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Application Type	Original Biologics License Application
STN	BLA 125806/0
CBER Received Date	August 1, 2023
PDUFA Goal Date	June 30, 2024 (Updated from March 31, 2024 after receipt of Major Amendment)
Division / Office	DCEGM/OCE/OTP
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Priority Review	Yes
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Applicant	Rocket Pharmaceuticals, Inc.
Established Name	marnetegrane autotemcel
(Proposed) Trade Name	KRESLADI
Pharmacologic Class	Autologous CD34+ Hematopoietic Stem cells that are transduced with an ex vivo lentiviral vector (Chim-CD18-WPRE LV)
Dosage Form(s) and Route(s) of Administration	KRESLADI is a cell suspension for intravenous infusion
Dosing Regimen	One-time treatment
Indication(s) and Intended Population(s)	Treatment of severe Leukocyte Adhesion Deficiency-I (LAD-I)

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GLOSSARY

AE	Adverse Event
AER	Annualized Event Rate
aGvHD	Acute Graft-versus-host Disease
BM	Bone Marrow
DCOD	Data Cutoff Date
EBMT	European Group for Blood and Marrow Transplantation
EFS	Event Free Survival
FDA	Food and Drug Administration
HSC	Hematopoietic Stem Cells
HSCT	Hematopoietic Stem Cell Transplant
HLA	Human Leukocyte Antigen
IND	Investigational New Drug
IR	Information Request
ITT	Intent-to-Treat
I.V.	Intravenous
LAD-I	Leukocyte Adhesion Deficiency-I
LTFU	Long-term Follow-up
LV	Lentiviral Vector
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
OS	Overall Survival
PB	Peripheral Blood
PPF	Per Protocol Final
PPT	Per Protocol Transplant
PT	Preferred Term
RMAT	Regenerative Medicine Advanced Therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
UK	United Kingdom
US	United States

1. Executive Summary

The original biologics license application (BLA) 125806/0 seeks traditional approval of RP-L201(also referred to as KRESLADI) for the treatment of severe Leukocyte Adhesion Deficiency-I (LAD-I). RP-L201 is a one-time, single-dose, investigational gene therapy product of autologous CD34+ hematopoietic stem cells transduced *ex vivo* with a lentiviral vector to encode for the ITGB2 gene. To support the efficacy and safety of RP-L201, the applicant included results from Study RP-L201-0318 (main study), a Phase I/II, open-label, single-arm, multi-site trial in severe LAD-I patients (age range: 10 months to 10 years) who were treated with RP-L201, and the results available by the data cut-off date in a long-term follow-up (LTFU) study (RP-L201-0121-LTFU) for those patients treated in the main study for a total follow-up of up to 15 years after the infusion. In addition, the applicant included the efficacy analysis results for comparison of patients treated in the RP-L201-0318 study with a subset of severe LAD-I patients in the European Group for Blood and Marrow Transplantation (EBMT) registry who underwent an allogeneic hematopoietic stem cell transplant (HSCT) at ages <12 years.

Efficacy

In Study RP-L201-0318, nine patients with severe LAD-I were treated with RP-L201 and were followed up for at least one year and up to 24 months post-infusion. Three patients were younger than one year of age when they were treated (the younger subgroup), while the other 6 patients ranged from age 2.6 to 9.8 years when they were treated (the older subgroup).

The primary efficacy endpoint was the proportion of survival responders, defined as a patient being alive for at least one year after RP-L201 infusion without receiving allogeneic HSCT. In addition, patients who are treated at less than one year of age need to be alive at age 2 (24 months) without allogeneic HSCT to qualify as a survival responder. The planned primary efficacy analysis was the observed survival response rate compared to a threshold survival rate of 39%. In the study, all nine treated patients were survival responders. The survival response rate was 100%, with a 95% two-sided confidence interval (CI) of (66%, 100%) and a p-value of 0.0002 when compared to a threshold rate of 39%.

The clinical reviewers consider the null survival response rate of 39% potentially acceptable for the younger subgroup (n=3), though there were some uncertainties with setting the threshold at 39%, because the supportive data were from developing countries and were not recent, which might not reflect current standard of care in the United States (US). With all three patients being survival responders, the 95% CI for the response rate is (29%, 100%), and the lower bound does not exceed the 39% threshold (p-value 0.059).

The clinical review team determined that there is no natural history data to support setting a null survival response rate for the older subgroup (n=6) at 39%.

Three patients are siblings, with the two younger siblings identified after the oldest one was identified first (diagnosed at 3.6 years of age). One of the siblings is in the younger subgroup. If conditioning on a patient surviving past age 2 would increase the chance of

younger siblings' also surviving past age 2, this sampling scheme might complicate the interpretation of the survival response in the younger subgroup.

In addition, the applicant reported the results for the following three key infection-related endpoints:

- Significant infection: Mean annualized event rate (AER) was 3.5 ± 0.3 events/year pre-infusion (baseline), compared to 0.5 ± 0.2 events/year from 91 days post-engraftment to data cut-off (efficacy period).
- Infection-related hospitalization: Baseline AER was 2.1 ± 0.3 while efficacy period AER was 0.5 ± 0.2 .
- Prolonged infection-related hospitalization (> 7 days): Baseline AER was 1.5 ± 0.2 while efficacy period AER was 0.3 ± 0.1 .

However, the clinical review team considers the within-subject comparison results reported by the applicant for these infection-related endpoints to be difficult to interpret due to several considerations:

- Determination of baseline infection-related events partially involves retrospective recalls by parents over a long period of years.
- Infection rates are expected to decrease with increased age.
- Considerable missing data, inconsistencies, and poor quality of infection-related endpoints.

We agree with the clinical team's evaluation regarding the data quality issues based on internal discussions and examples they identified. Please refer to the clinical review memo for more information.

Biomarker data on CD18 and CD11a were also reported in this submission. The evaluation of these results is deferred to the clinical pharmacology reviewer.

Finally, the applicant provided post-hoc analyses comparing several efficacy endpoints between the nine treated patients in Study RP-L201-0318 and three matched subsets of LAD-I patients identified from the EBMT Registry. Below are results for selected endpoints for comparisons with the subset of age-matched patients (N=51); results were similar to those in two other subsets matched on different criteria:

- Overall survival (OS) and event-free survival (EFS): RP-L201 treated patients showed numerically higher survival rates at 12 months post infusion (100% for both endpoints) than EBMT patients (OS: 83%, p-value > 0.05 ; EFS 59%, p-value < 0.05).
- Hospitalization-free and prolonged hospitalization-free survivals: EBMT patients showed numerically higher survival rates at 12 months post infusion than RP-L201 treated patients (difference of $\sim 12\%$, p-value > 0.05).

The comparison of various endpoints between RP-L201 treated patients and the matched patients from EBMT should be viewed as a comparison with an active control as the EBMT patients all received potentially curative allogeneic HSCT. Therefore, a statistically significant result from a superiority comparison is not expected to be a

requisite component, from a statistical perspective, to conclude the efficacy of RP-L201. However, no equivalence or non-inferiority margins were pre-specified prior to such analyses, nor proposed post-hoc to aid interpretation. Additional issues include data quality issues in the RP-L201 treated patients, the uncertainty in comparability between the compared patients in general in external-control based analyses. Based on the totality of these issues, the EBMT comparison does not provide compelling statistical evidence of effectiveness.

Safety results

There were no deaths in the studies. The applicant reported that there were no serious adverse events related to RP-L201, no graft-versus-host disease, and no secondary graft failures. Please refer to the clinical review memo for more information.

Conclusions

Efficacy evaluation of RP-L201 in treatment of severe LAD-I was based on data on nine patients treated with RP-L201 and followed up for at least one year (8 of them for at least 2 years). All patients met the survival response endpoint of surviving at least one year after infusion without allogeneic HSCT and in addition beyond 2 years of age for those treated at younger than one year of age. However, according to the clinical team, this endpoint was not interpretable in a single-arm study for the older subgroup (n=6) but may be interpretable in the younger subgroup (n=3) who were treated before they were one year old. The 95% CI for this survival response rate in the younger subgroup was (29%, 100%), which does not rule out the 39% null response rate. The applicant reported significant reduction in infection-related endpoints post RP-L201 treatment compared to baseline. However, in the clinical review team's opinion, study design and data quality issues render interpretation of infection data difficult. Findings comparing the RP-L201 treated patients with EBMT patients as an external control were inconclusive due to lack of pre-specified criteria for demonstration of efficacy and possible issues in population comparability, among other issues. Therefore, given the small sample size and above-mentioned challenges in interpreting the data, there is no conclusive statistical evidence of efficacy of RP-L201. However, it may be possible to conclude that there is substantial evidence of effectiveness based on a synthesis of multiple sources of information, including the mechanism of action, predictive biomarkers, and clinical perspectives of the data including benefit and risk considerations. Such a conclusion requires above all clinical judgment.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

LAD-I is a rare form (1 in 1,000,000 global prevalence) of primary immunodeficiency disorder. The clinical phenotype of severe LAD-I is characterized by recurrent, potentially life-threatening bacterial and fungal infections. Around 61% to 75% of patients with severe LAD-I are estimated to die prior to the age of 2 in the absence of allogeneic hematopoietic stem cell transplant (HSCT).

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Allogeneic HSCT is the only potentially curative therapy for LAD-I. Supportive treatments in LAD-I consist primarily of anti-microbials to prevent or treat acute and/or recurrent infections.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

RP-L201 is not currently marketed in any part of the world.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

Table 1. Regulatory Activity

Date	Regulatory Activity
November 9, 2016	Orphan drug designation for the treatment of Leukocyte Adhesion Deficiency-I (LAD-I) by FDA (OD #16-5430)
October 17, 2018	Original Submission of Investigational New Drug (IND) 18485 for the treatment of Severe LAD-I
November 30, 2018	Rare pediatric disease designation by FDA (RPD-2018-194)
December 12, 2018	Fast Track Designation by FDA
March 4, 2021	Regenerative Medicine Advanced Therapy (RMAT) designation by FDA
October 24, 2022	Pre-BLA Meeting Request denied
August 1, 2023	BLA 125806/0 submitted with data cut-off date of January 24, 2023
November 30, 2023	The applicant submitted 120-Day Safety and Efficacy Update to the BLA (125806/0/17), with a new data cut-off date of July 24, 2023, including the safety results as well as the dataset and computer programs for Study RP-L201-0121-LTFU.
December 7, 2023	The applicant submitted EBMT Registry data with 91 patients' information

Source: Reviewer's summary.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The clinical development program of RP-L201 for severe LAD-I consists of the main study RP-L201-0318 and the long-term follow-up study RP-L201-0121-LTFU. The efficacy and safety databases consist of data from both studies. See “Section 5.3 Table of Studies/Clinical Trials” for a summary of the studies. In addition, the applicant submitted data, analysis and report for external-control LAD-I patients who received allogeneic HSCT identified from the EBMT registry. My review will focus on the efficacy analyses.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The basis of this statistical review includes documents in the original BLA 125806/0.0 and information request (IR) responses from the applicant submitted as BLA amendments. Documents reviewed are listed below.

- STN 125806/0.0 Module 1.14 Labeling
- STN 125806/0.0 Module 1.2 Reviewer’s Guide
- STN 125806/0.0 Module 2.5 Clinical Overview
- STN 125806/0.0 Module 2.7.3 Summary of Clinical Efficacy
- STN 125806/0.0 Module 2.7.4 Summary of Clinical Safety
- STN 125806/0.0 Module 5.2 Tabular Listing of all Clinical Studies
- STN 125806/0.0 Module 5.3 Clinical Study Reports including the RP-L201-0318 study and the EBMT study report.
- STN 125806/0.2 Module 5.3.5.2. Clinical Information Amendment (Response to potential filing issues during the filing meeting and request for statistical programs of study RP-L201-0318)
- STN 125806/0.12 Module 5.3.5.2. Clinical Information Amendment (Response to provide the protocol for study RP-L201-0121-LTFU)
- STN 125806/0.14 Module 5.3.5.2. Clinical Information Amendment (Response to provide the correct dataset for correct CONSDT value)
- STN 125806/0.16 Module 1.11.3. Clinical Information Amendment (Response to provide the source of pre-treatment infections and hospitalization)
- STN 125806/0.17 Module 2.7. Clinical Information Amendment (Response to submit the clinical summary for the 120-day updates of efficacy and safety results of study RP-L201-0318 and RP-L201-0121-LTFU)

- STN 125806/0.17 Module 5.3.5.3. Clinical Information Amendment (Response to submit tables, figures and listings (TFLs) for the 120-day updates of efficacy and safety results of study RP-L201-0318 and RP-L201-0121-LTFU)
- STN 125806/0.17 Module 5.3.5.2. Clinical Information Amendment (Response to submit the datasets and the programs for studies RP-L201-0318 and RP-L201-0121-LTFU)
- STN 125806/0.18 Module 5.3.5.2. Clinical Information Amendment (Response to submit the post-marketing registry protocol synopsis)
- STN 125806/0.19 Module 2.7.3. Clinical Information Amendment (Response to submit the updated 120-day efficacy report with the correct swimmer plot and additional analyses to characterize the reduction in incidence of infections.)
- STN 125806/0.20 Module 5.3.5.4. Clinical Information Amendment (Response to submit the subject-level data of the 91 EBMT patients for the variables requested by the clinical reviewers)
- STN 125806/0.26 Module 5.3.5.2. Clinical Information Amendment (Response to submit the updated ADINF and ADPL datasets requested by clinical reviewer)
- STN 125806/0.27 Module 5.3.5.2. Clinical Information Amendment (Response to submit additional EBMT analysis requested by clinical reviewer)
- STN 125806/0.64 Module 1.11.3. Clinical Information Amendment (Response to submit the updated information on whether all treated patients are still alive and have not required HSCT)

5.3 Table of Studies/Clinical Trials

Table 2 summarizes the two RP-L201 studies and one external-control study report forming the basis of this BLA review.

- RP-L201-0318 study treated 9 pediatric patients aged at least 3 months (from 0.3 to 9.3 years at screening) and followed patients for 2 years after RP-L201 treatment.
- RP-L201-0121-LTFU study provided long-term follow-up, for up to 15 years in total after RP-L201 infusion for patients treated in the parent study RP-L201-0318. Six patients had enrolled in this study as of data cutoff.
- EBMT registry reports to compare outcomes between patients treated with RP-L201 and those in EBMT registry who received HSCT.

Table 2. Overview of Clinical Studies and External-Control Study Reports

Study Name	Study Description	Number of treated patients
RP-L201-0318	Main study for this BLA <ul style="list-style-type: none"> • Phase I/II • Safety and efficacy in patients with severe LAD-I 	9

	<ul style="list-style-type: none"> • Males and females with severe LAD-I aged 0.3 to 9.3 years at screening • United States (US), United Kingdom (UK), and Spain • Enrollment completed. Study Ongoing • The applicant initially submitted data with a data cutoff date (DCOD) on January 24, 2023. The applicant later submitted data with a new DCOD of July 24, 2023, in the 120-day update of efficacy and safety data for Studies RP-L201-0318 and RP-L201-0121-LTFU. 	
RP-L201-0121-LTFU	<ul style="list-style-type: none"> • Long-term follow-up study for a total of 15 years after infusion for patients treated in the parent study RP-L201-0318 after they complete or discontinue from the parent study. • US, UK, and Spain 	6 (treated in Study RP-L201-0318)
EBMT Registry Reports	<ul style="list-style-type: none"> • Compare outcomes between LAD-I patients in the EBMT Registry who received allogeneic HSCT and RP-L201 treated LAD-I patients from Study RP-L201-0318. • Consists of the EMBT Registry Report and the EBMT Comparator Cohort Report 	55 patients from EBMT Registry (aged from 0.12 to 11.12 years at HSCT) 9 patients from RP-L201-0318

Source: Reviewer's summary.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

The efficacy and safety database consists of data from the main study RP-L201-0318 and the long-term follow-up study RP-L201-0121-LTFU. In addition, comparisons between patients treated in the main study and those in the EBMT registry who received HSCT (external control) were reported. The review below is based primarily on a DCOD of July 24, 2023 for studies RP-L201-0318 and RP-L201-0121-LTFU. However, the comparison results with the EBMT registry were based on a DCOD of January 24, 2023 for the RP-L201-0318. This Section primarily reviews Study RP-L201-0318, incorporating Study RP-L201-0121-LTFU and EBMT registry comparison when needed.

6.1 Trial #1: Study RP-L201-0318

Study RP-L201-0318 is a single-arm trial. The protocol is entitled “Gene Therapy for Leukocyte Adhesion Deficiency-I (LAD-I): A Phase I/II Clinical Trial to Evaluate the Safety and Efficacy of the Infusion of Autologous Hematopoietic Stem Cells Transduced with a Lentiviral Vector Encoding the ITGB2 Gene.”

6.1.1 Objectives

Primary Objective:

- Trial Phase I:
 - To characterize the safety and toxicity associated with the investigational product.
- Trial Phase II:

- To assess the proportion of survival responders, defined as a patient being alive for at least one year after RP-L201 infusion without receiving allogeneic HSCT [for patients aged 1 year or above at enrollment], and [being alive] at age 2 (24 months) without allogeneic HSCT for patients less than 1 year of age at study enrollment.
- To characterize the safety and toxicity associated with the RP-L201.

Selected key Secondary Objectives:

- Determination of the incidence of significant infections, infection-related hospitalizations, and prolonged infection-related hospitalizations, comparing the incidences prior to RP-L201 infusion with those after hematopoietic reconstitution.
- Assessment of relevant biomarkers, including CD18.

Reviewer's Comments:

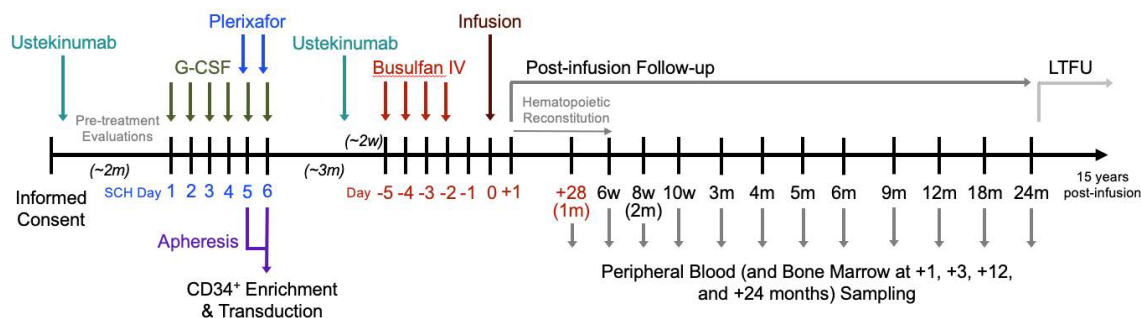
- *I have included additional texts in the brackets of the protocol-stated primary objectives for clarity.*
- *Age at enrollment has been used in the protocol. However, the FDA clinical reviewer considers using age at treatment (i.e., at infusion) to be more appropriate. This distinction does not change the numbers of patients in the age categories (<1 year, vs. ≥ 1 year old)*

6.1.2 Design Overview

The trial consisted of two phases. In Phase 1, 2 patients were treated. Seven additional patients were treated in Phase 2, for a total of 9 patients in the entire trial.

Figure 1 depicts a patient's journey in the trial, including in the LTFU study. Each patient would undergo stem cell mobilization, apheresis, and conditioning before receipt of RP-L201.

Figure 1. Overview of Study Design



Source: Adapted from BLA 125806/0, Clinical Study Report, Figure 2.

6.1.3 Population

Key Inclusion Criteria:

- A confirmed diagnosis of severe LAD-I as demonstrated by flow cytometry indicating neutrophil CD18 expression <2% (polymorphonuclear neutrophils)

- [PMNs]). Patients in whom CD18+ PMNs were >2% were considered eligible with CD11a or CD11b expressing PMNs <2% and if there is a documented *ITGB2* mutation and clinical history consistent with LAD-I (or known family history).
- At least one prior significant bacterial or fungal infection (National Cancer Institute – Common Terminology Criteria for Adverse Events Version 5.0 [NCI-CTCAE v5.0], Grade ≥ 2). This criterion was not required for patients with documented family history who met the above inclusion criteria.
 - Age ≥ 3 months.
 - Considered to be an appropriate candidate for autologous transplantation of hematopoietic stem cells (HSC).

Key Exclusion Criteria:

- Availability of a medically eligible human leukocyte antigen (HLA)-identical sibling donor transplant. If an HLA-identical sibling was identified, but peripheral blood (PB) or bone marrow (BM) HSC collection was not feasible (e.g., donor *in utero*, donor was a newborn from whom cord blood was not collected, or donor was unable to undergo donation procedure because of medical impairments), inclusion was permitted per Investigator discretion.
- Serious infections with persistent bloodstream pathogens at time of trial entry (patients with active infections – for example, unresolved ulcerative lesions, skin, or oral infections were permitted as long as appropriate antibiotic therapy was administered).

6.1.4 Study Treatments or Agents Mandated by the Protocol

Patient would undergo stem cell mobilization, apheresis, and conditioning before receipt of RP-L201.

6.1.6 Sites and Centers

The nine patients treated in this trial were from three countries, each including one clinical site: the United States (US), United Kingdom (UK), and Spain.

6.1.7 Surveillance/Monitoring

In Study RP-L201-0318, the patients were to be followed up weekly (or daily for some events) for the first month, and biweekly in the second month. From the third month, patients were to be followed up monthly until 6 months and then every 3 months up to one year after the infusion. From Month 12 to Month 24, patients were to be followed up every 6 months. Patients who completed the planned 24-month follow-up or discontinued early in the study were to be enrolled in the RP-L201-0121-LTFU Study, for a total of 15 years follow up. Patients were to be followed up every 6 months up to the first 5 years following RP-L201 infusion, and once a year until end of 15 years follow up.

6.1.8 Endpoints and Criteria for Study Success

Primary efficacy endpoint:

- The proportion of survival responders, defined as a patient being alive for at least one year after RP-L201 infusion without receiving allogeneic HSCT. In addition, patients who are treated at less than one year of age need to be alive at age 2 (24 months) without allogeneic HSCT to qualify as a survival responder.

Null hypothesis for the primary efficacy endpoint analysis:

The applicant proposed the null hypothesis for the survival response rate to be 39%, stating that a recent evaluation in the literature showed that 26 of 66 severe LAD-I patients (39%) survived to age 24 months, in the absence of allogeneic HSCT.

Key secondary efficacy endpoints:

- Infection related endpoints compared between the period pre-infusion and those following hematologic reconstitution after RP-L201 infusion:
 - Incidence of significant infections, defined as those requiring hospitalization or parenteral antimicrobials
 - Incidence of infection-related hospitalizations
 - Incidence of prolonged infection-related hospitalizations (≥ 7 days), analyzed per patient and across the entire cohort, comparing event rates
- Biomarker related endpoints

6.1.9 Statistical Considerations & Statistical Analysis Plan

Analysis sets

- **Intention to Treat (ITT)** population: Includes all patients for whom informed consent is provided and who undergo any trial procedure.
- **Per Protocol Transplant (PPT)** population: Includes all patients that have received the investigational product.
- **Per Protocol Final (PPF)** population: Includes all patients that complete the 24 months follow-up period.

Sample size estimation

With a null hypothesis on the survival response rate of 40% and an assumed 80% response rate in RP-L201 treated patients, a sample size of 9 provides approximately 70% power for a binominal test at a two-sided 5% significance level.

Reviewer's Comment:

The effect size assumed in the protocol and the statistical analysis plan (SAP) are inconsistent. In the protocol, the applicant assumed a historical survival rate of approximately 40% and a true survival rate of 90% among treated patients. With the planned sample size of 9, the study would have approximately 95% power via a binominal test with two-sided 5% significance level under these assumptions. There was also an inconsistency wherein both 39% and 40% were reported to be the null response rate. In what follows, I will use 39%.

Analysis plan for primary efficacy endpoint

The primary analysis of the primary efficacy endpoint was a test of the observed survival response rate against the null response rate of 39%, using an exact binomial test at the two-sided 5% significance level.

The primary analysis was to be performed with the PPT analysis set. Sensitivity analysis of the primary endpoint was to also be performed on the PPF population if the PPT and PPF populations are different.

Reviewer's comment: P-values presented in this review for the primary endpoint are one-sided.

Analysis plan for key secondary efficacy endpoints

Reviewer's Comment:

The key secondary endpoints are infection-related endpoints. These endpoints were compared between the period from 91 days after RP-L201 infusion and the period prior to RP-L201 infusion (baseline) using Poisson regression.

Evaluation of biomarker endpoints is deferred to the clinical pharmacology reviewer.

Handling of Dropouts or Missing Data

Any patient who withdrew from the study prior to treatment with the investigational product was to be replaced. Patients who received the investigational product but were subsequently withdrawn would not be replaced. No imputation was to be performed for missing data.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Nine patients were enrolled and treated, including two in the Phase 1 portion of the study and seven in the Phase 2 portion. No patients terminated participation early. All three analysis sets had the same patients.

6.1.10.1.1 Demographics

Patient demographics for the ITT population are summarized in Table 3. The age range of the 9 patients was from 10 months to 10 years at infusion. Three patients were under 12 months of age at the time of RP-L201 infusion. Six patients were from the United States.

Table 3. Demographics and Baseline Characteristics (ITT Population, N=9)

Characteristics	
Age at parent study Infusion – months	
Mean (SD)	41.9 (33.9)
Median [Min, Max]	42.3 [9.8, 117.4]
Age at parent study Infusion Category – n (%)	

<12 months	3 (33.3)
12 – 48 months	3 (33.3)
>48 months	3 (33.3)
Age at parent study Diagnosis – months	
Mean (SD)	21.9 (31.2)
Median [Min, Max]	6.8 [0.0, 95.9]
Age at parent study Diagnosis Category – n (%)	
<12 months	6 (66.7)
12 – 48 months	2 (22.2)
>48 months	1 (11.1)
Age at study LTFU informed consent – Years	
n	6
Mean (SD)	5.9 (3.5)
Median [Min, Max]	5.0 [2.9, 12.3]
Sex – n (%)	
Male	4 (44.4)
Female	5 (55.6)
Race – n (%)	
Asian	2 (22.2)
White	6 (66.7)
Unknown / Not Reported	1 (11.1)

Abbreviations: ITT=Intent-to-Treat; SD=standard deviation; Min=Minimum; Max=Maximum.

Source: Adapted from BLA 125806/0, Clinical Study Report, Table 6, and BLA 125806/0/17, Module 5.3.5.3 120-Day – Integrated Summary of Safety, Table 1.1.2.1.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Birth History

Of the nine patients, seven had peri-natal umbilical cord complications characteristic of LAD-I (including delayed detachment in each of these seven patients and omphalitis in four patients).

History of Infection

History of infections is summarized in Table 4. All nine patients experienced at least one infection prior to enrollment into the study, and eight patients experienced at least one infection necessitating hospitalization prior to enrollment into the study. A total of 170 infection events were reported, including 80 events requiring hospitalization, representing a mean of 8.9 infection-related hospitalizations per patient. Pre-enrollment infections were observed across a wide spectrum of organ systems; infectious preferred terms (PTs) reported for more than two patients included bronchiolitis, mouth ulceration, omphalitis, and otitis media. Treatment for infection varied by patient, mostly included intravenous (I.V.) (n=8; [88.9%]) and oral (n=8; [88.9%]) antibiotics.

Table 4. Prior Infection History (ITT Population, N=9)

Status	n (%)	Event Count
History of Infection		

Prior infections	9 (100)	170
Infections Involving Hospitalization	8 (88.9)	80
Treatment Required		
I.V. Antibiotics	8 (88.9)	63
Oral Antibiotics	8 (88.9)	57
I.V. Antivirals	1 (11.1)	1
Oral Antivirals	3 (33.3)	5
I.V. Antifungals	2(22.2)	3
Oral Antifungals	3(33.3)	7
Other	8(88.9)	45

Abbreviations: ITT=Intent-to-Treat; I.V.=intravenous.

Source: Adapted from BLA 125806/0, Clinical Study Report, Table 9.

Reviewer's comment: The duration of the data collection period for the events in Table 4 was variable.

6.1.10.1.3 Subject Disposition

Subject disposition is presented in Table 5. All nine patients have completed at least 1 year of follow-up, and eight patients have completed 2 years of follow-up.

Table 5. Overview of Subject Disposition (All Study Phases)

Status	Patients
Enrolled, n	9
ITT Population, n (%)	9 (100)
PPT Population, n (%)	9 (100)
PPF Population, n (%)	5 (55.6)
Subjects Who Completed Parent Study	8 (88.9)
Subjects Who Enrolled in LTFU Study	6 (66.7)
Subjects Who Discontinued LTFU Study due to AE	0
Duration of follow-up (months)	
n	9
Mean (SD)	29.8 (7.5)
Median [Min, Max]	29.3 [21.7, 44.8]
Patients in ITT Population (n=9) Who:	
Completed 1 Year, n (%)	9 (100)
Completed 2 Years, n (%)	8 (88.9)
Completed 2.5 Years, n (%)	5 (55.6)
Completed 3 Years, n (%)	2 (22.2)
Completed 3.5 Years, n (%)	1 (11.1)
Terminated Early from the Study	0

Abbreviations: ITT=Intent-to-Treat; n=number of patients in group; PPF=Per-Protocol Final; PPT=Per-Protocol transplant; AE=Adverse Event; Min=Minimum; Max=Maximum.

Source: Adapted from BLA 125806/0/17, Module 2.7.4 summary of clinical safety, Table 3.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

All 9 patients were survival responders, resulting in a 100% response rate with a p-value of 0.0002, and a 95% confidence interval (CI) of (66%, 100%).

Reviewer's Comment:

The clinical reviewers communicated that the primary efficacy endpoint was not interpretable for patients who were treated at older than one year of age due to lack of natural history information to support a null survival response rate in this group, which I term the "older subgroup". There were only 3 patients treated at younger than one year of age ("younger subgroup"). The clinical reviewers consider the survival response, as defined, interpretable for the younger group, although there are some uncertainties with the proposed null response rate of 39% due to the cited data being from developing countries during an earlier time period. For the younger subgroup, the response rate was 100% (3/3) with a p-value of 0.059 and a 95% CI of (29%, 100%).

6.1.11.2 Analyses of Secondary Endpoints

Significant Infections, Infection-related Hospitalizations and Prolonged Infection-related Hospitalizations

Annualized event rates for infection-related hospitalizations, prolonged infection-related hospitalizations, and significant infections are shown in Table 6. The results show a statistically significant decrease after hematopoietic reconstitution (from 91 days post-engraftment to end-of-study [EoS]) relative to pre-infusion incidences (p-value <0.0001). Figure 2 illustrates the significant infections per patient between the period prior to infusion (lifetime history of significant infections) and after hematopoietic reconstitution.

Table 6. Reduction in Incidence of Infection-Related Endpoints (PPT Population)

Endpoint and follow-up period	Number of patients with infection-related events (n/N (%))	Count of events	Follow-up duration (in years)	Annualized event rate (events/year) \pm SE [1]	Change compared to pre-infusion period [2]	p-value [3]
Infection-Related Hospitalizations						
Pre-infusion	9/9 (100)	65	31.5	2.1 \pm 0.3		
91 Days post-engraftment to EoS	4/9 (44.4)	8	15.2	0.5 \pm 0.2	-1.5	<0.0001
Overall post-infusion	4/9 (44.4)	10	17.9	0.6 \pm 0.2	-1.5	<0.0001
Prolonged Infection-Related Hospitalizations						
Pre-infusion	7/9 (77.8)	46	31.5	1.5 \pm 0.2		
91 Days post-engraftment to EoS	3/9 (33.3)	4	15.2	0.3 \pm 0.1	-1.2	<0.0001
Overall post-infusion	4/9 (44.4)	6	17.9	0.3 \pm 0.1	-1.1	<0.0001

Significant Infections (i.e., requiring Hospitalization/Prolong ed Hospitalization or I.V. Antimicrobial)						
Pre-infusion	9/9 (100)	110	31.5	3.5 ± 0.3		
91 Days post- engraftment to EoS	4/9 (44.4)	8	15.2	0.5 ± 0.2	-3.0	<0.0001
Overall post-infusion	8/9 (88.9)	24	17.9	1.3 ± 0.3	-2.2	<0.0001

Abbreviations: EoS=end of study; PPT=per protocol treated.

Note: Annualized Event Rate is calculated as the total number of events / total time in each time period for all patients. Results are adjusted event rate per year. Pre-infusion period includes pre-screening and screening to pre-infusion.

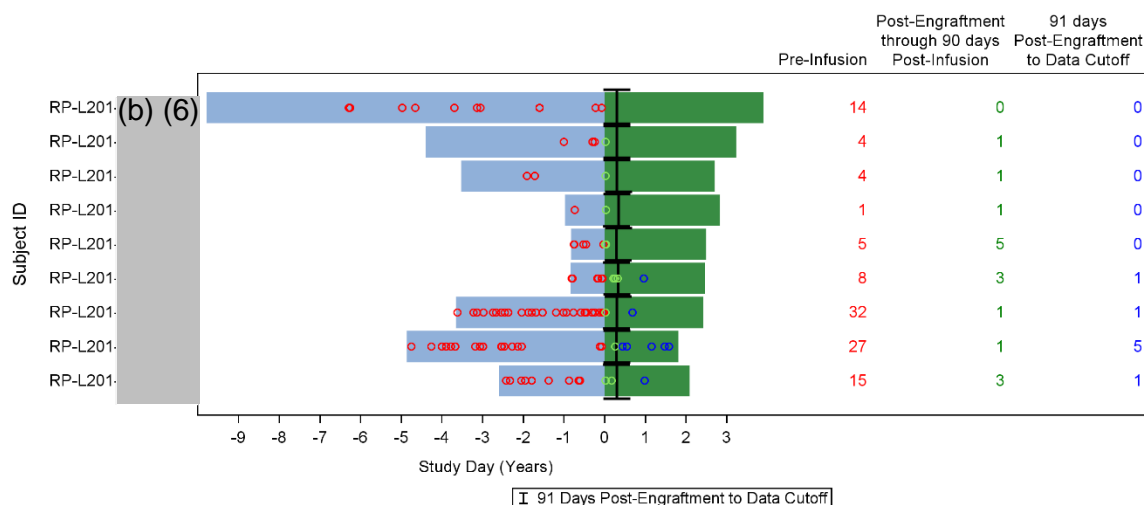
[1] SE = standard error by using Normal Approximation method, $\sqrt{\lambda / E}$ where λ is Poisson mean and E is total exposure in years.

[2] Reduction from pre-infusion = post-infusion - pre-infusion. Note that non-independent samples are modeled without taking into account the within patient correlation.

[3] P-value from Poisson regression with event and time period in the model with an offset of log of exposure.

Source: Adapted from BLA 125806/0/17, Module 2.7.3 summary of clinical efficacy, Table 4.

Figure 2. Swimmer Plots of Significant Infections (PPT Population)



Note: The bar represents the timeline in years; blue is lifetime history pre-infusion and green is post infusion. The dots represent Significant infection events (i.e., those requiring hospitalization, prolonged hospitalization or I.V. antimicrobials). Red dots are events occurring pre-infusion, green dots are events occurring post-infusion and prior to 91 days post-engraftment, blue dots are events occurring 91 days or more post engraftment. The numbers to the right of the graphic indicate the incidences of significant infections occurring pre-infusion (red), post-infusion and prior to 91-days post engraftment (green), 91 days or more post-engraftment (blue).

** Engraftment occurred between 12- and 33-days post infusion.

Source: Adapted from BLA 125806/0/17, Module 5.3.5.3 120-Day – Integrated Summary of Efficacy, Figure 2.1.6.

Reviewer's comment:

In the clinical review team's opinion, the infection-related analysis in this trial is uninterpretable in terms of efficacy assessment due to the following considerations involving both design and quality issues:

- *Reported pre-infusion (baseline) infection rate might not be reliable due to the following considerations:*
 - *Determination of infection-related events involves parent recalls over a long period of time which may be unreliable, in addition to medical records.*
 - *Considerable missing data, inconsistencies, and poor quality observed in the reporting.*
 - *Adjudication issues with respect to whether an antimicrobial use was for prophylaxis or for treatment of infections. This issue is also present for the infection-related events reported after infusion.*
- *Infection rate is expected to decrease with increased age, adding unquantifiable uncertainties to the within-subject comparison.*

This memo summarizes the infection-related analysis results submitted by the applicant. Please refer to the clinical review memo for results based on FDA's adjudication of events.

6.1.11.3 Subpopulation Analyses

I have included the subgroup analysis by age (<1 year vs. ≥ 1 year at infusion). As all nine patients were survival responders, subgroup analyses by sex and ethnicity/race all had 100% response rate.

6.1.11.4 Dropouts and/or Discontinuations

No patient discontinued from Study RP-L201-0318.

6.1.11.5 Exploratory and Post Hoc Analyses

EBMT Comparative Study:

The objective of this analysis was to compare outcomes in patients with severe LAD-I participating in Study RP-L201-0318 with outcomes in an external-control group of LAD-I pediatric patients enrolled in the EBMT registry who received an allogeneic HSCT between January, 2012 and December, 2021, and who also met the key inclusion/exclusion criteria matching those in Study RP-L201-0318.

Patient Selection

The following filters were applied for the selection of the 55 EMBT registry patients:

- There were 301,336 patients in the base allo1 registry.
- Of these, 287,049 had follow-up.
- Of these, 11,145 had inherited disorders.
- Of these, 7,423 had primary immune deficiencies.
- Of these, 164 had Leukocyte Adhesion Deficiency (LAD).
- **Of these, 91 had LAD Type-1 specifically.**
- Of these, 88 had transplants between the years 2007 and 2021 inclusively.
- Of these, 84 had 1 stem cell source.

- Of these, 65 were younger than 12 years old at the time of transplant.
- Of these, 56 had their transplant between the years 2012 and 2021 inclusively.
- Of these, one patient with high baseline neutrophil CD18, CD11a and CD11b expression was excluded.

Analysis Data

The applicant conducted analyses for three types of data: all patient unmatched data, all patient age-matched data, and low CD expressor age-matched data. Table 7 shows the numbers of patients in the three types of data from the EBMT and Study RP-L201-0318 cohorts.

Table 7. Analysis Data in the Study PR-L201-0318 and EBMT Registry Cohorts

Comparison types	# Patients treated with RP-L201	# Patients with Allo-HCT from EBMT
All patients - unmatched	9	55
All patients - age-matched	9	51
Low CD expressor patients - age-matched	9	30

^aLow CD expressor patients - age-matched: An analysis comparing outcomes in the nine RP-L201 patients to outcomes in age-matched EBMT patients who are recorded as having low (<2%) neutrophil CD18 expression (in the case of >2% CD18 with concomitant <2% CD11a or CD11b expression).

Source: Adapted from BLA 125806/0/0, Module 5.3.5.4 EBMT-comparative report.

Select Efficacy Endpoints

The efficacy endpoints included:

- Overall survival
- Event free survival (EFS) with events defined as graft failure, aGvHD grade II-IV or death
- Hospitalizations: infection-free hospitalization, cumulative incidence of hospitalization, prolonged hospitalization due to infection-free survival, cumulative incidence of prolonged hospitalization, number of prolonged hospitalizations, and number of prolonged hospitalizations after treatment.

Efficacy Results

The patients in the EBMT cohort had a median follow up time of 33.4 months ranging from 22.5 to 38.9 months. For the OS and EFS survival endpoints (Table 8), the RP-L201 treated patients showed numerically higher survival rates at 12 months post infusion (100% for OS and EFS) than EBMT patients (survival rates are between 56% and 85% for OS and EFS with three different comparative criteria) with p-value > 0.05 for OS and p-value < 0.05 for EFS.

Table 8. Summary of Overall Survival and Event-free Survival* Results

	Overall survival rate (95% CI) at 12 months post infusion	Event-free survival rate (95% CI) at 12 months post infusion
Unmatched		
RP-L201	100% (-, -)	100% (-, -)

Allo-HCT from EBMT	85% (75%, 94%)	59% (46%, 72%)
Age-matched		
RP-L201	100% (-, -)	100% (-, -)
Allo-HCT from EBMT	83% (72%, 93%)	59% (45%, 73%)
Age-matched low CD expression		
RP-L201	100% (-, -)	100% (-, -)
Allo-HCT from EBMT	82% (68%, 96%)	56% (38%, 74%)

*Includes Graft failure, aGvHD grade II-IV or death

Source: Adapted from BLA 125806/0/0, Module 5.3.5.4 EBMT-comparative report, OS and EFS results.

For the hospitalization-free survival endpoints (Table 9), the patients in the EBMT cohort exhibited numerically higher survival rates than those in patients treated with RP-L201. The observed differences were not statistically significant at 0.05 level.

Table 99. Summary of Hospitalization-free Survival* Results

	Hospitalization-free survival rate (95% CI) at 12 months**	Prolonged hospitalization-free survival rate (95% CI) at 12 months**
Unmatched		
RP-L201	56% (23%, 88%)	67% (36%, 97%)
Allo-HCT from EBMT	68% (52%, 84%)	80% (67%, 93%)
Age-matched		
RP-L201	62% (29%, 96%)	75% (45%, 100%)
Allo-HCT from EBMT	84% (72%, 96%)	87% (76%, 98%)
Age-matched low CD expression		
RP-L201	56% (23%, 88%)	67% (36%, 97%)
Allo-HCT from EBMT	78% (62%, 94%)	80% (64%, 95%)

*Include hospitalization due to infection or death

**From 91 days post engraftment

Source: Adapted from BLA 125806/0/0, Module 5.3.5.4 EBMT-comparative report, hospitalization results.

The comparison of various endpoints between RP-L201 treated patients and the matched patients from EBMT should be viewed as a comparison with an active control as the EBMT patients all received potentially curative allogeneic HSCT. Therefore, a statistically significant result from a superiority comparison is not expected to be a requisite component, from a statistical perspective, to conclude the efficacy of RP-L201. However, no equivalence or non-inferiority margins were pre-specified prior to such analyses, nor proposed post-hoc to aid interpretation. Additional issues include data quality issues in the RP-L201 treated patients, the uncertainty in comparability between the compared patients in general in external-control based analyses. Based on the totality of these issues, the EBMT comparison does not provide compelling statistical evidence of effectiveness.

Reviewer Comment:

We have summarized here results of post-hoc analysis in a select group of efficacy endpoints. Please refer to the clinical review memo for further evaluation of interpretability and reliability in such comparisons.

6.1.12 Safety Analyses

The safety analysis results include data from both the main and the LTFU studies.

6.1.12.3 Deaths

No deaths have been reported in the study.

6.1.12.4 Nonfatal Serious Adverse Events

A total of seven patients experienced at least one serious adverse event (SAE) in the pre-infusion period and four patients in the post-infusion period. Please refer to the clinical review memo for details.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

The original biologics license application (BLA) 125806/0 seeks traditional approval of RP-L201(also referred to as KRESLADI) for the treatment of severe Leukocyte Adhesion Deficiency-I (LAD-I). RP-L201 is a one-time, single-dose, investigational gene therapy product of autologous CD34+ hematopoietic stem cells transduced *ex vivo* with a lentiviral vector to encode for the ITGB2 gene. To support the efficacy and safety of RP-L201, the applicant included results from Study RP-L201-0318 (main study), a Phase I/II, open-label, single-arm, multi-site trial in severe LAD-I patients (age range: 10 months to 10 years) who were treated with RP-L201, and the results available by the data cut-off date in a long-term follow-up (LTFU) study (RP-L201-0121-LTFU) for those patients treated in the main study for a total follow-up of up to 15 years after the infusion. In addition, the applicant included the efficacy analysis results for comparison of patients treated in the RP-L201-0318 study with a subset of severe LAD-I patients in the European Group for Blood and Marrow Transplantation (EBMT) registry who underwent an allogeneic hematopoietic stem cell transplant (HSCT) at ages <12 years.

Efficacy

In Study RP-L201-0318, nine patients with severe LAD-I were treated with RP-L201 and were followed up for at least one year and up to 24 months post-infusion. Three patients were younger than one year of age when they were treated (the younger subgroup), while the other 6 patients ranged from age 2.6 to 9.8 years when they were treated (the older subgroup).

The primary efficacy endpoint was the proportion of survival responders, defined as a patient being alive for at least one year after RP-L201 infusion without receiving allogeneic HSCT. In addition, patients who are treated at less than one year of age need to be alive at age 2 (24 months) without allogeneic HSCT to qualify as a survival responder. The planned primary efficacy analysis was the observed survival response rate compared to a threshold survival rate of 39%. In the study, all nine treated patients were

survival responders. The survival response rate was 100%, with a 95% two-sided confidence interval (CI) of (66%, 100%) and a p-value of 0.0002 when compared to a threshold rate of 39%.

The clinical reviewers consider the null survival response rate of 39% potentially acceptable for the younger subgroup (n=3), though there were some uncertainties with setting the threshold at 39%, because the supportive data were from developing countries and were not recent, which might not reflect current standard of care in the United States (US). With all three patients being survival responders, the 95% CI for the response rate is (29%, 100%), and the lower bound does not exceed the 39% threshold (p-value 0.059).

The clinical review team determined that there is no natural history data to support setting a null survival response rate for the older subgroup (n=6) at 39%.

Three patients are siblings, with the two younger siblings identified after the oldest one was identified first (diagnosed at 3.6 years of age). One of the siblings is in the younger subgroup. If conditioning on a patient surviving past age 2 would increase the chance of younger siblings' also surviving past age 2, this sampling scheme might complicate the interpretation of the survival response in the younger subgroup.

In addition, the applicant reported the results for the following three key infection-related endpoints:

- Significant infection: Mean annualized event rate (AER) was 3.5 ± 0.3 events/year pre-infusion (baseline), compared to 0.5 ± 0.2 events/year from 91 days post-engraftment to data cut-off (efficacy period).
- Infection-related hospitalization: Baseline AER was 2.1 ± 0.3 while efficacy period AER was 0.5 ± 0.2 .
- Prolonged infection-related hospitalization (> 7 days): Baseline AER was 1.5 ± 0.2 while efficacy period AER was 0.3 ± 0.1 .

However, the clinical review team considers the within-subject comparison results reported by the applicant for these infection-related endpoints to be difficult to interpret due to several considerations:

- Determination of baseline infection-related events partially involves retrospective recalls by parents over a long period of years.
- Infection rates are expected to decrease with increased age.
- Considerable missing data, inconsistencies, and poor quality of infection-related endpoints.

We agree with the clinical team's evaluation regarding the data quality issues based on internal discussions and examples they identified. Please refer to the clinical review memo for more information.

Biomarker data on CD18 and CD11a were also reported in this submission. The evaluation of these results is deferred to the clinical pharmacology reviewer.

Finally, the applicant provided post-hoc analyses comparing several efficacy endpoints between the nine treated patients in Study RP-L201-0318 and three matched subsets of LAD-I patients identified from the EBMT Registry. Below are results for selected endpoints for comparisons with the subset of age-matched patients (N=51); results were similar to those in two other subsets matched on different criteria:

- Overall survival (OS) and event-free survival (EFS): RP-L201 treated patients showed numerically higher survival rates at 12 months post infusion (100% for both endpoints) than EBMT patients (OS: 83%, p-value > 0.05; EFS 59%, p-value < 0.05).
- Hospitalization-free and prolonged hospitalization-free survivals: EBMT patients showed numerically higher survival rates at 12 months post infusion than RP-L201 treated patients (difference of ~12%, p-value > 0.05).

The comparison of various endpoints between RP-L201 treated patients and the matched patients from EBMT should be viewed as a comparison with an active control as the EBMT patients all received potentially curative allogeneic HSCT. Therefore, a statistically significant result from a superiority comparison is not expected to be a requisite component, from a statistical perspective, to conclude the efficacy of RP-L201. However, no equivalence or non-inferiority margins were pre-specified prior to such analyses, nor proposed post-hoc to aid interpretation. Additional issues include data quality issues in the RP-L201 treated patients, the uncertainty in comparability between the compared patients in general in external-control based analyses. Based on the totality of these issues, the EBMT comparison does not provide compelling statistical evidence of effectiveness.

Safety results

There were no deaths in the studies. The applicant reported that there were no serious adverse events related to RP-L201, no graft-versus-host disease, and no secondary graft failures. Please refer to the clinical review memo for more information.

10.2 Conclusions and Recommendations

Efficacy evaluation of RP-L201 in treatment of severe LAD-I was based on data on nine patients treated with RP-L201 and followed up for at least one year (8 of them for at least 2 years). All patients met the survival response endpoint of surviving at least one year after infusion without allogeneic HSCT and in addition beyond 2 years of age for those treated at younger than one year of age. However, according to the clinical team, this endpoint was not interpretable in a single-arm study for the older subgroup (n=6) but may be interpretable in the younger subgroup (n=3) who were treated before they were one year old. The 95% CI for this survival response rate in the younger subgroup was (29%, 100%), which does not rule out the 39% null response rate. The applicant reported significant reduction in infection-related endpoints post RP-L201 treatment compared to baseline. However, in the clinical review team's opinion, study design and data quality issues render interpretation of infection data difficult. Findings comparing the RP-L201 treated patients with EBMT patients as an external control were inconclusive due to lack

of pre-specified criteria for demonstration of efficacy and possible issues in population comparability, among other issues. Therefore, given the small sample size and above-mentioned challenges in interpreting the data, there is no conclusive statistical evidence of efficacy of RP-L201. However, it may be possible to conclude that there is substantial evidence of effectiveness based on a synthesis of multiple sources of information, including the mechanism of action, predictive biomarkers, and clinical perspectives of the data including benefit and risk considerations. Such a conclusion requires above all clinical judgment.