Results of the First Completed Clinical Trial of an iPSC-Derived Product: CYP-001 in Steroid-Resistant Acute GvHD

Poster # 362

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INTRODUCTION

Mesenchymal stem cells (MSCs) isolated from donated tissue have been widely investigated as a treatment for graft versus host disease (GvHD), but with mixed results. Factors such as MSC donor variability and the effects of prolonged culture expansion may have contributed to inadequate outcomes.

Induced pluripotent stem cells (iPSCs) can proliferate indefinitely without loss of pluripotency. The novel Cymerus™ manufacturing process facilitates virtually limitless supply of well-defined and consistent MSCs from a single iPSC bank, using proprietary clonogenic progenitor-based technology. This avoids both inter-donor variability and the need for excessive culture expansion once MSCs are formed.

This is a multi-center, open label, dose escalation Phase I clinical trial (NCT02923375), to assess the safety, tolerability and efficacy of Cymerus iPSC-derived MSCs (CYP-001) in adults with grade II-IV steroid-resistant acute GvHD, following allogeneic hematopoietic stem cell transplantation.

METHODS

- All subjects had failed to respond to at least three days of steroid treatment (≥1 mg/kg/day), administered in accordance with standard management at each center.
- All subjects received two IV infusions of CYP-001 one week apart, as well as standard of care medications.
- CYP-001 doses were:
  - Cohort A: 1 x 10^6 cells/kg (max 1 x 10^8 cells)
  - Cohort B: 2 x 10^6 cells/kg (max 2 x 10^8 cells)
- An independent DSMB reviewed data from Cohort A before Cohort B was enrolled
- Primary evaluation was performed over eight study visits to day 100. Subjects then entered a follow-up phase of up to two years.
- Data for subjects with a minimum of six months after CYP-001 treatment are presented here.
- GvHD was staged and graded according to the 1994 Consensus Conference on Acute GvHD Grading.
- The primary objective was to assess the safety and tolerability of two infusions of CYP-001.
- Secondary objectives were efficacy, assessed by best response to treatment, by Day 28 and Day 100 and overall survival at Day 28 and Day 100.

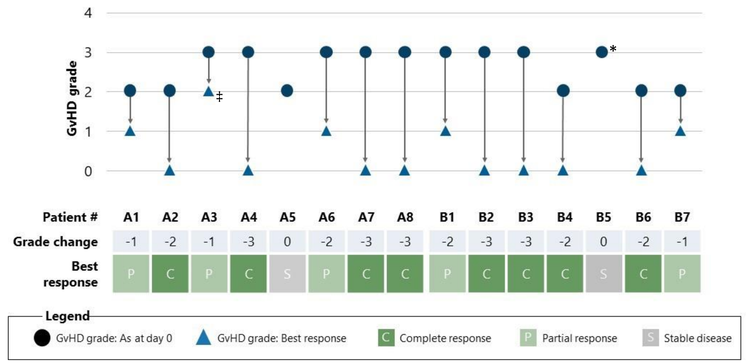
RESULTS

Best Response by Cohort

Outcome Measure	28 days		100 days	
	Cohort A	Cohort B	Cohort A	Cohort B
Complete Response	12.5%	57.1%	50.0%	57.1%
Overall Response	62.5%	85.7%	87.5%	85.7%
Overall Survival[1]	87.5%	85.7%	87.5%	85.7%

[1] *One subject in Cohort A died of pneumonia. The causality of this event was assessed by the investigator in accordance with the study protocol, and it was not considered to be possibly, probably or definitely related to CYP-001. One subject in Cohort B withdrew from the trial on Day 22 to commence palliative care. Reported overall survival rates are based on the assumption that this patient did not survive beyond the date of withdrawal.*

Best Response by Subject



‡ Subject A3 showed a PR at Days 14 and 21 but died due to pneumonia on Day 28
** Subject B5 did not improve after treatment and withdrew from the trial on Day 22 to commence palliative care*

Outcome	Definition
Complete Response	Absence of GvHD signs/ symptoms (GvHD Grade 0)
Partial Response	Improvement by at least 1 grade compared to baseline
Overall Response	Partial or Complete Response

- Eight subjects were enrolled in each cohort as planned but one subject in Cohort B withdrew prior to infusion of CYP-001.
- Seven females and eight males (average age 50 years) received CYP-001 infusions.
- All subjects had Grade 2 or 3 GvHD at baseline.
- There was an overall response in 13/15 (87%) subjects and a complete response in 8/15 (53%) subjects.
- The overall and complete response rates by Day 28 were higher in Cohort B than in Cohort A, but by Day 100, response rates were similar in both cohorts.
- Both CYP-001 dose levels were well-tolerated
- There were no serious adverse events (SAEs) assessed as possibly, probably or definitely related to CYP-001.
- A total of 5 treatment-emergent adverse events (TEAEs) reported in 4 (26.7%) participants were assessed as <u>possibly</u> related to CYP-001 (*Possibly related = TEAEs with a reasonable time relationship to CYP-001 administration, but which could also be explained by disease or other drugs*):
  - Abdominal pain, diarrhoea, febrile neutropenia, arthralgia and renal impairment
  - No TEAEs were assessed as probably or definitely related to CYP-001 treatment
- No participants discontinued treatment due to AEs.
- 13/15 subjects survived until Day 100:
  - 1 patient in Cohort A died of pneumonia on Day 28.
  - 1 patient in Cohort B withdrew on Day 22 to start palliative care

CONCLUSIONS

- Infusions of CYP-001 were safe and well tolerated in this patient cohort.
- Treatment response and overall survival rates are encouraging compared to previously published outcomes.
- Plans for a Phase II trial in this clinically challenging disease are underway.

DISCLOSURES: JEJR: GSK (Honoraria, Takeda (Honoraria), Cynata (Honoraria), Pfizer (Honoraria), Spark (Honoraria), Novartis (Honoraria), Celegene (Honoraria), Bluebird Bio (Honoraria), Genea (Honoraria), Rarecyte (consultancy and equity), Imago (consultancy) Australian Government, Chair of Gene Technology Technical Advisory (Advisory Board), Cure the Future (Board of Directors, FSHD Global Research Foundation (Board of Directors, scientific patron). **DTY**: Amgen (honoraria), Pfizer (honoraria), BMS (honoraria and research funding), Novartis (honoraria and research funding), Specialised Therapeutics Australia (honoraria). **IS**: Cynata (consultancy and equity ownership). **KK**: Cynata (employment and equity ownership). **AB** AbbVie (honoraria, member of advisory board, research funding), Janssen (research funding, speakers bureau), Roche (honoraria). **AP, JEG, MHG, RR** have no relationships to disclose.