Study Results Synopsis for Public Disclosure

Name of product: PHE885/INN Durcabtagene autoleucel

Protocol identification number: Clinicaltrials.gov: NCT04318327

Title of study: Phase I, open label, study of B-cell Maturation Antigen (BCMA)-directed CAR- T cells in adult patients with multiple myeloma.

Study center(s): The study was conducted globally across 4 countries. The countries (study centers) included Australia (1 center), Israel (2 centers), Singapore (2 centers), and USA (4 centers).

Publication (reference): Sperling A, Derman B, Nikiforow S, et al (2023). Updated Phase 1 Study Data results of PHE885, A T-Charge™ manufactured BMCA-directed therapy for patients with relapsed/Refractory (r/r) multiple myeloma (MM). J Clin Oncol; 41(suppl 16): abstr 8004.

Study period:

Study initiation date: 23-Jul-2020 (first participant first visit)

Early termination date: 21-Aug-2024

Phase of development (phase of this clinical study): I

Objectives:

Primary objectives

The primary objective of this study was to assess the safety and tolerability of the PHE885 in patients with relapsed and/or refractory multiple myeloma (r/r MM) (Part A) and newly diagnosed multiple myeloma (NDMM, Part B), and to provide a single-agent dose recommendation for future studies.

Secondary objectives

Evaluate feasibility of the manufacturing process.

To assess anti-MM activity of B-cell maturation antigen (BCMA) chimeric antigen receptor T-cell (CAR-T) cell therapy in subjects with r/r MM (Part A) and NDMM (Part B) by evaluating overall response rate (ORR) by International Myeloma Working Group (IMWG) as assessed by local investigator.

To assess the complete response rate (CRR), as determined by local investigator in subjects with r/r MM (Part A) and NDMM (Part B).

To evaluate duration of response (DOR) as assessed by local investigator with r/r MM (Part A) and NDMM (Part B).

Characterize in vivo cellular kinetics of BCMA CAR-T cells in peripheral blood and bone marrow by quantitative polymerase chain reaction (qPCR).

Characterize the incidence and prevalence of BCMA CAR-T cell therapy immunogenicity (humoral and cellular).

Study design and methodology: This was an open-label, Phase I study conducted to assess the safety and tolerability of anti-BCMA CAR-T cell therapy. Part A was a dose escalation evaluating four dose levels (2.5, 5, 10 and 20 × 10^6 CAR-positive viable T cells) in patients with r/r MM. Part B explored two doses of PHE885 (10 × 10^6 and 20 × 10^6 CAR-positive viable T cells) in patients with NDMM who had received a minimum of 4 and up to 6 cycles of standard induction therapy (VRd, D-VRd, and D-Rd).

In Part B of the study, only patients who achieved a response of ≥ partial response (PR) following standard induction therapy were administered PHE885 as consolidation therapy. Approximately 3 months after PHE885 administration, patients began standard maintenance therapy for a minimum of 2 years.

Approximately 40–50 patients were planned to be enrolled in Part B and randomized 1:1 to each dose level. Enrollment was expected to continue until at least 20 patients with a response of PR or very good partial response (VGPR) to induction therapy had been enrolled per group.

Diagnosis and main criteria for inclusion:

Part A

- Patients ≥18 years of age with MM were relapsed and/or refractory to at least 2 prior treatment regimens, including an Immunomodulatory drug (IMiD) (e.g., lenalidomide or pomalidomide), a proteasome inhibitor (e.g., bortezomib, carfilzomib), and an approved anti-CD38 antibody (e.g., daratumumab), if available, and had documented evidence of disease progression (IMWG criteria).
- Eastern Cooperative Oncology Group (ECOG) performance status that is either 0 or 1 at screening

Part B

- Patients ≥18 years of age with NDMM who had received 4–6 cycles of standard induction therapy with VRd, Dara-Rd, or Dara-VRd, and had achieved a response of PR or better. One cycle of Cy-Vd (or Cy or Vd alone) was allowed prior to induction.
- ECOG performance status was either 0 or 1 at screening (Part A), or 0–2 at screening

Test and reference therapies, dose and mode of administration: The study treatment refers to PHE885.

Table 2-1 Investigational drugs

Investigational drug (Name and Strength)	Pharmaceutical dosage form	Route of administration	Dose	Frequency and/or regimen
PHE885	Cell suspension	Intravenous use	As assigned	Single administration on Day 1

No reference therapy was administered.

Protocol amendments and other changes to study conduct:

The study protocol was amended 5 times. This CSR describes the conduct of the study according to the amended protocol (Amendment 5.0 dated 19 October 2023). The key rationale for this amendment was to revise the toxicity management sections for cytokine release syndrome (CRS), immune-effector cell-associated neurotoxicity syndrome (ICANS), and immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS) to align with evolving best practices, current clinical guidelines, and updated recommendations from recognized consensus groups. The amendment also incorporated additional supportive care measures for patients identified as being at high risk of bleeding due to hyperinflammatory states, as well as recommendations for antimicrobial prophylaxis. These revisions were implemented in response to Health Authority feedback to ensure greater consistency and standardization of treatment practices across participating centers.

Clinical trial quality risk management: Not applicable

Criteria for evaluation:

- Manufacture success rate
- **Efficacy**: BOR, ORR, CRR and DOR
- **Safety**: Dose limiting toxicity (DLT), adverse events (AEs), serious adverse events (SAEs), including changes in laboratory values, ECGs, and vital signs after PHE885 infusion
- **Pharmacokinetics**: In vivo cellular kinetics of anti-BCMA CAR-T cell therapy in peripheral blood and bone marrow aspirate by qPCR.
- **Immunogenicity:** Cellular and humoral immunogenicity of anti-BCMA CAR-T cell therapy.
- **Safety**: Incidence and nature of dose-limiting toxicities (DLTs) during the first 28 days after PHE885 administration.

Monitoring of AEs and SAEs, including changes in laboratory values, electrocardiograms (ECGs), and vital signs after PHE885 administration.

Statistical methods:

The following analysis sets were used to analyze and report the study results:

Screened Set: All the patients who signed the informed consent.

Enrolled Set: All the patients who were enrolled in the study. Enrollment was defined as the point at which the patient met all inclusion/exclusion criteria, and the patient's apheresis product was accepted for manufacturing.

Full Analysis Set (FAS): All the patients who received PHE885. Patients were analyzed according to the dose of PHE885 received.

Safety Set (SS): All the patients who received PHE885. Patients were analyzed according to the dose of PHE885 received, defined as the dose of PHE885 taken on Study Day 1.

- Patients whose actual infused dose differed from the planned dose by ≤2 million cells and did not experience a DLT during the evaluation period were analyzed at the next lower dose level for safety.
- Patients whose actual infused dose differed by >2 million cells and experienced a DLT during the evaluation period were analyzed at the next higher dose level for safety.

Efficacy Analysis Set (EAS): All the patients who received PHE885 in Part B with a response of VGPR or PR to induction therapy. The best response to induction therapy that had been recorded prior to PHE885 infusion was used to determine EAS eligibility.

- If a patient had not received the exact planned dose of PHE885, the patient was analyzed at the planned dose of PHE885 if the actual infused dose was within 2 million cells of the planned dose; otherwise,
- The patient was analyzed separately at the actual infused dose.

Dose-Determining Set (DDS): All the patients who had sufficient safety evaluations (as determined by Novartis and the Investigator) or experienced a DLT during the DLT-evaluation period (i.e., the first 28 days of dosing) in Part A.

Pharmacokinetic Analysis Set (PAS): All the patients who provided an evaluable PHE885 pharmacokinetic (PK) profile. A profile was considered evaluable if all of the following conditions were satisfied:

- Patient received PHE885
- Patient provided at least one primary PK parameter

Immunogenicity Analysis Set (IGS): All the patients with at least one available valid (i.e., not flagged for exclusion) IG concentration measurement, who had received study treatment and had no protocol deviations that impacted IG data.
The number (%) of patients in each analysis set was summarized by actual PHE885 dose level.

Summary - Results

Demographic and background characteristics:

Part A

The median patient age was 65 years (range: 43–81), with 45.5% younger than 65. Sex distribution was balanced, and most patients were White (76.4%). At screening, eastern cooperative oncology group (ECOG) performance status was 0 in 45.5% and 1 in 54.5%; pre- infusion, 65.5% had status 1.

At initial diagnosis, 40% were International Staging System (ISS) stage I and 30.9% in ISS stage II. Median time from most recent relapse/progression to treatment start was 1.9 months (range: 1–11). Disease burden: 63.6% had <50% plasma cells in bone marrow. High-risk cytogenetics were present in 47.3% (≥1 of: del17, t (14;16), t (4;14), or 1q gain/amplification).

Part B

The median age was 62.3 years (range: 43–79), with 52.0% younger than 65. Most patients were male (68.0%) and White (76.0%), with 20.0% Asian. At screening, ECOG performance status was 0 in 52.0% and 1 in 48.0%; pre-infusion, 40.0% had status 0 and 44.0% status 1.

At initial diagnosis, 40.0% of patients were in ISS stage I and 48.0% of patients in ISS stage II. Disease burden was low, with 88.0% having <50% plasma cells in bone marrow. High-risk cytogenetic abnormalities were observed in 8.0% (≥1 of: del17, t (14;16), t (4;14), or 1q gain/amplification).

Protocol deviations: There were no major protocol deviations that could impact the study conduct or results.

Exposure:

Part A

A total of **55 patients** were infused with PHE885 in following doses:

- PHE885 20×10^6: N = 18
- PHE885 10×10^6: N = 20
- PHE885 5×10^6: N = 13
- PHE885 2.5×10^6: N = 4

Part B

A total of **25 patients** were infused with PHE885:

- PHE885 20×10^6: N = 12 patients
- PHE885 10×10^6: N = 13 patients

Summary of Manufacturing Success Rate, Efficacy, Pharmacokinetics and Immunogenicity results

Manufacturing Success Rate (MSR):

Part A: The MSR was 98.2% (90% CI: 91.7, 99.9).

Part B: All the groups achieved 100% (90% CI: 88.7, 100) MSR.

Efficacy results:

Best Overall Response (including ORR and CRR)

Part A: The CRR was 58.2% (90% CI: 46.2, 69.5) and ORR (≥PR) was 98.2% (90% CI: 91.7, 99.9).

Part B: The CRR was 57.1% (90% CI: 37.2, 75.5) and ORR was 81.0% (90% CI: 61.6, 93.2).

Response rate at 3 and 6 months

Part A:

- The CRR was 30.9% (90% CI: 20.7, 42.7) and 30.9% (90% CI: 20.7, 42.7) at 3 and 6 months, respectively.
- ORR was 85.5% (90% CI: 75.3, 92.6) and 65.5% (90% CI: 53.5, 76.1) at 3 and 6 months, respectively.

Part B

- The CRR was 38.1% (90% CI: 20.6, 58.3) and 52.4% (90% CI: 32.8, 71.4) at 3 and 6 months, respectively.
- ORR was 71.4% (90% CI: 51.3, 86.8) and 71.4% (90% CI: 51.3, 86.8) at 3 and 6 months, respectively.

DOR

- **Part A:** The median DOR was 11.2 months (90% CI: 7.9 - 17.1). At month 12, 48.1% (90% CI: 36.6 - 58.7) of responders maintained response
- **Part B:** The median DOR was not estimable (NE) in either analyses because the majority of responders had no event at the time of data cut-off.

Pharmacokinetics results:

Part A: The time concentration profiles of PHE885 show comparable cellular expansion between all target dose levels for the cellular kinetic analysis set. Cellular expansion based on Cmax, AUC0-28d were comparable between the target dose levels. Longer persistence (Tlast) of PHE885 transgene was observed at dose level $5x10^6$, $20x10^6$ and $10x10^6$ with median Tlast of 189 days, 186 days and 139 days respectively compared to 46.0 days for dose level 2.5 $x10^6$.

Part B: The time concentration profiles of PHE885 show comparable cellular expansion between the $10x10^6$ and $20x10^6$ dose levels for the cellular kinetic analysis set. The cellular kinetic parameters were comparable between the two dose levels. Overall, the exposure (Cmax and AUC0-28) was 1.7-1.9-fold higher in the dose evaluation part (Part B) than the dose escalation part (Part A).

Immunogenicity results:

- **Part A**: Anti-drug antibodies (ADA) incidence was 56.4% in patients treated with PHE885. Cellular immunogenicity responses were low, with mean values <1% across the time points.
- **Part B**: ADA incidence was 48.0% in patients treated with PHE885. Cellular immunogenicity responses were low, with mean values <1% across the time points.

Safety results:

Part A

The overall median safety follow-up period (from infusion to death or last follow-up) was 22.4 months.

DLT: Nine patients (16.4%) were reported with at least 1 DLT. The most frequently reported DLTs were neutropenia (3.6%) and associated Preferred Terms (PTs) of neutrophil count decreased (1.8%), lipase increased, and neurotoxicity (3.6% each).

AEs: All patients (N=55) who received PHE885 were reported with at least one AE, regardless of relationship to PHE885, and all the reported AEs were suspected to be related to PHE885 by the investigator. The majority of patients (98.2%) had grade ≥3 AEs. The most frequently reported AEs at anytime post infusion were cytokine release syndrome (98.2%), anaemia (83.6%), neutropenia (70.9%) and associated PT of neutrophil count decreased (25.5%), pyrexia (60.0%), hypotension (52.7%).

SAEs: Thirty-five (63.6%) patients were reported with at least one SAE, 25 (45.5%) were suspected to be related to PHE885 by the investigator. The most frequently reported PTs were cytokine release syndrome (29.1%), pneumonia (12.7%), rhinovirus infection, myelodysplastic syndrome, dyspnoea (7.3% each), and pyrexia (5.5%).

Death: A total of 25 patients died during the study. Of these, 21 patients died due to underlying disease progression, and 4 patients due to adverse events. The causes of the 4 adverse event-related deaths were COVID-19 pneumonia (1 patient, 1.8%), pneumonia (2 patients, 3.6%), and haemorrhagic shock secondary to a surgical complication (1 patient, 1.8%). The death reported in 1 patient due to pneumonia was considered related to PHE885 infusion.

Adverse Events of Special Interest (AESI): Cytokine release syndrome (98.2%); Neurological events: immune effector cell–associated neurotoxicity syndrome (ICANS) (21.8%), cranial nerve disorders (9.1%), peripheral neuropathy (3.6%); immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome (IEC-HS) (12.7%); Haematological disorders including cytopenias (98.2%); Prolonged depletion of plasma cells and hypo/ agammaglobulinemia (12.7%); Infections: viral infections (49.1%), bacterial infections and fungal infections (16.4% each), sepsis (3.6%), infections-pathogen unspecified (52.7%); Second primary malignancies including vector insertion site (oligo or monoclonality) (10.9%) no cases of T-cell second primary malignancy or vector insertion site.

Part B

The overall median safety follow- up period (from infusion to death or last follow-up) was 12.5 months.

DLTs: Twelve patients (48.0%) were reported with at least 1 DLT. The most frequently reported (≥8%) DLTs were immune effector cell-associated HLH-like syndrome (6, 24.0%) and associated PT of hemophagocytic lymphohistiocytosis (2, 8.0%), neutropenia (2, 8.0%) and associated PT of neutrophil count decreased (1,4.0%), thrombocytopenia (2, 8.0%) and associated PT of platelet count decreased (1, 4.0%).

AEs: All (N=25) patients who received PHE885 were reported with at least one AE, regardless of relationship to PHE885, and all the reported AEs were suspected to be related to PHE885 by the investigator. All patients had grade ≥3 AEs. The most frequently reported AEs anytime post infusion were cytokine release syndrome (100%), neutropenia (72.0%) and associated PT of neutrophil count decreased (36.0%), anaemia (68.0%), thrombocytopenia (60.0%) and associated PT of platelet count decreased (28.0%), diarrhoea (44.0%), immune effector cell- associated hemophagocytic lymphohistiocytosis (HLH)-like syndrome (36.0%) and associated PT of haemophagocytic lymphohistiocytosis (20.0%).

SAEs: The most frequently reported PTs (all grades) in ≥5% of patients were immune effector cell-associated HLH-like syndrome (36.0%) and associated PT of haemophagocytic lymphohistiocytosis (12.0%), febrile neutropenia (16.0%), neutropenia (12.0%) and associated PT of neutrophil count decreased (4.0%), pneumonia (12.0%), thrombocytopenia, enterococcal bacteraemia, and septic shock (8% each).

Deaths: Four patients died at any time during the study. Of these 4 deaths, 1 patient died within 30 days, and 3 patients died more than 30 days after PHE885 infusion. Cause of deaths were AEs; bacterial sepsis, septic shock, soft tissue necrosis and distributive shock (1, 4.0% each). All four deaths were related to PHE885 infusion and considered complication of IEC-HS.

AESI: Cytokine release syndrome (100%); Neurological events: ICANS (4%), cranial nerve disorders and peripheral neuropathy (8.0% each); IEC-HS (56.0%), Haematological disorders including cytopenias (100.0%); Prolonged depletion of plasma cells and hypo/ agammaglobulinemia (16.0%); Infections: viral infections (40.0%), bacterial infections and sepsis (20.0% each), fungal infections (8.0%), infections-pathogen unspecified (36.0%); Second primary malignancies including vector insertion site oligo or monoclonality (12.0%), no cases of T-cell second primary malignancy or vector insertion site.

Conclusions: The study confirmed the feasibility of the T-Charge™ manufacturing process with a consistently high success rate in Part A and B and PHE885 demonstrated strong preliminary anti-myeloma activity, with overall response rates (ORR) of 98.2% for Part A and 81.0% for Part B, and complete response rates (CRR) of 58.2% for Part A and 57.1% for Part B, respectively. In addition, several patients in part B showed deepening responses between month 3 and month 6. DLTs and SAEs occurred more frequently in Part B of the study. In the NDMM population, high frequency of CRS and IEC-HS along with hematologic toxicities and infections were observed leading to prolonged and profound cytopenias, particularly neutropenia, and severe polymicrobial infections were observed including fatal complications of IEC-HS. IEC-HS with prolonged cytopenia was considered a new safety signal in the NDMM population.

Due to the IEC-HS safety signal, including fatal complications and the associated change in the benefit-risk profile for this population, the study was placed on voluntary clinical hold on 05- Jan-2024. Considering the rapidly evolving treatment landscape in multiple myeloma, a business decision was made on 21-August-2024 to discontinue further development of PHE885.