[redacted]

STATISTICAL ANALYSIS PLAN

A Phase II, multicenter, double blind, double dummy, randomized, 2 arms parallel study to evaluate the efficacy, safety and pharmacokinetics of CHF6563 in babies with Neonatal Opioid Withdrawal Syndrome

Protocol:	CLI-06563AA1-02
[redacted]**:**	[redacted]
Development phase:	II
Sponsor:	Chiesi Farmaceutici S.p.A.
Analysis purpose:	Final analysis
SAP version number:	Final 2.0
SAP version date:	07JUL2022

NCT no. NCT04104646

PROTOCOL HISTORY

Protocol:		
Version or ID	**Date (ddMMMyyyy)**	**Impact of the changes on the statistical analysis**
Final 1.0	04JUN2019	NAP
Final 2.0	26JUN2019	NAP
Final 3.0	11JUL2019	NAP
Final 4.0	24OCT2019	NAP
Final 5.0	28FEB2020	NAP
Final 6.0	18MAR2021	Sample size decreased from 99 to 57 subjects. Cardiorespiratory monitoring using continuous 3-lead ECG and pulse oximetry will be performed during treatment (starting before the first dose of study drug and continuing up to the initial stage of the weaning phase).

Protocol amendments:		
Version or ID	**Date (ddMMMyyyy)**	**Impact of the amendment on the statistical analysis**
NAP		

This statistical analysis plan (SAP) only considers the last version of the protocol, and of the protocol amendments, as listed above.

[redacted]

LIST OF ABBREVIATIONS

ADaM	analysis data model
ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
AST	aspartate transaminase
BL(O)Q	below the limit of quantification
CI	confidence interval
CRF	case report form
DBP	diastolic blood pressure
DRM	data review meeting
DRR	data review report
DY	relative day
ENR	enrolled set
FNAST	Finnegan Neonatal Abstinence Scoring Tool
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonization
MedDRA	Medical Dictionary for Regulatory Activities
NAP	not applicable
NOWS	neonate opioid-withdrawal syndrome
PK	pharmacokinetic
RND	randomized set
SAP	statistical analysis plan
SAF	safety set
SBP	systolic blood pressure
SD	standard deviation
SDTM	study data tabulation model
SE	standard error
[redacted]	[redacted]
SOP	standard operating procedure
STAT	statistics
TEAE	treatment-emergent adverse event
TLF	tables, listings and figures

VS	vital signs
WHO	World Health Organization
WI	work instruction

DEFINITION OF TERMS

case report form (CRF)	A printed, optical, or electronic document designed to record protocol required information to be reported to the sponsor for each trial subject.
display	Analysis table, figure or listing
phase	Interval of time in the planned conduct of a study associated with a specific purpose: for example, screening, treatment, follow-up.
round half away from zero tie-breaking rule	Convention to round values ending with 5 to the nearest digit away from zero. The round half away from zero is implemented in the SAS® ROUND function.

Examples:

Database value	Rounded value
-1.35	-1.4
-1.25	-1.3
1.25	1.3
1.35	1.4

significant digit	All digits of a number used to express it to the required degree of accuracy, starting from the first non-zero digit.
study drug	Pharmaceutical form of an active ingredient or placebo, being tested or used as a reference in a clinical study.

TABLE OF CONTENTS

1. INTRODUCTION

This SAP describes the final statistical analysis to be performed for the CLI-06563AA1-02 ([redacted]) study.

This SAP covers the efficacy, pharmacokinetic (PK), safety and general characteristics parts of the statistical analysis. It specifies the analysis displays to be presented and describes the methods and procedures in a more elaborated way than in the statistical methods section of the protocol.

The statistical analysis will process and present the results following the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) standards, in particular the ICH-E3, ICH-E6 and ICH-E9 guidelines.

1.1 STUDY OBJECTIVES

The primary objectives of this study are:

- To assess the efficacy of CHF6563 in babies with NOWS
- To assess the safety and tolerability of CHF6563 in babies with NOWS

The secondary objectives of this study are:

- To investigate the pharmacokinetics of CHF6563 in babies with NOWS
- To assess the use of the adjunctive therapy for NOWS

1.2 ESTIMAND FOR PRIMARY ANALYSIS

- Treatment: CHF6563
- Population: neonates with NOWS meeting eligibility criteria
- Variable of interest: duration of treatment for NOWS
- Summary measure: mean, 95% CI
- Intercurrent event handling
  - Discontinuation from study during the treatment period for any reason. These are the only foreseeable missing data. Every effort is made to minimize these withdrawals, but it can be anticipated that some missing data due to withdrawal of consent or Investigator's decision may be unavoidable in this patient population. These cases will be imputed as an extremely negative value (see section 5.3.1).
  - All other intercurrent events are treated as if they did not happen (treatment policy strategy). This includes, but not limited to:
    - the use of additional or alternative therapies
    - wrong treatment received
    - wrong dose received
    - rescue doses not as foreseen by protocol
    - adjunctive therapy not as foreseen by protocol

1.3 STUDY DESIGN

This is a randomized, multicenter, double blind, double-dummy, parallel group, controlled study.

Fifty-seven neonates with neonatal opioid-withdrawal syndrome (NOWS) with or without other concomitant drug withdrawal syndromes will be randomized to receive CHF6563 or morphine treatment. In order to maintain the blind, a double-dummy design will be used so that the subjects will receive either CHF6563 and morphine matched placebo, or morphine treatment and CHF6563 matched placebo. Due to the different lengths of weaning, functional unblinding will be possible following the last scheduled dose of CHF6563 up to the end of the study.

According to a randomization algorithm, neonates will be assigned to one of the two arms:

- Test arm: babies will receive a sublingual dose of CHF6563 at a starting dose of 10 µg/kg every 8 hours (±1 h) (using birth weight which should be rounded to the second decimal place) and the corresponding oral dose of morphine matched placebo q4.
- Reference arm: babies will receive an oral dose of morphine at a starting dose of 0.07 mg/kg every 4 hours (±1 h) (using birth weight which should be rounded to the second decimal place) and the corresponding sublingual dose of CHF6563 matched placebo q8.

The mothers of potential infants will be identified through the outpatient maternity, treatment clinics or upon admission to hospital. All babies for whom consent has been obtained will have NOWS graded according to Finnegan Neonatal Abstinence Scoring Tool FNAST (see protocol for details on FNAST).

Pharmacological treatment will start up to 7 days after delivery and consists of the following phases: initiation, escalation, stabilization, weaning and cessation. Assessment of the need for treatment and dose adjustments will be based upon clinical signs of withdrawal evaluated using a FNAST and continued until at least 48 hours after the last dose of opioid treatment. A review of the drug dose will take place on a daily basis or more frequently during the escalation phase to ensure timely dose adjustment.

The duration of follow up will be for 6 weeks after the final opioid treatment dose. Evidence of recurrence of significant withdrawal will be monitored for all babies who remain within the hospital. For babies discharged following the required period of inpatient observation (48 hours post last opioid treatment dose), daily telephone contact with the primary caregiver (parental/legal guardian or foster mother) will continue for the first 7 days and will record the baby's wellbeing and identify any escalation of withdrawal signs.

Thereafter weekly telephone contact will continue for the duration of the follow up period. The first weekly telephone contact will occur 7 days after the last daily phone call. Significant escalation of withdrawal signs will warrant clinical review and assessment for relapse severe enough to require pharmacological treatment and readmission.

The end of the trial is defined as the last follow-up at 6 weeks contact of the last subject in the trial.

The study will be conducted as follows for each baby:

- A pre-screening visit with the mother to explain the study and obtain the informed consent to participate in the study, and to confirm the use of opioid in the last month of pregnancy. This visit will be carried out during the last month of pregnancy or after delivery. The maternal screening questionnaire will also be completed.
- A screening visit on the neonates who show sign of NOWS. The visit will be carried out up to 7 days after delivery.
- A randomization visit to verify the eligibility of the neonate for inclusion in the study and to assign the neonates to a treatment and provide the first treatment administration.
- Treatment period: from randomization, up to 48 hours after the last dose. The treatment period can last up to 10 weeks (70 days) from the first treatment dose.
- Regular follow up will continue both before and after discharge from hospital to identify those babies who suffer recurrence of significant withdrawal. The duration of follow up will be for 6 weeks after the final opioid treatment dose. Evidence of recurrence of significant withdrawal will be monitored for all babies who remain within the hospital. For babies discharged following the required period of in-patient observation (48 hours post last opioid treatment dose), daily telephone contact with the primary caregiver (parental/legal guardian or foster mother) will continue for the first 7 days and will record the infant's wellbeing and identify any escalation of withdrawal signs. Thereafter weekly telephone contact will continue for the duration of the follow up period.

An 18-month (± 1 months) follow-up visit to assess neurodevelopmental and general health status and confirmation of the safety of the test treatment will be undertaken by the participating centers. This assessment will be evaluated separately from the main part of the study and will therefore not be described in this SAP. Since the study was early terminated the 18-month follow-up will not be conducted.

The schedule of assessments is in appendix 9.1.

1.4 EXPECTED SAMPLE SIZE

On the basis of the results of similar studies, it was determined that a sample size of 51 babies in (17 randomized to morphine and 34 randomized to CHF6563) will provide a power of 80% to detect a difference in duration of treatment of 13 days (312 hours), assuming a common standard deviation of 15 days and a two-sided significance level of 0.05. Assuming an early withdrawal rate of 10%, a total of 57 neonates will be randomized in order to reach a total of 51 evaluable babies completing the treatment period.

Based on an assumed screening failure rate of 80% it is anticipated that approximately 285 mothers should be pre-screened to achieve 57 randomized babies.

1.5 RANDOMIZATION AND BLINDING

Babies will be assigned in a 2:1 ratio to either CHF6563 or morphine. Randomization will be stratified according to the following variables, using a dynamic randomization algorithm (i.e. minimization) to balance treatment arms with respect to stratification factor levels, while maintaining an overall treatment balance:

- Neonate's feeding status at time of randomization (formula/any maternal breast- milk [including combination of breast milk and formula])
- Maternal primary opioid use (buprenorphine/methadone/other)
- Maternal concurrent use of benzodiazepines, antidepressants, or gabapentin (polypharmacy [yes/no]);

The minimization method is planned in order to maximize the balance of each stratification variable as well as the overall treatment balance across arms in a 2:1 ratio, considering the planned sample size. This method achieves a greater level of balance across multiple stratification variables compared to a traditional stratified randomization

Babies will be centrally assigned to one of the two treatment arms on randomization through an IRT system (Interactive Response Technology, combination of voice and web response system and also referred as IVRS/IWRS).

Following 2 consecutive FNAST with a sum ≥ 12, if all eligibility criteria except for Inclusion Criterion #5 are met, then babies will be pre-randomized in the IRT system to ensure treatment is available should Inclusion Criterion #5 be met (i.e. the sum of 3 consecutive FNAST scores ≥ 24 or a single score ≥12).

The IRT will allocate the patient to a certain treatment group using biased coin application of the Pocock and Simon minimization algorithm and assign the study medication kit number corresponding to the babies' treatment group. IRT specifications will be fully described in a specific document. The IRT will also generate a confirmation after every IRT transaction is performed.

The patient will be identified by a unique number of six digits: the investigational site number will be the first three digits and the following three digits will be the progressive numbering of the patient within each site (e.g. 101001, 101002 etc.).

1.6 INTERIM ANALYSIS

No interim analyses are foreseen.

1.7 SOFTWARE

SAS version 9.4 or later will be used for programming.

1.8 VALIDATION MODEL

[redacted] – Clinical Research statistics (STAT) standard operating procedures (SOPs) and work instructions (WIs) as effective at the project start will be followed throughout the project, provided the applicable regulatory requirements are still met.

[redacted]	

The analysis tables/listings will be validated according to model B (review by an independent person; see [redacted]).

In addition, the validation process followed for this study is summarized in the QC plan.

2. EFFICACY AND PHARMACOKINETIC ANALYSES

2.1 PRIMARY EFFICACY ENDPOINT

According to the protocol, the primary efficacy endpoint of this study is:

- Duration of treatment defined as the number of hours from first dose of study drug administration until the last dose of study drug.

2.1.1 Derivation rules

Duration of treatment (hours) = date/time of last study drug administration – date/time of first study drug administration

2.1.2 Presentation of results

All data relevant to the primary efficacy endpoint will be listed.

2.2 SECONDARY EFFICACY ENDPOINTS

According to the protocol, the secondary efficacy endpoints of this study are:

- Time to first weaning, defined as the number of hours from first dose of study drug administration until the first dose reduction
- Requirement for adjunctive drug therapy (phenobarbital) for signs of NOWS
- Total hours of treatment with adjunctive therapy
- Requirement for rescue doses (CHF6563 or morphine)
- Number of rescue doses administered per neonate
- Percentage of total amount of active study drug which is from rescue doses
- Length of opioid related hospital stay, defined as number of days from day of birth until 48 hours after the final dose of drug treatment for NOWS
- Relapse of NOWS, defined as experiencing recurrence of significant signs of withdrawal
- Incidence of readmissions, defined as readmission to hospital for NOWS relapse

2.2.1 Available data

The following parameters are collected per study visit or on the study termination form:

- Date/time of first dose reduction of study drug (SUPPDS.QVAL when SUPPDS.QNAM is 'FDREDDTC')
- Requirement for adjunctive drug therapy (phenobarbital): yes/no (SUPPSV.QVAL when SUPPSV.QNAM is 'PHENOBAR')

  Note: Only adjunctive drug therapy during the treatment period will be considered.
- Requirement for rescue doses: yes/no (SUPPSV.QVAL when SUPPSV.QNAM is 'RESCUEDO')

  Note: only rescue doses during the treatment phase will be considered.
- Escalation of opioid withdrawal: yes/no (FA.FASTRESC = 'Y' when FA.FAOBJ is 'ESCALATION OF OPIOID WITHDRAWAL' and FA.FATESTCD is 'EVIDENCE')
- Readmission to hospital: yes/no (FA.FASTRESC = 'Y' when FA.FAOBJ is 'ESCALATION OF OPIOID WITHDRAWAL' and FA.FATESTCD is 'READHOSP')

2.2.2 Derivation rules

- Time to first weaning (hours) = date/time of first dose reduction – date/time of first study drug administration

  Note: missing data will not be imputed.
- Number of rescue doses administered = sum of rescue dose administrations (SUPPEC.QVAL = 'Y' when SUPPEC.QNAM is 'RESCUEDO')

  Note: 0 for subjects not requiring rescue doses.

2.2.3 Inferential statistics

No inferential statistics will be performed.

2.2.4 Presentation of results

All data relevant to the following primary and secondary efficacy endpoints will be listed:

- Duration of treatment
- Time to first weaning
- Requirement for adjunctive drug therapy
- Number of rescue doses
- Relapse of NOWS

[redacted]

2.3 PHARMACOKINETICS

2.3.1 Available data

Blood samples will be collected for the determination of CHF6563 at the time points indicated in the schedule of assessments (see section 9.1).

2.3.2 Presentation of results

Individual CHF6563 blood concentrations and actual blood sampling times from drug administration for PK assessments will be listed.

3. SAFETY ANALYSES

3.1 ADVERSE EVENTS

3.1.1 Available data

Adverse events (AEs) are coded into system organ classes and preferred terms using the medical dictionary for regulatory activities (MedDRA). For each AE, start and stop date(time)s are collected as well as severity, a seriousness flag, treatment-relatedness, action taken towards the study drug and outcome.

3.1.2 Derivation rules

Pre-treatment AEs are defined as AEs starting between date(time) of informed consent and the date(time) of first study drug administration – 1 minute.

Treatment-emergent adverse events (TEAE) are defined as AEs starting on or after first administration of any study drug.

Peri-dosing TEAEs are defined as AEs included in the list below occurring during or shortly after study drug administration, i.e. within 10 minutes from the start of study drug administration:

- mouth irritation or inflammation,
- apnea, desaturation,
- brady/tachycardia,
- cough,
- immediate swallowing of sublingual drug,
- regurgitation,
- vomiting occurring after administration.

  Note: the list of preferred terms to be selected as peri-dosing TEAEs will be finalized prior to database lock and documented in the DRR. For AEs start dates with missing time information where no other database information indicates that AE started outside the peri-dosing interval, the worst-case principle will be applied and these AEs will be considered as peri-dosing.

Post-treatment AEs are defined as AEs starting on or after the start of the follow-up phase.

Based on their start date(time), AEs will be allocated to the phase during which they started. Phases are defined in section 5.2.1. In case the AE start date(time) is incomplete or missing and the AE could consequently be allocated to more than one phase, a worst-case allocation will be done as detailed below:

- Treatment phase vs. non-treatment phase: AE will be allocated to the treatment phase unless the available parts of the AE stop date(time) provide evidence for allocating to the non-treatment phase.

A fatal AE is defined as an AE with outcome ‘fatal’.

An AE for which the study drug was discontinued is defined as an AE with action taken ‘drug withdrawn’.

AE onset and duration will be calculated as follows when start and stop dates are fully known:

- AE onset day (vs. first administration) =
  - AE start date < date of first administration: AE start date – date of first administration
  - AE start date ≥ date of first administration: AE start date – date of first administration + 1 day
- AE duration (rounded as detailed in section 5.3.3) =
  - In minutes: AE end date/time – AE start date/time + 1 minute
  - In hours: AE end date/time – AE start date/time + 1 hour
  - In days:
    - AE end date – AE start date + 1 day
    - study discontinuation date – AE start date + 1 day (when the AE start date is fully known but the AE is not resolved at the end of the study)

      In this case the duration will be presented as ">x days".

Note: If AE duration is less than 1 hour, the duration will be presented in minutes. If the AE duration is 1 hour or more, but less than 1 day, it will be presented in hours. If AE duration is 1 day or more, it will be presented in days.

3.1.3 Presentation of results

Tables will present TEAEs and post-treatment AEs only. Pre-treatment AEs will only be listed.

An overview table will show the number and percentage of subjects with at least one event and the number of events by treatment for the following:

- TEAEs
- Serious TEAEs
- Non-serious TEAEs
- ADRs
- Serious ADRs
- Severe TEAEs
- TEAEs leading to study drug discontinuation
- TEAEs leading to death
- Peri-dosing TEAEs
- ADRs leading to study drug discontinuation
- ADRs leading to death
- Peri-dosing ADRs
- Post-treatment AEs

All AEs, including pre-treatment events and all coding information will be listed. AEs started after date of last study medication intake will be flagged. Blank system organ classes and preferred terms, if any will be shown as 'Not Available'.

3.2 CLINICAL LABORATORY EVALUATION

3.2.1 Available data

Per protocol, the following laboratory parameters are expected:

- Biochemistry: potassium, sodium, magnesium, phosphorus, C-reactive protein, urea nitrogen, calcium, creatinine, glucose, bilirubin (total serum bilirubin), bilirubin (direct or conjugated)
- Hematology: red blood cells count, hematocrit, total hemoglobin, white blood cells count, absolute neutrophils count, neutrophils count %, absolute lymphocytes count, lymphocytes count %, absolute monocytes count, monocytes count %, absolute eosinophils count, eosinophils count %, absolute basophils count, basophils count %, platelets count
- Liver function: alanine aminotransferase (ALT) and aspartate aminotransferase (AST)

Normal ranges are available as provided by the laboratory.

3.2.2 Derivation rules

- The following abnormality categories will be defined:
  - Low: value < lower limit of normal range
  - Normal: lower limit of normal range ≤ value ≤ upper limit of normal range
  - High: value > upper limit of normal range

Note: classification will be done in standardized units, using non-imputed values and normal ranges.

3.2.3 Presentation of results

The results will be presented in standardized units.

All laboratory data will be listed.

3.3 VITAL SIGNS

3.3.1 Available data

The following vital signs parameters are collected:

- Vital signs: heart rate (HR), respiratory rate (RR), peripheral oxygen saturation (SpO2), body temperature (BT), systolic (SBP) and diastolic blood pressure (DBP)
- Head circumference, body weight and body length.

3.3.2 Derivation rules

The following vital signs parameters will be derived:

- Head circumference percentile
- Body weight percentile
- Body length percentile

  Note: the head circumference, body weight and body length percentiles will be calculated based on the University of Calgary Fenton Pre-term Growth Charts for babies up to 50 weeks of gestational age. If a baby remains in the study beyond 50 weeks of gestational age, the WHO growth standards can be used for the calculation of the percentiles.
- Mean Blood Pressure (MBP) (mmHg) = (SBP + 2 * DBP)/3

3.3.3 Presentation of results

- Vital signs:

All vital signs (HR, RR, SpO2, BT, DBP, SBP, MBP) data will be listed.

- Head circumference, body weight and body length:

All head circumference, body weight and body length data (including the percentiles) will be listed.

[redacted]

3.4 ESCALATION OF OPIOID WITHDRAWAL

3.4.1 Available data

The following signs of escalation of opioid withdrawal are collected:

- Crying - excessive / continuous
- Persistent inability to sleep
- Tremors and jerks
- Sweating
- Fever
- Mottling
- Nasal stuffiness
- Sneezing
- Poor Feeding
- Regurgitation
- Projectile vomiting
- Loose stools
- Watery stools

3.4.2 Presentation of results

All available information concerning escalation of opioid withdrawal will be listed.

3.5 PHYSICAL EXAMINATIONS

Abnormal physical examination findings will be listed.

3.6 NEUROLOGICAL AND BEHAVIORAL ASSESSMENT

Abnormal neurological and behavioral examination findings will be listed.

4. GENERAL CHARACTERISTICS ANALYSES

4.1 SUBJECT DISPOSITION

The following subject data will be tabulated:

- The number of screen failures overall
- The number of subjects in each analysis set by treatment and overall
- The number and percentage of subjects for each analysis visit included in the list below by treatment and overall
    - Screening
    - Day 1
    - Every 5 days of the treatment phase (Day 5, Day 10, Day 15, ...)
    - Day of last dose
    - End of treatment visit
- The number and percentage of subjects who entered, completed or discontinued each study phase (initiation, escalation, stabilization, weaning and cessation)
- The number and percentage of subjects who completed or discontinued the study as documented on the study termination page and the number and percentage of subjects for each study discontinuation reason by treatment and overall

All information collected in the CRF concerning allocation, code breaking, study discontinuation and information on phases, dates of first signed informed consent, last visit and last contact (over the whole study) and comments will be listed.

4.2 PROTOCOL DEVIATIONS AND ELIGIBILITY

The number and percentage of subjects with major and minor protocol deviations, per category and type, will be tabulated separately, by treatment and overall.

All available information concerning protocol deviations, violations on eligibility criteria (only violated eligibility criteria having DV.DVDECOD = 'VIOLATION OF INCLUSION CRITERION' or 'VIOLATION OF EXCLUSION CRITERION') will be listed.

[redacted]

4.3 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

4.3.1 Available data

The following parameters will be available:

- Mother demographics: race, ethnicity and maternal characteristics as collected in the eCRF
- Mother drug screen
- Demographics: gestational age, sex, race, ethnicity, date of birth, and date of signing informed consent form (ICF), maternal smoking, alcohol consumption, mode of delivery, family history of prolonged QTc syndrome, unexplained sudden death in otherwise healthy family members and APGAR score
- Screening tests: head circumference, weight, length and vital signs, drug screen
- Baseline characteristics: primary feeding method, feeding type at randomization, maternal primary opioid use (buprenorphine / methadone / other) and use of other licit and illicit drugs, maternal concurrent use of benzodiazepines, antidepressants or gabapentin (polypharmacy)
- Feeding status: nasogastric feed (entire, partial, no), type (maternal breast milk only, formula or donor breast milk, mixed), breast fed (Y/N), estimated volume of maternal breast milk during breast feed (mL), volume of maternal breast milk given by bottle (mL) and volume of formula (mL)
- FNAST scores

4.3.2 Derivation rules

The following vital signs parameter will be derived:

- Mean Blood Pressure (MBP) (mmHg) = (SBP + 2 * DBP)/3

4.3.3 Presentation of results

Mother demographics and drug screen will only be listed.

Demographics will be presented by treatment and overall using descriptive statistics for age, head circumference, weight, and frequency tabulations for sex, race, ethnicity, maternal smoking, and alcohol consumption.

Baseline characteristics (primary feeding method, feeding type at randomization, maternal primary opioid use (buprenorphine / methadone / other) and use of other licit and illicit drugs, maternal concurrent use of benzodiazepines, antidepressants or gabapentin (polypharmacy)) will be presented by treatment and overall using frequency tabulations.

FNAST scores will be summarized by means of descriptive statistics at baseline only (as defined in section 5.2.2) by treatment.

Feeding status will be presented by treatment at Follow-up Day 7, Week 2, and Week 6 using descriptive statistics for estimated volume of maternal breast milk during

breast feed, volume of maternal breast milk given by bottle and volume of formula and frequency tabulations for nasogastric feed, type and breast fed.

In addition, the following parameters will be presented by treatment and overall using descriptive statistics:

- head circumference, weight and length at Screening
- vital signs at Screening

All demographic data, baseline characteristics, feeding status and FNAST scores and screening tests (except when listed in the safety part, i.e. head circumference, weight, length and vital signs) will be listed.

4.4 MEDICAL HISTORY AND CONCOMITANT DISEASES

4.4.1 Available data

Medical history and concomitant diseases findings are coded using the medical dictionary for regulatory activities (MedDRA) into system organ classes and preferred terms. For each finding (MH.MHCAT is 'GENERAL MEDICAL HISTORY'), a start and stop date or ongoing flag is collected.

4.4.2 Derivation rules

The following parameters will be derived:

- Medical history finding: not ongoing at screening (MH.MHENRTPT is 'BEFORE')
- Concomitant disease finding: still ongoing at screening (MH.MHENRTPT is 'ONGOING' or missing)

4.4.3 Presentation of results

Medical history and concomitant diseases will be tabulated separately by treatment and overall. Each table will show:

- The number and percentage of subjects with and without findings
- The number and percentage of subjects with findings by system organ class and preferred term

All medical history and concomitant diseases data will be listed separately.

4.5 PROCEDURES AND MEDICATIONS

4.5.1 Available data

All procedures are coded into system organ classes and preferred terms using the medical dictionary for regulatory activities (MedDRA). For each procedure start and stop date(time)s or ongoing flag are collected.

All medications are coded using WHO-DRUG. ATC selection is performed. ATC coding up to level 5 is available in the clinical database. For each medication, a start date(time) and stop date(time) or ongoing flag are collected.

4.5.2 Derivation rules

Based on their start and stop date(time), procedures and medications will be allocated to each phase during which they were performed/administered. A procedure/medication can therefore be reported in more than one phase.

Phases are defined in section 5.2.1. Procedures/medications with (partially) missing dates will be allocated to each phase unless the available parts of the procedure/medication start or stop date(time) provide evidence that the procedure/medication was not taken during that phase.

Based on their start and stop date(time) procedures and medications will be allocated to one of the following categories:

- Prior: the procedure/medication stopped prior to first study drug administration
- Maintained: the procedure/medication started before first study drug administration and was ongoing at first study drug administration
- Concomitant: the procedure/medication started at or after first study drug administration
- Post-treatment: the medication/procedure started on or after the start of follow-up phase

For procedures/medications with (partially) missing date(time)s not allowing allocation to any of the categories, a worst-case allocation will be done based on the available parts of the medication/procedure start or stop date(time). The medication/procedure will be allocated to the first category allowed by the available data, according to the following order:

- Concomitant
- Post-treatment
- Maintained
- Prior

Note: these procedures/medications will only be allocated to the phases that match the worst-case allocated category.

4.5.3 Presentation of results

Procedures:

The number and percentage of subjects with procedures and the number and percentage of subjects with procedures by system organ class and preferred term alphabetically sorted will be tabulated per category (prior, maintained, and concomitant); by treatment and overall (prior procedures only). Blank system organ classes, if any, will be shown as 'Not Available' in the tables.

Subjects having more than one procedure allocated to the same category within the same treatment, system organ class and preferred term will be counted only once.

All procedures data will be listed.

Medications:

The number and percentage of subjects with medications and the number and percentage of subjects with medications by anatomical main group (level 1), therapeutic subgroup (level 2), chemical subgroup (level 4), and generic term will be tabulated per category (prior, maintained, and concomitant); by treatment and overall (prior medications only). Blank ATC levels, if any, will be shown as 'Not Available' in the tables.

Subjects having more than one medication allocated to the same category within the same treatment, anatomical main group, therapeutic subgroup, chemical subgroup, and generic term will be counted only once.

All medications data will be listed.

4.6 EXPOSURE TO STUDY DRUG

4.6.1 Available data

For each study drug administration, the dates (time), the prescribed dose, the actual volume administered, rescue dose flag and issues occurred during dosing will be recorded.

4.6.2 Presentation of results

All exposure data will be listed.

5. GENERAL METHODOLOGY

5.1 ANALYSIS SETS

5.1.1 Analysis sets

The following analysis sets will be considered in the statistical analysis:

Enrolled Set (ENR):	all subjects for whom *informed consent was signed*
Randomized Set (RND):	all *randomized* subjects
Safety Set (SAF):	all randomized subjects who receive *at least one dose of study drug*

Notes:

- Having signed an informed consent is defined as having a complete informed consent signature date in the database.
- Randomized is defined as having a randomization date in the database or any information to confirm randomization.
- Having received at least one dose of study drug is defined as having an exposure date or any information confirming exposure present in the database.

Unless stated otherwise, the SAF analysis set will be used for demographics and baseline characteristics tables. All listings will be presented for the Randomized Set, unless states otherwise in section 8.2.

In case of local major protocol deviations, only the affected data at the specific time point will be excluded from the applicable analysis sets.

5.1.2 As planned versus as actual analysis

For analyses done on the safety analysis set (excluding general characteristics analyses), the actual treatment of the subject will be considered. In addition, the actual treatment will be presented in the general and safety listings.

For all other analyses, the planned treatment will be used.

5.2 PHASES AND TIME POINTS

5.2.1 Phases

Adverse events, medications, and procedures will be allocated to phases. For assessments, the visit and time point labels indicated on the subject's case report form (CRF) will be used to allocate to the correct treatment.

Adverse events, procedures and medications:

Phase	Start	End
Screening	Date of signing the ICF, with 00:00 added as time part	First administration date(time) – 1 minute
Treatment	First administration date(time)	Last administration date(time) + 48 hours
Follow-up	End date(time) of treatment phase + 1 minute	Date of last contact, with 23:59 added as time part

Per definition, and for each subject, the first phase starts on the date of the earliest available ICF signature, with 00:00 added as time part. The last available phase ends on the date of last contact, with 23:59 added as time part.

All tables and listings will present treatments rather than phases.

AEs, medications and procedures will be allocated to phases as described in sections 3.1.2 and 4.5.2 respectively.

In addition to the analysis phases described above, a subject will be considered to have entered a specific study phase based on the below definitions:

- Initiation phase: all subjects in the safety set
- Escalation phase: all subjects receiving at least one dose higher than the initial dose
- Stabilization phase: all subjects who receive at least 2 consecutive doses without escalation

  Note: Subjects can skip the escalation phase and directly enter the stabilization phase from the initiation phase.
- Weaning phase: all subjects who receive at least one dose lower than the previous
- Cessation phase: all subjects reaching the cessation dose (i.e. between 90-110% of the initial dose for CHF6563 or < 0.025 mg/kg for morphine) and having a decrease in dose frequency (only subjects receiving CHF6563, i.e. dosing frequency is decreased q24 hours)

Note: in addition to the above definitions, other information present in SDTM (i.e. flags or visits present indicating that a subject has entered a specific phase) could be used to determine whether a subject entered a specific phase. A phase (and all subsequent phases previously entered by the subject) will be considered discontinued whenever a subject discontinues the study during that study phase.

5.2.2 Baseline and change from baseline

The baseline value is a non-missing value before the first administration of any study drug.

Unless otherwise specified, Screening will be used as the baseline measurement. In case there are no assessments/measurements at Screening, the baseline value will be set to missing.

[redacted]	

The following table summarizes the baseline definition for each parameter:

Parameter	Baseline
Vital signs	Screening
Head circumference and body weight	Screening
Biochemistry, hematology and liver function	Screening
FNAST scores	Last non-missing value before the first administration of any study drug

Change from baseline is defined as:

Change from baseline at time point t = value at time point t – baseline value.

5.2.3 Relative day

Relative days (DY) will be calculated according to the following rule:

- Concerned date < reference date: DY = concerned date – reference date
- Concerned date ≥ reference date: DY = concerned date – reference date + 1

The reference date is the date of first administration of study drug

5.2.4 Analysis visits

The analysis will use the visits indicated on the subject's CRF. In addition, the vital signs assessments will be allocated to analysis time point windows as defined below based on the actual time of the assessment relative to the first dose (note: time points are not collected on the subject's CRF).

The screening value is the last available and non-missing value before the randomization visit (Day 1). This value corresponds to the screening visit, except in case of retesting. Reason for this approach is the use of retest results for subject eligibility assessment.

Unscheduled assessments will not be used in the analysis unless an unscheduled assessment was done to replace unavailable/unreliable data. The decision whether an unscheduled assessment should be used instead of the original assessment will be taken during the data review meeting before database lock. The selection of the unscheduled assessments to be included in the analysis instead of the original assessments will be done in the corresponding ADaM datasets using appropriate values for AVISIT(N) and ATPT(N). Hard coding (documented in the DRR and by a Note to File signed off by both [redacted] and Chiesi Farmaceutici S.p.A) will be implemented in the impacted analysis programs by including a comment.

Baseline is defined in section 5.2.2.

Scheduled and unscheduled assessments will be listed.

Follow-up visits will be summarized at selected time points only. All follow-up data will be listed.

The analysis visit labels will be assigned using the following rules:

- All planned screening, re-screening, eligibility recheck, etc. visits occurred during the screening phase will be presented as 'Screening'.

- All planned visits occurred during a scheduled day, will be presented as 'Day x' (x = study day, e.g. 'Day -1', 'Day 1', etc.)
- Early termination visits will be presented as 'Early Termination'
- Follow-up visits will be presented as 'Follow-up'. In case recurrent follow-up visits are planned, the label will include details of the repeated follow-up (e.g. 'Follow-up Day 1', 'Follow-up Week 2', etc.)
- Unscheduled visits that occurred during a planned visit day will be presented with the same label as the planned visit (see rules above)
- Unscheduled visits that occurred on a day different than a planned visit will be presented as 'Unscheduled'
- Other visits not covered by the rules above will be presented using similar labels to the ones used in SDTM (XX.VISIT)

5.3 IMPUTATION AND ROUNDING RULES

5.3.1 Missing values

Potential imputations of missing values will be discussed during the review of the data by the Chiesi team. Decisions on whether any imputation rules on missing values should be applied to the analysis will be fully documented in the DRR.

5.3.2 Values below or above a threshold

Safety values expressed as below (or above) the limit of quantification will be imputed by the value of the quantification limit itself.

PK concentrations below the quantification limit will be flagged as BLQ in the concentration listing. Listings will always show the non-imputed values.

5.3.3 Rounding of derived variables

Derived variables will be rounded to the appropriate number of decimals at TLF level:

- Duration of treatment/adjunctive therapy (hours) will be presented with 1 decimal.
- Time to weaning (hours) will be presented with 1 decimal.
- Percentage of total amount of active study drug which is from rescue doses will be presented with 1 decimal.
- Percentiles will be presented with 1 decimal.
- Mean blood pressure will be presented with 1 decimal.
- PK concentrations will be presented with 3 significant digits except values >1000, which will be presented without decimals.
- AE duration will be presented with 1 decimal.

Rounding will be done using the round half away from zero tie-breaking rule (see Definition of terms).

5.3.4 Outliers

No data will be excluded from the analysis.

5.4 PRESENTATION OF RESULTS

5.4.1 Calculation of descriptive statistics and percentages

For continuous parameters, full descriptive statistics will only be presented if there are at least 2 non-missing observations. Alternatively, only the number of non-missing data points and mean are shown.

Descriptive statistics will include the number of non-missing data points, the arithmetic mean, the standard deviation (SD), the median, minimum and maximum. For specific parameters, CI may be requested as well.

For all parameters except body temperature and head circumference, mean, median, SD and CI will be presented with one more decimal place than the individual values. For body temperature and head circumference, mean, median, SD and CI will be presented with one decimal place. Minimum and maximum will be presented with the same number of decimal places than the individual values.

For event-type data, the denominator will be all subjects in the analysis set and phase. All treatments will be shown, even if no events are present.

For frequency tabulations, missing values will not be included in the denominator count when computing percentages.

Percentages will be shown with one decimal place.

5.4.2 Presentation of treatments

The following treatment labels will be used in the tables and listings:

- CHF6563
- Morphine

An overall column, to summarize all subjects over treatments, will be presented only in tables showing data that are not affected by the study drug. The overall column will be shown last.

5.4.3 Ordering in tables and listings

If the treatments are presented as columns, tables will be sorted by analysis visit and time point. Otherwise, tables will be sorted first by treatment, then by analysis visit and time point.

The sorting of treatments will be kept as close as possible to the study design:

- The test treatment (CHF 6563) will be shown first and then the reference treatment (morphine)

All tables will be presented per treatment, unless specified otherwise.

All listings will be ordered by subject and then by analysis visit and time point (chronologically), unless specified otherwise.

In tables showing several parameters, each parameter will begin on a new page and parameters will be sorted alphabetically, within the parameter category if applicable.

5.4.4 Raw SAS output

Not applicable.

6. CHANGES TO THE PLANNED ANALYSIS

6.1 CHANGES TO THE PLANNED ANALYSIS

A total of 57 subjects were to be randomized in order to obtain 51 evaluable subjects (section 1.4). As only 7 subjects were randomized the study objectives of this study will not be evaluable. No statistical analysis will be performed on the collected data and no data derivation (i.e.: change from baseline) will be defined in the present SAP v2.0 (except for some safety parameters).

For the same reasons the following analysis sets planned in the study protocol, have not been defined in section 5.1.1:

- ITT set,
- PP set.

Duration of breast feeding will not be analyzed as stated in the CTP since these data are not collected at baseline.

The aforementioned changes, further detailed in section 6.3, and described in detail in this SAP (v2.0), will replace the analysis as proposed in the study protocol.

6.2 CHANGES IN THE CONDUCT OF THE STUDY

The clinical trial CLI-06563AA1-02 started with the first obtained signed informed consent and enrolment on 18 December 2020 and was terminated in February 2022 due to a very low recruitment rate, that is 7 neonates instead of planned 57 in one year and after a long setup phase which was actually unexpected and far from the original estimates. It leads to a projection of another 6 years to complete the trial, that does not fit with acceptable timelines within the Chiesi portfolio development. Consequently, Chiesi has decided to early terminate the trial.

6.3 CHANGES TO THE FINAL STATISTICAL ANALYSIS PLAN

In the table below, a detailed description of the changes and the impacted sections is provided.

SAP version number	SAP version Date (ddMMMyyyy)	Changes
Final 1.0	07MAY2021	Not applicable
Final 2.0	07JUL2022	Correction of typos, rephrasing, and addition of clarifications throughout text. Section (List of Abbreviations): • Removal of abbreviations related to the statistical analysis that will not be performed. • Addition of FNAST

		Sections 1.3/4 (Study Design / Expected Sample Size) • Aligned with protocol version 6.0. • Added note referring to protocol for FNAST assessment Section 1.8 (Validation Model) • Adjusted to reflect that only listings will be created, except for the general subject characteristics section of the analysis. Sections 2.1.1/2/3 (Derivation Rules / Inferential Statistics / Presentation of Results) • Only a subset of the primary efficacy endpoints will be derived and no statistical analysis will be performed. Sections 2.2.2/3/4 (Derivation Rules / Inferential Statistics / Presentation of Results) • No statistical analysis will be performed. • Only listings will be created. Sections 3.1.2/3 (Derivation Rules / Presentation of Results) • Except for a summary table only listings will be created. • Added worst-case derivation for peri-dosing AEs. Section 3.2.3 (Presentation of Results) • Only listings will be created. Sections 3.3.2/3 (Derivation Rules / Presentation of Results) • Only listings will be created. Sections 4.3.2/3 (Derivation Rules / Presentation of Results) • Parameter duration of breast feeding removed. • No figures will be created. Section 4.5.3 (Presentation of Results)

		• Correction: removal of 'treatment sequence'. Section 5.1.1 (Analysis Sets) • Removal of analysis sets (ITT & PP) that will not be used due to removal of eg. efficacy tables. Section 5.2.1 (Phases) • Removal of 'figures'. Sections 5.3.1/2 (Missing Values / Values Below or Above a Threshold) • Removal of imputation rules for efficacy analysis. Section 5.3.3 (Rounding of Derived Variables) • Addition of rounding rules for MBP and percentiles. Section 5.3.4 (Outliers) • Detection and use of outliers removed as not needed for the remaining analysis parts. Section 5.4.1 (Calculation of Descriptive Statistics and Percentages) • Specifications for descriptive statistics of efficacy parameters, p-values, and cross-tabulations removed. Section 5.4.2/3 (Presentation of Treatments / Ordering in Tables, Figures and Listings) • Reference to figures removed. Section 5.4.4 (Raw SAS Output) • Section set to 'not applicable'. Section 6.2 (Changes in the Conduct of the Study) • Added section to explain the rationale for the early termination of the study. Section 8 (List of Tables, Listings and Figures) • Updated list of output in line with the new scope of the analysis, updated titles where

		needed and updated analysis sets in order to display as much data as possible. Section 9.1 (SAS code) • Removed as no statistical analyses are kept in the study that require SAS example code.

7. REFERENCES

ICH Topic E6(R2) Guideline for Good Clinical Practice – Step 4, 9 November 2016.

8. LIST OF TABLES AND LISTINGS

8.1 TABLES

Number	Title	Analysis Set	TLFs Library Template Number
GENERAL CHARACTERISTICS			
14.1.1.1	**Screen Failures (Randomized Set)** Tabulation of completion/discontinuation and the reason for discontinuation.	**ENR**	**DST001**
14.1.1.2	**Disposition by Treatment (Randomized Set)** Tabulation of completion/discontinuation and the reason for discontinuation.	**RND**	**DST002**
14.1.1.3	**Analysis Sets (Randomized Set)** Tabulation of the number of subjects in each of the analysis sets defined in the SAP.	**RND**	**DST006**
14.1.1.4	**Attendance at Study Visits (Randomized Set)** Tabulation of the number and percentage of subjects that attended to each planned study visit (only visits defined in section 4.1) by treatment.	**RND**	**SVT001**
14.1.1.5	**Attendance at Study Phases (Randomized Set)** Tabulation of the number and percentage of subjects that entered, completed or discontinued each study phase (initiation, escalation, stabilization, weaning and cessation). The template SVT002 is used replacing the treatment periods by the study phases.	**RND**	**SVT002**
14.1.1.6	**Major Protocol Deviations (Safety Set)** Tabulation of the major protocol deviations (at least one), deviation category and deviation type by treatment and overall.	**SAF**	**DVT001**
14.1.1.7	**Minor Protocol Deviations (Safety Set)** Tabulation of the minor protocol deviations (at least one), deviation category and deviation type by treatment and overall.	**SAF**	**DVT001**
14.1.2.1	**Demographic Characteristics (Safety Set)** Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters.	**SAF**	**DMT001**
14.1.2.2	**Baseline Characteristics (Safety Set)** Frequency tabulation of baseline characteristics.	**SAF**	**DMT001**
14.1.2.3	**FNAST Scores at Baseline (Safety Set)** Descriptive statistics of FNAST scores at baseline.	**SAF**	**BLT001**
14.1.2.4	**Maternal Smoking Status (Safety Set)** Frequency tabulation of the maternal smoking status at screening.	**SAF**	**SUT001**
14.1.2.5	**Feeding Status (Safety Set)** Descriptive statistics of continuous parameters and frequency tabulation of categorical parameters.	**SAF**	**BLT001**

[redacted]

Number	Title	Analysis Set	TLFs Library Template Number
14.1.2.6	**Head Circumference and Weight at Screening (Safety Set)**	**SAF**	**BLT002**
	Descriptive statistics of head circumference and weight at Screening.		
14.1.2.7	**Vital Signs at Screening (Safety Set)**	**SAF**	**BLT002**
	Descriptive statistics of vital signs results at Screening.		
14.1.2.8	**Medical History (Safety Set)**	**SAF**	**MHT001**
	Tabulation of the number and percentage of subjects with medical history findings and number and percentage of subjects with medical history findings by system organ class and preferred term.		
14.1.2.9	**Concomitant Diseases (Safety Set)**	**SAF**	**MHT001**
	Tabulation of the number and percentage of subjects with concomitant diseases and number and percentage of subjects with concomitant diseases by system organ class and preferred term.		
14.1.2.10	**Prior Procedures (Safety Set)**	**SAF**	**MHT001**
	Tabulation of the number and percentage of subjects with prior procedures and number and percentage of subjects with prior procedures by system organ class and preferred term.		
14.1.2.11	**Maintained Procedures (Safety Set)**	**SAF**	**MHT002**
	Tabulation of the number and percentage of subjects with maintained procedures and number and percentage of subjects with maintained procedures by system organ class and preferred term.		
14.1.2.12	**Concomitant Procedures (Safety Set)**	**SAF**	**MHT002**
	Tabulation of the number and percentage of subjects with concomitant procedures and number and percentage of subjects with concomitant procedures by system organ classes and preferred terms.		
14.1.2.13	**Prior Medications (Safety Set)**	**SAF**	**CMT001**
	Tabulation of the number and percentage of subjects with prior medications and number and percentage of subjects with medications by ATC class (level 1), ATC class (level 2), ATC class (level 4) and preferred name.		
14.1.2.14	**Maintained Medications (Safety Set)**	**SAF**	**CMT001**
	Tabulation of the number and percentage of subjects with maintained medications and number and percentage of subjects with maintained medications by ATC class (level 1), ATC class (level 2), ATC class (level 4) and preferred name.		
14.1.2.15	**Concomitant Medications (Safety Set)**	**SAF**	**CMT002**
	Tabulation of the number and percentage of subjects with concomitant medications and number and percentage of subjects with concomitant medications by ATC class (level 1), ATC class (level 2), ATC class (level 4) and preferred name.		

Number	Title	Analysis Set	TLFs Library Template Number
SAFETY			
ADVERSE EVENTS			
14.3.1.1	**Summary of TEAEs (Safety Set)** Tabulation of the number and percentage of subjects with at least one of the events described in the SAP. The number of events will also be shown.	**SAF**	**AET001**

[redacted]

8.2 LISTINGS

Number	Title	Analysis Set	TLFs Library Template Number
GENERAL CHARACTERISTICS			
16.1.7	**Randomization Schedule (Randomized Set)** Listing of subject numbers and randomization information All discrepancies (as-randomized versus as-treated) will be presented.	**RND**	**DSL001**
16.2.1.1	**Screening Failures (Randomized Enrolled Set)** Listing of all subjects that discontinued after randomization. The study discontinuation reason will also be listed.	**ENR**	**DSL002**
16.2.1.2	**Study Discontinuation After Randomization (Randomized Set)** Listing of all subjects that discontinued after randomization. The study discontinuation reason will also be listed.	**RND**	**DSL003**
16.2.1.3	**Subject Disposition (Randomized Set)** Listing of the reasons for completion / discontinuation and the number of days since first study drug administration at study discontinuation. In case the discontinuation was due to AE, the AE will be presented in this listing. If there is another explanation on the discontinuation reason collected in the CRF, this will also be presented in this listing.	**RND**	**DSL004**
16.2.1.4	**Randomization Code Broken (Randomized Set)** Listing of the code breaking information. Only subjects for which the code was broken are presented in this listing.	**RND**	**DSL005**
16.2.1.5	**Analysis Set Disposition (Enrolled Set)** Listing of all subjects and analysis set indicators.	**ENR**	**DSL006**
16.2.1.6	**Subject Disposition: Analysis Phases and Periods (Enrolled Set)** Listing of the phases and periods in the study together with the start and end date(time)s.	**ENR**	**DSL008**
16.2.1.7	**Study Visits (Enrolled Set)** Listing per subject number of all subject visits, together with the start and end date of each visit. Listing is sorted chronologically by visit start date within each subject.	**ENR**	**SVL001**
16.2.1.8	**First and Last Contact in the Study (Enrolled Set)** List of the date of the first signed ICF, last visit date and last date of contact in the study. All dates are presented overall, not by treatment.	**ENR**	
16.2.2.1	**Violation of Eligibility Criteria (Enrolled Set)** Only violated in- and exclusion criteria will be listed. Only deviations with DVDECOD = "VIOLATION OF INCLUSION CRITERION" or "VIOLATION OF EXCLUSION CRITERION" will be selected.	**ENR**	**DVL001**
16.2.2.2	**Protocol Deviation (Enrolled Set)** Listing of all protocol deviations information	**ENR**	**DVL002**
16.2.4.1	**Demographic Characteristics (Mother) (Enrolled Set)** Listing of all demographic parameters. For layout purposes, a template presenting parameters as rows rather than columns could be used instead (similar to template SCL003).	**ENR**	**DML001**

[redacted]

Number	Title	Analysis Set	TLFs Library Template Number
16.2.4.2	**Urine Drug Screen (Mother) (Enrolled Set)**	**ENR**	**SCL003**
	Listing of all results of urine drug screen tests performed.		
16.2.4.3	**Demographic Characteristics (Enrolled Set)**	**ENR**	**DML001**
	Listing of all demographic parameters. For layout purposes, a template presenting parameters as rows rather than columns could be used instead (similar to template SCL003).		
16.2.4.4	**Baseline Characteristics (Enrolled Set)**	**ENR**	**SCL003**
	Listing of all baseline characteristics.		
16.2.4.5	**FNAST Scores (Enrolled Set)**	**ENR**	**SCL003**
	Listing of all FNAST scores results.		
16.2.4.6	**Drug Screen (Enrolled Set)**	**ENR**	**SCL003**
	Listing of all results of urine, meconium and umbilical cord drug screen tests performed.		
16.2.4.7	**Maternal Smoking Status (Enrolled Set)**	**ENR**	**SUL001**
	Listing of all smoking data available in the CRF		
16.2.4.8	**Feeding Status (Enrolled Set)**	**ENR**	
	Listing of all feeding status data available in the CRF		
16.2.4.9	**Medical/Surgical History (Enrolled Set)**	**ENR**	**MHL001**
	Listing of the medical history data findings available in the CRF		
16.2.4.10	**Concomitant Diseases (Enrolled Set)**	**ENR**	**MHL002**
	Listing of the concomitant diseases data findings available in the CRF		
16.2.4.11	**Procedures (Enrolled Set)**	**ENR**	**PRL001**
	Listing of all data on procedures		
16.2.4.12	**Medications (Enrolled Set)**	**ENR**	**CML001**
	Listing of all data on medications		
16.2.4.13	**Comments (Enrolled Set)**	**ENR**	**COL001**
	Listing of all remarks and comments written in the CRF		
16.2.5.1	**Exposure (Randomized Set)**	**RND**	
	Listing per subject number of all data related to exposure		
PHARMACOKINETICS			
16.2.5.2	**Actual Sampling Times and Concentrations (Randomized Set)** Listing per treatment, visit, subject and planned time point of actual blood sampling times and concentrations.	**RND**	**PCL001**
EFFICACY			
16.2.6.1	**Primary Efficacy Endpoint: Full Listing (Randomized Set)** Listing per subject number of all data related to the primary efficacy endpoint.	**RND**	**SCL002**

Number	Title	Analysis Set	TLFs Library Template Number
16.2.6.2	**Secondary Efficacy Endpoint: Time to First Weaning Full Listing (Randomized Set)** Listing per subject number of all data related to the secondary efficacy endpoint: time to first weaning.	**RND**	**SCL002**
16.2.6.3	**Secondary Efficacy Endpoint: Adjunctive Drug Therapy Full Listing (Randomized Set)** Listing per subject number of all data related to the secondary efficacy endpoint: requirement for adjunctive drug therapy.	**RND**	**SCL002**
16.2.6.4	**Secondary Efficacy Endpoint: Rescue Doses Full Listing (Randomized Set)** Listing per subject number of all data related to the secondary efficacy endpoint: requirement for rescue doses, number of doses.	**RND**	**SCL002**
16.2.6.5	**Secondary Efficacy Endpoint: Opioid Related Hospital Stay and incidence of Relapse of NOWS (Randomized Set)** Listing per subject number of all data related to the secondary efficacy endpoints: hospital stay and relapse of NOWS.	**RND**	**SCL002**
SAFETY			
ADVERSE EVENTS			
16.2.7.1	**Pre-Treatment Adverse Events (Enrolled Set)** Listing of all pre-treatment AE information collected in the CRF and of the onset day and duration. All information of one AE will be presented on the same line.	**ENR**	**AEL001**
16.2.7.2	**Treatment Emergent Adverse Events (Randomized Set)** Listing of all AE information collected in the CRF and of the phase / period dates and onset day and duration. All information of one AE will be presented on the same line.	**RND**	**AEL002**
16.2.7.3	**Serious Treatment Emergent Adverse Events (Randomized Set)** Same as listing 16.2.7.2, but listing serious TEAEs only.	**RND**	**AEL002**
16.2.7.4	**Non-Serious Treatment Emergent Adverse Events (Randomized Set)** Same as listing 16.2.7.2, but listing non-serious TEAEs only.	**RND**	**AEL002**
16.2.7.5	**Adverse Drug Reactions (Randomized Set)** Same as listing 16.2.7.2, but listing ADRs only.	**RND**	**AEL002**
16.2.7.6	**Serious Adverse Drug Reactions (Randomized Set)** Same as listing 16.2.7.2, but listing serious ADRs only.	**RND**	**AEL002**
16.2.7.7	**Severe Treatment Emergent Adverse Events (Randomized Set)** Same as listing 16.2.7.2, but listing severe TEAEs only.	**RND**	**AEL002**
16.2.7.8	**Treatment Emergent Adverse Events Leading to Study Drug Discontinuation (Randomized Set)** Same as listing 16.2.7.2, but listing TEAEs leading to study drug discontinuation only	**RND**	**AEL002**

[redacted]

Number	Title	Analysis Set	TLFs Library Template Number
16.2.7.9	**Treatment Emergent Adverse Events Leading to Death (Randomized Set)**	**RND**	**AEL002**
	Same as listing 16.2.7.2, but listing TEAEs leading to death only		
16.2.7.10	**Post-Treatment Adverse Events (Randomized Set)**	**RND**	**AEL001**
	Listing of all post-treatment AE information collected in the CRF and of the onset day and duration. All information of one AE will be presented on the same line.		
16.2.7.11	**Escalation of Opioid Withdrawal (Randomized Set)**	**RND**	
	Listing of all data on escalation of opioid withdrawal		
16.2.7.12	**Physical Examination Abnormalities (Randomized Set)**	**RND**	**PEL001**
	Listing of all data on abnormal physical examinations findings		
16.2.7.13	**Neurological and Behavioral Examination Abnormalities (Randomized Set)**	**RND**	**PEL001**
	Listing of all data on abnormal neurological and behavioral examination findings.		
LABORATORY DATA			
16.2.8.1	**Laboratory Results: Hematology Full Listing (Enrolled Set)**	**ENR**	**LBL001**
	Listing of all hematology results. The (non-imputed) values will be shown, as well as normal ranges, abnormality flags (L/H) and clinical significance flag.		
16.2.8.2	**Laboratory Results: Biochemistry Full Listing (Enrolled Set)**	**ENR**	**LBL001**
	Same as listing 16.2.8.1 but listing biochemistry results instead.		
16.2.8.3	**Laboratory Results: Liver Function Full Listing (Enrolled Set)**	**ENR**	**LBL001**
	Same as listing 16.2.8.1 but listing liver function results instead.		
VITAL SIGNS			
16.2.9.1	**Vital Signs: Full Listing (Enrolled Set)**	**ENR**	**VSL001**
	Listing of all vital signs results. The values will be shown but no changes from baseline will be shown.		
16.2.9.2	**Vital Signs: Head Circumference, Body Weight and Length (Enrolled Set)**	**ENR**	**VSL001**
	Listing of all head circumference, body weight and length results (including percentiles). The values will be shown but no changes from baseline will be shown.		

[redacted]

9. APPENDICES

9.1 SCHEDULE OF ASSESSMENTS

			Treatment Period		End of treatment	Follow Up	
	Pre-screening (Mother)	Screening (neonates)	Randomization up to stabilization	Weaning up to end of treatment	48h after last dose	Up to 6 weeks	18 months
Informed consent forms[1,2]	✔ 2						
Questionnaire	✔						
Maternal urine toxicology data (optional)	✔						
Baby toxicology data (optional)		✔					
Inclusion and exclusion criteria		✔	✔ 3				
Gestational Age, sex and race/ ethnicity		✔					
Weight		✔	✔	✔	✔		✔
Length		✔			✔		✔
Head circumference		✔			✔		✔
Randomization			✔				
Vital signs[4]		✔	✔	✔	✔		
NOWS scores[5]		✔	✔	✔	✔		
Escalation of withdrawal signs						✔	
hematology and blood chemistry (data recorded)		✔					
Liver Function[6]			✔ (x2)		✔		
PK CHF6563[7]			✔	✔			
Medical history		✔					
Concomitant medications/procedures		✔	✔	✔	✔	✔	
Drug administration			✔	✔			
Cognitive and behavioral development					✔		✔
Feeding status			✔	✔	✔	✔	
Adverse Events assessment[8]		✔	✔	✔	✔	✔	
General well-being						✔	
Health status							✔
Environmental / social factors							✔
Assessments of the mother / primary carer using standardized questionnaires							✔

1. Maternal urine toxicology data collection requires the mother to sign a separated Informed Consent form.
2. Informed Consent Form for the baby: this is required prior to screening and can be obtained at several time points i.e. during the last month of pregnancy, following birth, or when the baby shows signs of NOWS.
3. Inclusion and exclusion criteria will be checked at randomization.
4. Vital signs: heart rate (HR), respiratory rate (RR), peripheral oxygen saturation (SpO2), Body Temperature (BT). From randomization up to the stabilization they will be collected at the same time of the NOWS score, except for BT which will be collected at least once per day. Blood pressure (DBP; MBP; SBP) will be recorded if collected according to site clinical practice. From weaning until the end of the treatment they will be collected once a day at the time of NOWS score.
5. NOWS scores: FNAST will be used to assess withdrawal signs every 4 hours (±1 hour). After FNAST assessment has started, it should continue for at least 24 hours, even in case the baby is not randomized.
6. Liver function: Liver-function testing (AST, ALT) will be performed on 3 occasions: after the first dose, at stabilization and 48 hours after the last treatment dose
7. Blood sampling for PK will occur on the day of randomization and then every 5±1 days until end of treatment. The first blood sampling on randomization day might be taken after the first dose; in each subsequent other occasion sampling should occur after one of the morning doses and be timed to fit in with the following sampling windows; one blood sample should be taken in the 0-2h post-dose time window, one in the 2-4h post-dose time window and one in the 4-8h post-dose time window.
8. Non-serious AEs will not be collected for screening failure.