**Official Title:** A Phase II, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Safety, Efficacy, and Pharmacodynamics of 52 Weeks of Treatment With Basmisanil in Participants Aged 2 to 14 Years Old With DUP15Q Syndrome Followed by a 2-Year Optional Open-Label Extension

**NCT Number:** NCT05307679

**Document Date:** Protocol Version 3: 25-July-2023

**PROTOCOL**

| | |
|---|---|
| **TITLE:** | **A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO EVALUATE THE SAFETY, EFFICACY, AND PHARMACODYNAMICS OF 52 WEEKS OF TREATMENT WITH BASMISANIL IN** ***PARTICIPANTS AGED 2 TO 14 YEARS OLD*** **WITH DUP15Q SYNDROME** ***FOLLOWED BY A 2-YEAR OPTIONAL OPEN-LABEL EXTENSION*** |
| **PROTOCOL NUMBER:** | BP42992 |
| **VERSION:** | 3 |
| ***REGULATORY AGENCY IDENTIFIER NUMBERS:*** | **IND Number**: [redacted]<br>**EudraCT Number**: 2021-003791-13<br>***EU Trial Number:*** *2022-502165-20-00*<br>***Clinical Investigation Identification Number (CIV ID):*** *Not applicable* |
| **TEST PRODUCT:** | Basmisanil (RO5186582) |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |
| **DATE FINAL:** | Version 1: 29 July 2021 |
| **DATE AMENDED:** | Version 2: 25 January 2022<br>Version 3: See electronic signature and date stamp on the final page of this document |

## PROTOCOL ACCEPTANCE FORM

| | |
|---|---|
| **TITLE:** | **A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO EVALUATE THE SAFETY, EFFICACY, AND PHARMACODYNAMICS OF 52 WEEKS OF TREATMENT WITH BASMISANIL IN** *PARTICIPANTS AGED 2 TO 14 YEARS OLD* **WITH DUP15Q SYNDROME** *FOLLOWED BY A 2-YEAR OPTIONAL OPEN-LABEL EXTENSION* |
| **PROTOCOL NUMBER:** | BP42992 |
| **VERSION NUMBER:** | 3 |
| *REGULATORY AGENCY IDENTIFIER NUMBERS:* | **IND Number**: [redacted]<br>**EudraCT Number**: 2021-003791-13<br>***EU Trial Number:*** *2022-502165-20-00*<br>***Clinical Investigation Identification Number (CIV ID):*** *Not applicable* |
| **TEST PRODUCT:** | Basmisanil (RO5186582) |
| **SPONSOR:** | F. Hoffmann-La Roche Ltd |

**I agree to conduct the study in accordance with the current protocol.**

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please keep the signed original form in your study files, and return a copy to your local Site Monitor.

## PROTOCOL AMENDMENT, BP42992 VERSION 3
## RATIONALE

Trial readiness in the Dup15q syndrome patients and clinical communities is at an early stage. [redacted]. A shift in the clinical development plan for basmisanil in Dup15q syndrome, and consequently in the age range of the study population in BP42992, is required to generate data for the assessment of basmisanil across ages within a reasonable time frame.

The substantial changes described below thus aim to reduce patient and site burden, ease study execution and provide an opportunity for participants to receive active treatment in an open label extension (OLE). [redacted]

The following substantial changes have been implemented accordingly in Version 3:

1. **Addition of an optional open-label extension (OLE)** of 2 years (study Part 2). The OLE maximizes the long-term safety and tolerability data collected for basmisanil in this rare disorder by collecting data from all participants including those treated with placebo. As previously committed to by the Sponsor in the protocol (Section 6.7), the OLE provides an opportunity for participants who have completed the 52 weeks of blinded study treatment in Part 1 to receive active treatment with basmisanil with a direct prospect of benefit. This is considered a critical factor to raise interest in study participation in a placebo-controlled study and is anticipated to positively impact recruitment.

   **Changes related to the addition of the optional OLE have been implemented in the following sections:**

   Sections 1.2 Schematic of Study Design, 1.3 Schedule of activities (changes to Table 1 and Table 2; new Table 3 and Table 4), 2.1 Study Rationale, 2.3.2 Prospect of Direct Clinical Benefit for Pediatric Participants, 3 Objectives and Endpoints (new Table 6), 4.1 Overall Design, 4.1.1 Length of the Study, 4.2.2 Rationale for Study Duration, 4.3 Justification for Dose, 5 Study Population, 5.3 Lifestyle

Considerations, 6.1 Table 9 (new), Summary of Treatment Administered, 6.3.1 Method of Treatment Assignment, 6.5 Concomitant Therapy, 6.5.1 Permitted Therapy, 6.7 Treatment at the End of Part 1 of the Study, 8 Study Assessments and Procedures, 8.1.3.2 Devices, 8.1.4 Data Collection Methods for Clinical Outcome Assessments, [redacted] 8.10 Timing of Study Assessments, 8.10.4 Follow-Up Assessments, 9.4 Statistical Analyses of Part 2, and 9.5 Interim Analyses.

**2. Modification of upper age limit to 14 years, inclusive**

[redacted] of conducting a dedicated study in an adolescent population, the BP42992 study population has been extended to young adolescents aged 12 to 14 years, inclusive. Taking into account the significant delay in development associated with Dup15q syndrome, and the inclusion criterion of at least “moderate” disease severity as measured by CGI-S, inclusion of young adolescents aged 12 to 14 years is considered a reasonable extension of the pediatric study population. A positive impact to recruitment is anticipated to manifest rapidly, as the study will be open to a broader age range as of Stage 1 of the study, which is currently open to recruitment.

The integrity of the safety data, primary efficacy data (Vineland Adaptive Behavior Scales–Third Edition [Vineland-3, Adaptive Behavior Composite]) and quantitative EEG (qEEG) biomarker data is not impacted, and the statistical analysis plan remains unchanged. The expansion of the upper age limit was made taking into account the added baseline variability of neurodevelopmental outcomes in this age range (see Section 4.2.1 Rationale for Study Population) and the suitability of the different endpoints for individuals aged 12 to 14 years. The adequacy of the Mullen Scales of Early Learning (MSEL; secondary efficacy outcome measure) is not known in this older age group as few data are available. It is conceivable that a proportion of study participants, although at least moderately ill at screening (Dup15q syndrome Clinician Global Impression of Severity scale [CGI-S] inclusion criterion in Section 5.1), function at a developmental level exceeding those captured by the MSEL on one or more of the five domain scores (Section 3, Table 5 Objectives and Endpoints for Part 1). The data generated in BP42992 will support the characterization of the psychometric properties of the MSEL across ages and clinical severities for use in Dup15q syndrome clinical trials.

Additionally, the extension of the age range will provide open-label data for participants up to the age of 17 years (at the end of Part 2) and thus provide valuable bridging information to support future clinical development of basmisanil in adolescent and young adult populations.

**Changes related to the modification of the upper age range of the study population have been implemented in the following sections:**

Sections 2.1 Study Rationale, 2.2.2 Current Therapies and Unmet Medical Need, 2.3.1.3 Risk Evaluation of Measures Implemented in the Study, 3 Objectives and Endpoints, 4.1 Overall Design, 4.2.1 Rationale for Study Population, 4.3 Justification for Dose, 5 Study Population, 5.1 Inclusion Criteria, 6.1 (Table 8, Summary of Treatment Administered in Part 1), 6.3.1 Method of Treatment Assignment, and Section 1.3 of Appendix 1.

**3. Modification of staggered recruitment (see Section 4.1 including Figure 2)**

[redacted]

- The inclusion criteria for Stage 2 have been partially relaxed to allow inclusion of all participants meeting study eligibility criteria irrespective of their age or epilepsy diagnosis. Staggered recruitment thus occurs in two stages, instead of 3 previously.
- The interim analysis will be performed when approximately 24 participants recruited in Stages 1 and 2 reach 4 weeks of treatment, with a minimum of 9 participants aged 2-5 years.

The staggered approach by age and by presence or absence of epilepsy remains (see Section 4.1). The change, however, allows recruitment of both younger patients and patients without epilepsy simultaneously in Stage 2, rather than consecutively. There is no evidence for differences in epilepsy severity or presentation, nor a mechanistic rationale suggesting a different pro-epileptic risk with basmisanil treatment between age groups. The theoretical risk of worsening of seizures is related to the mechanism of action of basmisanil and should thus occur at a high frequency (Type A event). As such, the safety profile of basmisanil can be adequately assessed based on data from 9 participants aged 6 to 14 years presenting with epilepsy to safely ungate enrollment in Stage 2. Similarly, the interim analysis performed on approximately 24 participants recruited in Stages 1 and 2, with a minimum of 9 participants aged 2 to 5 years, will allow adequate evaluation of the overall safety profile of basmisanil in individuals representative of the study population. These changes therefore do not affect individual participants' safety and monitoring is in place at all times throughout the study.

The impact of the changes on staggered recruitment is anticipated to be significant. In fact, patients without epilepsy represent about 40% of the Dup15q population (see Section 2.2.1) and their inclusion opens earlier participation to a larger pool of patients. This is expected to accelerate decision-making in Study BP42992. A timely confirmation of age-dependent doses based on the safety and PK data by the Internal Monitoring Committee (IMC) + Scientific Oversight Committee (SOC) (see Section 4.1.2.2) is essential to maximize the number of participants who receive study treatment doses that reach the targeted exposures as early as possible in this

study: the target exposures are anticipated to offer the greatest likelihood of prospective benefit.

**Changes related to the study stages have been implemented in the following sections:**

Sections 1.2 Schematic of Study Design, 4.1 Overall Design, 4.1.2.2 Review Objectives and Procedures (IMC and SOC), 4.2.1 Rationale for Study Population, 4.2.3.1 Electroencephalography, 5.1 Inclusion Criteria, 6.1 (Table 8, Summary of Treatment Administered in Part 1), and 9.5 Interim Analyses.

**4. Alleviation of the study burden for participants and sites at the Day 1 visit:**

Taking into consideration the learnings gained from study execution and feedback from Investigators, the following changes have been implemented:

**EEG and PK assessments**

- The duration of the EEG recording on Day 1 has been reduced from 10 hours to 6.5 hours in total. The shorter recording duration decreases the number of pharmacodynamic (PD) timepoints collected (see Section 1.3) and will only marginally impede exploratory PK/PD analyses, without affecting study integrity, including the PD qEEG objectives of the planned interim analysis (see Section 4.1.2.2.). The change does not impact safety monitoring as the duration of the EEG recording required for safety review purposes is not reduced. Table 2 and Section 8.2.9 Seizures (EEG Monitoring) have been updated accordingly.
- To further reduce Day 1 visit burden, the timing of the last two PK samples has been amended to decrease the overall study visit duration by approximately 1 hour (see Table 2).

**Change in EEG safety review process**

- Section 8.2.9 Seizures (EEG Monitoring) and footnote "f" in Table 2 (Schedule of Activities for Part 1 – Detailed Table) have been amended to replace the requirement for a local review of the EEG by the site personnel with a central review process at the Day 1 visit. The sites will be provided with an EEG safety report based on review of the recording by a central reader (qualified neurologist independent of the site personnel). The report will be available to sites within 22 hours of receipt of the EEG recordings by the central reading vendor, and thus available before the end of the clinic visit the next day (Day 2 visit). [redacted] The central review process will additionally ensure consistency of the EEG safety review within a defined time-window. In addition, footnote “f” in Table 2 is applicable only at the Day 1 visit (addressed in Protocol Clarification Letter number 3 from 14 October 2022).

**Additional clarifications have been added to improve the clarity and consistency of the protocol and ease study execution:**

- To clarify genetic information required and genetic tests implemented in the study as per Protocol Clarification Letter number 2 from 14 October 2022

  Per protocol Section 8, “A previously established genetic diagnosis of Dup15q syndrome (medical history obtained before signing of the ICF) which contains the required information to determine eligibility may be utilized for screening.”

  Table 1 in Section 1.3, Section 8.2.1 Medical History and Demographic Data, and Section 8.6.1 Genetic and Genomic Analyses have been amended to specify that the genetic tests in the study are not mandatory and that Investigators decide on a case-by-case basis which genetic test(s) are required to be performed to obtain the full genetic information per study requirements.

- Section 1.3 Schedule of Activities
  - Table 1 has been amended to:
    - Add caregiver expectation guidance assessment at screening to ensure caregivers have the opportunity to discuss the requirements with the site personnel before the Baseline visit (footnote “u”). Section 8.1.2 Caregiver Expectations Guidance has been updated accordingly.
    - Add an Informed Consent Form (ICF) at the Day 365 visit for participants who continue study participation in Part 2 (footnote “t”).
  - Footnotes for SoA Table 1 have been updated as follows:
    - “a” has been amended to correct conflicting information in the protocol on the duration of the screening period, which lasts up to 5 weeks. Section 4.1.1 Length of the Study has been updated accordingly. This change has been addressed in Protocol Clarification Letter number 4 from 9 February 2023. It also indicated that all screening assessments required for eligibility must be completed with result available before the Baseline visit.
    - “g” has been updated to specify that the applicable age for the Tanner staging assessment is determined based on the participant’s age at the time of signing the ICF and to indicate that once Stage 5 on a scale is reached for a participant, the scale is not used anymore. Section 8.2.3 Tanner Staging has been updated accordingly.
    - “l” and Section 8.1.4.1 Clinician-Reported Outcome Assessments and Section 8.1.5.2 Vineland Adaptive Behavior Scales –Third Edition have been updated to specify that the Vineland-3 interview is performed by central raters independent of the site personnel and a time window of 5 days before the scheduled clinic visit has been specified for a remote assessment.
    - “o” has been amended to specify that the applicable age for the suicidality assessment is determined based on the participant’s age at

the time of signing the ICF. Section 8.2.8 Clinical Assessment of Suicidality has been updated accordingly.

- "p" and Section 8.1.5.12 (Wearable Device) have been updated to provide updated information on the technical and scheduling requirements for the wearable device in the study.
- "s" has been added to provide clarity that the caregiver exit interview should be performed within 4 weeks after the Day 365 visit and that the independent interviewers unrelated to the site personnel should perform this. Section 8.1.5.14 (Caregiver Exit Interview) has been updated accordingly. The optional caregiver exit interview has also been listed as an exploratory endpoint in Table 5 Objectives and Endpoints in Part 1.

- Table 2 has been amended to provide more clarity on the timing of assessments at the visits with EEG/qEEG, PK, and safety assessments.
- Footnotes for SoA Table 2 have been updated as follows:
  - "a" has been updated to provide information that the assessments should start in the morning, consistently across all study visits (addressed in Protocol Clarification Letter number 4 from 9 February 2023).
  - "g" and "h" have been removed and replaced as per below:
    - "g" and Section 6.4 Treatment Compliance have been amended to clarify that all doses administrated at site should be supervised and given within 30 minutes after the start of the meal.
    - "h" has been added to inform that the assigned assessments at the Day 365 visit will be performed only for participants who do not continue study participation in the optional OLE.
  - "i" to "m" have been added to provide instructions on the order of the assessments and blood draws.

- Section 3 Objectives and Endpoints, Table 5, Exploratory Objectives has been amended to list the optional Caregiver Exit Interview as per Table 1 Schedule of Activities for Part 1 and Section 8.1.5.14.
- Section 4.1.2.1 Administrative Structure paragraph "Scientific Oversight Committee (SOC)" has been amended to clarify the periods of SOC involvement in the study.
- Section 5.2, Exclusion Criterion 1 has been amended to clarify that the restrictions related to the use of rescue medication are limited to treatment of one seizure episode or seizure cluster per month on average in the past 6 months and that the concomitant use of more than 4 anti-epileptic medications is exclusionary in case of chronic use.

- Section 5.3 has been amended to clarify that a ketogenic diet needs to be on a stable regimen for 6 weeks prior to screening as initially stated in Section 6.5. As ketogenic diet is not a concomitant medication.
- Section 6 Treatments has been updated and a new Appendix 6 Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) Designations has been added to implement the requirements of the EU Clinical Trials Regulation (CTR) on the designations of the IMPs and auxiliary medicinal products (AxMPs)/NIMPs.
- Section 6.2 Preparation/Handling/Storage/Accountability has been updated to add that only unused stick-packs need to be returned by the caregiver at clinic visit or IMP shipment. The empty stick-packs will not be returned. This is to limit caregiver and site burden.
- Section 6.5.3 Therapy to be Used with Caution has been amended to allow for reschedule of a study visit with a 2-day window (even if it falls out of the protocol-defined visit window) in case an emergency occurs requiring treatment with benzodiazepines/benzodiazepine-related drugs.
- Section 8.1.4.2 Caregiver-Reported Assessments has been updated to provide more information about caregiver-reported data and requirements for reporting remotely.
- Section 8.1.5.3 Mullen Scales of Early Learning has been amended to further describe the MSEL.
- Section 8.1.5.10 Children's Sleep Habit Questionnaire (CSHQ) has been amended to further describe the CSHQ.
- Section 8.2.4 Seizure Status and Appendix 7 (new) have been updated with a list of seizure types to facilitate seizure diary entries.
- Section 8.3.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as Adverse Events or Serious adverse events has been amended to clarify when seizure activity should be reported as an AE/SAE.
- [redacted]
- Section 8.10 Timing of Study Assessments has been amended to provide further guidance on the order of assessments and to clarify that efficacy assessments related to primary and secondary objectives should be prioritized over exploratory assessments.
- Section 9.3.2 Efficacy Analyses has been updated to include the formal statistical hypotheses testing for Part 1 of the study as per FDA request.
- Appendix 1 Regulatory, Ethical, and Study Oversight Considerations has been updated to align with Clinical Trials Regulation (CTR) requirements.
- Section 5.2 Special Situations of Appendix 2 has been updated to clarify that special situations, regardless of whether they result in an AE, should be reported on the Special Situations eCRF.

Additional minor changes have been made to improve clarity and consistency. Substantial new information appears in *Book Antiqua* italics. This amendment represents cumulative changes to the original protocol.

## TABLE OF CONTENTS

## LIST OF TABLES

## LIST OF FIGURES



## LIST OF APPENDICES

## LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| **ABC-2-C** | Aberrant Behavior Checklist - Second Edition – Community Version |
| **ADOS-2** | Autism Diagnostic Observational Schedule, second edition |
| **AE** | adverse event |
| *AESI* | *adverse event of special interest* |
| **ASD** | autism spectrum disorder |
| **$AUC_{0-inf}$** | area under the concentration–time curve from time 0 to infinity |
| **$AUC_{0-12h}$** | area under the concentration-time curve from time 0 to 12 hours |
| **$AUC_{tau,ss}$** | area under the concentration–time curve during one dosing interval at steady state |
| **BID** | twice a day |
| **CA** | competent authority |
| **CBD** | cannabidiol |
| **C-CASA** | Columbia Classification Algorithm for Suicide |
| *CFB* | *change from baseline* |
| **CIAS** | cognitive impairment associated with schizophrenia |
| **ClinRO** | clinician-reported outcome |
| *CMA* | *chromosomal microarray* |
| **$C_{max}$** | maximum concentration |
| **$C_{max,ss}$** | maximum concentration at steady state |
| **COA** | clinical outcome assessment |
| **CRF** | case report form |
| **CSHQ** | Children's Sleep Habit Questionnaire |
| **CSR** | clinical study report |
| **CTCAE** | common terminology criteria for adverse events |
| **$C_{trough,ss}$** | trough plasma concentration at steady state |
| **DDI** | drug-drug interaction |
| *DOAC* | *direct-acting oral anticoagulant* |
| **Dup15q CaGI-C** | Dup15q syndrome Caregiver Global Impression *of* Change scale |
| **Dup15q CaGI-S** | Dup15q syndrome Caregiver Global Impression *of* Severity scale |
| **Dup15q CGI-C** | Dup15q syndrome *Clinician* Global Impression *of* Change scale |
| **Dup15q CGI-S** | Dup15q syndrome *Clinician* Global Impression *of* Severity scale |
| **EC** | Ethics Committee |
| **eCOA** | electronic clinical outcome assessment |
| **eCRF** | electronic case report form |
| **EDC** | electronic data capture |
| **EEA** | European Economic Area |
| **eGFR** | estimated glomerular filtration rate |
| **FDA** | Food and Drug Administration |
| *FISH* | *fluorescence in situ hybridization* |

| | |
|---|---|
| **GABA** | gamma-aminobutyric acid |
| **$GABA_A$** | GABA A receptor |
| **$GABA_AR$** | $GABA_A$ receptor protein |
| **$GABA_A$ α5R** | α5 subunit-containing GABA A receptor subtype |
| ***GABR*** | $GABA_A$ receptor subunit genes |
| **GCP** | Good Clinical Practice |
| **HIPAA** | Health Insurance Portability and Accountability Act |
| **ICF** | Informed Consent Form |
| **ICH** | International Council *for* Harmonisation |
| **idic(15)** | isodicentric 15 |
| **IEC** | Independent Ethics Committee |
| **IMC** | Internal Monitoring Committee |
| **IMP** | investigational medicinal product |
| **IND** | Investigational New Drug (application) |
| **int(15)** | interstitial 15 |
| **IQ** | intellectual quotient |
| **IRB** | Institutional Review Board |
| **ITT** | intent-to-treat |
| **IxRS** | interactive (voice/web) response system |
| **LPLO** | last participant, last observation |
| *MMRM* | *mixed effects model for repeated measures* |
| **MN** | mobile nurse |
| **MSEL** | Mullen Scales of Early Learning |
| *MS-MLPA* | *methylation specific-multiplex ligation-dependent probe amplification* |
| **NAM** | negative allosteric modulator |
| **NCI** | National Cancer Institute |
| **NDD** | neurodevelopmental disorder |
| *OLE* | *open-label extension* |
| **ORCA** | Observer-Reported Communication Ability |
| **OTC** | over-the-counter |
| **PBPK** | physiologically-based pharmacokinetic |
| **PD** | pharmacodynamic |
| **PedsQL-FIM** | Pediatric Quality of Life Inventory™ Family Impact Module |
| **PET** | positron emission tomography |
| **P-gp** | p-glycoprotein |
| **PI** | prediction interval |
| **PK** | pharmacokinetic |
| **PR** | PR interval |
| **PRO** | patient-reported outcome (also refers to participants) |
| **PTZ** | pentylenetetrazole |
| **qEEG** | quantitative EEG |
| **QRS** | QRS complex |

| | |
|---|---|
| **QT** | QT interval |
| **QTc** | QT corrected for heart rate |
| **QTcB** | QT corrected for heart rate using Bazett's formula |
| **QTcF** | QT corrected for heart rate using the Fridericia's correction factor |
| **RBR** | Research Biosample Repository |
| **RBS-R** | Repetitive Behavior Scale–Revised |
| **RO** | receptor occupancy |
| **SAE** | serious adverse event |
| **SMT** | Study Management Team |
| **SoA** | schedule of activities |
| **SOC** | Scientific Oversight Committee |
| **TID** | three times a day |
| **ULN** | upper limit of normal |
| **Vineland-3** | Vineland Adaptive Behavior Scales–Third Edition |
| **WES** | whole exome sequencing |
| **WGS** | whole genome sequencing |

# 1. PROTOCOL SUMMARY

## 1.1 SYNOPSIS

| | |
|---|---|
| **PROTOCOL TITLE:** | **A PHASE II, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL GROUP STUDY TO EVALUATE THE SAFETY, EFFICACY, AND PHARMACODYNAMICS OF 52 WEEKS OF TREATMENT WITH BASMISANIL IN *PARTICIPANTS AGED 2 TO 14 YEARS OLD* WITH DUP15Q SYNDROME *FOLLOWED BY A 2-YEAR OPTIONAL OPEN-LABEL EXTENSION*** |
| **PROTOCOL NUMBER:** | BP42992 |
| **VERSION:** | 3 |
| ***REGULATORY AGENCY IDENTIFIER NUMBERS:*** | ***IND Number:*** [redacted]<br>***EudraCT Number:*** *2021-003791-13*<br>***EU Trial Number:*** *2022-502165-20-00*<br>***Clinical Investigation Identification Number (CIV ID):*** *Not applicable* |
| **TEST PRODUCT:** | Basmisanil (RO5186582) |
| **PHASE:** | II |

**RATIONALE**

This *study consists of two parts. Part 1 is a* multi-center, randomized, double-blind, placebo-controlled, parallel group study *to* evaluate the safety, efficacy, and pharmacodynamics of 52 weeks of basmisanil treatment in children *and adolescents* with Dup15q syndrome aged 2 to *14* years. *Part 1 of* the study will test the hypothesis that negative allosteric modulation of the α5 subunit-containing $GABA_A$ receptor subtype ($GABA_A$ α5R) can address excessive $GABA_A$ receptor function driven by the additional *GABR* copy numbers, *as indexed by EEG,* and positively impact core neurodevelopmental disease features in *individuals* with Dup15q syndrome. *Part 2 of the study is an optional 2-year open-label extension (OLE) to evaluate long-term safety and tolerability and provide supportive evidence of continued treatment benefit in selected efficacy outcomes. The OLE presents an opportunity for all enrolled participants who have completed 52 weeks of treatment in the placebo-controlled part of the study (Part 1) to receive active treatment.*

**OBJECTIVES AND ENDPOINTS**

***Objectives and Endpoints for Part 1:***

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To evaluate the effects of *52 weeks of treatment with* basmisanil on core symptom domains of Dup15q syndrome (language and social skills) and daily functioning | • Vineland-3: Adaptive Behavior Composite |

| Objectives | Endpoints |
|---|---|
| **Secondary** | |
| **Efficacy** | |
| • To evaluate the effects of *52 weeks of treatment with* basmisanil on: | |
| ○ Motor function | • Vineland-3 gross and fine motor subdomains<br>• MSEL gross and fine motor domains |
| ○ Cognition | • MSEL visual reception domain |
| ○ Language | • Vineland-3 expressive and receptive *communication* subdomains<br>• MSEL expressive and receptive language subdomains |
| ○ Social skills | • Vineland-3 play and leisure time and interpersonal relationships subdomains |
| ○ *Clinician* global impression of *severity and change* | • Dup15q CGI-S and Dup15q CGI-C |
| ○ Challenging behaviors | • ABC-2-C domain scores |
| **Safety** | |
| • To evaluate the tolerability and safety of 52 weeks *of* treatment *with* basmisanil | • Incidence, nature, and severity of AEs and SAEs<br>• Incidence of treatment discontinuations due to AEs<br>• Incidence of laboratory abnormalities based on hematology, clinical chemistry, and urinalysis test results<br>• ECG changes from baseline; incidence of abnormal ECG assessments<br>• Change from baseline in all seizure frequency, duration, and type of seizure as reported in a seizure diary by caregivers<br>• Abnormal changes in EEG recordings compared to baseline with a focus on treatment-emergent epileptiform abnormalities<br>• Systolic and diastolic blood pressure and heart rate measurements<br>• Suicidality as assessed through questions from selected items adapted from the C-CASA in *participants* aged 6 years *and above*<br>• Height, weight, head circumference<br>• Tanner staging over time (in *participants* aged 9 years *and above*) |

| Objectives | Endpoints |
|---|---|
| **PK** | |
| • To characterize the PK of basmisanil and its metabolite M1 [redacted] | • Plasma concentration of basmisanil and its major metabolite M1 at specified timepoints.<br>• PK parameters for basmisanil: $AUC_{tau,ss}$, $C_{max,ss}$, $C_{trough,ss}$, CL/F, Vd/F<br>• Plasma concentration ratio of M1 to basmisanil at trough<br>• PK parameters for M1: $C_{max,ss}$, $C_{trough,ss}$<br>• Other PK parameters as appropriate |
| • To evaluate potential relationships between selected covariates and exposure to basmisanil | |
| **PD** | |
| • To evaluate the effects of basmisanil treatment on the characteristic Dup15q EEG phenotype acutely and at steady state | • qEEG beta-band power |
| *Exploratory* | |
| *Efficacy* | |
| • *To evaluate the effect of 52 weeks of treatment with basmisanil on:* | |
| ○ *Restrictive and repetitive behaviors* | • *RBS-R total score* |
| ○ *Health-related quality of life of the caregiver* | • *PedsQL-FIM* |
| ○ *Communication* | • *ORCA* |
| ○ *Caregiver global impression of severity and change* | • *Dup15q CaGI-S and Dup15q CaGI-C* |
| ○ *Autism symptoms* | • *ADOS-2* |
| ○ *Hypotonia* | • *Clinician rating of hypotonia* |
| ○ *Sleep* | • *CSHQ* |
| ○ *Gait (ambulant participants only)* | • *Stride length, stride speed and walking perimeter measured with wearable device*<br>• *Minimum and median distance measured with wearable device*<br>• *% of time of foot on the floor* |
| ○ *Qualitative changes in Dup15q symptoms or developmental skills* | • *Semi-structured, 1-hour (phone call) interview with caregivers of study participants* |

| Objectives | Endpoints |
|---|---|
| ***PK relationship to efficacy, safety, and PD*** | |
| • *To evaluate potential relationships between drug exposure and the efficacy, safety and PD of basmisanil* | • *Relationship between plasma concentration or PK parameters for basmisanil or M1 (if appropriate) and efficacy, safety, and PD endpoints* |
| ***PD*** | |
| • *To evaluate maintenance of EEG PD effect over the treatment period* | • *qEEG beta-band power* |

ABC-2-C = Aberrant Behavior Checklist - Second Edition – Community Version; *ADOS-2 = Autism Diagnostic Observational Schedule, second edition;* AE = adverse event; $AUC_{tau,ss}$ = area under the concentration–time curve during one dosing interval at steady state; C-CASA = Columbia Classification Algorithm for Suicide; CL/F = apparent clearance; $C_{max,ss}$ = maximum concentration at steady state; *CSHQ = Children's Sleep Habit Questionnaire;* $C_{trough,ss}$ = trough plasma concentration at steady state; *Dup15q CaGI-C = Dup15q syndrome Caregiver Global Impression of Change scale; Dup15q CaGI-S = Dup15q syndrome Caregiver Global Impression of Severity scale;* Dup15q CGI-C = Dup15q syndrome *Clinician* Global Impression *of* Change scale; Dup15q CGI-S = Dup15q syndrome *Clinician* Global Impression *of* Severity scale; *ECG = electrocardiogram; EEG = electroencephalogram;* MSEL = Mullen Scales of Early Learning; *ORCA = Observer-Reported Communication Ability;* PD = pharmacodynamics; *PedsQL-FIM = Pediatric Quality of Life Inventory™ Family Impact Module;* PK = pharmacokinetics; qEEG = quantitative EEG; *RBS-R = Repetitive Behavior Scale–Revised;* SAE = serious adverse event; Vd/F = apparent volume of distribution; Vineland-3 = Vineland Adaptive Behavior Scales–Third Edition.

***Objectives and Endpoints for Part 2:***

| *Objectives* | *Endpoints* |
|---|---|
| ***Exploratory*** | |
| ***Safety*** | |
| • *To evaluate the tolerability and safety of up to 3 years of treatment with basmisanil* | • *Incidence, nature, and severity of AEs and SAEs*<br>• *Incidence of treatment discontinuations due to AEs*<br>• *Incidence of laboratory abnormalities based on hematology, clinical chemistry, and urinalysis test results*<br>• *ECG changes from baseline; incidence of abnormal ECG assessments*<br>• *Change from baseline in all seizure frequency, duration, and type as reported in a seizure diary by caregivers*<br>• *Abnormal changes in EEG recordings compared to baseline with a focus on treatment emergent epileptiform abnormalities*<br>• *Systolic and diastolic blood pressure and heart rate measurements* |

| Objectives | Endpoints |
|---|---|
| | • *Suicidality as assessed through questions from selected items adapted from the C-CASA in participants aged 6 years and above*<br>• *Height, weight, head circumference*<br>• *Tanner staging over time (in participants aged 9 years and above)* |
| ***Efficacy*** | |
| • *To evaluate the effects of up to 3 years of treatment with basmisanil on core symptom domains of Dup15q syndrome (language and social skills) and daily functioning* | • *Vineland-3: Adaptive Behavior Composite* |
| • *To evaluate the effects of up to 3 years of treatment with basmisanil on* | |
| o *Motor function* | • *Vineland-3: gross and fine motor subdomains*<br>• *MSEL: gross and fine motor domains* |
| o *Cognition* | • *MSEL visual reception domain* |
| o *Language* | • *Vineland-3 expressive and receptive communication subdomains*<br>• *MSEL expressive and receptive language sub-domains* |
| o *Social skills* | • *Vineland-3 play and leisure time and interpersonal relationships subdomains* |
| o *Clinician global impression of severity and change* | • *Dup15q CGI-S and Dup15q CGI-C* |
| o *Challenging behaviors* | • *ABC-2-C domain scores* |
| o *Health-related quality of life of the caregiver* | • *PedsQL-FIM* |
| o *Caregiver global impression of severity and change* | • *Dup15q CaGI-S and Dup15q CaGI-C* |
| ***PK*** | |
| • *To characterize the PK of basmisanil and its metabolite M1* [redacted] | • *Concentration per timepoint for basmisanil and M1* |
| • *To evaluate potential relationships between selected covariates and exposure to basmisanil, if appropriate* | • *PK parameters as appropriate* |

| Objectives | Endpoints |
|---|---|
| *PD* | |
| • *To evaluate maintenance of EEG PD effect over the treatment period* | • *qEEG beta-band power* |
| ***PK relationship to efficacy, safety, and PD*** | |
| • *To evaluate potential relationships between drug exposure and the efficacy, safety and PD of basmisanil* | • *Relationship between plasma concentration or PK parameters for basmisanil or M1 (if appropriate) and efficacy, safety, and PD endpoints* |

*ABC-2-C = Aberrant Behavior Checklist - Second Edition – Community Version; AE = adverse event; C-CASA = Columbia Classification Algorithm for Suicide Assessment; Dup15q CaGI-C = Dup15q syndrome Caregiver Global Impression of Change scale; Dup15q CaGI-S = Dup15q syndrome Caregiver Global Impression of Severity scale; Dup15q CGI-C = Dup15q syndrome Clinician Global Impression of Change scale; Dup15q CGI-S = Dup15q syndrome Clinician Global Impression of Severity scale; ECG = electrocardiogram; EEG = electroencephalogram; MSEL = Mullen Scales of Early Learning; PD = pharmacodynamics; PedsQL-FIM = Pediatric Quality of Life Inventory™ Family Impact Module; PK = pharmacokinetics; qEEG = quantitative EEG; SAE = serious adverse event; Vineland-3 = Vineland Adaptive Behavior Scales–Third Edition.*

## OVERALL DESIGN

### STUDY DESIGN

This *study is composed of two parts. Part 1* is a multi-center, randomized, double-blind, placebo-controlled parallel group study to evaluate *the* safety, efficacy, and pharmacodynamics of 52 weeks of basmisanil treatment in children *and young adolescents* aged 2 to *14* years with Dup15q syndrome. *Part 2 is a 2-year optional OLE on basmisanil.*

*In Part 1,* approximately 90 participants will be randomized 2:1 to receive oral treatment with either basmisanil or placebo for 52 weeks (twice a day [BID] on the first day of treatment in the clinic (Day 1) and three times a day [TID] for the remaining study duration.

Randomization will be stratified by age *group* (2 to 5 years vs. 6 to *14* years), number of copies of the 15q11.2-q13.1 region (3 copies vs. 4 copies), and epilepsy (presence vs. absence).

*All participants who have completed 52 weeks of treatment in Part 1 will be offered the option to roll over directly to the OLE (Part 2) without completing the follow-up visit in Part 1 (no treatment gap). No new patients will be enrolled in the OLE. All participants in Part 2 will receive oral treatment with basmisanil for approximately 2 years.*

Efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD) assessments will be conducted throughout the study.

*In Part 1,* recruitment will be staggered as follows:

- By age to *determine* PK exposure and allow for potential dose adjustments and to assess safety in participants aged 6 to *14* years before exposing participants aged 2 to 5 years.
- By presence or absence of epilepsy to assess the effect of basmisanil on seizures before enrolling participants without epilepsy.

Staggered enrollment *by age and presence or absence of epilepsy* will be implemented as follows:

- **Stage 1**: Participants between ages 6 and *14* years *(inclusive)* with epilepsy will be enrolled.

  Data from *a minimum of 9 participants enrolled in* Stage 1 will be reviewed by an Internal Monitoring Committee (IMC) + Scientific Oversight Committee (SOC) prior to opening recruitment to participants aged 2 to 5 years *and participants without epilepsy* into Stage 2.

- **Stage 2**: *The remaining* participants aged 2 to *14* years with *or without* epilepsy will be enrolled *following IMC + SOC recommendation to reach a total sample size of approximately N=90.*

  Data from *participants enrolled into* Stage 1 and 2 will be included in *periodic* reviews by the IMC + SOC and a first interim analysis *will be performed when approximately N=24 participants reach 4 weeks of treatment.*

Overall, the study *aims* to enroll *a minimum of* approximately one-third of the *participants aged* 2 to 5 years *and a maximum of approximately one-fifth of participants aged 12 to 14 years.*

**TREATMENT GROUPS AND DURATION**

The investigational medicinal products in this study are basmisanil (immediate-release granules, packaged in stick-packs) and placebo (granules, packaged in stick-packs). One stick-pack of basmisanil [redacted].

Study treatment (basmisanil or placebo) will be administered orally BID during the first day of treatment in the clinic (Day 1) and TID for the remaining study duration (from Day 2 *onwards*), [redacted].

The planned study treatment starting doses are:

- [redacted]

*In Part 1, the starting dose is determined according to the participant's age at the time of signing of the Informed Consent Form (ICF) and maintained for the 52-week treatment duration.*

*In Part 2, the starting dose, dosing regimen and age-defined dose groups are* [redacted] *the same as for Part 1 (Day 2 and onwards) and determined based on the participant's age at the start of Part 2 (Day 366 visit). During Part 2, the dose will be adjusted according to the participant's actual age. If applicable, the dose must be changed at the latest on the first dispensation visit after a participant moves into a different age group.*

*Dose and dose regimen for participants aged 15 to 17 years are predicted to be similar to what has been determined as the starting steady state regimen in Part 1 for 10 to 14 years old* [redacted]

**LENGTH OF STUDY**

The *planned* total study duration is approximately 61 weeks *for participants who participate in Part 1 only and 165 weeks for those participating in Parts 1 and 2*, divided into the following periods:

- Screening period of *up to* 5 weeks (Day -35 to Day -2), which may overlap with the baseline period (Day -7 to Day -1)

- Double-blind 52-week treatment period (Day 1 to Day 365)
- *Optional OLE period of approximately 2 years/104 weeks (Day 366 to Day 1095/Year 3)*
- Follow-up period of approximately 4 weeks (*Part 1:* Day*s 365 to* 395 *or Part 2: Days 1095 to 1125*)

The screening period will start once the first actual screening assessment is performed (not with signing the Informed Consent Form). *All screening assessments required to confirm participant's eligibility for study participation need to be completed before the Baseline visit.* The Baseline visit can be done anytime between Day -7 and Day-1.

**END OF STUDY**

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last scheduled procedure per the schedule of *activities* or withdrawal of consent.

The end of the study is defined as the date when the last participant's last observation occurs.

**IMC AND SOC**

A Sponsor IMC will be responsible for regular reviews of accumulating safety, tolerability, and PK data to assess the adequacy of the selected doses in terms of tolerability and exposure. It will also oversee up to two interim analyses.

*During Part 1 of the study,* an SOC will help monitor safety and tolerability data *until all participants have completed or were prematurely withdrawn from Part 1. Specifically, the SOC will help* interpret any changes in seizure status and/or EEG findings in this patient population, to ensure that the study in its current form does not pose unacceptable safety risks to participants.

**PARTICIPANT POPULATION**

The participants in this study will be female and male children *and adolescents* aged 2 to *14* years *at the time of signing the ICF for Part 1* with genetically confirmed maternal duplications (3 copies) or triplications (4 copies) of chromosome 15q11.2-q13.1 (Dup15q syndrome), who fulfill all of the given inclusion criteria and do not meet *any* exclusion criteria.

**INCLUSION CRITERIA *(PART 1)***

**Informed Consent/Age**

1. Participants aged 2 to *14* years inclusive at the time the caregiver signs the informed consent.

**Type of Participants and Disease Characteristics**

2. In the investigator's opinion, able to participate and deemed appropriate for participation in the study.
3. Documented maternal duplication (3 copies) or triplication (4 copies) of the chromosome 15q11.2-q13.1 region that includes the Prader-Willi/Angelman critical region defined as [BP2-BP3] segment.
4. Dup15q syndrome *Clinician* Global Impression *of* Severity scale (Dup15q CGI-S) overall severity score ≥ 4 (at least moderately ill).
5. Stage 1 *specific inclusion criterion*: Participants *aged 6 to 14 years* with epilepsy.

**Weight**

6. Body weight equal to or above the third percentile for age.

**Sex and Contraception/Barrier Requirements**

7. Male and female participants

Some of the provisions that follow may have limited applicability based on the age range of study participants (i.e., up to the age of *14*) and the nature of the disease under study. These provisions are nonetheless included for purposes of completeness to make clear that individuals who are pregnant or are engaging in actions that may cause them to become pregnant, should not participate in this study. Consent must be provided by the legal representative for all participants.

a) Female Participants

A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

- Female participants of non-childbearing potential.
- Female participants of childbearing potential who agree to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods during the treatment period and for at least 28 days after the final dose of study treatment. The following are acceptable contraceptive methods: bilateral tubal occlusion/ ligation, male sexual partner who is sterilized, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices and copper intrauterine devices, male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide.

b) Male Participants

Male contraception is not required in this study because of the minimal seminal dose transmitted through sexual intercourse.

**Caregiver Requirements**

8. The participant has a parent, caregiver, or legally authorized representative (hereinafter "caregiver") of at least 18 years of age, who is fluent in the local language at the site, and capable and willing to provide written informed consent for the participant, according to International Council *for* Harmonisation and local regulations.
9. The participant's caregiver must be living with the participant and, in the opinion of the Investigator, able and willing to reliably assess the participant's ongoing condition, to accompany the participant to all clinic visits, and ensure compliance to study treatment throughout the study. The same caregiver is able and willing to complete the caregiver assessments and is available to the Investigational Site by telephone or email if needed.
10. The participant's caregiver is able and willing to use electronic devices to record information on the participant's condition and to complete assessments at home and agrees to home nursing visits, if local regulations allow for it and if home nursing service is available in the country/region.

**EXCLUSION CRITERIA** ***(PART 1)***

**Medical Conditions**

1. Uncontrolled epilepsy at screening as indicated by:
   a) Use of rescue medication*(s) to treat* more than *one seizure episode or seizure cluster* per month, on average in the past 6 months,

      OR

   b) Concomitant *chronic* use of more than four anti-epileptic medications,

      OR

   c) Status epilepticus within the past 6 months requiring hospitalization for treatment of the status epilepticus,

      OR

   d) Any implanted devices to treat drug-resistant epilepsy

2. Lymphoma, leukemia, or any malignancy within the past 5 years, except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
3. Clinically significant ECG abnormalities at screening, including an average triplicate QTcF > 450 ms for participants > 10 years or QTcB > 450 ms for children up to and including age 10 years (because Bazett's correction is more appropriate in young children).
4. Clinically significant abnormalities in laboratory test results at screening (including positive results for HIV, hepatitis B and/or hepatitis C). ALT values > 1.5 × the upper limit of normal (ULN; re-testing is allowed to confirm). GFR < 90 mL/min per 1.73 $m^2$ (Grade 1 CKD) as estimated using Schwarz formula.

**Prior/Concomitant Therapy**

5. Allowed prior existing medication should be on a stable regimen (or frequency of intervention) for at least 6 weeks, and at least 8 weeks for anti-epileptic treatment, prior to screening.
6. Non-pharmacological / behavioral therapies should not be stopped or newly started at least 6 weeks prior to screening and are expected to remain stable for the entire study duration (excluding changes related to standard age and educational interventional programs and minor interruptions such as illness or vacation).
7. Concomitant use of prohibited medications.

**Prior/Concurrent Clinical Study Experience**

8. Participation in an investigational drug study within one month or within 6 × the elimination half-life, whichever is longer, prior to dosing in the study.

**Other Exclusions**

9. Significant risk for suicidal behavior, as assessed through the suicidal behavior question adapted from the Columbia Classification Algorithm for Suicide Assessment (C-CASA) (participants ≥ 6 years of age only).
10. Known sensitivity to any of the study treatments or components thereof or drug or other allergy that, in the opinion of the Investigator, contraindicates the participation in the study, including severe lactose intolerance (e.g., unable to tolerate 250 mL [8 oz. or 1 cup] of milk, ice cream, or yogurt).
11. Concomitant clinically relevant disease or condition or any clinically significant finding at screening that could interfere with, or for which, the treatment might interfere with, the conduct of the study or that would pose an unacceptable risk to the participants in this study.
12. Known active or uncontrolled bacterial, viral, or other infection (excluding fungal infections of nail beds) or any major clinically significant episode of infection or hospitalization (relating to the completion of the course of antibiotics) within 6 weeks prior to the start of drug administration.

**NUMBER OF PARTICIPANTS**

Approximately 90 $participants$ with Dup15q syndrome are planned to be randomized 2:1 to basmisanil or placebo. Assuming approximately 10% of randomized participants may not be evaluable for efficacy, there will be approximately 81 evaluable participants. The sample size may be increased in case of higher-than-expected rates of early study withdrawals or number of participants requiring dose adjustments due to exposures substantially deviating from target trough plasma concentrations.

## CONCOMITANT THERAPY

Concomitant therapy includes any medication, e.g., prescription drugs, over-the-counter (OTC) drugs, vaccines (including COVID-19 vaccines) approved dietary and herbal supplements, nutritional supplements, and dietary restrictions used by a participant from 6 weeks prior to screening until the follow-up visit.

**Anti-epileptic medication** must be on a stable regimen 8 weeks prior to screening and for at least the first 4 weeks of treatment *in Part 1*. After the Day 28 visit, dose adjustments within the therapeutic range and changes within the same class of anti-epileptic medication may be allowed as part of routine clinical care, upon consultation with the Medical Monitor. *In Part 2, for the first 28 days (until Day 395) dose changes are not allowed.* Changes in the number or the class of anti-epileptic medications are not allowed until the *Part 1* follow-up visit *for participants who do not continue study participation in the optional OLE or until the Day 548 visit for participants who roll over to Part 2 of the study.*

**Non-pharmacological** (e.g., physiotherapy) / **behavioral therapies** should not be stopped or newly started at least 6 weeks prior to screening and are expected to remain stable *until the Part 1 follow-up visit or until the Day 548 visit for Part 2 participants* (excluding changes related to standard age and educational interventional programs or minor interruptions such as illness or vacation).

### Permitted Therapy

Permitted therapy includes all medication used by a participant to manage symptoms associated with Dup15q syndrome *that* is not specified as prohibited therapy*, taken* from 6 weeks prior to screening until the *Part 1* Follow-up visit *or until the Day 548 visit for participants in Part 2*.

Participants who use oral contraceptives with a failure rate of $<1\%$ per year, hormone-replacement therapy, or other maintenance therapy should continue their use.

### Prohibited Therapy

The below listed therapies are prohibited and should not be administered within 2 weeks (or within 5-times the elimination half-life, whichever is longer) prior to dosing and until the Follow-up visit, unless otherwise specified. Methods of administration which do not produce appreciable systemic drug exposure (e.g., topical administration for skin conditions) are permitted:

**Modulators of CYP3A4 Activity:** Basmisanil is predominantly cleared by metabolism via CYP3A4 and concomitant medications that significantly alter CYP3A4 activity will affect the pharmacokinetics of basmisanil.

Strong inhibitors of CYP3A4 (e.g., itraconazole, erythromycin, fluconazole, nefazodone, ritonavir, verapamil, grapefruit or grapefruit juice) taken within 2 weeks (or within 5-times the elimination half-life, whichever is longer) prior to dosing is prohibited. Moderate CYP3A4 inhibitors may be used after discussion with the Medical Monitor and eventual use of inhibitors of CYP3A should be accompanied by dedicated safety monitoring, in particular the QT interval (QT).

Inducers of CYP3A4 (e.g., rifampicin, carbamazepine, pioglitazone, rifampin, modafinil, systemic glucocorticoids, oxycarbazepine, carbamazepine, phenobarbital, phenytoin, St John's Wort) taken within 4 weeks prior to dosing (or within $5 \times$ the elimination half-life, whichever is longer) are not permitted.

**Dofetilide** use is not permitted because of the potential for interaction between basmisanil and renally cleared cationic drugs, as well as the very narrow therapeutic window of dofetilide.

**Benzodiazepines (chronic use):** Based on the potential for interactions to occur between basmisanil and other medications whose effects are mediated via $GABA_A$ receptors, chronic use of benzodiazepines, including as treatment for epilepsy (e.g., clobazam) is not allowed. Restrictions for acute use of benzodiazepines are described in the protocol.

**Direct-acting oral anticoagulants (DOACs):** In vitro assays of the DOACs dabigatran-etexilate, edoxaban, apixaban, and rivaroxaban in combination with basmisanil indicate the potential for in vivo drug-drug interaction at both gastrointestinal and systemic concentrations.

**OTC Cannabidiol (CBD):** Use of artisanal CBDs (products, derivatives, cannabis plants/extracts) is prohibited. Epidiolex/Epidyolex is not prohibited.

**Therapy to be Used With Caution**

**P-glycoprotein (P-gp) substrates** (with exception of DOACs which are prohibited): Basmisanil has been shown in in vitro assays to inhibit the activity of P-gp. Therefore, caution is advised when using basmisanil treatment with medications known to be P-gp substrates, especially those with a narrow therapeutic window (e.g., digoxin, colchicine, loperamide). Therapeutic drug monitoring of digoxin concentrations should be performed regularly but in particular when initiating and stopping basmisanil treatment.

**Concomitant medications with an effect on QT:** Drugs known to prolong the QT corrected for heart rate (QTc) interval will be allowed if stable at screening provided the screening QTc does not meet exclusion QTc criterion. Use of currently approved prokinetics (e.g., domperidone, metoclopramide) is not prohibited, but requires closer monitoring of QTc interval on ECG due to risk of arrhythmias.

**Benzodiazepines / GABAergic medications:** Benzodiazepines and benzodiazepine-related drugs may be exceptionally used with the following restrictions:

- For the **treatment of intermittent medical conditions** (e.g., for insomnia and anxiety / agitation, analgosedation)
  - Medications with a short half-life (e.g., lorazepam, alprazolam, or oxazepam) are preferred
  - Short-term use only (no more than 4 days per month)
  - Should not be taken within 2 days before a scheduled visit.
- For the **treatment of emergency situations** (e.g., for the acute management of a seizure)
  - *If benzodiazepines/benzodiazepine-related drugs are required in an emergency situation, the visit can be rescheduled to allow for a 2-day window between emergency medication and visit date (even if it falls out of the protocol defined visit window).*
  - If benzodiazepines, in particular diazepam, midazolam, or clonazepam are used, the Investigator should be aware that a higher-than-normal dose of the medication may be required to achieve clinical response.
  - Similarly, in case of acute use of anesthetics that are $GABA_A$ positive allosteric modulators (e.g., volatile anesthetics or hypnotics) in a participant treated with basmisanil, a higher dose of the anesthetics may be required to achieve the desired effect.

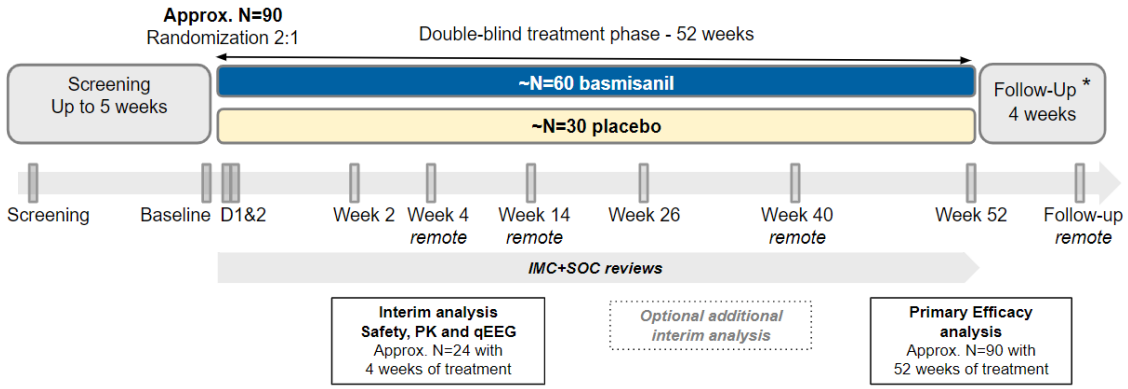
As described above, these recommendations are based on the potential for competition (PD interaction) at the $GABA_A$ receptor level.

## 1.2 SCHEMATIC OF STUDY DESIGN

An overview of the study design is provided in Figure 1.

### Figure 1 Overview of Study Design

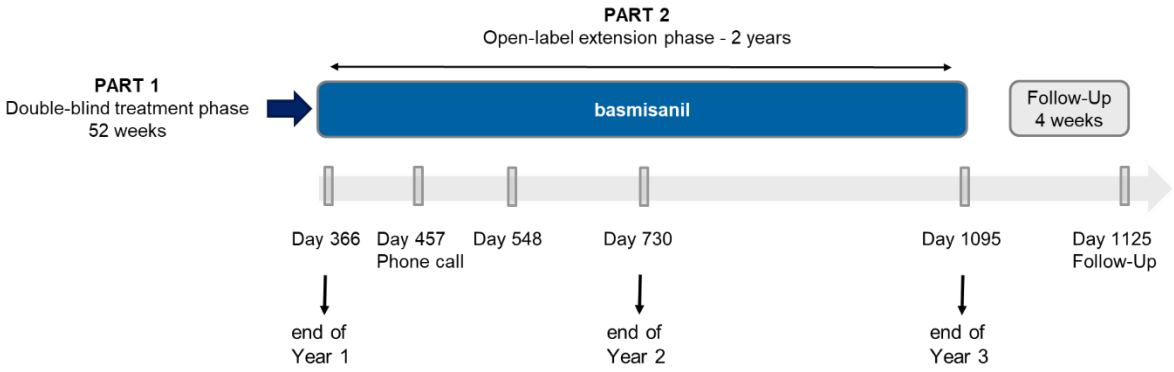
*A. PART 1 – 52-week double-blind placebo controlled (main study)*




D= Day; IMC = Internal Monitoring Committee; N = number of participants; PK = pharmacokinetics; qEEG = quantitative EEG; SOC = Scientific Oversight Committee.

** The follow-up period will not be completed for participants entering Part 2.*

*B. PART 2 – optional open-label extension (OLE) of 2 years*




## 1.3 SCHEDULE OF ACTIVITIES

The schedule of activities (SoA) *for Part 1* is provided in *Table 1* (overview *of Part 1*) *and Table 2 (Part 1 detailed table). The SoA for Part 2 is provided in Table 3 (Part 2 – optional open-label extension [OLE]) and Table 4 (Part 2 – optional OLE – detailed table).*

## Table 1 Schedule of Activities *for Part 1* – Overview

| Period | Screening [a] | Baseline [b] | Treatment Period/Visit | | | | | | | Final Visit | Follow-up [c, q] | Early Termination [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | Day -35 to Day -2 | Day -7 to Day -1 | Day 1 | Day 2 | Day 14 | Day 28 [d] | Day 92 [c] | Day 183 [b] | Day 274 [c] | Day 365 [b] | Day 395 | Anytime |
| Weeks (approximate) | Week -5 to Week -1 | Week -1 | Week 1 | Week 1 | Week 2 | Week 4 | Week 14 | Week 26 | Week 40 | Week 52 | Week 56 | |
| Visit window | | | | | ± 5 days | ± 5 days | ± 7 days | ± 7 days | ± 7 days | ± 7 days | ± 10 days | |
| Assessments | | | | | | | | | | | | |
| Informed consent | x | | | | | | | | | x [t] | | |
| Inclusion/Exclusion criteria | x | x | | | | | | | | | | |
| Caregiver expectation guidance [u] | x | x | | | | | | x | | x | | |
| Randomization | | x | | | | | | | | | | |
| Demography | x | | | | | | | | | | | |
| Medical history | x | | | | | | | | | | | |
| Physical examination [e] | x | x | | | | | | x | | x | | |
| Assessment of hypotonia | | x | | x | x | | | x | | x | | |
| Vital signs | x | x | x | x | x | | x | x | x | x [q] | x | x |
| Genetic test : CMA [r] | x | | | | | | | | | | | |
| Genetic test : MS-MLPA [r] | x | | | | | | | | | | | |
| Genetic test: FISH [r] | | | | | x | | | | | | | |
| Pregnancy test [f] | x | x | | | | | x | x | x | x [q] | x | x |
| Urinalysis | x | x | | | x | | x | x | x | x [q] | x | x |
| Hematology | x | x | | | x | | x | x | x | x [q] | x | x |
| Clinical chemistry | x | x | | | x | | x | x | x | x [q] | x | x |
| Coagulation | x | | | | | | | | | | | |
| Viral serology | x | | | | | | | | | | | |
| Thyroid hormones | x | | | | | | | | | x [q] | | |
| RBR whole blood sample (optional) | | x | | | | | | | | | | |
| Tanner staging [g] | | x | | | | | | | | x | | |
| 12-lead ECG (triplicate) | x | x | x | x | x | | | x | | x [q] | | |
| Seizure status [h] | | x | | | | x | x | x | x | x | x | x |
| EEG monitoring [i] | | x | x | x | x | | | x | | x [q] | | |
| Study drug administration [j] | | | ◄ | | | | | | | ► | | |
| PK sample [k] | | | x | x | x | | x | x | x | x [q] | | x |
| Dup15q CGI-S [h] | x | x | | | | x | x | x | x | x | x | x |
| Dup15q CGI-C [h] | | | | | | x | x | x | x | x | x | x |

## Table 1 Schedule of Activities *for Part 1* – Overview (cont.)

| Period | Screening [a] | Baseline [b] | Treatment Period/Visit | | | | | | | Final Visit | Follow-up [c, q] | Early Termination [c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Day | Day -35 to Day -2 | Day -7 to Day -1 | Day 1 | Day 2 | Day 14 | Day 28 [d] | Day 92 [c] | Day 183 [b] | Day 274 [c] | Day 365 [b] | Day 395 | Anytime |
| Weeks (approximate) | Week -5 to Week -1 | Week -1 | Week 1 | Week 1 | Week 2 | Week 4 | Week 14 | Week 26 | Week 40 | Week 52 | Week 56 | |
| Visit window | | | | | ± 5 days | ± 5 days | ± 7 days | ± 7 days | ± 7 days | ± 7 days | ± 10 days | |
| Assessments | | | | | | | | | | | | |
| VINELAND -3 [l] | | x | | | | | | x | | x | | x |
| MSEL [m] | | x | | | | | | x | | x | | |
| RBS-R [n] | | x | | | | | x | x | x | x | | x |
| ADOS [m] | | x | | | | | | | | x | | |
| PedsQL-FIM [n] | | x | | | | | | x | | x | | |
| ORCA [n] | | x | | | | | | x | | x | | x |
| ABC-2-C [n] | | x | | | | x | x | x | x | x | | x |
| Dup15q CaGI-S [n] | | x | | | | x | x | x | x | x | x | x |
| Dup15q CaGI-C [n] | | | | | | x | x | x | x | x | x | x |
| CSHQ [n] | | x | | | | x | x | x | x | x | | x |
| Clinical assessment of suicidality [h, o] | x | x | | | x | | x | x | x | x | x | x |
| Wearable device [p] | x | | | | | | x | x | x | x | | |
| Seizure diary | ◄ | | | | | | | | | ► | | |
| Palatability questionnaire | | | x | | x | | | | | | | |
| Meal record | | | x | x | x | | x | x | x | x | | |
| Drug diary | | | ◄ | | | | | | | ► | | |
| Exit interview (optional) [s] | | | | | | | | | | | x | |
| Adverse events | ◄ | | | | | | | | | | | ► |
| Previous and concomitant treatments | ◄ | | | | | | | | | | | ► |

## Table 1 Schedule of Activities *for Part 1* – Overview (cont.)

ABC-2-C = Aberrant Behavior Checklist - Second Edition – Community Version; ADOS = Autism Diagnostic Observational Schedule, second edition; BID = twice a day; *CMA = chromosomal microarray;* CSHQ = Children's Sleep Habit Questionnaire; Dup15q CaGI-C = Dup15q syndrome Caregiver Global Impression *of* Change scale; Dup15q CaGI-S = Dup15q syndrome Caregiver Global Impression *of* Severity scale; Dup15q CGI-C = Dup15q syndrome *Clinician* Global Impression *of* Change scale; Dup15q CGI-S = Dup15q syndrome *Clinician* Global Impression *of* Severity scale; *FISH = fluorescence in situ hybridization;* MSEL = Mullen Scales of Early Learning; *MS-MLPA = methylation specific-multiplex ligation-dependent probe amplification;* ORCA = Observer-Reported Communication Ability; PedsQL-FIM = Pediatric Quality of Life Inventory™ Family Impact Module; PK = pharmacokinetics; qEEG = quantitative EEG; RBR = Research biosample repository; RBS-R = Repetitive Behavior Scale–Revised; TID = three times a day; Vineland-3 = Vineland Adaptive Behavior Scales–Third Edition.

a Screening period starts once first screening assessment is performed; informed consent can be signed earlier. *All screening assessments required to confirm participant's eligibility for study participation need to be completed with results available before the Baseline visit*. The Baseline visit can be done anytime between Day -7 and Day -1.

b Visit can be split over two consecutive days if needed.

c Visit *can be* done remotely if local regulations allow for it and if home nursing service is available in the country/region.

d Telephone call only.

e Height and head circumference do not need to be recorded at Baseline.

f Urine pregnancy test for female participants of childbearing potential. If the urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.

g For participants aged 9 years *and above* at *the time of signing the Informed Consent Form. Once a participant reaches Stage 5, Tanner staging no longer needs to be performed.*

h Performed *by the clinician* either *at* the clinic *visit* or via *telephone*/video call *at the remote/telephone call visits.*

i See the detailed schedule in *Table 2* for length of EEG and timing of qEEG timepoints.

j Study treatment administration is BID on Day 1 and TID from Day 2 onward.

k See detailed schedule in *Table 2* for exact *PK* timings.

l *Vineland-3 interview will be performed by central raters, independent of the site personnel.* Caregivers may choose to complete the Vineland-3 *interview* at the clinic visit or remotely *within 5 days before the scheduled clinic visit*. The preferred method should be determined at Baseline and kept consistent throughout the study.

m Assessment will be video recorded.

n Caregiver-reported questionnaires can be completed either during the clinic visit or at home with support from the site within 5 days before the *scheduled clinic* visit *using a dedicated website (TrialMax)*. The preferred method should be determined at Baseline and kept consistent throughout the study.

## Table 1 Schedule of Activities *for Part 1* – Overview (cont.)

o Assessed in participants aged 6 years *and above at the time of signing the Informed Consent Form.*

p [redacted]

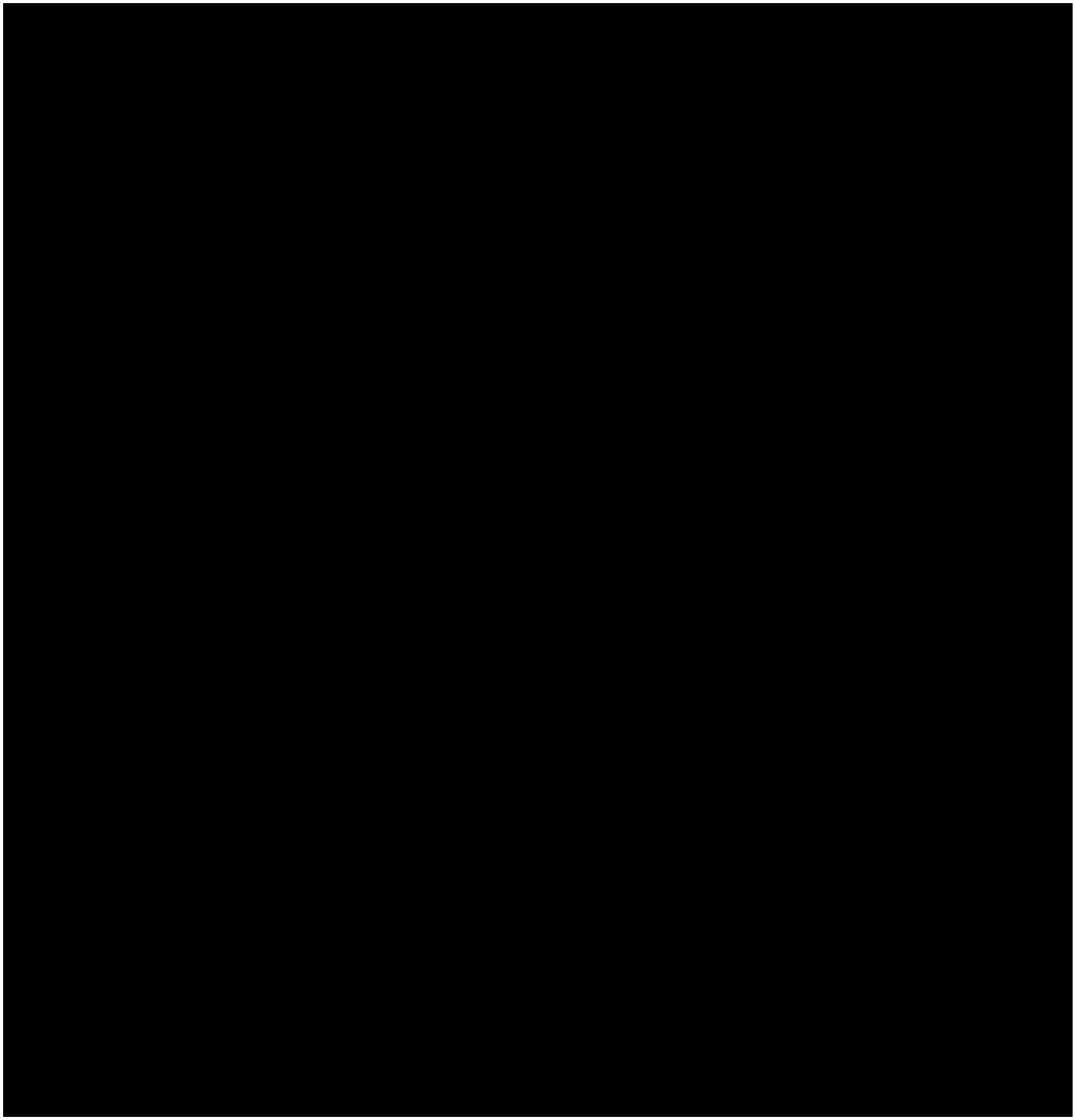
*q Only for participants who have either early terminated Part 1, or completed Part 1 but do not consent to enter the optional OLE.*

*r Genetic tests and associated samples are not mandatory assessments and do not need to be performed within the study in cases where the required genetic information is available in the patient's medical history.*

*s Optional exit interview, which should be performed within 4 weeks after the Day 365 visit (during the follow-up period if the participant does not enter Part 2 or during the first 4 weeks of Part 2), as applicable, will be performed by a trained interviewer independent of the site personnel. The exit interview can be performed whether or not the participant enters Part 2.*

*t Only for participants who enter Part 2 of the study. Should be signed before initiation of any activities at the Day 365 visit.*

*u The assessment should be done preferably before any other caregiver-reported assessments.*



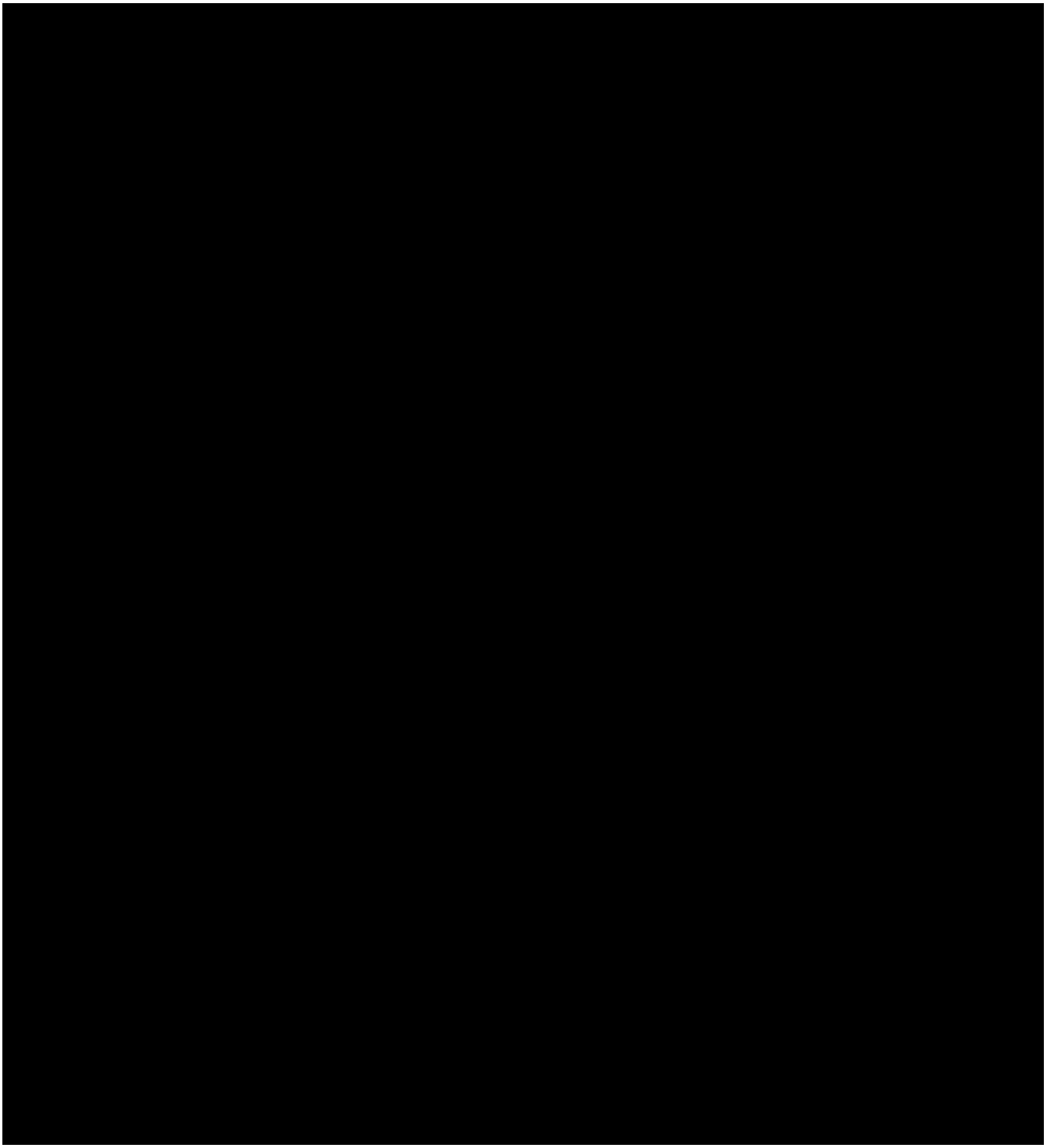


**Table 2 Schedule of Activities *for Part 1* – Detailed Table (cont.)**

*ECG = electrocardiogram; EEG = electroencephalogram; OLE = open-label extension;* PK = pharmacokinetics; qEEG = quantitative EEG; SoA = schedule of activities.

a [redacted]

b EEG is worn and recorded continuously during the specified time period. EEG technicians *will* periodically confirm that the signal quality is good and address any technical problems.

c This column lists sections of the EEG that will be used for quantitative analysis (qEEG blocks). For these blocks, the EEG technicians ensure *good impedances (checked at the start of the block) and that* the participant is awake and in a relatively calm state with limited movements (given the circumstances).

[redacted]

f EEG *recordings will be reviewed* for emergent abnormalities by the EEG *central reader (qualified neurologist independent of the site personnel). An EEG safety report will be provided to the site within 22 hours of receipt of EEG recordings by the central reading vendor. Site personnel must provide the EEG recording to the central reading vendor immediately after the completion of the recording at the site.*

g *All doses administered in the clinic are* to be taken under site *staff* supervision [redacted]

*h Only for participants who have completed Part 1 but do not consent to enter Part 2.*

*i To be performed before the blood draws.*

*j Safety laboratory blood samples to be collected prior to the PK blood samples.*

[redacted]

*m ECGs should be performed prior to any scheduled vital sign measurements.*

*Table 3 Schedule of Activities for Part 2 (Optional Open-Label Extension) – Overview*

| Period | Treatment Period/Visits | | | | | Follow-up [a] | Early Termination [a] |
|---|---|---|---|---|---|---|---|
| Day | Day 366 | Day 457 [b] | Day 548 [a] | Day 730 [a] | Day 1095 [a] | Day 1125 (30 days after the final dose) | Anytime |
| Weeks (approximate) | Week 52 | Week 65 | Week 78 | Week 104 | Week 156 | Week 160 | |
| Year | 1 | 1.25 | 1.5 | 2 | 3 | | |
| Visit window | | ± 7 days | ± 7 days | ± 7 days | ± 7 days | ± 10 days | |
| Assessments | | | | | | | |
| Caregiver expectation guidance [c] | | | x | x | x | | |
| Physical examination | | | x | x | x | x | x |
| Vital signs | x | | x | x | x | x | x |
| Pregnancy test [d] | x | | x | x | x | x | x |
| Urinalysis | x | | x | x | x | x | x |
| Hematology | x | | x | x | x | x | x |
| Clinical chemistry | x | | x | x | x | x | x |
| Coagulation | x | | | | | | |
| Viral serology | x | | | | | | |
| Thyroid hormones | x | | | | | x | x |
| Tanner staging [e] | | | | x | x | | |
| 12-lead ECG (triplicate) | x | | x | x | x | x | x |
| Seizure status [f] | | x | x | | | | |
| EEG monitoring [g] | x | | x | x | x | x | |
| Study drug administration [h] | ◄ | | | | ► | | |
| PK sample [i] | x | | x | x | x | | x |
| Dup15q CGI-S [f] | | x | x | x | x | x | x |
| Dup15q CGI-C [f] | | x | x | x | x | x | x |

*Table 3 Schedule of Activities for Part 2 (Optional Open-Label Extension) – Overview (cont.)*

| Period | Treatment Period/Visits | | | | | Follow-up [a] | Early Termination [a] |
|---|---|---|---|---|---|---|---|
| Day | Day 366 | Day 457 [b] | Day 548 [a] | Day 730 [a] | Day 1095 [a] | Day 1125 (30 days after the final dose) | Anytime |
| Weeks (approximate) | Week 52 | Week 65 | Week 78 | Week 104 | Week 156 | Week 160 | |
| Year | 1 | 1.25 | 1.5 | 2 | 3 | | |
| Visit window | | ± 7 days | ± 7 days | ± 7 days | ± 7 days | ± 10 days | |
| Assessments | | | | | | | |
| VINELAND -3 [j] | | | x | x | x | | x |
| MSEL [k] | | | x | x | x | | |
| PedsQL-FIM [l] | | | x | x | x | | |
| ABC-2-C [l] | | | x | x | x | | x |
| Dup15q CaGI-S [l] | | | x | x | x | x | x |
| Dup15q CaGI-C [l] | | | x | x | x | x | x |
| Clinical assessment of suicidality [f, m, n] | | x | x | x | x | x | x |
| Seizure diary | ◄ | ——— | ► | | | | |
| Drug diary | ◄ | ——— | ——— | ——— | ► | | |
| Meal record | x | | x | x | x | | |
| Adverse events [n] | ◄ | ——— | ——— | ——— | ——— | ——— | ► |
| Previous and concomitant treatments [n] | ◄ | ——— | ——— | ——— | ——— | ——— | ► |

## *Table 3 Schedule of Activities for Part 2 (Optional Open-Label Extension) – Overview (cont.)*

*ABC-2-C = Aberrant Behavior Checklist - Second Edition – Community Version; AE = adverse event; Dup15q CaGI-C = Dup15q syndrome Caregiver Global Impression of Change scale; Dup15q CaGI-S = Dup15q syndrome Caregiver Global Impression of Severity scale; Dup15q CGI-C = Dup15q syndrome Clinician Global Impression of Change scale; Dup15q CGI-S = Dup15q syndrome Clinician Global Impression of Severity scale; ECG = electrocardiogram; EEG = electroencephalogram; MSEL = Mullen Scales of Early Learning; OLE = open-label extension; PedsQL-FIM = Pediatric Quality of Life Inventory™ Family Impact Module; PK = pharmacokinetic; qEEG = quantitative EEG; TID = three times a day; Vineland-3 = Vineland Adaptive Behavior Scales–Third Edition.*

*a Visit can be split over two consecutive days if needed.*

*b Telephone call only.*

*c The assessment should be done preferably before any other caregiver-reported assessments.*

*d Urine pregnancy test for female participants of childbearing potential. If the urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.*

*e For participants aged 9 years and above at the time of the assessment. Once a participant reaches Stage 5, Tanner staging no longer needs to be performed.*

*f Performed by the clinician either at the clinic visit or via telephone/video call at the telephone call visits.*

*g See the detailed schedule in Table 4 for length of EEG and timing of qEEG recordings.*

*h Study treatment administration is TID throughout Part 2.*

*i See detailed schedule in Table 4 for exact timings for PK sampling.*

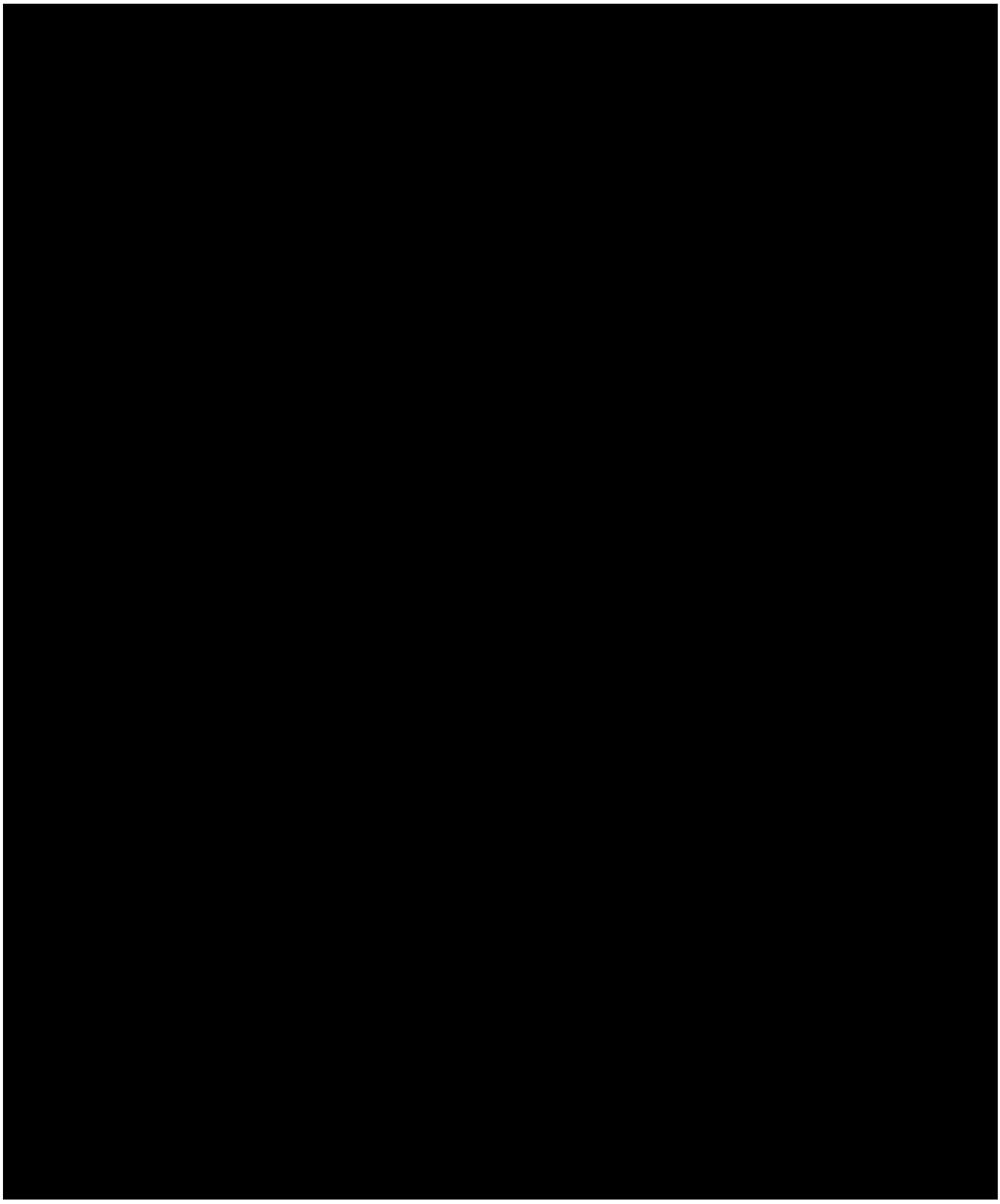
*j Vineland-3 will be performed by central raters, independent of the site personnel. Caregivers may choose to complete the Vineland-3 interview at the clinic visit or remotely within 5 days before the scheduled clinic visit. The preferred method determined at Baseline visit in Part 1 of the study should be kept consistent throughout Part 2 of the study.*

*k Assessment will be video recorded.*

*l Caregiver-reported questionnaires can be completed either during the clinic visit or at home with support from the site 5 days before the scheduled clinic visit using a dedicated website (TrialMax). The preferred method determined at Baseline visit in Part 1 of the study should be kept consistent throughout Part 2 of the study.*

*m Assessed in participants aged 6 years and above at the time of the assessment.*

*n Information on AEs, concomitant treatments, and suicidality assessment should be collected at minimum every 3 months via phone call.*



# 2. INTRODUCTION

## 2.1 STUDY RATIONALE

Dup15q syndrome is a rare and severe neurodevelopmental disorder (NDD) with a high unmet medical need (Section 2.2.3). It is caused by maternal duplication or triplication of the q11.2-q13.1 region of chromosome 15, which contains several genes and noncoding regions. The disease pathophysiology cannot be causally ascribed to any single gene (Finucane et al 2016). Genotype-phenotype associations in Dup15q syndrome suggest that the maternally expressed *UBE3A* gene is an important determinant of the clinical severity of the syndrome (Section 2.2.1).

A careful analysis of genotype-phenotype associations shows that core distinctive clinical features of the syndrome can manifest without the expression of *UBE3A* (paternal interstitial triplications, Castronovo et al 2015), and do not appear fully recapitulated in maternal duplications restricted to *UBE3A* only (Noor et al 2015). This points to an important contribution of other, non-imprinted genes in the 15q11.2-q13.1 region to the pathophysiology of Dup15q syndrome. Of particular relevance, the cluster of 3 $GABA_A$ receptor subunit genes (*GABRA5, GABRB3*, and *GABRG3*) are critical for normal neuronal development and function. Indeed, mutations in the *GABRB3* and *GABRA5* genes, including gain-of-function mutations have been causally linked to epilepsy, developmental delay, and hypotonia phenotypes (Menzikov et al 2021, Butler et al 2018, Hernandez et al 2019, Boonsimma et al 2020, Absalom et al 2020) reminiscent of Dup15q symptomatology.

The *GABRA* gene cluster encodes the α5, β3, and γ3 $GABA_A$ R subunits, which can co-assemble to form a $GABA_A$ α5-containing receptor subtype ($GABA_A$ α5R, Sur et al 1998). This receptor plays a central role in the control of neuronal excitability and inhibitory circuit formation early in CNS development (Jacob 2019). Emerging evidence from human postmortem studies and neuronal cellular models suggests increased $GABA_AR$ expression in people with Dup15q (Urraca et al 2018, Germain et al 2014). This is proposed to translate into increased $GABA_AR$-mediated inhibitory function as revealed by the characteristic EEG signature observed in patients with Dup15q syndrome (Urraca et al 2013, Frohlich et al 2019), which closely resembles the effects of $GABA_AR$ enhancing drugs (e.g., benzodiazepines; see the Basmisanil Investigator's Brochure for details).

Negative allosteric modulation of $GABA_A$ α5R with basmisanil is therefore proposed as the first therapeutic approach for the treatment of Dup15q syndrome. Intervention in early childhood, a critical period characterized by rapid maturation of the human brain (Kolb and Gibb 2011), may offer the opportunity to affect the trajectory of the disease and to maximize learning and socialization opportunities during key neurodevelopmental stages (Vivanti et al 2018), with a greater prospect of benefit than intervention later in life (see Section 4.2.1).

This study consists of two parts. Part 1 is a multi-center, randomized, double-blind, placebo-controlled, parallel group study to evaluate the safety, efficacy, and pharmacodynamics of 52 weeks of basmisanil treatment in children and adolescents with Dup15q syndrome aged 2 to 14 years. Part 1 of the study will test the hypothesis that negative allosteric modulation of $GABA_A$ α5R can address excessive $GABA_AR$ function driven by the additional *GABR* copy numbers, as indexed by EEG, and positively impact core neurodevelopmental disease features in individuals with Dup15q syndrome. Part 2 of the study is an optional 2-year open-label extension (OLE) to evaluate long-term safety and tolerability and provide supportive evidence of continued treatment benefit in selected efficacy outcomes. The OLE presents an opportunity for all enrolled participants who have completed 52 weeks of treatment in the placebo-controlled part of the study (Part 1) to receive active treatment (see Section 6.7).

The rationale for the study design is provided in Section 4.2.

## 2.2 BACKGROUND

### 2.2.1 Background on Disease

Dup15q syndrome is a rare genetic NDD, caused by copy number gains of the q11.2-q13.1 region on chromosome 15 that contains both *UBE3A* and *GABR* genes. The evidence on Dup15q syndrome incidence and prevalence is limited (Kirov et al 2014, Schinzel and Niedrist 2001); the birth incidence is estimated between 1 in 11,000 to 1 in 20,000. The majority (~60%–80%) and most affected individuals present with an isodicentric [idic(15)] supernumerary chromosome of maternal origin, resulting in triplication of the chromosomal segment (4 copies). The remaining 20%–40% of the population have interstitial tandem rearrangements [int(15)], resulting in duplication (3 copies) or very rarely in triplication (4 copies) of the 15q11.2-q13.1 region (Finucane et al 2016, Lusk et al 2021). Clinically, the syndrome is characterized by a distinctive but heterogeneous neurodevelopmental phenotype. Hypotonia in infancy, motor impairments, global developmental delay, language and speech impairments are the most frequent features (Finucane et al 2016, Kalsner et al 2015). Autism spectrum disorder (ASD), epilepsy, behavioral difficulties are also common in Dup15q syndrome (Finucane et al 2016, Kalsner et al 2015). People with Dup15q syndrome have low adaptive skills, impeding their independent day-to-day functioning.

Cognitive delays may manifest as intellectual disability ranging from mild (intellectual quotient [IQ] 50 to 70) to severe (IQ < 35), with most patients functioning in the moderate to severe range. Language is affected and speech difficulties include echolalia, pronoun reversal, and stereotyped utterances. While some may completely lack functional speech, a small subset of individuals can be highly verbal. Individuals with Dup15q syndrome typically also exhibit challenging behaviors. These include hyperactivity and non-compliance, irritability, anxiety, stereotyped behavior or emotional lability (Battaglia et al 1997, DiStefano et al 2020) and are particularly disruptive in early childhood.

Moderate to severe hypotonia in newborns and infants with Dup15q syndrome is associated with impaired sucking, feeding difficulties, and gross motor delays (delays in sitting and inability to walk independently at age 2 to 3 years). These aggregate with a typical wide-based or ataxic gait, slow pace and poor postural control. Persistent impairments in both fine and gross motor skills distinguish children with Dup15q syndrome from those with idiopathic ASD (Wilson et al 2020).

Approximately 60% of patients with Dup15q syndrome present with seizures (Kalsner and Chamberlain 2015) and most have EEG abnormalities. Epilepsy typically develops early in infancy or in later childhood, around 9 years of age (Battaglia 2008), according to an expert advisory panel consulted by the Sponsor. In some individuals, seizures can be well controlled; however, two-thirds of those with idic(15) have seizures into adulthood (Kalsner and Chamberlain 2015). Up to 8% of idic(15) cases with epilepsy may succumb to status epilepticus or sudden unexpected death in epilepsy (Conant et al 2014).

Other associated medical conditions include gastrointestinal problems, feeding difficulties and poor weight gain, and minor facial dysmorphisms (Shaaya et al 2015).

The clinical severity of Dup15q syndrome depends on multiple factors including the number of copies of the 15q11.2-13.1 region and the presence or absence of epilepsy. Idic(15) are typically more severely impaired than patients with int(15) (Cook et al 1997) across domains (DiStefano et al 2016, DiStefano et al 2020) and present more frequently with epilepsy (up to 80% vs. up to 25% *for Idic(15) vs int(15), respectively*) (Conant et al 2014, Beghi et al 2020, Battaglia et al 2016).

The recent approach to more systematic genetic testing of children with global developmental delay has facilitated the identification and earlier diagnosis of rare genetic syndromes. The *median* age of diagnosis of Dup15q syndrome is reported to be around 2 years of age *(Wheeler et al 2022)*. Dup15q syndrome patients with a severe clinical presentation (e.g., early onset epilepsy, severe infantile hypotonia, often idic[15] Dup15q) are more likely to be diagnosed in infancy.

### 2.2.2 Current Therapies and Unmet Medical Need

There is a high unmet medical need for people living with Dup15q syndrome, with no approved treatment and none in development *other than basmisanil*. Life-long supportive care may include occupational and physical therapy, alternative and augmentative communication, behavioral therapy, psychotropic medications for behavioral manifestations, and standard management for seizures. The overall clinical severity, including intellectual disability, functional motor impairments, behavioral difficulties, and for many, associated seizures, precludes most individuals with Dup15q syndrome from functioning independently. Children, *adolescents* and adults with Dup15q syndrome with impaired adaptive abilities require full time support and care to manage

daily living tasks. Dup15q syndrome carries a high and life-long burden for the affected individuals, their families and caregivers, ultimately impacting society.

### 2.2.3 Background on Basmisanil

Basmisanil is a clinically characterized, brain penetrant, and highly selective negative allosteric modulator (NAM) of the $GABA_A$ $\alpha$5R. Basmisanil has been developed for its high selectivity and specificity for the $\alpha$5-containing receptors versus the $\alpha$1-, $\alpha$2-, and $\alpha$3-containing receptors, and is devoid of the anxiogenic and pro-convulsant liabilities of non-selective $GABA_A$ NAMs and antagonists, as described below.

Previous clinical studies have demonstrated that basmisanil engages with $GABA_A$ $\alpha$5 receptors in the brain (positron emission tomography [PET] study) and induces a characteristic change of the EEG signature (Hipp et al 2021 and Basmisanil Investigator's Brochure), which opposes the EEG signature of $GABA_A$R–enhancing drugs (e.g., benzodiazepines, Greenblatt et al 1989).

Basmisanil was safe and well tolerated in all completed Phase I and Phase II clinical studies in other CNS disorders to date, including also a pediatric population aged ≥6 years *(see Sections 2.2.3.1 and 2.2.3.2)*.

A summary of non-clinical and clinical studies is provided in Section 2.2.3.1 and Section 2.2.3.2. Detailed information on non-clinical pharmacology studies including pro-cognitive effects; non-clinical pharmacokinetics and metabolism, toxicology, and safety studies; as well as clinical studies, is provided in the Basmisanil Investigator's Brochure.

#### 2.2.3.1 Non-Clinical Studies

Non-clinical studies were performed in vitro and in vivo to investigate the specificity, selectivity, and activity of basmisanil. In vitro studies examined binding and functional activities at different $GABA_A$R subtypes from rat and human, as well as non-specific interaction with other binding sites. The in vivo studies investigated the efficacy of basmisanil in several animal models (rat and monkey for cognition, Ts65Dn mouse model for Down syndrome, and rat and mouse for potential for anxiogenic and pro-convulsant effects).

Rat and dog were chosen for in vivo safety studies due to the similarity to humans with regard to their drug metabolism patterns, and suitable kinetic data including moderate oral bioavailability and comparable pharmacology. All in vivo studies were conducted using once daily oral administration unless otherwise specified.

Repeat-dose toxicity studies in Wistar rats of up to 26-week and in beagle dogs of up to 39-week duration have been completed. The potential effects of basmisanil on embryofetal development were assessed in mated female rats and rabbits, and

reproductive studies to investigate fertility and pre- and postnatal development were performed in rats. Juvenile toxicity studies in post weaning rats and dogs, approximately equivalent to 2 to 18 years of age in humans, were completed to explore effects on the developing organism. Dose-range finding studies in RasH transgenic mice have been conducted in preparation for a planned RasH transgenic mouse carcinogenicity study. The genotoxic potential of basmisanil was investigated in the standard battery of in vitro and in vivo tests. Safety pharmacology studies were performed to assess the potential for any side effects related to exaggerated pharmacological action or off-target effects related to vital functions. Toxicokinetic parameters for basmisanil were determined in all pivotal in vivo safety studies and adequate exposures were achieved.

Overall, as no serious safety concerns were identified for basmisanil nonclinically, and all risks can be managed clinically, the existing non-clinical package is considered to support *BP42992 Part 1 and Part 2 study duration* in *individuals aged* 2 years *and above*. Additional information and an overview of all non-clinical pharmacology and toxicology studies with basmisanil is provided in the Basmisanil Investigator's Brochure.

#### 2.2.3.2 Clinical Studies

Information is available from 11 completed Phase I clinical studies: nine studies in healthy adult participants (BP25129, WP25366, WP28214, WP28978, JP29312, WP29393, WP29394, WP29402, and BP29784); one study enrolling both healthy adult participants and adults with Down syndrome (BP25611), one study in young adults with Down syndrome (BP25543). Two Phase II studies were conducted in Down syndrome: BP27832 ["CLEMATIS"] in adults and adolescents was completed and Study WP28760 ["SEAHORSE"] in children was prematurely terminated due to the primary endpoint not being met in CLEMATIS. One Phase II study (BP39207) in adults was conducted to treat cognitive impairment associated with schizophrenia (CIAS).

*To date*, basmisanil was administered to more than 500 participants including healthy participants, individuals with Down syndrome, schizophrenia, and stroke. Experience with basmisanil includes pediatric *participant*s aged 6 to 11 years [redacted]) and adolescents aged 12 to 17 years [redacted]

##### 2.2.3.2.1 Safety and Tolerability

Overall, based on data acquired from Phase I and Phase II studies in various populations (healthy participants, participants with Down *syndrome*, participants with schizophrenia treated with antipsychotics, and special populations including children aged 6 to 11 years *and adolescents 12 to 17 years*), basmisanil appears safe and well tolerated with a favorable adverse event (AE) profile. Monitoring of hematology and chemistry safety laboratory data did not indicate any specific risks.

**Phase II studies**

In Study BP27832 (CLEMATIS) [redacted] adults and adolescents (aged 12 to 30 years) with Down syndrome were randomized to receive placebo, or low-dose basmisanil (120 mg twice a day [BID] for participants aged 14-30 years and 80 mg BID for participants aged 12-13 years), or high-dose basmisanil (240 mg BID for participants aged 14-30 years and 160 mg BID for participants aged 12-13 years) for 26 weeks. [redacted]

In Study WP28760 (SEAHORSE) [redacted] children (6 to 11 years) with Down syndrome were randomized to receive placebo, [redacted] mg basmisanil [redacted] for 26 weeks. No SAEs were reported from this study.

In Study BP39207, [redacted] adults with CIAS were randomized to receive placebo, [redacted] mg, or [redacted] mg basmisanil [redacted] for 24 weeks. [redacted]

For more details and summary of non-SAEs reported from these 3 studies, please see the Basmisanil Investigator's Brochure.

The three Phase II studies confirmed the favorable safety and tolerability profile of basmisanil, which was consistent with the overall profile from the phase 1 studies, with no new signal noted.

### 2.2.3.2.2 Pharmacokinetics

In adults, basmisanil is rapidly absorbed from the gastrointestinal tract after oral dosing. Peak plasma concentrations occur approximately 4.5 hours after administration of immediate-release granules with food. [redacted]. The average half-life after repeated dosing ranges from [redacted]. Food substantially increases basmisanil bioavailability in healthy adult participants.

Basmisanil is predominantly cleared by metabolism via CYP3A4 and [redacted]

[redacted]. Following inhibition of CYP3A with itraconazole, the systemic exposure to basmisanil 240 mg BID and the maximum plasma concentration of basmisanil were increased 4.7- and 4.1-fold, respectively.

[redacted]

## 2.3 BENEFIT/RISK ASSESSMENT

### 2.3.1 Risk Evaluation

Basmisanil is an orally administered drug with extensive prior clinical experience and an established safety and tolerability profile in more than [redacted] individuals without *an ongoing* medical history of seizures, aged 6 years old and above (see Section 2.2.3).

#### 2.3.1.1 Identified Risks for Basmisanil

QT corrected for heart rate (QTc) prolongation: pharmacokinetic (PK)/pharmacodynamic (PD) modeling using data from the itraconazole drug-drug interaction (DDI) Study WP29402 and from the multiple ascending dose (MAD) Study WP25366 indicates that basmisanil has an effect on the QT interval (QT) duration that is below the threshold considered to be of clinical significance by regulatory authorities (Jaminion et al 2020).

In these studies, median concentrations (5%-95% predicted interval) are predicted to be well below the exposure of clinical concern for QTc interval prolongation. ECG will be monitored at several timepoints during the study, and additional ECGs will be performed in case of a dose increase of basmisanil or in case of a concomitant administration of a drug (or a dose increase) known to increase the QTc interval (see Section 8.3.8). Clinical data in more than [redacted] participants do not indicate the potential for proarrhythmic risk.

#### 2.3.1.2 Potential Risks for Basmisanil

The potential for a pro-convulsive risk was evoked with the results of the pentylenetetrazole (PTZ) test, a potent pro-convulsant, in which sub-threshold doses of PTZ given with basmisanil were associated with convulsions at the highest dose tested (100 mg/kg) in female rats only. However, it has been proposed that the application of the PTZ test to assess the pro-convulsive activity of drugs that potentiate or antagonize GABA either directly or indirectly (as in the case with basmisanil, which interacts with the same $GABA_A$ receptor) may lead to false-positive conclusions (Löscher 2009).

Beside the PTZ test, non-clinical study results support the lack of pro-convulsant effect for basmisanil:

- No convulsions and no behavioral abnormalities were observed in the in vivo pharmacology experiments nor in Good Laboratory Practice toxicology experiments including the highest dose groups.
- No effect on audiogenic seizures was observed in DBA/2J mice (a strain that exhibits age-dependent susceptibility to seizure following an auditory stimulus).
- There were no convulsions and no liability for anxiety in $GABA_A$ $\alpha 5$ knock-out mice.

When basmisanil was used in clinical trials, clinical and EEG monitoring implemented in healthy participants (at doses of up to 1000 mg BID), in adults and children with Down syndrome, and in patients with stroke (at doses of up to 240 mg BID in Phase II studies) did not indicate an increased pro-convulsive liability.

Because epilepsy is present in more than half of the individuals with Dup15q syndrome and previous clinical trials excluded participants with a history of seizures or patients with epilepsy, the risk for basmisanil to exacerbate or trigger de novo seizures in individuals with Dup15q syndrome is not established. Therefore, careful clinical monitoring (including AEs, EEG recording, and determination of seizure status using caregiver reports and diaries) is implemented in this study.

In summary, based on cumulative clinical experience in healthy participants and in adults and children with Down syndrome the potential for basmisanil to trigger de novo seizures or increase the frequency of seizure is considered low and will be carefully assessed in this patient population with a high background incidence of seizures.

Other potential risks described for basmisanil are

- either not expected based on previous clinical experience in adolescents and children with Down syndrome and in CIAS (i.e., heart rate and blood pressure changes, lipids and cholesterol, effect on body weight) or
- deemed not clinically significant for the pediatric population with Dup15q syndrome (i.e., modest increase in serum creatinine related to the inhibition of its tubular secretion by basmisanil) included in this study.

For a complete summary, refer to the Basmisanil Investigator's Brochure.

Because of the effect of CYP3A4 inhibitors on the PK of basmisanil, there is a potential risk of QTc prolongation. However, because the use of strong CYP3A4 inhibitors is prohibited in this study (see Section 6.5.2), this risk of QTc prolongation is considered low for this study.

PK DDIs through inhibition of P-gp efflux are mitigated by prohibiting DOACs and advising that other P-gp substrates should be used with caution (see Section 2.2.3.2.2, Section 6.5.2, and Section 6.5.3).

PD DDIs through interaction with $GABA_A$ receptors are mitigated by advising that drugs acting through $GABA_A$ receptors may require a higher dose to reach the desired effect when participants are taking basmisanil (see the Basmisanil Investigator's Brochure, Section 6.5.3, and Table 12).

See the Basmisanil Investigator's Brochure for more details.

There is currently no known immunotoxic effect or increased risk of infection under basmisanil treatment. However, in the setting of a pandemic or epidemic, screening for active infections prior to and during study participation should be considered according to local/institutional guidelines, and basmisanil treatment should not be administered to participants with active, confirmed, or suspected, COVID-19 due to potential severity of this infection. In case of closing of the hospital facilities due to COVID-19, investigators should follow up with the participants as needed and at least follow the normal dosing schedule (i.e., call the participant for AE recording and ask for safety laboratory tests in local laboratories or other investigations (e.g., ECG) as a substitute for investigations scheduled at investigational facility if required).

Based on the eligibility criteria for this study protocol, and the measures that will be implemented to monitor participant safety (e.g., guidance regarding prohibited therapy [including CYP3A4 inhibitors/inducers], safety monitoring throughout the treatment period and follow-up period [laboratory tests, ECG, seizure status, and EEG], implementation of PK monitoring with dose adjustment, age-staggered approach for inclusion, implementation of dosing stopping rules at the individual participant level, and implementation of a Sponsor Internal Monitoring Committee [IMC] and Scientific Oversight Committee [SOC]), the risk to participants with Dup15q syndrome treated with basmisanil is considered small and will be re-evaluated on an ongoing basis.

#### 2.3.1.3 Risk Evaluation of Measures Implemented in the Study

The study design attempts to minimize harm or discomfort related to study assessments by limiting the number of direct evaluations of the participants to the minimum required to meet the study objectives. These include standard measures to ensure the participants' safety (EEG, ECG, blood draws, physical examination), as well as two neurodevelopmental assessments to assess efficacy. Novel EEG equipment will be used to allow *participants* to move freely, with restrictions during limited periods used for quantitative analyses. Although challenging for this population, these assessments are minimally invasive and ordinarily encountered in routine clinical care during the performance of physical and psychological examinations in children *and adolescents* with Dup15q syndrome.

Repeated PK sampling (*especially* first two days of dosing *[Day 1 and Day 2]* and at steady state [Day 14 visit]) will be performed *preferably* via a cannula to avoid multiple blood draws. [redacted]

The study design also is equally mindful of the burden of study participation for the caregivers and the families, taking into account the challenges associated with travelling to the study site and completing long study visits with children with Dup15q syndrome. Specific visits *can* be conducted fully remotely using home nursing and telehealth solutions, where local regulations allow doing so. Additional flexibility is incorporated for the completion of caregiver-reported assessments, which may be completed at home. Specific clinic visits may also be split over two consecutive days (as defined in the schedule of activities [SoA] in Section 1.3) if required to accommodate participants/families.

### 2.3.2 Prospect of Direct Clinical Benefit for Pediatric Participants

There is currently no clinical evidence with basmisanil to support a prospect of direct clinical benefit for patients with Dup15q syndrome. As summarized below, based on the mode of action, the clinically demonstrated PD effects of basmisanil at the $GABA_A$ α5R, as well as non-clinical efficacy data with RO4938581 (see below), a prospect of direct clinical benefit to the participants in this study is anticipated.

Basmisanil is the first treatment option in development to address the underlying pathophysiology of Dup15q syndrome, a severe NDD with high unmet medical need (see Section 2.2.2). Considerable progress in our understanding of the role of the copy number gains of *GABRB3, GABRA5 and GABRG3* genes and the downstream functional effects point to $GABA_A$ α5R as a valid and important target to treat Dup15q syndrome (see Section 2.1).

The direct genetic link with $GABA_A$ α5R in Dup15q syndrome contrasts with the previous indications in which basmisanil did not show efficacy (Studies BP27832 in Down syndrome and BP39207 in CIAS). Indeed, the pathomechanisms of schizophrenia and Down syndrome are multifactorial and poorly understood. Negative allosteric modulation of the $GABA_A$ α5R subtype has been postulated to have cognitive-enhancing properties (Rudolph and Knoflach 2011, Nutt et al 2007). Selective modulation at $GABA_A$ α5R was thus selected as a “safe mechanism” to restore excitation-inhibition balance and improve cognition (reducing GABAergic function in Down syndrome; indirectly enhancing N-methyl-D-aspartate receptor function in CIAS) (Martinez-Cue et al 2013, Redrobe et al 2011), without the safety liabilities associated with $GABA_A$a1,2,3 negative modulation (Rudolph and Knoflach 2011).

By contrast, in Dup15q syndrome, $GABA_A$ α5R are proximally involved in the core disease pathophysiology (see Section 2.1) and the mode of action of basmisanil directly

opposes the functional consequences of the genetic duplication of *GABR* genes (see Section 2.2.3). Therefore, it is deemed unlikely that lack of efficacy in previous phase II studies for this mode of action reliably informs effects in the Dup15q syndrome population.

Clinically, basmisanil decreases $GABA_A$ α5R function in the brain, as indexed by the decreases in EEG beta-band power (see the Basmisanil Investigator's Brochure). This provides PD evidence that basmisanil can directly target $GABA_A$-related pathomechanisms in Dup15q syndrome, namely excessive $GABA_A$ α5R activity. This study will use EEG beta-band power as a marker of excess $GABA_AR$ function in Dup15q syndrome (see Section 2.2.3). In particular, this study will test for treatment-related quantitative EEG (qEEG) normalizations to increase the confidence that the selected dose of basmisanil affects the $GABA_AR$-related pathophysiology. In case of lack of effects of basmisanil treatment on the Dup15q EEG phenotype at an early interim analysis, which would point to lack of beneficial effects on the GABA-related pathophysiology, the study would be stopped to ensure that participants are not treated unnecessarily (see the interim analyses in Section 4.1.2.2).

Non-clinical evidence further supports a prospect of clinical benefit in Dup15q syndrome following chronic $GABA_A$ α5 negative allosteric modulation. Indeed, beneficial effects were observed in a mouse model of Dup15q (patDp/+), following treatment with a $GABA_A$α5 NAM (RO4938581). RO4938581 has a comparable pharmacological profile to basmisanil (potency, selectivity, and inhibition of GABA-mediated currents, see the Basmisanil Investigator's Brochure). The patDp/+ mouse model shows good construct and face validity with duplication of syntenic mouse equivalent 15q region and models *GABR* copy number gains, as it does not over-express the *UBE3A* gene. In line with the excess *GABR* gene dose, the model recapitulates GABAergic signaling dysfunction in Dup15q syndrome with increased $GABA_A$ α5 receptor (subunits) expression and receptor activity, reflected in single-cell electrophysiology and an increased EEG beta-band power. Beneficial effects on learning inflexibility and abnormal social behavior were observed after chronic treatment with RO4938581 with partial normalization of electrophysiological phenotypes, including the EEG beta-band phenotype (see Basmisanil Investigator's Brochure). This suggests that selectively targeting $GABA_A$ α5Rs is sufficient to rescue impairments linked to $GABA_AR$ dysfunction in Dup15q.

The 52-week study duration *in Part 1* allows for a prospect of direct benefit for pediatric participants receiving basmisanil in this Phase II study across core neurodevelopmental symptoms with anticipated slow-paced changes (see the rationale for study duration in Section 4.2.2). *Additionally, the 2-year OLE (Part 2) allows for a prospect of direct benefit for all study participants who completed Part 1, including those randomized to placebo.*

Moreover, due to the proximal interplay between the disease mechanisms and $GABA_A$ α5Rs and their role in neural development and inhibitory synapse formation, early

intervention is proposed to provide prospect of clinical benefit to pediatric participants in the study (see the rationale for study population in Section 4.2.1 and Section 4.2.2).

### 2.3.3 Overall Benefit/Risk Assessment

The totality of the evidence outlined in Section 2.3 indicates that treatment with basmisanil has the potential to affect disease pathophysiology and core neurodevelopmental symptoms by normalizing the excessive $GABA_A$ α5R activity in Dup15q syndrome, with a prospect of direct clinical benefit for pediatric participants in this study. The thorough safety monitoring plan in place to continuously assess risks in this population (as compared to the established risk profile of basmisanil), with mitigation of the risk of unnecessary drug exposure in absence of an impact on a biomarker of the $GABA_AR$ pathophysiology are in place to safeguard study participants. The benefit/risk balance is thus considered to favorable for pediatric participants in this study, who are affected by a rare disease with no treatment options.

In addition, Study BP42992 will generate unprecedented evidence on the relative contribution of *GABR* genes to the disease and inform the development of therapeutic strategies in Dup15q syndrome. In the absence of natural history data, this study will also provide the first clinical characterization of the disease trajectory over 1 year *(placebo arm in Part 1)*. Independently of study outcome, the knowledge acquired will inform the development of endpoints for future clinical development in this indication and thus contribute to promoting the health of children with Dup15q syndrome.

## 3. OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are provided in Table 5 *for Part 1 and in Table 6 for Part 2.*

**Table 5 Objectives and Endpoints *for Part 1***

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| • To evaluate the effects of *52 weeks of treatment with* basmisanil on core symptom domains of Dup15q syndrome (language and social skills) and daily functioning | • Vineland-3: Adaptive Behavior Composite |
| **Secondary** | |
| **Efficacy** | |
| • To evaluate the effects *of 52 weeks* of *treatment with* basmisanil on: | |
| ○ Motor function | • Vineland-3 gross and fine motor subdomains<br>• MSEL gross and fine motor domains |
| ○ Cognition | • MSEL visual reception domain |
| ○ Language | • Vineland-3 expressive and receptive *communication* subdomains<br>• MSEL expressive and receptive language subdomains |
| ○ Social skills | • Vineland-3 play and leisure time and interpersonal relationships subdomains |
| ○ *Clinician* global impression of *severity and change* | • Dup15q CGI-S and Dup15q CGI-C |
| ○ Challenging behaviors | • ABC-2-C domain scores |
| **Safety** | |
| • To evaluate the tolerability and safety of 52 weeks *of* treatment *with* basmisanil | • Incidence, nature, and severity of AEs and SAEs<br>• Incidence of treatment discontinuations due to AEs<br>• Incidence of laboratory abnormalities based on hematology, clinical chemistry, and urinalysis test results<br>• ECG changes from baseline; incidence of abnormal ECG assessments<br>• Change from baseline in all seizure frequency, duration, and type of seizure as reported in a seizure diary by caregivers |

ABC-2-C = Aberrant Behavior Checklist – Second edition – *Community Version*; AE = adverse event; Dup15q CGI-C = Dup15q syndrome *Clinician* Global Impression *of* Change scale; Dup15q CGI-S = Dup15q syndrome *Clinician* Global Impression *of* Severity scale; MSEL = Mullen Scales of Early Learning; SAE = serious adverse event; Vineland-3 = Vineland Adaptive Behavior Scales–Third Edition.

**Table 5 Objectives and Endpoints *for Part 1* (cont.)**

| Objectives | Endpoints |
|---|---|
| **Secondary (cont.)** | |
| **Safety (cont.)** | |
| • To evaluate the tolerability and safety of 52 weeks of treatment with basmisanil | • Abnormal changes in EEG recordings compared to baseline with a focus on treatment-emergent epileptiform abnormalities<br>• Systolic and diastolic blood pressure and heart rate measurements<br>• Suicidality as assessed through questions from selected items adapted from the C-CASA in *participants* aged 6 years *and above*<br>• Height, weight, head circumference<br>• Tanner staging over time (in *participants* aged 9 years *and above*) |
| **PK** | |
| • To characterize the PK of basmisanil and its metabolite M1 [redacted]<br>• To evaluate potential relationships between selected covariates and exposure to basmisanil | • Plasma concentration of basmisanil and its major metabolite M1 at specified timepoints.<br>• PK parameters for basmisanil: $AUC_{tau,ss}$, $C_{max,ss}$, $C_{trough,ss}$, CL/F, Vd/F<br>• Plasma concentration ratio of M1 to basmisanil at trough<br>• PK parameters for M1: $C_{max,ss}$, $C_{trough,ss}$<br>• Other PK parameters as appropriate |
| **PD** | |
| • To evaluate the effects of basmisanil treatment on the characteristic Dup15q EEG phenotype acutely and at steady state | • qEEG beta-band power |

$AUC_{tau,ss}$ = area under the concentration–time curve during one dosing interval at steady state; C-CASA = Columbia Classification Algorithm for Suicide; CL/F = apparent clearance; $C_{max,ss}$ = maximum concentration at steady state; $C_{trough,ss}$ = trough plasma concentration at steady state; PD = pharmacodynamics; PK = pharmacokinetics; qEEG = quantitative EEG; Vd/F = apparent volume of distribution.

**Table 5 Objectives and Endpoints *for Part 1* (cont.)**

| Objectives | Endpoints |
|---|---|
| **Exploratory** | |
| **Efficacy** | |
| • To evaluate the effect of *52 weeks of treatment with* basmisanil on: | |
| ○ Restrictive and repetitive behaviors | • RBS-R total score |
| ○ Health-related quality of life *of the* caregiver | • PedsQL-FIM |
| ○ *C*ommunication | • ORCA |
| ○ Caregiver global impression of *severity and change* | • Dup15q CaGI-S and Dup15q CaGI-C |
| ○ Autism symptoms | • ADOS-2 |
| ○ Hypotonia | • Clinician rating of hypotonia |
| ○ Sleep | • CSHQ |
| ○ Gait (ambulant participants only) | • [redacted] |
| ○ *Qualitative changes in Dup15q symptoms or developmental skills* | • *Semi-structured, 1-hour (phone call) interview with caregivers of study participants* |
| **PK relationship to efficacy, safety, and PD** | |
| • To evaluate potential relationships between drug exposure and the efficacy, safety and PD of basmisanil | • Relationship between plasma concentration or PK parameters for basmisanil or M1 (if appropriate) and efficacy, safety, and PD endpoints |
| **PD** | |
| • To evaluate maintenance of EEG PD effect over the treatment period | • qEEG beta-band power |

ADOS-2 = Autism Diagnostic Observational Schedule, second edition; CSHQ = Children's Sleep Habit Questionnaire; Dup15q CaGI-C = Dup15q syndrome Caregiver Global Impression *of* Change scale; Dup15q CaGI-S = Dup15q syndrome Caregiver Global Impression *of* Severity scale; ORCA = Observer-Reported Communication Ability; PedsQL-FIM = Pediatric Quality of Life Inventory™ Family Impact Module; PD = pharmacodynamics; PK = pharmacokinetics; qEEG = quantitative EEG; RBS-R = Repetitive Behavior Scale–Revised.

*Table 6 Objectives and Endpoints for Part 2 – Optional OLE*

| Objectives | Endpoints |
|---|---|
| ***Exploratory*** | |
| ***Safety*** | |
| • *To evaluate the tolerability and safety of up to 3 years of treatment with basmisanil* | • *Incidence, nature, and severity of AEs and SAEs*<br>• *Incidence of treatment discontinuations due to AEs*<br>• *Incidence of laboratory abnormalities based on hematology, clinical chemistry, and urinalysis test results*<br>• *ECG changes from baseline; incidence of abnormal ECG assessments*<br>• *Change from baseline in all seizure frequency, duration, and type as reported in a seizure diary by caregivers*<br>• *Abnormal changes in EEG recordings compared to baseline with a focus on treatment emergent epileptiform abnormalities*<br>• *Systolic and diastolic blood pressure and heart rate measurements*<br>• *Suicidality as assessed through questions from selected items adapted from the C-CASA in participants aged 6 years and above*<br>• *Height, weight, head circumference*<br>• *Tanner staging over time (in participants aged 9 years and above)* |
| ***Efficacy*** | |
| • *To evaluate the effects of up to 3 years of treatment with basmisanil on core symptom domains of Dup15q syndrome (language and social skills) and daily functioning* | • *Vineland-3: Adaptive Behavior Composite* |

*AE = adverse event; C-CASA = Columbia Classification Algorithm for Suicide Assessment; ECG = electrocardiogram; EEG = electroencephalogram; OLE = open-label extension; SAE = serious adverse event; Vineland-3 = Vineland Adaptive Behavior Scales–Third Edition.*

*Table 6 Objectives and Endpoints for Part 2 – Optional OLE (cont.)*

| Objectives | Endpoints |
|---|---|
| ***Efficacy (cont.)*** | |
| • *To evaluate the effects of up to 3 years of treatment with basmisanil on:* | |
| ○ *Motor function* | • *Vineland-3: gross and fine motor subdomains*<br>• *MSEL: gross and fine motor domains* |
| ○ *Cognition* | • *MSEL visual reception domain* |
| ○ *Language* | • *Vineland-3 expressive and receptive communication subdomains*<br>• *MSEL expressive and receptive language subdomains* |
| ○ *Social skills* | • *Vineland-3 play and leisure time and interpersonal relationships subdomains* |
| ○ *Clinician global impression of severity and change* | • *Dup15q CGI-S and Dup15q CGI-C* |
| ○ *Challenging behaviors* | • *ABC-2-C domain scores* |
| ○ *Health-related quality of life of the caregiver* | • *PedsQL-FIM* |
| ○ *Caregiver global impression of severity and change* | • *Dup15q CaGI-S and Dup15q CaGI-C* |
| ***PK*** | |
| • *To characterize the PK of basmisanil and its metabolite M1* [redacted] | • *Concentration per timepoint for basmisanil and M1* |
| • *To evaluate potential relationships between selected covariates and exposure to basmisanil, if appropriate* | • *PK parameters as appropriate* |

*ABC-2-C = Aberrant Behavior Checklist - Second Edition – Community Version; Dup15q CaGI-C = Dup15q syndrome Caregiver Global Impression of Change scale; Dup15q CaGI-S = Dup15q syndrome Caregiver Global Impression of Severity scale; Dup15q CGI-C = Dup15q syndrome Clinician Global Impression of Change scale; Dup15q CGI-S = Dup15q syndrome Clinician Global Impression of Severity scale; MSEL = Mullen Scales of Early Learning; OLE = open-label extension; PD = pharmacodynamics; PedsQL-FIM = Pediatric Quality of Life Inventory™ Family Impact Module; PK = pharmacokinetics; qEEG = quantitative EEG; Vineland-3 = Vineland Adaptive Behavior Scales–Third Edition.*

*Table 6 Objectives and Endpoints for Part 2 – Optional OLE (cont.)*

| Objectives | Endpoints |
|---|---|
| ***PD*** | |
| • *To evaluate maintenance of EEG PD effect over the treatment period* | • *qEEG beta-band power* |
| ***PK relationship to efficacy, safety, and PD*** | |
| • *To evaluate potential relationships between drug exposure and the efficacy, safety and PD of basmisanil* | • *Relationship between plasma concentration or PK parameters for basmisanil or M1 (if appropriate) and efficacy, safety, and PD endpoints* |

*EEG = electroencephalogram; OLE = open-label extension; PD = pharmacodynamics; PK = pharmacokinetics; qEEG = quantitative EEG.*

# 4. STUDY DESIGN

## 4.1 OVERALL DESIGN

An overview of the study design is provided in Section 1.2.

This *study consists of two parts. Part 1* is a multi-center, randomized, double-blind, placebo-controlled, parallel group study to evaluate *the* safety, efficacy, and pharmacodynamics of 52 weeks of basmisanil treatment in children *and young adolescents* aged 2 to *14* years with Dup15q syndrome. *Part 2 is a 2-year optional OLE on basmisanil.*

*In Part 1,* approximately 90 participants will be randomized 2:1 to receive oral treatment with either basmisanil or placebo for 52 weeks (BID on the first day of treatment in the clinic (Day 1) and three times a day [TID] for the remaining study duration; see Section 4.3 for justification*)*.

Randomization will be stratified by age *group* (2 to 5 years vs. 6 to *14* years), number of copies of the 15q11.2-q13.1 region (3 copies vs. 4 copies), and epilepsy (presence vs. absence). *All participants who have completed 52 weeks of treatment in Part 1 will be offered the option to roll over directly to the OLE (Part 2) without completing the follow-up visit in Part 1 (no treatment gap). No new patients will be enrolled in the OLE. All participants in Part 2 will receive oral treatment with basmisanil for approximately 2 years (see Section 4.3 for justification).*

***Assessments for Part 1 and Part 2***

Efficacy, safety, PK, and PD assessments will be conducted throughout the study, as detailed in the SoA (*Section 1.3*). Participants will be closely monitored on the Day 1, Day 2 *(Part 1) and Day 366 (Part 2)* clinic visits, during which PK samples will be

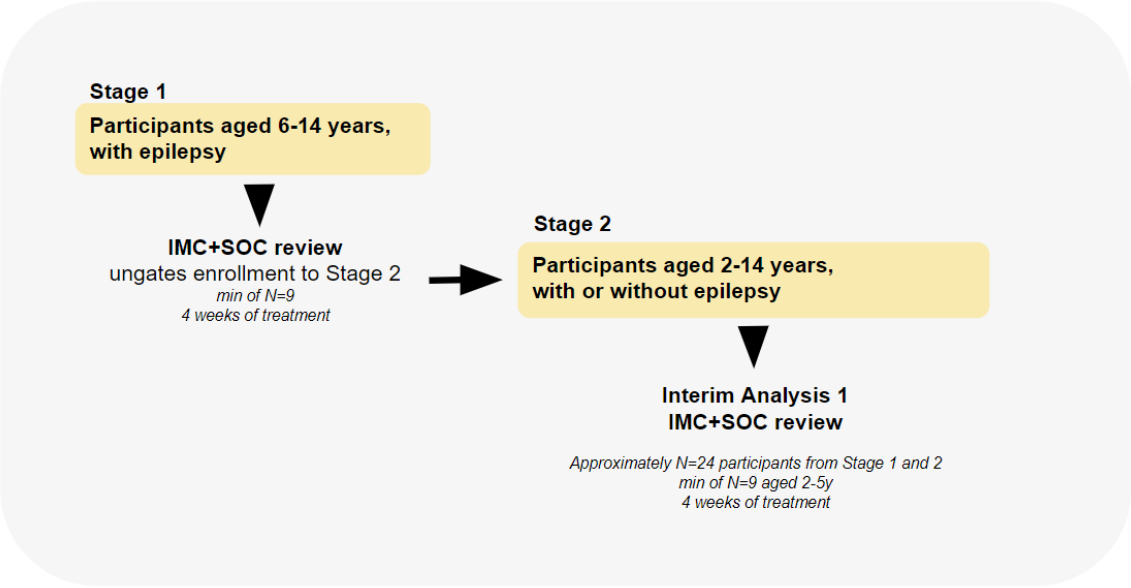
obtained, and EEG recordings and relevant safety assessments will be performed (see SoA *in Section 1.3*).

*In Part 1,* recruitment will be staggered as follows (see Figure 2):

- By age [redacted] to assess safety in participants aged 6 to *14* years before exposing participants aged 2 to 5 years, see Figure 2.
- By presence or absence of epilepsy to assess the effect of basmisanil on seizures before enrolling participants without epilepsy (for rationale see Section 4.2.1).

The study consists of *two* stages:

**Figure 2 Staggered Enrollment *in Part 1***




IMC = Internal Monitoring Committee; N = number of participants; SOC = Scientific Oversight Committee; y = years.

Staggered enrollment *by age and presence or absence of epilepsy* will be implemented as follows:

- **Stage 1**: Participants between ages 6 and *14* years *(inclusive)* with epilepsy will be enrolled.

  Data from *a minimum of 9 participants enrolled in* Stage 1 will be reviewed by an IMC + SOC as described in Section 4.1.2.2 prior to opening recruitment to participants aged 2 to 5 years *and participants without epilepsy* into Stage 2.

- **Stage 2**: *The remaining* participants aged 2 to *14* years with *or without epilepsy* will be enrolled *following IMC + SOC recommendation to reach a total sample size of approximately N=90*.

  Data from *participants enrolled into* Stage 1 and 2 will be included in *periodic* reviews by the IMC + SOC and a first interim analysis *will be performed when approximately N=24 participants reach 4 weeks of treatment,* as described in Section 4.1.2.2.

Overall, the study *aims* to enroll *a minimum of* approximately one-third of *participants aged* 2 to 5 years *and a maximum of approximately one-fifth of participants aged 12 to 14 years*.

**Treatment Groups and Duration**

Treatment with basmisanil or placebo granules, packaged in stick-packs, will be administered orally within 30 minutes after the start of a meal *(see Section 6.4)*.

**Table 7 Starting Doses According to the Age of the Participants:**

[redacted]

*In Part 1, the starting dose is determined according to the participant's age at the time of signing of the Informed Consent Form, and maintained for the 52-week treatment duration.*

*In Part 2, the starting dose, dosing regimen and age-defined dose groups are initially the same as for Part 1 (Day 2 and onwards) and determined based on the participant's age at the start of Part 2 (Day 366 visit). During Part 2, the dose will be adjusted according to the participant's actual age. If applicable, the dose must be changed at the latest on the first dispensation visit after a participant moves into a different age group.*

*Dose and dose regimen for participants aged 15 to 17 years are predicted to be similar to what has been determined as the starting steady state regimen in Part 1 for 10 to 14 years old* [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

### 4.1.1 Length of the Study

The *planned* total study duration is approximately 61 weeks *for participants who participate in Part 1 only and 165 weeks for those participating in Parts 1 and 2,* divided into the following periods:

- Screening period of *up to* 5 weeks (Day –35 to Day –2), which may overlap with the baseline period (Day –7 to Day –1)
- Double-blind 52-week treatment period (Day 1 to Day 365)
- *Optional OLE treatment period of approximately 2 years/104 weeks (Day 366 to Day 1095/Year 3)*
- Follow-up period of approximately 4 weeks *(Part 1: Days 365 to 395 or Part 2: Days 1095 to 1125)*

The screening period starts once the first screening assessment is performed (not with signing the Informed Consent Form [ICF]). *All screening assessments required to confirm participant's eligibility for study participation need to be completed with results available before the Baseline visit*. The Baseline visit can be done anytime between Day - 7 and Day -1.

### 4.1.2 Internal Monitoring Committee and Scientific Oversight Committee

#### 4.1.2.1 Administrative Structure

**Internal Monitoring Committee**

A Sponsor IMC will be responsible for regular reviews of accumulating safety, tolerability, and [redacted] in terms of tolerability and exposure. The IMC will consist of internal Sponsor experts representing Clinical Pharmacology, Pharmacometrics, Clinical Science, Drug Safety, Statistics, as

well as Biomarkers. Attendance at IMC meetings will be determined by the purpose of the IMC meeting; not all members are expected to be required for all meetings.

IMC members will review unblinded aggregated information as part of all reviews and interim analyses, i.e., summary information by treatment arm. As required by their functional expertise, selected IMC members (e.g., clinical pharmacology, drug safety) may be unblinded also at a participant level.

Individual study team members outside the IMC required to prepare information for IMC review will be unblinded to the treatment assignment of individual participants. Access to treatment assignment information will follow the Sponsor's standard procedures.

**Scientific Oversight Committee**

*During Part 1 of the study,* an SOC will help monitor safety and tolerability data *until all participants have completed or were prematurely withdrawn from Part 1. Specifically, the SOC will help* interpret any changes in seizure status and/or EEG findings in this patient population, to ensure that the study in its current form does not pose unacceptable safety risks to participants. The SOC will consist of one or more external neurologist/epileptologist with expertise in pediatric epilepsy in neurogenetic disorders and who is not an Investigator in this study. The SOC members will also review unblinded aggregated information and may be unblinded at the participant level if required.

A separate IMC+SOC agreement will include additional details on membership and procedures.

#### 4.1.2.2 Review Objectives and Procedures

*During Part 1, the* IMC will perform periodic reviews of all available PK exposure, safety, and tolerability data, including up to two interim analyses as described below. As part of these reviews, the SOC may be consulted on the interpretation of safety and tolerability data if required. "IMC+SOC" is used to refer to these reviews with the focus as described below.

***Periodic* reviews during enrollment of the first *24* participants in *Part 1* Stages 1 and 2**:

*The* objective*s* of *the IMC+SOC periodic reviews of* the initial PK and safety *data are* to:

[redacted]

(2) confirm that data support opening enrollment into Stage 2.

The clinical pharmacologist, supported by a pharmacometrician, will review exposure data on a continuous basis. [redacted]

Once a minimum of 9 participants have completed their first 4 weeks of dosing in **Stage 1**, the IMC+SOC will perform a review of all available PK exposure, safety, and tolerability data. Based on this review, the IMC may [redacted]

Periodic reviews of PK and safety data by the IMC+SOC will continue throughout the course of the study.

**Interim analyses**:

In addition to the aforementioned reviews of PK and safety data, the IMC+SOC will also oversee up to two interim analyses:

- The **first interim analysis** occurs once approximately 24 participants (i.e., the participants of Stages 1 and 2), with a minimum of 9 participants aged 2 to 5 years, have completed 4 weeks of treatment. In addition to PK, safety, and tolerability data, the IMC+SOC will review the effect of basmisanil treatment on the Dup15q EEG phenotype (qEEG beta-band power).

  The IMC may recommend continuing the study unchanged, to adapt the dose, to decrease PK and/or safety assessments, or to stop the study in case of significant safety findings or in case of lack of effect of basmisanil treatment on the Dup15q EEG phenotype.
- A **second interim analysis** may occur as described in Section 9.5. Following review of the data, the IMC may recommend to continue the study unchanged or to terminate the study if benefit / risk considerations make a continuation unethical.

The study will continue to enroll participants during the conduct of both interim analyses. Details of interim analyses will be described in a technical document, which will be stored in the Sponsor's trial master file.

### 4.1.3 Stopping Rules Criteria

Dosing will be stopped at any time during the study in a given individual participant if one of the following circumstances occurs:

- A QTc using the Fridericia's correction factor (QTcF) value > 480 msec (when confirmed in repeat measurement within 30 minutes) or a QTcF change from baseline > 60 msec (when confirmed in repeat measurement within 30 minutes) for participants **older than 10 years old**;

  OR

- A QTc using Bazett's formula (QTcB) value > 480 msec (when confirmed in repeat measurement within 30 minutes) or a QTcB change from baseline > 60 msec (when confirmed in repeat measurement within 30 minutes) for participants **up to, and including, the age of 10 years** (Bazett's correction is more appropriate in young children, see Section 8.2.6).
- Worsening of seizure frequency or occurrence of de novo seizures, which are considered clinically relevant in the opinion of the Investigator based on the following criteria:
  - persistent over time,

    OR

  - notably deviate from the expected fluctuations in seizure status based on the participant's medical history,

    OR

  - cannot be explained by the expected natural course of the disease,

    OR

  - making the benefit-risk ratio non-favorable for the individual.

Other AEs that may lead to discontinuation of study treatment following evaluation on a case-by-case basis are described in Section 8.3.8. Before permanently discontinuing study treatment, an interruption should be considered, and study treatment may be restarted as detailed in Section 6.6.1. Unless it is determined by the Investigator that the occurrence is not related to the administration of study treatment, study treatment should not be restarted (see Section 7.1).

## 4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study rationale is provided in Section 2.1.

### 4.2.1 Rationale for Study Population

The study will be conducted in male and female participants with maternal duplication or triplication of the chromosome 15q11.2-q13.1 region, aged 2 to *14* years *at the time of signing the Informed Consent Form*.

Participants with 3 or 4 copies of 15q11.2-q13.1 region, both int(15) and idic(15)

The study population includes patients with Dup15q syndrome, defined by a maternal duplication (resulting in 3 copies) or triplication (resulting in 4 copies) *containing* the Prader-Willi/Angelman Critical Region on chromosome 15q11.2-q13.1. It includes the $GABA_A$ subunit gene cluster encoding for 3 receptor subunits that together form $GABA_A$ α5-containing receptors. Both int(15) and idic(15) genetic subtypes present with the characteristic EEG signature that index excess $GABA_A$ function consequent to the copy

number gains (Section 2.2.1 and Section 2.2.3) and are thus expected to benefit from treatment with basmisanil. The effect of copy numbers on response to treatment will be explored in this study if applicable.

Participants aged 2 to *14* years

Dup15q syndrome is an NDD with symptoms such as central hypotonia, infantile spasm and feeding difficulties emerging early in infancy. Motor and cognitive developmental delays are typically recognized in early childhood. Because of the neurodevelopmental nature of the disorder, early symptoms in Dup15q syndrome likely contribute to poorer clinical outcomes, as suggested by greater clinical severity of children with infantile spasms compared with children with other epilepsy types which emerge later in childhood (DiStefano et al 2020). Hypotonia and impaired motor skills in early childhood may also negatively influence learning, language, and speech acquisition, and the development of social skills, as in other NDDs (Wilson et al 2018). Early intervention offers the opportunity to affect the trajectory of the disease by altering early brain development and maximizing learning and socialization opportunities during key neurodevelopmental stages (Vivanti et al 2018).

To which extent efficacy in adults with NDDs predicts treatment effects in children remains a matter of debate. Long-term neural adaptations and impact of the disease on brain function (e.g., decades of epilepsy for some patients), the difference in profiles of co-morbidities, and co-medications have been proposed as potential confounding factors. Early intervention during developmental stages in childhood, as early as possible following diagnosis (see Section 2.2.1) is thus proposed to provide greater prospect of benefit on neurodevelopmental outcomes in children. Greater effects may theoretically be expected for treatment with basmisanil at early developmental stages, when GABAergic control shapes inhibitory neuronal function (see Section 2.1) *but are anticipated to be beneficial throughout neurodevelopment into early adulthood.*

Adolescents (>11 years) *may present with more variable response to treatment, due to greater* heterogeneity in terms of developmental stages and to the interference of multiple factors emerging at adolescence such as the physiological changes linked to puberty, parent- and clinician-reported instability in symptoms (e.g., behavioral difficulties or anxiety), as well as important social and environmental changes during the teenage years. *Taking into account the significant delay in development associated with Dup15q syndrome, and the inclusion criterion of at least "moderate" disease severity as measured by Dup15q-CGI-S, inclusion of young adolescents aged 12 to 14 years is considered a reasonable extension of the pediatric study population. The effect of age on response to treatment will be explored in this study.*

Epilepsy

*Individuals* with uncontrolled epilepsy *(as defined for this study in Section 5.2)* are excluded from the study because of expected general instability from both safety and efficacy perspectives, and because of polypharmacy concerns, both of which may directly interfere with signal detection and reliable assessment of benefit/risk for the broader Dup15q syndrome population.

Study population for *Part 1* Stages 1 and 2 (see Figure 2)

The good safety and tolerability profile of basmisanil has been clinically established in more than 500 individuals (see Section 2.2.3.2), including pediatric patients with Down syndrome aged ≥6 years, but excluded patients with *an ongoing* medical history of epilepsy. The study population in Stage 1 will be restricted to *participants* aged 6 to *14* years with epilepsy, to establish the safety and tolerability profile of basmisanil in *older participants before enrolling younger participants aged 2 to 5 years, and to establish the safety and tolerability profile of basmisanil in participants who have epilepsy before enrolling* participants without epilepsy *into Stage 2*.

### 4.2.2 Rationale for Study Duration

Developmental progression is slowed in children affected by severe NDDs associated with intellectual disability, and meaningful improvements in core neurodevelopmental symptoms likewise likely require time to manifest. Beneficial treatment effects on neurodevelopmental gains are also anticipated to increase with treatment duration. Longer trials, particularly in pediatric populations, have been recommended by expert working groups for trials in rare NDDs based on the experience in other neurogenetic syndromes (e.g., Berry-Kravis et al 2018). A duration of 52 weeks, as recommended by an expert advisory panel consulted by the Sponsor, was selected to maximize the detection of meaningful changes on core neurodevelopmental features of the disorder *in the placebo-controlled part of the study*, as captured by the primary measure (Vineland-3: language, social skills and impact on daily functioning) and key secondary measures (Mullen Scales of Early Learning [MSEL]: motor and cognitive development). To ensure that the participants enrolled in this study are not treated unnecessarily for 52 weeks, at least one interim analysis will be performed to re-evaluate benefit/risk (see Section 4.1.2.2).

*The* 52-week study duration *in Part 1* will also generate the first longitudinal characterization of the *natural* trajectory of the disease in Dup15q syndrome, which is needed to support the determination of meaningful improvement on core disease domains.

*The OLE duration will allow the collection of long-term safety and tolerability data of a minimum of 2 years of basmisanil treatment in all Part 2 participants, and up to 3 years for those randomized to basmisanil in Part 1, and thus maximize the safety*

*information on basmisanil in this rare disorder. Additionally, it may provide supportive evidence of continued treatment benefit on key efficacy outcomes.*

### 4.2.3 Rationale for Assessments

#### 4.2.3.1 Electroencephalography

EEG will be assessed at several timepoints throughout the study (see the SoA in Section 1.3), and it serves several purposes.

Biomarker: Quantitative EEG

The background EEG in the awake state of individuals with Dup15q syndrome shows markedly abnormal (excess) beta-band power and is thought to index excess $GABA_A$ neurotransmission (Urraca et al 2013, Frohlich et al 2016, Frohlich et al 2019). This EEG abnormality will be quantified (qEEG) at several timepoints (qEEG blocks) to test for treatment-related changes (see Section 8.6.2).

Monitoring of *Epileptiform Activity*

Approximately *60%* of individuals with Dup15q syndrome have epilepsy, which affects patients with idic(15) (60% to 80%) more frequently than those with int(15) duplications (16 to 25%) (*Kalsner et al 2015,* Conant et al 2014, Beghi et al 2020, Battaglia et al 2016). Participants enrolled in Stage 1 of the study will have a medical history of epilepsy*, while participants enrolled in Stage 2 may or may not have epilepsy*.

*Clinical seizures* will be closely monitored during the study *in all participants to ensure participant safety (see Section 8.2.9) and also in order to investigate potential changes in seizure activity (see Section 8.2.4).*

*Seizure activity may be captured by the Investigator as* AEs *(see criteria in Sections 8.3.6 and 8.3.7)* and*/or entered in the* seizure status *section of the eCRF following joint review of the* caregiver-completed seizure diary *with the caregiver (*see Section 8.1.3).

Furthermore, EEG recordings will be *reviewed by a* central reader *(qualified neurologist independent of the site personnel)* for potential treatment-emergent epileptiform abnormalities *such as sharp wave, spike, spike-wave, or polyspike, and seizures (see Section 8.2.9).*

#### 4.2.3.2 Gait Assessment

Gait in Dup15q syndrome is impaired, characterized by poor postural control, and large gait variability (Wilson et al 2020). *In Part 1,* gait abnormalities and potential treatment-related changes will be quantified in the home setting, using wearable devices that will be attached to the [redacted]

### 4.2.4 Rationale for Control Group

The study is placebo controlled, as there is no approved treatment for the Dup15q syndrome. Given the lack of natural history data, a placebo-controlled design is required to assess benefits and risks of basmisanil treatment objectively. Improvements and developmental progress in the enrolled participants *are* expected over the one-year course of the study; therefore, *in Part 1 of the study* a placebo arm is essential to distinguish improvements due to natural development from the possible beneficial effects of basmisanil treatment. A placebo-controlled trial remains the most methodologically rigorous approach to assess the effect size of prospective new medicines (Di Pietro et al 2015).

[redacted] - in line with the envisaged mechanism of action of normalizing the gain-of-function of $GABA_A$ $\alpha$5 receptors - the aim is to block RO maximally [redacted].

Occupancy by basmisanil of the $GABA_A$ $\alpha$5-containing receptor subtype in the brain has been investigated using PET imaging in healthy volunteers and in individuals with Down syndrome. A direct relationship between basmisanil plasma concentrations and RO was established, [redacted]

Basmisanil is predominantly cleared by metabolism via CYP3A. [redacted]

A PBPK model integrating available pediatric data from two previous studies in participants with Down syndrome (Study WP28760 [SEAHORSE] and Study BP27832

[CLEMATIS]) and adult information was developed *(Basmisanil Investigator's Brochure)*. [redacted]. The pediatric PBPK model was used to simulate basmisanil exposure and variability in pediatric participants aged 2 to 11 years [redacted]. It predicted median $AUC_{0\text{-}12h}$ and $C_{max}$ values in this [redacted] TID dosing is predicted to result in higher plasma exposures than what can be achieved with BID due to absorption limitation.

[redacted]

*For the starting doses according to the age of the participants, see Section 4.1 (treatment groups and duration).*

A dosing algorithm has been defined utilizing available combinations of stick-packs with different dose strengths to provide a range of exposures comparable to those in adults across the full age range of children enrolled in this study.

**Dosing regimen**

[redacted] BID dosing was selected for the first dosing day *(in clinic)*. In addition, to characterize the exposure–EEG relationship (both acute safety (safety EEGs) and PD (qEEG beta-band power), a wide concentration range will be covered in the first two days of dosing. The dosing regimen changes to TID from Day 2 onwards to reach targeted exposure levels at steady state throughout the 52-week treatment period *in Part 1 and the 2-year treatment period in Part 2*.

Further details *on the justification for dose* are provided in the Basmisanil Investigator's Brochure.

## 4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last scheduled procedure per SoA or withdrawal of consent.

The end of the study is defined as the date when the last participant's last observation occurs.

# 5. STUDY POPULATION

The study population rationale is provided in Section 4.2.1.

The participants in this study will be female and male children *and adolescents* aged 2 to *14* years at *the* time of signing the *ICF for Part 1* with genetically confirmed maternal duplications (3 copies) or triplications (4 copies) of chromosome 15q11.2-q13.1 (Dup15q syndrome), who fulfill all of the given inclusion criteria and none of the exclusion criteria. *The criteria to participate in Part 2 optional OLE are described in Section 6.7.*

Prospective approval of protocol deviations, also known as protocol waivers or exemptions, is not permitted.

## 5.1 INCLUSION CRITERIA

Participants are eligible to be included in *Part 1 of* the study only if all of the following criteria apply:

**Informed Consent/Age**

1. Participants aged 2 to *14* years inclusive at the time the caregiver signs the informed consent.

**Type of Participants and Disease Characteristics**

2. In the investigator's opinion, able to participate and deemed appropriate for participation in the study.
3. Documented maternal duplication (3 copies) or triplication (4 copies) of the chromosome 15q11.2-q13.1 region that includes the Prader-Willi/Angelman critical region defined as [BP2-BP3] segment.
4. Dup15q syndrome *Clinician* Global Impression *of* Severity scale (Dup15q CGI-S) overall severity score≥4 (at least moderately ill).
5. Stage 1 *specific inclusion criterion*: Participants *aged 6 to 14 years* with epilepsy.

**Weight**

6. Body weight equal to or above the third percentile for age.

**Sex and Contraception/Barrier Requirements**

7. Male and female participants

Some of the provisions that follow may have limited applicability based on the age range of study participants (i.e., up to the age of $14$) and the nature of the disease under study. These provisions are nonetheless included for purposes of completeness to make clear that individuals who are pregnant or are engaging in actions that may cause them to become pregnant, should not participate in this study. Consent must be provided by the legal representative for all participants.

a) Female Participants

A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

- Female participants of non-childbearing potential, as defined in Appendix 5.
- Female participants of childbearing potential who agree to remain abstinent (refrain from heterosexual intercourse) or use acceptable contraceptive methods during the treatment period and for at least 28 days after the final dose of study treatment. The following are acceptable contraceptive methods: bilateral tubal occlusion/ ligation, male sexual partner who is sterilized, established proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices and copper intrauterine devices, male or female condom with or without spermicide; and cap, diaphragm, or sponge with spermicide.

b) Male Participants

Male contraception is not required in this study because of the minimal seminal dose transmitted through sexual intercourse.

**Caregiver Requirements**

8. The participant has a parent, caregiver, or legally authorized representative (hereinafter “caregiver”) of at least 18 years of age, who is fluent in the local language at the site, and capable and willing to provide written informed consent for the participant according to International Council $for$ Harmonisation and local regulations.
9. The participant’s caregiver must be living with the participant and, in the opinion of the Investigator, able and willing to reliably assess the participant’s ongoing condition, to accompany the participant to all clinic visits, and ensure compliance to study treatment throughout the study. The same caregiver is able and willing to complete the caregiver assessments and is available to the Investigational Site by telephone or email if needed.
10. The participant’s caregiver is able and willing to use electronic devices to record information on the participant’s condition and to complete assessments at home and agrees to home nursing visits, if local regulations allow for it and if home nursing service is available in the country/region.

## 5.2 EXCLUSION CRITERIA

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

**Medical Conditions**

1. Uncontrolled epilepsy at screening as indicated by:
   a) Use of rescue medication*(s) to treat* more than *one seizure episode or seizure cluster* per month on average in the past 6 months,

      OR

   b) Concomitant *chronic* use of more than 4 anti-epileptic medications,

      OR

   c) Status epilepticus within the past 6 months requiring hospitalization for treatment of the status epilepticus,

      OR

   d) Any implanted devices to treat drug-resistant epilepsy
2. Lymphoma, leukemia, or any malignancy within the past 5 years, except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
3. Clinically significant ECG abnormalities at screening, including an average triplicate QTcF > 450 ms for participants > 10 years or QTcB > 450 ms for children up to and including age 10 years (because Bazett's correction is more appropriate in young children).
4. Clinically significant abnormalities in laboratory test results at screening (including positive results for HIV, hepatitis B and/or hepatitis C). ALT values > 1.5 × the upper limit of normal (ULN; re-testing is allowed to confirm). GFR < 90 mL/min per 1.73 m2 (Grade 1 CKD) as estimated using Schwarz formula.

**Prior/Concomitant Therapy**

5. Allowed prior existing medication should be on a stable regimen (or frequency of intervention) for at least 6 weeks, and at least 8 weeks for anti-epileptic treatment, prior to screening.
6. Non-pharmacological / behavioral therapies should not be stopped or newly started at least 6 weeks prior to screening and are expected to remain stable for the entire study duration (excluding changes related to standard age and educational interventional programs and minor interruptions such as illness or vacation).
7. Concomitant use of prohibited medications (Section 6.5.2).

**Prior/Concurrent Clinical Study Experience**

8. Participation in an investigational drug study within one month or within 6 × the elimination half-life, whichever is longer, prior to dosing in the study.

**Other Exclusions**

9. Significant risk for suicidal behavior, as assessed through the suicidal behavior question adapted from the Columbia Classification Algorithm for Suicide Assessment (C-CASA) (participants ≥ 6 years of age only).
10. Known sensitivity to any of the study treatments or components thereof, or drug or other allergy that, in the opinion of the Investigator, contraindicates the participation in the study, including severe lactose intolerance (e.g., unable to tolerate 250 mL [8 oz. or 1 cup] of milk, ice cream, or yogurt).
11. Concomitant clinically relevant disease or condition or any clinically significant finding at screening that could interfere with, or for which, the treatment might interfere with, the conduct of the study or that would pose an unacceptable risk to the participants in this study.
12. Known active or uncontrolled bacterial, viral, or other infection (excluding fungal infections of nail beds) or any major clinically significant episode of infection or hospitalization (relating to the completion of the course of antibiotics) within 6 weeks prior to the start of drug administration.

## 5.3 LIFESTYLE CONSIDERATIONS

Throughout the study, due to a food effect on basmisanil exposure (see Section 2.2.3.2.2), a meal should be given before each study treatment administration. *In Part 1,* on Day 1, Day 2, Day 14*, and Day 365* study visits *and in Part 2, on Day 366 and Day 1095 study visits*, the meals should be taken as per the timings given in the detailed SoA (Table 2 *and Table 4 for Part 1 and Part 2, respectively*) to allow for adequate characterization of PK properties. Participants are allowed to eat additional snacks/meals and water is allowed ad libitum.

*A ketogenic diet should be on a stable regimen for 6 weeks prior to screening and should not be stopped or newly started throughout the study until the Part 1 follow-up visit for participants who do not continue study participation in Part 2 or until the Day 548 visit for participants who roll over to Part 2 of the study.* Any other dietary restrictions should be documented.

## 5.4 SCREEN FAILURES

Screen failures are defined as participants whose consent has been obtained via a caregiver to participate in the study but are not subsequently randomized to study treatment. Screen failures may be tracked separately.

The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

Screen-failed participants may be re-screened with Sponsor permission (Medical Monitor or designee) if there is a substantial change in the participant's general condition

(e.g., stabilization of medication or clinical status) and if recruitment for the study is still ongoing.

Re-screening is also allowed for participants who were screened in the study and met all inclusion/exclusion criteria but failed to be randomized within the combined screening (Day -35 to Day -2) and Baseline (Day -7 to Day -1) window because of a study halt, or logistical, personal, or technical reasons (including availability of screening test results).

Consultation with the Medical Monitor may be needed to identify whether repeat testing of any particular parameter is clinically relevant, on a case-by-case basis. The most current result prior to enrollment is the value by which study inclusion will be assessed, as it represents the participant's most current clinical state.

Re-screening is permitted once per participant. Samples of screen failures will not be retained for further analysis.

### 5.5 RECRUITMENT PROCEDURES

Participants will be identified for potential recruitment using pre-screening enrollment logs, clinical database, referrals from other clinicians, patient groups, and Institutional Review Board (IRB)/Independent Ethics Committees (IEC) approved participant-facing recruitment materials prior to consenting to take place in this study.

## 6. TREATMENTS

Study treatment is defined as any investigational product (including placebo) or marketed product intended to be administered to a study participant according to the study protocol.

The investigational medicinal products (IMP) for this study are basmisanil and placebo. *Appendix 6 identifies all IMPs and auxiliary medicinal products (AxMPs)/non-investigational medicinal products (NIMPs).* All IMPs required for completion of this study will be provided by the Sponsor.

Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated AEs, should be reported as described in Appendix 2, Section 5.2.

### 6.1 TREATMENTS ADMINISTERED

*Table 8 and Table 9* summarize the treatments administered *in Part 1 and Part 2, respectively*. Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 6.6 or Section 7, respectively.

**Table 8 Summary of Treatments Administered *in Part 1***

| Study Treatment Name: | Basmisanil (RO5186582) | Placebo |
|---|---|---|
| [redacted] | | |
| Dose[b]: | [redacted] | |
| Route of Administration: | oral | oral |
| Sourcing: | Provided centrally by the Sponsor | |
| Packaging and Labeling: | Study treatment will be provided in boxes. Each box will be labeled as required per country requirement. | |

BID = twice a day; NA = not applicable; TID = three times a day.

[a] Study treatment will be provided [redacted] The number of stick-packs to be *taken* per administration will depend on the participant's age at *the time of signing the Informed Consent Form.*

[b] *Doses are determined according to the age of the participant at the time of signing the Informed Consent Form and will not change if a participant moves into another age group. These are the starting doses for participants being enrolled in Part 1,* [redacted] *(see Sections 4.1 and 6.6).*

*Table 9 Summary of Treatments Administered in Part 2*

| *Study Treatment Name:* | *Basmisanil (RO5186582)* |
|---|---|
| *Use:* | [redacted] |
| *Dose Formulation:* | |
| *Unit Dose Strength:* | |
| *Dose[b]:* | |
| *Route of Administration:* | *oral* |
| *Sourcing:* | *Provided centrally by the Sponsor* |
| *Packaging and Labeling:* | *Study treatment will be provided in boxes. Each box will be labeled as required per country requirement.* |

*BID = twice a day; PBPK = physiologically-based pharmacokinetic; PK = pharmacokinetic; TID = three times a day.*

[a] *Study treatment will be provided* [redacted]. *No placebo is used in Part 2. The number of stick-packs to be taken per administration will depend on the participant's actual age.*

[b] *These are the starting doses for participants in Part 2. The starting dose will be determined according to the actual age of the participant at the start of Part 2 (Day 366 visit) and the dose must be changed at the latest on the first dispensation visit after the participant moved into a different age group (see Section 4.1).*

*Dose and dose regimen for participants aged 15 to 17 years are predicted to be similar to what has been determined as the starting steady state regimen in Part 1 for 10 to 14 years old* [redacted]

*Dose or dose regimen may be adapted during the study (see Sections 4.1 and 6.6).*

Please see Section 6.4 for details on *the requirements for* study treatment administration as well as the Basmisanil Investigator's Brochure for more details.

## 6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Study treatment packaging will be overseen by the Sponsor's clinical study supplies department and will bear a label with the identification required by local law, the protocol number, drug identification, and dosage.

The packaging and labeling of the study treatment will be in accordance with the Sponsor's standard and local regulations.

The study site should follow all instructions included with each shipment of IMP. The investigational site will acknowledge receipt of IMPs and confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all IMPs received, and that any discrepancies have been reported and resolved before use of the IMPs. All IMPs must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized staff.

Only participants enrolled in the study may receive IMPs, and only authorized staff may supply or administer IMPs. Study treatment will be dispensed at the study visits or shipped to the participant's home (where local regulations allow for home shipments). Caregivers will be instructed on IMP administration, storage and return. Returned study treatment should not be re-dispensed to the participants.

The study site (i.e., Investigator or other authorized personnel [e.g., pharmacist]) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol. The study site may also be responsible for shipping IMP to the participant's home. Upon arrival of the IMPs at the site, site personnel will complete the following:

- Check the IMPs for damage.
- Verify proper identity, quantity, integrity of seals and temperature conditions.
- Report any deviations or product complaints to the Study Monitor upon discovery.

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

All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). *Unused* IMP stick-packs will have to be returned by the caregiver at clinic visit *or via the shipping courier* to the study site for drug accountability and reconciliation.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. Local or institutional regulations may require immediate destruction of used

IMP for safety reasons. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form. Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the Basmisanil Investigator's Brochure for information on IMP formulation, IMP handling, including preparation and storage, and accountability.

## 6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

### 6.3.1 Method of Treatment Assignment

All participants will be centrally randomized to study treatment using an Interactive Voice/Web Response System (IxRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the login information and directions for the *IxRS* will be provided to each site.

Randomization will be stratified by

- Age *group* (2 to 5 years vs. 6 to *14* years)
- Number of copies of the15q11.2-q13.1 region (3 copies vs. 4 copies)
- Epilepsy (presence vs. absence)

*In Part 2 all participants are assigned to receive open-label basmisanil, regardless of their treatment assignment in Part 1.*

### 6.3.2 Blinding

*Part 1 is* a double-blind study, i.e., the study participants, the Investigators, all individuals in direct contact with the study participants at the investigative site, and the Sponsor Study Management Team (SMT) will be blinded to treatment assignment. PK data can be transferred and cleaned on an ongoing basis. The data will be handled and cleaned in a secure area that is not accessible by any blinded SMT member.

Members of the IMC and SOC will review unblinded aggregated information. Selected IMC and SOC members may be unblinded also at a participant level (see Section 4.1.2.1). Individual study team members outside the IMC and SOC required to prepare information for IMC and SOC review will be unblinded to the treatment assignment at the participant level. Access to treatment assignment information will follow the Sponsor's standard procedures.

#### Emergency Unblinding

If unblinding is necessary for participant management in the case of an SAE, the Investigator will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If the Investigator wishes to

know the identity of the study treatment for any other reason, he/she should contact the Medical Monitor directly. The Investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to an SAE).

As per Health Authority reporting requirements, the Sponsor will break the treatment code for all unexpected SAEs (see Section 8.3.3.1) that are considered by the Investigator to be related to study treatment. The participant may continue to receive treatment, and the Investigator, participant, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to participant treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

Whenever disclosure of the identity of the test medication is necessary, adequate procedures will be in place to ensure integrity of the data.

## 6.4 TREATMENT COMPLIANCE

The qualified individual responsible for dispensing the study treatment will write the date dispensed and participant number on the study treatment label and on the Drug Accountability Record. This individual will also record the study treatment number received by each participant during the study.

The study treatment granules are packaged in stick-packs, which have to be cut open with scissors and not ripped. [redacted]

*On the first day of treatment in Part 1 (Day 1), the study treatment is taken BID, in the morning and in the evening, at the clinical study site. Thereafter, the study treatment is taken TID, at least 3 hours apart and within 30 minutes after the start of a meal.*

*Caregivers will use a drug diary to record missed study treatment administration throughout the study (see Section 8.1.3.1)*. If a dose is missed (i.e., there would be less than *3* hours until the next dose), it must not be taken with the next dose and recorded as missed dose in the *drug* diary. The following dose should be taken at the usual time.

## 6.5 CONCOMITANT THERAPY

Concomitant therapy includes any medication, e.g., prescription drugs, over-the-counter (OTC) drugs, vaccines (including COVID-19 vaccines), approved dietary and herbal supplements *and* nutritional supplements used by a participant from 6 weeks prior to

screening until the follow-up visit. *See also stability requirements for a ketogenic diet in Section 5.3*.

**Anti-epileptic medication** must be on a stable regimen 8 weeks prior to screening and for at least the first 4 weeks of treatment *in Part 1*. After the Day 28 visit, dose adjustments within the therapeutic range, and changes within the same class of anti-epileptic medication may be allowed as part of routine clinical care, upon consultation with the Medical Monitor. *In Part 2, for the first 28 days (until Day 395) dose changes are not allowed.* Changes in the number or the class of anti-epileptic medications are not allowed until the *Part 1* follow-up visit *for participants who do not continue study participation in the optional OLE or until the Day 548 visit for participants who roll over to Part 2 of the study.*

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

All concomitant medications should be reported to the Investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF) along with reason for use, dates of administration (including start and end dates) and dosage information (including dose and frequency).

All medication administered to manage AEs should be recorded on the Adverse Event eCRF.

**Non-pharmacological** (e.g., physiotherapy) / **behavioral therapies** should not be stopped or newly started at least 6 weeks prior to screening and are expected to remain stable *until the Part 1 follow-up visit or until the Day 548 visit for Part 2 participants* (excluding changes related to standard age and educational interventional programs or minor interruptions such as illness or vacation).

Non-pharmacological / behavioral therapies should be reported on the *appropriate* eCRF *page*.

### 6.5.1 Permitted Therapy

Permitted therapy includes all medication used by a participant to manage symptoms associated with Dup15q syndrome *that is not specified as prohibited therapy in Section 6.5.2, taken* from 6 weeks prior to screening *until the Part 1 follow-up visit or until the Day 548 visit for participants in Part 2*.

Participants who use oral contraceptives with a failure rate of $<1\%$ per year; see Section 5.1 and Appendix 5, hormone-replacement therapy, or other maintenance therapy should continue their use.

### 6.5.2 Prohibited Therapy

The below listed therapies are prohibited and should not be administered within 2 weeks (or within 5-times the elimination half-life, whichever is longer) prior to dosing and until the Follow-up visit, unless otherwise specified. Methods of administration, which do not produce appreciable systemic drug exposure (e.g., topical administration for skin conditions), are permitted:

**Modulators of CYP3A4 Activity**

Basmisanil is predominantly cleared by metabolism via CYP3A4, and concomitant medications that significantly alter CYP3A4 activity will affect the pharmacokinetics of basmisanil.

Strong inhibitors of CYP3A4 (e.g., itraconazole, erythromycin, fluconazole, nefazodone, ritonavir, verapamil, grapefruit or grapefruit juice) taken within 2 weeks (or within 5-times the elimination half-life, whichever is longer) prior to dosing is prohibited. Moderate CYP3A4 inhibitors may be used after discussion with the Medical Monitor and eventual use of inhibitors of CYP3A should be accompanied by dedicated safety monitoring, in particular the QT.

Inducers of CYP3A4 (e.g., rifampicin, carbamazepine, pioglitazone, rifampin, modafinil, systemic glucocorticoids, oxycarbazepine, carbamazepine, phenobarbital, phenytoin, St John's Wort) taken within 4 weeks prior to dosing (or within 5 × times the elimination half-life, whichever is longer) are not permitted.

**Dofetilide**

Dofetilide use is not permitted because of the potential for interaction between basmisanil and renally cleared cationic drugs, as well as the very narrow therapeutic window of dofetilide.

**Benzodiazepines (chronic use)**

Based on the potential for interactions to occur between basmisanil and other medications whose effects are mediated via $GABA_A$ receptors, chronic use of benzodiazepines, including as treatment for epilepsy (e.g., clobazam) is not allowed.

Restrictions for acute use of benzodiazepines are described in Section 6.5.3.

[redacted]

**OTC Cannabidiol (CBD)**

Use of artisanal CBDs (products, derivatives, cannabis plants/extracts) is prohibited. Epidiolex/Epidyolex is not prohibited.

### 6.5.3 Therapy to be Used with Caution

[redacted]

**Concomitant medications with an effect on QT**

Drugs known to prolong the QTc interval will be allowed if stable at screening provided the screening QTc does not meet exclusion QTc criterion. Use of currently approved prokinetics (e.g. domperidone, metoclopramide) is not prohibited, but requires closer monitoring of QTc interval on ECG due to risk of arrhythmias.

**Benzodiazepines / GABAergic medications**

Benzodiazepines and benzodiazepine-related drugs may be exceptionally used with the following restrictions:

- **For the treatment of intermittent medical conditions** (e.g., for insomnia and anxiety / agitation, analgosedation)
  - Medications with a short half-life (e.g., lorazepam, alprazolam, or oxazepam) are preferred
  - Short-term use only (no more than 4 days per month)
  - Should not be taken within 2 days before a scheduled visit
- **For the treatment of emergency situations** (e.g., for the acute management of a seizure)
  - *If benzodiazepines/benzodiazepine-related drugs are required in an emergency situation, the visit can be rescheduled to allow for a 2-day window between emergency medication and visit date (even if it falls out of the protocol defined visit window).*
  - If benzodiazepines, in particular diazepam, midazolam, or clonazepam are used, the Investigator should be aware that a higher-than-normal dose of the medication may be required to achieve clinical response.
  - Similarly, in case of acute use of anesthetics that are $GABA_A$ positive allosteric modulators (e.g., volatile anesthetics or hypnotics) in a participant treated with

basmisanil, a higher dose of the anesthetics may be required to achieve the desired effect.

As described above, these recommendations are based on the potential for competition (PD interaction) at the $GABA_A$ receptor level.

## 6.6 DOSE MODIFICATION, TEMPORARY INTERRUPTION AND RECHALLENGE

[redacted]

### 6.6.1 Temporary Interruption

Before permanently discontinuing study treatment (regardless of whether initiated by the participant/*caregiver*, the Investigator or Sponsor), an interruption should be considered. Temporary study treatment interruption is an acceptable method to manage AEs related to the study treatment.

Participants who have temporarily interrupted should be considered for restarting study treatment as soon as medically justified in the opinion of the Investigator.

Study treatment should be interrupted if individual stopping rules are met (see Section 4.1.3) and to manage specific AEs and resumed as detailed in Section 8.3.8. Study treatment may be resumed with the joint agreement of the Investigator and the Sponsor's Medical Monitor when follow-up test results show that the participant no longer meets the dose interruption criteria. Unless it is determined by the Investigator that the occurrence is not related to the administration of the study treatment, study treatment should not be restarted.

## 6.7 TREATMENT AFTER THE END OF *PART 1 OF* THE STUDY

All participants who complete the 52 weeks of study treatment *in Part 1* will be offered the option to roll over into an *OLE to receive basmisanil treatment* for *a duration of*

*approximately 2 years (Part 2). Participants will be required to sign a separate ICF for participation in Part 2.*

A participant will not be eligible to receive study treatment after the end of *Part 1 of* the study if any of the following conditions are met:

- The study treatment is commercially marketed in the participant's country and is reasonably accessible to the participant (e.g., is covered by the participant's insurance or would not otherwise create a financial hardship for the participant).
- The Sponsor has discontinued development of the study treatment or data suggest that the study treatment is not effective for Dup15q syndrome.
- The Sponsor has reasonable safety concerns with regards to the study treatment.
- Provision of study treatment is not permitted under the laws and regulations of the participant's country.
- The participant discontinued prematurely from study treatment or withdrew from the study before completing 52 weeks of treatment.

## 7. DISCONTINUATION OF STUDY, STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Participants have the right to voluntarily discontinue study treatment or withdraw from the study at any time for any reason.

An excessive rate of withdrawals (either participants discontinuing study treatment or withdrawing from the study) can render the study non-interpretable. Therefore, unnecessary withdrawal of participants should be avoided and efforts should be taken to motivate participants to comply with all the study-specific procedures as outlined in this protocol.

Details on study and site closures are provided in Appendix 1, Section 4.

### 7.1 DISCONTINUATION OF STUDY TREATMENT

For data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed see the SoA (Section 1.3).

Reasons for discontinuation of study treatment may include, but are not limited to, the following:

- Any medical condition that the Investigator or Sponsor determines may jeopardize the participant’s safety if he or she continues study treatment.
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the participant.
- Participant suicidal behavior or active suicidal ideation with specific plan and intent.

- An event that meets the stopping criteria (see Section 4.1.3).
- Pregnancy.
- Specific AEs if discontinuation of study treatment is required to manage the event (see Section 8.3.8).
- Symptomatic participants with moderate or severe COVID-19 infection (as per WHO guidelines) with signs of pneumonia or hypoxia.

Every effort should be made to obtain information on participants who discontinue study treatment but have not withdrawn consent. Participants who discontinue study treatment prematurely *(Part 1 or Part 2)* will be asked to return to the clinic for a study early termination visit (see Section 8.10.3) and *will be asked to complete the* follow-up *visit* (see Section 8.10.4), unless the participant withdrew consent. The primary reason for premature study treatment discontinuation should be documented on the appropriate eCRF.

## 7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants have the right to voluntarily withdraw from the study at any time for any reason.

In addition, the Investigator has the right to withdraw a participant from the study for medical conditions that the Investigator or Sponsor determines, may jeopardize the participant's safety if he/she continues in the study.

If possible, information on reason for withdrawal from the study should be obtained. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Participants will not be followed for any reason after consent has been withdrawn. This includes the follow-up assessments.

When a participant voluntarily withdraws from the study, or is withdrawn by the Investigator, samples collected until the date of withdrawal will be analyzed, unless the participant specifically requests for these to be discarded or local laws require their immediate destruction. However, if samples have been tested prior to withdrawal, results from those tests will be used as part of the overall research data. A participant's withdrawal from this study does not, by itself, constitute withdrawal of samples donated to the Research Biosample Repository (RBR).

Participants who withdraw from the study will not be replaced (for sample size determination, see Section 9.1).

For data to be collected at the time of study discontinuation and for any further evaluations that need to be completed see SoA (Section 1.3).

## 7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if the participant 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 participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the caregiver of the participant and reschedule the missed visit as soon as possible.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the caregiver of the participant. These contact attempts should be documented in the participant's medical record.
- Should the caregiver of the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

Discontinuation of sites or of study as a whole are handled as part of Appendix 1.

# 8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timepoints are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

### *Remote visits*

*The* Day 92, *Day* 274*,* early termination*,* and follow-up visits *(Part 1) can be* done remotely at the participant's home, if local regulations allow for it. Visits at the participant's home will be conducted by a mobile nurse (MN) professional. The sponsor will select a healthcare company that will be responsible for providing MN services for participating sites. The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed.

*Visits on Day 28 (Part 1) and on Day 457 (Part 2) will be done as a telephone/video call.*

*In addition, during Part 2, mandatory phone calls every 3 months (at minimum) will be done to follow up on AEs, concomitant therapies and to assess suicidality.*

### *Blood sampling*

The volume of blood taken will follow the recommendations from the European Union on ethical considerations for clinical trials on medicinal products conducted with minors, which states 3% of total blood volume over 4 weeks and 1% of total blood volume at a single time. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Procedures conducted as part of the participant's routine clinical management (e.g., blood count) obtained before signing of the ICF may be utilized for screening purposes, provided the procedure met the protocol-specified criteria. A previously established genetic diagnosis of Dup15q syndrome (medical history obtained before signing of the ICF*, see Section 8.2.1*) which contains the required information to determine eligibility *(see Section 5.1)* may be utilized for screening.

## 8.1 EFFICACY ASSESSMENTS

### 8.1.1 Requirements and Instructions for Caregivers

To reduce variability in reporting, the same caregiver is asked to provide feedback on all informant-based assessments throughout the study, and the same caregiver should attend all on-site visits. If a visit cannot be completed as arranged (e.g., the caregiver is delayed in transit) visits should be rescheduled as soon as possible after the original appointment. The caregiver's relationship to the child (mother, father, etc.) will be captured for all caregiver-reported assessments. If the caregiver changes during the study, this should be captured in the medical records and transcribed into the eCRF with a reason for the change.

The caregiver must be able to attend the on-site visits and be available for the home visits when required. The caregiver must oversee the participant's compliance with protocol-specified procedures, including compliance to study treatment and report on the participant's status via completion of study diaries and assessments. *Caregiver-reported assessments can be completed at applicable clinic visits or remotely/at home throughout the study, if the requirements described in Section 8.1.4.2 can be fulfilled.*

### 8.1.2 Caregiver Expectations Guidance

Because of the important role of the caregiver as respondent in several key assessments, they will be provided with a short training on their role in the study prior to the administration of clinical scales. *The training can be provided either by the Investigator or as a self-read document on TrialMax* (see the SoA in Section 1.3). This aims to help caregivers accurately report on the participant's health and behaviors.

### 8.1.3 Equipment for Home Measurements

#### 8.1.3.1 *Dedicated Website (TrialMax)*

Diaries and outcome assessments can be completed at home or at site through a dedicated website *(TrialMax)* where caregivers can log in. The login will be created at screening *by the* site personnel. The *TrialMax* website can be accessed either through the caregiver's personal device or, if required, on a dedicated digital device (Section 8.1.3.2). *TrialMax* contains:

- the seizure diary (see Section 8.2.4)
- the *drug* diary to record missed study medication (Section 6.4)
- *the meal record to answer questions about whether the doses were given with the meal (see Section 8.5)*
- caregiver-reported assessments (see Table 10 and Section 8.1.5)
- *Caregiver expectation guidance (see Section 8.1.2)*

#### 8.1.3.2 Devices

To access the dedicated website *(TrialMax)* (Section 8.1.3.1) for diary entries or completion of caregiver-reported assessments, caregivers may use an appropriate personal device (with restrictions) or a dedicated digital device provided by the electronic clinical outcome assessment (eCOA) vendor for the duration of the study.

Two wearable devices will be provided to all caregivers of all participants who are able to walk 10 meters without assistance at screening. These wearable devices record the leg movements of the participant. One device will be worn on each ankle (see Section 8.1.5.12).

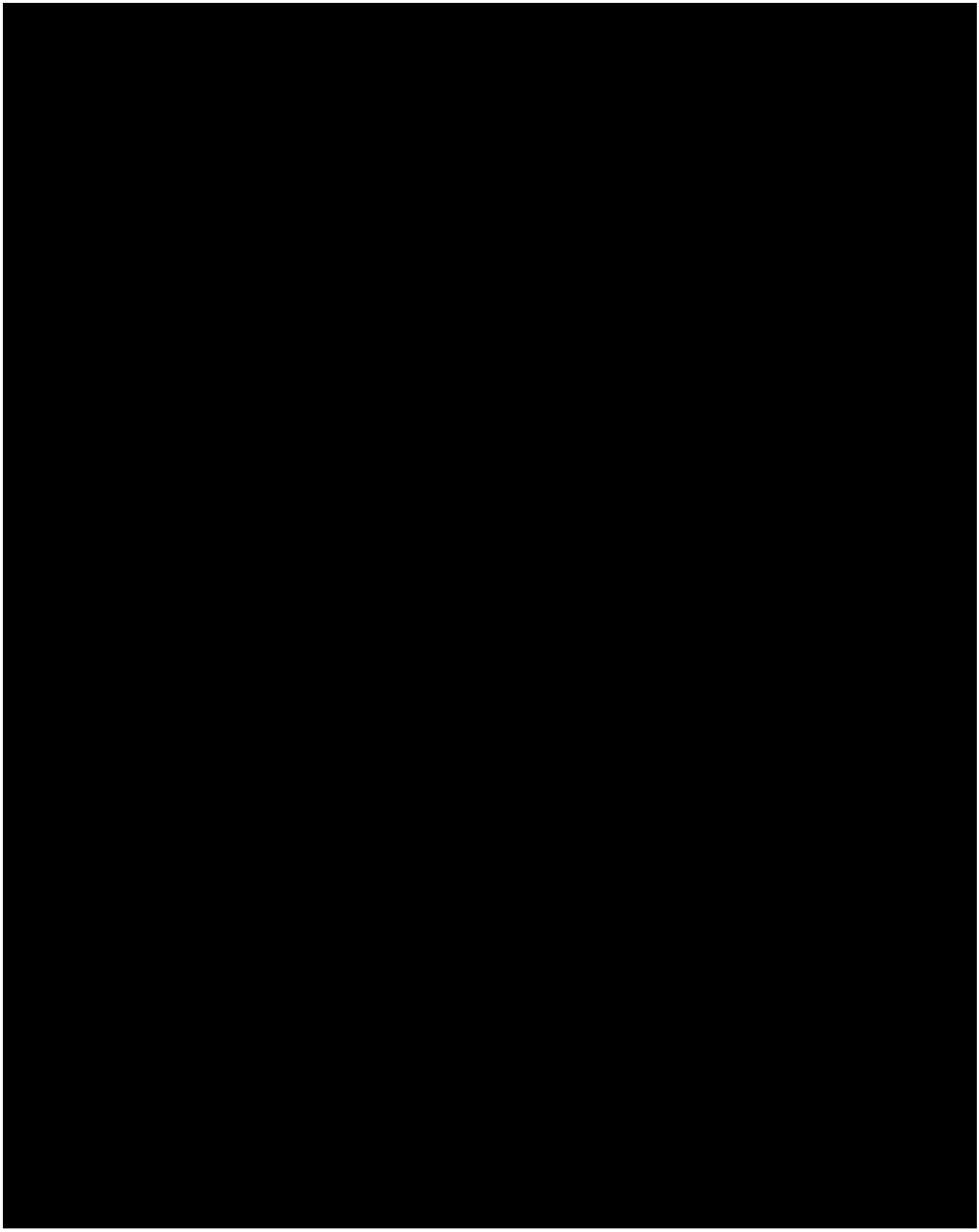
The equipment will be issued to the caregivers during the screening visit, as will educational materials and an instruction manual. Caregivers will be trained on the correct use of all devices.

All dedicated digital devices must be returned to the clinic *upon completion of study Part 1 for those who do not continue study participation in Part 2, or upon completion of study Part 2,* or upon early termination.

### 8.1.4 Data Collection Methods for Clinical Outcome Assessments

Clinical outcome assessments will be completed in the clinic or remotely at home as shown in Table 10.

To decrease the study burden for participants and their families and for the sites, some study visits *can be* performed entirely remotely (at Day 28 *[Part 1] and Day 457 [Part 2]* – telephone call only; and at Day 92, Day 274, Day 395 *[Part 1]* follow up, and early termination *[Part 1]* with home nursing and via telemedicine) (see the SoA in Section 1.3). Furthermore, caregiver-reported assessments scheduled at in-clinic visits (as specified in the SoA and per footnote “c” in Table 10) may also be performed remotely, consistently across visits, if all the requirements described in Section 8.1.4.2 can be fulfilled.



b Performed in the clinic by the clinician, except *Day 28 which will be a phone call visit and* Day 92, Day 274, Day 395 (follow up), and early termination visits which *can* be remote, if local regulations allow for it and if home nursing service is available in the country/region, via video call.

c Vineland-3 interview and completion of caregiver-reported scales can be done either at the clinic visit or at home under remote site supervision. The preferred method should be determined at Baseline and kept consistent throughout the study.

d Included in this outcome assessment table for completeness; but not used as efficacy assessment in this study (Section 8.2 and Section 8.1.5.13).

Training, guidance on rater qualifications, rating, and scoring procedures are described separately in the Rater Manual. An external company and external consultant will provide training to all site raters on the various scales and will provide all sites with the relevant record forms (paper or rater station device), instruction manuals, and kits as appropriate. Training and certification on the ADOS-2 will have to be performed through the scale owner (Western Psychological Services) directly, Roche *may facilitate access to* ADOS-2 training.

Rater qualification will be reviewed per the criteria established by the Sponsor. Only raters certified by the vendor to be qualified on those assessments should rate in this study. Efforts should be made to have the same rater or clinician perform the assessments *for a given participant* throughout the study as established at the screening and/or baseline visit.

#### 8.1.4.1 Clinician-Reported Outcome Assessments

Clinician-reported outcome (ClinRO) data will be collected through use of the following instruments: Dup15q CGI-S, Dup15q CGI-C, hypotonia assessment, and suicidality questions (completed by the clinician); MSEL and ADOS-2 completed by a certified rater *(site personnel), and Vineland-3 completed by a certified remote central rater (independent from the site personnel,* see Table 10 and Section 8.1.5). ClinRO instruments will be completed at the clinic or remotely during the study as specified in the SoA (see Section 1.3).

*The Vineland-3 interview may be completed remotely/at home or during the clinic visit, consistently throughout the study, based on the caregiver's preference as stated at Baseline. For interviews completed remotely/at home, the criteria for remote assessments described in Section 8.1.4.2 also apply.*

Remote centralized administration for the Vineland-3 (see Section 8.1.5.2) will be carried out via telephone and may be audio recorded. If a remote administration session cannot occur for an unforeseen reason, it will be rescheduled.

ADOS-2 and MSEL administration by a certified rater on site will be video recorded for quality control purposes.

A rater station device provided by the eCOA vendor will be used by site staff to capture or transcribe all ClinRO data. The instructions and training for completing the

assessments electronically will be provided by the eCOA vendor. The data will be transmitted to a centralized database maintained by the eCOA vendor. Paper booklets may be used to capture clinical outcome assessment data (if the digitalized scale version is not available or in case of technical issues).

#### 8.1.4.2 Caregiver-Reported Assessments

Caregiver-reported data *about the participants' health and behaviors* will be collected through *completion* of the following instruments: ABC-2-C, ORCA, RBS-R, CSHQ, Dup15q CaGI-S, and Dup15q CaGI-C. *Caregiver-reported data about caregiver and family functioning will be collected through administration of the PedsQL-FIM* (see Table 10 and Section 8.1.5).

The caregiver-reported assessments will be completed through a dedicated website *(TrialMax)* on an appropriate personal device, or a dedicated digital device provided by the eCOA vendor (see Section 8.1.3), or paper-based if the digital device is not available or feasible for a selected assessment and a paper-based alternative is available. Caregiver-reported data will also be collected through use of a seizure diary (Section 8.2.4) and a drug diary (Section 6.4) via *TrialMax*.

The assessments may be completed remotely/at home or during the clinic visit, consistently throughout the study, based on the caregiver's preference *as stated at Baseline*. For caregiver assessments completed *remotely/*at home, the following requirements apply:

- The caregiver must be able to dedicate sufficient time for completion (total approximately 2 hours, see Table 10).
- *The caregiver must have access to a location with limited distractions where privacy can be ensured.*
- *The assessments must be performed within a time window of 5 days before the scheduled clinic visit (see Section 8.10 and SoA in Section 1.3).*
- *The assessments can be performed with remote support from the site as needed.*

Detailed guidance will be provided by the eCOA vendor to the study sites for remote assessment completion/administration.

### 8.1.5 Clinical Outcome Assessments

#### 8.1.5.1 Dup15q Syndrome Clinician Global Impression *of* Severity and Clinician Global Impression *of* Change

The Dup15q CGI-S is a 10-domain, clinician-rated measure, which measures global severity of illness at a given point in time. Nine domains are seizures, expressive communication difficulties, fine motor skills difficulties, gross motor skills difficulties, cognitive/intellectual impairment, impairment in activities of daily living/self-care, socialization, maladaptive behavior, and sleep difficulties. The tenth domain is a score for overall severity. The Dup15q CGI-S is a 6-point scale with response options of none,

very mild, mild, moderate, severe, and very severe. Guidelines for rating will be provided to ensure consistency.

The Dup15q CGI-C is also a 10-domain, clinician-rated measure, assessing the clinician's impression of change in illness compared with baseline. The 10 domains are the same as the domains specified for the Dup15q CGI-S. The Dup15q CGI-C is a 7-point scale, with response options of very much improved, much improved, minimally improved, no change, minimally worse, much worse, and very much worse. Guidelines for rating will be provided to ensure consistency.

#### 8.1.5.2 Vineland Adaptive Behavior Scales–Third Edition

The Vineland-3 is an instrument that measures communication, daily living skills, socialization, and motor skills (Sparrow et al 2016). *The maladaptive behavior domain is not administered in this study.* The Comprehensive Interview Form (i.e., a semi-structured interview) will be administered *via telephone* to the participant's caregiver by a certified *remote central* rater *independent of the site personnel (see Section 8.1.4.1). The central rater* will ask the caregiver open-ended questions relating to the participant's activities and behavior. Items are either scored as 2 = Usually, 1 = Sometimes, 0 = Never, or scored as 2 = Yes, 0 = No in the case of items that require a binary response. Lower scores indicate lower adaptive behavior abilities.

#### 8.1.5.3 Mullen Scales of Early Learning

The MSEL are designed for a certified rater to provide an assessment of cognitive ability and motor development *of typically developing children from birth through age 68 months* (Mullen 1995). *The MSEL will be administered to all participants in the study, irrespective of their chronological age. They have previously been used outside of the standardized age norms to characterize the cognitive and developmental profiles of children and adolescents with Dup15q syndrome (DiStefano et al 2020). The instrument consists of 124* items across five scales measuring Gross Motor, Visual Reception, Fine Motor, Expressive Language, and Receptive Language. Each scale is comprised of interactive tasks that can be completed by the child or can be scored by the certified rater through interview of, or with assistance from, the caregiver. The scoring for each item ranges from 0 to 5 points. Lower scores indicate lower developmental abilities.

#### 8.1.5.4 Autism Diagnostic Observational Schedule, Second Edition

The ADOS-2 is a diagnostic tool used to document the presence of ASD (Gotham et al 2007, Lord et al 2000). During a semi-structured evaluation, the individual is observed in a naturalistic social situation and assessed by a certified rater across areas of social communication, imagination, and restricted and/or repetitive behaviors. The ADOS-2 includes four modules for use with different age groups and language levels.

#### 8.1.5.5 Aberrant Behavior Checklist-Community – Second Edition

The ABC-2 is an updated, empirically derived, validated 58-item caregiver-completed rating scale that measures the severity of a range of maladaptive behaviors commonly observed in children, adolescents, and adults with intellectual and developmental disabilities (Aman et al 2010, Aman and Singh 2017). The Community version of the scale (ABC-2-C) will be used. It is designed for use in individuals who are not residing in institutional settings. The checklist assesses symptoms across five domains: irritability, social withdrawal, stereotypic behavior, hyperactive/noncompliance, and inappropriate speech. Items are scored on a 4-point scale from 0 (never) to 3 (severe problem). Sub-scale scores and a total score can be calculated with higher scores indicating greater severity.

#### 8.1.5.6 Pediatric Quality of Life Inventory™ Family Impact Module

The PedsQL-FIM, Version 2, (Varni et al 2007) is a 36-item, informant-based measure that will be completed by the caregiver. The instrument was developed to measure parent and family functioning. It encompasses 6 scales covering Physical Functioning (6 items), Emotional Functioning (5 items), Social Functioning (4 items), Cognitive Functioning (5 items), Communication (3 items), and Worry (5 items) and 2 scales measuring parent-reported family functioning, Daily Activities (3 items) and Family Relationships (5 items). The acute form, using a recall period of 7 days, will be employed in this trial. Items are scored on a 5-point scale from 0 (never a problem) to 4 (almost always a problem) with higher scores indicating greater severity.

#### 8.1.5.7 Observer-Reported Communication Ability

The ORCA assesses the communication ability of an individual from the perspective of a caregiver. The instrument consists of 73 items representing 22 conceptual areas of communication capturing expressive, receptive and pragmatic communication skills, alongside a set of communication specific descriptive items that capture information about the individual's unique ways of communicating. All items, except "turns in conversation", have the same three response options of "No or only once", "Sometimes", and "Yes, almost all the time". "Turns in conversation" has 5 response options: 0, 1, 2, 3, 4 or more turns. A hierarchical ordering of communication ability level differentiates which behaviors represent lower ability (level 1) versus higher ability (greater than level 1) within each concept.

#### 8.1.5.8 Repetitive Behavior Scale–Revised

The RBS-R is a 43-item informant-based caregiver-reported questionnaire, assessing the variety of restricted and repetitive behaviors observed in individuals with ASD (Bodfish et al 2000). The scale is grouped into six subscales: Stereotyped, Self-Injurious, Compulsive, Ritualistic, Sameness, and Restricted Behaviors. Each item uses a 4-point response scale assessing the presence and severity of a restricted or repetitive behavior. Response options range from "Behavior does not occur" (0) to "Behavior occurs and is a severe problem" (3). A total score is generated for each subscale and an overall total score encompasses all the subscales.

#### 8.1.5.9 Assessment of Hypotonia

The Investigator *or designee* will perform an assessment of hypotonia (head control and truncal stability) including absence or presence of hypotonia, severity grading, and changes since the last visit at the timepoints specified in the SoA (Section 1.3).

#### 8.1.5.10 Children's Sleep Habit Questionnaire

The *Children's Sleep Habit Questionnaire (CSHQ), which* includes 45-items assessing sleep habits and possible difficulties with sleep, *was developed for typically developing children aged 4 to 10 years* (Owens et al 2000). *The CSHQ will be administered to all participants in the study, irrespective of their chronological age. The CSHQ has previously been used outside of the standardized age norms to characterize the sleep parameters of children and adolescents with ASD aged 5 to 20 years (Schnapp et al 2022).* The past week is the recall period, however if the last week is unusual for a specific reason, the most recent typical week will be chosen. Unless noted, "Always" refers to something occurring every night, "Usually" if it occurs 5 or 6 times a week, "Sometimes" if it occurs 2−4 times a week, "Rarely" if it occurs once a week, and "Never" if it occurs less than once a week. The questionnaire will be completed by the caregiver. Individual subscale scores as well as a total score can be calculated, with higher scores indicating more severe sleep disturbance.

#### 8.1.5.11 Dup15q Syndrome Caregiver Global Impression *of* Severity and Caregiver Global Impression *of* Change

The Dup15q CaGI-S is a nine domain, caregiver-rated measure, assessing the caregiver's impression of the impact of a participant's condition, in this case Dup15q syndrome (no other conditions/co-morbidities). This scale mirrors the Dup15q CGI-S described in Section 8.1.5.1. The nine concept-specific domains are seizures, non-verbal and verbal expressive communication, fine motor skills, gross motor skills, cognition, self-care, socialization, disruptive behavior, and sleep. The tenth domain is a score for overall severity. Guidelines will be provided to ensure consistency of rating.

The Dup15q CaGI-C is a 10-domain, caregiver-rated measure, assessing the caregiver's impression of change in the participant's condition, in this case Dup15q Syndrome (no other conditions or co-morbidities), compared with baseline. This scale includes the same domains as the Dup15q CaGI-S, and mirrors the Dup15q CGI-C described in Section 8.1.5.1. Guidelines for rating will be provided to ensure consistency of rating.

#### 8.1.5.12 Wearable device

Participants who are able to walk should wear a movement monitor during periods specified in the SoA in Section 1.3. All efforts should be made to ensure that *participants who are able to walk 10 meters without assistance at screening and can tolerate the wearable device* wear the device throughout the specified periods. The purpose of this device is to measure daily movement and activity levels of the participant accurately during normal daily living, outside of investigational site visits. The device consists of two sensors, one of which is worn on each ankle. As the device battery

requires recharging overnight, the device will not be worn at night. The device is *not* waterproof and *must not* be worn during bathing, swimming, or showering. The participant and caregiver will be trained on the correct use of the device, including correct fitting and wearing of the device, how to dock the device on the battery charging station, and when to return the wearable devices to the site. Detailed instructions as to use of the device are provided in the User Manual and Quick Start Guide.

#### 8.1.5.13 Palatability questionnaire

Palatability will be indirectly assessed by asking caregivers about the child's reaction to the administration of the study treatment and ease of drug administration:

1. On the basis of the reaction/facial expression of your child, do you think that the medication is: pleasant, not sure, or unpleasant?
2. Do you sometimes have problems in giving the medication to your child because he/she refuses to take it or throws it up? Yes/No

#### 8.1.5.14 Caregiver Exit Interview

If consent is provided, caregivers of study participants may be invited to participate in an optional, 1-hour, one-to-one interview, which will be recorded and transcribed. Interviews *will* be completed via telephone, in the caregiver's native language, and as soon as possible but no later than 4 weeks after the *Day 365 visit (during follow-up period if participant does not enter Part 2 or during the first 4 weeks of Part 2)*. Interviews are optional, and if a caregiver initially consents to participate in the interview, they can subsequently decide not to participate at a later time without any implications for their participation in the overall study. If a caregiver declines to participate at the start of the study this will not have any implication for the participation in the overall study.

These interviews will provide qualitative insights regarding among others: the daily life impact of Dup15q syndrome for the study participant; any key areas of change over the duration of the study; and the real-world impact of the changes that are most important. Caregivers will be asked to specifically consider areas such as developmental skills (including communication, motor function, cognition, behavior, and self-care), and seizures. Additionally, these interviews will capture information regarding how any change in Dup15q syndrome symptoms or functional ability may affect the daily life of the participant's caregivers and family. These interviews will *be performed by a trained interviewer independent of the site personnel to* explore whether there were additional *Dup15q syndrome* concepts that were not captured in the standard efficacy assessments. A semi-structured interview guide will be administered, including both open-ended and closed-ended questions.

### 8.2 SAFETY ASSESSMENTS

Planned timepoints for all safety assessments are provided in the SoA (Section 1.3).

Safety assessments will consist of monitoring and recording AEs, including SAEs and *AEs* of special interest (*AESIs*); and measurement of protocol-specified safety laboratory assessments, vital signs, ECGs, seizure status, and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

### 8.2.1 Medical History and Demographic Data

Medical history includes lifetime clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), including infantile hypotonia and infantile spasms and date of diagnosis of Dup15q syndrome. *Medical history should be recorded in the eCRF.*

*The following information will also be collected and recorded in the eCRF:*

- All medications (e.g., prescription drugs, OTC drugs, herbal or homeopathic remedies, nutritional supplements)
- Non-pharmacological interventions, including e.g., behavioral, physical, or speech therapies, within 6 weeks prior to the screening visit
- Demographic data will include age, sex, and caregiver−reported race/ethnicity
- Level of education and participation in special educational or day programs

[redacted]

### 8.2.2 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, throat, neck and lymph nodes, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Weight, height and head circumference: Body weight (using calibrated scales) will be measured to the nearest 100 g at the timepoints specified in the SoA (Section 1.3). Head circumference will be measured in children below the age of 5 years to the nearest 0.1 cm using a flexible, non-stretchable tape.

*Abnormal* changes from baseline should be recorded in participant's notes. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.

### 8.2.3 Tanner Staging

Tanner staging for pubertal status will be determined at the timepoints listed in the SoA (Section 1.3). *In Part 1, Tanner staging will be assessed for participants aged 9 years or above at the time of signing the Informed Consent Form. In Part 2, Tanner staging will be assessed for participants aged 9 or above at the time of the assessment.*

*Tanner staging will not be performed after participants achieve Stage 5.*

### 8.2.4 Seizure Status

The seizure diary (see Section 8.1.3) will be provided to caregivers for completion at home after initial training at the clinic. The *diary* entries are event driven, i.e., have to be completed *retrospectively* after a seizure occurred, and contain information on seizure type, duration, and frequency based on guidance from the International League Against Epilepsy (*ILAE;* Scheffer et al 2017, Fisher et al 2017). *A list of seizure types is provided for selection by the Investigator based on the "ILAE 2017 Classification of Seizure Types Expanded Version" (Appendix 7) to support the seizure diary entries.*

In addition, the seizure diary asks to confirm accurate entries at regular intervals.

The Investigator will determine the participant's recent seizure status at the timepoints specified in the SoA (*in Part 1 and for the first 6 months in Part 2; see* Section 1.3), based on caregiver report (time since last visit) and review of the information in the seizure diary (see Table 11 for *review* period for each assessment).

[redacted]

### 8.2.5 Vital Signs

Blood pressure, pulse rate, respiratory rate, and body temperature (oral or tympanic) will be recorded at the timepoints specified in the SoA (Section 1.3). Blood pressure, pulse rate, and respiratory rate should be obtained in a quiet room at a comfortable temperature, with the participant's arm unconstrained by clothing or other material. The participant should be asked to remove all clothing that covers the location of cuff placement. All measurements will be obtained from the same arm and, with the appropriate cuff size, using a well-calibrated automatic instrument with a digital readout, throughout the study (the “ideal” cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference [a length-to-width ratio of 2:1]). The individual should be comfortably in a semi-supine/supine position, with the legs uncrossed.

### 8.2.6 Electrocardiograms

At each specified timepoint, 12-lead ECG recordings must be obtained in triplicate (i.e., three useful ECGs without artifacts 2 to 3 minutes apart), per the SoA (see Section 1.3). The average of the three readings will be used to determine ECG intervals (e.g., PR, QRS complex [QRS], and QT). Whenever possible, the same brand/model of a standard high-quality, high-fidelity electrocardiograph machine equipped with computer-based interval measurements should be used for each participant. The conditions should be as close as possible to pre-dose timepoints; this includes but is not limited to food intake, activity level, stressors, and room temperature. To minimize variability, every effort should be made that participants be in a resting position for $\geq$ 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to any scheduled vital sign measurements and blood draws. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality.

For safety monitoring purposes, the investigator or designee must review, sign, and date all ECG tracings. Paper or electronic copies will be kept as part of the participant’s permanent study file at the site. If considered appropriate by Roche, ECGs may be analyzed retrospectively at a central laboratory. ECG characteristics, including heart rate, QRS duration, and PR, and QT, will be recorded on the eCRF. QTcB (Bazett’s correction; Phan et al 2015), QTcF (Fridericia’s correction), and RR will be recorded on the eCRF.

Both corrections of QTc will be tabulated and analyzed, although, in children, Bazett’s formula appears to provide a better correction of the QT. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented on the eCRF. T-wave information will be captured as normal or abnormal, U-wave information will be

captured in two categories: absent/normal or abnormal. Any medically relevant changes occurring during the study should be recorded in the AE section of the case report form (CRF).

### 8.2.7 Clinical Safety Laboratory Assessments

Normal ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts. A list of clinical laboratory tests to be performed is provided in Appendix 4, and these assessments must be conducted in accordance with the laboratories process. If analysis is required to be done centrally, the samples and assays should be clearly identified, and instructions may be provided by the central laboratory manual according to the requirements from the SoA (Section 1.3).

At any time, safety laboratory samples will be given priority over any other sample, such that the volume of blood taken at any single timepoint will not exceed 1% of total blood volume, and the volume collected over any 4-week period throughout the study will not exceed 3% of total blood volume, as per recommendations by the European Union. The Investigator must review the laboratory report, document this review, and record any medically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Medically relevant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

- In the event of unexplained, abnormal, medically relevant laboratory test values, the tests should be repeated immediately and followed up until values have returned to the normal range and/or an adequate explanation of the abnormality is found.
- If such values do not return to normal/baseline within a period judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- If laboratory values from non-protocol–specified laboratory assessments performed at the local laboratory require a change in participant management or are considered medically relevant by the Investigator (e.g., SAE or AE or dose modification), the results must be recorded in the CRF.

Results of clinical laboratory testing will be recorded on the eCRF or be received as electronically produced laboratory reports submitted directly from the local or central laboratory.

Additional blood or urine samples may be taken at the discretion of the Investigator if the results of any test fall outside the reference ranges or clinical symptoms necessitate additional testing to monitor participant safety.

Where the clinical significance of abnormal laboratory results at screening is considered uncertain, screening laboratory tests may be repeated before randomization to confirm eligibility.

Based on continuous analysis of the data in this study and other studies, any sample type not considered critical for safety may be stopped at any time if the data from the samples collected do not produce useful information.

### 8.2.8 Clinical Assessment of Suicidality

*In Part 1, suicidality will be assessed for participants aged 6 years and above at the time of signing the Informed Consent Form. In Part 2, suicidality will be assessed for participants aged 6 years and above at the time of the assessment.* The Investigator *or designee* will ask the caregiver of participants the following questions adapted from the C-CASA:

- Suicidal ideation: Has the participant wished he/she were dead or wished they could go to sleep and not wake up?
- Suicidal behavior: Has the participant made a suicide attempt? Has the participant done anything to harm him or herself?
- Self-injurious behavior: Has the participant engaged in non-suicidal self-injurious behavior?

If the Investigator determines that any of these questions can be asked directly to the participant, based on the participant's ability to understand and to react to the questions, then those questions should be directed to the participant; if not, these should be directed to the caregiver. If the answer to any of these three questions is "yes", then the investigator will further evaluate the suicidal risk of the participant.

### 8.2.9 Seizures (EEG Monitoring)

EEG will be measured according to the SoA (Section 1.3).

EEG monitoring will be implemented in this study as a safety parameter to detect treatment-emergent or changes in seizure activity. Abnormal changes in EEG recordings will be compared to baseline with a focus on:

- Treatment-emergent epileptiform abnormalities
- Occurrence of subclinical seizures and nonconvulsive status epilepticus

[redacted]

*The EEG safety report will indicate if any findings require the Investigator's attention in order to ensure patient safety and may be further discussed with the Medical Monitor if deemed necessary by the Investigator on a case-by-case basis.*

*Findings from the EEG safety report are to be considered within the full clinical context of the participant presentation for decision making on the continuation of dosing during the study, based on the stopping rules criteria listed in Section 4.1.3.*

For EEG to determine PD and biomarker parameters, see Section 8.6.2.

## 8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or SAE can be found in Appendix 2. The *AESIs* are discussed in Section 8.3.6.

The Investigator and any qualified designees are responsible for ensuring that all AEs (including assessment of seriousness, severity, and causality; see Appendix 2) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Appendix 2.

Procedures used for recording AEs are provided in Appendix 3.

### 8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2.

Investigators will seek information on AEs at each participant's contact. All AEs, whether reported by the participant or noted by study personnel, will be recorded in the participant's medical record and on the Adverse Event eCRF as follows:

**After informed consent** has been obtained, **but prior to initiation of study treatment**, only SAEs caused by a protocol-mandated intervention should be reported (e.g., SAEs related to invasive procedures such as biopsies). Any other AE should not be reported.

**After initiation of study treatment**, all AEs, regardless of relationship to study treatment, will be reported until 28 days after the final dose of study treatment.

**Post-study AEs and SAEs:** The Investigator is not required to actively monitor participants for AEs after the end of the AE reporting period of 28 days after the final dose of study treatment or until the start of another treatment, whichever comes first.

However, if the Investigator learns of any SAE (including a death) or other AEs of concern that are believed to be related to prior treatment with study treatment, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study treatment or study

participation, the Investigator must promptly notify the Sponsor. For the procedure of reporting, see Appendix 2.

### 8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all participant evaluation timepoints.

### 8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

#### 8.3.3.1 Investigator Follow-Up

The Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the event is otherwise explained, the participant is lost to follow up (Section 7.3), or the participant withdraws consent. Every effort should be made to follow all SAEs considered to be related to study treatment or study-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification. If, after follow up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome and reported according to the instructions provided in Section 8.3.5.

#### 8.3.3.2 Sponsor Follow Up

For SAEs, $AESIs$, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional event details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) to perform an independent medical assessment of the reported event.

### 8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Immediate notification by the Investigator to the Sponsor of an SAE regardless of relationship to study drug is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical

investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then, file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

For immediate (i.e., no more than 24 hours after learning of the event) and expedited reporting requirements from Investigator to Sponsor and from Sponsor to Health Authority, investigators, IRB and EC, see Appendix 2, Section 5.

#### 8.3.4.1 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours a day 7 days a week. Details will be available separately.

### 8.3.5 Pregnancy

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the pregnancy reporting process as detailed in Appendix 5. All pregnancies reported during the study should be followed until pregnancy outcome, with follow-up information on the infant collected according to procedures outlined in Appendix 5.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs (Appendix 5).

### 8.3.6 Adverse Events of Special Interest

*AESIs* are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Appendix 2 for reporting instructions).

*AESIs* for this study include the following:

- De novo seizure in participants who had no prior history of seizure
- New seizure type not reported prior to baseline
- Confirmed QTcF > 480 msec or confirmed QTcF change from baseline > 60 msec for participants older than 10 years.
- Confirmed QTcB > 480 msec or confirmed QTcB change from baseline > 60 msec for participants up to and including the age of 10 years.

- Confirmed increase of serum creatinine > 1.5 × ULN or eGFR <90 mL/min per 1.73 $m^2$ (Grade 1 CKD).
- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Appendix 3.
- Suspected transmission of an infectious agent by the study treatment, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

### 8.3.7 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events

*Seizure activity (i.e., convulsive and non-convulsive seizures) which are in line with the known medical history of the patient should not be reported as AEs unless they meet the seriousness criteria (see Appendix 2). Only convulsions requiring hospitalization or intubation should be reported as SAEs.*

### 8.3.8 Management of Specific Adverse Events

Treatment of specific AEs will be considered on a case-by-case basis according to local standard of care. Several measures are taken to ensure the safety of participants participating in this study. Eligibility criteria have been designed to exclude participants at potentially higher risk. Participants will undergo safety monitoring during the study. In addition, guidelines for managing AEs, including criteria for treatment interruption or discontinuation, are provided in Table 12.

- Increases in heart rate and blood pressure observed in pre-clinical studies and Phase I studies were not observed in subsequent clinical trials with basmisanil, including trials in children with Down syndrome. Vital signs will be monitored throughout the study.
- Increased in QTcF interval at supra-therapeutic plasma concentrations has been observed in the context of the basmisanil DDI study with itraconazole, a strong CYP3A4 inhibitor. In this study, basmisanil concentrations are predicted to be well below the exposure of clinical and regulatory concern for QTcF interval (see Section 2.3). ECG recordings are part of the safety monitoring of this study.
- Increase in serum creatinine has been reported previously and appears to reflect inhibitory effects of basmisanil on the tubular creatinine transporters since changes of other glomerular filtration rate markers remained unchanged. Serum creatinine *and eGFR* will be measured at various timepoints throughout the study.
- Seizure risk: The risk for basmisanil to exacerbate or trigger de novo seizures in individuals with Dup15q syndrome will be assessed but is considered low based on

non-clinical data and clinical experience in the patient population previously treated with basmisanil (see Section 2.3 and the Basmisanil Investigator's Brochure).

- Suicidality: clinical experience does not point to any suicidality liability of basmisanil. However, monitoring for suicidality is mandatory in clinical trials of CNS-active molecules and will be implemented as described in Section 8.2.8.

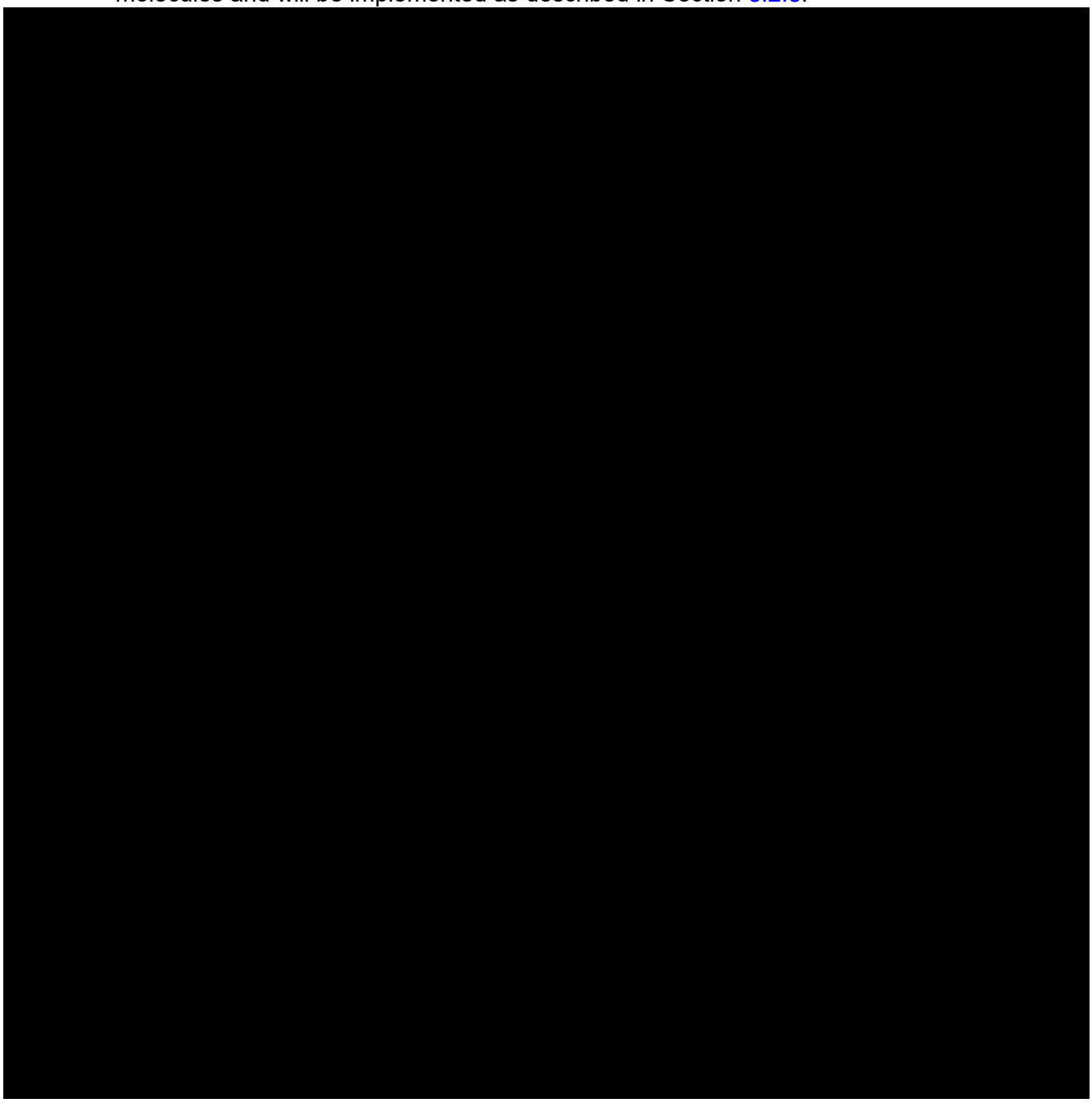


**Table 12 Guidelines for Managing Specific Adverse Events (cont.)**

| | |
|---|---|
| Elevated liver enzymes | • ALT or AST > 3 × ULN:<br>○ Monitor weekly until ALT and AST return to ≤ 1.2 × ULN.<br>○ Further investigation into the liver enzyme elevations may include hepatitis serologies and other diagnostic tests at the discretion of the investigator in consultation with the Medical Monitor.<br>• Interrupt the study treatment in the event of liver enzymes that meet the following criteria):<br>○ ALT or AST >5 ×ULN<br>○ ALT or AST > 3 × ULN and either total bilirubin > 2 × ULN or INR >1.5<br>○ ALT or AST > 3 × ULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity<br>○ Such abnormalities should be followed by repeat testing within 48 to 72 hours and repeated two to three times weekly based on the participant's clinical state. An evaluation by a hepatologist may be required if the abnormalities do not stabilize. All participants with possible drug-induced liver injury should be followed until abnormalities return to normal, even if the study treatment has been discontinued.<br>○ Discontinue study medication permanently if levels do not return to baseline after 30 days |

## 8.4 TREATMENT OF OVERDOSE

*Overdose is the accidental or intentional use of the study drug in an amount higher than the assigned dose throughout the treatment period.*

An overdose or incorrect administration of study treatment is not an AE unless it results in untoward medical effects (see Sections 5 and 5.2 of Appendix 2 for further details).

Decisions regarding dose-interruptions or modifications (if applicable) will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

In the event of an overdose, the Investigator should:

1. Contact the Sponsor's Medical Monitor immediately.

2. Closely monitor the participant for AE/SAE and laboratory abnormalities until resolved
3. Obtain a blood sample for PK and ECG analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose, as well as the duration of the overdose, in the CRF.

Appropriate supportive treatment should be initiated according to the individual's clinical signs and symptoms and in accordance with best medical practices. In vitro studies have shown that benzodiazepines compete with basmisanil for binding to $GABA_A$, and flumazenil was able to block the inhibitory effect of basmisanil on GABA-induced currents.

Benzodiazepines may therefore be considered as a treatment option for the management of basmisanil overdose.

## 8.5 PHARMACOKINETICS

Mandatory blood samples to evaluate plasma concentrations of basmisanil and its major metabolite, M1, will be collected from a vein. The date and time of each sample collection will be recorded in the eCRF. Basmisanil and M1 levels will be analyzed. The PK samples will be taken as outlined in the SoA (Section 1.3). [redacted] Additional PK samples will be taken at the time of treatment discontinuation or if an AE leading to dose-reduction or delay of basmisanil administration is reported (Section 6.6 Dose Modifications).

Due to the food effect of basmisanil the *information on the* meals *will* be recorded *by parent/caregiver at defined timepoints (tied to PK sampling, see SoA, Section 1.3).*

The PK blood samples will be destroyed no later than 2 years after the date of final clinical study report (CSR). Details on sampling procedures, sample storage, and shipment are given in the sample documentation. For participants who consent to RBR, leftover samples will be transferred to RBR (see Section 8.8).

A Sponsor IMC will perform unblinded reviews of PK data as described in Section 4.1.

Drug concentration information that would unblind the study, will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Any changes in the timing or addition of timepoints for any planned study assessments must be documented and approved by the relevant study team member and archived in the Sponsor and site study files. This will not constitute a protocol amendment. The

IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

## 8.6 PHARMACODYNAMICS AND BIOMARKERS ANALYSES

### 8.6.1 Genetic and Genomic Analyses

*Genetic tests can be performed within the study in cases where the required genetic information is not available in the participant's medical history (Section 8.2.1). In this case, the Investigator must ensure that the appropriate test(s) are performed within the study to obtain all of the following genetic information:*

- the number of copies of the 15q11.2-13.1 chromosomal region as well as breakpoints *coordinates in the human reference genome,* and *the* segment size*, determined by chromosomal microarray (CMA). CMA will be performed only if permitted by local regulations.*
- the parental origin of the duplication or triplication of 15q11.2-13.1 chromosomal region*, determined using methylation specific-multiplex ligation dependent probe amplification (MS-MLPA)*
- the int(15) vs. idic(15) nature of the copy number gain of the 15q11.2-13.1 chromosomal region*, determined by fluorescence in situ hybridization (FISH)*

*Where required, samples will be collected for DNA extraction at timepoints specified in the SoA (see Section 1.3).*

Data arising from all biosamples, including samples for analyses of inherited DNA, will be subject to the confidentiality standards described in Section 1.4 of Appendix 1.

### 8.6.2 Effect of Basmisanil on *the* EEG (qEEG) Assessments

EEG will be measured at clinic visits according to the SoA (see Section 1.3) using a clinical EEG system (10/20 montage comprising up to 32 electrodes plus auxiliary channels such as electrooculogram [EOG] or ECG).

Sections of the EEG data at pre-defined times (*qEEG blocks,* see Table 2 *and Table 4 for Part 1 and Part 2, respectively*) will be used for quantitative analyses. The impedance of electrodes will be checked *before starting each block* and participants will be instructed to *remain as* calm *as possible* and awake *during the qEEG block* with the goal to achieve good data quality for quantitative analysis. Recording good quality EEG data will be challenging but should be attempted. The EEGs will be used to evaluate the effect of basmisanil treatment on *EEG beta-band power,* acutely and at steady state, and to relate these signals to the PK *data*. In particular, the treatment-related change in the EEG beta-band power from Baseline to Day 2 and to Day 14 will be investigated (see Section 9.3.5). [redacted]

For EEG to monitor safety see Section 8.2.9.

## 8.7 PHARMACODYNAMICS AND BIOMARKER SAMPLES

*If required,* blood *and buccal swab* samples may *be* taken for DNA extraction for a full characterization of the Dup15q genotype (Section 8.6.1). *Where required,* samples will be collected according to the SoA (see Section 1.3). Additional samples may be requested in case of technical issues with the initial samples.

Blood *and buccal swab* samples will be destroyed no later than 2 years after the date of final CSR. For participants who consent to RBR, *an additional whole blood sample will be taken at Baseline and transferred to the RBR (see Section 8.8). Leftover blood and buccal swab* samples will be transferred to *the* RBR (Section 8.8).

Details on processes for collection and shipment of these samples can be found in a separate sample documentation.

## 8.8 SAMPLES FOR RESEARCH BIOSAMPLE REPOSITORY

### 8.8.1 Overview of the Research Biosample Repository

The Roche RBR is a centrally administered group of facilities for the long-term storage of human biologic samples, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of the RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from participants who give specific consent to participate in this optional RBR. Collected RBR samples can be used (but not limited to) to achieve the following objectives:

- To study the association of biomarkers with efficacy or progressive disease.
- To identify safety biomarkers that are associated with susceptibility to developing AEs or can lead to improved AE monitoring or investigation.
- To increase knowledge and understanding of disease biology and drug safety.
- To study treatment response, including drug effects and the processes of drug absorption and disposition.
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays.

### 8.8.2 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to study treatment, diseases, or drug safety:

- Leftover PK plasma samples
- Leftover genetic test sample prepared from whole blood *and buccal swab* (DNA)
- RBR whole blood sample

The sample collected for DNA extraction include, but is not limited to, genomic analysis and may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), next-generation sequencing, or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

Samples, upon RBR consent, may be used for DNA extraction to enable WGS/WES and other genomic analysis.

Samples may be sent to one or more laboratories for analysis of germline or somatic mutations via WGS or WES, or other genomic analysis methods. Genomics is increasingly informing researchers' understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop AE.

Participants will not be identified by name or any other personally identifying information. Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

If allowed by local laws, the caregiver may request access to the non-interpreted WGS and WES raw data from blood samples. Such a request must be conveyed to the Sponsor by the Investigator, using the email address: global.return-genomics-results@roche.com. The information, if available at the time of the request, would be shared with the Investigator in the form of a data file of raw genomic sequencing data. The Sponsor will not provide any interpretation of this raw genomic sequencing data. The interpretation of these data will require expertise in genomic and genetic analysis and an understanding of the variability of the technology used for data generation.

For all samples, dates of consent and sample collection should be recorded on the associated RBR page of the eCRF. Details on processes for collection and shipment of these samples can be found in separate sample documentation.

RBR samples will be stored and used until no longer needed, until they are exhausted but no longer than 15 years. The RBR storage period will be in accordance with the IRB/EC-approved ICF and applicable laws (e.g., Health Authority requirements).

The repository samples will be subject to the confidentiality standards (as described under Confidentiality and in Appendix 1).

## 8.9 HEALTH ECONOMICS

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

## 8.10 TIMING OF STUDY ASSESSMENTS

All assessments must be performed as per SoA (see Section 1.3).

As a rule, *efficacy assessments supporting primary and secondary objectives (Table 5) are to be prioritized over exploratory assessments. As much as possible* the sequence of assessments established for a given participant and their caregiver at the Baseline visit should be *kept the same on the Day 183 and Day 365 visits. Specifically, for MSEL administration, all efforts should be made to perform the assessments at about the same time of day.*

*The timings of the qEEG blocks (first block starts 30 minutes before the morning meal and lasts until the start of this meal as specified in the SoA) should be recorded at about the same time of day at every visit.*

Assessments *listed in Table 2 and Table 4 of the SoA (see Section 1.3) must be performed as specified at all indicated visits* as these *assessments* will be important to confirm the PK model and to establish the exposure-qEEG relationship in Dup15q syndrome.

Caregiver-reported questionnaires can be completed either in the clinic or remotely within a 5-day window *before* the *scheduled* clinic visit, with *remote* support from the site *as needed* (see the SoA in Section 1.3).

The Baseline, Day 183, Day 365 *(Part 1) and Day 548, Day 730, Day 1095 (Part 2), Day 1125, and early termination (Part 2)* visits can be split over 2 days if required to accommodate participants *and* families.

### 8.10.1 Screening and Pre-treatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. ICFs for enrolled participant and for participants who are not subsequently enrolled will be maintained at the study site. Assent should be obtained for *participants* who, in the opinion of the investigator, are judged to be capable of giving assent.

All screening, and all pre-treatment assessments (related to entry criteria), must be completed and reviewed by the Investigator to confirm that participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure.

The seizure diary and the wearable device should be handed out to the caregiver at screening to record baseline data as described in Section 8.2.4 and Section 8.1.5.12.

[redacted]

### 8.10.2 Assessments during Treatment

Under no circumstances will participants who enroll in this study and complete treatment as specified be permitted to be allocated a new randomization number and re-enrolled in the study.

All assessments must be performed as per SoA (Section 1.3).

### 8.10.3 Assessments at Early Termination Visit

Participants who discontinue from the study early will be asked to complete early termination assessments as per the SoA (Section 1.3) as soon as possible after the final dose of study treatment.

### 8.10.4 Follow-Up Assessments

Participants *who complete or who withdraw early from the study* will be asked to attend a safety follow-up visit as described in the SoA (Section 1.3). *For participants who consent to Part 2 OLE, the follow-up assessments will be completed at the end of Part 2 (see Section 4.1.1).*

After the study completion/early termination visit, AEs should be followed as outlined in Sections 8.3.1 and 8.3.3.

# 9. STATISTICAL CONSIDERATIONS

## 9.1 SAMPLE SIZE DETERMINATION

Approximately 90 $participants$ with $Dup15q$ syndrome are planned to be randomized 2:1 to basmisanil or placebo. Assuming approximately 10% of randomized participants may not be evaluable for efficacy, there will be approximately 81 evaluable participants. The sample size may be increased in case of higher-than-expected rates of early study withdrawals or number of participants requiring dose adjustments due to exposures substantially deviating from target trough plasma concentrations.

The primary efficacy analysis will compare the change in Vineland-3 Adaptive Behavior Composite score from Baseline to Week 52 of treatment between the basmisanil and the placebo arm.

[redacted]

## 9.2 SETS FOR ANALYSES

For purposes of analysis, the following analysis sets are defined in Table 13.

**Table 13 Analysis Sets**

| Analysis Set | Description |
|---|---|
| Intent-to-treat (ITT) | All randomized participants who received at least one dose of study treatment. The ITT population will be the primary population for the analysis of all efficacy endpoints. Participants will be allocated to the treatment arm they were randomized to. |
| Safety | The safety analysis population equals the ITT population assuming treatment is received as assigned at randomization. |
| Pharmacokinetic (PK) | All participants who have received at least one dose of study treatment and who have data from at least one postdose sample will be included in the PK analysis population. Participants will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete which may influence the PK analysis. Excluded cases will be documented with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure. |

If, at any time during $Part\ 1\ of$ the study, participants receive treatment different from the one they were randomized to, manual re-assignments of participants to treatment arms

for the purpose of *the* analysis *of safety data* may be made depending *on* the duration of such incorrect treatment. Such re-assignments, if any, can only be made after unblinding and will be described in detail.

## 9.3 STATISTICAL ANALYSES *OF PART 1*

### 9.3.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment group using means, standard deviations, medians, and ranges for continuous variables and proportions for categorical variables, as appropriate. Analyses will be performed in all randomized participants and in the intent-to-treat (ITT), if different.

Baseline will be defined as the latest available value prior to the first dose of study treatment.

### 9.3.2 Efficacy Analyses

The primary efficacy analysis will take place after all participants complete 52 weeks of *double-blind* treatment or *are* prematurely withdrawn.

*In addition,* results for *the* primary and secondary efficacy endpoints *in Part 1* will be presented in descriptive summary tables and graphs, as appropriate. Listings will be prepared as required. Change from baseline for continuous endpoints will be analyzed using *the same methodology as that for the primary endpoint*. All statistical analysis methodologies will be described in detail and documented in the Sponsor's trial master file prior to performing any of the planned interim or final analyses.

In addition to the primary analysis in the ITT, selected endpoints may be analyzed in subgroups, including by key demographic variables and stratification factors.

### 9.3.3 Safety Analyses

All safety analyses will be based on the safety analysis population. Safety endpoints will be described in appropriate summary tables and graphs. Individual outputs will be presented if required.

Descriptive summaries of exposure to study treatment will be prepared by treatment group (including treatment duration, total dose received, dose intensity).

Verbatim AE terms recorded in the eCRF will be mapped to MedDRA thesaurus terms. AE severity will be graded according to National Cancer Institute Common Terminology Criteria for AEs (v5.0). Data on AEs, SAEs, and deaths will be presented by treatment group in summary tables and in individual outputs, as appropriate.

Abnormal changes in EEG recordings compared to baseline will be presented in summaries and individual outputs with a focus on treatment-emergent epileptiform abnormalities. Seizure status as derived from the seizure diary entries by caregivers will be used to analyze changes from baseline in seizure types, frequency, and duration.

All clinical laboratory data will be stored on the database in the units in which they were reported. Laboratory test values will be presented in International System of Units (Système International d'Unités [SI] units;). Individual outputs will show flags for abnormal results. Summaries and shift tables will be prepared for selected laboratory tests to describe baseline and maximum post baseline severity grade.

Vital sign data will be presented *by individual listings* with flagging of values outside the normal ranges and flagging of abnormalities.

ECG data as well as data for height, weight, and head circumference will be presented using appropriate summaries and/or listings.

Suicidality questions adapted from the C-CASA will be analyzed descriptively in *participants* aged 6 years *and above.*

Tanner staging over time will be described in *participants from* age 9.

Concomitant Medications: The original terms recorded on the participants' eCRF by the Investigator for concomitant medications will be standardized by the Sponsor by utilizing a mapped term and appropriate drug dictionary level. Concomitant medications will be presented using appropriate outputs.

### 9.3.4 Pharmacokinetic Analyses

Analyses will be carried out on the PK analysis population. PK parameters will be estimated using a population PK model and presented by listings and descriptive summary statistics (mean, standard deviation, coefficient of variation, median, minimum, and maximum).

The plasma concentration of basmisanil and its major metabolite M1 will be determined. PK parameters for basmisanil are $AUC_{tau,ss}$, $C_{max,ss}$, $C_{trough,ss}$, CL/F, and Vd/F will be estimated by using population PK analysis. Plasma concentration ratio of M1 to basmisanil at trough will be determined as well as other PK parameters as appropriate.

Estimates for these parameters will be tabulated and summarized.

The population PK analysis analyses will be presented separately from the main CSR.

### 9.3.5 Pharmacodynamic Analyses

The main PD endpoint is the change in the characteristic Dup15q EEG phenotype, acutely and at steady state.

Results for change in EEG beta-band power from baseline will be presented in summary tables, graphs, and listings.

## 9.4 *STATISTICAL ANALYSES OF PART 2*

*Analyses using the complete database including both Parts 1 and 2 of the study will be performed when all participants complete the protocol-defined assessments or are prematurely withdrawn. Details on the statistical methodology will be described in a separate technical document prior to the analysis.*

## 9.5 INTERIM ANALYSES

Interim analyses *in Part 1* will be conducted as described in Section 4.1.2.2.

A first interim analysis is planned once approximately *24* participants (Stage 1 and Stage 2) have completed 4 weeks of treatment or withdrawn from treatment prior to that.

The Sponsor may choose to conduct an additional interim analysis *during Part 1*. The decision to conduct an optional interim analysis and the timing of the analysis will be documented in the Sponsor's trial master file prior to the conduct of the interim analysis.

The interim analyses will be performed and interpreted by members of the IMC and *may be shared with the* SOC *as needed and* as described in Section 4.1.2. Access to treatment assignment information will follow the Sponsor's standard procedures.

All statistical analysis methodologies will be described in detail and documented in the Sponsor's trial master file prior to performing any of the planned interim analyses.

*After completion of the primary analysis of Part 1 and prior to the end of the study, the Sponsor may conduct additional interim analyses combining the data collected in both Part 1 and Part 2. The timing of and the methods used in such analyses will be documented in the Sponsor's trial master file prior to the analysis.*

## 9.6 SUMMARIES OF CONDUCT OF STUDY

Protocol deviations will be summarized by treatment group; a participant listing will also be available.

Participant disposition, including number of participants randomized and discontinuations from study treatment or study will be reported.

Terms for concomitant medications recorded on the eCRF by the Investigator will be mapped to preferred terms by the Sponsor. Data on concomitant medication will be summarized and listed.

## 10. REFERENCES


Absalom NL, Liao VWY, Kothur K, et al. Gain-of-function *GABRB3* variants identified in vigabatrin-hypersensitive epileptic encephalopathies. Brain Commun 2020;2:fcaa162. doi: 10.1093/braincomms/fcaa162. PMID: 33585817; PMCID: PMC7869430.

Aman MG, Kasper W, Manos G, et al. Line-item analysis of the Aberrant Behavior Checklist: results from two studies of aripiprazole in the treatment of irritability associated with autistic disorder. J Child Adolesc Psychopharmacol 2010;20:415-22.

Aman MG, Singh NN. ABC-2 Aberrant Behavior Checklist. Community/residential manual. 2nd ed. East Aurora: Slosson Educational Publications Inc., 2017.

Battaglia A, Gurrieri F, Bertini E, et al. The inv dup(15) syndrome: a clinically recognizable syndrome with altered behavior, mental retardation, and epilepsy. Neurology 1997;48:1081-6.

Battaglia A. The inv dup (15) or idic (15) syndrome (Tetrasomy 15q). Orphanet J Rare Dis 2008;3:30.

Battaglia A, Bernardini L, Torrente I, et al. Spectrum of epilepsy and electroencephalogram patterns in idic (15) syndrome. Am J Med Genet A 2016;170: 2531–9.

Beghi E, Giussani G, Bianchi E, et al. A validation study of the clinical diagnosis of Dup15q syndrome: Which symptoms matter most? Seizure 2020;74:26–30.

Berry-Kravis EM, Lindemann L, Jønch AE, et al. Drug development for neurodevelopmental disorders: lessons learned from fragile X syndrome. Nat Rev Drug Discov 2018;17:280-99.

Bodfish JW, Symons FJ, Parker DE, et al.Varieties of repetitive behavior in autism: comparisons to mental retardation. J Autism Dev Disord 2000;30:237–43.

Boonsimma P, Suwannachote S, Phokaew C, et al. A case of GABRA5-related developmental and epileptic encephalopathy with response to a combination of antiepileptic drugs and a GABAering agent. Brain Dev 2020;42:546-50.

Butler KM, Moody OA, Schuler E, et al. De novo variants in GABRA2 and GABRA5 alter receptor function and contribute to early-onset epilepsy. Brain 2018;141:2392-405.

Castronovo C, Crippa M, Bestetti I, et al. Complex de novo chromosomal rearrangement at 15q11-q13 involving an intrachromosomal triplication in a patient with a severe neuropsychological phenotype: clinical report and review of the literature. Am J Med Genet A. 2015;167A:221-30.

Conant KD, Finucane B, Cleary N, et al. A survey of seizures and current treatments in 15q duplication syndrome. Epilepsia 2014;55:396-402.

Cook EH Jr, Lindgren V, Leventhal BL, et al. Autism or atypical autism in maternally but not paternally derived proximal 15q duplication. Am J Hum Genet 1997;60:928-34.

Di Pietro ML, Cutrera R, Teleman AA, et al. Placebo-controlled trials in pediatrics and the child's best interest. Ital J Pediatr 2015;41:11.

DiStefano C, Gulsrud A, Huberty S, et al. Identification of a distinct developmental and behavioral profile in children with Dup15q syndrome. J Neurodev Disord 2016;8:19.

DiStefano C, Wilson RB, Hyde C, et al. Behavioral characterization of dup15q syndrome: Toward meaningful endpoints for clinical trials. Am J Med Genet A 2020;182:71-84.

Finucane BM, Lusk L, Arkilo D, et al. 15q Duplication Syndrome and Related Disorders. 2016 Jun 16. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2021 [cited: 26 April 2021]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK367946/

Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:522-30.

Frohlich J, Senturk D, Saravanapandian V, et al. A quantitative electrophysiological biomarker of duplication 15q11.2-q13.1 syndrome. PLoS One 2016;11:e0167179.

Frohlich J, Reiter LT, Saravanapandian V, et al. Correction to: Mechanisms underlying the EEG biomarker in Dup15q syndrome. Mol Autism 2019;10:37.

Germain ND, Chen PF, Plocik AM, et al. Gene expression analysis of human induced pluripotent stem cell-derived neurons carrying copy number variants of chromosome 15q11-q13.1. Mol Autism 2014;5:44.

Gotham K, Risi S, Pickles A, et al. The Autism Diagnostic Observation Schedule: revised algorithms for improved diagnostic validity. J Autism Dev Disord 2007;37:613–27.

Greenblatt DJ, Ehrenberg BL, Gunderman J, et al. Pharmacokinetic and electroencephalographic study of intravenous diazepam, midazolam, and placebo. Clin Pharmacol Ther 1989;45:356-65.

Hernandez CC, XiangWei W, Hu N, et al. Altered inhibitory synapses in de novo GABRA5 and GABRA1 mutations associated with early onset epileptic encephalopathies. Brain 2019;142:1938-54.

Hipp, J.F., Knoflach, F., Comley, R., et al. Basmisanil, a highly selective GABA A -α5 negative allosteric modulator: preclinical pharmacology and demonstration of functional target engagement in man. Sci Rep 2021;11:7700. https://doi.org/10.1038/s41598-021-87307-7

Investigator’s Brochure RO5186582 (basmisanil).

Jacob TC. Neurobiology and Therapeutic Potential of α5-GABA Type A Receptors. Front Mol Neurosci. 2019;12:179.

Jaminion F, Bentley D, Wang K, et al. PKPD and cardiac single cell modeling of a DDI study with a CYP3A4 substrate and itraconazole to quantify the effects on QT interval duration. J Pharmacokinet Pharmacodyn. 2020;47(5):447-59.

Kalsner L, Chamberlain SJ. Prader-Willi, Angelman, and 15q11-q13 duplication syndromes. Pediatr Clin North Am 2015;62:587-606.

Kirov G., Rees E, Walters JTR, et al. The penetrance of copy number variations for schizophrenia and developmental delay. Biological Psychiatry 2014;75:378–85.

Kolb B, Gibb R. Brain plasticity and behaviour in the developing brain. J Can Acad Child Adolesc Psychiatry. 2011;20(4):265-76.

Lord C, Risi S, Lambrecht L, et al. The autism diagnostic observation schedule-generic: A standard measure of social and communication deficits associated with the spectrum of autism. J Autism Dev Disord 2000;30:205–23.

Löscher W. Preclinical assessment of proconvulsant drug activity and its relevance for predicting adverse events in humans. Eur J Pharmacol 2009;610:1-11.

*Lusk L, Vogel-Farley V, DiStefano C, et al. Maternal 15q Duplication Syndrome. 2016 Jun 16 [updated 2021 Jul 15]. In: Adam MP, Everman DB, Mirzaa GM, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2023 [cited: 22 February 2023]. Available from: https://pubmed.ncbi.nlm.nih.gov/27308687/*

Martinez-Cue C, Martínez P, Rueda N, et al. Reducing $GABA_A$ α5 receptor-mediated inhibition rescues functional and neuromorphological deficits in a mouse model of Down syndrome. J Neurosci 2013;33:3953-66.

Menzikov SA, Morozov SG, Kubatiev AA. Intricacies of $GABA_A$ Receptor Function: The Critical Role of the β3 Subunit in Norm and Pathology. Int J Mol Sci 2021;22:1457.

Mullen, EM. Mullen Scales of Early Learning. Circle Pines, MN: American Guidance Services, Inc., 1995.

Noor A, Dupuis L, Mittal K, et al. 15q11.2 Duplication encompassing only the UBE3A gene is associated with developmental delay and neuropsychiatric phenotypes. Hum Mutat 2015;36:689-93.

Nutt DJ, Besson M, Wilson SJ, et al. Blockade of alcohol's amnestic activity in humans by an α5 subtype benzodiazepine receptor inverse agonist. Neuropharmacology 2007;53:810-20.

Owens JA, Spirito A, McGuinn M. The Children's Sleep Habits Questionnaire (CSHQ): Psychometric properties of a survey instrument for school-aged children. Sleep 2000;23:1-9.

Phan DQ, Silka MJ, Lan YT, et al. Comparison of formulas for calculation of the corrected QT interval in infants and young children. J Pediatr 2015;166:960-64.

Redrobe JP, Elster L, Frederiksen K, et al. Negative modulation of GABAA α5 receptors by RO4938581 attenuates discrete sub-chronic and early postnatal phencyclidine (PCP)-induced cognitive deficits in rats. Psychopharmacology 2011;221: 451-68.

Rudolph U and Knoflach F. Beyond classical benzodiazepines: novel therapeutic potential of GABAA receptor subtypes. Nat Rev Drug Discov 2011;10: 685-97.

Salem F, Johnson TN, Abduljalil K, et al. A re-evaluation and validation of ontogeny functions for cytochrome P450 1A2 and 3A4 based on time data. Clin Pharmacokinet 2014;53:625-36.

Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:512-21.

Schinzel A, Niedrist D. Chromosome imbalances associated with epilepsy. Am J Med Genet 2001;106:119-24.

*Schnapp A, Harel M, Cayam-Rand D, et al. A Placebo-controlled trial of cannabinoid treatment for disruptive behavior in children and adolescents with autism spectrum disorder: effects on sleep parameters as measured by the CSHQ. Biomedicines. 2022;10:1685.*

Shaaya EA, Pollack SF, Boronat S, et al. Gastrointestinal problems in 15q duplication syndrome. Eur J Med Genet 2015;58:191-3.

Sparrow SS, Cicchetti DV, Saulnier CA. Vineland Adaptive Behavior Scales. Third Edition (Vineland-3). 2016 [cited: 26 April 2021]. Available from: https://www.pearsonclinical.ca/en/products/product-master.html/item-541.

Sur C, Quirk K, Dewar D, et al. Rat and human hippocampal alpha5 subunit-containing gamma-aminobutyric AcidA receptors have alpha5 beta3 gamma2 pharmacological characteristics. Mol Pharmacol 1998;54:928-33.

Upreti VV, Wahlstrom JL. Meta-analysis of hepatic cytochrome P450 ontogeny to underwrite the prediction of pediatric pharmacokinetics using physiologically based pharmacokinetic modeling. J Clin Pharmacol 2016;56:266-83.

Urraca N, Cleary J, Brewer V, et al. The interstitial duplication 15q11.2-q13 syndrome includes autism, mild facial anomalies and a characteristic EEG signature. Autism Res 2013;6:268-79.

Urraca N, Hope K, Victor AK, et al. Significant transcriptional changes in 15q duplication but not Angelman syndrome deletion stem cell-derived neurons. Mol Autism 2018; 27;9:6.

Varni JW, Limbers CA, Burwinkle TM. Parent proxy-report of their children's health-related quality of life: an analysis of 13,878 parents' reliability and validity across

age subgroups using the PedsQL™ 4.0 Generic Core Scales. Health Qual Life Outcomes 2007;5:2.

Vivanti G, Kasari C, Green J, et al. Implementing and evaluating early intervention for children with autism: Where are the gaps and what should we do? Autism Res 2018;11:16-23.

*Wheeler A, Gantz MG, Heidi Cope H, et al. Age of diagnosis for children with chromosome 15q syndromes. DOI: https://doi.org/10.21203/rs.3.rs-2022497/v1.*

Wilson RB, Enticott PG, Rinehart NJ. Motor development and delay: advances in assessment of motor skills in autism spectrum disorders. Curr Opin Neurol 2018;31:134-9.

Wilson RB, Elashoff D, Gouelle A, et al. Quantitative Gait Analysis in Duplication 15q Syndrome and Nonsyndromic ASD. Autism Research 2020;13:1102–10.

# 11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

# Appendix 1
# Regulatory, Ethical, and Study Oversight Considerations

## 1. REGULATORY AND ETHICAL CONSIDERATIONS

### 1.1. COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC) *or Clinical Trials Regulation (536/2014) (EEA sites only), and all other applicable local regulations*.

### 1.2. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the ICFs, any information to be given to the participant or caregiver (e.g. advertisements, diaries, etc.), and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any participant recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (Section 2.3.1 of this appendix).

The Investigator should follow the requirements for reporting all adverse events (AEs) to the Sponsor. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with Health Authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

### 1.3. INFORMED CONSENT

The Sponsor's Master Informed Consent Form *including the consent form for the optional open-label extension part of the study* (and ancillary sample ICFs such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. Participant's *caregiver or participant's legally authorized representative* must be informed that participation is voluntary. Participant's *caregiver* or legally authorized

representative will be required to sign a statement of informed consent 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 Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC‑approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes according to local requirements. Participant's *caregiver or participant' legally authorized representative* must be re-consented to the most current version of the ICF(s) during the *participant's* participation in the study. A copy of the ICF(s) signed by all parties must be provided to the *participant's caregiver* or the participant's legally authorized representative.

*Due to the nature of Dup15q syndrome, participants in this study will not be asked* to provide their own informed consent. The Informed Consent Form included in this study is for the caregiver *or the legally authorized representative* of the participant. The participant's ability to provide assent will not be dependent on their age. Assent should be obtained for all *participants* who, in the opinion of the Investigator, are judged capable of giving assent.

The ICFs must be signed and dated by the participant's *caregiver or* legally authorized representative before *the participant's* participation in the study. The case history or clinical records for each participant shall document the informed consent process *from the caregiver or participant's legally authorized representative* and that written informed consent was obtained prior to participation in the study.

The ICFs should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the participant*'s caregiver or participant's legally authorized representative* to take part. The final revised IRB/EC-approved ICFs must be provided to the Sponsor for Health Authority submission purposes if required as per local regulations.

If the ICFs are revised (through an amendment or an addendum) while a participant is participating in the study, the participant*'s caregiver* or a legally authorized representative may be re-consented by signing the most current version of the ICFs or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised ICFs, the case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained using the updated/revised ICFs for continued participation in the study. The study team will provide guidance for which participants need to re-consent in the event of an update to the ICF.

A copy of each signed ICF must be provided to the participant's *caregiver or participant's* legally authorized representative. All signed and dated ICFs must remain in

each participant's study file or in the site file and must be available for verification by study monitors at any time.

If a participant is re-screened, the caregiver *or the participant's legally authorized representative* is not required to sign another ICF if the re-screening occurs within 30 days from the previous ICF signature date.

### Consent to Participate in the Research Biosample Repository

The ICF will contain a separate section that addresses participation in the RBR. The Investigator or authorized designee will explain to each participant*'s caregiver or participant's legally authorized representative* the objectives, methods, and potential hazards of participation in the RBR. Participant*'s caregiver or participant's legally authorized representative* will be told that they are free to refuse to participate and may withdraw their samples at any time and for any reason during the storage period. A separate, specific signature will be required to document a participant's *caregiver or participant's legally authorized representative* agreement to provide optional RBR samples. Participant's *caregiver or participant's legally authorized representative* who declines to participate will not provide a separate signature.

The Investigator should document whether or not the participant*'s caregiver or participant's legally authorized representative* has given consent to participate by completing the RBR Sample Informed Consent eCRF.

In the event of death or loss of competence of a participant who is participating in the research, the participant's samples and data will continue to be used as part of the RBR.

For sites in the United States, each ICF may also include participant*'s caregiver's or participant's legally authorized representative's* authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for participant*'s caregiver's or participant's legally authorized representative's* authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study-site policies.

### Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the ICF by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol will not be applicable at that site.

### Withdrawal from the Research Biosample Repository

Participants whose caregiver *or legally authorized representative* gives consent to provide samples for the RBR have the right to withdraw their samples at any time for any

reason. If consent *is withdrawn for* the testing of *the* samples, the Investigator must inform the Medical Monitor and Site Monitor in writing of *the decision taken* using the RBR Withdrawal Form and, if the study is ongoing, must enter the date of withdrawal on the RBR Withdrawal of Informed Consent eCRF. The participant*'s caregiver or participant's legally authorized representative* will be provided with instructions on how to withdraw consent after the study is closed. A participant's withdrawal from Study BP41992 does not, by itself, constitute withdrawal of samples from the RBR. Likewise, a participant's withdrawal from the RBR does not constitute withdrawal from Study BP41992. Data already generated before time of withdrawal of consent to RBR will still be used.

## 1.4. CONFIDENTIALITY

*Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.*

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

The participant*'s caregiver or participant's legally authorized representative* must be informed that *the participant's* 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 participant.

Medical information may be given to a participant's personal physician or other appropriate medical personnel responsible for the participant's welfare, for treatment purposes.

The participant*'s caregiver or participant's legally authorized representative* must be informed that *the participant's* 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.

Study data, which may include data on germline mutations, may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and other summary reports will be provided upon request.

### Confidentiality for Research Biosample Repository

Data generated from RBR samples must be available for inspection upon request by representatives of national and local Health Authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Participant medical information associated with RBR samples is confidential and may only be disclosed to third parties as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the participant*'s caregiver or participant's legally authorized representative*, unless permitted or required by law.

Data derived from RBR sample analysis on individual participants will generally not be provided to study Investigators unless a request for research use is granted. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

Genetic research data and associated clinical data may be shared with researchers who are not participating in the study or submitted to government or other health research databases for broad sharing with other researchers. Participants will not be identified by name or any other personally identifying information. Given the complexity and exploratory nature of these analyses, genetic data and analyses will not be shared with Investigators or participants unless required by law.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR sample data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

### Monitoring and Oversight Research Biosample Repository

Samples collected for the RBR will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the ICF. The Sponsor's monitors and auditors will have direct access to appropriate parts of records relating to participant participation in RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and Health Authority inspections by providing direct access to source data and documents related to the samples.

## 1.5. FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study (i.e., LPLO).

# 2. DATA HANDLING AND RECORD

## 2.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

### 2.1.1. Data Quality Assurance

All participant data relating to the study will be recorded on electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.

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

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

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

Study monitors will perform ongoing source data verification 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 participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH Good Clinical Practice (GCP), and all applicable regulatory requirements.

### 2.1.2. Clinical Outcome Assessment Data

#### 2.1.2.1 Electronic Clinical Outcome Assessment

For this study, eCOA devices (dedicated digital device [Section 8.1.3.2] and a rater station device [Section 8.1.4.1]) provided by an eCOA vendor and through the dedicated website *(TrialMax)* on the caregiver's personal device will be used to capture COA data. The data will be transmitted to a centralized database maintained by the eCOA vendor. The data may be reviewed by site staff via secure access to a web server.

The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

#### 2.1.2.2. Paper Clinical Outcome Assessment Data

If paper booklets are used to capture COA data (e.g. ADOS-2, MSEL), all original forms on which responses are recorded are source documentation as described in Section 2.1.3 of this appendix.

### 2.1.3. Source Data Records

Source documents (paper or electronic) are those in which participant data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, COAs (paper or eCOA), evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, participant files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical study.

Before study initiation, data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data must be defined in the Trial Monitoring Plan.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described below.

To facilitate source data verification, the Investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable Health Authorities.

### 2.1.4. Use of Computerized Systems

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with Health Authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

## 2.2. RETENTION OF RECORDS

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for at least 15 years after study completion or discontinuation of the study, or for the length of time required by relevant national or local Health Authorities, whichever is longer. After that period, the documents may be destroyed, subject to local regulations. 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.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local Health Authorities.

Audio and video recordings will be maintained on a secure server throughout the duration of the study and destroyed 2 years after study completion on approval by the Sponsor.

For countries where Ethics Committees or the Ministry of Health will not approve video or audio recording of participant interviews, review of the scale worksheets, submitted as part of the assessment source information, will be performed to verify accuracy of scoring and compliance to study conventions.

## 2.3. STUDY RECORDS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully reconstructed, including but not limited to the protocol, protocol amendments, ICFs, and documentation of IRB/EC and governmental approval.

Roche shall also submit an Annual Safety Report once a year to the IEC and competent authorities (CAs) according to local regulatory requirements and timelines of each country participating in the study.

### 2.3.1. Protocol Amendments

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to participants or any non-substantial changes, as defined by regulatory requirements.

### 2.3.2. 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 for approval prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

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 multi-center trials only in their entirety and not as individual center data. In this case, a coordinating Investigator will be designated by mutual agreement.

Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Sponsor personnel.

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

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

### 2.3.3. Dissemination of Clinical Study Data

The results of the study may be communicated in scientific meetings and/or peer-reviewed literature. In addition, results of the study will also be included in submissions to regulatory agencies and other Health Authorities.

### 2.3.4. Management of Study Quality

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring participant safety and data integrity. Prior to first participant entry into the study, the Sponsor will identify and evaluate potential risks associated with critical $study$ processes and data and will implement controls for the communication, review, and reporting these risks. Details regarding the applied approach for the study will be provided in the integrated Risk Based Quality Management Plan.

### 2.3.5. Site Inspections

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, participants' medical records, and eCRFs. The Investigator will permit national and local Health Authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

## 3. ADMINISTRATIVE STRUCTURE

An IMC and a SOC will used in this study, see Section 4.1.2.

## 4. STUDY AND SITE CLOSURE

The Sponsor (or designee) has the right to close the study site or terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to participants.
- Participant enrollment is unsatisfactory.

The Sponsor will notify the Investigator and Health Authorities if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

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:

- 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 recruitment of participants by the Investigator.
- Discontinuation of further study treatment development.

# Appendix 2
# Adverse Events: Definitions and Procedures for Evaluating, Follow-up and Reporting

## 1. DEFINITION OF ADVERSE EVENTS

According to the E2A ICH guideline for Good Clinical Practice, an **adverse event** is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event can therefore be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

**Events Meeting the AE Definition:**

- Deterioration in a laboratory value (hematology, clinical chemistry, or urinalysis) or other clinical test (e.g., ECG, X−ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment (see Appendix 3, Section 4).
- Exacerbation of a chronic or intermittent preexisting 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.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE unless the progression is unexpectedly accelerated and not in line with the natural history of the disease. If the “Lack of efficacy” would not require safety reporting 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.

**Events NOT Meeting the AE Definition:**

- Any medically relevant abnormal laboratory findings or other abnormal safety assessments that 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 (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

## 2. DEFINITION OF SERIOUS ADVERSE EVENTS

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that at any dose:

- **Results in death**.
- **Is life-threatening**.

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant 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 was more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization** (see Appendix 3).

  In general, hospitalization signifies that the participant has been detained (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 fulfills 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 preexisting condition that did not worsen from baseline is not considered an AE.
- **Results in persistent or significant disability/incapacity**

  Disability means substantial disruption of the participant'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 (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**.

- **Other significant events**:

  Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant 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 in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or development of drug dependency or drug abuse.

  As epilepsy is part of the clinical presentation of Dup15q syndrome, only convulsions requiring hospitalization or intubation should be reported as SAEs.

## 3. RECORDING OF ADVERSE EVENT AND/OR SERIOUS ADVERSE EVENT

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information in the CRF.

It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Medical Monitor in lieu of completion of the eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

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.

### 3.1. ASSESSMENT OF SEVERITY

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 1 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

## Table 1 Adverse Event Severity Grading Scale

| Grade | Severity |
|---|---|
| 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated |
| 2 | Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living[a] |
| 3 | Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living[b,c] |
| 4 | Life-threatening consequences or urgent intervention indicated[d] |
| 5 | Death related to adverse event[d] |

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the NCI CTCAE (v5.0), which can be found at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 6 of this appendix for reporting instructions), per the definition of serious adverse event in Section 2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 6 for reporting instructions), per the definition of serious adverse event in Section 2. Grade 4 laboratory abnormalities would only be reported as SAEs if these meets one or more of the conditions outlined in Section 2 (Definition of Serious Adverse Events) of Appendix 2.

## 3.2. ASSESSMENT OF CAUSALITY

Investigators should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study treatment, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study treatment.
- Course of the event, considering especially the effects of dose-reduction, discontinuation of study treatment, or reintroduction of study treatment.
- Known association of the event with the study treatment or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the participant or use of concomitant medications known to increase the occurrence of the event.
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

For participant receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

## 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 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 participant dies during participation in the study or during a recognized follow-up period, when possible, the Investigator will provide the Sponsor with a copy of any postmortem findings including histopathology.

New or updated information will be recorded in the originally completed eCRF.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

## 5. IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The Investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the Investigator learns of the event. The following is a list of events that the Investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study treatment:

- Serious adverse events
- Adverse events of special interest ($AESI$)
- Pregnancies (see Section 8.3.5)

The Investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis.
- Significant new diagnostic test results.
- Change in causality based on new information.
- Change in the event's outcome, including recovery.
- Additional narrative information on the clinical course of the event.

Investigators must also comply with local requirements for reporting serious adverse events to the local Health Authority and IRB/EC.

## 5.1 REPORTING REQUIREMENTS OF SERIOUS ADVERSE EVENTS, AND ADVERSE EVENTS OF SPECIAL INTEREST

**Events that Occur prior to Study Treatment Initiation**

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

**Events that Occur after Study Treatment Initiation**

For reports of serious adverse events and adverse events of special interest (Section 8.3.6) that occur after initiation of study treatment (Section 8.3.1), Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the appropriate Adverse Event of Special Interest/ Serious Adverse Event eCRF form and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to the Sponsor's Safety Risk Management department.

In the event that the EDC system is unavailable, the Clinical Trial Adverse Event/ Special Situations Form provided to Investigators should be completed and submitted to the Serious Adverse Event Responsible immediately (i.e., no more than 24 hours after learning of the event).

Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

**Reporting of Post-Study Adverse Events and Serious Adverse Events**

If the Investigator becomes aware of any other SAE occurring after the end of the AE reporting period, and if the event is believed to be related to prior study treatment, the event should be reported directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Clinical Trial Adverse Event/Special Situations Form using the fax number or email address provided to Investigators.

## 5.2 *SPECIAL SITUATIONS* (OVERDOSE, MEDICATION ERROR, DRUG ABUSE, *AND*/OR DRUG MISUSE)

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug *(e.g., wrong drug, expired drug, accidental overdose, underdose, wrong dosing schedule, incorrect route of administration)*
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or *psychological* harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

    In cases where drug is to be self-administered by the participant, drug misuse could involve the drug being administered to someone other than the participant.

*After initiation of study drug, special situations associated with basmisanil/matching placebo and any associated AEs will be reported until 28 days after the final dose of study treatment.*

*Special situations, regardless of whether they result in an AE, should be reported on the Special Situations eCRF. If there are any associated AEs, each event should be recorded separately on the Adverse Event eCRF.*

*Special situations and any associated AEs should be reported within 30 days after the Investigator becomes aware of the situation. However, if an associated AE fulfills seriousness criteria or qualifies as an AESI, both the event and the special situation should be reported to the Sponsor immediately (i.e., no more than 24 hours after the Investigator becomes aware of the event), as described in Section 5.1 of this appendix.*

# 6. EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and *AESI* against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable Health Authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

| Drug | Document |
|---|---|
| Basmisanil | Basmisanil Investigator's Brochure |

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

# Appendix 3
# Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

## 1. DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

## 2. ADVERSE EVENTS OCCURRING SECONDARY TO OTHER EVENTS

In general, adverse events occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

## 3. PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the

Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent adverse event is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

## 4. ABNORMAL LABORATORY VALUES

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy.
- Medically relevant in the Investigator's judgment.

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a medically relevant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the upper limit of normal [ULN] associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a medically relevant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium", as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia".

Observations of the same medically relevant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

## 5. ABNORMAL VITAL SIGN VALUES

Not every vital sign abnormality qualifies as an adverse event. A vital sign result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention or a change in concomitant therapy.
- Medically relevant in the Investigator's judgment.

It is the Investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a medically relevant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same medically relevant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

## 6. ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN.
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Appendix 2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 8.3.6).

## 7. DEATHS

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5 of Appendix 2), regardless of relationship to study treatment, must be recorded

on the Adverse Event eCRF and immediately reported to the Sponsor. This includes death attributed to progression of Dup15q syndrome.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, “unexplained death” should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), “unexplained death” should be replaced by the established cause of death. The term "sudden death" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

## 8. PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

## 9. LACK OF EFFICACY OR WORSENING OF DUP15Q SYNDROME

Medical occurrences or symptoms of deterioration that are anticipated as part of Dup15q syndrome should be recorded as an adverse event if judged by the Investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of Dup15q syndrome on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., “accelerated Dup15q syndrome”).

## 10. HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Appendix 2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
    - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.
    - The participant has not suffered an adverse event. Prolonged hospitalization due to psychosocial issues such as lack of home care facilities, caregiver issues, transport issues, etc.

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available.

## 11. OBSERVER-REPORTED OUTCOME DATA (COA DATA REPORTED DIRECTLY BY CAREGIVER)

Adverse event reports will not be derived from patient-reported outcome (PRO) data by the Sponsor, and safety analyses will not be performed using PRO data. However, if any PRO responses suggestive of a possible adverse event are identified during site review of the PRO data, the Investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

# Appendix 4
# Clinical Laboratory Tests

The tests detailed in Table 1 will be performed by the central laboratory.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis be obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be captured in source documentation and entered as a comment into the eCRF.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2, respectively, of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

## Table 1 Protocol-Required Safety Laboratory Assessments

All study-required laboratory assessments will be performed by a central laboratory, with the exception of urine pregnancy test and urinalysis:

| Laboratory Assessments | Parameters |
|---|---|
| Hematology | • Leucocytes, erythrocytes, hemoglobin, hematocrit, platelets, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes) |
| Clinical chemistry | • Sodium, potassium, chloride, bicarbonate, glucose, urea, creatinine, $eGFR$, total protein, albumin, phosphate, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, γ-GT, CPK, total cholesterol (with HDL and LDL), triglycerides, urate, LDH |
| Coagulation | • PT (INR), aPTT |
| Viral serology | • HIV (specific tests HIV-1 antibody, HIV-1/2 antibody, HIV-2 antibody), hepatitis B surface antigen, total hepatitis B core antibody, hepatitis C virus antibody |
| Thyroid hormones | • Free T4, TSH |
| Pregnancy test | • Female participants of childbearing potential will have urine pregnancy tests. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test. |
| Urinalysis | • Dipstick: pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase<br>• If there is a medically relevant positive result, urine will be sent to the laboratory for microscopy and culture. If there is an explanation for the positive dipstick results (e.g., menses), it should be recorded and there is no need to perform microscopy and culture.<br>• Microscopic examination (RBCs, WBCs, casts, crystals, epithelial cells, bacteria), if blood or protein is abnormal. |

ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; CPK = creatine phosphokinase; γ-GT = gamma-glutamyltransferase; HDL = high-density lipoproteins; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoproteins; PT = prothrombin time; RBC = red blood cell; TSH = thyroid-stimulating hormone; WBC = white blood cell.

The results of each test may be entered into the CRF.

Investigators must document their review of each laboratory safety report.

## Additional Statistical Considerations for Clinical Laboratory Data

- Standard Reference Ranges and Transformation of Data

Potential analysis considerations for analyzing Laboratory data includes the use of Standard Reference Ranges and potential transformation of data for specific laboratory tests.

In this scenario, Roche standard reference ranges, rather than the reference ranges of the Investigator, can be used for specific parameters. For these parameters, the measured laboratory test result will be assessed directly using the Roche standard reference range. Certain laboratory parameters will be transformed to Roche's standard reference ranges.

A transformation will be performed on certain laboratory tests that lack sufficiently common procedures and have a wide range of Investigator ranges, e.g., enzyme tests that include AST, ALT, and alkaline phosphatase and total bilirubin. Because the standard reference ranges for these parameters have a lower limit of zero, only the upper limits of the ranges will be used in transforming the data.

- Definition of Laboratory Abnormalities

For all laboratory parameters included in the analysis described above, there exists a Roche pre-defined standard reference range. Laboratory values falling outside this standard reference range will be labeled "H" for high or "L" for low in participant statistical outputs of laboratory data.

In addition to the standard reference range, a marked reference range has been pre-defined by Roche for these laboratory parameters. The marked reference range is broader than the standard reference range. Values falling outside the marked reference range that also represent a defined change from baseline will be considered marked laboratory abnormalities (i.e., potentially medically relevant. If a baseline value is not available for a participant, the midpoint of the standard reference range will be used as the participant's baseline value for the purposes of determining marked laboratory abnormalities. Marked laboratory abnormalities will be labeled in the participant listings as "HH" for very high or "LL" for very low.

# Appendix 5
# Contraceptive and Barrier Guidance

## 1. DEFINITIONS

### Female Participants of Childbearing Potential

A female participant is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

### Female participants in the following categories are considered to be Female Participants of Non-Childbearing Potential

a) Pre-menarchal

b) Pre-menopausal female with one of the following:

- Documented hysterectomy.
- Documented bilateral salpingectomy.
- Documented bilateral oophorectomy.

  Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

## 2. CONTRACEPTION GUIDANCE

### Female Participants

Female participants of childbearing potential are eligible to participate if the caregiver agrees that the participant must use highly effective method of contraception consistently and correctly as described in Table 1 below.

Per ICH M3(R2), highly effective methods of birth control are defined as those, alone or in combination, that result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly as described in Table 1 below.

## Table 1 Highly Effective Contraceptive Methods

| **Highly Effective Contraceptive Methods That Are User-Dependent**[a]<br>(Failure rate of < 1% per year when used consistently and correctly) |
|---|
| • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:<br>  o Oral<br>  o Intravaginal<br>  o Transdermal<br>• Progestogen-only hormonal contraception associated with inhibition of ovulation:<br>  o Oral<br>  o Injectable |
| **Highly Effective Methods That Are User-Independent**<br>(Failure rate of < 1% per year) |
| • Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[a]<br>• Intrauterine device<br>• Intrauterine hormone-releasing system<br>• Bilateral tubal occlusion/ ligation<br>**Azoospermic partner (vasectomized or due to medical cause)**<br>A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the female participant of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.<br>**Sexual abstinence**<br>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 participant. |
| **Effective Birth Control Methods Which May Not Be Considered As Highly Effective**<br>(Failure rate of > 1% per year when used consistently and correctly) |
| • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action<br>• Male or female condom with or without spermicide [b]<br>• Cap, diaphragm or sponge with spermicide [b] |

**Table 1 Highly Effective Contraceptive Methods (cont.)**

a) Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.
Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

b) A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods. i.e., when the risk of teratogenicity and genotoxicity is unlikely.

## 3. PREGNANCY TESTING

For female participants of childbearing potential enrolled in the study, urine pregnancy tests will be performed according to Schedule of Activity tables (see Section 1.3). If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected and according to local practice.

## 4. COLLECTION OF PREGNANCY INFORMATION

### Male participants with partners who become pregnant

The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study (see Section 8.3.5 Pregnancy). This applies only to male participants who receive study treatment.

Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. The Investigator will record pregnancy information on the Clinical Trial Pregnancy Reporting Form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the Investigator should update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy when available. An Investigator who is contacted by the male participant or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician. The female partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Monitoring of the participant's partner should continue until conclusion of the pregnancy. Any termination of the pregnancy will be

reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

Additionally, attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

### Female participants who become pregnant

The Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study (see Section 8.3.5 Pregnancy). Information will be recorded on the Clinical Trial Pregnancy Reporting Form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, which will be forwarded to the Sponsor. Monitoring of the participant should continue until conclusion of the pregnancy. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, and should not be recorded on the AE eCRF, any pregnancy complication will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Appendix 2. While the Investigator is not obligated to actively seek this information in former study participants, he/she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will be withdrawn from the study.

Additionally, attempts should be made to collect and report infant health information. When permitted by the site, an Authorization for the Use and Disclosure of Infant Health Information would need to be signed by one or both parents (as per local regulations) to allow for follow-up on the infant. If the authorization has been signed, the infant's health status at birth should be recorded on the Clinical Trial Pregnancy Reporting Form. In addition, the Sponsor may collect follow-up information on the infant's health status at 6 and 12 months after birth.

## 5 ABORTIONS

Any spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2).

Any induced abortion due to maternal toxicity and/or embryofetal toxicity should also be classified as serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2).

Elective or therapeutic abortion not associated with an underlying maternal or embryofetal toxicity (e.g., induced abortion for personal reasons) does not require expedited reporting but should be reported as outcome of pregnancy on the Clinical Trial Pregnancy Reporting Form.

## 6 CONGENITAL ANOMALIES/BIRTH DEFECTS

Any congenital anomaly/birth defect in a child born to a female participant or female partner of a male participant exposed to study treatment should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

# *Appendix 6*
# *Investigational Medicinal Product and Non-Investigational Medicinal Product Designations*

## *Table 1 Investigational, Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for European Economic Area*

| *Product Name* | *IMP/AxMP Designation* | *Marketing Authorization Status in EEA* | *Used within Marketing Authorization* |
|---|---|---|---|
| *$GABA_A$ $\alpha$5 negative allosteric modulator (RO5186582)* | *IMP (test product)* | *Unauthorized* | *Not applicable* |

*AxMP = auxiliary medicinal product; EEA = European Economic Area; IMP = investigational medicinal product.*

## *Table 2 Investigational and Non-Investigational Medicinal Product Designations for the United Kingdom*

| *Product Name* | *IMP/NIMP Designation* | *Marketing Authorization Status in UK* | *Used within Marketing Authorization* |
|---|---|---|---|
| *$GABA_A$ $\alpha$5 negative allosteric modulator (RO5186582)* | *IMP (test product)* | *Unauthorized* | *Not applicable* |

*IMP = investigational medicinal product; NIMP = non-investigational medicinal product; UK = United Kingdom.*

# *Appendix 7*
# *International League against Epilepsy 2017 Classification of Seizure Types*

*(Fisher et al. 2017, Figure 2)*

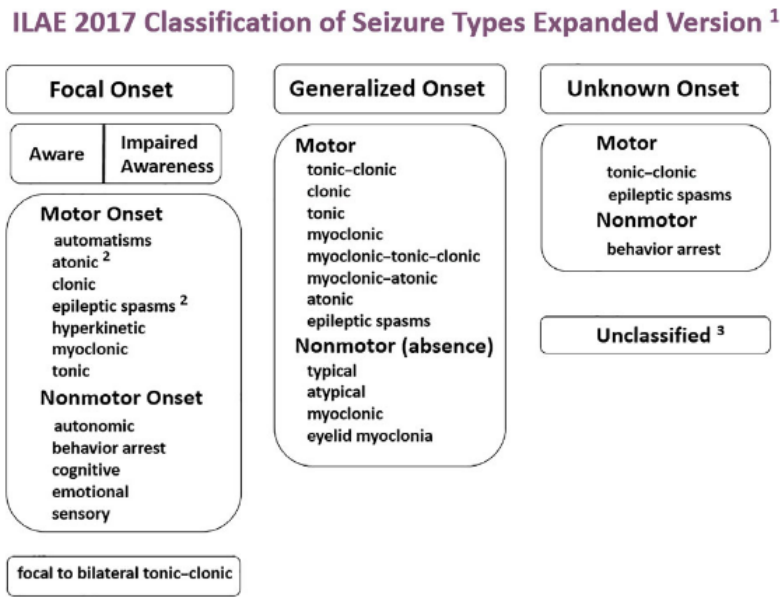



**Figure 2.**
The expanded ILAE 2017 operational classification of seizure types. The following clarifications should guide the choice of seizure type. For focal seizures, specification of level of awareness is optional. Retained awareness means the person is aware of self and environment during the seizure, even if immobile. A focal aware seizure corresponds to the prior term simple partial seizure. A focal impaired awareness seizure corresponds to the prior term complex partial seizure, and impaired awareness during any part of the seizure renders it a focal impaired awareness seizure. Focal aware or impaired awareness seizures optionally may further be characterized by one of the motor-onset or nonmotor-onset symptoms below, reflecting the first prominent sign or symptom in the seizure. Seizures should be classified by the earliest prominent feature, except that a focal behavior arrest seizure is one for which cessation of activity is the dominant feature throughout the seizure. In addition, a focal seizure name can omit mention of awareness when awareness is not applicable or unknown, and thereby classify the seizure directly by motor-onset or nonmotor-onset characteristics. Atonic seizures and epileptic spasms would usually not have specified awareness. Cognitive seizures imply impaired language or other cognitive domains or positive features such as déjà vu, hallucinations, illusions, or perceptual distortions. Emotional seizures involve anxiety, fear, joy, other emotions, or appearance of affect without subjective emotions. An absence is atypical because of slow onset or termination or significant changes in tone supported by atypical, slow, generalized spike and wave on the EEG. A seizure may be unclassified due to inadequate information or inability to place the type in other categories. [1]Definitions, other seizure types, and descriptors are listed in the accompanying paper and glossary of terms. [2]Degree of awareness usually is not specified. [3]Due to inadequate information or inability to place in other categories.
*Epilepsia* © ILAE

## *References:*


*Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58:522–30.*

Signature Page for Protocol - BP42992 - BASMISANIL - v3 - Global/Core - Publishe
System identifier: RIM-CLIN-496871

| | |
|---|---|
| Approval Task | [redacted]<br>Company Signatory<br>25-Jul-2023 15:15:18 GMT+0000 |