantial
	Adverse events and concomitant medications monitoring was added from screening.	This was to allow assessment of baseline characteristics.	Substantial
Section 1.2 Schedule of Activities Section 3 Objectives and Endpoints Section 8.2.3 Severity of Patient's Illness Section 9.4.4.2 Secondary Endpoint(s)	QIDS-16 assessment of mood was added.	To evaluate the effect of NOE-105 on change in mood as rated by the patient	Substantial
Section 1.2 Schedule of Activities	The term "neurological" was removed.	Neurological examinations were previously included in error and removed for consistency throughout the document.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 9.4.5 Safety			
Section 2.1 Study Rationale and Section 4.2 Scientific Rationale for Study Design	The term "serious motor, extrapyramidal, and metabolic antipsychotic side effects" was added.	This term was added to more clearly describe the common side effects of other treatments used for stuttering.	Non-substantial
Section 2.2 Background	Update of background with addition of a reference.	Updated to provide additional information	Non-substantial
Section 2.3.1 Risk Assessments	The term 'family' was replaced by 'household'.	This change was made in the event that patients do not live with family.	Non-substantial
	The number of patients with schizophrenia previously treated was updated from 26 to 59.	This change was made to correct a typographical error.	Non-substantial
Section 3 Objectives and Endpoints	Safety assessments were added.	Safety assessments had been omitted from this list previously in error.	Non-substantial
	"To evaluate the effect of NOE-105 on change in mood as rated by the patient using QIDS-16" was added	To evaluate the effect of NOE-105 on change in mood as rated by the patient	Substantial
Section 4.1 Overall Design	It was confirmed that patients will be randomized to NOE-105 or placebo 1:1.	Updated to provide additional clarity.	Non-substantial
	It was confurmed that the follow-up examination will be performed 28 (± 7) days after the last dose of study medication.	This was added to ensure consistency with the SoA.	Non-substantial
Section 4.2 Scientific Rationale for Study Design	The rationale for the endpoints, placebo control, 7-day run-in, variable randomization and parallel group design was added.	Details were added to provide additional rationale for the study design.	Non-substantial
	The dose previously administered to patients with schizophrenia was amended from 1 mg to 15 mg.	This change was made to correct a previous typographical error.	Non-substantial
Section 5.1 Inclusion criteria	Criterion 2 was updated to 'Patients who satisfy DSM-5 criteria for childhood onset fluency disorder and are suitable for pharmacotherapy' as opposed to 'requires pharmacotherapy'.	This change was made to provide a more relevant term for COFD.	Non-substantial
Section 5.3.2 Caffeine, Alcohol, and Tobacco	The time period to restrict consumption of alcohol was confirmed to be from screening until the end of treatment.	This change was made to provide clarity.	Non-substantial
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	It was clarified that 'patients who continue to meet all entry criteria will enter the treatment phase and will be randomized via an IVRS/IWRS to receive one of two treatments (NOE-105 or placebo) on Day 1, Day 15, or Day 29.'	This additional detail was added to provide clarity.	Non-substantial
	The term ~~'variable duration'~~ regarding the placebo run-in period was removed.	The placebo run-in is of fixed duration and orginal wording was included in error.	Substantial
Section 6.4 Study Intervention Compliance	It was added that drug accountability will be recorded in the eCRF.	This change was made to confirm the study procedures.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 6.5 Concomitant Therapy	It was added that the recording of concomitant therapy should commence from the start of screening rather than from the time of enrolment.	This change was made to provide additional clarity.	Non-substantial
Section 6.6 Dose Modification	The following was amended 'In case of **serious events** of ~~any~~ dystonia~~,~~ ~~including severe events~~ that necessitate pharmacological intervention' and 'In the event of dystonia that could threaten the airway the participant will discontinue participation in the study: **patient should complete EOT and FU visits per protocol'** (new text in bold)	This wording was amended to provide additional clarity.	Non-substantial
Section 6.7.1 Participant Level Stopping Criteria	The following was amended 'Discontinuation from study in case of severely abnormal clinical laboratory test abnormalities **in unscheduled assessments'** (new text in bold)	This wording was amended to provide additional clarity.	Non-substantial
Section 7.1 Discontinuation of Study Intervention	It has been added that discontinued patients may be replaced to ensure 54 evaluable patients.	This was added in case of unexpectedly high discontinuation rates.	Substantial
Section 8.1.1 Medical History and Physical Examinations	It was added that 'Relevant medical history should be obtained from the patient at screening, including stuttering and psychiatric conditions.'	This was added to provide clarity.	Non-substantial
Section 8.1.2 Vital signs	The assessment of weight and height (screening only) were added. Respiratory rate was removed.	Assessment of weight as part of the vital signs assessments was added to ensure patients are monitored for weight changes. Respiratory rate was removed as this is not required.	Substantial
Section 8.3.1 Clinical Laboratory Tests	It was confirmed that alcohol can be assessed using an alcohol breath test.	This change was made to document a change in process.	Non-substantial
	It was confirmed that clinically significant results obtained from non-protocol required laboratory assessments will be recorded in the patient's source notes.	This was added to provide clarity.	Non-substantial
	The recording of laboratory test results in the eCRF was removed.	Since the laboratory tests will be centrally assessed the results will be provided centrally.	Non-substantial
Section 8.5 Overdose	The reference to Overdose eCRF page was removed.	This was removed to correct a previous error as there is no specific overdose eCRF page.	Non-substantial
Section 9.2	The definition of an enrolled patient was updated.	This was updated to provide additional clarity.	Non-substantial
Section 9.4.2 Inferential Statistics Section 9.4.4.1 Primary Endpoint(s) Section 9.4.4.2 Secondary Endpoints	The definition of baseline was updated to the last measurement taken before randomization.	The definition was updated for clarification.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 9.4.4.1 Primary Endpoint(s)	The number of questions in the MLGSSS assessment was removed.	The number was removed since not all questions form part of the primary endpoint.	Non-substantial
Section 9.4.5 Safety	Urinalysis and ECG were added to list of assessments.	These were previously omitted in error.	Substantial
Appendix E4 Telemedicine visits to replace on-site visit (where applicable)	The term 'and skin biopsy' was removed.	This term was previously included in error.	Non-substantial

CGI-C, clinical global impression of change; COFD, childhood onset fluency disorder; C-SSRS, Columbia-suicide severity rating scale; ECG, electrocardiogram; eCRF, electronic case report form; IB, Investigator's Brochure; IDMB, independent data monitoring board; MLGSS, Maguire-Leal-Garibaldi Self-rated Stuttering Scale; MSQ, medication satisfaction questionnaire; PGI-C, patient global impression of change; PGI-S, patient global impression of severity; QIDS-16, quick inventory of depressive symptomology, SoA, schedule of activities.

Version 1.0 Amendment 1 Australia (05 May 2022)

This is a substantial amendment as it contains changes that will directly affect the study patients.

Overall Rationale for the Amendment:

The primary rationale for this amendment is provide additional safety measures to mitigate the risk of dystonia with NOE105.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Title Page	The title of the study was amended to change the treatment duration from "6 to 10 weeks" to "10 weeks".	The duration of treatment includes the entire double-blind period which is 10 weeks.	Substantial
Throughout	Minor typographical and editorial changes were made.	To correct previous typographical errors and to provide clarification.	Non-substantial
	The terms "subject" and "participant" (when used in the context of taking part in the study) were replaced with the term "patient".	This was made to ensure consistency throughout the document and to adhere to the Sponsor's SOPs.	Non-substantial
	Abbreviated terms and definitions are newly included in the list of abbreviations	New abbreviations included, consistent with the amended text.	Non-substantial
Synopsis	Changes were made to match those made in the body of the protocol.	Changes were made to ensure consistency.	Substantial
Section 1.2 Schedule of Activities	Details of whether visits will be conducted in clinic or remotely were added.	This addition was made to provide additional clarity regarding how assessments will be made.	Non-substantial
	It was updated to state that the end of treatment visit will be completed as soon	This was updated to provide additional clarity.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	as possible after the last dose of study medication rather than after completion of study medication.		
	Additional clinic visits were added at Days 8, 22, 36, 43, and 64, and remote visits at 50, and 57.	To mitigate the risk of intolerance, on site administration will take place for Dose 1, at each weekly dose increase, and at weekly intervals up to and including Week 8. In addition, MLGSSS will be conducted at weekly intervals throughout the study.	Substantial
	C-SSRS assessment has been added to every in-clinic visit and the baseline assessment will be made a Week -1.	In order to detect newly emerging suicidal ideation and behavior the C-SSRS will be assessed every week during study treatment.	Substantial
	SAS assessments have been added at D1, D50, and Day 71/EoT.	SAS has been added to investigate effects on motor function, coordination, and tremor.	Substantial
	SSI-4 assessment to be performed at Days 1 and 71 only.	The number of assessments was reduced to optimize the frequency of scales to provide relevant information and limit the burden to the investigator and study patients.	Substantial
	MLGSSS assessments to be performed every week during treatment.	The increase in the frequency of assessments will allow for assessment of post-randomization in patients who end treatment prematurely.	Substantial
	PGI-S to be performed every week during treatment.	The frequency of assessments was increased to allow for assessment of post-randomization in patients who end treatment prematurely.	Substantial
	PGI-C assessment to be performed at EoT/Day 71 and compared with the voice recording completed pre-dose on Day 1.	PGI-S is added as an appropriate tool to assess stuttering providing a good insight into the conditions and patients' perception of their condition.	Substantial
	CGI-C assessment to be performed on EoT/Day 71 only.	The clinical global assessment of change will use the investigator's notes for the baseline assessment and assess change over the duration of treatment.	Substantial
	SDS to be assessed on Days 1 and EoT/Day 71.	The number of assessments was reduced to optimize the	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
		frequency of scales to provide relevant information and limit the burden to the investigator and study patients.	
	Assessments of serology clinical laboratory assessments were added to the screening visit in SoA.	Serology at screening added as previously omitted in error from SoA.	Non-substantial
	The note for administration of IP was updated to state that 'If there is no clinic visit or if the clinic visit is scheduled for later in the day IP can be taken in the morning at home'.	This was added to provide clarity.	Non-substantial
	Assessment of IP accountability was added at all clinic visits following randomization.	The assessment of drug accountability was added to ensure compliance is monitored.	Non-substantial
Section 1.2 Schedule of Activities Section 4.1 Overall Design	It was added that eligibility assessment may include a video interview to confirm a minimal severity of moderate stuttering.	To ensure recruitment of patients with moderate stuttering, an independent confirmation will be made for the first patients.	Substantial
Section 1.2 Schedule of Activities Section 3 Objectives and Endpoints Section 8.2.3 Severity of Patient's Illness Section 9.4.4.2 Secondary Endpoint(s)	QIDS-16 assessment of mood was added.	This scale was added to capture psychological impacts of COFD.	Substantial
Section 1.2 Schedule of Activities Section 8.1.1 Medical history	Physical/neurological examinations have been split into separate assessments. Neurological examination at Screening, D50, Day 71/EoT, and at follow-up has been added. Addition of stuttering and psychiatric conditions as relevant conditions to be documented as Medical History.	In order to detect newly emerging neurological events, an additional neurological examination will be performed at Day 50.	Substantial
Section 2.1 Study Rationale	The term "language fluency" was replaced by "speech fluency".	This change was made to provide a more accurate description of the term.	Non-substantial
Section 2.1 Study Rationale and Section 4.2 Scientific Rationale for Study Design	The term serious motor, extrapyramidal, and metabolic antipsychotic side effects was added.	This term was added to more clearly describe the common side effects of other treatments used for stuttering.	Non-substantial
Section 2.2.1 NOE-105	The term "first line therapies" was replaced with currently used therapies".	There are no defined lines of treatment for COFD, so the original term was not accurate.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 2.2 Background	Update of background with addition of a reference and description of the males/females ratio in COFD.	Updated to provide additional information.	Non-substantial
Section 2.3 Risk Assessment	Details of additional mitigation measures in the event of dystonia were added.	Measures were added to provide further directions to investigators on how to mitigate the risk of dystonia.	Substantial
	Oral anti-cholinergic biperiden was added.	This was added to correct a previous omission.	Substantial
Section 3 Objectives and Endpoints	The secondary endpoints PGI-C was added.	PGI-C is added as an appropriate tool to assess overall wellbeing providing a good insight into the conditions and participant's perception of the change in their overall well-being.	Substantial
	Clarification of the CGI-C was made. The description of the SSI-4 was added as number of syllables stuttered and duration of hesitance.	Updates to secondary endpoints were made to provide additional clarity.	Non-substantial
	The ordering of secondary endpoints was updated.	The secondary endpoints were reordered according to importance.	Non-substantial
	Safety assessments were added.	Safety assessments had been omitted from this list previously in error.	Non-substantial
Section 4.1 Overall Design	The description of the run-in period and the treatment period were updated with clarification of when randomization will occur and that randomization will be 1:1.	The description of the run-in period and treatment period have been updated to provide additional clarity.	Non-substantial
	The maximum dose level for NOE-105 of 15 mg was added.	It was reiterated that patients will have their dose of NOE-105 increased until they reach a dose of 15 mg or their maximum tolerated dose.	Non-substantial
Section 4.2 Scientific Rationale for Study Design	The term "language fluency" was replaced by "speech fluency".	This change was made to provide a more accurate description of the term.	Non-substantial
	The rationale for the endpoints, placebo control, 7-day run-in, variable randomization and parallel group design was added.	Details were added to provide additional rationale for the study design.	Non-substantial
	The dose previously administered to patients with schizophrenia was amended from 1 mg to 15 mg.	This change was made to correct a previous typographical error.	Non-substantial
Section 5.1 Inclusion criteria	Criterion 2 was updated to 'Patients who satisfy DSM-5 criteria for childhood onset fluency disorder and are suitable for pharmacotherapy' as opposed to 'requires pharmacotherapy'.	This change was made to provide a more relevant term for COFD.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Criterion 10 "Fluency in the language of the investigator, study staff and the informed consent" was removed.	This criterion is no longer required since all patients and clinical staff are required to speak English which is included in Criterion 9.	Substantial
Section 5.3.2 Caffeine, Alcohol, and Tobacco	The time period to restrict consumption of alcohol was confirmed to be from screening until the end of treatment.	This change was made to provide clarity.	Non-substantial
Section 5.3.3 Activity	Watching television and reading were removed as examples of light recreational activities.	These examples were removed since they imply that all activities should be sedentary and light exercise is permitted.	Non-substantial
Section 6.1.1 Investigational Products	The unit dose strength of 7.5 mg NOE105 was added.	This was added to correct a previous omission.	Non-substantial
	It was updated that N0E-105 is supplied in blister wallets.	This update was made to reflect changes in the packaging.	Non-substantial
	Details of the NOE105 titration scheme were updated and moved to this section.	The titration scheme was amended to provide additional clarity.	Non-substantial
Section 6.2 Preparation/Handling/ Storage/Accountability	It was added that on site administration will take place for Dose 1, at each weekly dose increase, and at weekly intervals up to and including Week 8 and patients will be required to stay under supervision for 1 hour post dose.	Additional on-site administration of NOE105 was added to mitigate the risk of dystonia.	Substantial
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	The term "flexible" was removed when describing the duration of the run-in period and patients were denoted as entering the treatment phase.	The term flexible was removed as the run-in period is now a fixed duration of 7 days.	Non-substantial
	The person responsible for breaking the code was changed to "The pharmacovigilance function assigned by the Sponsor".	This change was made to reflect an administrative change in personnel.	Non-substantial
Section 6.4 Study Intervention Compliance	It was added that drug accountability will be recorded in the eCRF.	This change was made to confirm the study procedures.	Non-substantial
Section 6.5 Concomitant Therapy	It was added that the recording of concomitant therapy should commence from the start of screening rather than from the time of enrolment.	This change was made to provide additional clarity.	Non-substantial
Section 6.6 Dose Modification	Remote follow up of patients prior to dose escalation was removed as all dose increases will be performed at clinic visits.	To mitigate the risk of dystonia, each weekly dose increase will be performed at the clinical site.	Substantial
	Dose titration details were changed from tabular format to text format.	Dose titration details were moved to Section 6.1.1.	Non-substantial
	It was clarified that investigators will have the option to maintain patients at the same dose without further titration.	This was added to provide clarity.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	Specific details on how to modify the dose in case of dystonia were added.	Since dystonia has been noted as a risk with NOE105, specific instructions on how to dose modify in the case of dystonia are provided.	Substantial
Section 6.7 Stopping Criteria	This is a new section providing details of the IDMB. The IDMB will recommend termination of the study if the risk of treatment with NOE-105 exceeds the potential benefit of treatment. The IDMB will analyze the data before recommending if the study should continue or be stopped.	Details were added to provide greater clarity and to introduce the role of the IDMB.	Substantial
Section 6.7.1 Participant Level Stopping Criteria	This is a new section providing stopping criteria for an individual participant.	Details were added to provide clarity on criteria which would result in termination of a participant in the study.	Substantial
Section 6.7.2 Study Level Stopping Criteria	This is a new section providing stopping criteria for the entire study.	Details were added to provide clarity on criteria which would result in termination of the study.	Substantial
Section 7.1 Discontinuation of Study Intervention	It has been added that discontinued patients may be replaced to ensure 54 evaluable patients.	This was added in case of unexpectedly high discontinuation rates.	Substantial
Section 8.1.2 Vital signs	The assessment of weight and height (screening only) were added. Respiratory rate was removed.	Assessment of weight as part of the vital signs assessments was added to ensure patients are monitored for weight changes. Respiratory rate was removed as this is not required.	Substantial
Section 8.1.3 Electrocardiograms	It is confirmed that ECGs will be obtained after the patient has been resting in semi-supine position for at least 10 minutes. For each timepoint, 3 ECG recordings should be taken at about 5 minute intervals. All ECGs will be performed on equipment provided by the Sponsor (or designee) and reviewed by site personnel and a core/central laboratory.	Information was updated to provide additional clarity and to confirm a change in process that all ECGs will be reviewed and analyzed centrally.	Substantial
Section 8.2.1 Speech fluency	SSI-4 was added as an assessment.	This was added to correct a previous omission in this section.	Non-substantial
	The text “MLGSSS will be provided in the study manual” was removed.	The MLGSSS will be provided in electronic form to the study patients.	Non-substantial
Section 8.2.2 Overall functioning	The text “The SDS will be provided in the study manual” was removed.	Due to a change in procedure the SDS will no longer be provided in the study manual.	Non-substantial
Section 8.2.3 Severity of patient’s illness	The text “The PGI-S and CGI-C will be provided in the study manual” was	Due to a change in procedure the PCI-S, PGI-C and CGI-C no longer be provided in the	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	removed. PGI-C and QIDS-16 assessments were added.	study manual. PGI-C has previously been omitted in error.	
Section 8.2.4 Acceptability assessment	The text "The MSQ will be provided in the study manual" was removed.	Due to a change in procedure, the MSQ scales will no longer be provided in the study manual.	Non-substantial
Section 8.3.1 Clinical Safety Laboratory Assessments	It was confirmed that all samples will be analyzed at a central laboratory. Urine samples will be tested using dipsticks and only sent to the central laboratory in case of abnormal values.	This change was made to document a change in process.	Non-substantial
	It was confirmed that alcohol can be assessed using an alcohol breath test.	This change was made to document a change in process.	Non-substantial
	It was confirmed that clinically significant results obtained from non-protocol required laboratory assessments will be recorded in the patient's source notes.	This was added to provide clarity.	Non-substantial
Section 8.3.2 Other Safety Assessments	It was added that assessment of motor function, coordination, and tremor will performed using SAS.	The SAS was added to investigate effects on motor function, coordination, and tremor.	Substantial
Section 8.4.1 Adverse Events of Special Interest	This is a new section providing details on AESI for NOE-105.	This change was to provide the investigators with a summary of available data on dystonia, which is the AESI identified for NOE-105 in clinical trials, with reference to IB for further information.	Substantial
Section 8.5 Overdose	The reference to Overdose eCRF page was removed.	This was removed to correct a previous error as there is no specific overdose eCRF page.	Non-substantial
9.2 Sample size determination 9.3 Populations for Analysis	The definition patients enrolled was updated to state patients who sign the ICF.	The definition was updated for clarity.	Non-substantial
Section 9.4.4.1 Primary Endpoint(s)	The number of questions in the MLGSSS assessment was removed.	The number was removed since not all questions form part of the primary endpoint.	Non-substantial
Section 9.4.4.1 Primary Endpoint(s) Section 9.4.4.2 Secondary Endpoints	The definition of baseline was updated to the last measurement taken before first dose of study treatment following randomization.	The definition was updated for clarification.	Substantial
9.4.4.2 Secondary endpoint(s)	The endpoint CGI-C was added.	This endpoint had previously been omitted in error.	Substantial
	The secondary endpoint PGI-CQIDS-16 was added.	This scale was added to capture psychological impacts of COFD..	Substantial
Section 9.4.5 Safety	Urinalysis and ECG were added to list of assessments.	These were previously omitted in error.	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Appendix A.1.4 Data quality assurance	The reference to participant diaries and questionnaires has been replaced by electronic data capture.	The use of paper diaries and questionnaires has been replaced by electronic data capture methods.	Substantial
Appendix D.1 Chain of Custody	The paragraph "Samples retained for further use will be stored in ?????? biobanks and will be registered by the ????? during the entire life cycle" was removed.	This paragraph was removed to correct a previous error since there are no samples to be retained for further use in this study.	Non-substantial
Appendix E4 Telemedicine visits to replace on-site visit (where applicable)	The term 'and skin biopsy' was removed.	This term was previously included in error.	Non-substantial

CGI-C, clinical global impression of change; COFD, childhood onset fluency disorder; C-SSRS, Columbia-suicide severity rating scale; IB, Investigator's Brochure; IDMB, independent data monitoring board; MLGSS, Maguire- Leal-Garibaldi Self-rated Stuttering Scale; PGI-C, patient global impression of change; PGI-S, patient global impression of severity; QIDS-16, quick inventory of depressive symptomology, SAS, Simpson-Angus scale, SDS, Sheehan disability scale; SSI-4, Stuttering Severity Instrument – Fourth Edition.

Version 2 (03 March 2022)

This is a substantial amendment as it contains changes that will directly affect the study participants.

Overall Rationale for the Amendment:

The primary rationale for this amendment is provide additional safety measures to mitigate the risk of dystonia with NOE-105.

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Title Page	The title of the study was amended to change the treatment duration from "6 to 10 weeks" to "10 weeks".	The duration of treatment includes the entire double-blind period which is 10 weeks.	Substantial
Throughout	Minor typographical and editorial changes were made.	To correct previous typographical errors and to provide clarification.	Non-substantial
	The terms "subject" and "patient" (when used in the context of taking part in the study) were replaced with the term "participant".	This was made to ensure consistency throughout the document.	Non-substantial
	Abbreviated terms and definitions are newly included in the list of abbreviations	New abbreviations included, consistent with the amended text.	Non-substantial
Synopsis	Changes were made to match those made in the body of the protocol.	Changes were made to ensure consistency.	Substantial
Section 1.3 Schedule of Activities	Details of whether visits will be conducted in clinic or remotely were added.	This addition was made to provide additional clarity regarding how assessments will be made.	Non-substantial
	Additional visits were added at Days 8, 22, 36, 43, 50, 57, and 64.	To mitigate the risk of intolerence, on site administration will take place for Dose 1, at each weekly dose	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
		increase, and at weekly intervals up to and including Week 8. In addition, MLGSSS will be conducted at weekly intervals throughout the study.	
	C-SSRS assessment has been added to every in-clinic visit.	In order to detect newly emerging suicidal ideation and behavior the C-SSRS will be assessed every week during study treatment.	Substantial
	SSI-4 assessment to be performed at Days 1 and 71 only.	The number of assessments was reduced to optimize the frequency of scales to provide relevant information and limit the burden to the investigator and study participants.	Substantial
	MLGSSS assessments to be performed every week during treatment.	The increase in the frequency of assessments will allow for assessment of post-randomization in participants who end treatment prematurely.	Substantial
	PGI-S to be performed every week during treatment.	PGI-S is added as an appropriate tool to assess stuttering providing a good insight into the conditions and participants' perception of their condition.	Substantial
	PGI-C assessment to be performed on Day 71 and compared with the voice recording completed on Day 1.	The number of assessments was limited to last scheduled visit or upon treatment discontinuation.	Substantial
	CGI-C assessment to be performed on Day 71 only.	The clinical global assessment of change will use the investigator's notes for the baseline assessment and assess change over the duration of treatment.	Substantial
	SDS to be assessed on Days 1 and 71.	The number of assessments was reduced to optimize the frequency of scales to provide relevant information and limit the burden to the investigator and study participants.	Substantial
	AEs and concomitant medications to be assessed during the follow up period	This update was made to correct a previous error.	Substantial
Section 1.3 Schedule of Activities Section 4.1 Overall Design	It was added that eligibility assessment may include a video interview to confirm a minimal severity of moderate stuttering.	To ensure recruitment of participants with moderate stuttering, an independent confirmation will be made for the first participants.	
Section 2.1 Study Rationale	The term "language fluency" was replaced by "speech fluency".	This change was made to provide a more accurate description of the term.	Non-substantial
Section 2.2.1 NOE-105	The term "first line therapies" was replaced with currently used therapies".	There are no defined lines of treatment for COFD, so the original term was not accurate.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 2.3 Risk Assessment	Details of additional mitigation measures in the event of dystonia were added.	Measures were added to provide further directions to investigators on how to mitigate the risk of dystonia.	Substantial
	Oral anti-cholinergic biperiden was added.	This was added to correct a previous omission.	Substantial
Section 3 Objectives and Endpoints	The secondary endpoints PGI-C was added.	PGI-C is added as an appropriate tool to assess stuttering providing a good insight into the conditions and participant's perception of their condition.	Substantial
	Clarification of the CGI-C was made. The description of severity of stuttering as number of syllables stuttered and duration of hesitance.	Updates to secondary endpoints were made to provide additional clarity.	Substantial
	The ordering of secondary endpoints was updated.	The secondary endpoints were reordered according to importance.	Non-significant
Section 4.1 Overall Design	The description of the run-in period and the treatment period were updated.	The description of the run-in period and treatment period have been updated to provide additional clarity.	Non-substantial
	The maximum dose level for NOE-105 of 15 mg was added.	It was reiterated that participants will have their dose of NOE-105 increased until they reach a dose of 15 mg or their maximum tolerated dose.	Non-substantial
Section 4.2 Scientific Rationale for Study Design	The term "language fluency" was replaced by "speech fluency".	This change was made to provide a more accurate description of the term.	Non-substantial
Section 5.1 Inclusion criteria	Criterion 10 "Fluency in the language of the investigator, study staff and the informed consent" was removed.	This criterion is no longer required since all participants and clinical staff are required to speak English which is included in Criterion 9.	Substantial
Section 5.5.3 Activity	Watching television and reading were removed as examples of light recreational activities.	These examples were removed since they imply that all activities should be sedentary and light exercise is permitted.	Substantial
Section 6.1.1 Investigational Products	The unit dose strength of 7.5 mg NOE-105 was added.	This was added to correct a previous omission.	Non-substantial
	It was updated that both N0E-105 and placebo are supplied in blister wallets.	This update was made to reflect changes in the packaging.	Non-substantial
	Details of the NOE-105 titration scheme were updated and moved to this section.	The titration scheme was amended to provide additional clarity.	Non-substantial
Section 6.2 Preparation/Handling/ Storage/Accountability	It was added that on site administration will take place for Dose 1, at each weekly dose increase, and at weekly intervals up to and including Week 8 and participants will be required to stay under supervision for 3 hours post dose.	Additional on-site administration of NOE-105 was added to mitigate the risk of dystonia.	Substantial
Section 6.3 Measures to Minimize Bias: Randomization and Blinding	The term "flexible" was removed when describing the duration of the run-in period.	The term flexible was removed as the run-in period is now a fixed duration of 7 days.	Non-substantial
	The person responsible for breaking the code was changed to "The	This change was made to reflect an administrative change in personnel.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
	pharmacovigilance function assigned by the Sponsor".		
Section 6.6 Dose Modification	Remote follow up of participants prior to dose escalation was removed as all dose increases will be performed at clinic visits.	To mitigate the risk of dystonia, each weekly dose increase will be performed at the clinical site.	Substantial
	Dose titration details were removed from this section.	Dose titration details were moved to Section 6.1.1.	Non-substantial
	It was clarified that investigators will have the option to maintain participants at their previously tolerated dose without further titration.	This was added to provide clarity.	Substantial
	Specific details on how to modify the dose in case of dystonia were added.	Since dystonia has been noted as a risk with NOE-105, specific instructions on how to dose modify in the case of dystonia are provided.	Substantial
Section 6.7 Stopping Criteria	This is a new section providing details of the IDMB. The IDMB will recommend termination of the study if the risk of treatment with NOE-105 exceeds the potential benefit of treatment. The IDMB will analyze the data before recommending if the study should continue or be stopped.	Details were added to provide greater clarity and to confirm the role of the IDMB.	Substantial
Section 6.7.1 Participant Level Stopping Criteria	This is a new section providing stopping criteria for an individual participant.	Details were added to provide clarity on criteria which would result in termination of a participant in the study.	Substantial
Section 6.7.2 Study Level Stopping Criteria	This is a new section providing stopping criteria for the entire study.	Details were added to provide clarity on criteria which would result in termination of the study.	Substantial
Section 8.1.3 Electrocardiograms	It is confirmed that ECGs will be obtained after the participant has been resting semi-supine position for at least 10 minutes. For each timepoint, 3 ECG recordings should be taken at about 5 minute intervals. All ECGs will be performed on equipment provided by the Sponsor (or designee) and reviewed by site personnel and a core/central laboratory. In addition, all ECGs will be analyzed at the central laboratory.	Information was updated to provide additional clarity and to confirm a change in process that all ECGs will be reviewed and analyzed centrally.	Non-substantial
Section 8.2.1 Speech fluency	SSI-4 was added as an assessment.	This was added to correct a previous omission in this section.	Substantial
	The text "MLGSSS, the severity subset of the MLGSSS, and the SSI-4 will be provided in the study manual" was removed.	The MLGSSS and the severity subset of the MLGSSS will be provided in electronic form to the study participants, and the SSI-4 scales will be provided to the participant in a paper format and both will be filed in the trial master file.	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/Non-substantial
Section 8.2.2 Overall functioning	The text "The SDS will be provided in the study manual" was removed.	The SDS scale will be provided to the participant in an electronic format and will be filed in the trial master file.	Non-substantial
Section 8.2.3 Severity of participant's illness	The text "The PGI-S and CGI-C will be provided in the study manual" was removed.	The PCI-S, PGI-C and CGI-C will be provided to the participant in an electronic format and will be filed in the trial master file.	Non-substantial
Section 8.2.4 Acceptability assessment	The text "The MSQ will be provided in the study manual" was removed.	The MSQ scales will be provided to the participant in an electronic format and will be filed in the trial master file.	Non-substantial
Section 8.3.1 Clinical Safety Laboratory Assessments	It was confirmed that samples will be analyzed at a central laboratory. Urine samples will be tested using dipsticks and urine only sent to the central laboratory in case of abnormal values.	This change was made to document a change in process.	Non-substantial
Section 8.4.1 Adverse Events of Special Interest	This is a new section providing details on AESI for NOE-105.	This change was to provide the investigators with a summary of available data on dystonia, which is the AESI identified for NOE-105 in clinical trials, with reference to IB for further information.	Substantial
9.2 Sample size determination	The number of participants in the study has been updated.	The number of participants was updated to align with details in the table and to correct a previous error.	Non-substantial
9.4.4.2 Secondary endpoint(s)	The endpoint CGI-C was added.	This endpoint had previously been omitted in error.	Substantial
	The secondary endpoint PGI-C was added.	PGI-C is added as an appropriate tool to assess stuttering providing a good insight into the conditions and participant's perception of their condition.	Substantial
Appendix A.1.4 Data quality assurance	The reference to participant diaries and questionnaires has been replaced by electronic data capture.	The use of paper diaries and questionnaires has been replaced by electronic data capture methods.	Substantial
Appendix D.1 Chain of Custody	The paragraph "Samples retained for further use will be stored in ?????? biobanks and will be registered by the ????? during the entire life cycle" was removed.	This paragraph was removed to correct a previous error since there are no samples to be retained for further use in this study.	Non-substantial

CGI-C, clinical global impression of change; COFD, childhood onset fluency disorder; C-SSRS, Columbia-suicide severity rating scale; IB, Investigator's Brochure; IDMB, independent data monitoring board; MLGSS, Maguire- Leal-Garibaldi Self-rated Stuttering Scale; MSQ, medication satisfaction questionnaire; PGI-C, patient-reported clinical global impression of change; PGI-S, patient-reported clinical global impression of severity; SDS, Sheehan disability scale; SSI-4, Stuttering Severity Instrument – Fourth Edition.

ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ANCOVA	Analysis of covariance
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC_{inf}	Area under the curve to infinity
AUC_{tau}	Area under the curve over the dosing interval
BDRM	Blinded data review meeting
BL	Baseline
BMI	Body mass index
C	Clinic (visit)
cAMP	Cyclic adenosine monophosphate
CGI	Clinical Global Impression
CGI-C	Clinical Global Impression of Change
CONSORT	Consolidated standards of reporting trials
CPT	Continuous performance test
CRO	Contract research organization
CSR	Clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	Cytochrome P450
D1, D2	Dopamine 1, dopamine 2 receptor
DMTS	Delayed-match-to-sample
DS	Developmental stuttering
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EFD	Embryo fetal development
EoT	End of treatment
EPS	Extra pyramidal symptoms
FDA	Food and drug administration
GABA	γ-aminobutyric acid

Abbreviation	Definition
GCP	Good Clinical Practice
GGT	γ-glutamyl transferase
GI	Gastrointestinal
GLP	Good laboratory practice
HCP	Health care professional
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HV	Healthy volunteer
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMB	Independent data monitoring board
IEC	Independent Ethics Committee
INR	International normalized ratio
IP	Investigational Product
IQ	Intelligence quotient
IRB	Institutional Review Board
IVRS	Interactive voice response system
IWRS	Interactive web response system
MAD	Multiple Ascending Doses
MedDRA	Medical dictionary for regulatory activities
MLGSSS	Maguire-Leal-Garibaldi Self-rated Stuttering Scale
mRNA	Messenger ribonucleic acid
MSN	Medium spiny neuron
MSQ	Medication satisfaction questionnaire
MTD	Maximum tolerated dose
NMDA	N-methyl-D-aspartate
NOAEL	No observed adverse event level
NOEL	No observed event level
OD	Once daily
OGTT	Oral glucose tolerance test
PDE10A	Phosphodiesterase 10A
PET	Positron emission tomography
PGI-C	Patient global impression of change

Abbreviation	Definition
PGI-S	Patient global impression of severity
PI	Principal investigator
PK	Pharmacokinetic
PT	Prothrombin time
Q1, Q3	First quartile, third quartile
QIDS-16	Quick inventory of depressive symptomology
QIDS-C16	Quick inventory of depressive symptomology, clinician version
QIDS-SR16	Quick inventory of depressive symptomology, self-report version
R	Remote (visit)
RBC	Red blood cell
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
scPCP	Subchronic phencyclidine
SD	Standard deviation
SDS	Sheehan disability scale
SOP	Standard operating procedure
SOSS	Self-ordered spatial search
SSI-4	Stuttering Severity Instrument – Fourth Edition
SSS	Self-rated stuttering scale
SUSAR	Suspected unexpected serious adverse reaction
t½	Half-life
t_{max}	Time to maximum concentration
TPV	Third party vendor
ULNR	Upper limit of normal range
US	United States
W	Week
WBC	White blood cell
WOCBP	Women of childbearing potential

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