STATISTICAL ANALYSIS PLAN

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STATISTICAL ANALYSIS PLAN

APPROVAL SIGNATURES

(Final v. 2 November 20, 2024)

An Open-Label Extension of the HOPE-2 Duchenne Muscular Dystrophy Trial (HOPE-2-OLE)

REVISION HISTORY

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Explanation
AE	Adverse Event
ANCOVA	Analysis of Covariance Analysis
ATC	Anatomic Therapeutic Chemical
BMI	Body Mass Index
CDC	Cardiosphere-Derived Cells
CI	Confidence Interval
DMD	Duchenne Muscular Dystrophy
DSMB	Data Safety Monitoring Board
ECC	External Comparator Cardiac
ECP	External Comparator PUL 2.0 Combined Total
ET	Early termination
IP	Investigational Product
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
PT	Preferred Term
PUL	Performance of the Upper Limb
SD	Standard Deviation
SOC	System Organ Class
SOP	Standard Operating Procedures
TEAE	Treatment-Emergent Adverse Events
TLF	Tables, Listings and Figures
WHODrug Global	World Health Organization Drug Global Dictionary

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1 STUDY OVERVIEW

Duchenne muscular dystrophy (DMD) is a severe, X-linked, progressive disease that affects approximately 1 in 3600 to 9200 male births. It is caused by mutations in the dystrophin gene, which results in the absence of or non-functional dystrophin protein.

DMD symptoms begin in early childhood, with degeneration occurring progressively in the skeletal musculature and, ultimately, in the heart and respiratory muscles, resulting in premature death. Progressive weakness and muscle atrophy caused by degenerating muscle fibers begin in the lower extremities and pelvis before spreading into the upper extremities. Other symptoms include loss of some reflexes, a waddling gait, frequent falls, difficulty when rising from a sitting or lying position or when climbing stairs, changes to overall posture, and impaired breathing. Many children precipitously lose the ability to run or jump. The atrophied muscles, in particular the calf muscles, and less commonly, muscles in the buttocks, shoulders, and arms, may be enlarged by an accumulation of fat and connective tissue, causing them to look larger and healthier than they actually are ("pseudohypertrophy"). Bone thinning and scoliosis are common. Ultimately, a wheelchair becomes necessary, in most cases between 12 to 15 years of age.

No pharmacologic or biological therapies proven to stop or reverse the progression of DMD have been approved in the United States. Disease management consists primarily of preventive measures, as well as active interventions to address the primary and secondary aspects of the disorder.

Deramiocel is intended to be used as a therapy to improve the morbidities associated with DMD and, thus, to improve or prevent decline in muscle function through its composite immune-modulatory, anti-fibrotic, and regenerative mechanisms of action. [redacted] This clinical evidence suggests that deramiocel has the potential to address unmet medical needs for patients with DMD.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary

The primary objective of this trial is to provide deramiocel, previously referred to as CAP-1002, to subjects who were enrolled in the HOPE-2 trial and completed the 12-months of follow-up.

2.1.2 Secondary

The secondary objectives of this trial are to assess the safety and efficacy of intravenous (IV) administration of deramiocel every three months for a total of up to 20 doses administered over a period of approximately 60 months.

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2.2 Study Endpoints

2.2.1 Primary Safety Endpoint

The ***primary safety endpoint*** is the incidence and severity of all treatment-emergent adverse events (TEAEs) from baseline through Month 12.

2.2.2 Primary Efficacy Endpoint

The ***primary efficacy endpoint*** is the change from baseline at the 12-month timepoint in functional capacity as assessed by the PUL 2.0 Combined Total Score (high-level + mid-level + distal level dimensions).

2.2.3 Secondary Safety Endpoint

The secondary safety endpoint is the incidence and severity of all treatment-emergent adverse events from baseline through Month 60.

2.2.4 Secondary Efficacy Endpoints

The ***secondary efficacy endpoints*** include the change from baseline (PUL 2.0: HOPE-2-OLE Baseline, Cardiac MRI: HOPE-2 Screening Baseline) through Month 60 for the following:

- Upper body functionality using the PUL 2.0 assessment (i.e. Upper level PUL:2.0) at Months 24, 36, 48, and 60
- Distal level PUL 2.0 for subgroup of subjects with entry level PUL 2.0 scores of 2 and 3, at Month 12, 24, 36, 48, and 60
    - Entry level at baseline of HOPE-2-OLE
- Mid-level PUL 2.0 for subgroup of subjects with entry level PUL 2.0 scores of 4 and 5, at Month 12, 24, 36, 48, and 60
    - Entry level at baseline of HOPE-2-OLE
- Left Ventricular Ejection Fraction (LVEF (i.e. Cardiac MRI) at Month 24, 36, 48, and 60.
- Left Ventricular End Systolic Volume, Indexed (Cardiac MRI) at Month 24, 36, 48, and 60.
- Left Ventricular End Diastolic Volume, Indexed (Cardiac MRI) at Month 24, 36, 48, and 60
- Other cardiac parameters, including but not limited to mass, unindexed volumes, and end diastolic and end systolic wall thickness at 24, 36, 48, and 60

2.2.5 Exploratory Safety Endpoints

Exploratory safety endpoints include the analysis of the elevation of HLA antibodies against the donor cells (i.e., DSAs) to determine a level considered clinically significant using mean florescence intensity [MFI].

2.2.6 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include retrospective standard-of-care patient data from HOPE-2 to the beginning of HOPE-2-OLE and/or an external comparator pertaining to the following at appropriate timepoints:

- Upper body functionality (i.e., the PUL 2.0 Combined Total Score)
- Left ventricular Ejection fraction (LVEF) (i.e., cardiac MRI)

3 STUDY DESIGN

This Phase 2, multicenter, open-label extension trial will provide deramiocel to subjects who completed 12 months of follow-up in the HOPE-2 trial. The trial will assess the safety and efficacy of deramiocel, administered up to 20 IV infusions, each separated by 3 months. All subjects will undergo a targeted screening assessment within 30 days prior to first infusion, unless otherwise stated, to confirm eligibility based on protocol inclusion and exclusion criteria.

Administration of deramiocel (Day 1) should occur within a maximum of 30 days following confirmation of eligibility; if a delay of more than 30 days between enrollment and deramiocel administration is unavoidable, a conversation between the investigator and medical monitor should occur to determine the need for repeat screening prior to infusion.

Subjects will complete trial assessments at Screening; Day 1; Months 3, 6, 9, 12 (±14 days, each), 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, and 60 (±21 days, each). Baseline safety and efficacy assessments will be conducted prior to first infusion on Day 1. For subsequent infusions at Months 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, and 57 safety and efficacy assessments will be conducted prior to infusion, unless otherwise specified.

All IV infusions will be conducted in an outpatient setting at the investigative site on Day 1 and at Months 3, 6, and 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, and 57 trial visits. Prior to each investigational product (IP) infusion, medication(s) will be administered to the subject as determined by the Investigator based on the pre-treatment guidelines and/or institutional protocols to minimize the risk of potential severe allergic reactions, such as anaphylaxis. Subjects will be observed in the outpatient setting for at least 2 hours after infusion and then discharged on the same day if medically cleared by the site Investigator. If clinically indicated, an unscheduled in-person visit will be performed at the investigative site, with targeted assessments based on presentation of signs and symptoms after any infusion.

The schedule of assessments for the study is presented in Section 9.1 (Appendix A).

3.1 Sample Size

Thirteen subjects who were enrolled in and completed the 12-month randomized period in the HOPE-2 trial will be enrolled in this trial.

3.2 Deramiocel Treatment

This is not a randomized study. All subjects will receive open-label treatment with deramiocel (150M cardiosphere-derived cells [CDCs]) administered as an IV infusion on Day 1 and at Months 3, 6, and 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, and 57.

3.3 Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will review data and advise Capricor about any safety matters throughout the trial. The objectives, roles, and responsibilities of the DSMB, as well as the format and frequency of meetings, will be documented in the DSMB charter.

3.4 Interim Analyses

No formal interim analyses are planned.

4 GENERAL STRATEGIES FOR DATA PRESENTATION

Data with qualifiers (e.g., "<") will be listed with the qualifier but will be summarized without the qualifier. Subject data listings will include all data that are collected for all subjects. Listings will be sorted by site, subject number, nominal visit, date, and time (as applicable), unless otherwise indicated.

Categorical analyses will be summarized using counts and percentages. Percentages will be based on the number of subjects in the analysis set for whom there are non-missing data, unless otherwise specified. Continuous variables, including change from baseline, will be summarized using descriptive statistics [n, mean, standard deviation (SD), median, minimum, maximum].

All analyses will be performed using SAS v 9.3 or higher (SAS Institute, Inc, Cary, North Carolina, USA). Validation and quality control of the tables, listings and figures (TLFs) will follow the appropriate Innovative Analytics standard operating procedures (SOPs).

4.1 Study Phases

There will be three phases of the overall HOPE-2 study identified in the analysis, defined as follows:

1. **Main Phase**: The double-blind HOPE-2 study which followed subjects from baseline through 12 months of follow-up. Twenty subjects completed this study. Of these 20 subjects, 13 enrolled in the HOPE-2-OLE study.
2. **Gap Phase:** The gap period, approximately 1 year for each of the 13 subjects, between the end of HOPE-2 12-month visit and the Baseline visit of the OLE Phase.
3. **OLE Phase:** The unblinded open-label extension study (HOPE-2-OLE) described in this SAP and cited protocol, consisting of 13 subjects all treated with deramiocel for up to 57-months.

4.2 Treatment Groups

The treatment group to be presented will be composed of all subjects enrolled in this open label study. All subject in this study were assigned to receive deramiocel. The original treatment group (HOPE-2 Phase 2 study) for each of these subjects also will be considered. In addition, External Comparator (EC) data will be utilized to further examine the PUL 2.0 Combined Total Score and selected cardiac MRI parameters, labeled as ECP and ECC, respectively.

4.3 Study Day

The day of first IP administration is defined as Day 1. All other study days will be labeled relative to Day 1. Thus, study day for a particular event date on or after Day 1 is calculated as: *(Date of event – Date of first IP administration + 1)*. An event that occurs prior to Day 1 is calculated as: *(Date of event – Date of first IP administration)*.

The duration of an event will be calculated as *(Event end date – Event start date + 1)*. Day 0 will not be used.

The baseline value for each subject is the last non-missing value that is obtained prior to the time of the first IP administration on Day 1.

4.4 Handling of Dropouts or Missing Data

Subject-level listings will present data as reported. Missing or partially missing dates that are required for date-dependent definitions (e.g., TEAEs, concomitant medications) will be assumed to be the most conservative date possible.

An adverse event (AE) with a completely missing start date will be considered treatment-emergent; similarly, an AE that started the same month and year as IP administration, but with a missing start day, will be considered treatment-emergent.

When the PUL 2.0 Combined Total Score [high-level (shoulder) + mid-level (elbow) + distal level (wrist and hand] is calculated, there are subjects who cannot do the High-Level Shoulder regional assessment due to incapacity. In cases where sites left this subcategory blank rather than entering a 0, a 0 will be entered for analysis to permit calculation of the total. It should be noted that a higher score indicates higher functioning thus allowing a 0 for calculation purposes still reflects the overall incapacity of the subject.

Modest imputation of missing data is planned when modelling; this is to linearly impute missing item scores from the PUL 2.0, when those item scores are observed before and after the missing visit.

Medical history with missing stop dates will be considered ongoing. Medications with missing stop dates will be considered as concurrent use during the study and will be counted in the summary table of concomitant medications unless the start date is after the last IP administration.

Data from any subject who early terminates (ET) will be treated as follows:

- Map ET data to a scheduled visit according to the protocol defined windows (See Appendix A Section 9.1)

- If the ET data does not fall in any visit window, the ET data will be considered to have been collected at an unscheduled visit and excluded from analysis and summary tables.

4.5 Multiplicity

There are no pre-specified test hypotheses or assignments of statistical significance to study results requiring a consideration of adjustments for multiple testing.

4.6 Analysis Populations

The following analysis populations will be defined.

Enrolled Population: The enrolled population will include all subjects who signed the informed consent form and/or given assent.

Safety Population: The safety population will be defined as all subjects who received any amount of IP. All analyses will be based on the Safety Population, unless specified otherwise

For all efficacy analyses defined in this document, the *Safety Population* will be utilized.

Efficacy analyses combining HOPE-2-OLE data with either External Comparator for the PUL 2.0 Combined Total (ECP) or External Comparator for Cardiac (ECC) will use Safety Population for the HOPE-2-OLE subjects, and all subjects provided by ECP or ECC, unless specified otherwise

4.7 Subgroup Analyses

For select cardiac parameters, a subgroup analysis will be performed for subjects with >45% LVEF at baseline.

5 STUDY POPULATION PARAMETERS

5.1 Eligibility and Informed Consent

Eligibility and informed consent parameters will be listed for the enrolled population and will include date of informed consent/assent, version of the HOPE-2-OLE protocol under which the subject was enrolled, and inclusion and/or exclusion criteria that were not met.

The number of subjects who met all screening eligibility criteria and reasons for screen failure will be summarized for the enrolled population.

5.2 Protocol Deviations

Protocol deviations will be listed for the safety population and may include, but not be limited to, the following categories:

- Visit not done or out-of-window
- Assessment not completed or out-of-window
- Inclusion/exclusion

- Informed consent/assent
- IP administration

The number and percentage of subjects with at least 1 protocol deviation and the number and percentage of subjects with at least 1 protocol deviation in a deviation category will be summarized. Likewise, the number and percentage of subjects with at least 1 major protocol deviations will be tabulated.

5.3 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized for the safety population. Demographic characteristics will consist of sex, ethnicity, and race, as collected in the preceding HOPE-2 trial, and age in years at HOPE-2 OLE baseline.

Baseline characteristics will include ulna length, height, weight, body mass index (BMI), baseline PUL 2.0 entry item score, and baseline PUL 2.0 entry item score binary stratification (2, 3 vs 4, 5), where entry item score refers to the baseline OLE score, and length of Gap Phase in days.

Subject height will be calculated from the subject's ulna length: Height (cm) = [4.605 x Ulna Length (cm)] + [1.308 x Age (years)] + 28.003.

5.4 General Medical History

General medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 23.1. General medical history data will include the new relevant and significant medical history between the completing the HOPE-2 trial and the start of the HOPE-2-OLE trial.

Medical history will be listed and summarized for the safety population. The summary will be presented by MedDRA System Organ Class (SOC) and Preferred Term (PT). At each level of subject summarization, subjects who experience more than 1 medical history PT within an SOC will be counted only once in the SOC.

5.5 DMD Medical History

The following DMD medical history will be listed and summarized for the safety population:

- Age at diagnosis (years),
- Age at first use of chronic glucocorticoids (years),
- Loss of stair climb and age at loss of stair climb (years),
- Loss of stair descend and age at loss of stair descend (years),
- Use of a walker and age at first walker use (years),
- Part-time use of a manual/power wheelchair or scooter and age at first part-time use of a manual/power wheelchair or scooter (years),
- Transition to full-time use of a manual/power wheelchair or scooter and age at first full-time use of a manual/power wheelchair or scooter (years),

- Start of non-invasive ventilatory support and age at non-invasive ventilatory support started (years),
- Use of a mechanical cough assist device and age at first mechanical cough assist device use (years),
- History of spine surgery,
- History of symptomatic heart failure and age at first symptoms of heart failure (years), and
- History of medical (non-surgical) hospitalizations.

5.6 Prior and Concomitant Medications

Prescription and over-the-counter medication use will be coded to drug class, preferred drug name, and generic/trade drug name using the World Health Organization Drug Global (WHODrug Global) dictionary, version September 2020. A full medical chart review will be conducted in order to reconcile cardiac and systemic steroid medications received by subjects either prior to or on the HOPE-2 study with records of prior cardiac and systemic steroid medications on the HOPE-2 OLE study.

Frequencies and percentages of subjects in the safety population who report or receive any prior and/or concomitant medications will be displayed and listed together by WHODrug Global Anatomic Therapeutic Chemical (ATC) Level 2 and preferred name. In addition, systemic cardiac medication (omitting supplements), systemic steroids, and pre-treatment (pre-infusion) steroids medications will be summarized and listed separately. Systemic cardiac medications will be tabulated and listed by therapeutic subgroup (i.e., ATC Level 2) and preferred name, while systemic and pre-treatment steroids will be tabulated and listed by preferred name.

At each level of subject summarization, subjects who report use of one or more medication within that level will be counted once for that level.

5.7 Planned Medical/Surgical Procedures

All reported elective medical and/or surgical procedures (e.g., wisdom tooth extraction) that are not the result of an AE will be displayed for the safety population in a subject listing. For each procedure, the type of procedure, indication, and start/end date will be reported.

Any administered medication(s) related to the planned medical/surgical procedure(s) will be captured as a concomitant medication(s).

5.8 IP Administration

Details of IP administration will be summarized and listed for the safety population. The number of subjects who complete the IP infusion at each visit will be summarized. This is defined as subjects who receive (without interruption or syringe pump interrupted and restarted) both IP syringe administrations. For each visit and each IP syringe administration, the total dose delivered (mL) from both the first and second IP syringes, the number of subjects who receive the contents of both IP syringes, the reasons administration of both IP syringes was not completed, duration of IP administration (minutes), and total dose of IP syringe delivered (mL)

will be summarized. In addition, for the second IP syringe, the reasons the second IP syringe was not administered will also be summarized.

5.9 Subject Study Progress

A listing of study progress by subject will show dates of per-protocol study visits and unscheduled visits. The number of subjects who complete each visit will be summarized.

5.10 Subject Disposition

All screen failures will be listed, along with the primary reason for screen failure, for the enrolled population.

Subject disposition will be summarized for the safety population. The number of subjects who complete the study, the number of subjects who discontinue from the study, and the primary reason for discontinuation will be summarized.

6 EFFICACY ANALYSES

Listings and summaries of the efficacy parameters will be prepared for the Safety population, unless indicated otherwise, and summarized as described below for each efficacy parameter. This is an open-label extension study with a specified hierarchical testing order; however, for descriptive purposes, p-values will be calculated for each outcome even if the step in the hierarchy is not met. There will be no adjustment for multiplicity of analyses.

6.1 PUL Scale

The PUL 2.0 was designed specifically for assessing upper limb function in ambulant and non-ambulant DMD patients. All the tasks included in the PUL were selected to address patient-prioritized activities of daily living that are typical, regardless of age. The PUL includes an entry item to define the starting functional testing level for a subject. The remaining PUL items are divided into 3 regional dimensions: high-level (shoulder), mid-level (elbow), and distal level (wrist and hand). Trial subjects will complete testing for PUL 2.0 in the same preferred arm throughout the course of the trial.

All observed values will be listed. Observed totals and changes from baseline for each dimension [high-level (shoulder), mid-level (elbow), distal level (wrist and hand)] will also be listed.

6.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the change from baseline (Day 1) to Month 12 in the PUL 2.0 Combined Total Score (high-level + mid-level + distal level dimensions). Observed and change-from-baseline values will be summarized (n, mean, SD, minimum, and maximum). The 95% confidence intervals (CI) for the mean estimates also will be displayed.

To place the change from baseline (Day 1) for the PUL 2.0 Combined Total Score in context of the preceding HOPE-2 study and the Gap Phase, the following observed and change from baseline values, where not already tabulated, will be summarized (n, mean,

SD, minimum, and maximum) along with the 95% confidence intervals (CI) for the mean estimates. Figures will be provided for mean change for the four scenarios below.

- Non-treatment mean change HOPE-2 vs. Gap Phase: Change from the HOPE-2 baseline to Month 12 HOPE-2 [Main Phase] for the subjects in OLE study who were placebo subjects in HOPE-2 study and for these same subjects the change from Month 12 HOPE-2 to baseline (Day 1) HOPE-2-OLE [Gap Phase].
- On-treatment mean change HOPE-2 vs. HOPE-2-OLE:
    - Change from HOPE-2 baseline to Month 12 [Main Phase] for subjects in the OLE study who were deramiocel subjects in HOPE-2 study.
    - Change from HOPE-2-OLE baseline (Day 1) to Month 12 HOPE-2-OLE for subjects in the HOPE-2-OLE study who were on the placebo arm in HOPE-2 study.
- Gap Phase mean change comparison: Change from Month 12 HOPE-2 to baseline (Day 1) HOPE-2-OLE [Gap Phase] for the subjects in the HOPE-2-OLE study who were deramiocel subjects in the HOPE-2 study compared with the subjects in the HOPE-2-OLE study who were placebo subjects in the HOPE-2 study. As a reference, the change from HOPE-2 baseline to HOPE-2 Month 12 for subjects in the HOPE-2-OLE study who were deramiocel subjects in HOPE-2 study will be included.
- Year over year mean change during HOPE-2-OLE: For the safety population of the HOPE-2-OLE each year's change will be compared.

    - Change from HOPE-2-OLE baseline (Day 1) to Month 12 HOPE-2-OLE (Year 1).
    - Change from Month 12 HOPE-2-OLE to Month 24 HOPE-2-OLE (Year 2)
    - Change from Month 24 HOPE-2-OLE to Month 36 HOPE-2-OLE (Year 3)

6.3 Secondary Efficacy Endpoints

The ***secondary efficacy endpoints*** include the change from baseline (PUL 2.0: HOPE-2-OLE Baseline, Cardiac MRI: HOPE-2 Month 12) through Month 60 for the following:

- Upper body functionality using PUL 2.0 assessment (i.e. Upper level PUL:2.0) at Months 12, 24, 36, 48, and 60
- Distal level PUL 2. at Month 12, 24, 36, 48, and 60
- Mid-level (elbow) PUL 2.0 at Month 12, 24, 36, 48, and 60
- LVEF (i.e. Cardiac MRI) at Month~~,~~ 24, 36, 48, and 60.
- Left Ventricular End Systolic Volume, Indexed (Cardiac MRI) at Month, 24, 36, 48, and 60.
- Left Ventricular End Diastolic Volume, Indexed (Cardiac MRI) at Month, at Month 24, 36, 48, and 60.
- Other cardiac parameters, including but not limited to mass, unindexed volumes, and end diastolic and end systolic wall thickness at 24, 36, 48, and 60.

Observed values and change from baseline will be summarized (n, mean, SD, minimum, and maximum) for all secondary endpoints. Descriptive statistics for the External Comparators, ECP and ECC (section 6.4) will be presented for comparison with endpoints for which data are available.

Further comparisons will be formally made for the 24- and 36-month visits (if available) utilizing real-world evidence from external sources. The data and methods utilized for these comparisons is described in the next section.

6.4 External Comparators (Exploratory Efficacy Part 1)

For both the ECP and ECC, propensity score matching will first be attempted to produce an appropriate sample of real-world controls for comparison with the treated subjects from HOPE-2 OLE. If propensity score matching is not appropriate due to small sample size or other limiting factors, then cohort matching will be employed next. In either case, baseline characteristics available in both studies (e.g. baseline LVEF/PUL, age, etc.) will be utilized in the matching algorithm. External Comparator analyses will not be performed or reported if cell sizes are not sufficiently large for statistical analyses after either cohort or propensity score matching is performed. This will be determined separately and independently for the ECP and ECC datasets. If matching is not feasible summary level data may be analyzed.

If propensity score matching is feasible, the following parameterization will be utilized. Greedy nearest-neighbor matching using the logit of the propensity score and an appropriate caliper will be utilized to select matches. Up to 5 matches per treated subject will be used, given available data. Caliper width will be selected such that no treated samples are dropped from the analysis, i.e. at least one control subject will be selected per treated subject. Treated subject records will be sorted in ascending order by propensity score probability.

Baseline characteristics of matched subjects juxtaposed with treated subjects will be reported. In the case of propensity score matching, weighted statistics will be utilized including in analysis and modeling where appropriate.

Indexed volumes will be harmonized between studies: the body-surface area calculation utilized in the HOPE-2 study will be applied to the ECC to recalculate indexed volumes.

The HOPE-2 Month 12 visit will be utilized as the HOPE-2-OLE baseline visit for cardiac MRI parameters, as no cardiac MRI measurements were conducted at the HOPE-2-OLE baseline visit.

The treated and matched controls from the ECP/ECC will be compared using a continuous-time, random slope mixed model with age, baseline, and treatment-by-time interaction. If significant baseline imbalances persist after cohort matching, a baseline-by-treatment interaction term will be included in the model. Slope differences between groups will be presented along with the estimated treatment difference at 24 months (for ECC) and 36 months (for ECP) with corresponding 95% confidence intervals and associated two-sided p-values. The Kenward Roger approximation will be utilized to calculate denominator degrees of freedom. A percentile rank transformation will be applied to the change from baseline and baseline values in case model assumptions are violated.

Furthermore, a global statistical test (GST) may be employed to explore the totality of evidence across multiple cardiac endpoints, such as Left Ventricular Ejection Fraction, Indexed Left Ventricular End Systolic Volume, Indexed Left Ventricular End Diastolic Volume, and other

cardiac MRI measures collected in HOPE-2 OLE and in the ECC. The GST will be constructed as follows:

- For each distinct parameter in the GST, calculate the standardized change from baseline as follows:

$$chg'_{i,t,p} = \frac{x_{i,t,p} - \mu_p}{\sigma_{t,p}^{pooled}}$$

where i, t, p represent the i^{th} subject, the timepoint (visit) t, and the p^{th} parameter in the GST, x represents the raw score (analysis value), μ represents the mean baseline value for parameter, σ^{pooled} is the standard deviation of $x_{t,p}$ pooled between control and treatment arms, and chg' is the standardized change from baseline.

Then, by subject and visit, calculate the mean standardized change from baseline as:

$$chg_{i,t}^{gst} = \frac{1}{n}\sum_{p=1}^{n} chg'_{i,t,p},$$

where chg^{gst} represents the change from baseline score of the GST.

Baseline values will be calculated in the same manner using baseline analysis values for each parameter and only with the baseline visit. If any of the baseline components do not have a calculable baseline value, baseline will be calculated from the available measures. Scales will be directionally aligned in determination of the final score.

For percentile rank transformed variables, potentially (Left Ventricular Ejection Fraction, Indexed Left Ventricular End Systolic Volume, Indexed Left Ventricular End Diastolic Volume, Heart Chamber Volume End Diastolic Volume, and Heart Chamber Volume End Systolic Volume), the GST will be calculated using the average percentile rank instead of the process described above. Otherwise, all other rules for the construction of the GST will apply.

6.5 Sensitivity Analyses

Sensitivity analyses will be performed to test the robustness of the External Comparator analysis results for LVEF. Analyses exploring the hyperparameters of the propensity score matching algorithm will be presented. Random ordering will be employed to test the sensitivity of the match algorithm to sort order. Furthermore, results from an optimal propensity matching algorithm with appropriate *k* and caliper width will be presented.

The following outcome analyses will be performed using the matched set from the primary analysis:

- A Wilcoxon rank test comparing the change from baseline between the two groups,
- Change from baseline to Month 24 using an ANCOVA model with treatment as a factor and baseline and age as potential covariates.

6.6 Gap Phase (Exploratory Efficacy Endpoints Part 2)

Observed values and change from baseline will be summarized (n, mean, SD, minimum, and maximum) for PUL 2.0 Combined Total Score across the Gap Phase, which runs from Month 12 HOPE 2 (the baseline for these analyses) to Baseline/Day 1 HOPE-2-OLE.

7 SAFETY ANALYSES

Listings and summaries of the safety parameters will be done for the safety population. Safety parameters are described below.

7.1 Adverse Events

AEs will be coded using MedDRA coding system (Version 23.1).

The following AEs are defined as TEAEs:

- AEs that occur after the initiation of the IV catheter placement for the initial dose of IP
- AEs with a completely missing start date, or similarly, AEs that start the same month and year as IP administration but that have a missing start day.

TEAEs are considered to be related to IP/administration procedure if the relationship of the particular event is marked as “possible” or “probable”.

Subject listings of all AEs as reported will be provided. Serious AEs and TEAEs that are assessed as related to the IP or administration procedure, and hypersensitivity reactions/acute respiratory decompensation will be listed separately.

All summary tables will be reported using TEAEs. Additionally, TEAEs by maximum severity and TEAEs that are related to the IP or administration procedure and hypersensitivity reactions/acute respiratory decompensation will be summarized.

TEAEs will be displayed by MedDRA SOC and PT, with subjects who experience the same TEAE counted only once for that event and subjects who have more than one TEAE within a SOC counted only once in that SOC. The numbers and percentages of subjects with an event, as well as the number of events that were reported, will be calculated.

The summary tables will be prepared first for 12 months from the date of first IP administration during the OLE Phase and then again through 60 months in the OLE Phase.

7.2 Vital Signs, Height, Weight, and BMI

Vital signs will include systolic and diastolic blood pressures, pulse rate, respiratory rate, body temperature, and blood oxygen saturation (SpO_2). Observed and change-from-baseline values will be summarized at each post-baseline visit. Baseline will be defined as the pre-infusion samples that are collected on Day 1. Scheduled assessments will be summarized, and unscheduled events will only be listed.

Listings of vital signs, ulna length, height, weight, and BMI will be provided. Height will be calculated from the subject's ulna length.

7.3 Physical Examination

All physical examination results will be listed. A shift table will be presented by body system for physical examination findings.

7.4 Elevation of HLA antibodies against the donor cells (i.e., DSAs)

Mean fluorescence intensity (MFI) will be listed for donor specific antibodies. The listing will highlight MFIs >1000 with bold and italicized type.

8 DEVIATIONS FROM STATISTICAL METHODS IN THE PROTOCOL

The statistical methods in this statistical analysis plan are consistent with those described in the Amendment 5 of the study protocol with the following exceptions:

- The wall thickness percentages for the cardiac MRI parameters (secondary efficacy) were not collected and thus not available for descriptive analysis.
- Cardiac MRI parameters were not collected at 12-months for the HOPE-2-OLE study.
- The secondary analyses (Distal level PUL 2.0 and Mid-level (elbow) PUL 2.0) which involved subgroup analyses based on the entry level item of PUL 2.0 at baseline will be reported without the subgroups due to the small sample size of the subgroups.

9 APPENDICES

9.1 APPENDIX A: Schedule of Assessments

Procedure / Event	Screening[1]	Baseline[2] / Day 1	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24	Month 27	Month 30	Month 33	Month 36	Month 39	Month 42	Month 45	Month 48	Month 51, 54, 57	Month 60 Or Early Term
Trial Day (Visit Window)	*≤ 30 d prior to Day 1*	*1 d*	*(±14)*	*(±14)*	*(±14)*	*(±14)*	*(±21)*	*(±21)*	*(±21)*	*(±21)*	*(±21)*	*(±21)*	*(±21)*	*(±21)*	*(±21)*	*(±21)*	*(±21)*	*(±21)*	*(±21)*	*(±21)*
Intravenous Infusion #		*#1*	*#2*	*#3*	*#4*	*#5*	*#6*	*#7*	*#8*	*#9*	*#10*	*#11*	*#12*	*#13*	*#14*	*#15*	*#16*	*#17*	*#18, 19 20*	
Informed Consent / Assent	X					X				X				X						
Demographics	X																			
Medical History[4]	X																			
Eligibility Assessment	X																			
Pre-Treatment Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events[5]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Deramiocel (CAP-1002) Infusion[6]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ulna Length[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[8 9]										X				X				X		X
Hematology[8 10]										X				X				X		X
DSA[8]										X				X				X		X
Coagulation Panel[12]																		X[12]	X[12]	
PUL 2.0		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cardiac MRI	Standard-of-Care									X[11]				X[11]				X[11]		X[11]

[1] Some screening assessments may be conducted via telephone, but in-person assessments must be conducted prior to Baseline infusion.
[2] Baseline safety and efficacy assessments will be conducted prior to infusion on Day 1. Every effort should be made to have each subject complete all elements of the trial.
[3] If a subject has started at least one deramiocel infusion and withdraws prior to trial completion, all attempts must be made to perform a final comprehensive visit.
[4] Medical histories will be assessed for upper body functionality (i.e., PUL 2.0) and Left Ventricular Ejection Fraction (i.e., cardiac MRI). The assessment periods will cover the time from the end of HOPE-2 to the beginning of HOPE-2-OLE.
[5] A blood sample for tryptase should be obtained within 3 hours of the onset of allergic signs and symptoms and analyzed locally.
[6] All deramiocel infusions will be conducted in an outpatient setting at the investigative site. It occurs every 3 months anchored from the previous infusion for a total of up to 20 infusions (Day 1, Month 3, Month 6, Month 9, Month 12, Month 15, Month 18, Month 21, Month 24, Month 27, Month 30, Month 33, Month 36, Month 39, Month 42, Month 45, Month 48, Month 51, Month 54, and Month 57). Prior to each deramiocel infusion, medications will be administered to the subject as determined by the Investigator based on pre-treatment guidelines provided by Capricor and/or institutional protocols to minimize risk of potential severe allergic reactions such as anaphylaxis. Subjects will be observed for at least 2 hours post-infusion, including pulse oximetry monitoring for at least 30 minutes post-infusion. Sites will observe institutional policies related to parenteral infusions and post-infusion monitoring.
[7] Ulna length will be measured in all subjects and height will be calculated using a measurement of ulna length.
[8] Blood samples will be collected using trial-specific laboratory kits and then shipped to and tested at a central or local laboratory. Required sample collection for a visit may occur on multiple days; if the visit includes an IP infusion, sample collections should occur prior to IP administration.
[9] Basic metabolic panel (glucose, sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium), comprehensive hepatic panel (albumin, alkaline phosphatase, total protein, ALT, AST, GGT, direct bilirubin, total bilirubin).
[10] CBC with WBC differentials, hemoglobin, hematocrit, and platelet count.
[11] Cardiac MRI will be taken on all subjects at Month 24 or as soon as possible thereafter, Month 36, Month 48, and approximately 12 months after (at Month 60).
[12] Blood for a coagulation panel consisting of D-dimer, fibrinogen, PT/aPTT, INR, CRP, and ESR will be collected and analyzed locally at Months 48, 51, 54, and 57. During each visit, the coagulation panel will be drawn pre-dose, 2-hours (± 30 minutes) post dose, and 24 hours (± 12 hours) post dose.