CLINICAL STUDY PROTOCOL

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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

Version No.: 6.0
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Chiesi Farmaceutici S.p.A.
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GENERAL INFORMATION

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VERSION HISTORY

Version	Date	Change History
1.0	*04 June 2019*	*First version*
2.0	*26 June 2019*	*Second version - Changing CRP and minor formatting changes*
3.0	*11 July 2019*	*Third version– changing of volume of PK blood collection and minor typo errors*
4.0	*24 October 2019*	*Fourth version– changing of phenobarbital, packaging, addition of appendix and minor typo errors*
5.0	*28 February 2020*	*Fifth version -addition of functional unblinding description, appendix 3(List of psychotropic drugs), intensity of adverse event description and correction of minor typo errors*
6.0	*18 March 2021*	*Sixth version - For detailed list of changes see Summary of Changes from Protocol v 5.0 to Protocol v 6.0*

PROTOCOL OUTLINE

Study title	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
Sponsor	Chiesi Farmaceutici S.p.A. - Via Palermo 26/A 43122 Parma - Italy
Name of the Product	CHF6563 sublingual solution
Center(s)	Multicenter
Indication	Neonatal opioid-withdrawal syndrome (NOWS) with or without other concomitant drug withdrawal syndromes
Study design	Randomized, multicenter, double blind, double-dummy, parallel group, controlled study 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.
Study phase	II
Objectives	**Primary Objectives** • To assess the efficacy of sublingual CHF6563 in babies with NOWS • To assess the safety and tolerability of CHF6563 in babies with NOWS **Secondary Objectives** • To investigate the pharmacokinetics of CHF6563 in babies with NOWS • To assess the use of the adjunctive therapy for NOWS
Treatment duration	up to 10 weeks
Test product dose/route/regimen	**CHF6563** Sublingual administration of CHF6563 solution at concentration of 0.075 mg/mL

Regimen	**CHF6563**
Initial dose	10 µg/kg q8
Doses for up-titrations	15, 20, 25, 30 µg/kg q8
Maximum daily dose	90 µg/kg/day
Maximum # of up-titrations	4
Weaning rate	-15%
Cessation dose	between 90-110% of the initial dose
Dosing interval until cessation dose (hours)	8
Dose interval extension #1 at cessation dose (hours)	12
Dose interval extension #2 at cessation dose (hours)	24

<table>
<tr><td>Reference product dose/route/regimen</td><td>Morphine
Oral administration of a morphine solution at concentration of 0.5 mg/mL

<table>
<tr><th>Regimen</th><th>Morphine</th></tr>
<tr><td>Initial dose</td><td>0.07 mg/kg q4</td></tr>
<tr><td>Doses for up-titrations</td><td>0.09, 0.12, 0.16, 0.21 mg/kg</td></tr>
<tr><td>Maximum daily dose</td><td>1.25 mg/kg/day</td></tr>
<tr><td>Maximum # of up-titrations</td><td>4</td></tr>
<tr><td>Weaning rate</td><td>-15%</td></tr>
<tr><td>Cessation dose</td><td>≤ 0.025 mg/kg</td></tr>
<tr><td>Dosing interval until cessation dose (hours)</td><td>4</td></tr>
</table></td></tr>
<tr><td>Number of subjects</td><td>57</td></tr>
<tr><td>Study population</td><td>Babies with neonatal opioid-withdrawal syndrome (NOWS) with or without other concomitant drug withdrawal syndromes</td></tr>
<tr><td>Inclusion/exclusion criteria</td><td>Inclusion Criteria

Neonates must meet all of the following inclusion criteria to be eligible for randomization into the study:

1. Written informed consent obtained by parents/legal representative (according to local regulation) prior to or after birth.
2. Birth weight ≥ 3rd centile for gestational age (GA), according to the CDC growth chart
3. Gestational age ≥ 36 weeks
4. Exposure to opioids during the last month before delivery
5. Signs of neonatal opioid withdrawal syndrome requiring treatment, and the sum of 3 consecutive Finnegan assessment scores (FNAST) is ≥ 24 or a single score ≥12

Exclusion Criteria

The presence of any of the following exclusion criteria will exclude a neonate from study randomization:

1. Familial history of prolonged QT_C syndrome
2. Major congenital malformations or evidence of congenital infection
3. Signs of fetal alcohol spectrum disorders
4. Maternal alcohol abuse, defined as average of 3 or more drinks per week in the last 30 days
5. Medical illness at the time of randomization, including but not exclusively:
a. Neonatal hypoglycaemia requiring intravenous glucose therapy
b. Neonatal respiratory illness requiring non-invasive or invasive respiratory support
c. Neonatal encephalopathy (including hypoxic ischemic encephalopathy or seizures
d. Severe hyperbilirubinemia - bilirubin at or above the exchange transfusion threshold as defined by the AAP</td></tr>
</table>

	e. Severe elevation of serum aminotransferases (more than twice the upper limit of the age appropriate aminotransferases reference range of the investigational site). f. Proven or suspected early onset neonatal infection which will require more than 48 hours treatment with antibiotics 6. Unable to tolerate an oral or sublingual medication 7. Need for medications forbidden in this study protocol 8. Any condition that, in the opinion of the Investigator, would place the neonate at undue risk 9. Participation in another clinical trial of any medicinal product, placebo, experimental medical device or biological substance conducted under the provisions of a protocol on the same therapeutic target. The participation in studies involving diagnostic devices or treatments for conditions other than NOWS and NAS may be permitted following an agreement with the Sponsor. Non-interventional observational studies are allowed.
Study plan	Neonates 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: • Feeding status at time of randomization (exclusive formula versus [maternal breast milk [including a combination of maternal 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 will balance each stratification variable as well as the overall treatment balance across the arms in a 2:1 ratio. This method achieves a greater level of balance across multiple stratification variables compared to a traditional stratified randomization Following 2 consecutive FNAST with a sum ≥ 12, if all eligibility criteria except for Inclusion Criterion #5 are met, then neonates 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). **Treatment period** Pharmacological treatment will start up to 7 days after birth in neonates who show signs of NOWS and have failed to respond to non-pharmacologic care. Withdrawal signs will be assessed using a predefined Finnegan Neonatal Abstinence Scoring Tool (FNAST). If all the inclusion/exclusion criteria are met the baby will be randomized in one of the following groups: *CHF6563*: babies will receive a sublingual dose of CHF6563 at a starting dose of 10 µg/kg q8 (using birth weight) and the corresponding oral dose

	of morphine matched placebo q4. *Morphine*: babies will receive an oral dose of morphine at a starting dose of 0.07 mg/kg q4 (using birth weight) and the corresponding sublingual dose of CHF6563 matched placebo q8. Signs of withdrawal will be assessed and recorded every 4 hours (±1 hour). *CHF6563 treatment* From initiation through cessation dose, CHF6563 will be administered every eight hours (±1 h). In the up-titration phase, dose escalation will occur if the sum of the 3 consecutive FNAST scores is ≥ 24 or a single score is ≥ 12. No more than one dose escalation can take place each day unless a rescue dose is required after which a dose increase will occur. During the up-titration phase, doses will increase by 5 ug/kg steps, i.e. after the initial 10 ug/kg dose there can be consecutive dose increases to 15, 20, 25 and 30 ug/kg, if signs of withdrawal persist (i.e. FNAST scores remain ≥ 24 as the sum of three consecutive scores or a single score is ≥ 12). The stabilization phase begins when no further drug treatment escalation is required. A stabilization period of 48 hours (without need for further drug treatment escalation) is required before weaning of drug treatment can begin. The initiation of weaning will begin after a 48 hour stabilization period, providing the sum of the previous 3 scores is < 18 and no single score is ≥8: doses will be decreased by 15% once per day. If during a 24 hour period, the sum of the previous 3 scores is ≥ 18 or a single score is ≥ 8, (even if no dose escalation has been required), weaning will not take place, the current dose will continue to be administered. Once the sum of the previous 3 scores is < 18 and no single score is ≥ 8, weaning can resume. No more than one dose reduction is permitted in one calendar day. The cessation dose will be around the initial dose, i.e. between 90-110% of 10 ug/kg. The maximum dose of 90 µg per kilogram of body weight per day is reached after 4 increases in dose. *Morphine treatment* From initiation through cessation dose, morphine will be administered every four hours (±1 h). In the up-titration phase, dose escalation will take place if the sum of the 3 consecutive FNAST scores is ≥ 24 or a single score is ≥ 12. No more than one dose escalation can take place each day unless a rescue dose is required after which a dose increase will occur. During the up-titration phase, after the initial 0.07 mg/kg dose the consecutive dose increases are 0.09, 0.12, 0.16 and 0.21 mg/kg, if signs of withdrawal persist (i.e. FNAST scores remain ≥ 24 as the sum of three consecutive scores or a single score is ≥ 12). The stabilization phase begins when no further drug treatment escalation is

	required. A stabilization period of 48 hours (without need for further drug treatment escalation) is required before weaning of drug treatment can begin. The initiation of weaning will begin after a 48 hour stabilization period, providing the sum of the previous 3 scores is < 18 and no single score is ≥ 8: doses will be decreased by 15% once per day. If during a 24 hour period, the sum of the previous 3 scores is ≥ 18 or a single score is ≥ 8, (even if no dose escalation has been required), weaning will not take place, the current dose will continue to be administered. Once the sum of the previous 3 scores is < 18 and no single score is ≥ 8, weaning can resume: doses will continue to be decreased by 15% once per day. No more than one dose reduction is permitted in one calendar day. The cessation dose is ≤ 0.025 mg/kg q 4 hours. The maximum dose of 1.25 mg per kilogram per day is reached after 4 increases in dose. *Additional rescue dose during the escalation phase* At the discretion of the physician, a rescue dose of CHF6563 or morphine may be given during the up-titration phase to a neonate who has a single score ≥ 12. A rescue dose should not be administered within 1 hour of the previous dose or 1 hour before the next scheduled dose. Rescue dose will be the same as the previous dose. A rescue dose must not be given once the maximum dose has been reached. The administration of a rescue dose in the up-titration period will trigger a dose escalation at the next scheduled dose. *Additional rescue dose during the weaning phase* If patient evaluation is consistent with worsening NOWS, at the discretion of the physician, a rescue dose of CHF6563 or morphine may be given during the weaning phases to a neonate who has a single score ≥ 12. A rescue dose should not be administered within 1 hour of the previous dose or 1 hour before the next scheduled dose. Rescue dose will be the same as the previous dose. The administration of a rescue dose in the weaning period will not trigger a dose escalation. If after 24 hours the sum of the previous 3 scores is < 18 and no single score is ≥ 8 weaning (i.e. further dose reduction) can resume. If after cessation of therapy a rescue dose is given, the neonate must be observed for at least 48 hours. *Adjunct phenobarbital therapy* If in either group, withdrawal as assessed by the FNAST is not controlled at the maximum dose of primary therapy (CHF6563 / morphine), phenobarbital will be initiated with an oral loading dose of 20 mg/kg, followed by a daily oral dose of 5 mg/kg/day. Birth weight will be used for the calculation of phenobarbital loading and maintenance dose. Treatment with adjunctive phenobarbital will continue for at least two days and stabilization should be achieved before weaning of the opioid. Weaning will commence with reduction of the primary therapy (CHF6563 / morphine) according to the same rules as indicated above. When the primary therapy (CHF6563 / morphine) has been weaned to 50% of the

	maximal dose and the sum of the previous three scores is < 18 and no single score is ≥ 8, the phenobarbital dose will be reduced to 2.5 mg/kg/day. The primary therapy (CHF6563 / morphine) dose will not be weaned on the day phenobarbital is weaned. Phenobarbital will be discontinued 72 hours after the dose reduction to 2.5 mg/kg/day, provided the sum of the previous three scores is < 18 and no single score is ≥ 8, and prior to the discontinuation of the primary therapy (CHF6563 / morphine). The primary therapy (CHF6563 / morphine) will not be weaned on the day when phenobarbital is discontinued. *Follow up* Following discontinuation of opioid treatment, babies will be observed for at least 48 hours during which time scoring of NOWS signs will continue. Regular follow up will continue during the inpatient admission and following discharge from the hospital, to identify those babies who suffer recurrence of significant withdrawal. The duration of this 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 (at least 48 hours post last opioid 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 well-being and identify any escalation of withdrawal signs. Thereafter weekly telephone contact will continue for the duration of the follow up period. Significant escalation of withdrawal signs will warrant clinical review and assessment for relapse severe enough to require pharmacological treatment and readmission. An additional long-term assessment at 18-months (± 1 months) of age will be performed for confirmation of the safety of the test treatment. *Adverse events* Adverse events (AEs) and serious adverse event (SAEs) will be collected starting from the Informed Consent signature or from the neonate's birth (if the Informed consent is signed before birth). Ongoing AEs/SAEs will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the Investigator. For neonates who will not be randomized, only SAEs will be collected. An Independent Safety Monitoring Board (ISMB) will review the safety profile of CHF6563 / morphine treatment.
Most relevant allowed concomitant treatments	Phenobarbital (only as adjunctive therapy). Acetaminophen administration for analgesia or treatment of pyrexia should not exceed 48 hours, with a maximum daily permitted dose of 60 mg/kg/day. During the weaning phase only: sedative and analgesia medications (including general and spinal anesthesia, skeletal muscle relaxants, benzodiazepines, and short acting opioids) required prior to or during

	surgical, investigational and imaging procedures. Any concomitant medication required for the standard care of babies will be permitted during the study. Wherever possible post-operative analgesia should avoid systemic opioids; spinal / epidural analgesia, oral / parenteral acetaminophen and NSAIDS are permissible
Most relevant forbidden concomitant treatments	Metabolic enzyme-inducing or inhibiting drugs, or drugs known to have a well-defined potential for hepatotoxicity should not be taken. Other drugs which may give additive CNS/respiratory depression if used in combination with opioids (benzodiazepines, skeletal muscle relaxant, anticholinergics, etc.) unless required prior to or during surgical, investigational and imaging procedures undertaken. Other drugs or biological substance to be administered under the provisions of a protocol on the same therapeutic target. Treatments for different conditions than NOWS and NAS may be permitted following an agreement with the Sponsor.
Breastfeeding	Breastfeeding is allowed. Current feeding status (formula or maternal breast milk [including combination of maternal breast milk and formula]) will be recorded just prior to randomization. During the study, actual feeding will be collected in terms of breastfeeding, formula feeding, mixed feeding, and the proportion of feeding which is breast milk for subjects receiving both formula and breast milk.
Efficacy variables (and/or pharmacokinetics variables)	**Primary endpoint** Duration of treatment defined as the number of hours from first dose of study drug administration until the last dose of study drug. **Secondary endpoints:** • 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 (yes/no) • Total hours of treatment with adjunctive therapy • Requirement for rescue doses (CHF6563 or morphine) (yes/no) • Number of rescue doses administered per neonate • Percentage of total amount of active study drug which is from rescue doses per neonate • 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 (yes/no) • Incidence of readmissions, defined as readmission to hospital for NOWS relapse (yes/no)

Safety variables	**During administration of sublingual CHF6563 or oral morphine:** Number and percentage of babies with peri-dosing adverse events (AEs) (i.e., mouth irritation or inflammation, apnea, desaturation, brady/tachycardia, cough, immediate swallowing of sublingual drug, regurgitation, vomiting occurring after administration) **During the study** • Hematology and blood chemistry: full blood count (FBC), urea, creatinine and electrolytes (sodium, potassium, magnesium calcium, phosphorus), glucose, C-reactive protein if collected before randomization according to site clinical practice. • Adverse events and adverse drug reactions (ADRs) will be collected. • Liver enzymes analysis-function testing (AST, ALT) will be performed on 3 occasions: after first dose, at stabilization and 48 hours (±4 h) after the last treatment dose. • Vital signs: heart rate (HR), respiratory rate (RR), peripheral oxygen saturation (SpO_2), body temperature (BT) will be monitored, and data collected during the escalation and stabilization phases. • Weight, head circumference • Blood pressure (SBP, MBP, DBP) will be monitored according to individual site clinical practice. **End of treatment period (48 hours ±4 h after last dose)** • Vital signs: heart rate (HR), respiratory rate (RR), peripheral oxygen saturation (SpO2), body temperature (BT). Blood pressure (SBP. MBP. DBP) if collected according to site clinical practice. • General physical and neurological examination. • Assessment of growth: head circumference, body weight, length. • Further adverse events as well as changes in those already reported.
Pharmacokinetics	An opportunistic sampling strategy combined with population pharmacokinetic modelling will be adopted. Blood sampling for PK will occur the day of randomization and then every 5±1 days until the last dose. The analysis of this data will follow a population pharmacokinetic modelling approach, to be described in a separate analysis plan and report.
Sample size calculation	Based on the results of similar studies, it was determined that a sample size of 51 babies (17 morphine; 34 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 babies (19 morphine; 38 CHF6563) will be randomized to obtain a minimum of 51 evaluable babies completing the treatment period.
Statistical methods	**Primary efficacy analysis:** An ANCOVA model based on log-transformed data will be performed to test the treatment effect as **duration of treatment (hours)**. The model

	will include treatment (CHF6563 and morphine) as a fixed effect, primary feeding method (formula / any maternal breast milk), maternal primary opioid use (buprenorphine/methadone/other), and concurrent maternal use of benzodiazepines, antidepressants or gabapentin (polypharmacy [yes/no]) as covariates. In cases where observed primary feeding method during the treatment period (formula / any maternal breast milk) differs from the feeding method at time of randomization, the observed primary feeding method will be used for analysis. The adjusted ratio of geometric means between treatments, its 95% CI and associated p-value will be estimated by the model. Babies who discontinue study medication prior to end of the study treatment will be allowed to remain in the study and receive standard of care according to clinical practice. Handling of such cases will be described in the SAP. Babies who discontinue completely (including withdrawal due to treatment longer than 10 weeks) will be imputed using the maximum of the observed value (10 weeks for patients withdrawn due to treatment longer than 10 weeks) or the value of the 90th percentile of duration of any subject completing the study, regardless of treatment group. **Secondary efficacy analyses:** In cases where observed primary feeding method during the treatment period (formula / any maternal breast milk) differs from the feeding method at time of randomization, the observed primary feeding method will be used for analysis. **Time to first weaning (hours)** An ANCOVA model based on log-transformed data will be performed to test the treatment effect as **time to first weaning (hours)**. The model will include treatment (CHF6563 and morphine) as a fixed effect, primary feeding method (formula / any maternal breast milk), maternal primary opioid use (buprenorphine/methadone/other), and maternal use of benzodiazepines, antidepressants or gabapentin (polypharmacy [yes/no]) as covariates. The adjusted ratio of geometric means between treatments, its 95% CI and associated p-value will be estimated by the model. Requirement for **adjunctive drug therapy (phenobarbital) for signs of NOWS (yes/no)** during the treatment period will be analyzed using logistic regression. The Odds ratio and corresponding 95% CI and p-value will be presented, adjusting for primary feeding method (formula / any maternal breast-milk), maternal primary opioid use (buprenorphine/methadone/other), and maternal use of benzodiazepine, antidepressants or gabapentin (polypharmacy [yes/no]). **Total hours of treatment with adjunctive therapy** will be analyzed using an ANCOVA model. The model will include treatment (CHF6563 and morphine) as a fixed effect and primary feeding method (formula/any maternal breast-milk), maternal primary opioid use (buprenorphine/methadone/other), and maternal use of benzodiazepine, antidepressants or gabapentin (polypharmacy [yes/no]) as covariates. Babies not requiring adjunctive therapy will be included with a value of 0.

	Requirement for **rescue doses of CHF6563 or morphine (yes/no)** during the treatment period will be analyzed using logistic regression, adjusting for primary feeding method (formula/any maternal breast-milk), maternal primary opioid use (buprenorphine/methadone/other), and maternal use of benzodiazepine, antidepressants or gabapentin (polypharmacy [yes/no]). The odds ratio of incidence between treatment groups will be presented together with the 95% CI and corresponding p-value. The **mean number of rescue doses per neonate and the mean percentage of total amount of active study drug which is from rescue doses** will be analyzed using an ANCOVA model. The model will include treatment (CHF6563 and morphine) as a fixed effect and primary feeding method (formula/any maternal breastmilk), maternal primary opioid use (buprenorphine/methadone/other), and maternal use of benzodiazepine, antidepressants or gabapentin (polypharmacy [yes/no]) as covariates. Babies not requiring rescue dose(s) of active study drug will be included with a value of 0. **Length of opioid related hospital stay** will be analyzed using an ANCOVA model based on log transformed data. The model will include treatment (CHF6563 and morphine) as a fixed effect and primary feeding method (formula/ any maternal breastmilk), maternal primary opioid use (buprenorphine/methadone/other), and maternal use of benzodiazepine, antidepressants or gabapentin (polypharmacy [yes/no]) as covariates. Incidence of **relapse of NOWS (yes/no)** will be analyzed using logistic regression, adjusting for primary feeding method (formula/ any maternal breastmilk), maternal primary opioid use (buprenorphine/methadone/other), and maternal use of benzodiazepine, antidepressants or gabapentin (polypharmacy [yes/no]). The odds ratio of incidence between treatment groups will be presented together with the 95% CI and corresponding p-value. Incidence of **readmissions (yes/no)** during the study period will be analyzed using logistic regression, adjusting for primary feeding method (formula/ any maternal breastmilk), maternal primary opioid use (buprenorphine/methadone/other), and maternal use of benzodiazepine, antidepressants or gabapentin (polypharmacy [yes/no]). The odds ratio of incidence between treatment groups will be presented together with the 95% CI and corresponding p-value. **Pharmacokinetics** The relative low number of blood samples per baby, the opportunistic sampling strategy and the continuous variation of the administered dose prevent the application of standard non-compartmental analysis for the characterisation of CHF6563 pharmacokinetics in the neonate population. Instead, a population pharmacokinetic modelling approach will be applied. Separated analysis plan and report will be produced.

	Safety variables • The number and percentage of subjects experiencing Treatment-emergent adverse events (TEAE), drug-related AE, serious TEAE, serious related TEAE, TEAE leading to study discontinuation, TEAE leading to death and peri-dosing adverse events, as well as the number of events, will be presented by treatment group and overall. Each of these groups of adverse events will also be summarized by System Organ Class and Preferred Term. • Liver-function test parameters and their changes from baseline will be summarized using descriptive statistics. • Vital signs: heart rate (HR), respiratory rate (RR), peripheral oxygen saturation (SpO_2), body temperature (BT), blood Pressure (SBP. MBP. DBP) will be monitored if collected according to site clinical practice. These variables will be presented as descriptive statistics only. • Head circumference and body weight (and percentile) and its change from baseline will be summarized using descriptive statistics. The following parameters collected at end of treatment will be listed only: • Growth parameters: head (and percentile), and length (and percentile) • General physical and neurological examination

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AAP	American Academy of Pediatrics
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical classification
BT	Body temperature
CDC	Center for Disease and Control
CI	Confidence Interval
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
DBP	Diastolic Blood pressure
DMPKA	Drug Metabolism and PharmacoKinetics
CBC	Complete blood count
FSFV	First Subject First Visit
FNAST	Finnegan Neonatal Abstinence Scoring Tool
eCRF	Electronic case report form
GA	Gestational age
GCP	Good Clinical Practices
GLP	Good Laboratory Practice
HR	Heart rate
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISMB	Independent Safety Monitoring Board
ITT	Intention to Treat
LSLV	Last Subject Last Visit
MBP	Mean Blood pressure
MedDRA	Medical Dictionary for Regulatory Activities
NAS	Neonatal Abstinence syndrome
NOWS	Neonatal opioid-withdrawal syndrome
NSAIDS	Nonsteroidal anti-inflammatory drugs
PK	Pharmacokinetics
PP	Per-Protocol
RR	Respiratory rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood pressure
SmPC	Summary of Product Characteristics
SpO2	Peripheral oxygen saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment emergent adverse event

CONTENT

1. INTRODUCTION

1.1 Background information

Neonatal opioid withdrawal syndrome (NOWS) is a subset of Neonatal abstinence syndrome (NAS) and refers to neonatal withdrawal from opioid drugs and can occur in the presence of other drug withdrawal syndromes. In the United States, neonatal withdrawal following in-utero opioid exposure is typically the result of prolonged maternal use and/or abuse of illicit or prescribed opioids during pregnancy. Birth leads to the abrupt cessation of fetal substance exposure and can precipitate acute withdrawal symptoms that can result in severe health complications with prolonged recovery and longer hospitalization. Withdrawal can be both severe and intense, with an estimated 60% to 80% of exposed neonates requiring pharmacological intervention to control symptoms [1][2].

While the signs and symptoms of NOWS are similar to those experienced by adults undergoing acute opiate withdrawal, they present a higher risk to the neonate due to the babies' dependence on others for all aspects of well-being.

NOWS presenting signs include central nervous system hyperirritability (tremors, jitteriness, irritability, hyperactive muscle reflexes, and excessive high-pitched cry), autonomic nervous system deregulation and instability (tachypnea, nasal flaring, hyperphagia, temperature instability, insomnia, sweating, mottle skin, yawning, and sneezing), and gastrointestinal symptoms (diarrhea, vomiting, and poor feeding) [3][4][5]. Seizures are generally rare, although they have been reported occurring in 2% to 11% of neonate cases in the early stage of severe opioid withdrawal [6][7], especially if medical treatment has been delayed. A recent large observational cohort study of Medicaid babies in 46 US States reported an incidence of seizures was 2.7% among the 1705 observed cases of NAS [8]. Neonates with NOWS can also experience weight loss or failure to thrive, which often results from a combination of poor feeding, vomiting, nausea, and diarrhea [4] [5]. If left untreated, some cases of NOWS may even lead to death [5]. Some of the less severe signs and symptoms of opiate withdrawal may persist for several months [3].

The onset, duration, and the severity of NOWS are dependent on several factors: the type of opiate exposure, maternal-fetal drug transferability, poly-drug exposure, time and duration of opiate exposure, placental and fetal drug concentrations, the rate of excretion, spatial representation and density of opiate receptors, and gestational age [4][1][9][10].

The management of neonates at risk of this withdrawal syndrome is based on the following [11]:

- Identification of neonates at risk, preferably by identification of maternal substance exposure during pregnancy;
- Early initiation of non-pharmacological care (this first-line treatment provides a suitable, supportive environment for both the mother and baby, which minimizes exposure to stress, and encourages breastfeeding where appropriate);
- Monitoring for signs of withdrawal;
- Pharmacological care, which is instituted when the signs of withdrawal become too severe to be managed with non-pharmacological care

There are no FDA-approved drugs for the treatment of NOWS with or without other concomitant drug withdrawal syndromes; however, there is consensus within the neonatology community that

opioid replacement should be the first-line pharmacotherapy treatment [3][4][12]. Morphine is the most often used opioid for the treatment of neonatal withdrawal following in-utero opioid exposure, followed by methadone, with some hospitals using buprenorphine. While morphine is used in morethan 80% of NAS cases requiring pharmacological treatment [11], there is no agreed standard of care [13] or treatment regimens [1][14] and the optimal pharmacological treatment protocols have not been established in large, well-controlled studies.

Commercially available liquid formulations of morphine and methadone are unsuitable for the neonatal population for several reasons. They contain inappropriately high concentrations of opioid, necessitating local compounding of extemporaneous formulations or dilution prior to administration within the hospital pharmacy or by neonatal nursing staff, increasing the risk of medication errors [15][16][17][18]. Commercially available liquid formulations frequently contain alcohol and other preservatives and excipients that are contraindicated or undesirable in the neonatal population. Whilst an alcohol-free morphine solution is available, commercial methadone solutions contain alcohol. Therefore, the currently available pharmacological treatments for NOWS leave the neonate at risk of medication errors, other hazards related to local compounding of extemporaneous formulations, and exposure to alcohol, other preservatives, and excipients that are contraindicated or undesirable in the neonatal population.

Buprenorphine has several characteristics that make it an attractive agent in the treatment of NOWS. Buprenorphine is a long acting μ-opioid receptor partial agonist and κ-opioid receptor antagonist. The long half-life and duration of action prevents the rapid change in receptor occupancy that can precipitate withdrawal and should allow a simplified dosing regimen to be developed. Sublingual buprenorphine shows a lack of the cardiovascular liability that is associated with methadone. Related to the lack of cardiovascular liability, sublingual buprenorphine possesses a well-established safety profile in adults. Moreover, buprenorphine has the lowest incidence of respiratory depression among opioids, which is dose-dependent and has a ceiling effect in relation to the long half-life of buprenorphine [19][20][21][22].

The CHF6563 development program is intended to develop a neonate-specific formulation of buprenorphine. CHF6563 does not contain ethanol, naloxone, or any excipients considered contraindicated, unsafe, or inappropriate for use in the neonatal population. CHF6563 is intended to control or reduce withdrawal symptoms, decrease duration of treatment, and reduce length of hospital stay in neonates diagnosed with NOWS with or without other concomitant drug withdrawal syndromes.

1.2 Study rationale

Chiesi is developing CHF6563 (sublingual buprenorphine) for the treatment of NOWS with or without other concomitant drug withdrawal syndromes.

The safety and efficacy of buprenorphine as a treatment for NOWS with or without other concomitant drug withdrawal syndromes has been investigated in 5 published studies [23][24][25][26][27] using an extemporaneous formulation containing 30% ethanol. Across the 5 studies, sublingual buprenorphine demonstrated a significant reduction in duration of treatment and stay compared to the standard of care (oral morphine or methadone). The extemporaneously prepared ethanolic buprenorphine sublingual formulation was generally well tolerated in the target population and demonstrated a similar safety profile to oral morphine.

The CHF6563 development program is focused on finding an appropriate, safe, and efficacious buprenorphine formulation, and establishing a buprenorphine-dosing regimen that provides effective control of the clinical signs of NOWS when non-pharmacological therapy has failed. The PK profile of buprenorphine should enable a dosing regimen to be developed that will increase the

interval between doses compared with morphine and simplify the weaning regimen, potentially bringing safety and efficacy benefits to the neonate, their families, and healthcare systems.

This study will evaluate the efficacy and safety of a model-derived CHF6563 dosing regimen as a treatment for NOWS with or without other concomitant drug withdrawal syndromes when non-pharmacological therapy has failed.

1.3 Risk/benefit assessment

Sublingual buprenorphine shows a lack of the cardiovascular liability that is associated with methadone. Related to the lack of cardiovascular liability, sublingual buprenorphine possesses a well-established safety profile in adults. Moreover, buprenorphine has the lowest incidence of respiratory depression among opioids, which is dose-dependent and has a ceiling effect in relation to the long half-life of buprenorphine [19][20][21][22].

Buprenorphine is a long-acting, partial μ-opioid receptor agonist and κ-opioid receptor antagonist. Due to its favorable pharmacological characteristics of long half-life and duration of action, buprenorphine has been shown to significantly reduce the median duration of treatment and a median length of stay when compared to morphine and methadone in both retrospective and in RCT study [23][24][25][26][27]. The long half-life and duration of action prevents the rapid change in receptor occupancy that can precipitate withdrawal seen with shorter acting opioids (i.e. morphine). In contrast to the full μ-opioid agonists (morphine and methadone) commonly used to treat NOWS, increasing buprenorphine serum concentration results in a ceiling effect for important opioid agonistic side effects, namely respiratory depression (morphine and methadone) or cardiovascular liability including QTc interval prolongation (methadone) [19][20][21][22]. In Kraft's 2017 study, a model based analysis demonstrated that at any time during treatment the mean respiratory rate in morphine treated infants was lower by 4.4 breaths per minute (95% Cl: 0.7, 8.1; p=0.020) as compared to buprenorphine treated infants in the same strata. Although all the respiratory rates recorded were within the normal range, these data suggest a possible safer profile for buprenorphine. In this same study, 13 adverse events occurred in 7 infants in the buprenorphine group and 10 events in 8 infants in the morphine group (P = 0.79 for the no. of events by Fisher's exact test) [28]. Cough, tachycardia, umbilical granuloma, involvement of skin conditions and of gastrointestinal conditions have been observed. There were two serious adverse events. One was an inguinal hernia repair in the morphine group, and one was a supraglottoplasty associated with the Pierre Robin syndrome in the buprenorphine group. There were no elevations in levels of alanine aminotransferase or aspartate aminotransferase in any infant.

The results of the available toxicology studies showed that buprenorphine possess less adverse reactions over other opioids. Single and repeated dose of buprenorphine significantly decreased adverse clinical observations associated with opioid withdrawal. Main acute toxic signs in animals associated with buprenorphine treatment were CNS and cardiorespiratory depression. Subchronic toxicity studies of buprenorphine in rat, dog and monkey showed decreased body weight, inflammatory reaction at the injection site, and clinical biochemistry and hematology parameters changes that reflect this inflammatory reaction. No adverse findings were observed during histology. Positive findings were noted in few genotoxicity assays and an increased incidence of testicular interstitial cell tumors was observed in rats. No effects on fertility and no teratogenic effects were noted, although some developmental effects were observed. During a 4 weeks study in

juvenile rats transient increased activity, excessive behaviors and decreased body weight were noted[29][30][31][32][33][34][35][36][37].

Considering the safety profile of the treatments, the measures in place to ensure the patients' safety and the expected scientific value, the overall risk/benefit assessment can be considered acceptable for the proposed trial.
This trial will be conducted in compliance with the Declaration of Helsinki (1964 and amendments) current ICH E6 Good Clinical Practices and all other applicable laws and regulations.

2. STUDY OBJECTIVES

2.1 Primary Objective(s)

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

2.2 Secondary Objective(s)

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

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.

The weaning period requires a lower number of weaning steps for CHF6563 compared to morphine. In order to avoid maintaining babies randomized to CHF6563 in the hospital following completion of study drug, only to receive placebo for several days (about 5, depending on the severity of the withdrawal), the unblinded pharmacist will advise the clinical staff that the baby has completed active study treatment following the last active dose of CHF6563 and babies will be eligible for discharge (at least insofar as the clinical trial is concerned) 48 hours after the last active dose. Since the cessation dose will not occur at the same weaning step for the 2 treatment arms, it will be possible to ascertain the treatment for each baby after the weaning step which corresponds to the cessation dose of CHF6563. This is considered a "functional unblinding" since, after this point, it will be possible for members of the blinded team to ascertain the treatment arm.

Prior to the last scheduled dose of CHF6563, all members of the blinded study team will remain completely blinded. Following the last scheduled dose of CHF6563/placebo, members of the blinded study team will not have access to the explicit treatment codes, but it will be possible to ascertain the treatment arm. Similarly, data review will occur without access to explicit treatment codes, since the explicit treatment codes will be maintained in a confidential manner. The randomization list and explicit treatment codes will be disclosed to blinded study team members only after the database is locked.

Withdrawal signs will be assessed using a predefined Finnegan Neonatal Abstinence Scoring Tool (FNAST). FNAST assessments will commence in neonates who show signs of withdrawal despite appropriate non-pharmacological care and recorded every 4 hours (±1 hour). Pharmacological treatment will start up to 7 days after delivery in neonates who show signs of NOWS (sum of 3 consecutive FNAST scores ≥24 or a single score ≥12) and have failed to respond to non-pharmacologic care. After FNAST assessment has started, it should continue for at least 24 hours, even in case the baby is not randomized.

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.

Pharmacological treatment 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.

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.

4. SUBJECT SELECTION CRITERIA

4.1 Subject Recruitment

57 neonates with neonatal opioid-withdrawal syndrome (NOWS) with or without other concomitant drug withdrawal syndromes will be randomized.

4.2 Inclusion Criteria

Neonates must meet all of the following inclusion criteria to be eligible for randomization into the study:

1. Written informed consent obtained by parents/legal representative (according to local regulation) prior to or after birth.
2. Birth weight ≥ 3rd centile for gestational age (GA), according to the CDC growth chart
3. Gestational age ≥ 36 weeks
4. Exposure to opioids during the last month before delivery
5. Signs of neonatal opioid withdrawal syndrome requiring treatment, and the sum of 3 consecutive FNAST scores is ≥ 24 or a single score ≥ 12

4.3 Exclusion Criteria

The presence of any of the following will exclude a subject from study randomization:

1. Familial history of prolonged QTc syndrome
2. Major congenital malformations or evidence of congenital infection
3. Signs of fetal alcohol spectrum disorders
4. Maternal alcohol abuse, defined as average of 3 or more drinks per week in the last 30 days
5. Medical illness at the time of randomization, including but not exclusively:
   a) Neonatal hypoglycemia requiring intravenous glucose therapy
   b) Neonatal respiratory illness requiring non-invasive or invasive respiratory support
   c) Neonatal encephalopathy (including hypoxic ischemic encephalopathy or seizures
   d) Severe hyperbilirubinemia–bilirubin at or above the exchange transfusion threshold as defined by the AAP
   e) Severe elevation of serum aminotransferases (more than twice the upper limit of the age appropriate aminotransferases reference range of the investigational site).
   f) Proven or suspected early onset neonatal infection which will require more than 48hours treatment with antibiotics
6. Unable to tolerate an oral or sublingual medication
7. Need for medications forbidden in this study protocol
8. Any condition that, in the opinion of the Investigator, would place the neonate at undue risk
9. Participation in another clinical trial of any medicinal product, placebo, experimental medical device or biological substance conducted under the provisions of a protocol on the same therapeutic target. The participation in studies involving diagnostic devices or treatments for conditions other than NOWS and NAS may be permitted following an agreement with the Sponsor. Non-interventional observational studies are allowed

More details on the characteristics of mothers whose babies are allowed to be recruited are provided in section 0 and in APPENDIX 2 – Maternal Screening Questionnaire.

4.4 Subject Withdrawal

Babies must be discontinued from the study for any of the following reasons:

- An adverse event occurs that, in the opinion of the investigator, makes it unsafe for the subject to continue in the study
- Additional drug therapy is required when withdrawal signs as assessed by the FNAST are not controlled with the maximum dose of the study drug in combination with phenobarbital.
- Prolonged requirement for opioid therapy defined as > 10 weeks (> 70 days) i.e. inability to wean from opioid therapy.
- The baby is lost to follow-up.
- Parents or legal guardian withdraws consent.
- The baby's safety is affected by use of not-permitted concomitant medication.
- The baby transfers to another inpatient facility during the phase of administration of study drug
- The sponsor or the regulatory authorities or the Ethics Committee(s), for any reason, terminates the entire study, or terminates the study for this trial site or this particular subject.

It is understood by all concerned that an excessive rate of withdrawals can render the study uninterpretable; therefore, unnecessary withdrawals of subjects should be avoided.
However, should a baby discontinue study medication, data collection will continue and all efforts will be made to complete and report the observations as thoroughly as possible.

In case of withdrawal, the Investigator must fill in the "Study Termination" page in the eCRF, reporting the main reason for withdrawal.

If a baby is withdrawn/drops-out of the study after receiving the test treatment, the subject study number and corresponding test treatments should not be reassigned to another subject.

5. CONCOMITANT MEDICATIONS

5.1 Permitted concomitant Medications

Phenobarbital (as adjunctive therapy only, see section 6.2.2.4)

Acetaminophen administration for analgesia or treatment of pyrexia should not exceed 48 hours, with a maximum daily permitted dose of 60 mg/kg/day.

During the weaning phase only: sedative and analgesia medications (including general and spinal anaesthesia, skeletal muscle relaxants, benzodiazepines, and short acting opioids) required prior to or during surgical, investigational and imaging procedures.

Any concomitant medication required for the standard care of babies will be permitted during the study.

Investigators are required to record all medications in the eCRF with the exception of the drugs listed below, unless these drugs are administered to treat an adverse event:

Multivitamins or single vitamins, iron, folic acid, calcium and phosphorus, simethicone, cream for napkin dermatitis, glycerin suppository, reflux medications, sucrose solution, dextrose gel, oral glucose gel, vaccines.

Wherever possible post-operative analgesia should avoid systemic opioids; spinal / epidural analgesia, oral / parenteral acetaminophen and NSAIDS are permissible

5.2 Non-permitted concomitant Medications

Metabolic enzyme-inducing or inhibiting drugs, or drugs known to have a well-defined potential for hepatotoxicity should not be taken.

Other drugs which may give additive CNS/respiratory depression if used in combination with opioids (benzodiazepines, skeletal muscle relaxant, anticholinergics, etc.) unless required prior to or during surgical, investigational and imaging procedures undertaken.

Other drugs or biological substances to be administered under the provisions of a protocol on the same therapeutic target. Treatments for different conditions than NOWS and NAS may be permitted following an agreement with the Sponsor. However urgent treatment should not be withheld or delayed.

6. TREATMENT(S)

The study medications will be supplied to the clinical site under the responsibility of the Sponsor, who will also provide the Pharmacist/Investigator with appropriate certificates of analytical conformity.

6.1 Appearance and Content

- **CHF6563, Chiesi liquid preparation 0.075 mg/mL for sublingual administration (Test treatment & rescue medication)**
    - Active ingredient: Buprenorphine
    - Excipients: Citric buffer pH 6, Hydroxyethylcellulose
    - Presentation: transparent solution
- **CHF6563 matched placebo, Chiesi liquid preparation, for sublingual administration**
    - Excipients: Citric buffer pH 6, Hydroxyethylcellulose
    - Presentation: transparent solution
- **Morphine sulfate injection USP 0.5 mg/mL to be used for oral administration (Reference treatment & rescue medication)**
    - Active ingredient: morphine sulfate pentahydrate

- Excipients: water for injection USP, sodium chloride. May contain HCl/or NaoH for pH adjustment.

- **Morphine matched placebo: Sterile water for injection to be used for oral administration**

Sterile water for injection USP is a sterile, nonpyrogenic preparation of water for injection which contains no bacteriostatic, antimicrobial agent or added buffer and is supplied only in 20 mL single-dose containers.

- **Phenobarbital oral solution USP 20 mg/5mL (adjunctive therapy)**

- Active ingredient: phenobarbital
- Excipients: alcohol, FD&C Red no.40, flavors, glycerin, sucrose, water
- Presentation: red-orange clear solution

6.2 Dosage and Administration

6.2.1 Selection of doses in the study

Based on the results of the NCT01452789 study [26], a pharmacokinetic/pharmacodynamic (PK/PD) model has been created and published [29][38][38].
The PK/PD model allowed a number of observations to be made regarding buprenorphine in NOWS:

- Efficacy of time to stabilization is driven primarily by buprenorphine exposure, implying that most of the variability in dose response has a PK basis.
- Exposure is driven primarily by changes in clearance, with no clearly identified covariates that can predict PK variability.
- There were no identifiable changes in respiratory rate associated with buprenorphine exposure.

Since in NCT01452789 there was no evidence of decline in respiratory rate in infants treated with higher doses of buprenorphine compared to lower doses, a higher initial dose may allow therapeutic buprenorphine concentrations to be reached more quickly, ultimately leading to shorter lengths of treatment and hospital stay. This hypothesis has been tested by exploring *in silico* a variety of dosing-related factors: initial buprenorphine doses (from 0.1 to 15 µg/kg), up titration rates (25%, 33% and 50%), maximum buprenorphine doses (up to 25 µg/kg) and weaning rates (10%, 15% and 25%).

Simulations results showed that the best combinations of dosing factors are the following:

- Initial dose: 8 µg/kg
- Uptitration rate: 33%
- Maximum dose: 25 µg/kg
- Weaning rate: 15%

Results of this pharmacometric approach refer to the ethanolic formulation used in NCT01452789. To account for the difference in absorption showed by CHF6563, doses derived by the PK/PD modelling were increased by a 20% factor. This CHF6563-adjusted regimen has been further adapted and simplified to avoid calculation errors, by imposing up-titration steps based on a fixed 5 µg/kg rise rather than a percentage-based rate.

6.2.2 Dosage

All doses of CHF6563, morphine, respective matched placebos and phenobarbital are adjusted according to the birth weight which should be rounded to the second decimal place.

6.2.2.1 Test treatment dosage

Starting dose
The starting dose for CHF6563 is 10 µg/kg (30 µg/kg/day).

Frequency of administration
CHF6563 will be administered every 8 hours (±1 h), together with oral morphine matched placebo. Oral morphine matched placebo will be administered also every 4 hours (±1 h), to match the morphine administration schedule.
There is a ± 1hour interval around each nominal time point to account for sleeping and feeding schedule.
If dosing occurs at a time different from the specified nominal time (± 1 hour), the next dose will be scheduled to take place 8 hours following the actual dose administration.

Lost doses: if a baby spits or vomits soon after administration, the administration will not be repeated to avoid potential overmedication.

Dose escalation
In the up-titration phase, dose escalation will occur if the sum of 3 consecutive FNAST scores is ≥ 24 OR a single score is ≥ 12 OR a rescue dose was administered.

- No more than one dose escalation can take place each day unless a rescue dose is required.
- During the up-titration phase, doses will increase by 5 ug/kg steps, i.e. after the initial 10 ug/kg dose there can be consecutive dose increases to 15, 20, 25 and 30 ug/kg, if signs of withdrawal persist.
- The maximum dose (90 ug/kg/day) is therefore reached, if needed, after 4 up-titration steps.

Stabilization
The stabilization phase is defined as the period of treatment when no further drug treatment escalation is required. A stabilization period of 48 hours (without need for further drug treatment escalation) is required before weaning of drug treatment can begin.

Weaning
The initiation of weaning will begin after a 48 hour stabilization period, providing the sum of the previous 3 FNAST scores is < 18 and no single score is ≥ 8.

- Doses will be decreased by 15% once per day providing the sum of the previous 3 scores is < 18 and no single score is ≥ 8.
- If during a 24 hour period the sum of the previous 3 scores is ≥ 18 or a single score is ≥ 8, (even if no dose escalation has been required), weaning will not take place, the current dose will continue to be administered.
- If the sum of the previous three scores is ≥ 28 and at the discretion of the treating physician, the standing dose may revert to the previous dose or dose interval at which signs were controlled.
- Once the sum of the previous 3 scores is < 18 and no single score is ≥ 8, weaning can resume, and doses will continue to be decreased by 15% once per day.

- No more than one dose reduction is permitted in one calendar day.

Dose cessation
The cessation dose will be around the initial dose, (i.e. between 90-110% of the 10 ug/kg initial dose). Once this is reached, the dosing frequency is decreased from q8 to q12 hours for 24 hours, followed by a further decrease in dosing frequency from q12 to q24 hours prior to stopping.

Following cessation of dosing, babies will be observed in an inpatient setting for at least 48 hours, during which time scoring of NOWS signs will continue.

6.2.2.2 Reference treatment dosage

Starting dose
The starting dose for morphine is 0.07 mg/kg (0.42 mg/kg/day).

Frequency of administration
Morphine will be administered every 4 hours (±1 h) together with sublingual CHF6563 matched placebo. Sublingual CHF6563 matched placebo will be administered every 8 hours (±1 h), to match the CHF6563 administration schedule.
There is a ±1 hour interval around each nominal time point to account for sleeping and feeding schedule. If dosing occurs at a time different from the specified nominal time (±1 hour), the next dose will be scheduled to take place 4 hours following the actual dose administration.
Lost doses: if a baby spits or vomits soon after administration, the administration will not be repeated to avoid potential over medication.

Dose escalation
In the up-titration phase, dose escalation will occur if the sum of the 3 consecutive FNAST scores is ≥ 24 OR a single score is ≥ 12 OR a rescue dose was administered.

- No more than one dose escalation can take place each day unless a rescue dose is required.
- During the up-titration phase, after the initial 0.07 mg/kg dose there can be consecutive dose increases to 0.09, 0.12, 0.16 and 0.21 mg/kg, if signs of withdrawal persist.
- The maximum dose (1.25 mg/kg/day) is therefore reached, if needed, after 4 up-titration steps.

Stabilization
The stabilization phase is defined as the period of treatment when no further drug treatment escalation is required. A stabilization period of 48 hours (without need for further drug treatment escalation) is required before weaning of drug treatment can begin.

Weaning
The initiation of weaning will begin after a 48 hour stabilization period, providing the sum of the previous 3 scores is < 18 and no single score is ≥ 8.

- Doses will be decreased by 15% once per day providing the sum of the previous 3 scores is < 18 and no single score is ≥ 8.
- If during a 24 hour period, the sum of the previous 3 scores is ≥ 18 or a single score is ≥ 8, (even if no dose escalation has been required), weaning will not take place, the current dose will continue to be administered.

- If the sum of the previous three scores is ≥ 28 and at the discretion of the treating physician, the standing dose may revert to the previous dose or dose interval at which signs were controlled.
- Once the sum of the previous 3 scores is < 18 and no single score is ≥ 8, weaning can resume, and doses will continue to be decreased by 15% once per day.
- No more than one dose reduction is permitted in one calendar day.

Dose cessation
The cessation dose will be ≤0.025 mg/kg q4 hours.
Following cessation of dosing, babies will be observed in an inpatient setting for at least 48 hours, during which time scoring of NOWS signs will continue.

6.2.2.3 Rescue dose (CHF6563 0,075 mg/mL or morphine 0.5 mg/mL)

If, between scheduled doses, a baby has a single score ≥ 12, a rescue dose of CHF6563 or morphine may be administered at the discretion of the treating physician.

- The rescue dose will be the same as the previous dose.
- A rescue dose must be given at least 1 hour after the previous dose and 1 hour before the next scheduled dose.
- The rescue dose must not be given once the maximum dose has been reached.
- The administration of a rescue dose in the up-titration period will trigger a dose escalation at the next schedule dose.
- The administration of a rescue dose in the weaning period will not trigger a dose escalation.
- If after cessation of therapy a rescue dose is given, the baby must be observed for 48 hours.

To maintain the blinding, both active drug as well as placebo will be administered at the same time. Chiesi Farmaceutici S.p.A. will supply the rescue medication. Rescue medication will be packed for the trial as the test treatment (CHF6563/its matched placebo) and the reference treatment (morphine/its matched placebo).

6.2.2.4 Adjunctive therapy (phenobarbital USP 20 mg/mL)

If in either group, withdrawal as assessed by the FNAST is not controlled at the maximum dose of primary therapy (CHF6563 / morphine), phenobarbital will be initiated with an oral loading dose of 20 mg/kg, followed by a daily oral dose of 5 mg/kg/day.

Birth weight will be used for the calculation of phenobarbital loading and maintenance dose.

- Treatment with adjunctive phenobarbital will continue for at least two days and stabilization should be achieved before weaning of the opioid. Weaning will commence with reduction of the primary therapy (CHF6563 / morphine) according to the same rules as indicated above in the CHF6563 and in the morphine treatment section.
- When the primary therapy (CHF6563 / morphine) has been weaned to 50% of the maximal dose and the sum of the previous three scores is <18 and no single score is ≥ 8, the phenobarbital dose will be reduced to 2.5 mg/kg/day.
- The primary therapy (CHF6563 / morphine) dose will not be weaned on the day phenobarbital is weaned.

- Phenobarbital will be discontinued 72 hours after the dose reduction to 2.5 mg/kg/day, provided the sum of the previous three scores is < 18 and no single score is ≥ 8, and prior to the discontinuation of the primary therapy (CHF6563 / morphine).
- The primary therapy (CHF6563 / morphine) will not be weaned on the day when phenobarbital is discontinued.

Lost doses: if a baby spits or vomits soon after administration, the administration will not be repeated in order to avoid potential over medication. A replacement dose of study medication may be considered at the discretion of the treating physician in consultation with the site Principal Investigator.
Chiesi Farmaceutici S.p.A. will supply the adjunctive therapy.

6.2.2.5 Randomized Treatment period:

- **Test treatment: CHF6563 arm**

  CHF6563 0.075 mg/mL sublingual administration every 8 hours

  Morphine matched placebo, oral administration every 4 hours

The maximum CHF6563 dose is 90 μg per kilogram of (birth) body weight per day.

- **Reference treatment: morphine arm**

  Morphine solution 0.5 mg/mL oral administration every 4 hours

  CHF6563 matched placebo, sublingual administration every 8 hours

The maximum morphine dose is 1.25 mg per kilogram of (birth) body weight per day.

6.2.3 Administration

The study medication will be prepared for each individual baby by the pharmacist within the hospital's pharmacy department. The procedure for the preparation of the syringe is reported in the leaflet of both CHF6563 and its matched placebo and morphine and its matched placebo. CHF6563 or CHF6563 matched placebo will be administered sublingually and will be differentiated from oral study medication morphine / morphine placebo using oral syringes with marks differently colored. Each baby will be administered with:

- CHF6563 or CHF6563 matched placebo
  - A number of clear transparent 1 mL [redacted] oral sterile syringes of 1 mL with color 1 marks, calculated on the basis of birth weight and FNAST score containing CHF6563 **or** CHF6563 matched placebo, prepared by the pharmacist at the hospital's pharmacy.

  Each syringe will be filled with CHF6563 or CHF6563 matched placebo up to the 1 mL marking.

or

- Morphine or morphine matched placebo

- A number of clear transparent 1 mL [redacted] oral sterile syringe with color 2 marks, calculated on the basis of birth weight and FNAST score containing morphine solution at the concentration of 0.5 mg/mL **or** water INJ (morphine matched placebo), prepared by the pharmacist at the hospital's pharmacy.

Each syringe will be filled with morphine solution (concentration of 0.5 mg/mL) or morphine matched placebo (water INJ) up to the 1 mL marking.

Following preparation, the filled syringes will be dispensed to the neonatal service and stored as per hospital standard operational procedures for opioid medication. For investigational drug specific storage information and in-use storage condition please refer to the leaflet. Immediately prior to administration and according to the hospital standard operational procedures for opioid administration, members of the clinical staff will together prepare the correct dose of CHF6563 or CHF6563 matched placebo (color 1 mark syringes) AND morphine or morphine matched placebo (color 2 mark syringes) by adjusting the volume within the syringes. The correct dose is based on birth weight (which should be rounded to the second decimal place), FNAST and treatment regime. Information on how to calculate and administer the dose are reported in the leaflet of both CHF6563 and its matched placebo and morphine and its matched placebo.

Administration of the sublingual medication (CHF6563 or CHF6563 matched placebo) should always precede the oral medication (morphine or morphine matched placebo).

In accordance with the hospital standard operational procedures for opioid administration the clinical staff will administer the study drugs to the neonate following the correct administration practices for an oral and a sublingual drug.

In order to ensure the blinding between the two study drugs, one of which is administered by the sublingual route and the other orally, the trial has double dummy design, so a baby randomized to receive CHF6563 will also receive morphine matched placebo (water for injection) and a baby randomized to receive morphine will also receive CHF6563 placebo.

The two-different colored marks of the oral syringes will reduce the chances of the pharmacist preparing the incorrect study medication / placebo syringes, avoid a mismatch between the two solutions available: CHF6563/matched placebo and morphine/matched placebo when the volume of drug in the prefilled syringe is adjusted to the correct dose, and will allow the clinical staff to distinguish and administer the correct drug via the oral or sublingually route.

The frequency of administration is 8 hours for test treatment and of 4 hours for reference treatment, therefore the matched placebo of morphine will be administered every 4 hours in the CHF6563 arm and the matched placebo of CHF6563 will be administered every 8 hours in the comparator arm.
To allow for alteration in sleeping and feeding schedules, each dose of drug can be administered ± 1 hour around nominal time point for that dose.
Administration of CHF6563 or CHF6563 placebo will be as follows: the nurse will hold the neonate's head at approximately 45 degrees, gently move the tongue to the side and administer the drug under the tongue. The use of a pacifier to reduce swallowing of drug is permitted. If the volume of the drug is > 0.5 mL, the drug will be administered in two (or more) aliquots of no more than 0.5 mL, separated by 2 minutes.

If in either group, withdrawal as assessed by the FNAST is not controlled at the maximum dose of primary therapy (CHF6563 / morphine), phenobarbital will be initiated with a loading dose of 20 mg/kg, followed by a daily oral dose of 5 mg/kg/day. Birth weight will be used for the calculation of phenobarbital loading and maintenance dose (see section 6.2.2.4).

6.3 Packaging

All investigational medicinal product will be prepared according to the Good Manufacturing Practices (GMP) as required by the current Good Clinical Practices (GCP). Chiesi Farmaceutici S.p.A. will supply the study drug for the treatment period.

After randomization, at starting dose, at each step of up-titration and of weaning and in case the rescue dose is needed, for each baby, the pharmacist will be provided with the kits according to the randomization arm. The pharmacist will prepare the study medication in the pharmacy prior to the administration. The administration will be performed by the clinical staff at the bed side. Dispensing and administration will be done according to the package instruction leaflets and hospital standard operational procedures for opioid administration.
A package leaflet will be included in each kit with study medications in local language.

If the syringe drops on the floor during the filling procedure a new kit shall be used. In case the vial content has not been contaminated, it can still be used, the user needs to take a new syringe from the back up syringes kit provided for the study.

6.3.1 CHF6563 or CHF6563 matched placebo kit:

One labelled vial containing 2 mL of CHF6563 or matched placebo co-packed with one labelled pouch containing [redacted]- Oral syringe 1 mL, transparent, with color 1 marks, in a labelled holder.

Primary packaging: labelled vial containing 2 mL of CHF6563 or matched placebo plus one labelled pouch containing [redacted]- Oral syringe 1 mL transparent with color 1 marks.

Secondary packaging: labelled box containing one vial of 2 mL of CHF6563 or matched placebo plus one [redacted]- Oral syringe 1 mL transparent with color 1 marks plus the instruction for use.

6.3.2 Morphine kit

A labelled box containing one labelled commercial vial of 10 mL of morphine sulfate injection solution 0.5 mg/mL.

Primary packaging: one labelled vial of 10 mL.
Secondary packaging: one labelled box containing a 10 mL vial of morphine sulphate injection 0.5 mg/mL plus the instruction for use.

6.3.3 Morphine matched placebo (water for injection) kit

A labelled box containing one labelled commercial vial of 20 mL of water for injection.

Primary packaging: one labelled vial of 20 mL.
Secondary packaging: one labelled box containing a 20 mL vial of water for injection plus the instruction for use

6.3.4 Syringes kit

Two separate labelled boxes containing respectively a set of [redacted]- Oral syringe 1 mL transparent, with color 1 marks for CHF6563/matched placebo administration and a set of [redacted]- Oral syringe 1 mL transparent with color 2 marks for morphine/Water For Injection USP administration.

Primary packaging: one labelled pouch containing each one [redacted]- Oral syringe 1 mL transparent syringe

Secondary packaging: one labelled box containing labelled [redacted]- Oral syringes 1 mL transparent syringes.

The syringe kit containing the set of [redacted]- Oral syringes 1 mL transparent, with color 1 marks **is a back up kit**, in case the syringe drops on the floor.

The syringe kit containing the set of [redacted]- Oral syringe 1 mL transparent, with color 2 marks is **NOT a backup kit**, but it must be used for every preparation of morphine/matched placebo.

6.3.5 Adjunctive therapy kit

A 473 mL labelled commercial bottle of phenobarbital oral solution 20 mg/mL.
*Primary packaging***:** labelled plastic bottle of 473 mL. Instruction for use secured to the bottle with a rubber band.

*Secondary packaging***:** not present.

6.4 Labeling

All labeling will be in local language and according to local law and regulatory requirements and will be compliant with *21 CFR 312.6 "Labelling of an Investigational New Drug", for US trials*.

6.5 Treatment allocation

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]); please refer to APPENDIX 3 – List of PSYCHOTROPIC DRUGS for the list of drugs to be checked.

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 [37]. 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 [37], 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.).

6.6 Treatment Code

The kit list will be provided to the labeling facility. Neither the kit list, nor any randomization list will be available to subjects, investigators, monitors or employees of the center involved in the management of the trial before unblinding of the data, unless in case of emergency. Pharmacists will be unblinded.

The Sponsor's clinical team will also be blinded during the study as they will not have direct access to the randomization list. Of note, it will be possible following the last scheduled dose of CHF6563/placebo to ascertain the treatment for each subject. However, the randomization list and explicit treatment codes will not be available to the blinded team until after the database is locked.

In case of emergency, unblinding of the treatment code will be done through IRT. The treatment group will be disclosed, and confirmation will follow (by fax and/or notification email). The IRT will be designed to send a confirmation (by fax and/or notification email) to the site for every transaction performed by the Investigators. The Investigator will be provided with credentials for randomization purposes and separate credentials to unblind the study treatment in case of emergency situation, where he/she considers essential to know what treatment the patient was taking. The IRT will promptly notify the Sponsor and the Clinical Monitor whenever a treatment code is unblinded.

Users from Chiesi Global Pharmacovigilance will have their own credentials to unblind babies in case of SUSARs to be reported to the competent Regulatory Authorities and Ethic Committees/IRB.

6.7 Treatment compliance

Not applicable.

6.8 Drug Storage

The Pharmacist/Investigator will be responsible for the safe storage of all medications assigned to this study, in a secure place with restricted access, and maintained within the appropriate ranges of

temperature. For investigational drug specific storage information and in-use storage condition please refer to the leaflet. In addition, the hospital's standard operational procedures for the storage, handling and administration of opioids will be followed.

- **CHF6563 and its matched placebo vials** must be stored between 2°- 8° C (36° to 46°F) protected from light. Once withdrawn from the vial, the solution must be stored in the syringe below 25°C (77°F) and protected from the light.
- **Morphine sulphate IV solution 0.5 mg/mL vials** must be stored at controlled room temperature, protected from light at 20° to 25°C (68° to 77°F). Once withdrawn from the vial, the solution must be stored in the syringe below 25°C (77°F) and protected from the light.
- **Water for injection 20 mL** must be stored at 20° to 25°C (68° to 77°F). Once withdrawn from the vial, the solution must be stored in the syringe below 25°C (77°F).
- **Phenobarbital oral solution must be stored** at 20° to 25°C (68° to 77°F) protected from light.

6.9 Drug Accountability

The Investigator, or the designated/authorized representative, is responsible for the management of all the study medications to be used for the study. Study medications should be stored in a locked, secure storage facility with access limited to those individuals authorized to dispense the study medications and according to the hospital's standard operational procedures for the storage, handling of opioids.
An inventory will be maintained by the Investigator or pharmacist (or other designated individual), to include a signed account of all the study medication(s) received, dispensed and returned to the pharmacist by each Investigator/nurse during the trial.
At the conclusion or termination of the study, the Investigator or the pharmacist shall conduct and document a final drug supply inventory. An explanation will be given for any discrepancies.
All the study medications supplied, used or unused, will be returned to Chiesi or to the designated CRO under Sponsor's responsibility or destroyed directly at the site (hospital pharmacist). In this case, a destruction certificate must be completed by the investigational center and filed both at site and at Sponsor. Return and destruction will not occur until authorized by Chiesi.

6.10 Provision of additional care

Not applicable

7. STUDY PLAN

7.1 Study Schedule

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 FNAST. Pharmacological treatment will start up to 7 days after delivery in neonates who have persisting signs of NOWS despite the implementation of appropriate non-pharmacologic care. If all the inclusion/exclusion criteria are met the baby will be eligible for the randomization.
Following 2 consecutive FNAST with a sum ≥ 12, if all eligibility criteria except for Inclusion Criterion #5 are met, then neonates 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). If eligibility is confirmed, the randomization will be confirmed in the IRT system and the baby will be treated.

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.

A 18-months (± 1 months) follow-up visit for a further long-term assessment and confirmation of the safety of the test treatment.

The study plan and scheduled tests are summarized in the following table:

			Treatment Period		End of treatment	Follow Up	
	Pre-screening (Mother)	**Screening (neonates)**	**Randomization up to stabilization**	**Weaning up to end of treatment**	**48h±4 h 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. Cardiorespiratory monitoring using continuous 3-lead ECG and pulse oximetry should be performed during treatment (starting before the first dose of study drug and continuing up to the initial stage of the weaning phase).
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 (±4 h) 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 the last dose. 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.

7.1.1 Pre-screening visit

A pre-screening visit will be carried out in order to identify mothers with history of opioid use in the last month of pregnancy, obtain information on additional drugs or substance use during the pregnancy and exclude a family history of prolonged QTc syndrome (this should include questions on unexplained sudden death in otherwise healthy individuals). Use of opioid could be licit or illicit. Mothers who have been using other substances and/or are on prescribed medications can take part in this study.

The mother will be asked to undertake the following:

- Prior to birth (if possible) or following birth, or when the baby shows signs of NOWS:
  a) written informed consent for the completion of the maternal screening questionnaire
  b) written informed consent for access to the maternal electronic medical record to collect demographic information
  c) written informed consent for access to maternal urine toxicology data collected during pregnancy and labor (optional within the consent)
- Written informed consent for the baby to enter the treatment phase can be obtained at this visit.

  This should be signed by the parent /legal representative, following full explanation of the study by the investigator. The investigator or his/her designee should provide them ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. Once their written informed consent has been obtained (either prior to or after birth), inclusion and exclusion criteria will be evaluated, and neonate's eligibility assessed.

The investigator or his/her designee will complete the maternal screening questionnaire in discussion with the mother (refer to APPENDIX 2 – Maternal Screening Questionnaire)

7.1.2 Screening Visit

After delivery, a screening visit will be carried out up to 7 days after birth to identify neonates with signs of NOWS who may be eligible for the study.

The following information will be collected:

- NOWS score: FNAST will be used to assess withdrawal signs every 4 hours (±1 hour)
- Gestational age, sex
- Race/ ethnicity
- Birth weight, head circumference, birth length (or length captured during Screening)
- Baby toxicology data, if available (optional)
- Vital signs: heart rate (HR), respiratory rate (RR), peripheral oxygen saturation (SpO_2), body temperature (BT). Blood pressure (DBP; MBP; SBP) will be recorded if collected according to site clinical practice
- Hematology and blood chemistry data: the results of investigations performed prior to randomization will be recorded; these can include complete blood count (CBC), urea, creatinine and electrolytes (sodium, potassium, magnesium calcium, phosphorus), glucose, C-reactive protein, if collected before randomization according to clinical practice
- Medical history

- AEs and concomitant medication/procedures to be checked and recorded. Non-serious AEs will not be collected for screening failure.

After FNAST assessment has started, it should continue for at least 24 hours, even in case the baby is not randomized.

7.1.3 From randomization to stabilization

Once the baby's eligibility to take part in the study is confirmed, the Investigator will randomize the baby to the assigned treatment by using the IRT system. Pharmacological treatment will start up to 7 days after delivery in neonates who show signs of NOWS and have failed to respond to non-pharmacologic care.

All neonates enrolled in the study should receive routine cardiorespiratory monitoring using continuous 3-lead ECG and pulse oximetry This should commence before the first dose of study drug (CHF6563 or morphine) is administered and continue throughout the dose-escalation phase, stabilization phase and the initial stage of the weaning phase. During the later stages of weaning, the continuous ECG monitoring may be discontinued at the investigator's discretion, to allow nonpharmacological care strategies to be maximized.
If an abnormal rhythm is detected by the continuous 3-lead ECG, the neonate should be evaluated with a 12-lead ECG and dosing interrupted. If a pediatric cardiologist confirms a QTc interval of ≥500 ms on a 12-lead ECG, the study treatment should be discontinued.

The following procedures will take place only at randomization:

- Inclusion/ exclusion criteria
- Randomization: neonates with a GA ≥36 weeks and the sum of 3 consecutive FNAST assessment scores ≥ 24 or a single score ≥12 will be assigned in a 2:1 ratio to either CHF6563 or morphine. Treatment doses will be calculated according to birth weight which should be rounded to the second decimal place.

The following procedures will take place from randomization to stabilization:

- NOWS score: FNAST will be used to assess withdrawal signs. Signs of withdrawal will be assessed and recorded every 4 hours (±1 hour)
- Vital signs: heart rate (HR), respiratory rate (RR), peripheral oxygen saturation (SpO_2), and body temperature (BT) 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. Routine cardiorespiratory monitoring will be performed using continuous 3-lead ECG and pulse oximetry.
- Body weight – all body weights recorded as part of standard of care will be collected (minimum requirement - once a week)
- Treatment administration: treatment doses will be calculated according to birth weight (which should be rounded to the second decimal place) and the NOWS score which will be assessed and recorded every 4 hours.
- Feeding status: breastfeeding, formula feeding, mixed feeding, and the proportion of maternal breastmilk intake during this period of time i.e. randomization to stabilization will be recorded.
- Liver function test (AST, ALT): will be performed after first dose and following treatment stabilization prior to the first weaning dose and recorded.
- Blood sampling for CHF6563 pharmacokinetics will be performed.
- Further concomitant medications/procedures and adverse events as well as changes in those already reported will be recorded.

7.1.4 From weaning to the end of treatment

The following procedures will take place:

- NOWS score: signs of withdrawal will be assessed and recorded every 4 hours (±1 hour) using FNAST
- Vital signs: heart rate (HR), respiratory rate (RR), peripheral oxygen saturation (SpO_2), body temperature (BT) will be collected at the same time of the NOWS score but only once a day. Blood pressure (DBP; MBP; SBP) will be recorded if collected according to site clinical practice. Cardiorespiratory monitoring will be continued during the initial stage of weaning and can be discontinued at the investigator's discretion during later stage.
- Body weight – all body weights recorded as part of standard of care with be collected (minimum requirement - once a week).
- Treatment administration: treatment doses will be calculated according to birth weight (which should be rounded to the second decimal place) and the NOWS score which will be assessed and recorded every 4 hours.
- Feeding status: breastfeeding, formula feeding, mixed feeding, and the proportion of maternal breastmilk intake during this period of time i.e. weaning to end of treatment will be recorded.
- Blood sampling for CHF6563 pharmacokinetics will be performed.
- Further concomitant medications/procedures and adverse events as well as changes in those already reported will be recorded.

7.1.5 End of treatment period Visit (48 hours ±4 h after the last dose)

The following procedures will take place:

- NOWS score
- Vital signs: heart rate (HR), respiratory rate (RR), peripheral oxygen saturation (SpO_2), body temperature (BT), will be collected; blood pressure (DBP; MBP; SBP) will be recorded if collected according to site clinical practice
- Head circumference, and body weight and length
- General physical and neurological examination
- Liver function test (AST, ALT) will be performed and recorded
- Feeding status: breastfeeding, formula feeding, mixed feeding, and the proportion of maternal breastmilk intake during this period of time i.e. end of treatment to discharge will be recorded.
- Further concomitant medications and adverse events as well as changes in those already reported.

7.1.6 Functional unblinding

The weaning period requires a lower number of weaning steps for CHF6563 compared to morphine. In order to avoid maintaining babies randomized to CHF6563 in the hospital following completion of study drug, only to receive placebo for several days (about 5, depending on the severity of the withdrawal), the unblinded pharmacist will advise the clinical staff that the baby has completed active study treatment following the last active dose of CHF6563 and babies will be eligible for discharge (at least insofar as the clinical trial is concerned) 48 hours after the last active dose. Since the cessation dose will not occur at the same weaning step for the 2 treatment arms, it will be possible to ascertain the treatment for each baby after the weaning step which corresponds to the cessation dose of CHF6563. This is considered a "functional

unblinding" since, after this point, it will be possible for members of the blinded team to ascertain the treatment arm.

Prior to the last scheduled dose of CHF6563, all members of the blinded study team will remain completely blinded. Following the last scheduled dose of CHF6563/placebo, members of the blinded study team will not have access to the explicit treatment codes, but it will be possible to ascertain the treatment arm. Similarly, data review will occur without access to explicit treatment codes, since the explicit treatment codes will be maintained in a confidential manner. The randomization list and explicit treatment codes will be disclosed to blinded study team members only after the database is locked.

7.1.7 Follow-up

Regular follow up will continue both before and after discharge from the hospital to identify those babies who suffer recurrence of significant withdrawal.

- During the first 7 days after the initial 48 hours observation period following the last dose:
    a) If the baby has already been discharged from the hospital, daily telephone contact with the primary caregiver (parental/legal guardian or foster mother). The following information will be recorded:
        - General well-being
        - Escalation of withdrawal signs
        - Feeding status: breastfeeding, formula feeding or mixed feeding
        - Further concomitant medications and adverse events as well as changes in those already reported.
    b) If the baby stays in the hospital, the following information will be recorded:
        - General well-being
        - Escalation of withdrawal signs
        - Feeding status: breastfeeding, formula feeding, mixed feeding, and the proportion of maternal breastmilk intake during this period of time i.e. first 7 days.
        - Further concomitant medications and adverse events as well as changes in those already reported.
- From 10 days and until 6 weeks after the last treatment dose, weekly telephone contact with the primary care will continue. The following information will be recorded:
        - General wellbeing
        - Escalation of withdrawal signs
        - Feeding status: breastfeeding, formula feeding or mixed feeding
        - Further concomitant medications and adverse events as well as changes in those already reported.

7.1.8 Follow-up: 18 months (±1 months)

A further clinical assessment at 18 months (±1 months) will be performed by a multidisciplinary team at the participating study centers to assess the general wellbeing, growth and long-term neurodevelopmental assessment and growth parameters.

The clinical assessment will collect information on the following domains:

- Health status (general medical history and physical examination, including growth parameters, medical illness, developmental issues, medications and hospital admission)
- Environmental / social factors (foster care, domestic violence exposure, substance use / treatment)
- Cognitive and behavioral development (Bayley Scales of Infant Development – all 5 domains)
- Assessments of the mother / primary carer using standardized questionnaires (e.g. Brief Symptom Inventory (BSI), Quick Inventory of Depressive Symptomatology (QIDS), Parenting Stress Index (PSI), Child Behavior Checklist (CBCL))

This 18-month clinical assessment will be analyzed and evaluated separately from the initial part of the study and be object of an addendum to the initial core clinical study report. Individual assessments will be described in more detail in an additional document.

7.2 Investigations

7.2.1 NOWS score

FNAST (refer to APPENDIX 4 – Finnegan Neonatal Abstinence Scoring Tool (FNAST)) will be used to assess the severity of NOWS.
Details on FNAST, training package and site validation will be provided in a separate report document.

7.2.2 Feeding Status

Feeding status will be collected daily from the electronic patient record. (Formula /breast milk or a mixed feeding and proportion of maternal breast milk intake).

7.2.3 Toxicological collection

It will only be performed in those hospitals where this is common clinical practice, according to site procedures.

7.2.4 Vital signs

At screening and from the randomization until the end of the treatment, heart rate (HR), respiratory rate (RR), peripheral oxygen saturation (SpO_2), body Temperature (BT) will be collected. Blood pressure (DBP; MBP; SBP) will be recorded if collected according site clinical practice.

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.

From weaning until the end of the treatment they will be collected once a day at the time of NOWS score.

Cardiorespiratory monitoring using continuous 3-lead ECG and pulse oximetry should be performed during treatment (starting before the first dose of study drug and continuing up to the initial stage of the weaning phase).

7.2.5 Hematology/blood chemistry and liver function

The results of investigations - if performed according to site clinical practice - prior to randomization will be recorded; these can include full blood count (FBC), urea, creatinine and electrolytes (sodium, potassium, magnesium, calcium, phosphorus), glucose, C-reactive protein.

Liver-function test analysis (aspartate aminotransferase [AST], alanine aminotransferase [ALT]),) will be performed on 3 occasions: after the first dose, at stabilization and 48 hours (±4 h) after the last treatment dose.

7.2.6 Pharmacokinetics

Blood sampling for PK will occur the day of randomization and then every 5±1 day until the last dose. The first blood sampling should be taken after the first dose. Subsequent sampling should occur after the morning dose and be timed to fit in with the following sampling windows: one blood sample should be taken in the 0-2 h post-dose time window, one in the 2-4 h post-dose time window and one in the 4-8 h post-dose time window.
If possible, in order to minimize discomfort for the babies, PK samples should be collected simultaneously to routine blood sample collection.

Twenty µl aliquot of blood will be spotted onto DMPK-A cards and allowed to dry at room temperature on an open non-absorbent surface for at least two hours (at least three spots per sample). Cards will be then stored at room temperature in a sealed plastic bag containing desiccant until shipment to the central Laboratory for determination of CHF6563.
Around 300-360 µl will be collected every 5±1 day until end of last dose.

[redacted] is allocated as reference laboratory in charge for the study bioanalysis.
CHF6563 blood concentrations will be determined using validated HPLC-MS/MS methods.
The laboratory analysis will be carried out following Good Laboratory Practice (GLP) regulations of the OECD. The analytical procedure will be described in a separate analytical study plan.

7.2.7 Neurological and behavioral assessment

Neurological and behavioral assessment will be performed at the end of treatment period and at 18 months.

At the end of treatment period (48h ±4 h after last dose), general physical and neurological examination will be performed.

At 18 months, cognitive and behavioral development will be assessed using the Bayley Scales of Infant Development– all 5 domains. Moreover, standardized questionnaires will be administered to the mother/primary carer (e.g. Brief Symptom Inventory (BSI), Child Behavior Checklist (CBCL)).

8. EFFICACY ASSESSMENTS

8.1 Primary Efficacy endpoint

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

8.2 Secondary Efficacy endpoints:

- 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

9. SAFETY ASSESSMENTS

During administration of sublingual CHF6563 or oral morphine:

- Number and percentage of babies with peri-dosing adverse events (AEs) (i.e., mouth irritation or inflammation, apnoea, desaturation, brady/tachycardia, cough, immediate swallowing of sublingual drug, regurgitation, vomiting occurring after administration)

During the study

From the randomization to the end of the treatment the following information will be collected and presented using summary statistics:

- Adverse events and adverse drug reactions (ADRs).
- Liver enzymes analysis-function testing (AST, ALT,) will be performed on 3 occasions: after the first dose, at stabilization and 48 hours (±4 h) after the last treatment dose.
- Vital signs: heart rate (HR), respiratory rate (RR), peripheral oxygen saturation (SpO2), body temperature (BT) will be monitored, and data collected during the escalation and stabilization phases.
- Body Weight and head circumference
- Hematology and blood chemistry: full blood count (FBC), urea, creatinine and electrolytes (sodium, potassium, magnesium calcium, phosphorus), glucose, C-reactive protein if collected before randomization according to site clinical practice.
- Blood pressure (SBP, MBP, DBP) will be monitored according to individual site clinical practice

End of the treatment period

After 48 hours (±4 h) from the last dose the following will be recorded and presented using summary statistics:

- Vital signs: heart rate (HR), respiratory rate (RR), peripheral oxygen saturation (SpO_2), body temperature (BT). Blood pressure (SBP. MBP. DBP) if collected according to site clinical practice
- Neurological and behavioral assessment
- Body weight, length and head circumference
- All the Adverse Events, and adverse drug reactions, and concomitant medications as well as changes in those already reported.

End of 6 week Follow up

- Signs of / escalation of withdrawal
- All the Adverse Events, and adverse drug reactions, and concomitant medications as well as changes in those already reported.

Follow up to 18 months

- Health status (general medical history and physical examination, including growth parameters, medical illness, developmental issues, medications and hospital admission)
- Environmental / social factors (foster care, domestic violence exposure, substance use / treatment)
- Cognitive and behavioral development (Bayley Scales of Infant Development - all 5 domains)
- Assessments of the mother / primary carer using standardized questionnaires (e.g. Brief Symptom Inventory (BSI), Quick Inventory of Depressive Symptomatology (QIDS), Parenting Stress Index (PSI), Child Behavior Checklist (CBCL))

10. ADVERSE EVENT REPORTING

10.1 Definitions

An **Adverse Event** is "any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment".
An adverse event can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An **Adverse Drug Reaction** is an "untoward and unintended response to an investigational medicinal product related to any dose administered".
All adverse events judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression "reasonable causal relationship" means to convey in general that there are facts (evidence) or arguments meant to suggest a causal relationship.
The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

A **Serious Adverse Event (SAE)/Serious Adverse Drug Reaction** is any untoward medical occurrence or effect that at any dose falls in one or more of the following categories:

- **Results in death**

Death is not an adverse event but an outcome. It is the cause of death that should be regarded as the adverse event. The only exception to this rule is "sudden death" where no cause has been established; in this latter instance, "sudden death" should be regarded as the adverse event and "fatal" as its reason for being serious.

- **Is life-threatening**

Life-threatening refers to an event in which the subject was at risk of death at the time of the event (e.g., aplastic anaemia, acute renal failure, and anaphylaxis). The term does not refer to an event which hypothetically might have caused death if it were more severe.

- **Requires hospitalisation or prolongation of existing hospitalisation**

Hospitalization refers to a situation whereby an AE is associated with unplanned formal overnight admission into hospital, usually for purpose of investigating and/or treating the AE. Hospitalization for the treatment of a medical condition that occurs on an "elective" or "scheduled" basis or for a pre-existing condition that did not worsen during the study should not necessarily be regarded as a AE. Complications that occur during the hospitalisation are AEs. If a complication prolongs hospitalisation, the event is an SAE. Emergency room visits that do not result in a formal admission into hospital should be evaluated for one of the other seriousness criteria (e.g., life-threatening; persistent or significant disability or incapacity; medically significant).

- **Results in persistent or significant disability or incapacity.**

The term significant disability should be viewed as any situation whereby an AE has a clinically important effect on the subject's physical or psychological well-being to the extent that the subject is unable to function normally.

- **Is a congenital anomaly or birth defect**

- **Is a medically significant adverse event**

This criterion allows for any situations in which important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation may jeopardise the subject's health or may require intervention to prevent one of the above outcomes.

Examples of such events are: intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.
Medical and scientific judgment should be exercised in deciding whether an event is serious because medically significant.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

A **Non-Serious Adverse Event/Non-Serious Adverse Drug Reaction** is an adverse event or adverse drug reaction that does not meet the criteria listed above for a serious adverse event/serious adverse drug reaction.

10.2 Expectedness

An expected adverse reaction is an adverse reaction, the nature or severity of which is consistent with the applicable reference safety information (Investigator's Brochure for CHF6563 and USPI for Morphine), otherwise it is considered unexpected.

Reports which add significant information on specificity or severity of a known, already documented serious adverse drug reaction constitute unexpected events. For example, an event more specific or more severe than described in the Investigator's Brochure would be considered as "unexpected". Examples of such events are: (a) acute renal failure as a labelled ADR with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.
In the event an exacerbation is interpreted as due to lack of efficacy, it should not be classified as drug related.

10.3 Intensity of Adverse Event

The investigator is asked to assess the intensity of all the adverse events and to report them in the eCRF.

The intensity (severity) of a specific event is defined as mild, moderate, or severe; the event itself, however, may be of relatively minor medical significance. This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Each Adverse Event must be rated on a 3-point scale of increasing intensity:

- **Mild:** asymptomatic or mild symptoms; clinical or diagnostic observations only; no change in baseline age-appropriate behavior (e.g. oral feeding behavior, voluntary movements and activity). The event does not lead to either modification of test treatment dosage or establishment of a correcting treatment.
- **Moderate:** resulting in minor changes of baseline age appropriate behavior; requiring minor changes in baseline care or monitoring (e.g. oxygenation, ventilation, tissue perfusion, metabolic stability and organ functioning). The event leads to a diminution of dosage of the test treatment, or a temporary interruption of its administration or to the establishment of a correcting treatment.
- **Severe:** resulting in major changes of baseline age-appropriate behavior; requiring major change in baseline care or monitoring; requiring major change in baseline care or monitoring (e.g. brief, local, non-invasive or symptomatic treatments). The event causes severe discomfort and it may be of such severity to cause the definitive interruption of test treatment.

For the classification of AEs intensity, the ''Development of a neonatal adverse event severity scale through a Delphi consensus approach'' article released on September 19, 2019 may be used as a guidance.

Since the above-mentioned guidance is based on a 5-grade table, the following conversion will be performed:

AEs grade 1→ Mild
AEs grade 2 → Moderate
AEs grade 3, 4 and 5→ Severe

In order to guarantee objectivity and consistency in the evaluation of AEs (including classification of intensity), the proposed guidance should be followed in alignment with best medical practice. Moreover, clinical abnormalities and other assessments will be reported as AEs if are judged by the Investigator as being clinically significant.

10.4 Causality Assessment

The following "binary" decision choice will be used by the Investigator to describe the causality assessment:

- Reasonable possibility of a relatedness
- No reasonable possibility of relatedness

The expression "reasonable possibility of relatedness" is meant to convey, in general, that there are facts (evidence) or arguments meant to suggest a causal relationship.

The Investigator will be asked to consider the following before reaching a decision on causality assessment:

- Time relationship between study drug intake and event's onset;
- De-challenge (did the event abate after stopping drug?);
- Re-challenge (did the event reappear after reintroduction?);
- Medical history;
- Study treatment(s);
- Mechanism of action of the study drug;
- Class effects;
- Other treatments-concomitant or previous;
- Withdrawal of study treatment(s);
- Lack of efficacy/worsening of existing condition;
- Erroneous treatment with study medication (or concomitant);
- Protocol related process.

10.5 Action taken with the study drug due to an AE

- Dose not changed
- Drug permanently withdrawn
- Drug temporarily interrupted
- Unknown
- Not applicable

10.6 Other actions taken

- Specific therapy/Medication
- Concomitant Procedure
- N/A

10.7 Outcome

Each Adverse Event must be rated by choosing among:

- Recovered/resolved
- Recovering/resolving
- Not recovered/not resolved
- Recovered with sequelae/resolved with sequelae
- Fatal
- Unknown

10.8 Recording Adverse Events

All Adverse Events occurring during the course of the study must be documented in the Adverse Event page of the electronic Case Report Form (eCRF). Moreover, if the Adverse Event is serious, the Serious Adverse Event Form must also be completed.
It is responsibility of the Investigator to collect all adverse events (both serious and non-serious). Signs of NOWS (the condition under study) are efficacy endpoints in this study. Since detailed information on these events will be collected on the relevant page (refer to APPENDIX 4 – Finnegan Neonatal Abstinence Scoring Tool (FNAST)), these events therefore do not require to be reported as AEs unless their occurrence, severity or unresponsiveness to treatment (both study arms) is considered by the investigator unusual or abnormal or suggest another clinical diagnosis or pathology.
Additionally, those events should be reported as SAEs if they fulfill the definition of an SAE as in section 10.1

All AEs, regardless of seriousness, severity or presumed causality must be recorded in the subject's medical records and in the CRF. AEs that occur in subjects who have screen failed and are not entered into the CRF will be captured on the AE Reporting Log in the Investigator Site File. All SAEs occurring in subjects who have screen failed will be reported from informed consent and recorded in eCRF.

The investigator should carefully check inclusion and exclusion criteria because some of these morbidities may not allow the neonate to be randomized.
Clinically significant abnormalities detected at Screening visit not due to a pre-existing condition or clinically significant changes at the following visits in the medical opinion of the investigator must be reported as adverse events in the eCRF, taking into consideration the above assessment.

A diagnosis, if known, or clinical signs and symptoms if diagnosis is unknown, rather than the clinically significant abnormal laboratory finding, should be reported on AE *eCRF* page. If no diagnosis is known and clinical signs and symptoms are not present, then the abnormal finding should be recorded.

For pharmacovigilance purposes, all SAEs should be followed-up in order to elucidate as completely and practically as possible their nature and/or causality until resolution of all queries, clinical recovery is complete, laboratory results have returned to normal, stable condition is reached or until the subject is lost to follow-up. Follow-up may therefore continue after the subject has left the study. In this case, the follow-up will continue with no timelines for related SAEs, while for unrelated SAEs the type and extent of follow-up undertaken will be determined for each individual case and will depend upon the nature (e.g. events with poor prognosis or which do not resolve), severity and medical significance of the event.

10.9 Reporting Serious Adverse Events to Chiesi

The Investigator must report all Serious Adverse Events to the [redacted] Safety Contact listed below within 24 hours of awareness. The information must be sent by providing the completed paper *Serious Adverse Event*

form. At a later date, the [redacted] Safety Contact will report all information to Chiesi Global Pharmacovigilance, the Clinical Project Manager and the Clinical Research Physician.

Name and Title	Telephone no.	Mobile no.	Fax no.	E-mail
[redacted] Associate Safety Project Manager [redacted] Safety Contact	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] Global Pharmacovigilance Operation Specialist Chiesi Farmaceutici S.p.A. Parma (Italy)	[redacted]	-	[redacted]	[redacted]

- Reporting of SAEs from the investigator site is from the time of subject's signature of informed consent and until the subject's study participation ends. After this date, even if no active monitoring of subjects is required, only related SAEs occurring to a subject should be reported if the investigator becomes aware of them.
- Up to the closure of the site, SAE reports should be reported to the [redacted] Safety Contact. New related serious adverse events occurring after the site is closed should be reported directly to the Chiesi Safety Contact.

10.10 Reporting Serious Adverse Events to Regulatory Authorities/Ethics Committees/IRB

The Sponsor or [redacted] will report adverse events to the regulatory authorities in compliance with the timelines and standards of reporting according to local regulations (Guidance for industry and Investigators-Safety Reporting Requirements for INDs and BA/BE studies, December 2012). All suspected unexpected serious adverse reactions (SUSARs), which occur with the investigational medicinal product or marketed active comparator, within or outside the concerned clinical trial, will be reported by the Sponsor or [redacted] to regulatory authorities, as required, as well as to the Investigators and Central IRB, if applicable, by MedWatch/CIOMS form. The Investigator (or Sponsor/CRO where required) must inform the IRB per Sponsor instruction upon receipt of the SUSAR notification. An IND and/or NDA Safety Report will be submitted to regulatory authorities unblinded. Participating Investigators and IRB will receive a blinded IND Safety Report, unless otherwise specified. Regarding regulations in force for Pharmacovigilance, the Investigator must fulfill his/her obligation according to the law in force in his country.

10.11 General Notes

- In case of death, a comprehensive narrative report of the case should be prepared by the Investigator and sent to the [redacted] Safety Contact by fax together with the Serious Adverse Event form, retaining a copy on site.
- If an autopsy is performed, copy of autopsy report should be actively sought by the Investigator and sent to the [redacted] Safety Contact as soon as available, retaining a copy on site.
- All source documents provided by the Investigator or site staff to the [redacted] Safety Contact must be carefully checked for respect of confidentiality. All personal patient's data must be redacted.

10.12 Independent Safety Monitoring Board

An Independent Safety Monitoring Board (ISMB) will be established to ensure the safety of study subjects on an on-going basis. The involvement of independent expert advisors will provide an unbiased evaluation

of the overall safety in the study, with particular regard to the incidence of major adverse outcomes (i.e. Serious Adverse Events) during and following study treatment administration.
Independent Clinicians (2 or 3) and one independent Biostatistician will compose the ISMB.
The Sponsor (and other study personnel) may be involved in some blinded parts of the ISMB meetings.
All ISMB members will keep as confidential all information and data deriving from the ISMB activity, without disclosing them to others.
The ISMB will have periodical face-to-face or telephone meetings, as appropriate, and meeting minutes will be issued after each meeting.
The complete ISMB guidelines including details regarding the members, duties and responsibilities, work and communication processes, frequency of meetings will be established by the ISMB members during the first meeting and reported in a separate charter.

11. DATA MANAGEMENT

An electronic CRF (eCRF) will be filled-in by the Investigator and/or his/her representative designee.
Front-end edit checks will run at the time of data collection and back-end edit checks will be used by the Data Manager to check for discrepancies and to ensure consistency and completeness of the data.
Subject questionnaires will be collected on paper and data will be entered at the site into the eCRF.
Medical history, adverse events and concomitant procedures will be coded using the MedDRA dictionary; medications will be coded using the WHO Drug dictionary and Anatomical Therapeutic Chemical classification (ATC). Access to electronic systems used for data collection will be granted to the study personnel only after appropriate training.
After the completion of data collection and cleaning, one or more data review meetings will be held to determine the occurrence of any protocol violation and to define the subject populations for the analysis. Although it will be possible to derive the treatment arm for patients who have reached or surpassed the end of the weaning phase, the explicit treatment codes will not be disclosed to the blinded team who are reviewing the data. All data review will occur without explicit access to treatment codes. Once the database has been declared to be complete and accurate, it will be locked, the randomization codes will be opened, and the planned statistical analysis will be performed. Of note, the randomization list will remain confidential from the blinded study team until after database lock, even for patients who are functionally unblinded.
If the database is unlocked after the initial lock, the process must be carefully controlled and documented; updates to the study data must be authorized by Chiesi.
At the study conclusion, a complete copy of the study data will be created for archival purposes at Chiesi. The investigators will receive copies of the patient data for retention at the investigational sites.

The 18-months (± 1 month) follow up data will be recorded in a separate database.

12. STATISTICAL METHODS

12.1 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.

12.2 Populations for analysis

- **Enrolled Population:** all subjects for whom informed consent was signed.
- **Randomized Population:** all randomized subjects.
- **Intention-to-Treat population (ITT):** all randomized subjects who receive at least one dose of the study treatment and with at least one available evaluation of efficacy after the baseline.
- **Per-protocol population (PP):** all subjects from the ITT population without any major protocol deviations (i.e., wrong inclusions, non-permitted medications). Exact definition of major protocol deviations will be discussed by the study team during the review of the data and described in the Data Review Report.
- **Safety population:** all randomized subjects who receive at least one dose of study treatment.

  - The primary analysis population for efficacy will be the ITT. Analysis on the primary variable(s) will be repeated in the PP population
  - The Safety population will be used in the analysis of all safety variables.
  - In case of deviation between as-randomised treatment and treatment actually received, the treatment actually received will be used in the safety analyses (i.e. an as-treated analysis will be performed).

12.3 Statistical analysis

A detailed statistical analysis plan will be described in the Statistical Analysis Plan. The plan might be reviewed and updated as a result of the blind review of the data and will be finalized before breaking the blind.

12.3.1 Descriptive Statistics

General descriptive statistics for numeric variables will include the n (number of observed values), the mean, the standard deviation, the median, the minimum, and the maximum values. For categorical variables, the number and percent of subjects with a specific level of the variable will be presented.

12.3.2 Missing data

Babies for whom the parent/legal guardian wishes to discontinue treatment with study medication will be encouraged (via the parent/guardian) to remain in the study for collection of safety and efficacy data until the patient is discharged from the hospital or consent is otherwise withdrawn. These babies will receive standard of care according to clinical practice but will continue to contribute to study assessments. Handling of such cases will be described in the SAP.

Primary Efficacy Variable: Duration of treatment for babies who discontinue from the study prior to end of study treatment for any reason, including withdrawal due to treatment longer than 10 weeks, will be imputed using for the primary efficacy analysis. The imputed value will be the maximum of:

- the actual value for duration of treatment for the neonate (10 weeks for patients withdrawn due to treatment longer than 10 weeks) or
- the 90th percentile value for duration of treatment of all neonates, regardless of treatment group.

Further details on dealing with missing data, along with the handling of possible outliers, will be described in the Statistical Analysis Plan (SAP). Other critical missing data, if any, will be discussed during the review of the data. Decisions will be fully documented in the Data Review Report.

12.3.3 Patient demographics and baseline characteristics

Demographics and baseline variables will be summarized by treatment arm using descriptive statistics for the ITT population.

The following variables will be presented: gestational age, sex, race/ ethnicity, head circumference and percentile, weight and percentile, medical history, concomitant diseases, FNAST scores, primary feeding

method, feeding type at randomization, duration of breastfeeding, maternal smoking, alcohol consumption, primary opioid and use of other licit and illicit drugs, prior medications (baby), and vital signs (neonate). Summary statistics of demographic and baseline characteristics will be presented for the Safety Population (if different from the ITT population) and the PP.

12.3.4 Primary efficacy variable

The primary efficacy variable is the duration of treatment defined as the number of hours from start of the treatment until the last dose of study drug.

An ANCOVA model based on log-transformed data will be performed to test the treatment effect as duration of treatment (hours).

The model will include treatment (CHF6563 and morphine) as a fixed effect and covariates for primary feeding method (formula/ any maternal breast- milk), Maternal primary opioid use (buprenorphine/ methadone / other), and maternal use of benzodiazepines, antidepressants or gabapentin (polypharmacy [yes/no]). In cases where observed primary feeding method during the treatment period (formula / any maternal breast milk) differs from the feeding method at time of randomization, the observed primary feeding method will be used for analysis. The adjusted geometric mean in each treatment group, the adjusted ratio of geometric means between treatments, together with its 95% CI and associated p-value will be estimated by the model.

Missing data handling for the primary efficacy analysis is described in Section12.3.2.

Sensitivity analyses will be performed as described in the SAP.

12.3.5 Secondary efficacy variables

In cases where observed primary feeding method during the treatment period (formula / any maternal breast milk) differs from the feeding method at time of randomization, the observed primary feeding method will be used for analysis.

Time to first weaning
Time to first weaning is defined as the number of hours from start of the treatment until the first dose reduction.
An ANCOVA model based on log-transformed data will be performed to test the treatment effect as time to first weaning (hours).

The model will include treatment (CHF6563 and morphine) as a fixed effect and covariates for primary feeding method (formula/ any maternal breast- milk), Maternal primary opioid use (buprenorphine/ methadone / other), and maternal use of benzodiazepines, antidepressants or gabapentin (polypharmacy [yes/no]). The adjusted geometric mean in each treatment group, the adjusted ratio of geometric means between treatments, together with its 95% CI and associated p-value will be estimated by the model.

Requirement for adjunctive drug therapy (phenobarbital) for signs of NOWS
Only adjunctive drug therapy during the treatment period will be considered. Odds ratios and corresponding 95% CIs will be presented, based on logistic regression, adjusting for primary feeding method (formula / any maternal breast milk), maternal primary opioid use (buprenorphine /methadone / other), and maternal use of benzodiazepines, antidepressants or gabapentin (polypharmacy [yes/no]).

Total hours of treatment with adjunctive therapy (phenobarbital)
Total hours of treatment with adjunctive therapy is defined as the sum of time on each occasion when adjunctive therapy is required (since babies may require adjunctive therapy on separate occasions). For each

occasion requiring adjunctive therapy, the time of treatment is defined as the time of first dose until the last dose.
Total hours of treatment with adjunctive therapy will be analysed using an ANCOVA model. The model will include treatment (CHF6563 and morphine) as a fixed effect and primary feeding method (formula/any maternal breast- milk), maternal primary opioid use (buprenorphine/ methadone/ other), and maternal use of benzodiazepines, antidepressants or gabapentin (polypharmacy [yes/no]) as covariates. Babies not requiring adjunctive therapy will be included as 0 hours.

Requirement for rescue doses (CHF6563 or morphine)

Only rescue doses during the treatment period will be considered. Odds ratios and corresponding 95% CIs will be presented, based on logistic regression, adjusting for primary feeding method (formula / any maternal breast milk), maternal primary opioid use (buprenorphine /methadone / other), and maternal use of benzodiazepines, antidepressants or gabapentin (polypharmacy [yes/no]).

Number of rescue doses administered

Number of rescue doses administered will be analyzed using an ANCOVA model. The model will include treatment (CHF6563 and morphine) as a fixed effect and primary feeding method (formula / any maternal breast milk), maternal primary opioid use (buprenorphine / methadone / other), and maternal use of benzodiazepines, antidepressants or gabapentin (polypharmacy [yes/no]) as covariates. Babies not requiring rescue dose(s) will be included with a value of 0.

Percentage of total amount of active study drug which is from rescue doses

The percentage of total amount of active study drug which is from rescue doses will be analyzed using an ANCOVA model. The model will include treatment (CHF6563 and morphine) as a fixed effect and primary feeding method (formula / any maternal breast milk), maternal primary opioid use (buprenorphine / methadone / other), and maternal use of benzodiazepines, antidepressants or gabapentin (polypharmacy [yes/no]) as covariates. Babies not requiring rescue dose(s) of active study drug will be included with a value of 0.

Length of opioid related hospital stay

Length of opioid related hospital stay is defined as number of days from day of birth until 48 hours after the final dose of drug treatment for NOWS.
Length of opioid related hospital stay (days) will be analyzed using an ANCOVA model based on log-transformed data. will be performed to test the treatment effect as length of opioid-related hospital stay (days).

The model will include treatment (CHF6563 and morphine) as a fixed effect and primary feeding method (formula / any maternal breast milk), maternal primary opioid use (buprenorphine / methadone / other), and maternal use of benzodiazepines, antidepressants or gabapentin (polypharmacy [yes/no]) as covariates. The adjusted mean in each treatment group, the adjusted ratio of geometric means between treatments, its 95% CIs and associated p-value will be estimated by the model.

Incidence of relapse of NOWS, defined as experiencing recurrence of significant signs of withdrawal

Odds ratios and corresponding 95% CIs will be presented, based on logistic regression, adjusting for primary feeding method (formula/ any maternal breast milk), maternal primary opioid use (buprenorphine /methadone / other), and maternal use of benzodiazepines, antidepressants or gabapentin (polypharmacy [yes/no]). The odds ratio of incidence between treatment groups will be presented together with the 95% CI and corresponding p-value.

Incidence of readmissions, defined as readmission to hospital for NOWS relapse

Odds ratios and corresponding 95% CIs will be presented, based on logistic regression, adjusting for primary feeding method (formula/any maternal breast milk), maternal primary opioid use (buprenorphine

/methadone / other), and maternal use of benzodiazepines, antidepressants or gabapentin (polypharmacy [yes/no]). The odds ratio of incidence between treatment groups will be presented together with the 95% CI and corresponding p-value.

12.3.6 Pharmacokinetic variables

The relative low number of blood samples per baby, the opportunistic sampling strategy and the continuous variation of the administered dose prevent the application of standard non-compartmental analysis for the characterization of CHF6563 pharmacokinetics in the neonate population.
Instead, a population pharmacokinetic modelling approach will be applied. A separate analysis plan and report will be produced.

12.3.7 Safety variables

Adverse Events
Safety analysis will be based on Safety population. All adverse events starting on or after the time of first study drug intake will be classified as treatment emergent adverse event (TEAE). Any adverse events started after the informed consent signature and before the time of first study drug intake will be classified as pre-treatment adverse events.
The number of babies who experienced at least one TEAE, drug-related TEAE, serious TEAE, serious related TEAE, TEAE leading to study discontinuation, TEAE leading to death, and peri-dosing TEAEs will be summarized by treatment arm. Summaries will be presented overall (number and percentage of babies having at least one event, total number of events) and by system organ class and preferred term (number and percentage of babies having at least one occurrence of that event).
All adverse events will be listed.
Pre-treatment adverse event will be listed only.

The peri-dosing AEs are defined as adverse events occurring during or shortly after administration of study treatment, i.e. within 10 minutes from the start of study drug administration.

Vital signs
Vital signs will be summarized at each planned time point by means of descriptive statistics. At each timepoint when vital signs are collected, mean, min, max and standard deviation of the observed values and change from baseline will be presented, in addition to being listed.

Laboratory data
Sites will use local labs to obtain liver enzymes analysis-function testing. When consistent with site clinical practice, sites will use local labs to collect hematology and blood chemistry. The laboratory values and the change from baseline for continuous laboratory parameters will be summarized by descriptive statistics at each planned time point. All laboratory data will be listed with abnormal values flagged.

Head circumference (and percentile) and body weight (and percentile)
Head circumference (and percentile) and body weight (and percentile) and their corresponding changes from baseline will be summarized using descriptive statistics at each planned time point.

Additional Safety Variables
The following parameters collected only at the end of the treatment period will be listed only:

- Neurological and behavioral assessment

Analysis of safety variables collected at the 18-month follow up visit will be described in the SAP.

12.3.8 Interim analysis

A blinded sample size re-assessment (BSSR) will be performed when approximately 23-28 babies (40-50% of the planned sample size) have completed the treatment period. At this time, the overall variance based on

all completed patients (without knowledge or consideration of treatment arm) will be evaluated and the sample size may be increased if the variability is higher than anticipated beyond a certain threshold.

The BSSR may be adjusted for an assumed minimum effect size. The minimum effect size assumed for BSSR may be lower than the effect size assumed for the sample size calculation in order to avoid underestimation of the within-group variance. The BSSR will be restricted such that the sample size may be unchanged or increased, but not reduced, as a result of the BSSR.

The methodology planned for this BSSR has been shown to generally control type 1 error (Kieser and Friede, 2003). Therefore, no adjustment will be made to the end-of-study analysis, considering an alpha of 0.05.

13. ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD APPROVAL

The study proposal will be submitted to the Institutional Review Board in accordance with the local requirements.
The IRB shall give its opinion in writing clearly identifying the study number, study title and informed consent form approved, before the clinical trial commences.
A copy of all communications with the IRB will be provided to the Sponsor.
The Investigator should provide written reports to the IRB annually or more frequently if requested on any changes significantly affecting the conduct of the trial and/or increasing risk to the subjects (according to the requirements of each country).

14. REGULATORY REQUIREMENTS

The study will be notified to the Health Authorities (or authorized by) according to the legal requirements in each participating country.
Selection of the subjects will not start before the approval of the Institutional Review Board has been obtained and the study notified to Health Authorities (or authorized by).

15. INFORMED CONSENT

Informed consent must be written in a language understandable to the mothers/parent/legal guardians. It is the responsibility of the Investigator to obtain written consent from each mother/parent/legal guardian prior to any study related procedures taking place, by using the latest IRB approved version of the document.
Adequate time shall be given to the mother/parents of each neonate or from the neonate's legal representative to enquiry ask the PI about for any clarification needed and to consider his or her decision to participate to the trial.
If the parent and his/her legal representative are unable to read, the informed consent will be obtained in the presence of an impartial witness, e.g., a person independent of the study who will read the informed consent form and the written information for the neonate.
Consent must be documented by the parents/legal representative's dated signature. The signature confirms that the consent is based on information that has been understood. Moreover, the Investigator must sign and date the informed consent form.
Each signed informed consent must be kept on file by the Investigator. One copy must be given to the neonate's parents/legal representative.

16. SOURCE DOCUMENTS/DATA

16.1 Recording of source data

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

16.2 Direct access to source document/data

The Investigators or designated must permit trial-related monitoring, audits, Ethics Committee/Institutional Review Board review or regulatory inspection, providing direct access to source data/documents.

17. STUDY MONITORING

Monitoring will be performed by [redacted] who has been designated by Chiesi.
It is understood that the monitor(s) will contact and visit the Investigator/center before the study, regularly throughout the study and after the study had been completed, and that they will be permitted to inspect the various study records: case reports form, Investigator study file and source data, (source data is any data that is recorded elsewhere to the case report forms), provide independent that neonate confidentiality is respected.
The purposes of these visits are:

- to assess the progress of the study;
- to review the compliance with the study protocol;
- to discuss any emergent problem;
- to validate the contents of the CRFs against the source documents;
- to assess the status of drug storage, dispensing and retrieval.
- Prior to each monitoring visit, the Investigator or staff will record all data generated since the last visit on the case report forms. The Investigator and/or study staff will be expected to be available for at least a portion of the monitoring visit to answer questions and to provide any missing information.
- It is possible that the Investigator site may be audited by Sponsor personnel or regulatory national and/or international regulatory agencies during and after the study has been completed.

18. QUALITY ASSURANCE

The R&D Quality Assurance Department of Chiesi may perform an audit at any time according to the Sponsor's Standard Operating Procedures, in order to verify whether the study is being conducted in agreement with Good Clinical Practices and the protocol.

19. INSURANCE AND INDEMNITY

Chiesi holds and will maintain an adequate insurance policy covering damages arising out of Chiesi's sponsored clinical research studies.
Chiesi will indemnify the Investigator and hold him/her harmless for claims for damages arising out of the investigation, in excess of those covered by his/her own professional liability insurance, providing that the

drug was administered under his/her or deputy's supervision and in strict accordance with accepted medical practice and with the study protocol.
The Investigator must notify Chiesi immediately upon notice of any claims or lawsuits.

20. CONFIDENTIALITY

All study documents are provided by the Sponsor in confidence to the Investigator and his/her appointed staff. None of this material may be disclosed to any party not directly involved in the study without written permission from Chiesi.
The Investigator must assure the subject's anonymity will be maintained. The Investigator will keep a separate list with at least the initials, the subject's study numbers, names, and (optional) addresses and telephone numbers. The Investigator will maintain this for the longest period of time allowed by his/her own institution and, in any case, until further communication from Chiesi.

21. PREMATURE TERMINATION OF THE STUDY

Both the Sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, the procedures for an early termination or temporary halt will be arranged after consultation by all involved parties.
The Sponsor should submit a written notification to the Regulatory Authority concerned and Ethics Committee/Institutional Review Board providing the justification of premature ending or of the temporary halt.

22. CLINICAL STUDY REPORT

At the end of the trial a summary of the clinical study report will be provided to all Ethics Committees/Institutional Review Boards, to the Competent Authority of the EU Member State or the US concerned and to Investigators.

23. RECORD RETENTION

After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file.
Regulations require that essential documents must be retained for at least two years after the final marketing approval in an ICH region or until two years have elapsed since the formal interruption of the clinical development of the product under study. It is the responsibility of the Sponsor to inform the Investigator of when these documents can be destroyed. The Investigator must contact Chiesi before destroying any trial-related documentation. In addition, all subjects' medical records and other source documentation will be kept for the maximum time permitted by the institution.

24. PUBLICATION OF RESULTS

Chiesi is entitled to publish and/or present any results of this study at scientific meetings, and to submit the clinical trial data to national and international Regulatory Authorities. Chiesi furthermore reserves the right to use such data for industrial purposes. In the absence of a Study Steering Committee, Investigators will inform Chiesi before using the results of the study for publication or presentation and agree to provide the Sponsor with a copy of the proposed presentation. Data from individual study sites must not be published separately. Negative as well as positive results should be published or otherwise made publicly available according to the relevant regulatory requirements.

25. REFERENCES

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APPENDIX 1 - Approval of the protocol by clinical investigator(s)

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

Product: CHF6563

Pharmaceutical Form: sublingual

Approval of Clinical Study Protocol by the Investigator:

I have carefully read this protocol and I agree that it contains all the necessary information required to conduct the study and I agree to conduct it as described.

I understand that this trial will not be initiated without Ethics Committee/Institutional Review Board approvals and that the administrative requirements of the governing body of the institution will be fully complied with.

Written informed consent will be obtained from the mother/parents/legal guardians and appropriately documented, prior to their enrolment in the study.

The undersigned agrees that the trial will be carried out in conformity with the Declaration of Helsinki (as applicable, with attention being drawn to Section concerning freely given consent), ICH E6 Good Clinical Practices and with all the other local laws and regulations relevant to the use of new and approved therapeutic agents in subjects.

Investigator's Name: _____,MD

Centre No. :_____

_____ _____

Signature Date

Chiesi Farmaceutici S.p.A.
Via Palermo 26/A
43122 Parma - Italy

APPENDIX 2 – Maternal Screening Questionnaire

A Phase 2, Multicenter, Double-blind, Double-dummy, Randomized Study to Evaluate the Efficacy, Safety and Pharmacokinetics of CHF6563 in Neonates with Neonatal Opioid Withdrawal Syndrome

Maternal Screening Questionnaire

Clinical Study Code No.: CLI-06563AA1-02	Version No.:6.0
IND No.: 131,339	Date: 18 March 2021

[redacted]

A Phase 2, Multicenter, Double-blind, Double-dummy, Randomized Study to Evaluate the Efficacy, Safety and Pharmacokinetics of CHF6563 in Neonates with Neonatal Opioid Withdrawal Syndrome

Maternal Screening Questionnaire

Name: _____Age ___ Number of Weeks Pregnant _____

[redacted]

[redacted]	[redacted]	[redacted]
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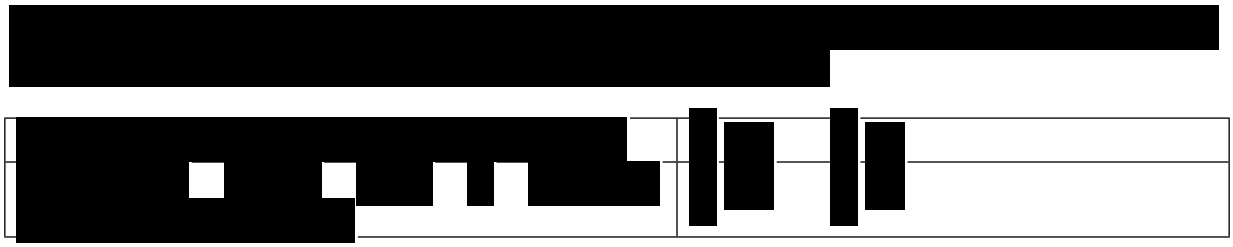

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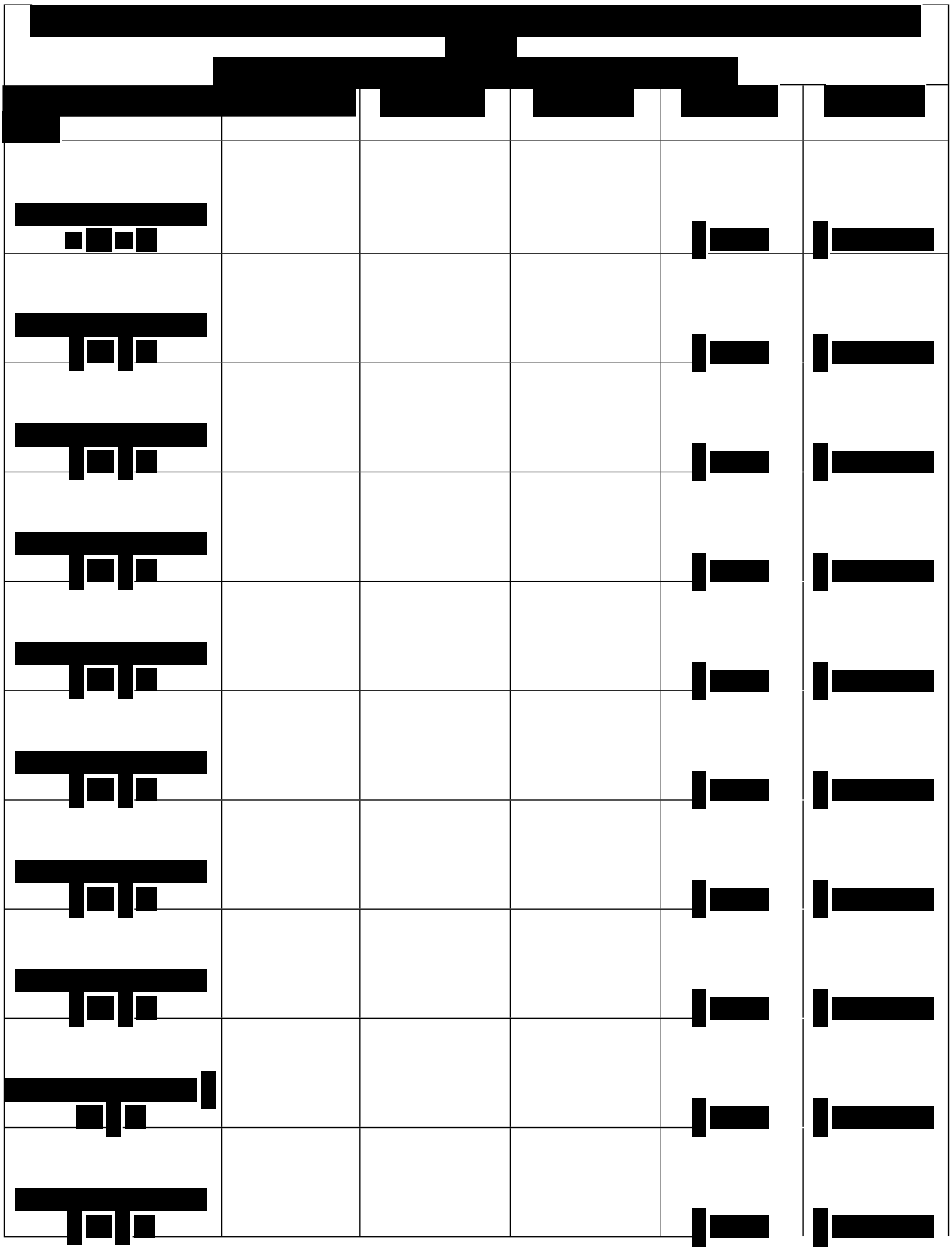

APPENDIX 3 – List of PSYCHOTROPIC DRUGS

The following drugs have been associated to increased relative risk of neonatal withdrawal among women who were co-exposed to opioids (Huybrechts et al, Risk of neonatal drug withdrawal after intrauterine co-exposure to opioids and psychotropic medications: cohort study. BMJ 2017 Aug 2;358:j3326). This table is to be used for the identification of stratification criterion #3 (*Maternal concurrent use of benzodiazepines, antidepressants or gabapentin (polypharmacy [yes/no])*, see *6.5 Treatment allocation*).

Antidepressants	
Selective serotonin reuptake inhibitors	citalopram, escitalopram. fluoxetine, fluvoxamine, paroxetine, sertraline
Serotonin and norepinephrine reuptake inhibitors	duloxetine, venlafaxine, desvenlafaxine, levomilnacipran
Tricyclic antidepressant	amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine
others	isocarboxazid, phenelzine, tranylcypromine, bupropion, mirtazapine, nefazodone, trazodone, vilazodone, vortioxetine
Benzodiazepines	
Long-acting	chlordiazepoxide, clobazam, clorazepate, diazepam, flurazepam, quazepam
Short-acting	alprazolam, midazolam, triazolam, clonazepam, estazolam, lorazepam, oxazepam, temazepam
Gabapentin	

APPENDIX 4 – Finnegan Neonatal Abstinence Scoring Tool (FNAST)

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