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Title:

A Safety Study of Intravenous Infusion of Bone Marrow Mesenchymal Stem Cell-derived Extracellular Vesicles (UNEX-42) in Preterm Neonates at High Risk for Bronchopulmonary Dysplasia

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ABBREVIATIONS AND DEFINITIONS

AE	Adverse event
ATC	Anatomical Therapeutic Chemical
BPD	Bronchopulmonary dysplasia
eCRF	Electronic Case Report Form
GA	Gestational age
IV	Intravenous
PMA	Postmenstrual age

1 PREFACE

This Statistical Analysis Plan provides further details of the planned analyses for Study UNX-BP-101, as presented in the study protocol.

1.1 CHANGES TO PLANNED ANALYSES

This study was terminated early by United Therapeutics Corporation. The first dose cohort was partially enrolled with 3 subjects randomized prior to study termination. Therefore, only listings will be provided. No summary or inferential analyses will be provided.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 OBJECTIVES

2.1.1 Primary Objective

To assess the safety and tolerability of intravenous (IV) infusion of UNEX-42 in infants born at <27 weeks of gestational age (GA) and exhibiting respiratory distress.

2.1.2 Secondary Objectives

To assess the effect of UNEX-42 on the following:

1. Incidence and severity (mild, moderate, severe) of bronchopulmonary dysplasia (BPD) or death at 36 weeks postmenstrual age (PMA)
2. Short-term outcomes including oxygen utilization and ventilation exposure in the first 28 days after treatment.
3. Long-term outcomes up to 1 year corrected age.

2.2 ENDPOINTS

2.2.1 Primary Endpoints

The primary endpoints are the following safety assessments during the Post-treatment Phase:

- Incidence of treatment-emergent adverse events (AEs)
- Incidence of all-cause mortality through Week 36 PMA
- Incidence of treatment-related AEs
- Absolute and changes from Baseline in laboratory parameters
- Absolute and changes from Baseline in vital signs

2.2.2 Secondary Endpoints

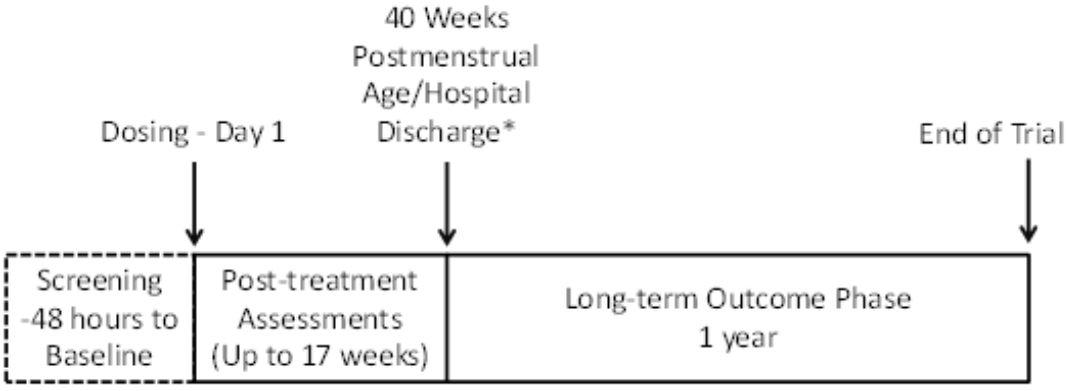
The secondary endpoints are the following assessments:

- Incidence of BPD or death at 36 weeks PMA
- Severity of BPD (mild, moderate, severe) at 36 weeks PMA
- Complications of prematurity during the Post-treatment Phase (diagnosis of sepsis, pneumothorax, clinically significant patent ductus arteriosus requiring treatment or ligation, necrotizing enterocolitis requiring treatment or surgery, intraventricular hemorrhage [including highest grade], periventricular leukomalacia, and retinopathy of prematurity [including stage])

3 STUDY DESIGN

This is a multicenter, placebo-controlled, randomized, dose escalation, safety, and tolerability study of UNEX-42 in infants born at <27 weeks of GA at high risk for BPD. UNEX-42 will be administered via IV infusion to 3 cohorts at 20, 60, and 200 pmol phospholipid/kg body weight. Within each cohort, eligible subjects will be randomly assigned to receive either UNEX-42 or placebo treatment (2:1 allocation ratio). A schematic presentation of the study design is presented in Figure 3-1.

Figure 3-1 Schematic of Study Design for an Individual Subject



*Subjects that discontinue the study prematurely should have the 40 Weeks Postmenstrual Age/Hospital Discharge assessments performed if possible. Subjects that complete the 40 Weeks PMA Assessment or are discharged from hospital will continue into the Long-term Outcome Phase.

Study assessments will occur during the study at the following time points: Screening, Baseline, 24 and 72 hours postdose, 7 days postdose, weekly until 35 weeks PMA, 36 weeks PMA, and 40 weeks PMA/hospital discharge during the Post-treatment Phase. For subjects that complete the Post-treatment Phase, the Long-term Outcome Phase will occur at 6 months (phone contact) and 1 year of corrected age (site visit).

4 RANDOMIZATION

The study will be randomized 2:1 UNEX-42 to placebo. Within each dose cohort, subjects will be randomly allocated to receive UNEX-42 or placebo through the Interactive Response Technology using a centrally administered block randomization.

5 SEQUENCE OF PLANNED ANALYSES

Unblinding of all data from the Post-treatment and Long-term Outcome Phases will occur after the database has been locked.

6 SAMPLE SIZE CONSIDERATIONS

No formal sample size calculations were performed.

7 ANALYSIS POPULATIONS

No analysis populations will be specified. All enrolled subjects will appear in the listings unless otherwise specified.

8 GENERAL CONSIDERATIONS FOR DATA ANALYSES

All the data collected in the electronic Case Report Form (eCRF) will be listed. In general, listings will be sorted by subject number and scheduled assessment (if applicable). Listings will include assessment date, assessment time (if available), study day, and all relevant data collected in the eCRFs. For data collected on a fixed schedule, the assessment identifier or the nominal time point will also be included on the listing. Repeat or redundant observations within an assessment window and observations that do not fall within any predefined assessment window will be flagged in these listings.

8.1 PREMATURE DISCONTINUATION AND MISSING DATA

A subject's parent/guardian may voluntarily withdraw the subject, or the subject may be withdrawn from the study and/or study drug by the Investigator at any time for reasons including, but not limited to, the following:

- The subject's parent/guardian wishes to withdraw the subject from further participation.
- Any medically appropriate reason, in the opinion of the Investigator, or significant protocol violation likely to undermine the validity of results.
- The Sponsor terminates the study.

All available data from all subjects will be used as detailed in this analysis plan. No imputation for missing data will be performed.

8.2 MULTIPLE COMPARISONS AND MULTIPLICITY

No inferential analyses are planned.

9 STUDY POPULATION

Unless otherwise specified, all subjects will appear in the listings.

9.1 SUBJECT ACCOUNTABILITY

The listing of subject disposition will include the subject number, treatment group, date/time of randomization, dates of last Post-treatment Phase and last Long-term Outcome Phase assessments, reason for study discontinuation, and dates of hospital discharge and neonatal intensive care unit discharge.

9.2 ELIGIBILITY CRITERIA

The status of the entry criteria will be listed for all subjects. The listing will include the date of the initial screening assessment, whether all eligibility criteria were met (Yes/No), and a list of any specific entry criteria not met.

9.3 PROTOCOL DEVIATIONS

Protocol deviations will be documented throughout the study. All deviations will be reviewed by the clinical team and those that might affect subject safety or efficacy outcomes will be considered 'Major.' All other deviations will be classified as 'Minor.' Protocol deviations will

be listed, including the date of the deviation, the type of deviation, the severity of the deviation (Major/Minor), and a description of the deviation.

9.4 OTHER DESCRIPTIONS OF STUDY POPULATION

9.4.1 Demographics

The listing of subject demographics will include the subject number, treatment group, date of birth, postnatal age (days), GA at birth (weeks/days), sex, race, and ethnicity.

9.4.2 Maternal History

The listing of maternal history will include the subject number, treatment group, maternal age, maternal race, maternal ethnicity, reason for delivery, mode of delivery, receipt of IV magnesium during pregnacy, diagnosis of chorioamnionitis during pregnancy, and any recorded medications received during pregnancy/delivery.

9.4.3 Infant Measurements

The listing of infant measurements will include the subject number, treatment group, assessment date, weight (g), length (cm), and head circumference (cm).

9.4.4 Infant Medical Conditions

The listing of infant medical conditions will include the subject number, treatment group, medical condition, date started, date stopped, and whether the medical condition was ongoing at the end of the study.

9.4.5 Concomitant Medications

All concomitant medications recorded on the eCRF will be mapped to a standard name and Anatomical Therapeutic Chemical (ATC) Levels 1 to 4 using the World Health Organization WHODrug Global drug dictionary. The ATC Levels 2 and 4 and verbatim term of all concomitant medications will be listed for all subjects. This listing will include the date started (or indication that drug was ongoing at randomization), date discontinued (or indication that drug was ongoing at end of Post-treatment Phase), and the condition(s) treated/indication(s). If ATC Level 4 is not available for a medication, ATC Level 3 will be substituted. If ATC Level 3 is not available, ATC Level 2 will be substituted. If ATC Level 2 is not available, ATC Level 1 will be substituted.

10 EFFICACY ANALYSES

Only listings will be provided. No summaries or inferential analyses will be conducted.

10.1 BPD ASSESSMENT

The listing for the BPD assessment at 36 weeks PMA will include the subject number, treatment group, date of assessment, whether BPD occurred, the severity of BPD (mild, moderate, severe), and predefined complications of prematurity during the Post-treatment Phase (diagnosis of sepsis, pneumothorax, clinically significant patent ductus arteriosus requiring treatment or ligation, necrotizing enterocolitis requiring treatment or surgery, intraventricular hemorrhage [including highest grade], periventricular leukomalacia, and retinopathy of prematurity [including stage]). The dates started/stopped will also be included for the predefined complications of prematurity, if available and indication of ongoing if known.

Additionally, a listing of Respiratory Severity Score will be provided. It will include the subject number, treatment group, date/time of assessment, Respiratory Severity Score, mean airway pressure, and fraction of inspired oxygen.

10.2 POST-NATAL STEROIDS

The listing of post-natal steroids will include the subject number, treatment group, steroid taken, date started or ongoing at randomization, date stopped or ongoing at end of Post-treatment Phase,dose, form, unit, frequency, route, and condition treated/indication.

10.3 GENERAL HEALTH ASSESSMENT

The general health assessment listing will include the subject number, treatment group, nominal time point, date/time, person interviewed, and the response to each question at the assessment.

11 SAFETY ANALYSES

The safety data collected in this study will be presented in listings. No summaries or inferential statistical analyses are planned. Assessments are treatment-emergent if they occur on or after the infusion of study drug.

11.1 EXTENT OF EXPOSURE

The exposure listing will include the subject number, treatment group, infusion start/stop dates and times, flow rate, and any other available details associated with the infusion.

11.2 ADVERSE EVENTS

All AEs will be coded to the appropriate Preferred Term and System Organ Class using the Medical Dictionary for Regulatory Activities. AEs will be listed by treatment group including all details recorded on the eCRF plus an indicator of whether the event was treatment emergent. The AE listings will include the AE verbatim term and its corresponding Preferred Term and System Organ Class.

11.3 DEATHS

The listing of all deaths will include the subject number, treatment group, date of death, and cause of death for all deaths occurring between administration of study drug and the end of study, or within 4 weeks after study drug infusion, if the subject prematurely terminates.

11.4 CLINICAL LABORATORY PARAMETERS

The listing of laboratory parameters will include the subject number, treatment group, nominal time point, date/time, and the analyte value.

11.5 VITAL SIGNS

The listing of vital signs will include the subject number, treatment group, nominal time point, date/time, diastolic blood pressure, systolic blood pressure, heart rate, respiratory rate, and oxygen saturation at all collected assessment time points.

11.6 RESPIRATORY SUPPORT

A listing for respiratory support will include the subject number, treatment group, type of respiratory support, percent of oxygen at start and stop, and start date and stop date or ongoing at 40 weeks/hospital discharge.

12 APPENDICES

12.1 LIST OF LISTINGS

Listing Number	Listing Title
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