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CLINICAL ARTICLE

A phase 1/2a dose-escalation study of oligodendrocyte progenitor cells in individuals with subacute cervical spinal cord injury

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OBJECTIVE The primary objective of this study was to evaluate the safety of 3 escalating doses of oligodendrocyte progenitor cells (LCTOPC1; previously known as GRNOPC1 and AST-OPC1) administered at a single time point between 21 and 42 days postinjury to participants with subacute cervical spinal cord injuries (SCIs). The secondary objective was to evaluate changes in neurological function following administration of LCTOPC1.

METHODS This study was designed as an open-label, dose-escalation, multicenter clinical trial. Twenty-five participants with C4–7 American Spinal Injury Association Impairment Scale grade A or B injuries received a single dose of either 2×10^6, 1×10^7, or 2×10^7 LCTOPC1 delivered via intraparenchymal injection into the spinal cord at the site of injury using a custom-designed syringe positioning device. Low-dose tacrolimus was administered until day 60. Outcome measures included adverse event (AE) monitoring and neurological function as measured by the International Standards for Neurological Classification of Spinal Cord Injury.

RESULTS All 25 participants experienced at least one AE, with a total of 534 AEs (32 study-related vs 502 study-unrelated anticipated complications of SCI) reported at the completion of 1-year follow-up. There were 29 serious AEs reported. Two grade 3 serious AEs (CSF leak in one participant and a bacterial infection in another) were considered related to the injection procedure and to immunosuppression with tacrolimus, respectively. The CSF leakage resolved with sequelae, including self-limited altered mental status, and the infection resolved with antibiotic therapy. For all participants, MRI scans demonstrated no evidence of an enlarging mass, spinal cord damage related to the injection procedure, inflammatory lesions in the spinal cord, or masses in the ventricular system. At 1-year follow-up, 21/22 (96%) of the intention-to-treat group recovered one or more levels of neurological function on at least one side of their body, and 7/22 (32%) recovered two or more levels of neurological function on at least one side of their body.

CONCLUSIONS LCTOPC1 can be safely administered to participants in the subacute period after cervical SCI. The injection procedure, low-dose temporary immunosuppression regimen, and LCTOPC1 were well tolerated. The safety and neurological function data support further investigation to determine the efficacy of LCTOPC1 in the treatment of SCI.

Clinical trial registration no.: NCT02302157 (ClinicalTrials.gov)

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KEYWORDS cervical spinal cord injury; GRNOPC1; AST-OPC1; LCTOPC1; human embryonic stem cells; clinical trials; central nervous system; trauma

ABBREVIATIONS AE = adverse event; AIS = ASIA Impairment Scale; ASIA = American Spinal Injury Association; HED = human equivalent dose; hESC = human embryonic stem cell; ISNCSCI = International Standards for Neurological Classification of Spinal Cord Injury; ITT = intention-to-treat; NLI = neurological level of injury; OPC = oligodendrocyte progenitor cell; SAE = serious AE; SCI = spinal cord injury; UEMS = upper-extremity motor score.

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The Lineage Cell Therapeutics oligodendrocyte progenitor cells (LCTOPC1, previously known as GRNOPC1 and AST-OPC1) are derived from a single cell line of self-renewing human embryonic stem cells (hESCs), and are intended for one-time administration for the treatment of traumatic spinal cord injury (SCI). In nonclinical studies, LCTOPC1 has been shown to produce neurotrophic factors, migrate in the spinal cord parenchyma, stimulate vascularization, and induce remyelination of denuded axons, all of which are critical functions of oligodendrocyte progenitor cells (OPCs) and are important for survival, regrowth, and function of axons.[1,2] In animal models of SCI, the cells led to improvement in locomotor function as measured by standardized behavioral testing.[3]

In January of 2009, LCTOPC1 entered "the world's first clinical trial of a therapy generated by human embryonic stem cells."[4] The thoracic clinical trial (NCT01217008)[5] was designed to evaluate the safety and efficacy of intraparenchymal injection of 2×10^6 LCTOPC1 in individuals with a neurological level of injury (NLI) between T3 and T11 and with American Spinal Injury Association (ASIA) Impairment Scale (AIS) grade A.[6] The thoracic trial has completed 10-year follow-up and has reported safety data without any serious adverse events (SAEs) related to LCTOPC1, the injection procedure, or the low-dose temporary immunosuppression regimen, as well as no findings of concern on scheduled neurological examinations and/or MRI.[6]

The favorable safety profile of the thoracic trial led to the initiation of the current clinical trial of individuals with cervical SCI:[7] a phase 1/2a study of escalating doses of LCTOPC1 in participants with subacute (21–42 days postinjury) sensorimotor complete (AIS grade A) or incomplete (AIS grade B) traumatic cervical SCI with NLI between C4 and C7. Individuals with severe cervical SCI face considerable unmet medical needs due to the loss of motor function in all four limbs, and other sequelae.[8] These individuals frequently require significant assistance for self-care and activities of daily living.[8]

In a pivotal animal study, rats with cervical contusion injuries that received a dose of 2.4×10^5 LCTOPC1 exhibited significantly greater recovery of locomotor function, as assessed by the TreadScan system (Clever Sys, Inc.), than did vehicle-injected control animals.[9] Given that each segment of the human spinal cord has roughly a 50-fold larger volume than the corresponding rat spinal cord segment, it was estimated that the human equivalent dose (HED) for efficacy would be approximately 1.2×10^7 LCTOPC1. However, it was anticipated that the optimal therapeutic dose in humans may need adjustment in the clinical setting, because LCTOPC1 has several potential mechanisms of action, which may translate separately and collectively from rodents to humans. Therefore, 1×10^7 and 2×10^7 cells were selected for this study's intention-to-treat (ITT) population in order to bracket the estimated HED with a sufficient range to maximize the probability of detecting neurological change, while maintaining an acceptable safety profile based on the aggregate preclinical and clinical data.[9,10]

To date, there are no FDA-approved treatments to induce neurological recovery following SCI. Thus, there remains a significant unmet medical need in SCI, particularly for individuals with more severe injuries who are initially classified as motor complete (AIS grade A or B).[8] The current clinical trial provides critical safety data necessary for enabling future trials to investigate novel stem cell therapeutics or combination therapies for individuals with SCI. This study was registered with the ClinicalTrials.gov database (http://clinicaltrials.gov), and its registration no. is NCT02302157.

Methods

Study Design

This study was an open-label, staggered dose-escalation, multicenter phase 1/2a clinical trial (Fig. 1). At the inception of the trial, the intervention was administered at a single time point between 14 and 30 days postinjury to participants with C5–7 AIS grade A SCI. The inclusion criteria were later modified to include individuals with C4 AIS grade B as well as a change of the injection time window to 21–42 days. Participants with cervical AIS grade A SCI received 1 of 3 sequential doses (2×10^6, 1×10^7, or 2×10^7) of LCTOPC1. Participants with cervical AIS grade B SCI received 1×10^7 or 2×10^7 LCTOPC1. All participants, who received LCTOPC1, also received low-dose tacrolimus for 60 days to prevent potential immune rejection (Supplemental Materials section *Immunosuppression*). Participants were followed for 1 year under this protocol and were then required to participate in a separate long-term safety follow-up protocol for an additional 14 years. An overview of study visits for the 1-year protocol is presented in the study schema (Fig. 2) and in Supplemental Table 1. For details regarding staggered enrollment and rules for advancement within cohorts, see Supplemental Materials section *Staggered Enrollment Within Each Cohort*. For detailed inclusion and exclusion criteria, see Supplemental Materials section *Inclusion and Exclusion Criteria*.

Dose and Mode of Administration

Each participant received a single administration of LCTOPC1 delivered by injection into the SCI site by a neurosurgeon using a custom-designed syringe positioning device during a dedicated surgical procedure. The low dose (cohort 1; Table 1) was 2×10^6 LCTOPC1, matched to the dose used in a previous thoracic SCI study[6] and designed to establish the safety of LCTOPC1 and its delivery in cervical SCI. The middle and high doses were 1×10^7 (cohorts 2 and 4; Table 1) and 2×10^7 (cohorts 3 and 5; Table 1) LCTOPC1, and were expected to be the HED of the therapeutic range observed in preclinical studies of rats with SCI.[1,9] The low and middle doses were delivered in a volume of 50 μL at a depth of 6 mm via a single injection located 5 mm caudal to the epicenter and within a region of damaged, but nonhemorrhagic, spinal cord tissue as determined by MRI. The high dose of 2×10^7 LCTOPC1 was delivered via 2 injections of 50 μL each. Similarly, the second injection site was located within a region of damaged tissue, 5–10 mm rostral to the first site, preferably on the side of the midline opposite to the first injection. For

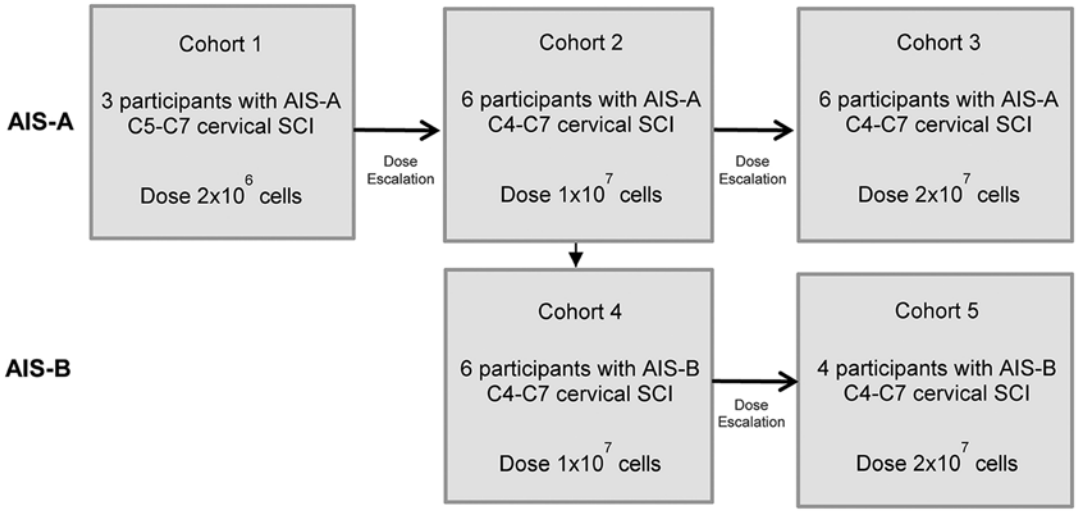

FIG. 1. Study design. One participant enrolled in cohort 3 received only the 1×10^7 dose due to an error during dose preparation. One participant enrolled in cohort 5 received only the 1×10^7 dose due to inadequate lesion volume to identify 2 injection locations.

the needle to enter the spinal cord without deformation, the surgeon made an approximately 1-mm longitudinal incision in the pia mater at the site(s) of injection.

Safety Assessments

The primary endpoint of the trial was safety, as measured by the frequency and severity of adverse events (AEs) and SAEs within 1 year of LCTOPC1 injection that were related to LCTOPC1, the injection procedure used to administer LCTOPC1, and/or the concomitant immunosuppression administration. Measurements used to assess safety included physical examinations; vital signs; electrocardiography; neurological examinations; International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) examinations; MRI scans; pain questionnaire; concomitant medications; AEs; and laboratory tests for hematology, blood chemistry, and immunosuppression safety monitoring. All AEs were monitored in an ongoing fashion by the medical monitor who worked for the study's sponsor (Asterias Biotherapeutics, Inc., which was acquired by Lineage Cell Therapeutics, Inc.), and by an independent Data and Safety Monitoring Board. Based on the frequency, severity, and relatedness of AEs, the sponsor at the time of the study could have determined, or the Data and Safety Monitoring Board could have recommended, that the trial be suspended or discontinued. For additional details, see the following Supplemental Materials sections: *Safety Assessment*; *Adverse Event: Definition, Reporting, and Evaluation*; and *Magnetic Resonance Imaging*.

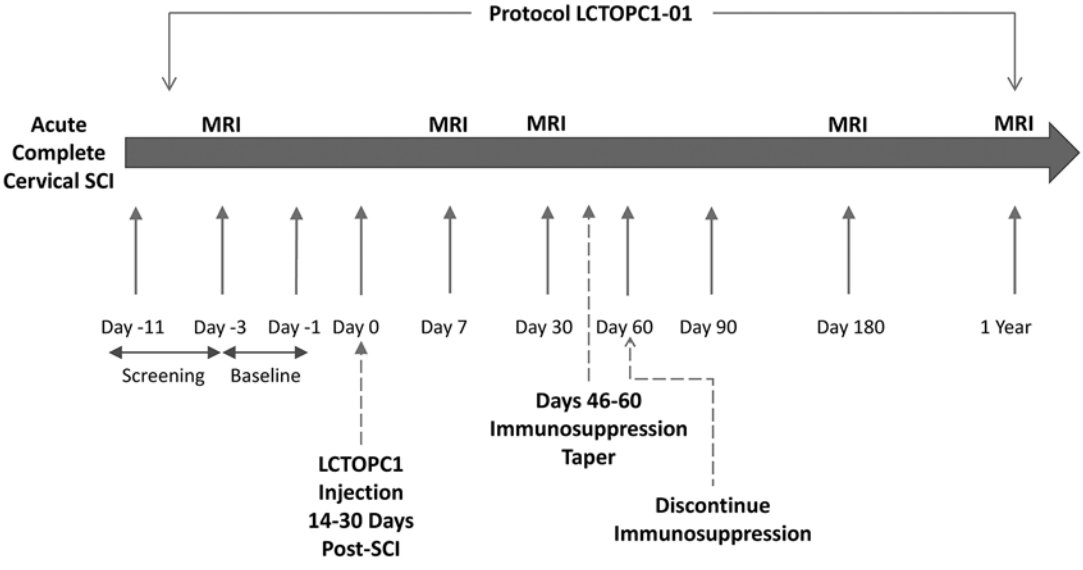

FIG. 2. Study schema for cervical SCI study LCTOPC1-01.

TABLE 1. Dose cohorts

Cohort	Dose (no. of cells)	Concentration (cells/μL)	Vol per Injection (μL)	No. of Injections	Total Vol Administered (μL)
1	2×10^6	4×10^4	50	1	50
2	1×10^7	2×10^5	50	1	50
3	2×10^7	2×10^5	50	2	100
4	1×10^7	2×10^5	50	1	50
5	2×10^7	2×10^5	50	2	100

Neurological Assessments

The secondary endpoint was neurological function as measured by the ISNCSCI. The ISNCSCI is a highly reproducible research and clinical assessment of neurological impairment for individuals with SCI, and has been used as a tool to evaluate the effectiveness of acute SCI clinical interventions.[11,12] ISNCSCI assessors were physicians or physical therapists who had at least 2 years of experience routinely administering the examination. To maximize interrater and intrarater reliability, all assessors completed the 4-hour online training (International Standards Training e-Learning Program [InSTeP]) offered by ASIA. Additionally, a number of assessors attended an in-person, half-day, site-specific training led by an external expert, including examination of individuals and a competency assessment. During the first year of the study, ISNCSCI examinations were performed at 30, 60, 90, 180, 270, and 365 days after injection of LCTOPC1. The 365-day follow-up visit was prespecified as the time for the secondary endpoint.

Statistical Methods

General Methodology

Conventional descriptive statistics were used to summarize participant demographics, baseline characteristics, disposition, and history. Continuous data tabulations used a standard set of summary statistics: number of observations available, mean, SD, median, and range (minimum, maximum). Categorical or dichotomous data were tabulated using counts and percentages (see Tables and Supplemental Tables).

Statistical Analysis for Efficacy

The efficacy endpoint, neurological function, was evaluated by characterizing the upper-extremity motor score (UEMS) and motor level on the ISNCSCI examination (point estimate and 95% CI) by time point at 30, 60, 90, 180, 270, and 365 days after injection of LCTOPC1. The baseline for the ISNCSCI assessment was defined as the baseline visit performed between 24 and 48 hours prior to injection. UEMS and change from baseline were summarized by participant, mean, SD, 95% CI, median, minimum, and maximum.

Statistical Analysis for Safety

The collection period for AEs began once the participant had signed the informed consent form and ended after 365 days of observation. Statistical analysis of AEs started on or after the date and time of the LCTOPC1 injection, or an AE that started before the LCTOPC1 injection, and worsened after the administration of the investigational product. AEs were tabulated by system organ class and by preferred term within system organ class according to the Medical Dictionary for Regulatory Activities (MedDRA, version 18), and reported by participants. A topline summary of AEs with the number of events, number of participants, and percentage of participants for each category was tabulated by cohort and overall. Categories for possible relationship included the following: LCTOPC1, injection procedure, and tacrolimus. Tabulations were prepared for all AEs, related events, grade 3 and higher events, and SAEs.

Results

Study Participants

The study was initiated (first dose) in the summer of 2015 and completed enrollment (last dose) in the winter of 2017. There were 9 study centers that screened potential participants, with 5 of those centers administering LCTOPC1. A total of 33 participants enrolled across 5 cohorts. Of these 33 enrollees, 7 failed screening, and 1 terminated their participation in the study prior to dosing. The failure of 7 participants to pass screening was due to MRI findings of spinal cord laceration and cerebral infarction, inability to lie flat on the MRI table, conversion to AIS grade C, NLI of C4, investigator judgment, and withdrawal of consent (Fig. 3). Over a total of 29 months, 25 participants in 5 cohorts received LCTOPC1 as shown in Fig. 1. Of note, 1 participant enrolled in cohort 3 received only 1×10^7 cells due to an error during dose preparation. Participant 22, who was enrolled in cohort 5, received a dose of only 1×10^7 cells due to inadequate lesion volume to identify 2 injection locations within a region of damaged tissue. The 25 participants who were administered LCTOPC1 were a mean age of 31.8 years, predominantly male (21 participants), and predominantly White (22 participants), and most injuries were the result of a diving accident or a vehicular accident (8 participants each). Additional demographic information by cohort is provided in Supplemental Table 2.

Evaluation of Safety

Summary of AEs

All 25 participants experienced at least one AE. No participant discontinued the study due to AEs. An overview and breakdown by grade of the 534 AEs and 29 SAEs in

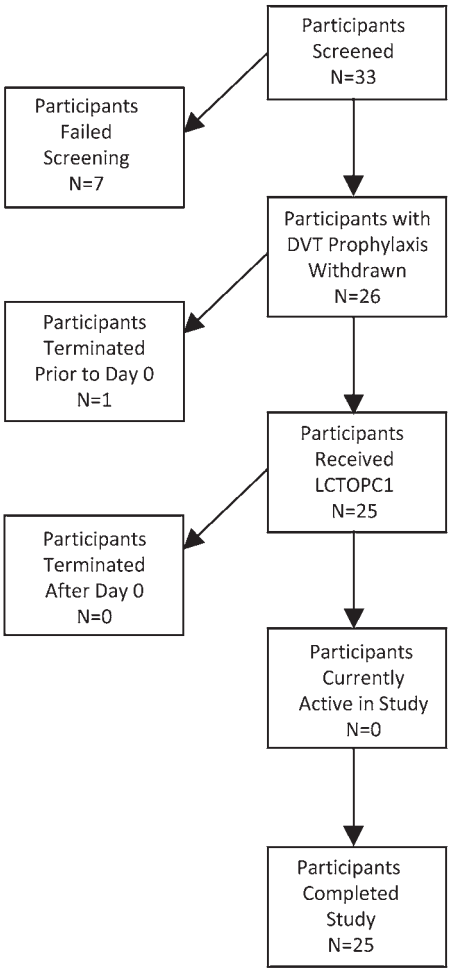

FIG. 3. CONSORT diagram. DVT = deep venous thrombosis.

participants who received LCTOPC1 are presented in Table 2. A summary of all related AEs is presented in Table 3, and a summary of all AEs that occurred in more than 3 participants is provided in Supplemental Table 3. No trend was observed between cohorts in severity or number of reported AEs. Cohort 3 presented with a higher number of SAEs due to 1 participant who reported 7 SAEs (bilateral pyelonephritis, altered mental status, urinary tract infection, pulmonary embolism, gastrointestinal hemorrhage, buttock cellulitis, and hypokalemia), all unrelated to LCTOPC1 (Table 4).

Analysis of AEs

No participant discontinued the study due to an AE. The most frequently reported AEs were urinary tract infection (23 participants), decubitus ulcer (14 participants), hypomagnesemia (13 participants), musculoskeletal pain (10 participants), and nausea (10 participants) (Supplemental Table 3). Of the 534 AEs reported, 1 AE possibly related to LCTOPC1 was a grade 2 dysesthesia that began 47 days postinjection and resolved by the year 2 follow-up visit (Table 3). There were 20 AEs related to the injection procedure (nausea, vomiting, postoperative wound infection, autonomic dysreflexia, procedural pain, myalgia, neck pain, headache, incision drainage, CSF retention, and CSF leakage) (Table 3). The events related to the injection procedure were mostly grades 1–2 in severity and were expected events following a surgical intervention of this nature. One report of autonomic dysreflexia occurred during the injection procedure. This AE was rated as grade 3 and was an anticipated cause of physiological instability, which resolved with a brief pause in the surgery. A total of 11 AEs were judged as possibly related to tacrolimus; 4 AEs were grade 1, 6 AEs were grade 2, and 1 AE was grade 3 (Table 3). These AEs were primarily known common adverse reactions to tacrolimus (hypomagnesemia [n = 8], nausea [n = 1], bacterial infection [n = 1]). No evidence of any adverse neurological changes or adverse changes on MRI was reported during tacrolimus tapering or after tacrolimus discontinuation. Overall, the tacrolimus regimen was well tolerated, and most participants completed the regimen per protocol.

Analysis of Deaths, SAEs, and Significant AEs

No participant discontinued the study due to an SAE, and none died during study follow-up. A total of 29 SAEs

TABLE 2. Overview of AEs and SAEs in all treated participants

	Total Participants, n = 25	Total AEs, n = 534	Total SAEs, n = 29
Participants reporting ≥1 related & severe (≥ grade 3) AE	4	4	2
Total no. reported	25	534	29
By severity			
Mild (grade 1)	25	343	0
Moderate (grade 2)	21	161	15
Severe (grade 3)	12	30	14
Life-threatening (grade 4)	0	0	0
Death (grade 5)	0	0	0
Related to			
LCTOPC1	1	1	0
Injection procedure	9	20	1
Tacrolimus	8	11	1

TABLE 3. Summary of related AEs in all treated participants

Preferred Term	AE (no.)	SAE (no.)	Causality	Days From Injection	Outcome	Severity
Dysesthesia	1	None	OPC1	47	Resolved*	Grade 2
CSF leakage	2	1	Injection procedure	11–15	Resolved w/ sequelae†	Grade 2–3
CSF retention	5	None	Injection procedure	6–7	Resolved	Grade 1
Pain (neck, muscular, incisional)	5	None	Injection procedure	0–1	Resolved	Grade 1–3
Headache	3	None	Injection procedure	0–84	Resolved	Grade 1–2
Nausea	1	None	Injection procedure	0	Resolved	Grade 2
Postop wound infection	1	None	Injection procedure	7	Resolved	Grade 1
Vomiting	1	None	Injection procedure	0	Resolved	Grade 2
Autonomic dysreflexia	1	None	Injection procedure	0	Resolved	Grade 3
Incision drainage	1	None	Injection procedure	1	Resolved	Grade 1
Hypomagnesemia	8	None	Tacrolimus	5–43	Resolved	Grade 1–2
Bacterial infection	1	1	Tacrolimus	30	Resolved	Grade 3
Decreased appetite	1	None	Tacrolimus	NK	Resolved	Grade 2
Nausea	1	None	Tacrolimus	7	Resolved	Grade 2

NK = not known.
* Dysesthesia resolved at year 2 follow-up.
† One CSF leakage required lumbar drainage. Participant returned to rehabilitation on day 22.

TABLE 4. Summary of SAEs in all treated participants

Participant Identifier	SAE (preferred term)	Days From Dosing	Severity	Relationship to Procedure	Outcome
3	Urinary tract infection	126	Grade 2	Unrelated	Resolved
3	Femur fracture	323	Grade 3	Unrelated	Resolved
19	CSF leakage	15	Grade 3	Injection procedure	Resolved w/ sequelae*
19	Urinary tract infection	276	Grade 2	Unrelated	Resolved
1	Urinary tract infection	199	Grade 2	Unrelated	Resolved
1	Sepsis	322	Grade 2	Unrelated	Resolved
15	Aspiration pneumonia	5	Grade 2	Unrelated	Resolved
15	Pulmonary embolism	6	Grade 2	Unrelated	Resolved
13	Urinary tract infection	53	Grade 2	Unrelated	Resolved
13	Joint effusion	63	Grade 2	Unrelated	Resolved
13	Mental status changes	72	Grade 3	Unrelated	Resolved
12	Pyelonephritis	44	Grade 3	Unrelated	Resolved
12	Mental status changes	57	Grade 2	Unrelated	Resolved
12	Urinary tract infection	151	Grade 2	Unrelated	Resolved
12	Pulmonary embolism	178	Grade 3	Unrelated	Resolved
12	Gastrointestinal hemorrhage	206	Grade 2	Unrelated	Resolved
12	Hypokalemia	258	Grade 2	Unrelated	Resolved
12	Abscess	281	Grade 3	Unrelated	Resolved
23	Atrial fibrillation	15	Grade 3	Unrelated	Resolved
23	Renal injury	330	Grade 3	Unrelated	Resolved
17	Bacterial infection	30	Grade 3	Tacrolimus	Resolved
17	Acute kidney injury	56	Grade 3	Unrelated	Resolved
17	Urinary tract infection	84	Grade 3	Unrelated	Resolved
10	Acute respiratory failure	3	Grade 2	Unrelated	Resolved
5	Wound infection	120	Grade 2	Unrelated	Resolved w/ sequelae
5	Urosepsis	178	Grade 3	Unrelated	Resolved
5	Decubitus ulcer	225	Grade 3	Unrelated	Resolved w/ sequelae
5	*Escherichia* sepsis	326	Grade 3	Unrelated	Resolved
4	Urinary tract infection	248	Grade 3	Unrelated	Resolved

* CSF leakage required lumbar drainage. Participant returned to rehabilitation on day 22.

TABLE 5. Percent motor level improvement from baseline

Time of Visit (no. of participants)	% (no.) w/ ≥2 Motor Levels on ≥1 Side	% (no.) w/ ≥1 Motor Level on Both Sides	% (no.) w/ ≥1 Motor Level on ≥1 Side	% (no.) w/ No Change	% (no.) w/ Ascending Motor Level
Day 7 (22)	0 (0)	0 (0)	45.5 (10)	54.5 (12)	0 (0)
Day 30 (22)	9.1 (2)	18.2 (4)	45.5 (10)	54.5 (12)	0 (0)
Day 60 (21)	14.3 (3)	28.6 (6)	61.9 (13)	38.1 (8)	0 (0)
Day 90 (22)	18.2 (4)	36.4 (8)	81.8 (18)	18.2 (4)	0 (0)
Day 180 (22)	13.6 (3)	54.5 (12)	86.4 (19)	13.6 (3)	0 (0)
Day 270 (20)	25.0 (5)	45.0 (9)	85.0 (17)	10.0 (2)	5.0 (1)
Day 365 (22)	31.8 (7)	59.1 (13)	95.5 (21)	4.5 (1)	4.5 (1)

were reported by 11 of the 25 participants who were administered LCTOPC1 (Table 4). The 29 SAEs included urinary tract infections (7 participants), urosepsis (2 participants), sepsis (1 participant), pyelonephritis (1 participant), femur fracture (1 participant), wound infection (1 participant), decubitus ulcer (1 participant), abscess (1 participant), bacterial infection (1 participant), acute respiratory failure (1 participant), CSF leakage (1 participant), pulmonary embolism (2 participants), aspiration pneumonia (1 participant), altered mental status (2 participants), acute renal failure (1 participant), hypokalemia (1 participant), atrial fibrillation (1 participant), hip effusion (1 participant), gastrointestinal hemorrhage (1 participant), and renal injury (1 participant) (Table 4).

None of the SAEs were related to LCTOPC1; 1 SAE was deemed possibly related to tacrolimus (bacterial infection) and 1 was deemed possibly related to the injection procedure (CSF leakage) (Table 4). The bacterial infection SAE, in participant 17, was reported 30 days after injection as grade 3 in severity and resolved with antibiotic treatment. The CSF leak SAE, in participant 19, resulted in a prolongation of hospitalization and was complicated by self-limited sequelae including altered mental status. The CSF leak was identified on the MRI obtained on day 7 and managed with a lumbar drain. At the time of the initial FDA reporting this event was listed as "resolved with sequelae," which has been maintained in this publication; however, this event subsequently resolved completely. The participant returned to inpatient rehabilitation 22 days after injection. This individual's ISNCSCI examinations demonstrated progressive improvement (Supplemental Table 4). For all participants, MRI scans demonstrated no evidence of an enlarging mass, spinal cord damage related to the injection procedure, inflammatory lesions in the spinal cord, or masses in the ventricular system.

Neurological Function Change Following LCTOPC1 Administration

The trial consisted of 5 cohorts including cohort 1, which included 3 individuals, receiving a low dose of 2×10^6 cells. The study's ITT population was defined as participants who received the middle and high dose of LCTOPC1 in cohorts 2–5. All 22 participants in the ITT population, including 6 in cohort 2 (AIS grade A, 1×10^7 LCTOPC1); 6 in cohort 3 (AIS grade A, 2×10^7 LCTOPC1); 6 in cohort 4 (AIS grade B, 1×10^7 LCTOPC1); and 4 in cohort 5 (AIS grade B, 2×10^7 LCTOPC1), completed 1 year of follow-up. The baseline mean UEMS for these 22 individuals was 28.4 points (minimum 7, maximum 46), with a mean improvement from baseline of 8.9 points (minimum 3, maximum 20) by day 365. The average UEMS improvement at 1 year relative to baseline per cohort is as follows: cohort 2, 12.3 points; cohort 3, 9.2 points; cohort 4, 6.7 points; and cohort 5, 6.8 points. There were 3 participants (18, 21, and 25) from cohorts 4, 4, and 5, respectively, who experienced conversion from AIS grade B to AIS grade C, with limited improvement in lower-extremity motor scores and without apparent correlation with the degree of improvement in UEMS.

A total of 7 (32%) of 22 ITT participants attained a two-motor-level improvement on at least one side of the body at the day 365 visit (Table 5). Most ITT participants (21/22; 96%) attained at least a one-motor-level improvement on at least one side of the body at the day 365 visit relative to baseline (Table 5). There was no correlation between the level of improvement with sex, age, cell dose (10 million cells vs 20 million cells), manufacturing cell lot, number of days from injury, and time of intervention.

No participant exhibited evidence of unexpected neurological deterioration on ISNCSCI UEMS through 1 year of follow-up. For participant 13, the NLI changed from C7 at day 180 to C5 at day 270. On consultation with the examiner, they noted that "considering the spastic influence, it [motor strength] could have been scored a 5* indicating a normal neurological innervation and not a decline in function." We have maintained the language from communications with the FDA in Tables 3 and 4; however, it should be noted that at day 365, the UEMS for this individual had increased from a baseline of 18 to 35 and the motor zone of partial preservation had improved from C6 at baseline to T1.

Sensory scores exhibited small fluctuations for most participants, but overall were stable. A few participants exhibited significant improvements in sensory scores. Participant 11 had a light touch score of 22 at baseline, which improved to a score of 59 at the day 365 visit. Participant 21's light touch sensory score improved from 43 at baseline to 109 on day 365. Participant 25 had a light touch score of 44 at baseline that improved to a score of 97 on day 365, and a pinprick score of 42 at baseline that improved to a score of 80 at day 365. Participants 5 and 6 improved more than two sensory levels from baseline

to day 365. Supplemental Table 4 provides the results of ISNCSCI examinations for all participants.

Discussion

Ten-year safety data have been previously published in this journal for the first-in-human trial of direct injection of OPCs in patients with acute thoracic SCI.[5,6] The current trial[7] was authorized by the FDA following review of the 1-year safety data from the thoracic trial. In this trial of LCTOPC1, treating more rostral injuries in the cervical spinal cord represents a potential increase in both the risk and reward of treatment. Treatments that produced two or more levels of recovery for individuals with cervical SCIs hold the promise of improving functional independence.[13]

The safety data from this study suggest that LCTOPC1 can be safely administered to participants in the subacute period after cervical SCI. None of the 25 participants who received LCTOPC1 showed evidence of neurological deterioration. There were no SAEs reported as being directly related to LCTOPC1, and evaluation of the AEs did not show an increase in incidence for commonly reported SCI complications, such as urinary tract infections, muscle spasms, or neuropathic pain.[14] One potential issue in the 2 participants with the least UEMS improvement (1 from cohort 4 who had gained only 3 motor points at 1 year, and 1 from cohort 5 who had gained only 4 points at 1 year) is that both had postoperative extradural fluid collections that were found to be compressing the spinal cord caudal to the LCTOPC1 injection sites on the day 30 and day 7 MRI scans, respectively. It should be noted that extradural fluid collections are common in these patients even prior to LCTOPC1 administration, due to the presence of stabilizing surgical hardware such as rods and pedicle screws that are used for internal fixation of the spine following SCI. Based on the findings in these 2 individuals, we suggest the use of subfascial drainage with the collection bag maintained at the level of the dural incision in future trials.

Regarding spontaneous recovery, Steeves et al. reported that the proportion (%) of people living with cervical (C4–7) sensorimotor complete (AIS grade A) SCI spontaneously recovering 1 or ≥ 2 upper-extremity motor levels on either the right or left side, whichever is greater after 48 weeks postinjury, is 68% for one level and 26% for two levels, respectively.[15] In this study involving participants with cervical C4–7 AIS grade A and AIS grade B, at 1-year follow-up, 21/22 (96%) of the ITT group recovered one or more levels of motor function on at least one side of their body and 7/22 (32%) recovered two or more levels of motor function on at least one side of their body. Given the limited sample size in this open-label clinical trial, it is difficult to specifically attribute the degree of recovery to cellular therapy versus natural recovery.

This clinical trial had limitations that will inform future clinical trials. This study was neither designed nor properly controlled to study neurological improvement or functional gains relating to LCTOPC1; there is no control group for tacrolimus or the surgical injection procedure (e.g., no vehicle control). This study was not powered to evaluate neurological improvement related to LCTOPC1. The accurate implementation of the ISNCSCI examination is critical in studies assessing neurological recovery. Future studies should consider training commensurate with the trial phase and outcomes. ASIA offers online training programs as well as in-person training through the organization. For subsequent trials, certification from ASIA through the International Standards Training e-Learning Program (InSTeP) with renewal to maintain ongoing certification as well as ISNCSCI in-person training should be considered.

Conclusions

The data, from both the thoracic and cervical trials, have provided evidence that hESC-derived treatments can be safely delivered into the spinal cord. The 30 individuals who have participated in these two trials[5–7] provide evidence for regulatory agencies to consider trials investigating hESC-derived interventions for individuals with AIS grade A or B injuries in the cervical spine up to the level of C4. Given the data collected in these studies, we believe that continued development of LCTOPC1 in a larger clinical trial studying efficacy is warranted. As a future direction, we recommend maximizing the benefit of cellular treatments through studies incorporating a period of rehabilitation in which novel strategies designed to augment the potential of hESC base therapies to promote functional recovery are used.

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Disclosures

Dr. Jones was employed by Geron, Inc., during the thoracic study. Dr. Lebkowski was employed by Asterias, Inc., at the time of the execution of the clinical trial. She is no longer employed there and has no financial relationship with the sponsor. Dr. Wirth was employed by Asterias, Inc., at the time of the study. He is a consultant for Lineage Cell Therapeutics, was formerly employed by that company, and was clinical lead on this study.

Author Contributions

Conception and design: all authors. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Fessler. Statistical analysis: all authors. Administrative/technical/material support: all authors. Study supervision: Fessler, Ehsanian, Liu, Steinberg, Lebkowski, Wirth, McKenna.

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