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## **BLA Clinical & Clinical Pharmacology Review Memorandum**

Application Type	351(a)
STN	125806/0
CBER Received Date	August 1, 2023 (Original submission) September 26, 2026 (Resubmission)
PDUFA Goal Date	March 26, 2026
Division /Office	DCEGM/ OCE/ OTP/ CBER
Priority Review	Yes
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Review Completion Date	March 26, 2026
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Applicant	Rocket Pharmaceuticals, Inc.
Established Name	marnetegrane autotemcel
Proposed Trade Name	KRESLADI
Pharmacologic Class	autologous hematopoietic stem cell-based gene therapy
Formulation	Transduced autologous CD34+ cells; washed, suspended in a solution containing 5% dimethyl sulfoxide (DMSO), and cryopreserved
Dosage Form/ Route of Administration	Cell suspension for intravenous (IV) infusion
Dosing Regimen	Single dose for infusion containing a minimum recommended dose of $10^{(b)(4)} \times 10^6$ CD34+ cells/kg
Indication	For the treatment of pediatric patients with severe leukocyte adhesion deficiency type I (LAD-I) due to biallelic variants in <i>ITGB2</i> without an available human leukocyte antigen (HLA)-matched sibling donor for allogeneic hematopoietic stem cell transplant
Orphan Designated	Yes

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**GLOSSARY**

AC	acceptance criteria
aGVHD	acute graft-versus-host disease
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ALC	absolute leukocyte count
Allo-HSCT	allogeneic hematopoietic stem cell transplant
ANC	absolute neutrophil count
AR	adverse reaction
AST	aspartate aminotransferase
BIMO	Bioresearch Monitoring
BLA	Biologics License Application
BM	bone marrow
BMA	bone marrow aspirate
cAUC	cumulative area under the curve
CBC	complete blood count
CBER	Center for Biologics Evaluation and Research
CD	cluster of differentiation
CFR	Code of Federal Regulations
CFU	colony forming units
cGVHD	chronic graft-versus-host disease
CI	confidence interval
CMC	Chemistry, Manufacturing, and Controls
CRO	contract research organization
CSR	clinical study report
DCEGM	Division of Clinical Evaluation General Medicine
ddPCR	droplet digital polymerase chain reaction
DMSO	dimethyl sulfoxide
DP	drug product
EBMT	European Society for Blood and Marrow Transplantation
eCRF	electronic case report form
EFS	event-free survival
FDA	Food and Drug Administration
GF	graft failure
GGT	gamma-glutamyltransferase
GT	gene therapy
GVHD	graft versus host disease
HLA	human leukocyte antigen
HSC	hematopoietic stem cell
HSCT	hematopoietic stem cell transplant
ICF	informed consent form
IDMC	Independent Data Monitoring Committee
IL	interleukin
IND	Investigational New Drug
IP	investigational product
IR	information request
IRB	Institutional Review Board
ISA	integration site analysis

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ITT	intent-to-treat
IV	intravenous
LAD-I	leukocyte adhesion deficiency type I
LDH	lactate dehydrogenase
LFA-1	lymphocyte function-associated antigen-1
LOD	limit of detection
LOQ	limit of quantitation
LTFU	long-term follow-up
LVV	lentiviral vector
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MSD	matched sibling donor
n	number
NA	not applicable
NAI	no action indicated
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NH	natural history
OCE	Office of Clinical Evaluation
OS	overall survival
OTP	Office of Therapeutic Products
PAH	pulmonary arterial hypertension
PB	peripheral blood
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic
PI	Principal Investigator
PK	pharmacokinetic
PMN	polymorphonuclear neutrophil
PMR	post-marketing requirement
PPF	per protocol final
PPT	per protocol transplant
PT	preferred term
qPCR	quantitative polymerase chain reaction
RMAT	Regenerative Medicine Advanced Therapy
RCL	replication-competent lentivirus
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SIN-LV	self-inactivating lentivirus
SN	sequence number
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
UK	United Kingdom
US	United States
USPI	United States Prescribing Information
VAI	voluntary action indicated
VCN	vector copy number
VOD	veno-occlusive disease
WBC	white blood cell



## 1. EXECUTIVE SUMMARY

On August 1, 2023, Rocket Pharmaceuticals, Inc. (the Applicant) submitted an original Biologics License Application (BLA), STN BL 125806, for licensure of marnetegrane autotemcel (also known as RP-L201; proprietary name KRESLADI) with the proposed indication “for the treatment of severe Leukocyte Adhesion Deficiency-I (LAD-I).” During the initial review cycle, the BLA did not satisfy CMC requirements for biological product licensure, and thus a complete response letter was issued on June 14, 2024. The BLA was resubmitted on September 26, 2025.

LAD-I is a rare, autosomal recessive primary immunodeficiency syndrome caused by biallelic variants in the *ITGB2* gene which results in impairment of leukocyte (neutrophil) adhesion on endothelial cells which is critical for their function. Loss of function of *ITGB2* results in low production and functional impairment of its protein product, CD18 which normally forms a heterodimer with another protein, CD11a. The CD18/CD11a complex known as lymphocyte function-associated antigen-1 (LFA-1) serves as a cell surface receptor on neutrophils and it plays a critical role in adhesion of neutrophils to endothelial cells and extravasation to sites of infection. The level of CD18 expression (in addition to level of CD11a) determines the severity of disease with level <2% defining severe LAD-I. Clinically, patients experience recurrent serious and life-threatening infections and reduced survival. There are no FDA-approved treatments for LAD-I, with allogeneic hematopoietic stem cell transplant (allo-HSCT) being the standard of care for severe disease. Allo-HSCT has favorable outcomes if performed early using a human leukocyte antigen (HLA)-matched donor, but it is estimated that less than 25-30% of patients have an available matched sibling donor (MSD). There is a substantial unmet need for effective treatment for severe LAD-I.

KRESLADI is an autologous CD34+ hematopoietic stem cell -based gene therapy, transduced *ex vivo* with a self-inactivating lentivirus (SIN-LV) containing functional copies of the *ITGB2* gene and administered as a one-time intravenous infusion. KRESLADI is intended to enable expression of functional CD18 on leukocytes to form LFA-1 and restore leukocyte adhesion to endothelial cells thereby improving or curing LAD-I.

The Applicant has provided substantial evidence of effectiveness based on a single adequate and well-controlled clinical investigation, Study RP-L201-0318, with confirmatory evidence for KRESLADI for the treatment of pediatric patients with severe LAD-I with biallelic variants in *ITGB2* and without an available HLA-matched sibling donor for allogeneic HSCT. The clinical evidence from Study 0318 demonstrates substantially improved expression of both CD18 and CD11a on neutrophils indicating restoration of the CD18/CD11a heterodimer (leukocyte function-associated antigen-1; LFA-1) function post-KRESLADI administration. Functional restoration of LFA-1 serves as a surrogate endpoint that is reasonably likely to predict clinical benefit of improved survival in severe LAD-I for purposes of accelerated approval. The overall benefit-risk profile of KRESLADI is favorable in a disease associated with premature death in childhood due to life-threatening complications when untreated.

Study RP-L201-0318 (Study 0318) was a single-arm, open label, 24-month clinical trial assessing the safety and efficacy of a single dose of KRESLADI in 9 pediatric patients (median age 42 months; range: 9.8 to 117 months) with severe LAD-I and without an HLA-matched sibling donor for allogeneic hematopoietic stem cell transplant (HSCT). Interpretation of the Applicant-proposed clinical efficacy endpoints including allo-HSCT-free survival and incidence of serious infections was limited due to several design and statistical limitations (see section 6). Given these limitations, only objective measures of treatment response, CD18 and CD11a expression on neutrophils, were evaluable and interpretable. Substantial improvement in both CD18 and CD11a surface expression was observed in

all treated patients at months 12 and 24 which was sustained over at least 42 months of follow up. These improvements reflect restoration of the CD18/CD11a (LFA-1) heterodimer function, whose deficiency causes LAD-I and are expected to result in improved neutrophil endothelial cell adhesion and recruitment to sites of infections, thereby reducing the risk of serious and life-threatening infections and improving survival.

Confirmatory evidence includes mechanistic evidence from nonclinical studies demonstrating transduction of CD18-deficient hematopoietic stem cells with the lentiviral vector (LVV) in KRESLADI leading to CD18 and CD11a surface expression and functional correction of leukocyte adhesion defects. Because LAD-I pathogenesis is well-established and caused by dysfunction of a single molecular pathway and a single molecular defect, CD18/CD11a heterodimer deficiency, the established natural history knowledge that heterodimer function is not restored in the absence of treatment serves as additional confirmatory evidence.

The safety database includes 9 patients followed for up to 42 months from product administration. The available safety database is limited as expected for a rare disease; however, it is considered sufficient for purposes of a safety evaluation. Treatment with KRESLADI involved not only administration of the product, but also administration of chemotherapeutic agents for myeloablative conditioning prior to product administration. These agents are associated with serious safety risks, such as cytopenias and serious infections, which were observed in the clinical study. Overall, the observed adverse events are attributable to the myeloablative conditioning and the underlying disease. The safety profile of KRESLADI administration is acceptable for this life-threatening disease with limited treatment options. There is a theoretical risk of insertional oncogenesis with KRESLADI given it is based on a LVV with genomic integration potential. There were no cases of insertional oncogenesis or hematologic malignancy observed in the KRESLADI clinical program, and this risk will be monitored during a post-marketing, long term follow up study.

## **Regulatory Flexibility**

LAD-I is a very rare disease with only about 450 cases reported in the literature. Due to the serious clinical manifestations including life-limiting severe infections and other inflammatory sequelae, LAD-I causes substantial morbidity, especially in the severe form with early death in childhood without definitive treatment. The only available therapeutic option currently is supportive care and allogeneic hematopoietic stem cell transplantation (HSCT) which is associated with serious toxicities and life-threatening complications. In this therapeutic context, regulatory flexibility in the review and approval decision of this BLA is warranted and was exercised in the following ways:

- 1) Acceptance of a single adequate and well controlled clinical investigation in a very small number of pediatric patients (N=9) with severe LAD-I along with confirmatory evidence;
- 2) Acceptance of objective measures of treatment effect that are central to the disease pathogenetic mechanism, CD18 and CD11a expression on neutrophils, as novel surrogate endpoints that are reasonably likely to predict clinical benefit on survival under the accelerated approval provisions. Verification of clinical benefit on survival will be assessed as a post-marketing requirement;
- 3) Acceptance of a safety database of 9 patients followed over a long duration (up to 42 months) as sufficient to support the product's safety assessment.

## 1.1 Demographic Information: Subgroup Demographics and Analysis Summary

Nine pediatric patients with severe LAD-I were treated with KRESLADI in Study RP-L201-0318 and long-term follow up Study 0121-LTFU. Baseline patient characteristics are shown in Table 1. There was insufficient information to draw conclusions about differences in effectiveness or safety outcomes by subgroup based on age, sex, race, ethnicity, or national origin.

**Table 1: Demographic Information for Treated Patients in Studies RP-L201-0318 and 0121-LTFU**

Parameter	N=9
Age at diagnosis (months)	-
Median	6.8
Minimum - Maximum	0.0 - 95.9
Age at enrollment (months)	-
Median	36.0
Minimum - Maximum	3.0 - 112.0
Age group at enrollment, n (%)	-
<12 months	3 (33)
≥12 months	6 (67)
Age at treatment (months)	-
Median	42.3
Minimum - Maximum	9.8 - 117.4
Age group at treatment, n (%)	-
<12 months	3 (33)
≥12 months	6 (66)
Sex, n (%)	-
Female	5 (56)
Male	4 (44)
Race, n (%)	-
White / Caucasian	6 (67)
Asian	2 (22)
Unknown / Not Reported	1 (11)
National origin, n (%)	-
United States	5 (56)
Great Britain	1 (11)
India	1 (11)
Sri Lanka	1 (11)
Turkey	1 (11)
Site of treatment, n (%)	-
002 / Spain	1 (11)
003 / United States	6 (67)
004 / United Kingdom	2 (22)

Source: Adapted from Original BLA 125806; SN0001, Module 5.3.5.2, RP-201-0318 CSR v1.0, Table 6.

## 1.2 Patient Experience Data

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
<input type="checkbox"/>	Patient-reported outcome	-
<input checked="" type="checkbox"/>	Observer-reported outcome <ul style="list-style-type: none"> <li>Caregiver questionnaire</li> </ul>	<a href="#">Section 7.1.5.1</a>
<input checked="" type="checkbox"/>	Clinician-reported outcome <ul style="list-style-type: none"> <li>Local medical provider questionnaire</li> </ul>	<a href="#">Section 7.1.5.1</a>
<input type="checkbox"/>	Performance outcome	-
<input type="checkbox"/>	Patient-focused drug development meeting summary	-
<input type="checkbox"/>	FDA Patient Listening Session	-
<input checked="" type="checkbox"/>	Qualitative studies <ul style="list-style-type: none"> <li>Expert and referring provider survey: "Current Practices in the Diagnosis and Management of Leukocyte Adhesion Deficiency Type I (LAD-I)"</li> <li>Patient/family testimonials</li> </ul>	<a href="#">Section 6.1.10.1.2</a> , <a href="#">Section 6.1.11.1</a>  <a href="#">Section 7.1.5.1</a>
<input type="checkbox"/>	Observational survey studies	-
<input type="checkbox"/>	Natural history studies	-
<input type="checkbox"/>	Patient preference studies	-
<input checked="" type="checkbox"/>	Other: <ul style="list-style-type: none"> <li>EBMT Registry Report</li> <li>EBMT Registry Comparator Report</li> <li>Applicant literature review</li> </ul>	<a href="#">Section 6.1.11.5</a> <a href="#">Section 6.1.11.5</a> <a href="#">Section 2.1</a>
<input type="checkbox"/>	If no patient experience data were submitted by Applicant, indicate here.	-
Check if Considered	Type of Data	Section Where Discussed, if Applicable
<input type="checkbox"/>	Perspectives shared at patient stakeholder meeting	-
<input type="checkbox"/>	Patient-focused drug development meeting summary report	-
<input type="checkbox"/>	FDA Patient Listening Session	-
<input type="checkbox"/>	Other stakeholder meeting summary report	-
<input type="checkbox"/>	Observational survey studies	-
<input checked="" type="checkbox"/>	Other: <ul style="list-style-type: none"> <li>FDA/clinical team literature review</li> </ul>	<a href="#">Section 5.5</a> , <a href="#">Section 6.1.11.1</a>

Abbreviations: EBMT, European Society for Bone and Marrow Transplantation

## 2. CLINICAL AND REGULATORY BACKGROUND

### 2.1 Disease Background

LAD-I is a rare, autosomal recessive, primary immunodeficiency syndrome. The exact prevalence is unknown but published estimates note the condition to occur in approximately 1 per 1 million people worldwide (Cox and Weathers 2008) with approximately 450 unique cases reported in the scientific literature (Bondarenko et al. 2023). LAD-I is caused by biallelic pathogenic variants in the *ITGB2* gene located on chromosome 21q22.3. *ITGB2* encodes the protein CD18, which is the common beta subunit of the leukocyte beta-2 integrin family (Roos et al. 2023). CD18 forms a heterodimer with one of the alpha integrin subunits CD11a, CD11b, or CD11c forming a cell surface receptor. The CD18/CD11a heterodimer called lymphocyte function-associated antigen 1 (LFA-1) is necessary for neutrophil adhesion to endothelial cells and migration from the blood stream to sites of infection. The absence or impairment of CD18 function leads to degradation of CD18 and CD11a and other alpha integrin subunits.

#### Diagnosis and Disease Progression

LAD-I is characterized by recurrent, serious bacterial and fungal infections starting from birth, without a marked increase in susceptibility to viral infections. A classic presenting infection is omphalitis with delayed separation of the umbilical cord. Infections are primarily localized to the skin and mucosal surfaces, but bacterial sepsis may also occur. Additional clinical manifestations include impaired wound healing, absence of pus formation, and persistent neutrophilic leukocytosis (van de Vijver et al. 2013). Severe gingivitis and periodontitis are common in those who survive infancy, with complete loss of dentition by late adolescence in most patients (Cox and Weathers 2008; Dababneh et al. 2008; Hanna and Etzioni 2012). Some literature points to a potential shift from an infectious to an inflammatory picture as patients age (Geroldinger-Simic et al. 2022).

A clinically suspected diagnosis of LAD-I is confirmed via flow cytometry demonstrating low or absent expression of the CD18 subunit and associated CD11 subunits in neutrophils. *ITGB2* mutations resulting in abnormal but still expressed CD18 have been described but, in these cases, normal CD11a co-dimers are degraded without formation of a functional integrin heterodimer, and levels of CD11a are consistently low or absent. As such, measurement of both CD18 and CD11a is recommended to increase the likelihood of early diagnosis and treatment (Levy-Mendelovich et al. 2016; Wolach et al. 2019; Fazlollahi et al. 2023). In most cases, severe LAD-I is defined by neutrophil CD18 expression <2%, but in cases where non-functional CD18 is still expressed, CD11a levels have been used to identify severe cases, which tend to have a poor prognosis in the absence of definitive therapy (Etzioni 2010; Almarza Novoa et al. 2018; Fazlollahi et al. 2023). In an Applicant-initiated review of all LAD-I cases published through 2017, the reported survival rate to the age of 2 years for severe LAD-I without allogeneic hematopoietic stem cell transplant (allo-HSCT) was 39% (Almarza Novoa et al. 2018).<sup>1</sup> However, this may be an underestimate secondary to publication biases, underreporting, and differences in medical care over time and by location (see also [Section 6.1.11.1](#)).

Survival estimates for patients with severe LAD-I who survive beyond 2 years of age without allo-HSCT are not well-defined. The Applicant notes that mortality for severe LAD-I beyond age 2 years “remains extremely high, with most not surviving into adolescence.” However, findings from an independent literature review indicate that a significant number of severe LAD-I patients survive into adolescence and even into adulthood without transplant. This suggests that demonstration of short-term survival in

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<sup>1</sup> Of 323 LAD-I cases identified between 1975 and 2017, 66 severe cases included survival to 2 years of age, with 40 deaths reported.

older patients may not be meaningful when evaluating the effectiveness of treatment. Please refer to [Section 6.1.11.1](#) for further discussion of the natural history (NH) of severe LAD-I.

#### LFA-1 role and function

LAD-I is caused by genetically absent or dysfunctional (but present) neutrophil CD18 expression with resultant absent/minimal expression of the alpha integrin subunits CD11a, CD11b, and CD11c. Limitations with the interpretability of CD11b and CD11c expression include the inducible nature of the CD11b/CD18 and CD11c/CD18 heterodimers such as is seen in states of inflammation or coagulable events. As such, use of CD11b and CD11c expression as a biomarker for diagnosis or monitoring of LAD-I is of limited value. By contrast, CD11a expression is stable and non-inducible given the constitutive expression of the CD11a/CD18 heterodimer on the surface of neutrophils. Given the central role that CD18 and CD11a play in the pathogenesis of LAD-I as a functional heterodimer (LFA-1) which has a single, well-established molecular pathway, there is a high biological plausibility that restoring expression of those proteins in neutrophils through a cell-based gene therapy approach like with KRESLADI treatment, will improve leukocyte adhesion to blood vessels and migration to sites of infection. These improvements at the cellular and tissue level will, in turn, reduce patients' susceptibility to serious infections and inflammation and improve survival.

Published literature shows a strong correlation between CD18 expression and survival (Fischer and Lisowska-Groszpiere 1988; Almaraz Novoa et al. 2018) with an estimated 39% survival to the age of 2 years without allo-HSCT for severe LAD-I (<2% CD18 expression). Many patients with expression between 2 and 4% may live longer with survival up to approximately 10 years of age. CD18 expression >4% is associated with survival beyond childhood. Overall, the severity of LAD-I, as defined by CD18 and CD11a expression, correlate with allo-HSCT free survival, with improved outcomes seen in moderate versus severe disease. Published literature documents "restoration" or "normalization" of CD18 expression in severe LAD-I patients following successful allo-HSCT. In these cases, patients have been noted to have concurrent improvement in clinical outcomes, with one report noting the patient to be "disease-free" (Chakraborty et al. 2020) and others indicating an absence of new infections and/or resolution of prior infections following transplant (Al-wahadneh et al. 2006; Zhu et al. 2025). Additionally, allogeneic transplant experience shows that even with mixed chimerism, children with severe LAD-I can remain alive and free of significant symptoms following transplant (Thomas et al. 1995; Qasim et al. 2009). In canine models of LAD-I treated with gene-modified cells with resultant CD18 expression in the range of 5-10%, treated animals showed long-term protection against infection up to 7 years following treatment (Bauer et al. 2008; Bauer et al. 2013). More details are provided in [Appendix C](#).

Although LAD-I is not due to a primary defect in CD11a with no reports of isolated CD11a deficiency in humans (Levy-Mendelovich et al. 2016), and no reports of disease-causing mutations in any of the alpha chains (Roos et al. 2023), a lack of CD11a expression reflects a CD18 defect and deficient activity of the necessary CD18/CD11a heterodimers. When CD18 is abnormal or absent, there is no assembly of the CD11a/CD18 heterodimer and there is hastened degradation of both the abnormal CD18 and normal CD11a. Additionally, levels of CD11a expression are constant and non-inducible with constitutive expression of the CD11a/CD18 heterodimer on the surface of neutrophils. By contrast, the CD11b/CD18 heterodimer is stored within intracellular granules and only migrates to the cell surface upon receipt of inflammatory signals (Levy-Mendelovich et al. 2016). Published literature supports using CD11a to identify LAD-I patients, with all affected patients having low or undetectable CD11a, even in the setting of variable levels of CD18 or other CD11 co-dimers (Levy-Mendelovich et al. 2016;

Wolach et al. 2019; Chakraborty et al. 2020; Fazlollahi et al. 2023). Measurement of CD11a may also predict early treatment response in cases where pre-existing CD18 expression precludes its use as a biomarker. Following successful allo-HSCT, patients have been noted to have increased and/or normal CD11a expression and phenotypic reversal of disease whereas CD11a expression remains at 0% in cases of failed engraftment (Levy-Mendelovich et al. 2016; Chakraborty et al. 2020; Zhu et al. 2025). More details are provided in [Appendix D](#).

LFA-1 (CD18/CD11a heterodimer) functional restoration as a surrogate endpoint reasonably likely to predict clinical benefit in severe LAD-I

The following lines of evidence support the predictive ability of LFA-1 (the CD18/CD11a heterodimer) functional improvement (reflected in increases in both CD18 and CD11a surface expression) in severe LAD-I supporting its use as a surrogate endpoint that is reasonably likely to predict clinical benefit on survival and clinical outcomes in severe LAD-I:

- 1) there is strong biologic plausibility of improved neutrophil CD18 and CD11a surface expression leading to functional restoration of the LAD-I molecular pathway with resultant improved clinical symptoms and improved survival.
- 2) available scientific evidence reports improved survival and infectious complications in association with increased functional CD18/CD11a surface expression from genetic restoration of neutrophil function through allo-HSCT (see sections 7.1.5.2 and 7.1.5.3).
- 3) mechanistic evidence in LAD-I animal models following treatment with genetically modified cells demonstrates improved survival and clinical outcomes.

## **2.2 Currently Available Treatments/Interventions for the Proposed Indication**

There are currently no FDA-approved treatments for LAD-I. Allo-HSCT is the standard of care, as it is the only curative treatment for LAD-I, and is recommended as early as possible, particularly for the severe phenotype (Thomas et al. 1995; Qasim et al. 2009; Al-Dhekri et al. 2011; Hamidieh et al. 2012; Horikoshi et al. 2018; Bakhtiar et al. 2021). In a 2021, multicenter, retrospective study of data collected using the European Society of Blood and Marrow Transplantation (EBMT) Registry, Bakhtiar et al. reported outcomes for LAD-I patients from 33 centers who received allo-HSCT between 2007 and 2017 (n=69). Overall survival (OS) at 3 years was found to be 84%, which is comparable to the 81% OS seen in the 2018 literature review by Almarza Novoa et al. Event-free survival (EFS), defined as survival in the absence of graft failure (GF) and acute graft-versus-host disease (aGVHD) Grades 2-4, was 58%, with 24% developing aGVHD and 18% experiencing primary or secondary GF. Age at transplant <13 months was associated with significantly better EFS, which is thought to be due to better baseline health prior to the occurrence of repeated serious infections.<sup>2</sup>

Success of transplantation appears to be related to the degree of human leukocyte antigen (HLA) matching with the donor, with excellent survival outcomes for patients with a matched sibling donor (MSD) or other 10/10 matched donor (family or unrelated), as compared to unmatched donors. In earlier analyses of EBMT data from 14 centers between 1993 and 2007, 82% of patients with matched donors survived (n=28), while survival was only 50% for 8 patients with a haploidentical donor (Qasim et al. 2009). Similarly, literature review demonstrated 83% OS for matched donors (n=71) but only 68% for haploidentical donors (n=22), with 55% of haploidentical recipients receiving at least one subsequent transplant (Almarza Novoa et al. 2018).<sup>3</sup> It is estimated that only 25-30% of patients

<sup>2</sup> This analysis included a subset of patients with LAD-III (13% in the entire sample but unclear exactly how many were analyzed for EFS).

<sup>3</sup> Of 323 LAD-I patients, 101 received allo-HSCT. OS for those with an MSD was 89% (32 of 36).

requiring allo-HSCT have the option of an MSD and when you add in a hereditary component to the disease, the availability of a suitable MSD may decrease even further. Despite the presence of international registry databases, approximately 50% of unrelated donor searches will not yield a suitable matched unrelated donor, with an even lower likelihood of success for patients of non-northern European ancestry (Acevedo et al. 2019).

## 2.4 Previous Human Experience with the Product

KRESLADI is not approved for use in any country.

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

Throughout development, the FDA engaged with the Applicant regarding the development program for KRESLADI. FDA expressed concerns related to the proposed primary endpoint and comparator for the pivotal trial. Alignment with the Applicant on the pivotal trial design was not reached. A pre-BLA meeting was not held. The BLA was originally submitted on August 1, 2023, and received a CR action due to major CMC deficiencies. The BLA was resubmitted on September 26, 2025 and contained longer team safety and biomarker data.

**Table 2: Regulatory Milestones**

Date	Milestone
Nov 9, 2016	Orphan drug designation granted
Mar 19, 2018	Pre-IND meeting (PS003612)
Nov 17, 2018	IND 18485 allowed to proceed
Nov 30, 2018	Rare pediatric disease designation granted
Dec 12, 2018	Fast track designation granted
Mar 4, 2021	RMAT designation granted
Sep 29, 2023	BLA filed, priority review granted
Jan 25, 2024	Major amendment filed – CMC
Jun 14, 2024	Complete response letter issued – CMC
Oct 15, 2024	Incomplete response letter issued
Sep 26, 2025	BLA resubmission, priority review granted

Source: Clinical review of original BLA 125806 and IND 18485.

Abbreviations: BLA, Biologics License Application; CMC, Chemistry, Manufacturing, and Controls; IND, investigational new drug; RMAT, Regenerative Medicine Advanced Therapy.

## 3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

### 3.1 Submission Quality and Completeness

The Applicant's submission contained the elements required to support filing of the BLA, but the quality of the submission was poor. A large quantity of material was submitted for review, and navigating the application was difficult due to poor organization.<sup>4</sup> Key efficacy data was spread across multiple datasets, with nearly all datasets containing extraneous categories not helpful to the review. There was both a large amount of duplicate data and missing/incomplete data. In addition, there were numerous instances of incongruity between datasets, listings, and reports/summaries (e.g., lab value documented in listings but absent from datasets). Even following interactions with the Applicant to obtain missing data, seek clarification, and request that data be presented in alternative formats, a significant amount of time was required to compile data from multiple sources and organize data in such a way that it could be analyzed. Specific examples of review challenges related to issues with submission quality

<sup>4</sup> e.g., Analysis Data Reviewer's Guide contained several inaccurate dataset descriptions (i.e., dataset did not support what it claimed to support), as well as parameters that were missing definitions or were poorly defined.



and completeness can be found throughout this review, including those related to references to the literature ([Appendix A](#)), secondary infection endpoints ([Section 7.1.5.1](#)), and protocol deviations (see below).

#### Protocol Deviations and Missing Data

While the vast majority of major protocol deviations in Study 0318 were related to informed consent (see [Section 3.2](#) below), 2 of 9 subjects had major deviations due to “multiple sequential missed visits or protocol procedures, including safety parameters.”<sup>5</sup> For the first subject, visits at Months 4-9 were conducted remotely, with delays of up to 10 months in identifying missing assessments. The second subject was noted to have no visit at Month 4, care at a local clinic abroad from Months 5-9 (with numerous missing assessments), and documentation of deviations being identified before they were even reported to have occurred. A number of missed assessments outside of missed study visits were also identified during review, with many appearing to be connected to remote or local visits without Applicant oversight or clear record (see also [Section 3.2](#)). Deviations were also inconsistently categorized, with identical deviations being related to efficacy for one subject but related to safety for another (despite both leading to missed safety assessments). While the protocol states that all assessments may not be performed at all timepoints, it also notes that “evaluations that are considered essential for optimizing safe care of human subjects (for example, monitoring of blood counts and chemistries) should be prioritized whenever required.” However, nearly 90% of all deviations were categorized as related to safety assessments, but less than 10% were noted to be “important” or “major,” despite some having a reasonable potential to affect subject safety or the scientific value of the trial (e.g., missed monitoring for thrombotic microangiopathy [TMA], pulmonary arterial hypertension [PAH], or oncogenesis; multiple missing assessments integral to the analysis of secondary efficacy endpoints).

**Reviewer Comment:** *While it is unclear how much control the Applicant had over missed visits and assessments, there appears to be little to no acknowledgment of these protocol deviations or their potential impact on data quality or safety monitoring. Specifically, there is no discussion of the potential impact that local site visits without Applicant oversight could have on the frequency of missed assessments or the collection of study data in general. In most instances, it remains unclear whether remote visits occurred at the same time as visits to local sites, as documentation related to assessment location is poor. During a significant portion of the study, monitoring appears to have been inadequate to detect protocol deviations in a timely manner and prevent recurrence, with the consequence of missed visits and missing data. Ultimately, the greatest area of impact in terms of efficacy was found to be in the collection of data for infection-related outcomes, with less impact seen for more objective assessments of survival and biomarker endpoints. While the missing safety assessments are clearly concerning, there do not appear to have been any missed safety events, based on available data from subsequent follow-up. In addition, following the initial BLA review cycle, the Applicant incorporated a mobile health service to facilitate more standardized collection of safety and efficacy data, as discussed in [Section 3.2](#) in the context of protocol deviations related to local study visits.*

### **3.2 Compliance with Good Clinical Practices and Submission Integrity**

The Applicant indicated that their single interventional trial, Study 0318, was conducted under IND 18485 and in compliance with good clinical practice. However, following review of submitted materials, there are concerns related to compliance with good clinical practices regarding informed consent, with more than 30 protocol deviations related to the informed consent process and delays in identification of

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<sup>5</sup> Original BLA 125806; SN0018, Module 5.3.5.3, Integrated Summary of Safety, Listing 1.2.1.

at least one year for over 90% of the noted deviations.<sup>6</sup> It is also noted that the most recent version of the Applicant's protocol (v3.0) was still pending Independent Ethics Committee approval at the UK clinical site at the time of BLA submission.<sup>7</sup> Additionally, concerns related to inadequate study monitoring and documentation were identified following a full review of protocol deviations (outlined in [Section 3.1](#) above) and via inspections, described below.

Bioresearch Monitoring (BIMO) inspections were issued for one domestic and one international clinical investigator site, the Applicant, and a contract research organization (CRO). These sites were selected for inspection based upon subject enrollment, Applicant-reported AEs, prior inspection histories, and the specific testing performed (in the case of the CRO). The BIMO inspection findings are summarized in Table 3. Specifically, BIMO inspection revealed that 7 of 9 subjects completed study assessments (to include bone marrow aspiration in 3 subjects) at 5 local sites outside of the main study sites, without any oversight from the Applicant. Approximately 30 assessments occurred, starting as early as November 2019, while the provision for a single local visit at Week 10 was not added to the study protocol (v2.3) until June 2021. When 2 local sites were reported by the Principal Investigator (PI) for Site 003 in June 2023, these sites were noted to be laboratories, not clinical sites. In addition to failing to ensure proper monitoring and oversight for their clinical trial, the Applicant did not ensure that the study was conducted in accordance with the protocol, with 7 of 9 subjects receiving RP-L201 between 4 and 21 hours after the protocol-defined window for administration. These protocol deviations were not discovered until more than a year following their occurrence and do not appear in the Applicant's listed protocol deviations submitted to the BLA.<sup>8</sup>

**Table 3: Summary of Inspections**

<b>Firm (Type)</b>	<b>Location (Site ID)</b>	<b>Enrolled Subjects</b>	<b>Form 483 Issued</b>	<b>Final Inspection Classification</b>	<b>Inspectional Findings</b>
Donald Kohn, MD (PI)	Los Angeles, CA (Site 003)	6	No	VAI	Failure to report local sites  Misrepresentation of local sites  Failure to follow protocol (local sites)
Claire Booth, MBBS, MSc, PhD (PI)	London, UK (Site 004)	2	No	VAI	Failure to follow protocol (local sites)
Rocket Pharmaceuticals, Inc. (Applicant)	Cranbury, NJ	NA	Yes	VAI	Failure to obtain Form FDA 1572 for PI at Site 004 or any local sites  Failure to ensure proper study monitoring and conduct
GOSH Immunology Laboratory (CRO)	London, UK	NA	No	NAI	NA

<sup>6</sup> Original BLA 125806; SN0018, Module 5.3.5.3, Integrated Summary of Safety, Listing 1.2.1.

<sup>7</sup> Original BLA 125806; SN0001, Module 5.3.5.2, RP-L201-0318 CSR v1.0, Appendix 16.1.3.

<sup>8</sup> Original BLA 125806; SN0003, Module 5.3.5.2, RP-L201-0318 CSR v1.0, Listing 16.2.2.1; SN0018, Module 5.3.5.3, Integrated Summary of Safety, Listing 1.2.1.

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Source: Original BLA 125806; review of BIMO inspection findings.

Abbreviations: BIMO, Bioresearch Monitoring; CRO, contract research organization; FDA, Food and Drug Administration; GOSH, Great Ormond Street Hospital; NA, not applicable; NAI, no action indicated; PI, Principal Investigator; UK, United Kingdom; VAI, voluntary action indicated.

Following issuance of a Form FDA 483 to the Applicant, it is reported that the identified issues were adequately addressed. As inspection of the two clinical sites did not reveal any data integrity concerns, no Form FDA 483 was issued at the conclusion of these inspections. However, the aforementioned protocol deviations were identified during review of the establishment inspection reports and exhibits collected from the sites, and a Response Review Letter was issued to each PI to address the deviations; it is reported that the identified concerns were adequately addressed.<sup>9</sup>

**Reviewer Comment:** *Data quality issues combined with the identification of local sites not overseen by the Applicant preclude the interpretation of subject-level data for endpoints which are more subjective in nature (i.e., those related to infection or inflammatory outcomes; see also [Section 7.1.5.1](#)). It is evident that there was inadequate data monitoring during the study and when preparing documents submitted to the BLA. However, it is also acknowledged that no major data integrity issues were identified during inspections and that some of the issues may have been compounded by the COVID-19 pandemic. Additionally, despite delays in the identification of protocol deviations related to RP-L201 administration (and the lack of documentation of these deviations), the deviations themselves do not preclude data interpretability. Specifically, none of the noted concerns preclude interpretation of data for the biomarker endpoints that were ultimately recommended as the basis for AA. Following inspections, the identified deviations appear to have been addressed and, in the case of the local sites, the Applicant has specifically incorporated a mobile health service into their LTFU protocol to enable more uniform data collection and reporting (see [Section 6.2.7](#)).*

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<sup>9</sup> Per BIMO Review Memo, dated Jan 12, 2026.

### 3.3 Financial Disclosures

<b>Covered clinical study</b> (name and/or number): <b>RP-L201-0318</b>
Was a list of clinical investigators provided? <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Total number of investigators identified: <u>12 to 14</u> (see below)
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category [as defined in 21 CFR 54.2(a), (b), (c) and (f)]:</p> <p style="padding-left: 40px;">Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>1</u></p> <p style="padding-left: 40px;">Significant payments of other sorts: <u>2</u></p> <p style="padding-left: 40px;">Proprietary interest in the product tested held by investigator: <u>1</u></p> <p style="padding-left: 40px;">Significant equity interest held by investigator in sponsor of covered study: <u>0</u></p> <p style="padding-left: 40px;">Is an attachment provided with details of the disclosable financial interests/arrangements?</p> <p style="padding-left: 80px;"><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p> <p style="padding-left: 40px;">Is a description of the steps taken to minimize potential bias provided? <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<p>Number of investigators with certification of due diligence (Form FDA 3454, box 3): <u>0</u></p> <p style="padding-left: 40px;">Is an attachment provided with the reason? <u>N/A</u></p>

The Applicant provided a list of clinical investigators in Module 1.3.4 (to include Form FDA 3454) and Appendix 16.1.4 of the CSR for Study 0318. There are discrepancies between the lists, but the investigators with disclosable financial interests appear consistent. Form FDA 3455 was submitted for one PI (Julian Sevilla Navarro, MD, PhD) and one sub-investigator (Adrian Thrasher, MD, PhD), with both receiving consultancy payments from the Applicant. From March 1, 2018, to May 4, 2022, Dr. Sevilla Navarro received consultancy payments of (b) (4). Effective May 5, 2022, he receives (b) (4) for no more than 5 hours per week. There is no documentation of payments received by Dr. Thrasher. One subject was treated at the clinical site where Dr. Sevilla Navarro is the PI (002), and two subjects were treated at the clinical site where Dr. Thrasher is the PI (004).

Additional disclosures note that Dr. Sevilla Navarro is an inventor on two patent applications that are related to licensed rights granted to the Applicant. According to the license agreement, he receives a portion of the revenue income paid to institutions upon meeting agreed-upon milestones, and royalty payments for commercialized products. It is unclear if these patents are related only to the Fanconi anemia program licensed to the Applicant or to RP-L201 as well. Due to a lack of information provided (including a description of steps to minimize potential bias), the potential for impact to data integrity is unclear.

In 2009, Dr. Elena Almarza developed the SIN-LV vector containing the *ITGB2* gene which was licensed by the Applicant in 2017 and formed the basis of their IND application submitted in October

2018.<sup>10</sup> Dr. Almarza is noted to be the Director of CMC and Analytics in teleconference summaries with the Applicant.<sup>11</sup> She is not an investigator for the clinical trial but was the first author on the comprehensive literature review published in July/August 2018 that is the primary source of NH data for children with LAD-I and the benchmark for survival to which the Applicant compares the outcomes on their primary efficacy endpoint. The Applicant did not provide any disclosures related to Dr. Almarza, but the publication contains a disclosure that “E. Almarza has received personal fees for lecturer participation and has patent licensing agreements for the development of LAD gene therapies from Rocket Pharmaceuticals.”

#### **4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES**


##### **4.1 Chemistry, Manufacturing, and Controls (CMC)**

Following initial review, the CMC team concluded that the information contained within the original BLA submission did not demonstrate adequate control of the manufacturing process or critical quality attributes. As such, the BLA did not satisfy CMC requirements for biological product licensure, and thus a complete response letter was issued (Jun 14, 2024). Upon BLA resubmission in October 2024, CMC determined that the Applicant did not completely address the noted deficiencies, and an incomplete response letter was issued. Following review of the Applicant’s most recent resubmission (Sep 26, 2025), all CMC major deficiencies were adequately addressed. Please refer to the CMC Review for full details.

##### **4.2 CD18 and CD11a Assay Validation**

The assay integral to the interpretation of the biomarker data includes the single assay measuring CD18 and CD11a expression on the cell surface of neutrophils. This assay was used to quantify expression of CD18 and CD11a on the neutrophil surface and was validated by the Applicant prior to use in the trials, with a validation report submitted to the BLA for FDA review.<sup>12</sup> This assay was also evaluated by the CMC team through detailed data assessment and found to be sufficiently validated at higher levels of expression for both biomarkers to allow accurate and reliable interpretation of the CD18 and CD11a post-treatment data.

(b) (4)



Please refer to the CMC Review for further information regarding validation of the Applicant’s assay.

<sup>10</sup> Original BLA 125806; SN0001, Module 1.2, Reviewer’s Guide, pp.1-2.

<sup>11</sup> FDA Mid-Cycle Communication Summary, dated Jan 8, 2024.

<sup>12</sup> Original BLA 125806; SN0001, Module 5.3.5.2, Appendix 16.1.10 (GOSH LAD-I Flow Cytometry Assay Validation Report).

**Reviewer Comment:** Based on Applicant-provided data and review by the CMC team, there is confidence in the results obtained using the CD18 assay component above a threshold of (b) (4) expression. As such, it is anticipated that this assay accurately captured most post-treatment CD18 values obtained in the Applicant's clinical studies (see [Section 7.1.5.2](#) for CD18 results by subject and a discussion of CD18 limitations). Similarly, there is confidence in the results obtained using the CD11a assay component above a threshold of (b) (4) (see [Section 7.1.5.3](#) for CD11a results by subject and a discussion of implications of this LOQ). It is suspected that the true LOQ for both assay components is lower than (b) (4) but, to confirm this, the Applicant will need to generate additional data (with additional (b) (4) points), which was thought to be untenable under the current BLA review schedule. However, supplemental assay validation studies for both assay components will be conducted in the post-marketing setting, as a PMR outlined in [Section 11.6](#).

The Applicant's CD18 and CD11a assays were also used to measure baseline/pre-treatment values. Based on the Applicant's validation studies, at levels of CD18 and CD11a expression (b) (4), the variability is unacceptably high to provide confidence in the results obtained. This is acknowledged as a potential challenge to any assessments of change that would be dependent on pre-treatment and post-treatment values. However, as noted in [Section 7.1.5.2](#) and [Section 7.1.5.3](#), achievement of post-treatment CD18 and CD11a expression at levels (b) (4) (which is the case for the majority of treated patients) is thought to be sufficiently accurate to allow reliable interpretation and use as an efficacy endpoint for approval. As such, the baseline value does not carry the same level of importance as it would if it were to be used to directly measure response on the biomarker endpoint (i.e., response defined as a specific change from baseline) and therefore, additional uncertainty can be tolerated as related to the measurement of baseline values. Additionally, the changes from baseline following treatment are large enough to overcome the uncertainties inherent to the assay itself for low baseline values (see Figure 8 and Figure 9) and, as noted above, there is confidence that the high levels of post-treatment expression are accurate based on the assay validation at high expression levels.

Lastly, it is recognized that the Applicant's CD18 and CD11a assay was used to confirm eligibility for Study 0318 and that the levels of expression used to define severe LAD-I are below the LOQ for both assays (b) (4). However, it is notable that, while not required, nearly all subjects met criteria for severe LAD-I based on multiple aspects typically considered in diagnosis, including confirmation of pathogenic ITGB2 variants and clinical and family history of the disease. In fact, all patients were diagnosed by outside providers prior to being referred for study enrollment, as evidenced by accounts of referring providers<sup>13</sup> and historical testing for

<sup>13</sup> Original BLA 125806; SN0001, Module 2.5, Survey Current Standard of Care in the Treatment of Severe LAD-I.

*CD18/CD11a and genetic mutations,<sup>14</sup> and all results were confirmed for study eligibility. Commercially available assays for CD18 and CD11a expression exist and are routinely used for LAD-I diagnostic purposes and in the allo-HSCT setting. It is thus expected that those assays will continue to be used to identify severe LAD-I patients for KRESLADI treatment in the post-marketing setting and for clinical follow-up after product administration. Therefore, the uncertainty regarding CD18 and CD11a expression at baseline is unlikely to confound their interpretation for diagnostic purposes and study enrollment given several lines of evidence establishing patients' diagnosis for enrollment.*

#### **4.3 Nonclinical Pharmacology/Toxicology (P/T)**

*In vitro* and *in vivo* nonclinical studies conducted by the Applicant demonstrated proof-of-concept, with CD34+ cell transduction following KRESLADI administration leading to CD18 expression and expression of CD11a, functional correction of leukocyte adhesion defects, and improvement in clinical outcomes in treated animals.<sup>15</sup> Please refer to the P/T Review for full review of the Applicant's nonclinical data.

#### **4.4 Clinical Pharmacology**

The clinical pharmacology assessment focused on the pharmacodynamic (PD) effects of KRESLADI and on assessment of the Applicant's proposed recommended dose. Due to the nature of the product, conventional studies on pharmacokinetics, absorption, distribution, metabolism, and elimination are not applicable. The data supporting the product's clinical pharmacology assessment for the proposed indication was obtained from clinical study RP-L201-0318. As part of PD assessment, engraftment parameters for transduced cells (i.e., vector copy number, VCN) and expression of mechanistically relevant markers such as CD18 and CD11a were monitored longitudinally.

##### **4.4.1 Mechanism of Action**

KRESLADI adds functional copies of the *ITGB2* gene into patients' hematopoietic stem cells (HSCs) through transduction of autologous CD34+ cells with LV-RP-201. After KRESLADI infusion, transduced CD34+ HSCs engraft in the bone marrow and differentiate into various cell types, including leukocytes capable of expressing functional CD18 protein. Functional CD18 protein enables formation of the CD18/CD11a heterodimer (Lymphocyte Function-Associated Antigen-1, LFA-1) which facilitates leukocyte adhesion to endothelial surfaces and extravasation to infectious and inflammatory sites.

##### **4.4.2 Human Pharmacodynamics**

The pharmacodynamic assessment of KRESLADI included engraftment parameters for transduced cells (i.e., vector copy number, VCN) and expression of mechanistically relevant markers such as CD18 and CD11a.

###### **4.4.2.1. Engraftment of transduced cells**

The vector copy number (VCN) was monitored longitudinally in peripheral blood mononuclear cells (PBMC) and in a subpopulation of PBMC expressing CD15+ (neutrophils). The Applicant defined an engraftment threshold of VCN as 0.1 copies per cell. All 9 patients achieved >0.1 copies per cell in PBMC from Month 1 to 24. The VCN in PBMC was variable among the 9 patients and the median VCN appears to increase between Month 1 to 3 (range: 0.14 to 2.4) and remains stable from Month 6 to 24

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<sup>14</sup> Eight of 9 subjects had prior CD18 and/or CD11 testing consistent with severe LAD-I and 8 of 9 had historical genetic testing identifying a variant in the *ITGB2* gene. Source: Original BLA 125806; SN0001, Module 5.3.5.2, RP-201-0318 CSR v1.0, Listings 16.2.4.8 and 16.2.4.12.

<sup>15</sup> Original BLA 125806; SN0003, Module 2.4 (Nonclinical Overview).

(range: 0.49 to 3.6) following product administration. The median (range) VCN in CD15+ cells was 1.63 (range: 0.53 to 2.23) and 1.12 (range: 0.01 to 3.25) at Month 6 and Month 24, respectively.

#### 4.4.2.2. CD18 Expression in Neutrophils

CD18 expression in neutrophils was analyzed by Flow Cytometry using CD18 monoclonal antibody clone 6.7, and clone L130. The limit of detection (LOD) for CD18 (clone 6.7) was (b) (4) and it was (b) (4) for clone L130. Based on published scientific studies, the Applicant proposed to employ a threshold of (b) (4) CD18 expression based on clone 6.7 assay.

The CD18 expression results using clone 6.7 assay are summarized below. At baseline (screening), seven out of nine patients had CD18 expression in neutrophils below LOD. Two patients had CD18 expression at baseline of 5.8% and 63.4% (indicating production of a dysfunctional CD18 protein as the patients still had severe LAD-I given CD11a <2%, molecular confirmation, and clinical symptomatology). These two patients were excluded from CD18 assessment. Seven of nine patients had baseline neutrophil CD18 expression <2% and thus were evaluable for post-treatment CD18 assessment. CD18 expression increased in all 7 patients after product infusion and stabilized by Month 3 post-infusion with median CD18 expression of 51% (range: 26% to 84%). Median CD18 expression at Month 12 and Month 24 post-infusion were 54% (range: 20% to 87%) and 45% (range: 16% to 82%), respectively signifying marked improvements. Neutrophil CD18 expression was sustained through at least Month 42 post-infusion (Table 5).

**Table 5: Expression of CD18 in Neutrophils After Product Administration (Clone 6.7 Assay)**

Variable	Week 4	Month 3	Month 6	Month 12	Month 24	Month 36	Month 42
N	7	7	7	7	7	7	7
Mean (SD)	63.6 (20)	52.0 (18)	64.4 (16)	55.2 (24)	47.4 (22)	59.2 (18)	42.7 (12)
Median	58.9	51.2	65.7	54.0	45	56.8	44.7
Min, Max	40.4, 88.6	25.6, 83.8	47.2, 86.6	19.6, 87.4	16.2, 81.7	36.5, 85.3	22.5, 54.7

Source: Clinical pharmacology reviewers' (Drs. Million Tegenge and Xiaofei Wang) analysis

#### 4.4.2.3. CD11a Expression in Neutrophils

Expression of CD11a was monitored using the same flow cytometry assay. The limit of detection for CD11a was (b) (4) and all 9 patients had CD11a expression below LOD at baseline. The results of CD11a are summarized in Table 6. Increase in CD11a production was observed in all 9 treated patients. In addition, seven of the 9 patients had CD11a expression above 25% from Month 1 to Month 42 following product administration.

**Table 6: Expression of CD11a in Neutrophils After Product Administration**

	Week 4	Month 3	Month 6	Month 12	Month 24	Month 36	Month 42
CD11a	--	--	--	--	--	--	--
N	9	9	7	9	9	9	7
Mean (SD)	62.1 (19)	47.9 (17)	50.0 (21)	42.5 (20)	41.7 (17)	43.4 (17)	36.1 (14)
Median	61.7	49.8	54.6	45.3	39.4	45.1	38.3
Min, Max	32.5, 89.7	20.5, 67.9	15.1, 73.8	18.4, 74.8	17.4, 65	17.0, 73.6	18.6, 59.4

Source: Clinical pharmacology reviewers (Drs. Million Tegenge and Xiaofei Wang) analysis

#### 4.4.2.4. Correlative Analyses

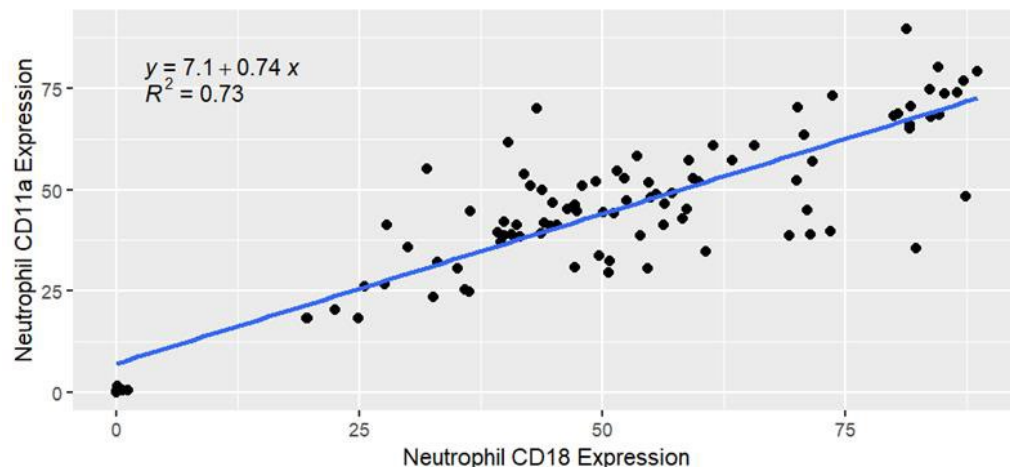
##### Expression of CD18 and CD11a

Correlative analysis for neutrophil CD18 and CD11a expression was conducted using pooled post-treatment data from 7 patients who were evaluable for CD18 assessment (baseline CD18 levels <2%).



The results indicate a strong positive correlation between post-treatment CD18 and CD11a expression indicating restoration of the LFA-1 heterodimer function (Figure 1).

**Figure 1: Correlation Between CD18 and CD11a Expression in Neutrophils After Product Administration**



Source: Reviewer's analysis.

Please refer to [Section 7.1.5.2](#) and [Section 7.1.5.3](#) for further information pertaining to CD18 and CD11a expression.

#### VCN in PBMC and Expression of CD18 and CD11a

Additional correlative assessments between the engraftment/PD parameters were conducted to understand the quantitative relationship and consistency among the different PD parameters. Strong correlations were observed between VCN in PBMC and expressions of CD18 and CD11a using data at Month 24 indicating that the biomarker improvements were secondary to KRESLADI administration and successful engraftment (Table 7). Similar associations were observed using pooled post-treatment data.

**Table 7. Correlative Assessment between VCN in PBMC and Expression of CD18 and CD11a at Month 24**

-	N	R <sup>2</sup>
VCN PBMC vs CD18*	9	0.82
VCN PBMC vs CD11a	9	0.87

Source: Dr. Million Tegenge's analysis

\* CD18 (clone 6.7 assay)

#### 4.4.2.5. Dose Justification

The median CD34+ cell dose was  $4.3 \times 10^6$  CD34+cells/kg (range:  $2.8 \times 10^6$  CD34+cells /kg to  $10.0 \times 10^6$  CD34+cells/kg). No dose-response relationship was observed. Exploratory analysis of the limited data showed that none of the product characteristics (e.g., dose, vector copy number, (b) (4) and transduction efficiency) correlated with pharmacodynamic parameters (i.e., VCN in

PBMC, CD18 or CD11a). Also, busulfan cAUC and patient age at KRESLADI treatment did not correlate with pharmacodynamic parameters.

#### 4.4.3 Human Pharmacokinetics

KRESLADI is an autologous cell-based gene therapy (GT) which includes HSCs that have been genetically modified *ex vivo*. The nature of KRESLADI is such that conventional pharmacokinetic (PK) studies on absorption, distribution, metabolism, and excretion are not applicable.

PK analysis was performed for the myeloablative conditioning agent (busulfan) that was used in the clinical study. Busulfan's pharmacodynamic activity in myeloablation is dependent on cumulative exposure (cumulative area under the concentration versus time curve, cAUC) over 4 days of dosing. Published studies of allogeneic HSCT have shown an association between high busulfan exposure and increased toxicity and low busulfan exposure has been shown to correlate with more frequent graft rejection. PK blood samples were collected after the initial dose and following at least one subsequent dose to adjust dosing in the 3rd and 4th day of conditioning so that the net AUC for all 8 doses would average 18,462  $\mu\text{Mol}\cdot\text{minute}$  (equivalent to 75  $\text{mg}\cdot\text{hour/L}$ ). The target cumulative AUC for busulfan was initially 65.0  $\text{mg}\cdot\text{h/L}$  and later modified to 75.0  $\text{mg}\cdot\text{h/L}$ . In the 9 treated patients, the median busulfan cAUC was 74.9  $\text{mg}\cdot\text{h/L}$  (range 63-77). Based on the limited data, no relevant relationship was observed between individual patient time to neutrophil/platelet engraftment and busulfan cAUC. Please refer to [Section 6.1.4](#) for further information related to busulfan conditioning.

#### 4.5 Statistical

Please see [Section 6.1.11.1](#) for a discussion of statistical analyses related to the Applicant's proposed primary efficacy endpoint (HSCT-free survival) and [Section 6.1.11.5](#) for a discussion of statistical analyses pertaining to EBMT NH data. The team did not perform analyses of the primary or secondary endpoints on incidence of infections due to significant limitations to data interpretability (see [Section 7.1.5.1](#)). Please refer to the Statistical Review for additional details.

#### 4.6 Pharmacovigilance

The clinical review team agrees with the Division of Pharmacovigilance's recommendation for a post-marketing requirement (PMR) study under the Food and Drug Administration Amendments Act of 2007 Title IX. The PMR will require the Applicant to conduct a post-marketing, prospective, observational study to assess and characterize the long-term safety and risk of secondary malignancies following treatment with KRESLADI. Although no malignancies were reported in this study, this class of products based on LVV carries a risk of insertional oncogenesis with cases of hematologic malignancies reported with other LVV-based cell-based gene therapy products. Furthermore, given the small size of the safety database currently available, additional long-term safety data will be helpful to ensure the continued favorable benefit-risk assessment of KRESLADI. Please refer to [Section 6.1.12](#) and [Section 8](#) for additional discussion of the safety findings and analyses and [Section 11.6](#) for an outline of the PMR safety study. Please also refer to the Pharmacovigilance Review for additional details of the PMR safety study and the Applicant's pharmacovigilance plan.

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

#### 5.1 Review Strategy

The Applicant's single interventional trial (RP-L201-0318) and corresponding LTFU study (RP-L201-0121-LTFU) are discussed individually in [Section 6.1](#) and [Section 6.2](#), respectively. Analysis of the primary efficacy endpoint (as proposed by the Applicant) is discussed in [Section 6.1.11.1](#), as it was

assessed during the parent study. The secondary efficacy endpoints (including the biomarker endpoints ultimately recommended as the basis for AA) are discussed in the context of the Integrated Overview of Efficacy in [Section 7.1.5](#), as data from both studies were included in the analyses. Upon BLA resubmission in September 2026, the Applicant provided updated efficacy data (data cut: Jun 18, 2025), which has been incorporated into the aforementioned sections of this memo.

The majority of the safety analysis is within the context of the parent study in [Section 6.1.12](#), as there was minimal AE reporting in the LTFU study. As certain clinical assessments, such as vital signs and laboratory assessments, were provided by the Applicant inclusive of the LTFU study, these aspects of the safety review are discussed in the Integrated Overview of Safety in [Section 8](#). Limited updates to safety data were provided upon BLA resubmission, with all interval events outlined in [Section 8.4.8](#).

The clinical review of the BLA was performed jointly by Dr. Erica Glancy, who conducted the clinical efficacy review, and Dr. Shelby Elenburg, who conducted the clinical safety review. Both reviewers contributed to the synthesis and documentation of the overall conclusions for the application. However, due to the complex analyses that led to determinations about efficacy (compared to relatively clearer albeit serious risks with RP-L201), Dr. Glancy as the primary clinical reviewer was responsible for the overall conclusions and benefit-risk determination.

Initial clinical pharmacology review was conducted by Dr. Million Tegenge. Clinical pharmacology review related to BLA resubmission was conducted by Dr. Xiaofei Wang, with her review incorporated into this review memo.

## **5.2 BLA/IND Documents That Serve as the Basis for the Clinical and Clinical Pharmacology Review**

Source documents for this review include documents filed under the original BLA 125806, documents under IND 18485, and Applicant responses to information requests (IRs) sent during the initial and resubmission review cycles. Specific literature searches were performed per [Section 5.5](#).

## **5.3 Clinical Trials in the BLA**

The BLA includes data from one interventional trial, Study RP-L201-**0318** (NCT03812263), and one LTFU study, Study RP-L201-**0121-LTFU** (NCT06282432):

- **Study 0318** was a global, single-arm, open-label, Phase I/II study in 9 subjects with severe LAD-I evaluating the safety and efficacy of a single dose of RP-L201 over a 2-year period. The first subject was treated with RP-L201 on August 30, 2019, and the ninth subject was treated on October 2, 2021. As of the BLA resubmission data cut (Jun 18, 2025), all study subjects had completed the primary study.
- **Study 0121-LTFU** is an ongoing global observational study designed to evaluate the long-term safety and efficacy of RP-L201 in the 9 subjects treated in Study 0318 over a total of 15 years. As of the BLA resubmission data cut (Jun 18, 2025), all study subjects were enrolled in the LTFU trial with approximately 42 to 60 months of follow-up data available.

## **5.4 Consultations**

### **5.4.1 Advisory Committee Meeting**

An advisory committee meeting was not held because the information submitted, including updated trial results, did not raise concerns that would benefit from advisory committee discussion.

#### 5.4.2 External Consults/Collaborations

Not applicable.

### 5.5 Literature Reviewed

Clinical review of this BLA included the review of a substantial number of publications, some included in the BLA submission<sup>16</sup> and some pulled independently. In total, 96 publications pertaining to humans were pulled during the initial review cycle, with an additional 3 involving canine LAD reviewed. A portion of the review was prompted by specific clinical questions regarding the NH of disease and the potential use of biomarkers in predicting clinical outcomes (as outlined in the paragraphs below), with the remainder of the publications pulled to answer additional questions arising throughout the review period and to guide data analyses.

Assisted by FDA librarian, Gwendolyn Halford, the clinical review team conducted a literature search with the following aim: to identify case reports/series describing patients with severe LAD-I who survived beyond the age of 2 years without allo-HSCT. Selected publications (16) and similar publications (4) were identified for further review. Additional publications (14) were identified by FDA reviewers as relevant to the research question and were also reviewed. Of the 20 publications originally identified by Ms. Halford, 7 were cited in the 2018 literature review by Almarza Novoa et al. Of the 14 reviewer-identified publications, 5 were cited in the above review and an additional 4 were submitted as either non-clinical or clinical literature with the BLA.

A second literature review was conducted by the clinical review team with the following aim: to obtain information related to the utility of potential biomarkers (CD11a and leukocyte/neutrophil counts) to predict clinical outcomes in patients with severe LAD-I. A total of 10 publications were identified as having relevant information, including 5 that were not included in the above library review. Of the 5 new publications, 2 had been cited in the review by Almarza Novoa et al. (2018), with an additional publication submitted to the BLA.

Upon BLA resubmission, an abbreviated literature search was conducted to identify updated literature related to the NH of disease, standard of care, and/or biomarkers examined during the prior review cycle (i.e., CD18, CD11a). Eight additional publications were pulled for review, including 5 related to the questions examined in the previous literature searches.

Publications pertinent to discussions found in this BLA review are cited throughout and can be found in the [References](#) section at the end of this Clinical Review Memorandum.

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<sup>16</sup> Approximately 10 publications reviewed can be found in Module 4.3 (Nonclinical Study Reports, Literature References) and approximately 15 publications reviewed can be found in Module 5.4 (Clinical Study Reports, Literature References).

## 6. DISCUSSION OF INDIVIDUAL CLINICAL TRIALS

### 6.1 Trial #1 – Study RP-L201-0318

Title: “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 (RP-L201-0318, v3.0)”

#### 6.1.1 Objectives

##### Primary Objectives

- Characterize the safety and toxicity associated with KRESLADI.
- Evaluate allo-HSCT survival

##### Secondary Objectives

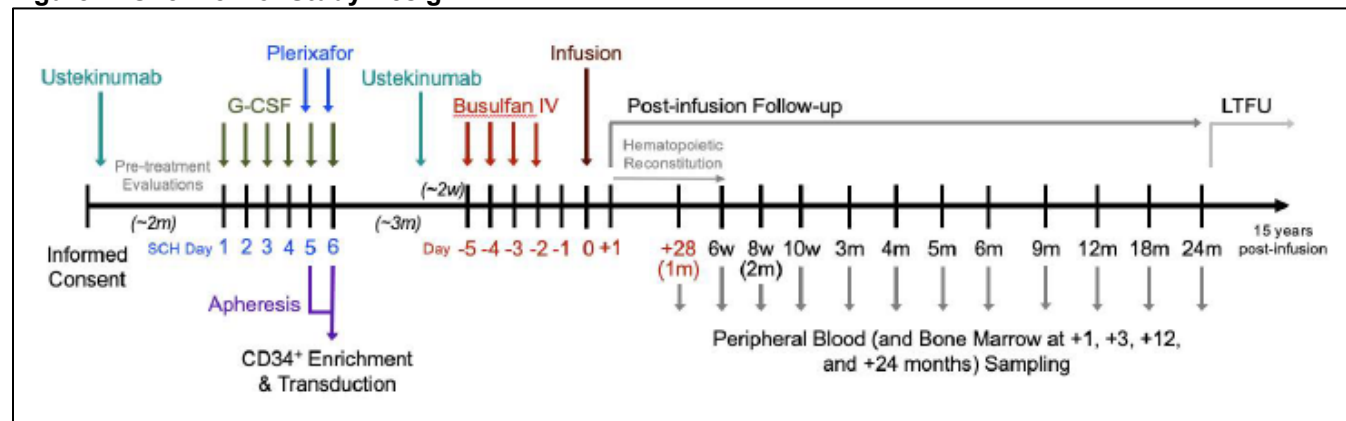
Determine:

- The incidence of significant infections, infection-related hospitalizations, and prolonged infection-related hospitalizations
- The percentage of subjects with an increase in neutrophils expressing CD18
- Percentage of patients with increased CD11a expression post-treatment
- EFS, defined as survival without GF and without aGVHD Grades 2-4.
- The percentage of subjects in whom infusion results in genetic correction of PB cells as demonstrated by VCN of  $\geq 0.1$  in PBMCs and PB CD15+ granulocytes at 6 months.
- Decreases (partial or to normal levels) of LAD-I-associated neutrophilia and leukocytosis.
- Resolution (partial or complete) of any underlying LAD-I-related skin rash or periodontal abnormalities.

#### 6.1.2 Design Overview

Study 0318 is a global, single-arm, open-label, Phase I/II study in subjects with severe LAD-I evaluating the safety and efficacy of a single dose of RP-L201 over a 2-year (24-month) period. As shown in Figure 2, trial days are numbered for the initial stem cell harvest (SCH) and transduction sequence starting at Day 1 (SCH D1) and running forward until conditioning and infusion of the IP. At the time of conditioning, trial day numbering is reset such that the IP is administered on Day 0, and any trial day thereafter represents the number of days following IP infusion. At the end of this study, subjects were enrolled into Study 0121-LTFU (Trial #2) for long-term follow up for an additional 13 years.

**Figure 2: Overview of Study Design**



Source: Original BLA 125806; SN0001, Module 5.3.5.2, RP-L201-0318 CSR v1.0, Figure 2.

Abbreviations: CD, cluster of differentiation; G-CSF, granulocyte-colony stimulating factor; IV, intravenous; LTFU, long-term follow-up; m, month; SCH, stem cell harvest; w, week.

### 6.1.3 Population

#### Key Inclusion Criteria

- Confirmed diagnosis of severe LAD-I as demonstrated by flow cytometry indicating CD18 expression on <2% of polymorphonuclear neutrophils (PMNs). Subjects in which CD18+ PMNs are >2% are considered eligible with <2% CD11a or CD11b expression, a documented *ITGB2* mutation, and a clinical history consistent with LAD-I (or a known family history).
- At least one prior significant bacterial or fungal infection, defined as Grade 2 or higher using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI-CTCAE v5.0). Criterion not required for subjects with a documented family history who met above inclusion criteria.
- Age ≥3 months.

#### Key Exclusion Criteria

- Availability of a medically eligible HLA-identical sibling donor for HSCT
- Hepatic, renal, or pulmonary dysfunction.
- Active metastatic or locoregionally advanced malignancy (including hematologic) for which survival is anticipated to be <3 years.
- Serious infections with persistent bloodstream pathogens.
- Significant medical conditions to include human immunodeficiency virus (HIV) infection; poorly controlled diabetes, hypertension, cardiac arrhythmia, or congestive heart failure; or arterial thromboembolic events (including stroke or myocardial infarction) within the prior 6 months.

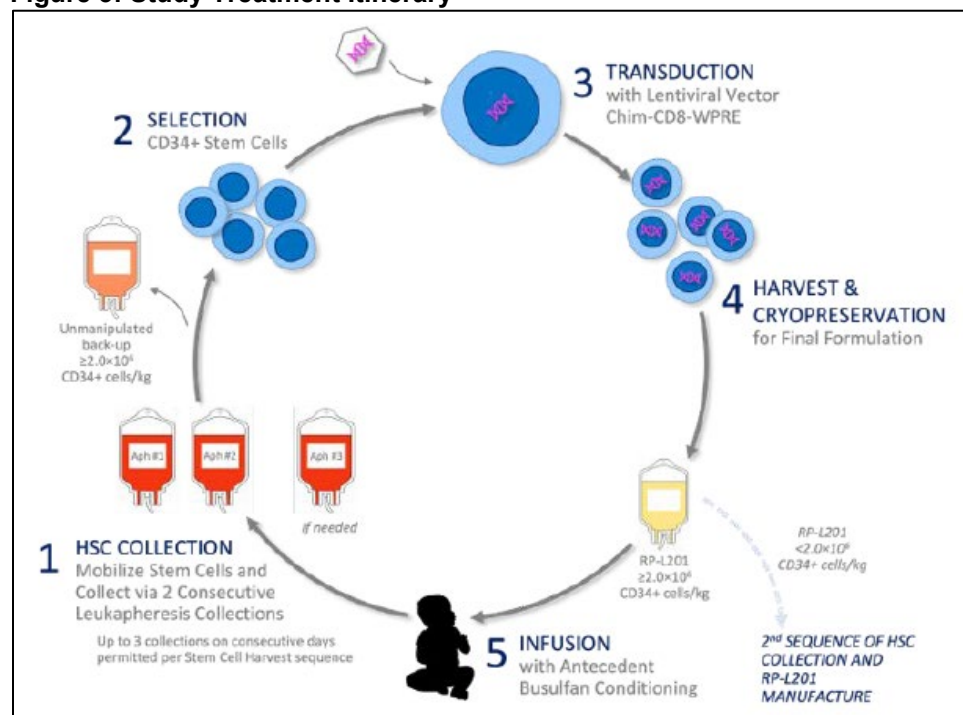
**Reviewer Comment:** Based on review of the literature, defining severe LAD-I based on low CD11b expression alone is unreliable, as levels were noted to be “highly variable,” “not appropriate for diagnosing LAD-I,” and inducible (Levy-Mendelovich et al. 2016; Fazlollahi et al. 2023; Simon et al. 2010). Despite the eligibility criterion allowing for the enrollment of subjects with isolated low CD11b, no subjects qualified for inclusion based on low CD11b alone; all subjects also had low CD11a if they had CD18 expression >2%. The inclusion criterion for diagnosis are appropriate to identify patients with severe LAD-I.

### 6.1.4 Study Treatments or Agents Mandated by the Protocol

Study treatments were mandated by the protocol for different phases including: 1) HSC mobilization and collection (via PB apheresis); 2) CD34+ cell enrichment for pre-stimulation; 3) transduction with LVV; 4) cryopreservation of the IP (as well as unmanipulated back-up cells); and 5) busulfan conditioning, followed by thawing and infusion of the IP. The study treatment itinerary is illustrated in Figure 3.



Figure 3: Study Treatment Itinerary



Source: Original BLA 125806; SN0001, Module 5.3.5.2, RP-L201-0318 CSR v1.0, Figure 3.  
Abbreviations: CD, cluster of differentiation; HSC, hematopoietic stem cell.

### Ustekinumab

Instructions for administration of ustekinumab at a dose of 0.75 mg/kg subcutaneously (SC) approximately 2 weeks prior to initiation of mobilization and 1 to 2 weeks prior to infusion of the IP (prior to conditioning), were added to the study protocol with v1.5 (dated Dec 19, 2019).<sup>17</sup> Ustekinumab is a mAb that blocks IL-12 and IL-23 and was added to the protocol to minimize the potentially deleterious effects of LAD-I-associated hyperinflammation (as described in [Section 2.1](#)) on long-term HSC viability (i.e., optimize the potential for collection of viable long-term HSCs and facilitate engraftment of gene-corrected long-term repopulating hematopoietic cells).<sup>18</sup> The Investigator, in consultation with the Medical Monitor, was permitted to adjust the dose or schedule of ustekinumab based on clinical judgement.

**Reviewer Comment:** One subject treated prior to the implementation of protocol v1.5 did not receive the pre-mobilization dose of ustekinumab but did receive the pre-conditioning dose, as well as two interval doses between mobilization and the pre-conditioning dose. One subject did not receive ustekinumab at all during the study. Six of the seven other subjects received additional doses of ustekinumab prior to IP administration (i.e., more than the two specified doses).

### Mobilization and Apheresis

The following medications were administered prior to apheresis:

- Granulocyte-colony stimulating factor (G-CSF) 10 µg/kg SC every 24 hours for up to 6 doses.
  - A seventh dose could be administered if a third apheresis collection was planned.

<sup>17</sup> IND 18485; SN0016, Module 5.3.5.2.

<sup>18</sup> Original BLA 125806; SN0001, Module 5.3.5.2, RP-L201-0318 CSR v1.0, Section 9.5.1.1.

- To minimize the potential for splenic rupture associated with severe leukocytosis, doses were reduced to 5 µg/kg for WBC (white blood cell count) >50,000/mm<sup>3</sup> or omitted if >75,000/mm<sup>3</sup>.
- Doses could be reduced or omitted at WBC values lower than those above at the discretion of the Investigator, based on clinical judgement.
- Plerixafor 240 µg/kg/day SC 16-20 hours after the fourth and fifth administration of G-CSF.
  - A third dose could be administered after the sixth dose of G-CSF when a third apheresis collection was planned.
  - In the event of dose reductions or omissions of G-CSF, plerixafor (and apheresis) could be commenced earlier than scheduled or administered according to schedule, at the discretion of the Investigator in consultation with the Medical Monitor.

The first apheresis collection commenced 4 to 10 hours following plerixafor administrations, or earlier if PB CD34+ counts met or exceeded 10 cells/µL. Generally, up to 2 apheresis collections were permitted, with the second collection commencing within 24 hours of the first. A third apheresis collection was permitted in select circumstances, commencing within 24 hours of completion of the second collection.

**Reviewer Comment:** *Three of nine subjects underwent a third apheresis collection.*

#### CD34+ Cell Enrichment, Transduction, and Cryopreservation

Enriched CD34+ hematopoietic cells were purified and transduced *ex vivo* with LV-RP-201 encoding the human *ITGB2* gene, followed by cryopreservation of the IP (utilizing dimethyl sulfoxide [DMSO]). A minimum of 2×10<sup>6</sup> viable CD34+ cells/kg were required for release for infusion. If the IP did not meet established release specifications, an additional sequence of mobilization/apheresis could be initiated no earlier than 2 weeks following the final collection of the first sequence.

**Reviewer Comment:** *Three of nine subjects underwent a second sequence of mobilization and apheresis, with one requiring the two sequences to obtain adequate cell numbers for product manufacturing.*

#### Cryopreservation of CD34+ Rescue Cells

An aliquot of least 2×10<sup>6</sup> unmanipulated CD34+ cells/kg was cryopreserved to remain available as hematologic rescue (back-up) in the event of engraftment failure or compromise of the IP.

#### Busulfan Conditioning

Conditioning would only commence once it was verified that the IP met established release specifications and rescue cells had been cryopreserved. Conditioning busulfan was administered twice daily (i.e., every 12 hours) as a 2-hour IV infusion on 4 consecutive days (3-hour infusion was permitted if required by institutional standards), commencing at a dose based on subject weight (1.6 to 2.0 mg/kg) and with multiple PK samples collected after the initial dose and following at least one subsequent dose (subsequent to any PK-guided dose-adjustment). Institutional guidelines could be implemented to determine points for PK analysis, where applicable. Anti-emetic and anti-seizure medications were given prior to and during busulfan administration according to institutional guidelines. Please see [Section 4.4.3](#) for additional details of busulfan PK parameters.



#### 6.1.5 Directions for Use (Thawing and Infusion of the product)

Subjects were hospitalized during the treatment portion of the trial and until hematologic reconstitution was documented. During hospitalization, subjects were managed according to institutional clinical practice protocols for autologous HSCT, which may include general and supportive measures; infection prophylaxis; antiemetic, anti-seizure, and analgesic therapy; growth factor support prior to and after engraftment; and post-transplant re-vaccination. After confirmation of release specifications being met, the IP was to be thawed at 37°C approximately 24 to 48 hours (but no less than 22 hours) after the final busulfan dose according to standard operating procedures. The IP was administered within 30 minutes of thawing, as a single IV infusion with a minimum cell dose of  $2 \times 10^6$  CD34+ cells/kg on Day 0. If more than one DP was manufactured (e.g., if a second mobilization and apheresis sequence was required to meet the minimum total cell dose), bags were infused 1 to 2 hours apart. No maximum IP dose was specified.

**Reviewer Comment:** Seven of 9 subjects received the IP between 4 and 21 hours after the protocol-defined window for administration (see also [Section 3.2](#)). One study subject was infused with IP from two DP lots.

#### 6.1.6 Sites and Centers

This multi-center study was performed at three clinical sites in the United States, United Kingdom, and Spain. The main study sites are outlined in Table 8 and a complete list of investigators was provided per [Section 3.3](#). A single local site visit was permitted at Week 10 following an amendment to the study protocol on June 7, 2021 (v2.3). Please refer to [Section 3.2](#) and the BIMO Review for further details of additional local study sites where study subjects completed assessments.

**Table 8: Study Sites and Principal Investigators**

Site	Location	Principal Investigator
002	Hospital Infantil Universitario Niño Jesús Avenida Menéndez Pelayo, 65 28009 Madrid, Spain	Julián Sevilla Navarro, MD, PhD
003	University of California Los Angeles 3163 Terasaki Life Sciences Building 610 Charles E. Young Dr. E Los Angeles, CA 90095-1489 (US)	Donald B. Kohn, MD
004	University College London Great Ormond Street Institute of Child Health 30 Guilford St. London WC1N 1EH, UK	Claire Booth, MBBS, PhD, MSc

Source: Original BLA 125806; SN0001, Module 5.3.5.2, RP-L201-0318 CSR v1.0, Table 1.  
Abbreviations: CA, California; UK, United Kingdom; US, United States.

#### 6.1.7 Surveillance/Monitoring

Subjects were monitored per the Schedules of Events in [Section 6.1.7.1](#), with any notable changes occurring with protocol amendments outlined in the relevant sections of this review. Data was collected on electronic case report forms (eCRFs).

With protocol v3.0 (dated Feb 3, 2023), the Applicant defined events that would not be considered a serious adverse event (SAE) to include: 1) a visit to the emergency room or other hospital department lasting <24 hours that does not result in admission (unless considered an important medical event or a

life-threatening event); and 2) Grade 4 laboratory values, unless they are deemed clinically significant by the Investigator or result in clinical sequelae.<sup>19</sup>

Adverse events of special interest (AESI) requiring expedited reporting (within 24 hours of awareness) were also added in this protocol amendment, to include:<sup>20</sup>

- Any new severe or otherwise significant infection.
- Any new skin or oral lesion of infectious etiology or otherwise caused by underlying LAD-I.
- Any new aGvHD, particularly those Grade 2 to 4.
- Any primary GF.
- Any secondary GF, defined as a sustained decrease in VCN <0.1 or neutrophil CD18 (using mAb 6.7) <10% on 2 consecutive evaluations separated by an interval of at least 1 month, and not considered related to a concurrent infection or non-IP drug-related toxicity.
- Any predominant clone, determined by ISA of ≥10% clonal contribution in setting of VCN ≥0.1.

An Independent Data Monitoring Committee (IDMC) was used to make decisions regarding trial modification, termination, and activation of Phase II following completion of Phase I. Members of the IDMC were individuals with expertise in gene therapy, immunology, hematology, and/or life-threatening primary immunodeficiencies who were neither study investigators nor representatives of the Applicant.

#### 6.1.7.1 Schedules of Events

The Schedules of Events for Study 0318 can be found in [Appendix E](#).

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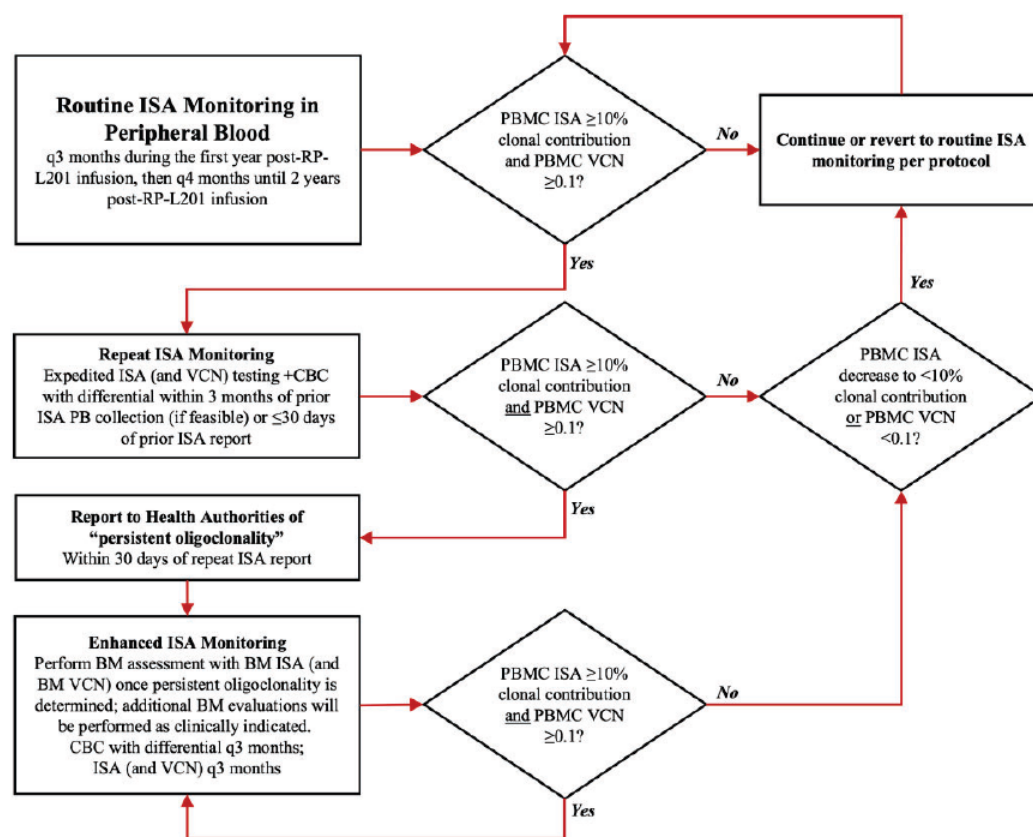
<sup>19</sup> "Clinically significant laboratory values are those that require medical intervention to correct or otherwise deemed important by the Investigator. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an AE." Source: Original BLA 125806; SN0001, Module 5.3.5.2, RP-201-0318 protocol v3.0, Section 10.2.3.

<sup>20</sup> Original BLA 125806; SN0001, Module 5.3.5.2, RP-201-0318 protocol v3.0, Section 10.2.5.

### 6.1.7.2 Integration Site Analysis (ISA)

PB cells were routinely evaluated for clonality and insertion site genomic localization by ISA according to the Schedules of Events in [Appendix E](#). When feasible, ISA in bone marrow (BM) cells was also performed. The identification of a predominant clone in PBMCs, defined as clonal contribution of  $\geq 10\%$  with a PBMC VCN  $\geq 0.1$ , warranted additional monitoring as illustrated in Figure 4.<sup>21</sup> The target turnaround time for results from repeat ISA and VCN analysis was within 30 days of sample collection. In the event of “persistent oligoclonality,” subjects underwent a BM evaluation and enhanced PB monitoring. Other indications for performing BM evaluation for BM ISA included leukocytosis or cytopenias that cannot be explained by other factors (e.g., medication or acute illness). Subsequent BM evaluations, including gene expression studies, were performed if the predominant clone was an oncogene or tumor suppressor gene. If multiple insertion sites were identified within the same clone, single-cell sequencing or genome sequencing approaches were used to perform further evaluations in PB and/or BM, to potentially include assessment of BM colony-forming units.

**Figure 4: Integration Site Analysis Algorithm**



Source: Original BLA 125806; SN0001, Module 5.3.5.2, RP-L201-0318 protocol v3.0, Figure 5.

Abbreviations: BM, bone marrow; CBC, complete blood count; ISA, integration site analysis; PB, peripheral blood; PBMC, peripheral blood mononuclear cell; VCN, vector copy number.

<sup>21</sup> In RP-L201-0318 protocol v3.0 (dated Feb 3, 2023), Section 8.2.8.5 (Bone marrow evaluation) was expanded, and Section 8.2.9.5 (Integration Site Analysis) was added to “incorporate recommendations from the FDA on monitoring of insertional mutation analysis (ISA).” Specifically, ‘predominant clone’ was defined and additional monitoring in the event of a predominant clone was specified, to include addition of the ISA algorithm shown in Figure 4. Any incidence of a predominant clone was also included as an AESI in v3.0. Changes appear to be in response to an abnormal clone identified in one study subject in April 2022 (see Section [6.1.12.4](#)).

#### 6.1.7.3 Monitoring for Pulmonary Arterial Hypertension (PAH) and Thrombotic Microangiopathy (TMA)

Following an SAE of PAH and concern for potential TMA,<sup>22</sup> Study 0318 protocol v2.3 (dated Jun 7, 2021) incorporated recommendations from the IDMC for additional assessments to monitor for PAH and TMA. Additionally, the development of PAH in two or more subjects and evidence of TMA were added to the study stopping rules. These events were later included in a new protocol section for AESI in protocol v3.0 (dated Feb 3, 2023).

#### 6.1.8 Endpoints and Criteria for Study Success

##### Primary Endpoint

The primary efficacy endpoint was allo-HSCT-free survival, defined as the proportion of subjects alive at least 1-year post-IP infusion without allo-HSCT and at age 2 (24 months) without allo-HSCT for subjects <1 year of age at study enrollment. Success on the primary endpoint was defined as improved HSCT-free survival over a historical survival rate of 39% (specific only to patients treated at < 2 years of age), as defined by Almarza Novoa et al. (2018) and described in [Section 2.1](#).

**Reviewer Comment:** FDA did not agree with the Applicant's primary efficacy endpoint of HSCT-free survival prior to BLA submission given the limitations of the comparator rate. Please refer to [Section 6.1.11.1](#) (Analysis of Primary Endpoint).

##### Secondary Endpoints

Secondary efficacy endpoints include:

- Reduction in the incidence of 1) significant infections, defined as infections requiring hospitalization or parenteral antimicrobials; 2) infection-related hospitalizations; and 3) prolonged infection-related hospitalizations (≥7 days); analyzed per subject and across the entire cohort, comparing event rates pre-infusion to those following hematologic reconstitution.
- EFS without GF and without aGvHD Grade 2-4.
- LV VCN in blood and BM cells, as determined via digital droplet polymerase chain reaction (ddPCR) at specified time points pre- and post-infusion, including assessment of the percentage of subjects with PBMC and PB CD15+ cell VCN ≥0.1.
- Post-treatment CD18, CD11a, and CD11b expression in PB PMNs, as determined by flow cytometry.
- Decrease (from pre-infusion) of LAD-I-associated neutrophilia and leukocytosis.
- Resolution (partial or complete) of any underlying LAD-I-related skin rash or periodontal abnormalities, as determined by the treating investigator. Lesions graded based on interval changes from baseline to show worsening, no change, partial improvement, or resolution of lesions.

Safety endpoints include:

- Incidence of AEs, SAEs, suspected adverse reactions (ARs), suspected unexpected serious ARs (SUSARs), and toxic death.
- Insertional mutagenesis: Evaluation of gene-modified clonal repertoire and LV ISA in blood and, if feasible, BM cells.
- Replication competent lentivirus (RCL) in blood, as required and in settings where there is clinical suspicion of unexplained viral illness.

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<sup>22</sup> See [Section 6.1.12.4](#).

- Immunogenicity: Evidence of antibodies against CD18 (or other beta-2 integrin components CD11a or CD11b, or LV components) in serum, if indicated in settings where there is clinical suspicion of immunogenic response or evidence of decreasing PMN CD18 expression.
- Incidence of respiratory complications (including, but not limited to, pneumonitis).
- Incidence of hepatic complications (including, but not limited to, VOD).
- Incidence of bacterial, fungal, and viral (including cytomegalovirus [CMV]) infections pre- and post-IP infusion.
- Incidence of primary and secondary GF post-IP infusion.

**Reviewer Comment:** *Some, but not all, secondary efficacy endpoints were pre-specified. Of note, key infection-related endpoints were not fully defined until all subjects had been enrolled and most were well into post-treatment monitoring. Additionally, secondary endpoints were not hierarchically ordered, with changes noted between protocols and between v3.0 and the CSR. A primary safety endpoint was not specified. Please refer to [Section 7.1.5](#) for further discussion of secondary efficacy endpoints.*

#### 6.1.9 Statistical Considerations and Statistical Analysis Plan (SAP)

##### Applicant's Sample Size Calculation

A total of 9 subjects were planned for study enrollment, including 2 subjects in Phase I and 7 subjects in Phase II. Assuming a historical survival rate of approximately 40%<sup>23</sup> and a true survival rate of 80% among treated subjects, a sample size of 9 results in approximately 70% power that the true survival rate is 80% using an exact binomial test at a two-sided 5% significance level (per SAP v2.0, dated May 18, 2023).<sup>24</sup> The CSR and protocol v3.0 assume a historic survival rate of approximately 40% and a true survival rate of 90% among treated subjects, resulting in approximately 95% power via a binomial test at a two-sided 5% significance level for a sample size of 9.

##### Null Hypothesis

The null hypothesis is that the proportion of subjects alive at 24 months of age and at least 1 year following IP who have not received HSCT is not different from the assumed historical survival rate of 40%.

##### Analysis Populations

- Intent-to-Treat (ITT): Includes all subjects for whom informed consent was obtained and who underwent any trial procedure.
- Per Protocol Transplant (PPT): Includes all subjects who received the IP.
- Per Protocol Final (PPF): Includes all subjects who completed the 24-month follow-up period.

##### Baseline

The last observation recorded before mobilization (SCH D1) was used as the baseline observation for all calculations of change from baseline.

##### Imputed Dates

Conventions for replacing missing dates are outlined in Section 6.1.6 of the SAP. Conventions were applied, as applicable, to AEs, medications (prior infection history), hospitalizations, and dates for clinical course analysis.

<sup>23</sup> Based upon literature review by Almarza Novoa et al. (2018), discussed in [Section 2.1](#).

<sup>24</sup> Original BLA 125806; SN0001, Module 5.3.5.2, RP-L201-0318 CSR v1.0, Appendix 16.1.9. Unable to locate SAP v1.0.

### Primary Efficacy Analysis

Survival (time-to-event) was defined as the time from date of infusion to either death due to any cause or HSCT. Subjects who survived to the end of the study without HSCT were censored at the date of last contact.

### Secondary Efficacy Analysis<sup>25</sup>

- Change in CD18 and CD11 expression, including percentage of subjects with CD18 expression  $\geq 10\%$
- EFS (time-to-event) analysis for:
  - Hospitalization-free survival
  - Infection-related hospitalization-free survival
  - Prolonged infection-related hospitalization-free survival
  - Prophylactic antimicrobial-free survival
    - Time to end of prophylactic antimicrobial use (summarized)
  - GF-free survival
  - GVHD-free survival
  - GF- and GVHD-free survival
  - GF- and GVHD- and prolonged infection-related hospitalization-free survival
- Reduction in events:<sup>26</sup>
  - Hospitalizations
  - Infection-related hospitalizations
  - Prolonged infection-related hospitalizations
  - Infections
  - Infections requiring IV antimicrobials or hospitalization
  - Surgical interventions (debridement, drainage, and resection)
- Resolution in any underlying skin or periodontal abnormalities (summary)
- Change in VCN, including percentage of subjects with PB PMN VCN  $\geq 0.1$
- Summary of neutrophil and platelet engraftment
- Decrease in LAD-associated neutrophilia (and leukocytosis added later)

The frequency of qualitative endpoints was described by the cumulative incidence and its 95% CI. Kaplan-Meier survivor function and Nelson-Aalen cumulative hazard function were estimated for endpoints for which time-to-event occurrence is recorded. Descriptive statistics (mean, median, standard deviation [SD], quartiles, minimum and maximum) were presented for values of quantitative endpoints with absolute and relative changes from baseline at scheduled visits. The 95% CI was presented for both mean and median values.

**Reviewer Comment:** *The Applicant's plan for analysis of the primary efficacy endpoint was based on a historical HSCT-free survival rate of approximately 40%. However, the review team believes it is inappropriate to apply this analysis to the entire sample because 6 of 9 subjects were not representative of the population used to calculate this survival rate. Additionally, the Applicant appears to have changed their assumption of true survival in the CSR versus the "a priori" SAP. Please refer to [Section 6.1.11.1](#) (Analysis of Primary Endpoint) for further discussion of the primary efficacy endpoint. Secondary efficacy endpoints as outlined in the SAP differ slightly from those in the CSR and protocol (primarily, additional analyses for EFS*

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<sup>25</sup> As outlined in SAP v2.0, dated May 18, 2023.

<sup>26</sup> Annualized event rate (AER) by cohort and by subject.



*and event reduction as compared to baseline). Due to a lack of NH data in older patients, analyses of time-to-event endpoints involving survival are not applicable to the entire population and, are, thus not reliable. As only 3 of the 9 treated patients were treated with the product at <2 years of age, the endpoint of allo-HSCT survival to age 2 years is only evaluable in these 3 patients. Please refer to [Section 7.1.5](#) for further discussion of secondary endpoints, including issues with infection-related endpoints.*

#### 6.1.10 Study Population and Disposition

##### 6.1.10.1 Populations Enrolled/Analyzed

Nine subjects were enrolled in Study 0318 between March 2019 and February 2021, with the last subject receiving RP-L201 on October 4, 2021. Three of 9 subjects enrolled were siblings with the same *ITGB2* mutation, and 2 of the siblings met the study inclusion criterion of severe LAD-I using CD11 levels rather than CD18 levels. The study was originally designed to enroll younger patients with severe LAD-I, but 6 of 9 subjects were >2 years of age at the time of treatment (see also Table 1).

The analysis populations are defined in the study SAP as outlined in [Section 6.1.9](#). All subjects are included in the ITT and PPT population. As related to the PPF population, at the time of BLA submission (data cut: Jan 24, 2023), 5 of 9 subjects had completed 24 months of follow-up, and at the 120-Day Update (data cut: Jul 24, 2023), 8 of 9 subjects had completed 24 months of follow-up. At BLA resubmission (data cut: Jun 18, 2025), all 9 subjects had completed 24 months of follow-up in the primary study.

##### 6.1.10.1.1 Demographics

Demographics and baseline characteristics of the 9 subjects enrolled and treated in Study 0318 are outlined in [Section 1.1](#) (Table 1).

##### 6.1.10.1.2 Medical Characterization of the Enrolled Population

Age and CD18/CD11 levels at baseline are summarized in Table 9. All subjects met diagnostic criteria for severe LAD-I, as defined in [Section 6.1.3](#) and shown below. The presence of pathogenic or likely pathogenic *ITGB2* variants was confirmed in all subjects. Information related to baseline infection history and hospitalizations is not included here due to difficulties with interpretation, as outlined in [Section 7.1.5.1](#).

None of the enrolled subjects had previously undergone allo-HSCT (trial exclusion criterion). Based on a survey provided to the referring physicians, 7 of 8 respondents indicated that their patient was at significant risk of developing a life-threatening/life-ending infection in the absence of HSCT, and all 8 respondents indicated that their patient needed allo-HSCT from a non-MSD as soon as feasible (within the next 12 months). Three of 8 respondents indicated that their decision to refer patients for study enrollment was based on the presence of significant, recurring infections.<sup>27</sup>

**Table 9: Age and Baseline CD18/CD11a Expression in Enrolled Population (N=9)**

Subject	Age at Diagnosis	Age at Treatment	CD18 Baseline (%)	CD11a Baseline (%)	CD11b Baseline (%)
(b) (6)	8 y	9.8 y	0.7	0.5	0.9
	3.6 y	4.4 y	63.4 <sup>b</sup>	0.2	0.4

<sup>27</sup> Original BLA 125806; SN0001, Module 2.5, Survey Current Standard of Care in the Treatment of Severe LAD-I.

(b) (6)	2.3 y	3.5 y	0.0	0.3	1.1
	1 d	11.7 m	5.8 <sup>b</sup>	0.9	0.6
	2.8 m	9.8 m	0.2	1.5	0.9
	2.2 m	10 m	0.0	0.2	0.1
	11.9 m	3.6 y	0.0	0.0	0.0
	6.8 m	4.9 y	1.2	0.6	0.6
	6.3 m	2.6 y	0.2	0.4	0.2

Source: Reviewer analysis; derived from ADSL and ADEFF datasets (original BLA 125806, SN0018).

Abbreviations: CD, cluster of differentiation; d, days; m, months; y, years.

<sup>a</sup> Siblings with the same *ITGB2* mutation.

<sup>b</sup> Subjects did not meet inclusion criterion for severe LAD-I based on CD18 expression <2%. In conjunction with CD11a and CD11b expression <2%, presence of an abnormal/unstable protein was suspected, and subjects otherwise met inclusion criteria based on presence of *ITGB2* mutations and medical history consistent with severe LAD-I and/or family history.

### 6.1.10.1.3 Subject Disposition

All subjects completed the study and enrolled in the LTFU study (Trial #2). Subject disposition is summarized in the Integrated Overview of Efficacy ([Section 7.1.3](#), Table 15).

### 6.1.11 Efficacy Analyses

#### 6.1.11.1 Analysis of Primary Endpoint

The primary efficacy endpoint was survival (proportion of subjects alive without allo-HSCT at least 1-year post-IP infusion and at age 2 years for subjects <1 year of age at study enrollment), with success based on improvement over a historical benchmark estimate of 39% survival to age 2 years in the absence of HSCT. All 9 patients survived to the end of study (24 months) with a survival rate of 100% (9 of 9).<sup>28</sup> However, only 3 patients were treated at < 1 year of age and survived to 2 years of age during the study. Six out of the 9 treated patients were >2 years of age at the time of treatment and for those, the historical threshold of 39% survival is not applicable or appropriate for analysis of the primary endpoint. Even looking at the Applicant's clinical trial, 50% of the older subjects (3 of 6) were diagnosed prior to 1 year of age but survived beyond age 2 years without HSCT. Therefore, the results of the Applicant's primary efficacy analysis are not interpretable for the entire enrolled population and not reliable for purposes of establishing efficacy. The study was not designed to demonstrate a survival benefit in only 3 patients and was underpowered for this endpoint when evaluating results based on the 3 patients alone.

As described in [Section 2.1](#), the authors of the literature review on which the historical benchmark is based note that they were unable to calculate survival curves for severe LAD-I patients older than age 2 years because precise survival duration was not noted for most cases. As such, the HSCT-free survival rate for patients with LAD-I who survive beyond age 2 years is unknown. Furthermore, there is concern that a 39% survival rate may be an underestimate secondary to publication biases due to preferentially reporting more severe cases or underreporting from regions with high disease incidence but poor access to diagnostics, or where LAD-I management is a standard part of medical practice.

In a response to an FDA IR requesting NH data for these older patients, the Applicant states, "The disease course...has not been well-characterized as there is an extremely limited number of patients to characterize." They further note, "Mortality for patients surviving beyond age 2 remains extremely high, with most not surviving into adolescence (Li 2010; Hinze 2010)."<sup>29</sup> The Applicant cites two case reports of patients with severe LAD-I who survived beyond age 2 years without HSCT, with mortality at ages 5

<sup>28</sup> Two-sided 95% CI of (66%, 100%) and a p-value of 0.0002 when compared to a null threshold of 39%.

<sup>29</sup> Original BLA 125806; SN0008, Module 1.11.3, Response to FDA IR, p.4.



and 11 years, respectively. However, independent literature review completed by the clinical review team identified at least 15 patients with severe LAD-I who survived into adolescence or adulthood in the absence of HSCT.<sup>30</sup> Additionally, in response to an Applicant-developed survey designed to evaluate current practices in the evaluation and management of severe LAD-I, 5 of 15 (33%) respondents indicated that they had encountered at least one patient with severe LAD-I who was  $\geq 10$  years of age and had not received allo-HSCT.<sup>31</sup>

As noted in [Section 2.1](#), some literature points to a potential shift from an infectious to an inflammatory picture as patients age, even suggesting that inflammatory processes (e.g., periodontitis) manifesting in childhood may be a positive prognostic indicator for reaching adulthood (Geroldinger-Simic et al. 2022). Abuzaitoun et al. (2005) documented a decreased frequency of hospitalizations with age in a case series of 4 severe LAD-I patients, where limited resources necessitated conservative management (i.e., no HSCT). It was noted that diagnosis at a young age, compliance with prophylactic antibiotics, and prompt treatment of infections played a role in the outcomes of these patients. Three of the 4 patients who were compliant with treatment were documented to be 19, 15, and 15 years of age in a 2019 retrospective review by Wolach et al. Of note, all 3 patients had signs of chronic inflammation including inflammatory bowel disease (3 of 3), psoriasis, and gingivitis.

As described in [Section 6.1.10.1.1](#) (Table 11), only 3 of 9 subjects in Study 0318 were  $<1$  year of age at the time of treatment. The remaining 6 of the 9 subjects had already survived beyond 2 years of age without allo-HSCT which yields a survival rate (in this study cohort) of 67% (much higher than the Applicant's survival threshold used for statistical hypothesis testing in this trial).

HSCT-free survival in the 3 subjects treated at  $<1$  years of age was 100% (95% CI: 29%,100%) with the lower bound of the CI not exceeding the 39% survival benchmark selected by the Applicant as a success criterion. As such, the interpretability of the survival endpoint in the enrolled population is limited at best.

**Reviewer Comment:** *Measurement at 1-year post- infusion is not meaningful in subjects treated after 2 years of age (and thus were alive at age 2 years without transplant). The historical benchmark of 39% survival is not applicable to the 6 subjects in this older population, and the expected clinical course in this population is unclear, with an expected natural decrease in infections (including life-threatening infections) as children get older and a potential shift from an infectious to inflammatory symptoms with older age. While evaluation of the primary efficacy endpoint as compared to the historical benchmark may be reasonable for subjects  $<1$  year of age at product administration,<sup>32</sup> the sample size for this population (n=3) is too small to provide confidence in the results. Even in the 3 youngest subjects, the lower bound of the CI for survival rate at 2 years of age (29%) is lower than the historical survival rate selected by the Applicant as a trial success criterion indicating failure of the trial to demonstrate a survival benefit.*

<sup>30</sup> See publications by Bauer and Hickstein (2000), Farinha et al. (2002), Dababneh et al. (2008), Parvaneh et al. (2010), De Rose et al. (2018), Wolach et al. (2019), Qian et al. (2020), Celiksoy et al. (2021), Geroldinger-Simic et al. (2022), Bondarenko et al. (2023), and Norouzi-Barough et al. (2025).

<sup>31</sup> Survey included anonymous respondents from the Primary Immune Deficiency Treatment Consortium (n=9) and non-anonymous respondents who were study PIs and other experts in the treatment of primary immune deficiency (n=6). Source: Original BLA 125806; SN0001, Module 2.5, Survey Current Standard of Care in the Treatment of Severe LAD-I.

<sup>32</sup> Reference is also made to a single-center study of 34 pediatric LAD-I patients (31 severe) evaluated in Egypt between 2009 and 2023 in which a 58% mortality rate was observed in the first 2 years of life (Saad et al. 2024); this study was published following the initial BLA review cycle and identified following resubmission (see [Section 5.5](#)). While there are challenges to extrapolating this study to the wider LAD-I population, it provides some support for the proposed 40% benchmark for younger patients derived from the 2018 review by Almarza Novoa et al., and it appears to include unique patients (only one Egyptian patient noted in prior review).

*However, the trial was likely underpowered to show a treatment effect on survival based on only 3 patients.*

*Overall, the data on HSCT-free survival is difficult to interpret for purposes of establishing efficacy.*

#### 6.1.11.2 Analyses of Secondary Endpoints

Because longitudinal data spanning Study 0318 and Study 0121-LTFU were used in analyses of the Applicant's secondary efficacy endpoints, discussion of these endpoints (including the biomarker endpoints which were ultimately used as the basis for AA), are found in the Integrated Overview of Efficacy ([Section 7.1.5](#)).

#### 6.1.11.3 Subpopulation Analyses

Analysis of the primary endpoint was completed for the subset of subjects enrolled at <1 year of age (see [Section 6.1.11.1](#)). Due to the very small sample size, no additional subpopulation analyses were performed.

#### 6.1.11.4 Dropouts and/or Discontinuations

There were no dropouts.

#### 6.1.11.5 Post Hoc Analyses – Allo-HSCT Natural History Data

The Applicant utilized the EBMT Registry to conduct a retrospective analysis of 56 LAD-I patients <12 years of age who received their first allo-HSCT from a single stem-cell source between the years of 2012 and 2021. This was followed by a matched analysis of RP-L201 and EBMT Registry patients, with subgroup analyses matching for age at treatment and low baseline CD18/CD11 expression across cohorts. A summary of the findings from the EBMT Registry Report and EBMT Registry Comparator Report are found in this section.

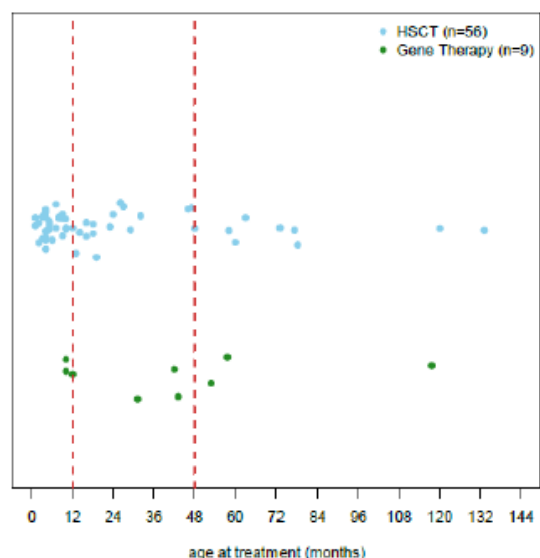
#### Comparability and Matching

The Applicant plotted the age of EBMT patients at the time of allo-HSCT and the age of RP-L201 patients at the time of treatment per Figure 5. The Applicant designated 3 subgroups for age at treatment with the following cut-offs (noted by red dashed lines): ≤12 months, >12 to ≤48 months, and >48 months. Despite there not being a statistically significant difference in age between the two cohorts ( $p=0.12$ ), the distribution of ages was skewed more heavily toward the youngest age subgroup (≤12 months of age at transplant) in the HSCT cohort than in the RP-L201 cohort, which resulted in variable ratios between the 3 age subgroups (Table 10). When patients were split into 2 age subgroups of <2 years of age and ≥2 years of age at the time of treatment, differences were more pronounced, with ratios of 13.3 and 2.5, respectively ( $p=0.05$ ; not shown).<sup>33</sup>

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<sup>33</sup> Original BLA 125806; SN0001, Module 5.3.5.4, EBMT Registry Comparator Report, p.4.

**Figure 5: Age at Treatment – EBMT Registry Population (HSCT) and RP-L201 Population (Gene Therapy)**



Source: Original BLA 125806; SN0001, Module 5.3.5.4, EBMT Registry Report, Figure 1.  
Abbreviations: EBMT, European Society for Bone and Marrow Transplantation; HSCT, hematopoietic stem cell transplant.

**Table 10: Distribution of HSCT and RP-L201 Patients by Age at Treatment**

	≤12 months, n	>12 to ≤ 48 months, n	>48 months, n	Total
HSCT (EBMT)	31	17	8	n=56
RP-L201 (GT)	3	3	3	n=9
Ratio	10.3	5.7	2.7	6.2

Source: Adapted from original BLA 125806; SN0001, Module 5.3.5.4, EBMT Registry Report, Table 1.  
Abbreviations: EBMT, European Society for Bone and Marrow Transplant; GT, gene therapy; HSCT, hematopoietic stem cell transplant.

When the EBMT population was limited to only those with low CD18 or CD11 expression <2% (n=31), there was an even larger difference in ratios between the first 2 age subgroups, as demonstrated in . Ratios remained unbalanced when the low CD expressors were separated into 2 subgroups of <2 years of age and ≥2 years of age at the time of treatment, with ratios of 8.3 and 1, respectively (not shown). It is unclear if these differences in age are statistically significant, as analyses were not performed, but once again a clear skewing of age toward a younger population in the EBMT cohort is noted when matching for low CD expression.<sup>34</sup>

**Table 11: Distribution of HSCT and RP-L201 Patients with Low CD Expression by Age at Treatment**

	≤12 months, n	>12 to ≤ 48 months, n	>48 months, n	Total
HSCT (EBMT)	22	6	3	n=31
RP-L201 (GT)	3	3	3	n=9
Ratio	7.3	2	1	3.4

Source: Derived from original BLA 125806; SN0001, Module 5.3.5.4, EBMT Registry Comparator Report, p.8.  
Abbreviations: EBMT, European Society for Bone and Marrow Transplant; GT, gene therapy; HSCT, hematopoietic stem cell transplant.

Based on the above analyses, the Applicant concluded that the age distribution of RP-L201 subjects is comparable to that of the real-world age distribution of LAD-I patients receiving allo-HSCT. However, using the above ratios, matching between the HSCT and RP-L201 cohorts resulted in more HSCT patient matches per RP-L201 patient for those in the younger subgroup of RP-L201 patients. RP-L201

<sup>34</sup> Derived from original BLA 125806; SN0001, Module 5.3.5.4, EBMT Registry Comparator Report, p.8.

patients treated at  $\leq 12$  months of age had 7 or 8 matching HSCT patients, whereas 5 out of 6 of the RP-L201 patients treated at  $\geq 12$  months of age had only one match (with the other having 3).<sup>35</sup> Due to overall small sample sizes and a large amount of missing data, no further matching or subgroup analyses (e.g., based on prior infection history, WBC) were performed.

**Reviewer Comment:** Overall, there is a clinically significant difference in the age of EBMT patients as compared to patients treated with RP-L201, with patients in the Registry more likely to be younger ( $\leq 12$  months of age) at the time of treatment. While the intention behind the age subgroups is understood, NH data suggests that expected clinical outcomes likely change once patients surpass the age of 2 years. As such, it is unclear what would be expected in the middle group of patients who were between 1 and 4 years of age at treatment. During review, FDA requested data for all EBMT patients who had LAD-I (91 patients total) in an attempt to identify additional older patients. Unfortunately, no CD18/CD11 data was available for any of the additional patients, which limited further matching and analyses.<sup>36</sup> As noted, patients were not able to be matched based on prior infection history or other laboratory values because these are not routinely collected as part of the EBMT Registry (it is not a disease- or immunodeficiency-specific registry). The noted age difference between the two cohorts increases the amount of caution needed when interpreting data obtained from these already small subgroups.

### Outcomes

In the EBMT/HSCT cohort, 39% of patients had an available MSD, 25% had a CMV mismatch, 80% received lympho-suppressive serotherapy, and over 98% received GVHD prophylaxis. Eight patients died throughout the course of follow-up, for a 3-year OS rate of 85% (75,95). All 8 deaths were in patients from regions other than Western Europe, with causes of death listed as GVHD (n=2), septic shock (n=3), infection (n=2) and organ damage/failure (n=1). CMV recipient/donor status (n=52) was a significant predictor of OS ( $p=0.003$ ), with recipient negative/donor positive mismatch (n=10) showing the lowest OS at 57% (25,89). The 3-year EFS rate was 58% (45,71), with all events (death, GF, or GVHD Grade 2-4) occurring within 1 year of transplant. Patient age, HLA match (MSD 86%), and time from diagnosis to transplantation were significant predictors of EFS ( $p=0.012$ , 0.01, and 0.045, respectively). The number of infections pre-transplantation was a significant predictor of GF ( $p=0.009$ ). The Applicant concluded that the results of the EBMT Registry Report confirm literature-based evidence highlighting the considerable risks of morbidity and mortality associated with allo-HSCT secondary to HLA mismatching, CMV mismatching, and use of serotherapy and GVHD prophylaxis.

**Reviewer Comment:** This reviewer agrees that the findings in the EBMT Registry Report support the significant risks of morbidity and mortality that accompany allo-HSCT. Findings also highlight the importance of early transplantation prior to the onset of serious infections. However, it is noted that the occurrence of all events within 1 year of allo-HSCT does not translate to 1 year of follow-up being sufficient to detect outcomes in RP-L201 patients, with this point being particularly relevant to those who are older at the time of treatment.

In the EBMT Registry Comparator Report, outcomes in the RP-L201 cohort (n=9) were compared to outcomes in the EBMT cohort (n=55, with one patient excluded due to high CD18/CD11 at baseline). OS at 1 and 2 years were 100% for the RP-L201 cohort compared to 82-85% for the EBMT cohort, depending on matching for age and/or low CD expression ( $p=0.19$  to 0.24). EFS was 100% in the RP-L201 cohort compared to 56-59% in the EBMT cohort ( $p=0.03$  for all 3 subgroups). There was no

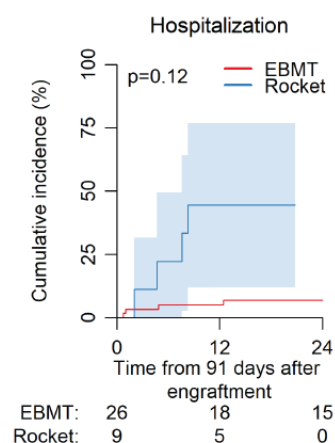
<sup>35</sup> Derived from original BLA 125806; SN0001, Module 5.3.5.4, EBMT Registry Comparator Report, Table 3.

<sup>36</sup> Original BLA 125806; SN0021 and SN0028.

statistically significant difference in GF or GVHD of any type between the cohorts for any subgroup, although there were trends towards significant differences, particularly for aGVHD ( $p=0.09$  to  $0.12$ ).

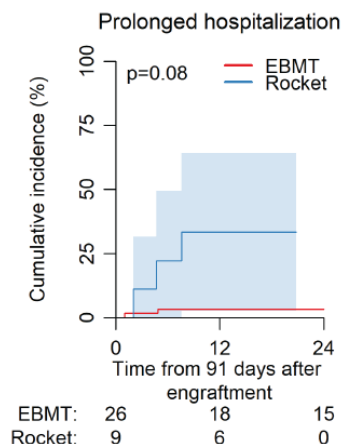
Analysis of infectious endpoints focused on patients matched for age and low CD expression ( $n=56$ ). Analysis of cumulative incidence of hospitalization and prolonged hospitalization, with death as a competing event, showed trends towards significance ( $p=0.12$  and  $p=0.08$ , respectively), as illustrated in Figure 6 and Figure 7. The rate of prolonged hospitalizations from 91 days post-engraftment to within 2 years from baseline was shown to be 0.31 hospitalizations per year for RP-L201 patients (4 total hospitalizations over 12.83 years of follow-up) and 0.09 hospitalizations per year for HSCT patients (3 total hospitalizations over 33.59 years of follow-up) with a relative risk of prolonged hospitalizations (RP-L201 versus allo-HSCT patients) of 3.49 (0.78,15.59) with a  $p$ -value of 0.10.

**Figure 6: Cumulative Incidence of Hospitalizations – Matched for Age and Low CD Expression**



Source: Adapted from Original BLA 125806; SN0001, Module 5.3.5.4, EBMT Registry Comparator Report, p.46.  
Abbreviations: EBMT, European Society for Blood and Marrow Transplantation.

**Figure 7: Cumulative Incidence of Prolonged Hospitalizations – Matched for Age and Low CD Expression**



Source: Adapted from Original BLA 125806; SN0001, Module 5.3.5.4, EBMT Registry Comparator Report, p.52.  
Abbreviations: EBMT, European Society for Blood and Marrow Transplantation.

**Reviewer Comment:** Rates of OS and EFS are consistent with other literature, which is not surprising considering use of the same registry in some cases (e.g., Bakhtiar et al. 2021). There was a statistically significant difference between populations as related to EFS, which includes

events of death, GF, and GVHD Grade 2-4. As highlighted in [Section 6.1.11.1](#), interpretation of any endpoint that involves survival in a population where the NH of disease is unclear is challenging (i.e., severe LAD-I patients >2 years of age). Additionally, in the EBMT cohort, all 8 deaths occurred in patients from regions outside Western Europe, raising questions about the comparability of healthcare in different regions of the world. However, it is expected that there will be differences in EFS driven by risks of GF and GVHD present with allo-HSCT that are largely absent with autologous transplant.

While there were no statistically significant differences seen between the two cohorts on infection endpoints (and incomplete data for both cohorts), the trends seen in Figure 6 and Figure 7 and the relative risk of prolonged hospitalization are concerning, as it appears that despite not requiring serotherapy or GVHD prophylaxis, patients receiving RP-L201 may be at higher risk for infectious complications post-treatment. Unfortunately, post-treatment values for CD markers and/or WBC are not routinely collected as part of the EBMT Registry, preventing any comparisons on these important biomarkers.

Of note, no equivalence or non-inferiority margins were pre-specified or proposed post-hoc to aid interpretation of the EBMT comparisons. In combination with data quality issues in the RP-L201 cohort and general uncertainty regarding comparability between cohorts in external control-based analyses, the comparisons were not found to provide compelling statistical evidence of effectiveness by the statistics team.

## 6.1.12 Safety Analyses

### 6.1.12.1 Methods

The safety population consists of all 9 subjects who received treatment with RP-L201 after enrollment in Study 0318. Monitoring for AEs was ongoing from time of enrollment. An assessment of safety was conducted by analyzing safety events reported for all subjects treated in the RP-L201 clinical development program, inclusive of time in Study 0318 and Study 0121-LTFU. Adverse events were evaluated by system organ class (SOC) and preferred term (PT). Although AEs were assessed by timepoint, challenges in safety data interpretation due to inconsistent safety data recording in the submission precluded assessment of timing with confidence.

### 6.1.12.2 Overview of Adverse Events

AEs occurring in at least 2 subjects and considered to be at least possibly related to RP-L201 or other study treatments or procedures for the entire safety population are shown in Table 12 as adverse reactions (ARs), presented by SOC. For subjects who experienced multiple of the same event, the highest grade (by CTCAE) event was considered for the purposes of this table. This includes all ARs that occurred from the initiation of busulfan conditioning to last follow-up in the primary study.

The majority of AEs occurred early in the study, between the start of conditioning and the time of engraftment. Infection-related events were common throughout all study time points.

Most AEs were Grade 1 or 2. Grade 3 or 4 AEs that occurred in at least one subject included: abnormal clone, anemia, febrile neutropenia, leukopenia, neutropenia, thrombocytopenia, sensorineural deafness, stomatitis, COVID-19 infection, device-related infection, gastroenteritis, lower respiratory

tract infection (including pneumonia), cough, pulmonary arterial hypertension (PAH), stridor, generalized edema, and veno-occlusive disease (VOD).

Some AEs were attributable to underlying LAD-I, but some, such as infections and oral lesions, may have been related to LAD-I or to study drugs and procedures. These AEs are accounted for in this section and in [Section 8](#), but are also addressed, where relevant, in the efficacy review. Because attribution was challenging for these events and because some LAD-I related outcomes (e.g., skin lesions) worsened shortly following treating, for the purposes of this review these AEs were considered as ARs in Table 12. The Applicant attributed most AEs as not related to RP-L201 or other study medications or procedures; however, there was inconsistency in the datasets and AE narratives regarding attribution of events to busulfan. The only AE regularly attributed to busulfan conditioning across sources was mucositis/stomatitis.

**Reviewer Comment:** *The assessment of AEs and thus the safety of KRESLADI is limited by the very small size of the safety population subjects. Many of the AEs that occurred between KRESLADI administration and neutrophil engraftment, including febrile neutropenia, cytopenias, elevated liver enzymes, and mucositis/stomatitis, were related to busulfan conditioning and thus attributable to study medications/procedures and not to the product itself. As conditioning is a requirement for successful product administration, conditioning-related AEs should be considered in the context of risks of product administration and the overall assessment of safety of the product.*

*Important events for which KRESLADI may have a causal role include AEs that do not align with the expected timeframe for engraftment and hematologic recovery, including later-occurring cytopenias (which were relatively rare and primarily in the context of subjects who had pre-existing anemia at baseline) and the finding of abnormal integration events or clones, as discussed in [Section 6.1.12.4](#). However, due to the small safety database and relatively short follow-up, there remains significant uncertainty about the potential long-term risks of the gene therapy, such as insertional oncogenesis that is a known potential risk of LVV-based gene therapies. This will be further evaluated in the post-marketing setting through a PMR study.*



Table 12: Adverse Reactions Occurring in >20% in Study 0318 (N=9)

System Organ Class Adverse Event	Any Grade, n (%)	Grade 3 or Higher, n (%)
<b>Gastrointestinal disorders</b>	-	-
Constipation	2 (22)	0
Nausea/vomiting	4 (44)	0
<b>General disorders and administration site conditions</b>	-	-
Febrile neutropenia	6 (67) <sup>a</sup>	6 (67) <sup>a</sup>
Mucositis <sup>b</sup>	8 (89)	5 (56)
Pyrexia	4 (44)	0
<b>Infections and infestations</b>	-	-
COVID-19	5 (56)	1 (11)
Device-related infection <sup>c</sup>	3 (33)	2 (22)
Gastroenteritis	2 (22)	1 (11)
Lower respiratory tract infection <sup>d</sup>	2 (22)	1 (11)
Skin candidiasis <sup>e</sup>	2 (22)	0
Skin infection <sup>f</sup>	3 (33)	0
Upper respiratory tract infection <sup>g</sup>	8 (89)	2 (22)
Urinary tract infection <sup>h</sup>	2 (22)	0
Viral infection <sup>i</sup>	4 (44)	0
<b>Skin and subcutaneous tissue disorders</b>	-	-
Alopecia	2 (22)	0
Skin lesions <sup>j</sup>	6 (66)	1 (11)
Rash <sup>k</sup>	4 (44)	0

Source: Clinical review of 120-day safety update ADAE, ADLB, and ADVS datasets, SAE/AESI narratives (Section 14.3.3), and 120 Day Integrated Summary of Safety - Tables, Listings and Figures (all submitted in BLA 125806 SN0018)

<sup>a</sup> Values differed from those presented by applicant due to what appear to be coding errors

<sup>b</sup> Includes events of "mucositis" and "stomatitis"

<sup>c</sup> Includes events of "Staphylococcal bacteraemia" (with central line in place), "vascular device infection," and "device related bacteraemia"

<sup>d</sup> Includes events of "bronchiolitis," "pneumonia viral," and "pneumonia"

<sup>e</sup> Includes events of "candida diaper dermatitis" and "candida infection of flexural skin"

<sup>f</sup> Includes events of "catheter site cellulitis," "ear piercing site infection," "impetigo" and "folliculitis"

<sup>g</sup> Includes events of "upper respiratory tract infection," "viral upper respiratory tract infection," "upper respiratory tract infection bacterial," "nasopharyngitis," "tonsillitis," "laryngitis," "sinusitis," "respiratory syncytial virus infection," "adenoviral upper respiratory tract infection," "respiratory tract infection viral," and "otitis media"

<sup>h</sup> Includes events of "urinary tract infection" and "urinary tract candidiasis"

<sup>i</sup> Includes events of "metapneumovirus eye infection," "roseolovirus test positive," "respiratory syncytial virus test positive," "respirovirus test positive," "parainfluenza test positive," and "adenovirus test positive"

<sup>j</sup> Includes events of "pyoderma gangrenosum," "skin lesion," "vesicles-pathogen unknown," "hyperpigmentation," "erythema," catheter site erythema," "papulopustular rash non-infectious," and "lip erythema" – it is not clear if any may be overlapping with skin infections or may be skin infections themselves due to methods of AE recording

<sup>k</sup> Includes events of "eczema," "dermatitis atopic," "diaper dermatitis," and "rash"

**Reviewer Comment:** Because of date imputations and inconsistencies in reporting of AEs, it was challenging to determine where there may have been splitting or duplication of events. There is quite a bit of uncertainty regarding accuracy of reporting and categorization of infections, skin, and oral AEs, which are also important aspects of the underlying disease. AE



*start and end dates were inconsistently recorded, which precluded a comprehensive assessment of the timing of AEs and ARs for the purposes of this review.*

#### 6.1.12.3 Deaths

There were no deaths during the course of Study 0318 or Study 0121-LTFU as of the date of last follow-up in the BLA resubmission.

#### 6.1.12.4 Nonfatal Serious Adverse Events

The protocol notes an adverse event will be considered “serious” and thus a serious adverse event (SAE) if, in the view of either the Principal Investigator or Sponsor, it results in any of the following outcomes:

- Death of a subject
- Immediate risk of subject death at the time the event was observed
- Hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly or birth defect
- Any other significant medical condition that may endanger the subject or require intervention to prevent any of the above outcomes

It should be noted that, with the most recent Study 0318 protocol v3.0 (dated Feb 3, 2023) after all subjects had already been treated, the following exceptions were added to note that the following would not be considered SAEs for the purposes of the study:

- A visit to the emergency room or hospital visit lasting less than 24 hours and that doesn't result in admission
- Elective surgery planned before informed consent
- Admission as per protocol for planned medical or surgical procedures
- Routine health assessment requiring admission for trending of health status
- Medical surgical/admission for purposes of non-LAD-I-related illness or malformations that were planned before study entry (with appropriate documentation required for these cases)
- Admission conducted for other life circumstances (e.g., psychosocial) that are not related to health status and for which there is no medical or surgical intervention
- Grade 4 laboratory abnormalities (including those consistent with busulfan toxicity) not considered by the Investigator to be clinically significant and without clinical sequelae

SAEs reported throughout the course of the study include the following:

#### Serious Infections

Serious infections could be considered SAEs and/or AESI, depending on the infection and circumstances. Increased susceptibility to serious infections is inherent with underlying LAD-I as well as with myeloablative conditioning agents such as busulfan.

Infection-related SAEs were not clearly defined between datasets and listings, and the datasets contain SAEs not discussed in the SAE narratives. It is not clearly noted when serious infections should be recorded as SAEs, AESI, or both, perhaps because AESI were not defined in the protocol until after many of these events occurred. Between the various sources, 10 events between 4 subjects were identified as shown in Table 13. Of note, the table reflects infections reported as SAEs in the original BLA submission. Three additional SAEs (all Grade 3) occurring in the LTFU study were reported in the

resubmission across 2 subjects - 2 lower respiratory tract infections in 1 subject, and RSV infection in 1 subject. Additional details are found in [Section 8.4.8](#).

**Reviewer Comment:** *Inconsistencies between protocols and judgment of the Investigator about the relatedness of infections to busulfan, LAD-I, both, or neither may have impacted recording of infections as SAEs. Furthermore, AESI were not defined until after a majority of the infectious events had already occurred, and similarly, the SAE exclusions noted above were in the same protocol revision. It is not clear if revisions to SAEs and AESI were done retrospectively, and whether this may have impacted recording and analysis of infections as SAEs and/or AESI. This is further complicated by previously mentioned data integrity concerns related to documentation of infections, which indicate post-treatment infectious complications may be underestimated. Interestingly, the 4 subjects for whom infection-related SAEs were recorded were the last 4 subjects treated in the study, though they were treated at 3 different study sites. It is unclear if there may be more accurate documentation of events for these subjects due to the proximity of events to protocol changes defining infection-related AEs, and whether events for other subjects may not have been accurately recorded and reported.*

**Table 13: Infections Reported as Serious Adverse Events (SAEs)**

Infection	Subjects, n (%) (N=9)	Total Events, n	Events Grade <3, n (%)	Events Grade ≥3, n (%)	Events Associated with Hospitalization, n (%)	Occurred within 1 Year, n (%)	Occurred >1 year, n (%)
Upper respiratory infection*	1 (11)	2	2 (100)	0	2 (100)	1 (50)	1 (50)
Bronchiolitis*	1 (11)	1	1 (100)	0	1 (100)	1 (100)	0
Tonsillitis*	1 (11)	1	0	1 (100)	1 (100)	0	1 (100)
Viral pneumonia*	1 (11)	1	0	1 (100)	1 (100)	0	1 (100)
Vascular device associated infection*	2 (22)	2	0	2 (100)	2 (100)	2 (100)	0
COVID-19*	1 (11)	1	0	1 (100)	1 (100)	1 (100)	0
Gastroenteritis*	2 (22)	2	1 (50)	1 (50)	2 (100)	2 (100)	0

Source: Clinical review of 120-day safety update ADAE, ADLB, and ADVS datasets, SAE/AESI narratives (Section 14.3.3), and 120 Day Integrated Summary of Safety- Tables, Listings and Figures (all submitted in BLA 125806 SN0018).

\*Events were also considered severe or significant infection adverse events of special interest (AESI).

### Veno-occlusive Disease

VOD is a recognized complication of busulfan conditioning. One subject developed VOD (Grade 3) on Study Day 14 in the context of acute weight gain with hyperbilirubinemia, and VOD was confirmed with ultrasound. The VOD was managed with fluid restriction, diuretics, and defibrotide, and resolved study Day 30 without clinical sequelae. The event was attributed to busulfan conditioning.

### Pulmonary Arterial Hypertension

One subject with underlying comorbidity of congenital heart disease developed pulmonary arterial hypertension (PAH) requiring hospitalization (Grade 3) on study Day 92. The subject initially presented with respiratory distress and received IV antimicrobials without improvement. Echocardiogram revealed PAH. On Day 94, event severity increased to Grade 4, with support escalating to mechanical ventilation and pulmonary antihypertensive therapies. During the course of the event, the subject received eculizumab and defibrotide, and the event resolved after a total of 7 weeks. At the time of the SAE, the differential diagnosis included thrombotic microangiopathy (TMA) due in part to elevated terminal

complement C5b-9; however, the event was ultimately characterized as PAH without TMA. The event was attributed to a combination of busulfan therapy, underlying respiratory compromise from repeated lower respiratory infections from underlying LAD-I, and tracheal compression from the underlying congenital heart defect.

**Reviewer Comment:** *The event was consistent with PAH, and aside from moderately elevated terminal complement did not appear consistent with TMA, including clinical presentation and timing of the event relative to study procedures and medications. The subject's medical history, including congenital heart defect and recurrent respiratory infections from LAD-I increased the risk of PAH following busulfan therapy. While the incidence of concomitant congenital heart disease in patients with LAD-I is unclear, some patients with LAD-I may have respiratory compromise from repeated respiratory infections, particularly if treated beyond infancy, and thus PAH is an important risk to consider in this patient population and is included in the product label.*

#### Neurosensory Deafness

One subject developed bilateral neurosensory deafness (Grade 3) confirmed by auditory brainstem response testing approximately 9 months after RP-L201 infusion. Ototoxicity is a known risk of busulfan and amikacin use. The SAE of neurosensory deafness was assessed as possibly related to repeated courses of amikacin prior to and following GT administration. The event was considered resolved upon the subject receiving a hearing aid. It is noted that sensorineural deafness is once again listed as an AE occurring in Study 0121-LTFU within the 120-day safety update, but there were no narrative updates provided and it is unclear if this is recorded merely as a continuation from the previously recorded AE from the primary study.

#### Stridor

Approximately 10 months after KRESLADI infusion, one subject had a “floppy episode,” was unresponsive and had difficulty breathing with increased respiratory rate and stridor (Grade 3). Oxygen saturation was 82% and improved with supplemental oxygen. The subject was hospitalized for observation and received dexamethasone for suspected croup. Blood bacterial and fungal cultures were negative, and the subject was discharged the next day, with the event considered resolved. The Investigator attributed the event to aortic arch repair surgery that had occurred a month prior, as such surgery is associated with respiratory symptoms due to maldevelopment of the trachea from prior compression. The event was attributed as not related to RP-L201 or other study medications or procedures.

#### Abnormal Clone

Approximately 1 year after KRESLADI infusion, one subject experienced an SAE of an abnormal clone (Grade 3) detected on routine bone marrow assessment. An abnormal clone with add (15)(q11.2) and der (19)t(15;19)(q21;q13.3) was detected by G-banded analysis. Fluorescent *in situ* hybridization (FISH) analysis demonstrated material from chromosome 15 (PML) located on the der(19p) similar to the G-banded analysis. Repeat bone marrow aspiration (BMA) approximately 2 months later demonstrated no abnormal clone and no evidence of hematologic malignancy. Complete blood count assessments remained unremarkable over longer follow up. The event was considered resolved. The Investigator attributed the event as unlikely related to KRESLADI and potentially related to concurrent infection at time of BMA and to myeloablative conditioning prior to KRESLADI therapy.

**Reviewer Comment:** *Only one abnormal clone has been identified to date in the safety population but given the small safety database and relatively short duration of follow-up for*

*study subjects, the implication of identification of an abnormal clone in one subject is unclear. No further investigation of the clone is currently warranted given the clone was only observed at one time point and had resolved 2 months later, and no hematologic consequences or other concerns for malignancy have arisen in the subject. However, routine continued surveillance per protocol is warranted and further investigation may be warranted for hematologic abnormalities, signs or symptoms of malignancy, re-emergence of the abnormal clone, or identification of an abnormal clone in any additional patients. The risk of insertional oncogenesis resulting in hematologic malignancy will be monitoring post-marketing through a PMR observational study.*

#### 6.1.12.5 Adverse Events of Special Interest (AESI)

Adverse events of special interest (AESI) were not defined for the study until the latest protocol version (v3.0, dated Feb 3, 2023), after all subjects had already been treated (between August 2019 and October 2021) and many were already quite far along in follow-up.

As defined in Study 0318 protocol v3.0 (dated Feb 3, 2023), AESI include:

- Any new severe or otherwise significant infection (requiring hospitalization, surgical intervention, parenteral “antibiotics” [defined as antibacterial, antifungal, or antiviral therapy], or IV anti-inflammatory agents (including monoclonal antibodies or corticosteroids)
- Any new skin or oral lesion of an infectious etiology or otherwise caused by underlying LAD-I
- Any new incidence of aGVHD, “particularly those with an Overall Grade of 2 to 4 as determined by MAGIC criteria,” and cGVHD
- Any incidence of primary graft failure (defined as failure to achieve neutrophil and platelet engraftment following busulfan conditioning and subsequent administration of RP-L201
- Any incidence of secondary graft failure, defined as sustained decrease in PBMC VCN <0.1 or PB neutrophil CD18 expression by monoclonal antibody (mAb) 6.7 (or clone 6.7) of <10% on 2 consecutive evaluations separated by at least 1 month
- Any incidence of predominant clone as determined by PBMC ISA of ≥10% clonal contribution in the setting of PBMC VCN ≥0.1

AESI that occurred in Study 0318 per the SAE/AESI narratives and ADAE dataset included the following:

#### Severe/Significant Infection

Within the ADAE dataset, additional events are flagged as severe or significant infections, but are addressed as SAEs (bronchiolitis, tonsillitis, viral pneumonia, COVID-19, 1 device-related infection [the other is addressed below due to context], 2 events of gastroenteritis and 2 events of upper respiratory infection) or in the skin or oral lesion AESI section (pyoderma gangrenosum, lip erythema) and thus are not addressed separately here.

Infection-related AESI reported in the SAE/AESI narratives include the following, which all resolved after treatment with IV antimicrobial therapy:

- Pneumonia: One event (Grade 2)
- Urinary tract infection: One event (Grade 1)
- “Streptococcal infection”: One subject experienced both a Streptococcal upper respiratory infection and a *Streptococcus viridans* device-related bacteremia (each Grade 3), the latter of which required hospitalization and is one of the two device-related infection SAEs already

referenced. Within the narratives, these appear to be grouped as a single event, but in the dataset are coded separately, which could lead to splitting or duplication of related events.

- Staphylococcal bacteremia: One event (Grade 2) of *Staphylococcus epidermidis* bacteremia that occurred while the subject had a central line.
- "Infection": Three events of "infection" (each Grade 1 or 2) in three subjects (1 event each) were recorded for fever in the absence of a known pathogen. It is important to note that one event of fever coincided with the event of "staphylococcal bacteremia" and thus appears to be splitting or duplication of the same event. One additional event occurred in an additional subject but occurred between conditioning and RP-L201 administration and thus was not included in the SAE/AESI narratives.
- "Neutropenic infection" or febrile neutropenia: Four Grade 3 events in four subjects (one event each) of fever during period of neutropenia in the first month following treatment with RP-L201 were classified as infections. One event occurred concurrently with the urinary tract infection and thus appears to be splitting or duplication of the same event.

**Reviewer Comment:** *The infectious AESI add little new information to infectious events categorized as SAEs, and in fact many events are counted as both. It appears most of the infectious AESI are events that occurred during the first month following treatment and were not generally associated with hospitalization as subjects were already hospitalized. The majority appear to be due to conservative management of an immunocompromised population (from both underlying LAD-I and myeloablative conditioning) with labeling events of fever or febrile neutropenia (that are expected with conditioning) as infections and treating with IV antimicrobials. Numerous events appear to be duplications or mischaracterization of events as infections without evidence of a body site or source of infection. The potential mis-recording of post-treatment events is particularly concerning as recording of events post-treatment (especially in the early post-treatment period where subjects are still expected to be at the study site) is theoretically protocolized, and yet there are several noted errors just within the AESI data. This lends the infectious data as a whole (pre- and post-treatment) to scrutiny, particularly when subjects are seen remotely or at local sites for study visits, and decreases confidence in the data on infections. The infection data is largely uninterpretable for purposes of assessing either safety or efficacy.*

### Skin/Oral Lesions

There were a few inconsistencies between the AE dataset and SAE/AESI narratives, but between the two sources, the following skin and oral lesion AESI occurring between the start of conditioning and last follow-up were identified by the Applicant:

- In 3 subjects each: oral pain, skin erythema
- In 2 subjects each: alopecia, atopic dermatitis/ eczema, rash
- In 1 subject each: pruritus, aseptic pustule, stomatitis, blister, skin hyperpigmentation, pyoderma gangrenosum, diaper dermatitis, and skin lesion

Pyoderma gangrenosum and stomatitis were each Grade 3; all other skin and oral AESI were Grade 1 or 2 in severity. Each of the skin/oral lesion AESI was assessed as not attributed to study treatment; however, it was specifically noted that stomatitis, blister, and alopecia in one subject were likely attributable to busulfan.

The one skin/oral lesion AESI clearly consistent with underlying LAD-I is pyoderma gangrenosum, which was a pre-existing recurrent condition in the subject prior to treatment with RP-L201 and improved following engraftment with no new lesions developing after 91 days post-engraftment. The same subject also experienced “erythema” that had an unknown start date but resolved on the same date as the pyoderma gangrenosum, so is presumed to be a related symptom. Both resolved without intervention and did not recur. The AEs were assessed by the Investigator as not related to any study treatment.

Skin or oral lesion AESI that were also labeled as infection-related events included pyoderma gangrenosum, all 3 AEs of skin erythema, the blister, and the “skin lesion.” In the datasets, only the AE of lip erythema is noted to have required IV antimicrobial therapy. However, the SAE/AESI narratives indicate the event of “blister” required IV antimicrobial therapy for resolution, indicating a possible infection-related AESI for which data may have been incorrectly coded in the datasets.

**Reviewer Comment:** *There are several inconsistencies in the identification and recording of skin and oral lesion AESI that make interpretation of these AEs challenging. Investigators appear to have varied interpretation of the AESI and thus also varied significantly in reporting skin and oral findings as AESI as some reported any skin or mucosal AEs as even if they were clearly not related to underlying LAD-I (e.g., oral pain secondary to teething). Other reported AESI, such as alopecia and stomatitis that occurred within the first month after treatment, appear more likely to be related to busulfan conditioning than LAD-I, particularly considering stomatitis/mucositis occurred in most treated subjects, though only one event was reported as an AESI. Eczema and atopic dermatitis are common even in children without LAD-I. The identified skin and oral lesion AESI are thus not very informative to the safety (or efficacy) of RP-L201. Reporting of overall skin and mucosal AEs (as per [Section 6.1.12.2](#)) may be more informative.*

#### Other AESI

There were no reports of acute or chronic GVHD or primary or secondary graft failure. The single event of an abnormal clone was described in [Section 6.1.12.4](#).

**Reviewer Comment:** *The AESI are particularly interesting given many appear to be mischaracterized/miscategorized. For example, febrile neutropenia is likely related to busulfan conditioning, but was counted as a new infectious complication, as was fever that primarily occurred during the first 30 days following treatment. Many of the skin/oral AESI (e.g., atopic dermatitis) may be unrelated to any study medications or procedures. Additionally, it is not clear why some infections and skin/oral lesions were counted as AESI, but others weren't. Given concerns about documentation, late definitions of AESI after subjects had already been treated and followed at least a year, and general data integrity concerns, there is not confidence in estimates of infectious or inflammatory outcomes relevant to LAD-I that challenge the evaluation of these outcomes as they relate to safety and efficacy of the product.*

#### 6.1.12.6 Clinical Test Results

Discussion of clinical test results can be found in [Section 8.4.5](#).

#### 6.1.12.7 Dropouts and/or Discontinuations

There were no subject dropouts or discontinuations.

### 6.1.13 Study 0318 Summary and Conclusions

Study 0318's primary endpoint was the proportion of patients alive and without allogeneic HSCT at least 1-year post-infusion and at age 2 years for patients <1 year old at study enrollment (allo-HSCT-free survival). Success on the primary endpoint was defined by the Applicant as improved HSCT-free survival over a historical rate of 39% at age 2 years (based on published literature review by Almarza Novoa et al. (2018)). The authors of that literature review note that they were unable to calculate survival curves for severe LAD-I patients older than 2 years of age because precise survival duration was not noted for most cases in their study. Given this limitation and the limited support for the chosen historical comparator rate (based only on a single publication and on data only to age 2 years), the comparison of HSCT-free survival is only applicable to patients enrolled at <1 years old and who reached at least 2 years of age during the study. Of the 9 enrolled patients in Study 0318, only 3 were <1 years of age at study enrollment and were evaluable for the primary endpoint. HSCT-free survival in these 3 patients was 100% (95% CI: 29%,100%) at 24 months with the lower bound of the CI below the 39% survival benchmark selected by the Applicant as a success criterion. In the remaining 6 patients, the endpoint of HSCT-free survival at 24 months is not interpretable as it lacks an appropriate comparator threshold or control group. Across both studies, all 9 patients remained alive without allogeneic HSCT up to at least 42 months of follow up post-product administration.

One of the secondary endpoints was the change in incidence of significant infections and hospitalizations pre- and post-infusion (using historical data for comparisons). For the infectious endpoint, the definition of infections and hospitalizations changed throughout different protocol versions and there was inconsistent data collection and missing data pre- and post-infusion with insufficient and incongruous documentation of infection incidences in the historical (pre-infusion) records. The clinical data review also revealed conflicting data among datasets, listings, reports/summaries, and caregiver testimonials (designed to fill data gaps) for infectious endpoints. As a result, the infectious endpoints were uninterpretable.

Study 0318 had several design and conduct limitations. The primary endpoint of HSCT-survival was compared to a pre-specified historical threshold which was based on a cohort of LAD-I patients followed up to 2 years of age. Therefore, the primary endpoint assumption for study success was only specific to those patients who were younger than 2 years of age at treatment. In Study 0318, only 3 out of the 9 patients were <2 years of age at product administration and, thus, the study was underpowered to show an effect on HSCT-free survival in the entire cohort of 9 treated patients. In fact, even though all 3 patients survived to the end of study (24 months), the lower bound of the 95%CI for the primary endpoint (29%) in this subgroup of 3 patients was below the pre-specified historical threshold of 39%. This finding is not unexpected given that the study was likely underpowered to show an effect on HSCT-free survival in the 3-patient subgroup on which the comparison was based on. Furthermore, the secondary endpoint of incidence of infections was not interpretable due to significant limitations in the comparison between pre- and post-treatment data. Endpoint definitions changed during the course of the study and data collection was inconsistent with high rates of missing data.

Due to these limitations, only objective measures of neutrophil adhesion in the form of CD18 and CD11a expression on neutrophils (representing heterodimeric LFA-1 function), which were assessed as secondary endpoints, were interpretable and form the basis of the efficacy evaluation and regulatory action. Treatment effects on these 2 objectively ascertained biomarkers were substantial and much less prone to bias compared to clinical measures (See sections 7.1.5.2 and 7.1.5.3 for analyses and results of the post-treatment CD18 and CD11a data).

## 6.2 Trial #2 – Study 0121-LTFU

Title: “Long-Term Follow-Up (LTFU) for Gene Therapy of Leukocyte Adhesion Deficiency-I (LAD-I) (RP-L201-0121-LTFU, v3.0-v5.0)”

**Reviewer Comment:** v3.0 was in place during the initial BLA review cycle. Amendments submitted to IND 18485 in the interval prior to BLA resubmission (v4.0 and v5.0) have been incorporated into this section, given v5.0 will be used in a portion of the efficacy PMR outlined in [Section 11.6](#).

### 6.2.1 Objectives

To evaluate long-term safety and efficacy following infusion of RP-L201.

### 6.2.2 Design Overview

Study 0121-LTFU is an ongoing global observational study designed to evaluate the long-term safety and efficacy of RP-L201 in the 9 subjects treated in Study RP-L201-0318 over a total of 15 years.

### 6.2.3 Population

All 9 subjects treated with RP-L201 in Study RP-L201-0318.

### 6.2.4 Study Treatments or Agents Mandated by the Protocol

All subjects had previously received RP-L201 in Study RP-L201-0318.

### 6.2.5 Directions for Use

Not applicable.

### 6.2.6 Sites and Centers

The study sites for the LTFU protocol are the same as those for the parent study, as outlined in [Section 6.1.6](#) (Table 8).

### 6.2.7 Surveillance and Monitoring

The Schedule of Events for Study 0121-LTFU protocol v5.0 is outlined in Table . Changes from prior protocol versions were largely based on changes made in the parent study (Study 0318). Study visits will occur every 6 months up to Year 5 and then yearly until Year 15 post-infusion.

Beginning with v4.0, study visits at local sites are no longer permitted, but an optional mobile nursing service has been introduced to support protocol-required visits. The procedures performed will be the same as those performed at the study site, with the exception of any bone marrow assessments (if required) and assessment of AEs, which will be performed by the PI. If a mobile health service visit is conducted, the PI must schedule a follow-up telehealth visit as soon as possible after the mobile health service visit and within the protocol-defined visit window. The PI will review the data collected during the mobile health service visit along with information gathered during the accompanying telehealth visit.

There is no requirement to return to the clinical site at any minimum frequency, but subjects should return to the study site for assessment in the event of any of the following:



- Any new malignancy
- Secondary GF
- GVHD
- Persistent oligoclonality
- Any other clinical concern that in the opinion of the PI would warrant a return to the clinical site for additional evaluation and follow-up (e.g., RCL evaluation)

AEs are only collected if they meet the criteria for an AR, SAE, and/or AESI. Events that do not meet criteria for an SAE are the same as for the parent study (see [Section 6.1.7](#)). AESI include any severe (Grade  $\geq 3$ ) infection, any new skin or oral lesion of infectious etiology or otherwise caused by underlying LAD-I, any new malignancy, any new cGVHD, any secondary GF, and predominant clone.

Study 0121-LTFU uses the same algorithm for ISA outlined for Study 0318 in [Section 6.1.7.2](#).

**Table 14: Schedule of Events (Study 0121-LTFU)**

Assessment	Early d/c q6- 12M	2y 6m	3y	3y 6m	4y	4y 6m	5y	6y	7y	8y	9y	10y	11y	12y	13y	14y	15y
Physical examination, vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Skin examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Oral examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications/ allogeneic HSCT documentation <sup>1,2</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy status <sup>3</sup>	-	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event assessment <sup>4</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Performance Status <sup>5</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
<b>Laboratory evaluations (blood):</b>	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CBC w differential <sup>*</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
VCN in PBMC & subsets <sup>6*</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
RCL <sup>7</sup>	X	-	X	-	X	-	X	X	X	X	X	X	X	X	X	X	X
ISA: PBMC & subsets <sup>8*</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CD18/CD11a/CD11b expression	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Exploratory assays <sup>9</sup>	X	X	X	X	X	X	X	-	X	-	-	X	-	X	-	-	X

Source: Adapted from IND 18485; SN0088, Module 5.3.5.2, RP-L201-0121-LTFU protocol v5.0, Table 1.

Note: Follow-up assessments may be performed w/in 2 mos prior or following specified post-infusion date through Y5, and w/in 3 mos prior or following post-infusion date for Y6-15.

- Concomitant medications will include all relevant medications since prior assessment, including antimicrobial use or other treatment for infection. A detailed description of any malignancies diagnosed, including treatments provided, should be obtained.
- At each visit, occurrence of allo-HSCT will be documented in the eCRF, along w/reason for and outcome of transplant.
- Validated pregnancy test will be obtained from all females of childbearing potential annually after menarche. All males  $\geq 14$  should be asked about pregnancy status of partners.
- Assessment of AEs will be performed throughout LTFU study. All AEs that occur between interim visits will be evaluated to determine if they meet criteria for reporting.
- Lansky Play/Performance Score should be determined for subjects  $< 16$  years of age per the schedule. If Lansky Score cannot be obtained (e.g., too young), FSS should be obtained; should be continued at specified timepoints with Lansky in addition to FSS when patients of sufficient age. For patients  $\geq 16$  years of age, Karnofsky performance status.
- For malignancy, sample to determine whether malignant clone developed from gene-corrected lineage or uncorrected cell population; additional analyses prior to HSCT.
  - For secondary GF, w/o gene-marking (VCN) for 2 consecutive assessments  $\geq 1$  mo apart, subsequent laboratory evaluations only conducted per investigator discretion in consultation with Sponsor medical representatives, or as required by health authority or institutional requirement.
- RCL assays will be conducted on archived samples when clinically relevant, to include PCR-based evaluation of PBMCs and may include serologic detection of RCL-specific antibodies in serum.
- ISA will be performed on any malignancy sample in which VCN meets or exceeds lower limit of detection.
- Serum and whole blood will be obtained and stored from consenting patients at designated timepoints.

\* Additional VCN and ISA evaluations in PB and clinical monitoring will be performed in setting of clonal predominance. BM assessments also warranted when multiple insertion sites identified within same clone or in proximity to oncogenic loci. BMA/biopsy and cytogenetic and mutation analysis should be performed on each BM assessment (when required based on abnormalities on ISA).

#### 6.2.8 Endpoints and Criteria for Study Success

##### Safety endpoints:

- Safety assessments include ISA, RCL, and AESI.
- Any significant infection (requiring hospitalization or IV antimicrobials).
- Any new skin or oral lesion potentially caused by underlying LAD-I disease.
- Any late occurring (>2 years post-IP) SAE considered at least possibly related to IP.
- Any malignancy.
- Any new concern for secondary GF, defined as a sustained decrease in PBMC VCN <0.1 or neutrophil CD18 expression <10% on 2 consecutive evaluations, separated by an interval of ≥1 month, and not considered related to concurrent infection or non-IP drug-related toxicity.
- Any new concern for GVHD.

##### Efficacy endpoints:

- HSCT-free survival.
- EFS in the absence of GF and GVHD.
- Reduction in incidence of significant infections, infection-related hospitalizations, and prolonged infection-related hospitalizations.
- Improvement or resolution of LAD-I-related neutrophilia and leukocytosis.
- Resolution of LAD-I-related skin rash or periodontal abnormalities.
- Persistence of transgene, as demonstrated by VCN ≥0.1 in PBMCs and CD15+ granulocytes.
- Persistence of neutrophil CD18 expression, defined by expression ≥10% of normal.
- Persistence of neutrophil CD11a/b co-expression.

**Reviewer Comment:** As with the parent study (Study 0318), endpoints for the LTFU study were not clearly defined (particularly in the case of infection-related endpoints) and often differed in order depending on their location in the protocol. Endpoints appear to have been updated over time to reflect changes in the parent study. With amendments to the protocol following the initial BLA review cycle (v4.0 and v5.0), study endpoints were updated “for concision and clarity,” as reflected above.

#### 6.2.9 Statistical Considerations and Statistical Analysis Plan (SAP)

No formal statistical hypothesis testing was conducted. Analyses are descriptive.

#### 6.2.10 Study Population and Disposition

Subject demographics and baseline characteristics are summarized in [Section 1.1](#) (Table 1) and [Section 6.1.10.1.2](#). Subject disposition is summarized in the Integrated Overview of Efficacy ([Section 7.1.3](#), Table 15).

#### 6.2.11 Efficacy Analyses

Please refer to the Integrated Overview of Efficacy ([Section 7](#)) for efficacy analyses related to data obtained in Study 0121-LTFU.

#### 6.2.12 Safety Analyses

Safety analyses inclusive of events in Study 0121-LTFU are addressed in [Section 6.1.12](#) (Safety Analyses) and in the Integrated Overview of Safety ([Section 8](#)).

## 7. INTEGRATED OVERVIEW OF EFFICACY

### 7.1 Indication: Severe leukocyte adhesion deficiency type I (LAD-I)

#### 7.1.1 Methods of Integration

For all 9 subjects, data collected during the 2-year interventional trial (Study 0318) and available data from the subsequent 13-year LTFU trial (Study 0121-LTFU) were integrated to analyze the Applicant's secondary efficacy endpoints. The Applicant's primary efficacy endpoint was measured during Study 0318; please refer to [Section 6.1.11.1](#) for a discussion of the primary efficacy endpoint.

#### 7.1.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics can be found in [Section 1.1](#) (Table 1) and [Section 6.1.10.1.2](#).

#### 7.1.3 Subject Disposition

Per Table 15, all 9 subjects treated with RP-L201 completed the parent study (Study 0318) and enrolled in the LTFU study (Study 0121-LTFU), with 42 to 60 months of follow-up at last data cut.

**Table 15: Subject Disposition**

Parameter	N=9
Screened, n (%)	9 (100)
Enrolled in Study 0318, n (%)	9 (100)
Completed mobilization/apheresis (ITT population)	9 (100)
Received pre-treatment conditioning	9 (100)
Received RP-L201 (PPT population)	9 (100)
Successful neutrophil engraftment	9 (100)
Completed study (PPF population)	9 (100)
Discontinued study	0
Enrolled in ongoing Study 0121-LTFU, n (%)	9 (100)
Discontinued	0
Duration of follow-up (months)	-
Median	50.9
Minimum – Maximum	42.5 - 67.8
Visits completed, n (%)	-
Year 1	9 (100)
Year 2	9 (100)
Year 2.5	9 (100)
Year 3	9 (100)
Year 3.5	9 (100)
Year 4	8 (89)
Year 4.5	4 (44)
Year 5	2 (22)

Source: Adapted from Original BLA 125806; SN0003, Module 5.3.5.2, RP-L201-0318 CSR v1.0, tables and listings; SN0085, Module 5.3.5.2, Listing 1.1.1. Data cut of June 18, 2025.

Abbreviations: ITT, intent-to-treat; LTFU, long-term follow-up; PPF, per protocol final; PPT, per protocol transplant.

#### 7.1.4 Analysis of Primary Endpoint

The primary efficacy endpoint proposed by the Applicant (HSCT-free survival) was analyzed as part of Study 0318 and discussed in [Section 6.1.11.1](#).

#### 7.1.5 Analysis of Secondary Endpoint(s)

Secondary endpoints as defined in [Section 6.1.8](#) and [Section 6.2.8](#), for Studies 0318 and 0121-LTFU, respectively, were largely modified in tandem. Due to issues with interpretation of the primary efficacy endpoint for the parent study, the clinical team conducted an in-depth review of the secondary efficacy data provided in both the parent and LTFU study focusing on the objective endpoints of post-treatment CD18 and CD11a expression.

##### 7.1.5.1 Infection-Related Endpoints

The Applicant provided pre- and post-treatment data on infection-related endpoints for all subjects. Endpoints identified in the most recent study protocols (v3.0) include: 1) significant infections, 2) infection-related hospitalizations, and 3) prolonged infection-related hospitalizations ( $\geq 7$  days). Numerous review issues were encountered when analyzing the infection-related efficacy data, which have been summarized below.

##### Protocol Modifications

The Applicant notes that v3.0 of the Study 0318 protocol (dated Feb 3, 2023) “clarified endpoints and the associated definitions” and that “modifications did not substantively modify the efficacy and safety objectives and endpoints.” However, between v2.3 (dated Jun 7, 2021) and v3.0, secondary objectives and efficacy endpoints related to infectious and inflammatory outcomes received substantial modifications (with corresponding changes to the LTFU protocol), and instructions related to the collection of pertinent infectious and inflammatory history were expanded upon in v3.0.<sup>37</sup> With the first subject enrolled in March 2019 (under v1.2, dated Nov 2018) and the last enrolled in February 2021 (under v2.2, dated Oct 2020), capture of prior infection history and most post-treatment data occurred prior to these modifications. Additionally, infection-related endpoint definitions vary both within and between the most recent protocol versions for the parent and LTFU studies. This includes variable use of the following defining factors for “significant infection”: 1) severity, as defined by NCI-CTCAE v5; 2) surgical interventions; and 3) use of anti-inflammatory agents.<sup>38</sup>

##### Source Data

The organization of the eCRF is thought to have negatively impacted collection of prior infection history and infection-related outcome data. For historical events, the eCRF includes both medical history and prior infection history sections, with instances of similar entries being removed from these sections. Prior infection history entries include options to check if there is an associated hospitalization (and if date unknown) and the types of treatment required, but there is no field for documentation of specific dates or treatments (e.g., antibiotic name, dose, duration). Hospitalization dates and medication and treatment details are found elsewhere within the eCRF. For infection-related outcomes occurring after enrollment (classified as AEs), all protocols state that, “Because endpoints are specifically defined in the protocol, they are often not collected on the AE pages of the CRFs.”<sup>39</sup> Given the aforementioned endpoint changes, the degree of completeness of data collection is unclear. The eCRF includes options to check if medication and/or non-medication therapies were given and if the event was infection-related, required IV antimicrobials, or required hospitalization or prolonged hospitalization (same check box). However, like prior infection history entries, there is no option for the provision of further details.

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<sup>37</sup> Of note, protocol 0318 v3.0 was never submitted to IND 18485 and was first available for review at the time of BLA submission. Similarly, there was no record of the related LTFU protocol (0121-LTFU) being submitted prior to BLA review (requested in SN0012).

<sup>38</sup> Further details of protocol modifications pertaining to infection-related endpoints are provided in Table 23 in [Appendix B](#).

<sup>39</sup> As found in RP-L201-0318 protocol v3.0, Section 10.4.1 submitted with original BLA 125806 and review of RP-L201-0318 protocol v1.0, v1.2, v1.5, v2.1, v2.2, and v2.3 submitted to IND 18485.

The eCRF does not include a section specific to infection-related data collection, despite this being a study endpoint that had not been “substantively modified” during the study.<sup>40</sup>

**Reviewer Comment:** *The absence of fully defined infection-related endpoints prior to study initiation, a lack of consistent definitions for these endpoints, and the organization of the eCRF raise concerns regarding the Applicant’s ability to collect complete and unbiased infection-related data. These deficiencies limit the interpretability of the infection-related endpoints.*

#### Limitations of Submitted Datasets on Infection Endpoints

Secondary to the data collection methods described above and general issues with data quality,<sup>41</sup> initial datasets containing infection-related outcomes were largely uninterpretable. Specifically, numerous infection-related outcomes for all subjects were contained in a single dataset, while other information needed for interpretation (e.g., hospitalization and medication data) was in separate datasets, with all datasets containing extraneous and duplicate information. As such, the Applicant was asked to provide subject-level datasets containing only infection-related outcome data.<sup>42</sup> During review of the new datasets, it became apparent that infection-related events were linked with any hospitalization or treatment occurring during the date range for the event. This was especially problematic due to missing/incomplete dates and the Applicant’s conventions for the imputation of missing dates, which led to overlapping and conflicting events. In addition, there were numerous instances of incongruity between datasets, listings, and reports/summaries, as well as conflicts with caregiver testimonials, which were designed to fill gaps. Despite reanalysis of data in several different formats, infection data remained uninterpretable. The extent to which poor data quality contributed to suspected overestimations of significant infections and prolonged infection-related hospitalizations remains unclear.<sup>43</sup>

#### Additional Challenges to Interpretation

While there is a prevailing lack of understanding of the expected clinical course for older severe LAD-I patients (see [Section 6.1.11.1](#)), all children are expected to have less infections with age, creating a time bias favoring RP-L201; this may be particularly problematic if recorded infections are not classic for LAD-I. Additionally, the identification of inflammatory complications and their differentiation from infections was not emphasized in the study protocol. There is concern that this lack of differentiation may have led to some pre-treatment events being attributed to infection rather than inflammation. There is also the possibility that inflammatory events post-treatment could be underreported if they do not require the same level of care as an infectious event; events that would have been recorded pre-treatment may not meet criteria of significance in the LTFU study. While inflammatory complications are unlikely to carry the same mortality risk as serious infections or require the same level of care, they remain impactful and may require an alternative assessment to show meaningful change following treatment.<sup>44</sup>

Other pre-existing concerns include a propensity for more conservative management in younger patients or in those who have not received definitive treatment. Related to this issue, the Applicant provided no distinction between serious bacterial or fungal infections characteristic of LAD-I (and used to determine eligibility) and viral infections common in childhood when defining “significant” infections.

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<sup>40</sup> Original BLA 125806; SN0001, Module 5.3.5.2, RP-L201-0318 protocol v3.0, p.3.

<sup>41</sup> See also [Section 3.1](#).

<sup>42</sup> Original BLA 125806; SN0027, Module 5.3.5.2 (dated Dec 22, 2023).

<sup>43</sup> Further information related to specific data quality issues surrounding infection-related endpoints is provided in [Appendix B](#).

<sup>44</sup> See also [Section 6.1.11.1](#) for discussion of inflammatory complications of LAD-I.

As per [Section 2.1](#), LAD-I does not result in increased susceptibility to viral infections. However, viral infections are common in young children (e.g., RSV) and may lead to hospitalization due to respiratory distress or biases related to age or underlying illness (i.e., LAD-I without HSCT). Issues specific to this cohort include a lack of clear “significant” infectious events at baseline in three subjects (either due to age or poor detail of limited pre-treatment events) and the impact of the COVID-19 pandemic on behavior and infectious exposures.

**Reviewer Comment:** *The infection-related data submitted by the Applicant are of poor quality and essentially uninterpretable. Data quality issues are in the context of other concerns with interpretability that preceded BLA submission. These issues combined with the discovery of local sites being involved in the collection of this often-subjective data, and without any oversight from the Applicant (see [Section 3.2](#)), preclude the use of infection-related endpoint data to support any efficacy conclusions for RP-L201.*

*Furthermore, findings on clinical review are in stark contrast to the Applicant’s claims that: 1) potential confounding factors from the use of baseline comparators have been mitigated; 2) pre-treatment infection data has been confirmed by source data verification, with baseline rates “consistent with those reported in the literature (Madkaikar 2012);”<sup>45</sup> and 3) differences in pre- and post-treatment care have been “largely mitigated,” with care “largely conducted by the same local medical team given the geographic distribution of patients and distances to clinical sites.”<sup>46</sup>*

#### 7.1.5.2 Neutrophil CD18 Expression

The Applicant provided baseline/pre-treatment and longitudinally collected post-treatment values for CD18. CD18 is used clinically for preliminary diagnosis and severity classification in LAD-I, and a CD18 expression level  $\geq 10\%$  following treatment has been consistently presented as one of the Applicant’s efficacy endpoints throughout product development. The use of CD18 as a biomarker to support accelerated approval was discussed several times during product development in the IND stage, with the most recent discussion at the Type A meeting in October 2022. During this interaction, the Applicant provided data to support the biologic plausibility of the relationship between LAD-I, CD18, and clinical outcomes.<sup>47</sup>

The Applicant measured neutrophil CD18 expression with assays using mAb 6.7 and mAb L130. Two subjects did not meet the study inclusion criterion of severe LAD-I based on CD18  $< 2\%$  using the Applicant’s preferred assay (6.7).<sup>48</sup> Normal CD18 expression is seen in LAD-I patients with deleterious mutations where the CD18 protein is produced but is truncated or misfolded, thereby making it dysfunctional<sup>49</sup> (Levy-Mendelovich et al. 2016). There is also the potential for commonly used antibiotics to correct certain nonsense mutations via a read-through mechanism.<sup>50</sup> In addition, interpatient (in patients with the same mutation) and within-patient variability has been noted in the literature, which may be due to the inducible nature of the CD11b/CD18 and CD11c/CD18 heterodimers. Specifically, inflammation or coagulable events may induce levels of these integrins, increasing CD18 expression.

<sup>45</sup> See also [Appendix A](#).

<sup>46</sup> Original BLA 125806; SN0003, Module 2.5, Clinical Overview, p.24.

<sup>47</sup> Data supporting the correlation between CD18 expression and clinical outcomes, as well as the 10% threshold, are found in [Appendix C](#).

<sup>48</sup> See also [Section 6.1.10.1.2](#) (Table 12) for baseline CD18 values.

<sup>49</sup> Dim (weak) baseline CD18 expression in 63.4% of PMNs for (b) (6) and baseline CD18 expression of 5.8% noted for (b) (6). In conjunction with PMN CD11a/b expression  $< 2\%$ , abnormal/unstable protein suspected; otherwise eligible based on *ITGB2* and history (see [Section 6.1.3](#)).

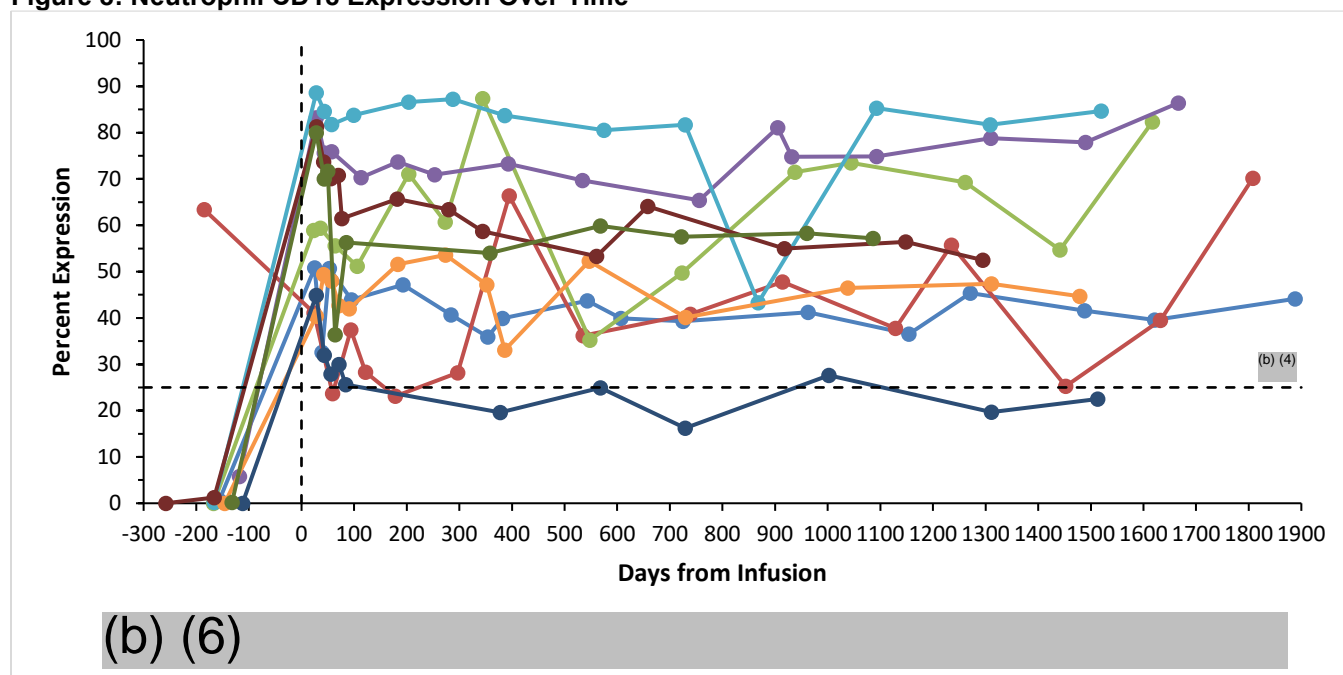
<sup>50</sup> Specifically, gentamicin has been shown to increase expression of a full-length but dysfunctional or mislocalized CD18 subunit. Despite expression, there is no improvement in leukocyte adhesion/chemotaxis or clinical manifestations. The integrity of the CD18/CD11 complex at the cell surface is impaired due to abnormal CD18 and possibly due to a lack of CD11a expression (Simon et al. 2010).



Other potential mechanisms for variability include subjective interpretation when determining cut-offs for positive cells and technical pitfalls (Levy-Mendelovich et al. 2016; Wolach et al. 2019).

CD18 expression data, as measured at the Great Ormond Street Hospital (GOSH) Immunology Laboratory using mAb 6.7,<sup>51</sup> are summarized in Figure 8 for all 9 subjects. Seven of 9 subjects had CD18 <2% at baseline and were thus evaluable for post-treatment CD18 expression. Following treatment with RP-L201, CD18 expression increased and generally stabilized by Month 3, with all 7 evaluable subjects maintaining expression ≥10% and 6 of 7 maintaining expression ≥25% (the (b) (4) for the assay; see also [Section 4.2](#)) through last follow-up (Month 42 to 60; Day 1278 to 1825). Expression generally remained stable throughout the post-treatment period, although Subject (b) (6) had a significant decrease at Month 30, which was noted by the Applicant to be “incongruous” with CD11 and VCN values measured at the same time point.<sup>52</sup> At BLA resubmission, CD18 expression for Subject (b) (6) was observed to have increased back to the level of prior values, remaining stable through Month 48. See also [Section 4.4.2](#) (Human PD) for additional CD18 data.

**Figure 8: Neutrophil CD18 Expression Over Time**



Source: Reviewer analysis; derived from ADPHC datasets by-subject (original BLA 125806; SN0029) and updated at resubmission (SN0085).

Abbreviations:

Notes: All assays completed at Great Ormond Street Hospital (GOSH) Immunology Laboratory using monoclonal antibody (mAb) 6.7. Subjects (b) (6) had CD18 expression >2% prior to treatment (63.4 and 5.8%, respectively). Data cut of June 18, 2025.

### 7.1.5.3 Neutrophil CD11a Expression

As with CD18, baseline/pre-treatment values and post-treatment values at multiple timepoints were provided for review.

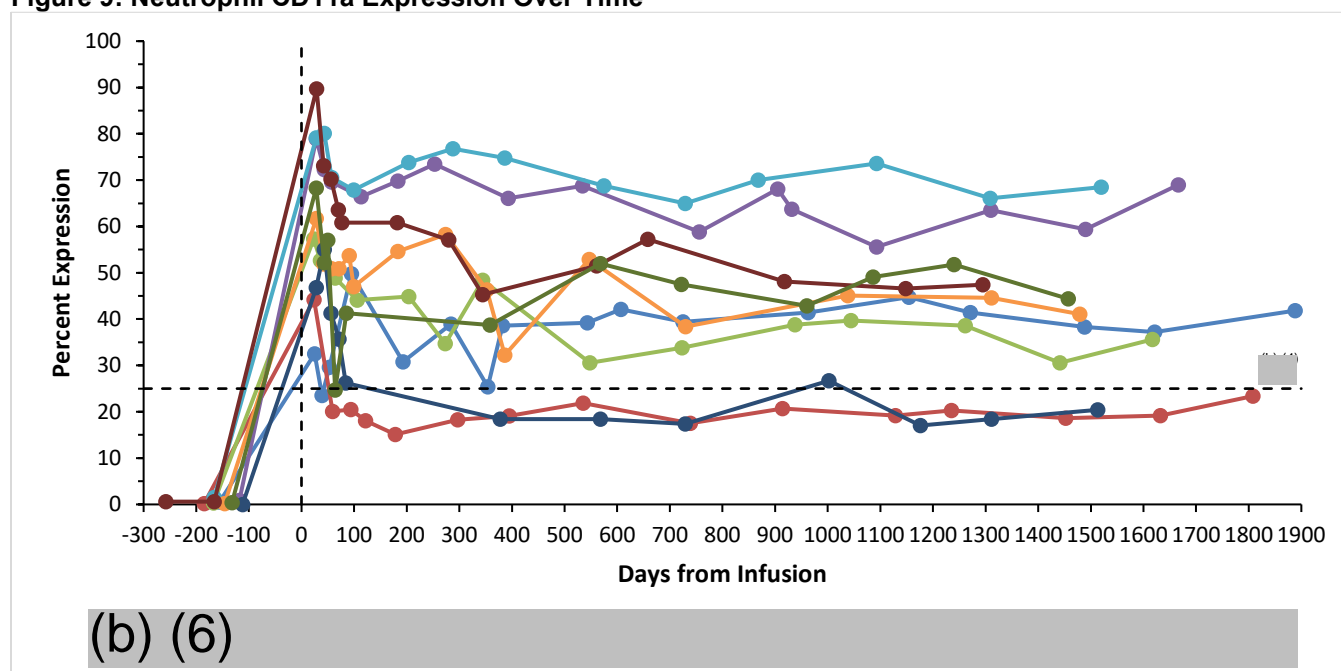
<sup>51</sup> Assay acceptably validated at a range of (b) (4) expression. See [Section 4.2](#) for a review of assay validation.

<sup>52</sup> Original BLA 125806; SN0020, Module 2.7.3, 120-Day Clinical Efficacy Update, p.39.



As shown in Figure 9, all study subjects (9 of 9) had neutrophil CD11a expression <2% at baseline, similar to what is documented in the literature.<sup>53</sup> Following treatment with RP-L201, CD11a expression increased and stabilized by Month 12,<sup>54</sup> with 9 of 9 (100%) subjects maintaining CD11a expression  $\geq 10\%$ <sup>55</sup> (range: 20.4 to 69.0 at last follow-up). Seven of 9 (68%) subjects had sustained post-treatment CD11a expression  $\geq 25\%$  (the (b) (4) of the assay) to the end of the primary study (Month 24; Day 730), with persistence through last follow-up (Month 42 to 60; Day 1278 to 1825).

**Figure 9: Neutrophil CD11a Expression Over Time**



Source: Reviewer analysis; derived from ADPHC datasets by-subject (original BLA 125806; SN0029) and updated at resubmission (SN0085).

Abbreviations:

Notes: All assays completed at Great Ormond Street (GOSH) Immunology Laboratory. Data cut of June 18, 2025.

## Conclusions:

Overall, the substantial improvements in post-treatment CD11a and CD18 through 42 months of follow up in conjunction with the finding of a strong correlation between CD18 and CD11a post-treatment values demonstrate functional restoration of the heterodimer LFA-1, whose absence on neutrophils is the root molecular cause of LAD-I. The median expression of both CD18 and CD11a approximate the approximately half normal expression expected in healthy (asymptomatic) biomarker response on both components of the heterodimer is large and durable over long term follow up which provides a strong scientific basis for concluding that KRESLADI administration resulted in restoration of the underlying molecular defect. Therefore, it is appropriate to consider the functional restoration of LFA-1 as reflected in CD18 and CD11a improved expression as a surrogate endpoint that is reasonably likely to predict clinical benefit in severe LAD-I.

<sup>53</sup> See also [Section 6.1.10.1.2](#) (Table 12) for baseline CD11a values by subject.

<sup>54</sup> Two subjects (b) (6) were missing CD11a assessments at Month 6 and Month 9.

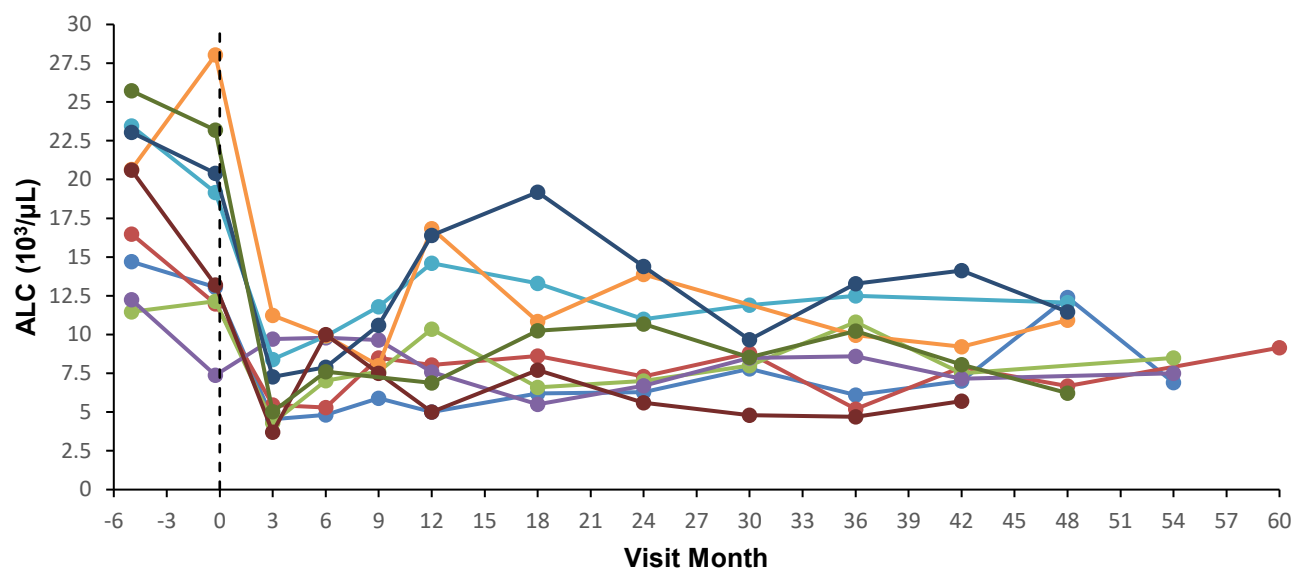
<sup>55</sup> Threshold for CD18 expression proposed by Applicant, based on literature.

#### 7.1.5.4 Neutrophilia and Leukocytosis

Patients with LAD-I typically exhibit mild to moderate leukocytosis (particularly granulocytosis) in the absence of overt infection, but neutrophil counts may be >100,000/mL during episodes of acute infection (Hanna and Etzioni 2012; van de Vijver et al. 2013). To demonstrate an improvement and/or resolution of the neutrophilic leukocytosis commonly seen in these patients, the Applicant provided pre- and post-treatment values for absolute leukocyte count (ALC) and absolute neutrophil count (ANC) in their BLA submission. Pre-treatment values were limited to those collected during the Screening Visit and Treatment Pre-Conditioning Visit.<sup>56</sup>

Overall trends in ALC are shown in Figure 10 and outlined in Table 16. For Figure 10, pre-treatment values are plotted at baseline (typically from the Screening Visit) approximately 5 months prior to infusion (range: 118-177 days) and at the Treatment Pre-Conditioning Visit approximately 1 week prior to infusion. Post-treatment values are plotted at visits from Month 3 to last follow-up (Month 42 to 60). Normal values vary with age and several reference ranges were available for interpretation of these values.<sup>57</sup> Overall pretreatment values for ALC ranged from 7.4 to 28.0 x 10<sup>3</sup> cells/μL, with abnormal values ranging between 14.7 in the oldest subject and 28.0 in one of the youngest subjects.

**Figure 10: Absolute Leukocyte Count (ALC) by Visit Month**



(b) (6)

Source: Reviewer analysis; derived from ADPHC datasets by-subject (original BLA 125806; SN0029) and updated at resubmission (SN0085).

**Table 16: Subject-Level ALC Classification by Study Visit**

	(b) (6)									
Screening	H	U <sup>a</sup>	U	N	H	H	H	H	H	H
Pre-Conditioning	U	U	U	N	H	H	H	U	H	H

<sup>56</sup> During the initial review cycle, additional pre-treatment values were sought via IR, but the Applicant stated that “additional efforts to gather further CBC (data) from patients’ medical records (would) take many weeks and (would) not be likely to generate useful new information.” Source: Original BLA 125806; SN0045, Module 1.11.3, Response to FDA IR, p.4.

<sup>57</sup> The Applicant provided reference ranges for ALC from a publication by Shearer et al. (2003) and for ANC from a textbook by Cairo and Brauho (2003). Lab-provided reference ranges were also used in review and were largely consistent with values from a 2023 publication by Pabon Rivera et al.

<b>Post-Treatment</b> (M3 to M36-48)	U (M48)	N	U (M36)	N	U (M12,18,30,42)	<sup>H</sup> (M12) U (M24)	<sup>H<sup>b</sup></sup> (M12,18,42) U (M24,30,36)	N	N
<b>Last Follow-Up</b>	N <sup>c</sup> (M54)	N (M60)	N (M54)	N (M54)	U (M48)	N (M48)	U (M48)	N (M42)	N (M48)

Source: Reviewer analysis; derived from ADPHC datasets by-subject (original BLA 125806; SN0029) and updated at resubmission (SN0085).

Abbreviations: ALC, absolute leukocyte count; H, high; M, month; N, normal; U, unclear – normal per lab reference range but high per Applicant reference range.

<sup>a</sup> Lab value likely elevated; reference range for this laboratory appeared to have a high upper limit of normal.

<sup>b</sup> Subject likely had viral infections at M12 and 18; Grade 3 lower respiratory tract infection documented at M42 (SN0085).

<sup>c</sup> No M60 value; last value unscheduled at D1964 (U).

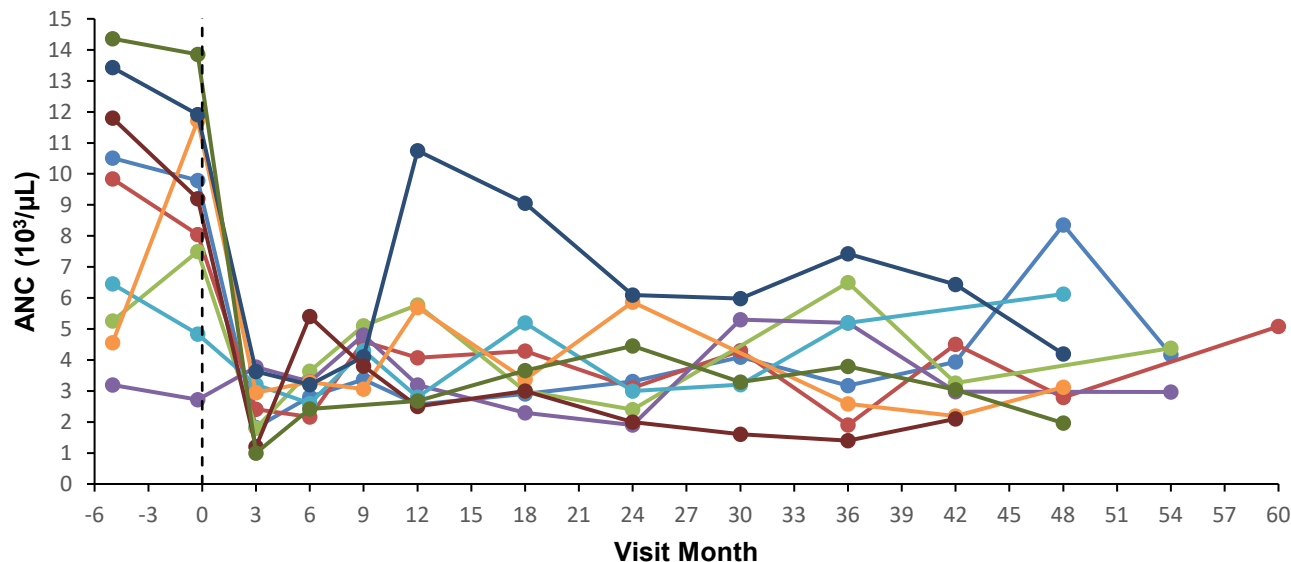
Note: Following BLA resubmission, 6 of 9 subjects were missing one ALC value, versus 1 of 9 in initial review cycle.

Per Table 16, utilizing lab-provided reference values only, at least 2 subjects (b) (6), and possibly a third (b) (6); see footnote “a”), did not have elevated ALC values at baseline, resulting in the potential for 7 (or 6) subjects to demonstrate an improvement in leukocytosis following treatment with RP-L201. Two subjects (b) (6) had at least one instance of elevated ALC post-treatment.

Using the Applicant-provided reference range, which generally has lower thresholds for leukocytosis, only one subject doesn't have leukocytosis at baseline (b) (6), but 5 subjects have instances of elevated ALC post-treatment (b) (6) including 4 instances in Subject (b) (6).

Overall trends in ANC are shown in Figure 11 and outlined in Table 17. Pretreatment values ranged from 2.7 to 14.4 x 10<sup>3</sup> cells/μL, with abnormal values ranging between 9.2 and 14.4 cells/μL.

**Figure 11: Absolute Neutrophil Count (ANC) by Visit Month**



(b) (6)

Source: Reviewer analysis; derived from ADPHC datasets by subject (original BLA 125806; SN0029) and updated at resubmission (SN0085).

**Table 17: Subject-Level ANC Classification by Study Visit**

	(b) (6)								
<b>Screening</b>	<sup>H</sup>	<sup>H</sup>	N	N	N	N	<sup>H</sup>	<sup>H</sup>	<sup>H</sup>
<b>Pre-Conditioning</b>	<sup>H</sup>	N	N	N	N	<sup>H</sup>	<sup>H</sup>	<sup>H</sup>	<sup>H</sup>
<b>Post-Treatment</b> (M3 to M36-48)	<sup>H</sup> (M48)	N	N	N	N	N	<sup>H<sup>a</sup></sup> (M12,18)	N	N

<b>Last Follow-Up</b>	N (M54) <sup>b</sup>	N (M60)	N (M54)	N (M54)	N (M48)	N (M48)	N (M48)	N (M42)	N (M48)

Source: Reviewer analysis; derived from ADPHC datasets by subject (original BLA 125806; SN0029) and updated at resubmission (SN0085).

Abbreviations: ANC, absolute neutrophil count; H, high; M, month; N, normal.

<sup>a</sup> Subject likely had viral infections during these visits.

<sup>b</sup> No M60 value; last value unscheduled at D1964 (N).

Note: Following BLA resubmission, 6 of 9 subjects were missing one ANC value, versus 2 of 9 in initial review cycle.

Per Table , 3 subjects (b) (6) did not have any elevated ANC values at baseline, and 2 subjects (b) (6) only had neutrophilia at one of the pre-treatment time points. Two subjects (b) (6) had at least one instance of elevated ANC post-treatment.

**Reviewer Comments:** Interpretation of ALC/ANC values was complicated by limited pre-treatment values and a lack of context surrounding lab draws (e.g., unclear if drawn during a period of active infection or inflammation). Because the most dramatic episodes of neutrophilic leukocytosis for LAD-I patients are noted to occur with infection, as neutrophils are produced but unable to exit the circulation, additional pre-treatment values (with knowledge of context) would be incredibly helpful in both showing trends and in documenting persistently high levels in these subjects. Post-treatment context is also important, as children frequently have infections which can cause elevations into abnormal ranges, and there are causes of leukocytosis beyond infection (e.g., inflammation, injury, medications).

Another challenging aspect of interpretation of these values is that reference ranges change with age in childhood. There were also some substantial differences in lab-based reference ranges noted, but attempts were made to identify these outliers. Interpretation of ALC values was particularly difficult, as designations regarding an abnormal value were highly dependent on whether lab-provided reference ranges or Applicant-provided reference ranges were used.

Due to the challenges outlined above, use of ALC/ANC data to support efficacy is difficult. However, it appears that there is at least a trend towards normalization in ALC and ANC in most subjects who had elevated levels at baseline (using laboratory reference ranges). Additionally, none of the post-treatment elevations in ALC or ANC surpassed baseline levels and no subjects appear to show a persistent neutrophilic leukocytosis. As such, it is felt that improvement in ALC/ANC in select subjects could be used as supportive evidence in the context of AA based on CD11a and CD18 expression as surrogate endpoints.

#### 7.1.5.5 VCN

The Applicant provided longitudinal measurements of VCN in PBMCs and CD15+ granulocytes (to include neutrophils)<sup>58</sup> to demonstrate genetic correction following hematopoietic reconstitution post-IP infusion. Through last follow-up of 42 to 60 months, all subjects had VCN  $\geq 0.1$  copies/cell in both PBMCs and CD15+ cells.<sup>59</sup> During the initial review period, one subject (b) (6) had a low value for CD15+ VCN at Month 24 (0.0087), which was thought to be due to an error given the stable PBMC VCN and neutrophil CD18/CD11 expression noted at this timepoint.<sup>60</sup> At timepoints beyond Month 24, VCN in CD15+ cells was subsequently observed to be well-above 0.1 copies/cell and consistent with

<sup>58</sup> VCN was also measured in CD3+ (T lymphocytes) and CD19+ (B lymphocytes) subpopulations, but this data is not discussed in this review.

<sup>59</sup> The Applicant notes that a "targeted peripheral blood VCN of at least 0.1 was established because it was believed that this was most likely to correspond to CD18 expression on at least 10% of neutrophils, especially over protracted (i.e., 6 months or greater) follow-up" (Original BLA 125806, SN0003, Module 2.4, Nonclinical Overview, p.4).

<sup>60</sup> Original BLA 125806; SN0020; Module 2.7.3, 120-Day Clinical Efficacy Update, p.39.

VCN measured in other cell types.<sup>61</sup> Please see [Section 4.4.2](#) for further information regarding VCN assessments.

**Reviewer Comment:** *VCN data may provide supportive mechanistic evidence of the observed treatment effect of increased CD11a/CD18 expression.*

#### 7.1.6 Other Endpoints

Other secondary endpoints did not weigh significantly into the efficacy analysis, so they will only briefly be addressed here.

##### Event-Free Survival (EFS)

The secondary efficacy endpoint of EFS was added with Study 0318 protocol v3.0. No events of death, GF, or GVHD occurred for any subject through the last data cut (Jun 18, 2025).<sup>62</sup>

**Reviewer Comment:** *Because this endpoint includes survival as a component, interpretation is limited due to the issues discussed in [Section 6.1.11.1](#) and in other portions of this review.*

##### LAD-I-Related Skin and Oral Lesions

A secondary endpoint of resolution (partial or complete) of any underlying LAD-I-related skin rash or periodontal abnormalities was defined in the protocol for Study 0318 and carried over to the protocol for Study 0121-LTFU. Lesions were graded by the Investigator based on interval changes from baseline. There is limited data regarding this endpoint found in the datasets. The CSR for Study 0318 includes discussions of individual subjects, with information included on this endpoint in cases of available longitudinal data and photos of “sufficient resolution.” Photo assessments were only obtained during scheduled study visits, with resolution of events potentially occurring between visits. The Applicant concludes that improvement or resolution of LAD-I related skin and oral lesions occurred in all study subjects.

Upon review of the individual summaries, photos were available for skin lesions in three subjects and oral lesions in two subjects.<sup>63</sup> In at least one instance, it is difficult to visualize the skin lesion noted to be captured in the photos provided. The first set of oral lesion photos appear to be inappropriately labeled, with both photos of the first lesion being labeled as “Baseline” and both photos of the second lesion noting times of resolution. The second set of oral photos appear to depict two lesions at baseline but the follow-up photos showing resolution at Month 18 do not allow for visualization of one of the prior lesions. Minimal detail is included in the individual summaries to provide context for the lesions in these photos, and the limited information provided in the datasets/listings is poorly organized.<sup>64</sup> The subject summaries appear to be incomplete, with events in the datasets/listings that document photos were taken and that events are “related” to LAD-I, but these events are absent from the summaries. Labeling of anatomic location for the images in the datasets/listings is inconsistent (e.g., same lesion documented on “back” versus “other” at different time points), and the name of the photograph sometimes describes the location of a lesion or assessment rather than providing a name. The Applicant does not provide any information regarding how skin and oral lesions were designated as “related” versus “unrelated” to LAD-I.

<sup>61</sup> Original BLA 125806; SN0085, Module 5.3.5.2, Listing 2.3.3.

<sup>62</sup> Original BLA 125806; SN0085, Module 1.11.3, Response to FDA IR.

<sup>63</sup> Original BLA 125806: RP-L201-0318 CSR v1.0; Figures 23, 24, 30, 51, 52, 58, and 59.

<sup>64</sup> Original BLA 125805; SN0003, Module 5.3.5.2, Listings 16.2.6.7.1.1, 16.2.6.7.1.2, and 16.2.6.7.2; SN0018, Module 5.3.5.3, ADPH integrated dataset.

**Reviewer Comment:** *The data provided regarding improvement/resolution of LAD-I -related oral/skin lesions are incomplete, contain errors, and lack context. As such, these data were found to be uninterpretable and are unable to be used to support the effectiveness of RP-L201 in the treatment of severe LAD-I. Updated patient narratives provided following BLA resubmission do not contain any new data pertaining to resolution of LAD-I- related oral/skin lesions that alter the conclusions made during the initial review cycle. However, it is notable that one subject is recorded as having normal wound healing following corrective thoracotomy for congenital double aortic arch with tracheal compression at 9 months post-IP infusion. While there is no other evidence for normal wound healing provided in the submission (e.g., photos), it is the opinion of this reviewer that this is unlikely to have occurred without treatment.*<sup>65</sup>

#### 7.1.7 Subpopulations

Analysis of the primary endpoint was completed for the subset of subjects enrolled at <1 year of age (n=3), as outlined in [Section 6.1.11.1](#). A more in-depth analysis of secondary infectious endpoints was performed for the older subpopulation (n=6), as discussed in [Appendix B](#). Given the small sample size, no other subgroup analyses were completed based on sex, race, ethnicity, country of origin, or site of treatment.

#### 7.1.8 Persistence of Efficacy

All subjects were noted to be alive and without allo-HSCT at 5.2 to 15.6 years of age as of the last data cut (Jun 18, 2025).<sup>66</sup> However, as outlined in [Section 6.1.11.1](#), the duration of follow-up is insufficient to assess survival benefit in subjects >1 year of age at treatment. Specifically, all subjects have maintained increased CD11a and CD18 expression over a duration of follow-up ranging from 42 to 60 months.<sup>67</sup> All subjects have maintained VCN  $\geq 0.1$  and those with initial elevations in ALC/ANC have not shown a return to baseline levels or concerns for persistent neutrophilic leukocytosis.

#### 7.1.9 Product-Product Interactions

Although concomitant medications were documented for all subjects, no product-product interactions were expected or observed during the clinical studies.

#### 7.1.11 Efficacy Conclusions

In summary, this clinical reviewer concludes that there is substantial evidence of effectiveness of RP-L201 on surrogate clinical endpoints of CD11a and CD18 expression in patients with severe LAD-I based on evidence from a single adequate and well-controlled trial (Study 0318 and the associated Study 0121-LTFU) and confirmatory evidence, as compared to the NH of disease documented in the medical literature. Seven of 9 subjects enrolled in the Applicant's pivotal study demonstrated sustained CD11a expression  $\geq 25\%$  (the assay (b) (4) through last follow-up at 42 to 60 months post-infusion).<sup>68</sup> Six of 7 evaluable subjects (those with baseline pre-treatment expression <2%) demonstrated sustained post-treatment neutrophil CD18 expression  $\geq 25\%$  (the assay (b) (4)).<sup>69</sup> Supportive data include preclinical studies demonstrating proof of concept, as outlined in [Section 4.3](#). Additional supportive data

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<sup>65</sup> Original BLA 125806; SN0085, Module 1.11.3, Response to FDA IR.

<sup>66</sup> Original BLA 125806; SN0085, Module 1.11.3, Response to FDA IR, p.5.

<sup>67</sup> Exclusive of 2 subjects not measuring above the (b) (4) for CD11a for the first analysis and 2 subjects not having CD18<2% at baseline for the second analysis.

<sup>68</sup> As discussed in [Section 7.1.5.3](#).

<sup>69</sup> Measured using mAb 6.7, in the setting of the known limitations of CD18 measurement noted in [Section 7.1.5.2](#).

includes mechanistic evidence in the form of neutrophil VCN  $\geq 0.1$  in 9 of 9 subjects<sup>70</sup> and trends towards resolution of persistent neutrophilic leukocytosis in subjects with elevated ALC and/or ANC at baseline.<sup>71</sup>

## OVERVIEW OF SAFETY

### 8.1 Safety Assessment Methods

Analyses were conducted for total duration of follow-up in clinical studies and by study timepoint. As AE reporting is sparse in Study 0121-LTFU, safety is primarily addressed as related to the primary study 0318 in [Section 6.1.12](#) (Safety Analyses).

### 8.2 Safety Database

#### 8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The safety database consisted of all 9 subjects treated with RP-L201 in Study 0318. Safety data from Study 0318 and available data from continued follow-up in Study 0121-LTFU were analyzed in the assessment of safety.

#### 8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Demographics and duration of follow-up for the safety population is the same as for the efficacy population in Table 1 and Table 15, respectively.

#### 8.2.3 Categorization of Adverse Events

The Applicant utilized MedDRA version 26.0 to code all AEs. AEs were evaluated by SOC and PT. Severity of AEs was graded according to the NCI CTCAE v5.0.

### 8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

No subjects have yet completed Study 0121-LTFU and follow up data were available up to month 42 for most subjects. Definitions for relevant AEs, such as AESI and SAEs were characterized differently across various protocol versions within a study (see discussion in [Section 6.1.12](#) for Study 0318) and between Study 0318 and Study 0121-LTFU. However, because Study 0121-LTFU only requires collection of AE data if the AE meets criteria for an AR, SAE, and/or AESI, sparse AE data was reported from Study 0121-LTFU and thus the differences between the primary study and LTFU study did not significantly affect the analysis of safety when data was pooled.

### 8.4 Safety Results

#### 8.4.1 Deaths

There were no deaths through date of last follow-up.

#### 8.4.2 Nonfatal Serious Adverse Events

Three new SAEs (2 lower respiratory tract infections and 1 RSV infection) occurred in the LTFU study and were provided as part of the BLA resubmission. These events are discussed in [Section 8.4.8](#). All other nonfatal SAEs occurred during the primary study and are discussed in [Section 6.1.12.4](#).

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<sup>70</sup> As discussed in [Section 7.1.5.5](#).

<sup>71</sup> As discussed in [Section 7.1.5.4](#).



#### 8.4.3 Study Dropouts/Discontinuations

There were no study dropouts or discontinuations in either study.

#### 8.4.4 Common Adverse Events

As AEs were primarily recorded for the primary study, common AEs are discussed in [Section 6.1.12.2](#).

#### 8.4.5 Clinical Test Results

##### Vital Signs

##### *Temperature*

Methods of obtaining temperature (e.g., rectal, tympanic, temporal) were not specified within the datasets and may vary significantly between methods. Although several subjects experienced fever (with and without neutropenia), only one instance of temperature >38.3 degrees Celsius is noted in the datasets. No instances of low temperature <35 degrees Celsius were reported.

##### *Blood Pressure*

No AEs of hypertension or hypotension were noted in treated subjects. Blood pressure readings were reviewed and there were no persistent elevations or other trends in blood pressure readings following treatment with RP-L201.

##### *Heart Rate*

Transient elevations in heart rate were recorded with no persistent tachycardia noted in study subjects. One subject had a recorded AE of bradycardia that was Grade 1 and resolved same day.

##### *Weight*

One subject experienced weight loss during the course of the study, but this was relatively minor and resolved back to baseline weight in less than a month. No concerning variations in weight were noted in study subjects per review of relevant data.

##### Complete Blood Count

The majority of Grade 3 or 4 complete blood count (CBC) abnormalities occurred within the first 30 days after RP-L201 administration, with cytopenias common and expected with myeloablative busulfan conditioning. CBC abnormalities commonly associated with underlying LAD-I (neutrophilia, leukocytosis) are addressed in the efficacy analysis.

##### *Anemia*

Seven (78%) subjects had anemia prior to conditioning, including 2 who had  $\geq$  Grade 3 anemia at baseline. All 9 (100%) subjects experienced Grade 3 or 4 anemia within the first 30 days after treatment, either new onset anemia or worsening/persistence of pre-existing anemia. All subjects received at least one red blood cell transfusion between conditioning and 30 days after RP-L201 infusion. Anemia persisted beyond 30 days for all subjects but generally lessened in severity. One subject who had comorbid congenital heart disease who received surgical repair following RP-L201 administration and who experienced SAEs of VOD and PAH continued to have anemia requiring intermittent transfusions until nearly one-year post- RP-L201. Two (22%) subjects had persistent or recurrent anemia beyond one-year post-treatment; both improved to Grade 1 after one year without need for transfusions.



### *Leukopenia*

Five (56%) subjects developed Grade 3 or 4 leukopenia in the first 30 days following treatment. Leukopenia generally resolved with engraftment, except in one subject who continued to have Grade 1 leukopenia through Day 204.

### *Neutropenia*

Coding within the AE dataset and thus the AE tables and listings was inconsistent so that the Applicant reported events separately as “Neutrophil count decreased” or “Neutropenia.” When combined, the Applicant reported Grade 3 or 4 neutropenia in all but one study subject. Examination of the laboratory data, including neutrophil counts, indicated the subject did in fact have neutropenia (Grade 4) in the initial month following treatment, suggesting the AE was not recorded. Grade 3 or 4 neutropenia thus occurred in 100% of study subjects within the first 30 days following treatment with RP-L201. Neutropenia generally resolved quickly following engraftment, with all resolved beyond the Month 3 study visit.

There also appear to be coding errors related to febrile neutropenia. The Applicant reported AEs of febrile neutropenia in 4 subjects, but review of the AE and laboratory data indicated 2 additional subjects had concurrent fever and neutrophil counts  $<1000/\mu\text{L}$ , meeting criteria for febrile neutropenia rather than fever. Thus, 6 (67%) subjects experienced Grade  $\geq 3$  febrile neutropenia within the first 30 days following treatment. Many instances of febrile neutropenia were coded as infections for the purposes of adverse events of special interest (AESI) and are discussed in further detail in [Section 6.1.12.5](#).

### *Thrombocytopenia*

Coding within the AE dataset and thus the AE tables and listings was inconsistent so that the Applicant reported events separately as “Platelet count decreased” or “Thrombocytopenia,” but when combined all 9 (100%) subjects experienced thrombocytopenia. Three (33%) subjects had  $<$ Grade 3 thrombocytopenia prior to conditioning. All 9 (100%) subjects experienced Grade 3 or 4 thrombocytopenia within the first 30 days after treatment, and all subjects received at least one platelet transfusion between conditioning and 30 days after RP-L201 infusion. One subject who had comorbid congenital heart disease who received surgical repair following RP-L201 administration and who experienced SAEs of VOD and PAH continued to have thrombocytopenia requiring intermittent transfusions through approximately 3 months post- RP-L201 administration.

### Chemistries

No significant or persistent derangements in electrolytes were observed in treated subjects. Mild abnormalities observed in study subjects quickly resolved and are noted in [Section 6.1.12.2](#).

### Liver Function Tests

Elevations in hepatic enzymes (ALT, AST, and GGT) typically occurred early after treatment within the first 30 days (3 subjects, 33%). One additional subject developed elevated liver enzymes after 90 days post-treatment. Hepatotoxicity is a known side effect of busulfan conditioning. All ALT, AST, and GGT elevations were Grade 1 or 2 severity and were not persistent.

#### 8.4.6 Systemic Adverse Events

Refer to the discussion of AEs in [Section 6.1.12](#) (Safety Analyses) and the rest of this integrated safety section.

#### 8.4.7 Local Reactogenicity

Not applicable

#### 8.4.8 Adverse Events of Special Interest

AESIs are primarily addressed in discussion of the primary study in [Section 6.1.12.5](#). Within the BLA resubmission (data cut: Jun 18, 2025), the Applicant reported 4 new AESI of significant infection across two subjects: one subject experienced a Grade 3 RSV infection from Day 1407 to 1409 that required hospitalization and IV antimicrobials; a second subject experienced two Grade 3 lower respiratory tract infections from Day 990 to 1002 and Day 1062 to 1068, respectively, with both requiring outpatient IV antimicrobials, and one Grade 1 viral infection that required outpatient IV antimicrobials. All 4 events were noted to resolve without sequelae.<sup>72</sup> None of the events are included in Table 12, and based on occurrence beyond 2 years post-treatment are felt unlikely to be related to study treatments and more likely to be typical childhood infections or related to underlying LAD-I.

### 8.5 Additional Safety Evaluations

#### 8.5.1 Dose Dependency for Adverse Events

No dose dependency for AEs was identified. However, due to the small study population, AEs largely related to conditioning as would be expected, and limited duration of follow-up for some study subjects, assessments for possible dose relationship for AEs are not possible.

#### 8.5.2 Time Dependency for Adverse Events

The majority of AEs (e.g., transient cytopenias) appeared to be related to conditioning, generally occurring within the first 30 days. AEs that occurred outside this timeframe and were potentially related to the product or conditioning include infections, which could also be attributed to the underlying disease. Each of these topics is discussed elsewhere.

#### 8.5.3 Product-Demographic Interactions

No product-demographic interactions were identified, but the assessment of product-demographic interactions was limited by small size of the trial, absence of a control arm, limited understanding of the underlying disease course after 2 years of age in the absence of treatment (impacting 67% of study subjects), and enrollment of 3 (33%) siblings with the same genetic mutation.

#### 8.5.4 Product-Disease Interactions

The product is intended to restore functional CD18, and thus a favorable product-disease interaction is expected regarding efficacy, but no product-disease interaction is expected regarding AEs. The assessment of product-disease interactions was limited by the same limiting factors discussed for product-demographic interactions in Section 8.5.3.

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<sup>72</sup> Original BLA 1252806; SN0085, Module 1.11.3, Response to FDA Clinical Request for Information, Table 11.

#### 8.5.5 Product-Product Interactions

Safety concerns resulting from PK-based product interactions are not expected to occur with RP-L201. RP-L201 is not expected to interact with the hepatic cytochrome P450 family of enzymes or drug transporters. There is a possibility of product-product interactions between conditioning agents and other concomitant medications. Because the concomitant medications varied between subjects, describing those potential interactions is beyond the scope of this review.

#### 8.5.6 Human Carcinogenicity

No cases of malignancy were identified following treatment with KRESLADI to date. Carcinogenicity is a potential risk of integrating vectors such as the LV contained in KRESLADI, and subjects will continue to be monitored for malignancy throughout the LTFU study and in a post-marketing study as a PMR (see [Section 6.2.7](#)).

One subject developed an abnormal clone that later resolved without hematologic or malignant consequences, which is not concerning and is discussed in [Section 6.1.12.4](#).

#### 8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable.

#### 8.5.8 Immunogenicity (Safety)

Not applicable

#### 8.5.9 Person-to-Person Transmission, Shedding

Person-to-person transmission and viral shedding are not commonly identified risks of LVV-based products, and is not applicable to this product.

### 8.6 Safety Conclusions

The safety database includes 9 patients, all followed for up to 42 months from product administration. The available safety database is limited as expected for a rare disease; however, it is considered sufficient for purposes of a safety evaluation of KRESLADI. Treatment with KRESLADI involved not only administration of the product, but also administration of busulfan, a chemotherapeutic agent for myeloablative conditioning prior to product administration. Myeloablative conditioning with busulfan is known to be associated with serious safety risks, such as cytopenias and serious infections, which were observed in the clinical study. Overall, the observed adverse events appear attributable to the myeloablative conditioning and the underlying disease. There is a theoretical risk of insertional oncogenesis with KRESLADI given it is based on a LVV with genomic integration potential. There were no cases of insertional oncogenesis or hematologic malignancy observed in the KRESLADI clinical program, and this risk will be monitored during a post-marketing, long term follow up study.

The safety profile of KRESLADI (in conjunction with busulfan pre-conditioning) is sufficiently characterized considering the life-threatening nature of this rare disease with limited treatment options and is appropriate to inform the benefit-risk assessment for a regulatory decision on this BLA.

### 9. ADDITIONAL CLINICAL ISSUES

## 9.1 Special Populations

### 9.1.1 Human Reproduction and Pregnancy Data

There are no available data with KRESLADI administration in pregnant women. However, it is expected that the product will be administered in children making this risk non-applicable. The long-term sequelae of this therapy on future pregnancy are unknown, but it is unclear in the absence of treatment that women with severe LAD-I have healthy pregnancies.

### 9.1.2 Use During Lactation

There are no available data with KRESLADI administration during lactation, including no information regarding presence of the product in human milk, effect on the breastfed infant, or effects on milk production.

### 9.1.3 Pediatric Use and PREA Considerations

The clinical program only included pediatric patients, and the product will be indicated for the pediatric population with severe LAD-I without HLA-matched sibling donor for allogeneic HSCT. Additionally, as KRESLADI has been granted orphan drug designation, this BLA is exempt for PREA requirements.

### 9.1.4 Immunocompromised Patients

All study subjects were immunocompromised as related to their underlying primary immunodeficiency. There are no available data with KRESLADI administration in patients who are immunocompromised for reasons other than as related to severe LAD-I.

### 9.1.5 Geriatric Use

There are no available data in a geriatric population.

## 10. CONCLUSIONS

The Applicant has provided substantial evidence of effectiveness for KRESLADI in the treatment of pediatric patients with severe LAD-I without an HLA-matched sibling donor for allo-HSCT based on a single adequate and well-controlled trial, Study 0318, with confirmatory evidence. The available scientific evidence supports the use of neutrophil CD18 and CD11a improvement as reflecting LFA-1 functional restoration as a surrogate endpoint reasonably likely to predict clinical benefit (improved survival) in pediatric patients with severe LAD-I who do not have an available HLA-matched sibling donor for allogeneic HSCT.

Study 0318's primary endpoint was the proportion of patients alive and without allogeneic HSCT at least 1-year post-infusion and at age 2 years for patients <1 year of age at study enrollment (HSCT-free survival). Success on the primary endpoint was defined by the Applicant as improved HSCT-free survival over a historical HSCT-free survival rate of 39% at age 2 years (based on a single, published literature review by Almarza Novoa et al. (2018)). The authors of the literature review note that they were unable to calculate survival curves for severe LAD-I patients older than age 2 years because precise survival duration was not noted for most cases. Therefore, the proposed historical threshold of HSCT-free survival is only applicable to patients enrolled at <1 year of age. Of the 9 enrolled patients in Study 0318 and subsequently in Study 0121-LTFU, 3 were <1 year of age at study enrollment and were evaluable for the primary endpoint based on the proposed historical survival threshold. HSCT-free survival in these 3 patients was 100% (95% CI: 29%, 100%) at 24 months with the lower bound of the CI not exceeding the 39% survival benchmark selected by the Applicant as a success criterion. In the

remaining 6 patients, the endpoint of HSCT-free survival at 24 months is not interpretable as it lacks an appropriate comparator threshold or control group. Across both studies, all 9 patients remained alive without allogeneic HSCT up to at least 42 months of follow-up post-product administration.

A secondary endpoint was the change in incidence of significant infections and hospitalizations pre- and post-infusion (using historical data for comparisons). For the infectious endpoint, the definition of infections and hospitalizations changed throughout different protocol versions and there was inconsistent data collection and missing data pre- and post-infusion with insufficient and incongruous documentation of infection incidences in the historical (pre-infusion) records. The clinical data review also revealed conflicting data among datasets, listings, reports/summaries, and caregiver testimonials (designed to fill data gaps) for infectious endpoints. As a result, the infectious endpoints were uninterpretable. Other secondary endpoints included VCN in peripheral blood mononuclear cells (PBMC) and expression of CD18 and CD11a in neutrophils.

Expression of CD18 and CD11a in neutrophils were evaluated as secondary endpoints in Study 0318. Seven of 9 patients had baseline CD18 expression <2% and all 9 patients had baseline CD11a expression <2%. Seven of the 9 enrolled patients had baseline neutrophil CD18 expression <2% and thus were evaluable for post-treatment CD18 expression. CD18 expression increased in all evaluable patients after KRESLADI infusion with median CD18 expression at Month 12 and Month 24 post-infusion of 54% (range: 20% to 87%) and 50% (range: 16% to 82%), respectively. Neutrophil CD11a expression increased after KRESLADI infusion in all 9 patients. Median CD11a expression at Month 12 and Month 24 post-infusion were 45% (range: 18% to 75%) and 39% (range: 17% to 65%), respectively. The observed improvements in neutrophil CD18 and CD11a expression were sustained through at least Month 42 post-infusion in all patients. Median levels at months 12 and 24 approached levels observed in asymptomatic, *ITGB2* heterozygotes (healthy individuals) for both biomarkers.

Study 0318 had several design limitations that preclude the interpretation of the clinical endpoints, HSCT-free survival and incidence of serious infections. The primary endpoint of HSCT-survival was compared to a pre-specified historical threshold which was based on a cohort of LAD-I patients followed up to 2 years of age. Therefore, the primary endpoint assumption for study success was only specific to those patients who were younger than 2 years of age at treatment. In Study 0318, only 3 out of the 9 patients were < 2 years of age at product administration and, thus, the study was underpowered to show an effect on HSCT survival in the entire cohort of 9 treated patients. In fact, even though all 3 patients survived to the end of study (24 months), the lower bound of the 95%CI for the primary endpoint (29%) in this subgroup was below the pre-specified historical threshold of 39%. This finding is not unexpected given that the study was likely underpowered to show an effect on HSCT-survival in the 3-patient subgroup on which the comparison was based on. Furthermore, the secondary endpoint of incidence of infections was not interpretable due to significant limitations in the comparison between pre- and post-treatment data in each patient and in the cohort as a whole. Endpoint definitions changed during the course of the study and data collection was inconsistent with high rates of missing data. Due to these limitations, only objective data were interpretable in the 2 studies and were the focus of our review. Treatment effects on the 2 objectively ascertained biomarkers, CD18 and CD11a expression in neutrophils, were substantial and much less prone to bias compared to data on clinical outcomes. In fact, the observed treatment effect on CD18 (which underlies the pathogenesis of LAD-I and mediates the downstream molecular deficiency in neutrophil adhesion and recruitment at sites of infection) was pronounced and showed a strong correlation with the improvement seen in the second part of the heterodimer that is necessary for neutrophil adhesion, CD11a. Similarly, the observed treatment effect on CD11a was substantial and the medial post-treatment expression levels for both CD18 and CD11a reached levels expected in asymptomatic (healthy) *ITGB2* heterozygotes (about half normal expression). The CD18 and CD11a expression data

taken together provide a strong basis for concluding that CD18/CD11a heterodimer function is restored post-product administration which is reasonably likely to predict a clinical benefit on survival in pediatric patients with severe LAD-I.

As confirmatory evidence, nonclinical studies demonstrated transduction of RP-L201 leading to CD18 expression, regulated by the endogenous expression of CD11a, and resulting in the functional correction of leukocyte adhesion defects. Because LAD-I is based on a single molecular pathway with established pathophysiology due to CD18/CD11 heterodimer deficiency, the established natural history knowledge that heterodimer function is not restored in the absence of treatment serves as additional confirmatory evidence.

The safety database includes 9 patients followed up to 42 months from product administration. The available safety database is limited which is expected given the rarity of LAD-I but it is considered sufficient for purposes of a safety evaluation. Treatment with RP-L201 involved not only administration of the product, but also administration of chemotherapeutic agents for myeloablative conditioning. These agents are associated with potentially serious safety risks, such as cytopenias and serious infections, which were observed in the clinical study and are unlikely related to the product itself. However, the safety profile of RP-L201 administration appears acceptable, particularly in the context of life-threatening infections that are already a part of the underlying disease. There is a theoretical risk of insertional oncogenesis with KRESLADI but the uncertainty and risks are reasonable in the context of severe LAD-I. The overall benefit-risk profile of KRESLADI is favorable in a disease associated with premature death due to life-threatening complications when untreated.

## **11. BENEFIT-RISK ASSESSMENT**

### **11.1 Benefit-Risk Considerations**

Considerations are outlined in Table 18.

Table 1818: Benefit-Risk Considerations

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	<ul style="list-style-type: none"> <li>Leukocyte adhesion deficiency type I (LAD-I) is a rare autosomal recessive (AR) primary immunodeficiency caused by mutations in the <i>ITGB2</i> gene, resulting in decreased expression or function of CD18, the common beta subunit of the leukocyte beta-2 integrin family. Defects in CD18 prevent normal dimerization with alpha integrin subunits (including CD11a) and expression on the cell surface, leading to an impairment in leukocyte endothelial adhesion and extravasation to sites of infection and inflammation.</li> <li>Recurrent bacterial and fungal infections are typically apparent from birth, with additional clinical manifestations of impaired wound healing, persistent neutrophilic leukocytosis, and severe gingivitis and periodontitis in patients who survive infancy.</li> <li>In most cases, the severity of disease is directly related to CD18 expression, with severe disease defined as expression &lt;2%. <i>ITGB2</i> mutations resulting in abnormal but expressed CD18 have been described but, in these cases, normal CD11a subunits are degraded without formation of a functional heterodimer, resulting in consistent CD11a expression &lt;2%.</li> <li>Based on available natural history (NH) data, patients with the severe phenotype have a 39% survival probability to the age of 2 years in the absence of allogeneic hematopoietic stem cell transplant (allo-HSCT). The NH for severe LAD-I patients who survive beyond age 2 years without allo-HSCT is not well-established, but there are reports of survival into adolescence and some even into adulthood.</li> </ul>	<ul style="list-style-type: none"> <li>Severe LAD-I is a serious and ultimately fatal disease.</li> <li>The period of greatest risk of mortality in the absence of allo-HSCT appears to be within the first 2 years of life (approximately 60%).</li> <li>The clinical course for those alive at age 2 years without allo-HSCT (approximately 40%) is not well-established; while patients appear to have high morbidity in the form of infections and inflammatory complications and ultimately a reduced life expectancy, it is unclear that they would have substantial mortality in the short-term (i.e., within 1-2 years) in the absence of definitive treatment.</li> </ul>
Current Treatment Options	<ul style="list-style-type: none"> <li>There is no FDA-approved treatment for severe LAD-I.</li> <li>The standard of care for severe LAD-I is allo-HSCT, which carries significant risks of morbidity and mortality, primarily due to transplant complications of graft failure and graft-versus-host disease (GVHD).</li> <li>Optimal outcomes for allo-HSCT are dependent on donor matching. However, only 25-30% of patients have the option of a matched sibling donor (possibly less given the autosomal recessive inheritance of LAD-I), and approximately 50% of unrelated donor searches do not yield a suitable matched unrelated donor. Risks of graft failure and GVHD are increased with mismatched donors.</li> <li>Event-free survival (without graft failure or GVHD) has been shown to be increased in those transplanted at less than 13 months of age.</li> </ul>	<ul style="list-style-type: none"> <li>There is a significant unmet medical need for effective therapy to reduce morbidity and prevent premature mortality in all patients with severe LAD-I, but especially for those without a suitable matched sibling donor for allo-HSCT.</li> <li>The inability to identify a suitable donor can increase morbidity and mortality in patients with severe LAD-I. There is also increased risk of morbidity and even mortality in very young children with severe LAD-I for whom identification of a donor is delayed.</li> </ul>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	<ul style="list-style-type: none"> <li>• In Study RP-L201-0318, all subjects had a clinical and molecular diagnosis of severe LAD-I based on CD18 expression &lt;2% (7 of 9 patients) and CD11a expression &lt;2% (all 9 patients) and molecular genetic confirmation.</li> <li>• Seven of the 9 enrolled patients had baseline CD18 expression &lt;2% and CD11a &lt;2% indicating severe CD18 deficiency. The remaining 2 patients had high CD18 expression but very low CD11a expression (&lt;2%) indicating a present but non-functional CD18 protein and severe LAD-I.</li> <li>• All 7 subjects with baseline CD18 expression &lt;2% experienced improved expression seen as early as 3 months after treatment. The median CD18 expression at Month 12 and Month 24 post-infusion were 54% (range: 20% to 87%) and 50% (range: 16% to 82%), respectively.</li> <li>• Neutrophil CD11a expression increased after KRESLADI infusion in all 9 treated patients. Median CD11a expression at Month 12 and Month 24 post-infusion were 45% (range: 18% to 75%) and 39% (range: 17% to 65%), respectively.</li> <li>• The observed improvements in neutrophil CD18 and CD11a expression were sustained through at least Month 42 post-infusion in all patients. Median levels of both biomarkers at months 12 and 24 were high enough to expect functional restoration of the CD18/CD11a heterodimer (LFA-1) whose absence causes LAD1.</li> <li>• The observed improvements in CD18 and CD11a expression post-treatment showed a strong correlation at all tested timepoints further strengthening the overall favorable treatment effect on the CD18/CD11a heterodimer.</li> </ul>	<ul style="list-style-type: none"> <li>• KRESLADI led to restoration of CD18/CD11a heterodimer (LFA-1) function in neutrophils whose absence on the surface of neutrophils is the root molecular cause of LAD-I.</li> <li>• Available epidemiologic evidence demonstrates that CD18/CD11a heterodimer restoration is associated with improved clinical outcomes including improved survival and supports its use as a surrogate endpoint that is reasonably likely to predict clinical benefit in severe LAD-I.</li> <li>• The submitted evidence supports accelerated approval of KRESLADI based on functional restoration of LFA-1 in neutrophils.</li> <li>• The post-marketing confirmatory study to verify and describe clinical benefit will enroll additional younger severe LAD-I patients (minimum n=4) for which the expected short-term survival in the absence of allo-HSCT is better established (i.e., &lt;1 year of age at treatment with assessment of HSCT-free survival at 2 years of age). Continued follow-up of older, previously treated patients (n=6) will occur in the ongoing long-term follow-up study, with assessment of longer-term survival once all patients have reached at least 10 years of age.</li> </ul>



Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk & Risk Management	<ul style="list-style-type: none"> <li>• Serious risks identified during the clinical development program include serious infections, veno-occlusive disease, pulmonary arterial hypertension, sensorineural deafness, and identification of an abnormal clone (without evidence of hematologic malignancies).</li> <li>• The most common adverse reactions were anemia, thrombocytopenia, neutropenia, mucositis, upper and lower respiratory tract infections, febrile neutropenia, leukopenia, viral infections, pyrexia, increased hepatic enzymes, and dermatitis.</li> <li>• There were no deaths and no cases of hematologic malignancy which is a risk associated with LVV products.</li> <li>• The observed adverse reactions were likely caused by the required myeloablative condition treatment prior to product administration and/or the underlying disease (predisposing to infectious and inflammatory complications).</li> </ul>	<ul style="list-style-type: none"> <li>• Given the rarity of LAD-I, this safety database is deemed reasonable for purposes of the benefit-risk assessment of KRESLADI.</li> <li>• The observed risks are largely due to busulfan pre-conditioning and the underlying disease causing increased infectious complications.</li> <li>• Safety risks are included in the product label and further post-marketing long-term safety follow-up will occur as part of an observational safety study (PMR).</li> <li>• The PMR study will enroll a minimum of 10 newly treated subjects to provide additional information on the long-term risks of KRESLADI, specifically secondary hematologic malignancies.</li> </ul>

## 11.2 Benefit-Risk Summary and Assessment

The submitted clinical evidence demonstrates substantial and durable improvement in the CD18/CD11a heterodimer expression in neutrophils indicating restoration of LFA-1, which is necessary for neutrophil adhesion and recruitment to sites of infection. Given the identified risks that are largely due to the myeloablative conditioning treatment and the underlying disease, the overall benefit-risk evaluation for KRESLADI is favorable and supports approval. Clinical benefit will be evaluated in the post-marketing setting through a PMR assessing HSCT-free survival and overall survival in treated patients over a longer duration of follow-up.

## 11.3 Discussion of Regulatory Options

Given the substantial uncertainties about the natural history of patients who survive past 2 years of age with severe LAD-I, the small sample size of Study 0318, and the data quality issues with the submission, the clinical team considers that traditional approval based on clinical outcomes assessed in the trials is not scientifically supported. The clinical team determined that functional restoration of LFA-1 supports accelerated approval. The clinical team did not believe that interpretability of these biomarkers was impacted by concerns about data integrity, as there was protocolized collection, limited missing data for these values, the values themselves are less prone to bias or subjective interpretation, and the assays used were sufficiently validated at high expression thresholds to permit data interpretation and reliability.

Lastly, the clinical team considered the appropriateness of restricting the indication to patients without an appropriate allo-HSCT match. Challenges to the comparison of outcomes for like patient populations following treatment with allo-HSCT and uncertainties regarding complications related to both therapies factored into the decision-making (see [Section 6.1.11.5](#)). Ultimately, the clinical team determined that it was most appropriate to restrict the indication to patients without an available HLA-matched sibling donor (MSD) for allo-HSCT, which is the current gold standard for the treatment of severe LAD-I, and reflects the population studied in the Applicant's pivotal trial. Given the potential for delays in treatment related to identification of a suitable matched unrelated donor, which may be of particular significance for patients treated at a young age and who are the most seriously affected, treatment decisions for severe LAD-I patients without an MSD will be left to clinician discretion.

## 11.4 Recommendations on Regulatory Actions

The clinical review team recommends accelerated approval.

## 11.5 Labeling Review and Recommendations

Labeling negotiations with the Applicant did not begin during the initial review cycle due to the CR recommendation from CMC. Following BLA resubmission, the clinical and clinical pharmacology review teams recommended substantial changes to the proposed United States Prescribing Information (USPI), as summarized in Table 19 below.

**Table 1919: Summary of Significant Changes to USPI**

Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
Section 1: Indication and Usage	KRESLADI is indicated for the treatment of pediatric patients with severe Leukocyte Adhesion Deficiency-I (LAD-I).	The indication was revised to specify that KRESLADI is indicated for pediatric patients with severe LAD-I due to biallelic variants in <i>ITGB2</i> without an available human leukocyte antigen (HLA)-matched sibling donor for allogeneic hematopoietic stem cell

		transplant. Limiting the indication to patients without an available HLA-matched sibling donor appropriately positions KRESLADI as a treatment option when the established standard of care is not available, rather than as a replacement for HSCT.
Section 2: Dosage and Administration	-	<p>Section revised for active command language.</p> <p>Specific recommendations included pretreatment mobilization and myeloablative conditioning based on clinical trial data.</p> <p>Steps for KRESLADI administration revised for clarity with numerical bullet points.</p>
Section 5: Warnings and Precautions	-	<p>Sections were added based on serious adverse reactions reported in the clinical trial.</p> <p>Subsections re-ordered based on clinical significance.</p>
Section 6: Adverse Reactions	-	<p>Section revised to describe safety database and KRESLADI exposure in the clinical study 0318.</p> <p>Adverse reaction table revised to include events analyzed and adjudicated by the review team with possible or probably causal relationship with KRESLADI treatment.</p> <p>Adverse reactions are defined as adverse events that occurred from myeloablative conditioning administration through year 2 following KRESLADI administration in Study 0318.</p>
Section 7: Drug Interactions	The safety and effectiveness of immunization with live viral vaccines during or following KRESLADI treatment has not been studied.	Added recommendations on vaccination schedule to ensure hematological recovery following treatment with KRESLADI.
Section 8: Use in Specific Populations	-	Revised to describe data supporting pediatric indication.

		Sections 8.6 (hepatic impairment) and section 8.7 (Renal impairment) were deleted as no specific recommendations were included in these sections.
Section 12: Clinical Pharmacology	-	A cross-reference to section 14 was added for PD data described in the referenced section.
Section 14: Clinical Studies	-	Revised to describe the study design, patient eligibility, intervention, patient demographics and characteristics, endpoints, and significant results that serve as the basis for accelerated approval of KRESLADI.
Section 17: Patient Counseling Information	-	This section was revised for clarity, use of command language, and to include important risks listed in section 5 (Warning and Precautions).

Source: Created by FDA Clinical Reviewers and Associate Director of Labeling

## 11.6 Recommendations on Post-marketing Actions

The following 3 PMRs will be issued which the Applicant has agreed to.

- A. Accelerated approval regulations at 21 CFR 601.41 Subpart E require that the Applicant conduct adequate and well-controlled clinical trial(s) to verify and describe the clinical benefit of KRESLADI. The Applicant agreed to the following 2 PMRs to satisfy these requirements:
  1. Submit analyses of clinical outcomes including, at a minimum, overall survival, allogeneic HSCT-free survival, and infectious outcomes, as well as biomarker changes (e.g., neutrophil CD18 expression, CD11a expression) from: 1) all treated patients with severe LAD-I currently enrolled in Study RP-L201-0121-LTFU with each patient followed to at least 10 years of age; and 2) at least 4 newly treated pediatric patients with *ITGB2*-associated severe LAD-I who are ≤1 year of age at the time of marnetegrane autotemcel administration with each patient followed to at least 2 years of age. All endpoints should be well defined, and data should be collected systematically and consistently considering potential confounding variables to enable data interpretation, e.g., antibiotic use in relation to incidence of serious infections, etc. Biomarker assessments should be based on appropriately validated bioanalytical assays (as assessed in PMR 2). All analyses should include comparisons to a suitable comparator for purposes of verifying and describing the clinical benefit of marnetegrane autotemcel in *ITGB2*-associated severe LAD-I.

Milestone dates include:

- Final protocol submission: June 30, 2026
- Interim study report submission: October 31, 2030
- Study completion: December 31, 2033

- Final study report submission: June 30, 2034
2. To enable interpretation of data under PMR 1, submit data from supplemental validation studies performed on the LAD-1 Flow Cytometry assay described in SOP-778817. This validation is needed to enable data interpretation of your confirmatory study and specifically evaluate the performance of the CD18 (6p7) and CD11a assays throughout the complete analytical range, including low cell surface expression levels, and should include assessments of repeatability, linearity, accuracy, intermediate precision, and specificity.

Milestone dates:

- Final protocol submission: July 31, 2026
- Study completion: December 31, 2026
- Final study report submission: February 27, 2027

- B. Because of the small safety population and the known risk of secondary malignancy with lentiviral-based gene therapy products, the Applicant agreed to the following safety post-marketing requirement PMR under Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA):

Submit analyses of safety data from a post-marketing, prospective, longitudinal, observational study assessing and characterizing the long-term safety risks of marnetegrane autotemcel in patients with severe LAD-I including the risk of secondary malignancies. This study will enroll a minimum of 10 patients with severe LAD-I who receive marnetegrane autotemcel and safety data will be collected in each patient for at least 15 years after product administration. The protocol number is RP-L201-0224-PMRS.

Milestone dates include:

- Final protocol submission: June 30, 2026
- Study completion date: June 30, 2047
- Final study report submission: December 31, 2047

## APPENDIX A: ISSUES RELATED TO LITERATURE REFERENCES CONTAINED IN THE BLA

The Applicant provided scientific information related to LAD-I throughout their BLA submission. However, the same overarching concepts were often presented in different, and sometimes conflicting ways, and with inconsistency in the sources cited. This necessitated frequent confirmation of cited information or return to other study documents to find a source. Missing and improper source citations (either where the cited source did not appear to support the statement to which it was attached or where there appeared to be misinterpretations of the cited literature) led to a decrease in confidence in some of the Applicant's assumptions and/or conclusions and necessitated extensive independent review of the literature (see also [Section 5.5](#)). Three examples of concepts expressed in different ways throughout the BLA and not appearing to reflect the scientific literature are presented below, along with their impact on the clinical review.

1. *Severe LAD-I patients experience 3 or more serious infections per year*, sometimes citing a publication by Madkaikar et al. (2012).

Despite the Applicant frequently citing this “statistic,” there does not appear to be sufficient information from this publication (or any other identified source) to inform a benchmark for infection history for severe LAD-I patients, with this information being integral to decisions related to the ability of infection-related data to support approval.<sup>73</sup>

2. *Serious, resistant, disseminated, and/or fatal infections occur despite antimicrobial prophylaxis and/or treatment.*

There are few citations attached to these statements and the publications that are cited do not appear to support the generalizations made by the Applicant.<sup>74</sup> Further research was required to assess the potential impact of antimicrobial prophylaxis and prompt treatment of infections on the NH of disease. See also [Section 6.1.11.1](#).

3. *HSCT-free survival of severe LAD-I patients beyond the age of 2 was 6% in a cohort from India*, citing a 2020 publication by Kambli et al.

While the publication does state that patients had a survival rate of 6%, the survival curve for these patients does not show a 6% survival rate. In one instance where the Applicant cites this 6% rate, they immediately follow their statement with a survival curve from this publication alongside curves from other literature reviews (including the review by Almarza Novoa et al. referenced in [Section 2.1](#)), noting that they are “not dissimilar.” Survival to age 2, as demonstrated by figures in the publication by Kambli et al. and those provided by the Applicant, appears to be between 30-40%.<sup>75</sup> These benchmarks were fundamental to several parts of the clinical team's review (e.g., HSCT-free survival endpoint, post-marketing requirements).

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<sup>73</sup> Original BLA 125806; SN0001, Module 5.3.5.2, RP-L201-0318 CSR v1.0, pp.19-20; SN0012, Module 1.11.3, Response to FDA IR, p.4.

<sup>74</sup> Original BLA 125806; SN0001, Module 1.2, Reviewer's Guide, p.12; SN0001, Module 5.3.5.2, RP-L201-0318 CSR v1.0, p.20; SN0003, Module 1.2, Addressing FDA Questions, p.9; SN0012, Module 1.11.3, Response to FDA IR, p.4.

<sup>75</sup> Original BLA 125806; SN0008, Module 1.11.3, Response to FDA IR, p.4.

## APPENDIX B: SUPPLEMENTAL INFORMATION RELATED TO INFECTION DATA

**Table 2020: Infection- and Inflammation-Related Efficacy Data by Protocol Version (Study 0318)<sup>76</sup>**

Protocol Section	Protocol v2.3 (Dated Oct 2, 2020)	Protocol v3.0 (Dated Feb 2, 2023)
Demographics and medical history (Section 8.2.7 in v2.3 and Section 8.2.1 in v3.0)	A complete medical history, including history of LAD-I will be obtained during Screening and Pre-Treatment Evaluation period. The medical history is to include all prior and current medical history and history of prior infections, including documentation of any hospitalizations and outpatient-based treatments for the management of infection.	A complete medical history, including <i>birth history</i> and history of LAD-I diagnosis and resultant medical events will be obtained during the Screening and Pre-Treatment Evaluation period. Medical history should include all prior and current medical and infection history, including documentation of any hospitalizations, <i>medical and non-medical interventions</i> , infections, <i>surgical procedures</i> , and outpatient-based treatments for the management of infections or <i>inflammatory</i> complications.
Secondary objectives (Section 3.2)	Determination of the incidence and severity of bacterial or other <i>infections</i> (subsequent to hematopoietic reconstitution).	Determination of the incidence of <u>significant infections</u> , infection-related hospitalizations, and prolonged infection-related hospitalizations, <i>comparing</i> the incidences prior to investigational product infusion and subsequent to hematopoietic reconstitution.
Efficacy endpoints (Section 3.3.1)	Overall survival and overall health status.	Statistically significant reduction in the incidence (of) <u>severe infections</u> , <sup>a</sup> infection-related hospitalizations, and prolonged infection-related hospitalizations; analyzed per patient and across the entire cohort, <i>comparing</i> event rates prior to RP-L201 infusion and following hematologic reconstitution after RP-L201.
Efficacy assessments/parameters (Section 8.2.19 in v2.3 and Section 9.1.1 in v3.0)	Incidence of hospitalizations or <i>outpatient-based treatments</i> for <i>systemic</i> bacterial, fungal, or viral infections (including, but not limited to, CMV infections).  Note: Only mention of “significant infection” prior to v3.0 (and included in v3.0) is in context of inclusion criterion of the occurrence of at least one prior <u>significant bacterial or fungal infection</u> ( <b>defined</b> as Grade 2 or higher by NCI-CTCAE v5).	Incidence of <u>significant infections</u> , <b>defined</b> as those requiring hospitalization, parenteral (IV or intramuscular) antimicrobials (including antibacterial, antifungal, or antiviral therapy), and/or IV <i>anti-inflammatory</i> agents (including monoclonal antibodies or corticosteroids) [emphasis added].  Incidence of infection-related hospitalizations.  Incidence of <i>infection-related prolonged hospitalizations</i> ; hospitalizations that are ≥7 days in duration are considered prolonged.
Adverse Events of Special Interest (added Section 10.2.5 in v3.0)	NA	Any new <u>severe</u> or otherwise <u>significant infection</u> , defined as those requiring hospitalization, <i>surgical intervention</i> , parenteral (IV or intramuscular) antibiotics (including antibacterial, antifungal, or antiviral therapy), or IV <i>anti-inflammatory</i> agents (including monoclonal antibodies or corticosteroids).

Source: Clinical review of RP-L201-0318 protocols submitted to original BLA 125806 and IND 18485.

Abbreviations: IV, intravenous; LAD-I, leukocyte adhesion deficiency type I; NA, not applicable; NCI-CTCAE v5, National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0.

<sup>a</sup> Per NCI-CTCAE v5 criteria, Grade 3 events are **classified** as severe.

Notes: Use of “significant” and “severe” emphasized with underlining with attention to definitions in **bold**. Other pertinent differences noted in *italics*.

<sup>76</sup> A summary of protocol amendments for Study RP-201-0318 can be found in CSR v1.0, Table 3.

### Infection-Related Endpoints – Subgroup Analysis for Older Patients >2 Years of Age at Treatment

As discussed in [Section 7.1.5.1](#), review of secondary efficacy endpoints related to infections uncovered issues with data quality that significantly hindered the interpretation of this data. During a more intensive review of data related to the six older subjects (for which the historical benchmark used in analysis of the primary efficacy endpoint was not applicable), data quality issues were split into seven categories to allow for the provision of subject-level examples from the data of these older subjects. A summary of the issues and some general examples are provided below. Following review, multiple issue types (i.e., 1-7) were identified within the data for each of the six older subjects.

Issue #1: Suspected overestimation of significant infections.

3. Example #1: Events that are likely the same categorized as separate events.
4. Example #2: Multiple events (up to 4 in some cases) linked to a hospitalization, but unclear which event(s) is the primary reason for the hospitalization.
5. The exact degree of overestimation is unclear, despite seeking additional information from the Applicant.

Issue #2: Suspected overestimation of prolonged infection-related hospitalizations.

6. Primarily due to the frequent use of imputed dates when dates were missing.
7. Led to overlapping hospitalizations in some cases.
8. The exact degree of overestimation is unclear, despite seeking additional information from the Applicant.

Issue #3: Conflicting data between Applicant materials and outside sources.

9. Example #1: Missing dates provided by a local physician in questionnaire from Applicant deleted from the CRF.
10. Example #2: Medication with missing dates that had been clarified by local physician deleted from or not included in CRF/datasets.
11. Example #3: Listings note a specific event to be associated with a specific hospitalization, but parental report suggests hospitalization is related to a different event (and in this case, was not a hospitalization at all, with patient being sent home the same evening).
12. Example #4: No hospitalization associated with an event in datasets, but parent testimonial indicates prolonged hospitalization.
13. Source of data in CRF not specified in most instances, often unclear when information from different sources was collected, and unclear how similar events were reconciled.

Issue #4: Conflicting data within Applicant materials.

14. Example #1: Therapies in CRF/listings that do not match those in the datasets.
15. Example #2: Events present in CRF/listings but absent from datasets.
16. Example #3: Data deleted from CRF but remaining in datasets.
17. Example #4: Dates for event not matching those of associated hospitalization.
18. Example #5: Hospitalizations without a clear associated event.
19. Example #6: Change in need for pre-treatment hospitalization/IV treatments between initial submission and efficacy update without explanation.

Issue #5: Insufficient detail to determine the nature of events or management.

20. Example #1: Absence of location of a problem (e.g., skin lesion).
21. Example #2: Missing or nonspecific treatment dates for an event/treatment (often leading to imputations and overlap).



22. Example #3: Non-specific descriptions of events which do not justify the level of treatment provided (e.g., viral URI treated with IV antibiotics and for an entire year due to imputed dates; IV treatment also documented in duplicate).
23. This issue is largely why the degree of overestimation of significant infections and prolonged hospitalizations is unknown.
24. Related issues: Indications for therapies having varying levels of similarity to description of event, and similar but not identical indications for therapies under a single event.

Issue #6: Therapies linked to events by date rather than indication.

- General problem, as noted in [Section 7.1.5.1](#).
- Related issues: Presence of duplicate therapies and therapies being noted as both treatment (medical history) and prophylaxis in the CRF, leading to it appearing in multiple places within datasets.

Issue #7: Variation in definition of “significant infection” endpoint, leading to difficulty in classification.

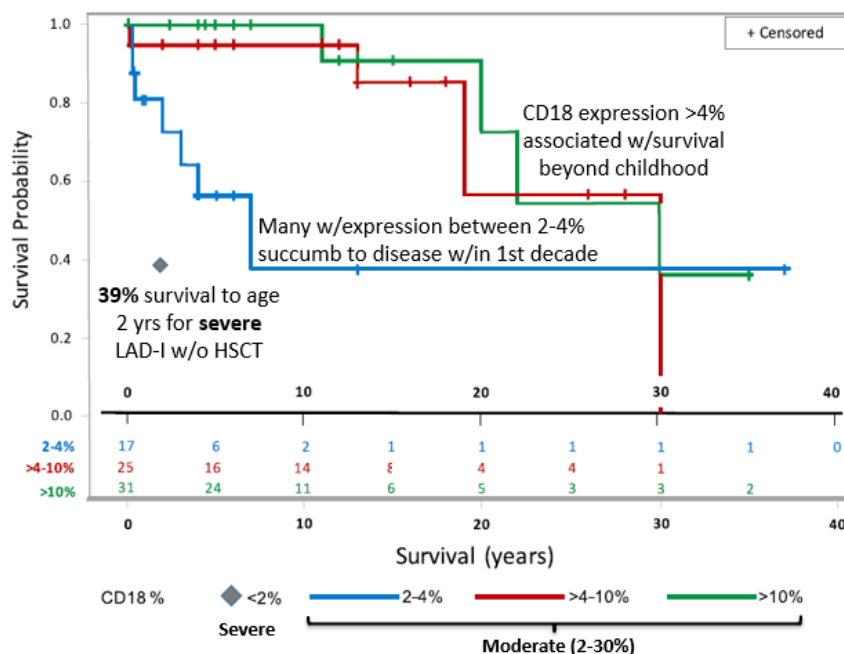
- As outlined in [Section 7.1.5.1](#), key infectious endpoints, including “significant infection,” were not fully defined until after subjects had been enrolled and treated. Initial references to “significant infection” referred to bacterial/fungal infections only.
- Some documents (including columns in datasets) note whether IV antimicrobials were given, not whether any parenteral therapy was provided (which is what the current definition specifies to define an infection as significant).

## APPENDIX C: SUPPLEMENTAL INFORMATION RELATED TO CD18 EXPRESSION

### Survival in the Absence of Allo-HSCT

Literature reviews have demonstrated a correlation between CD18 expression and survival (Fischer and Lisowska-Groszpiere 1988; Almarza Novoa et al. 2018). Figure 12 is adapted from a literature review of 323 cases of LAD-I published globally between 1975 and 2017 and includes cases where affected patients did not receive allo-HSCT (Almarza Novoa et al. 2018). CD18 expression of <2% is defined as severe disease, with the survival probability for this population noted by the gray diamond (n=66). CD18 expression of 2-30% is defined as moderate disease, with Kaplan-Meier survival curves provided for patients with expression between 2-4% (blue), >4-10% (red), and >10% (green). CD18 is shown to correlate with survival, with an estimated 39% survival to the age of 2 years for severe LAD-I (<2% CD18 expression).<sup>77</sup> Many with expression between 2 and 4% are seen to succumb to disease within the first decade of life. CD18 expression >4% is associated with survival beyond childhood. The Applicant attributes increased OS in these patients to a correlation between increased CD18 expression and a reduced risk of infection.

**Figure 12: HSCT-free Survival by CD18 Expression**



Source: Adapted from Almarza Novoa et al. (2018), Figure 1.

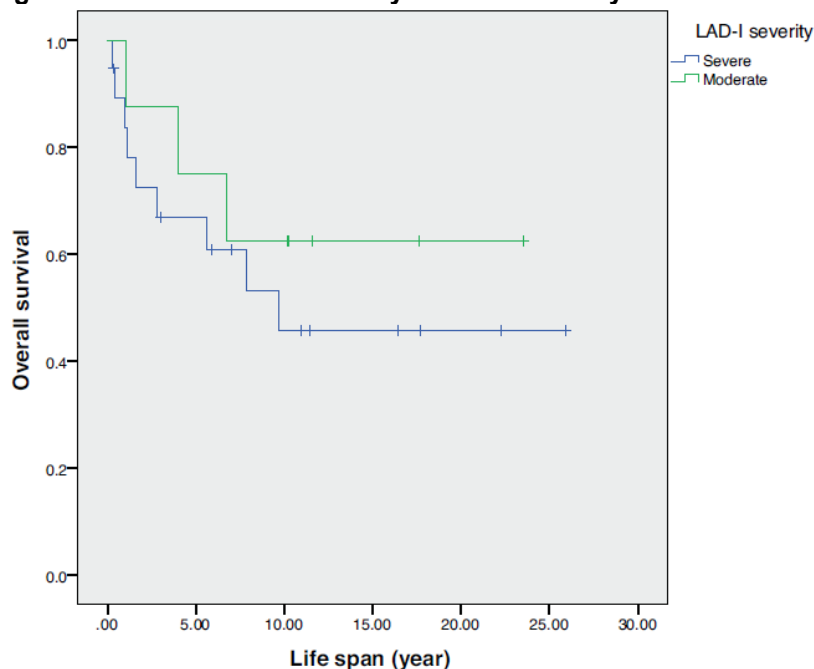
Abbreviations: HSCT, hematopoietic stem cell transplant; LAD-I, leukocyte adhesion deficiency type I.

Survival was also reported by disease severity in a cohort of 69 LAD-I patients referred to an Iranian medical center between 2007 and 2022 (Fazlollahi et al. 2023). Kaplan-Meier survival curves were generated based on 26 severe (CD18 and/or CD11a expression <2%) and 12 moderate (CD18 and/or CD11a expression 2-30%) LAD-I patients who did not undergo allo-HSCT (Figure 13). Severity, as

<sup>77</sup> Survival probability of 39% is for severe patients defined by CD18 <2% or investigator assessment; unclear if investigator assessment included consideration of CD11a <2%, as observed in 8 patients who had CD18 >30%, or if associated with temporal or geographic factors. When only CD18 <2% is used to define severe disease, survival probability is 44% (n=48); rate is the same when also only considering cases diagnosed after 2000 (n=43), which may be related to increased availability of diagnostics. Source: Almarza Novoa et al. (2018), Table I.

defined by CD18 or CD11a expression, appears to correlate with survival, with improved outcomes seen in moderate versus severe disease.

**Figure 13: HSCT-free Survival by Disease Severity<sup>a</sup>**



Source: Fazlollahi et al. (2023), Figure 3.

Abbreviations: HSCT, hematopoietic stem cell transplant; LAD-I, leukocyte adhesion deficiency type I.

<sup>a</sup> Severity defined by CD18 and/or CD11a expression.

### Allo-HSCT for the Treatment of Severe LAD-I

Literature reports document “restoration” or “normalization” of CD18 expression (up to 100% in one case) in severe LAD-I patients following successful allo-HSCT. In these cases, patients have been noted to have concurrent improvement in clinical outcomes, with one report noting the patient to be “disease-free” (Chakraborty et al. 2020) and others indicating an absence of new infections and/or resolution of prior infections following transplant (Al-wahadneh et al. 2006; Zhu et al. 2025).

Additionally, allogeneic transplant experience shows that even with mixed chimerism, children with severe LAD-I can remain alive and free of significant symptoms following transplant (Thomas et al. 1995; Qasim et al. 2009). In one case cited by Qasim et al. (2009), even a very low level of CD18 expression (incomplete chimerism with <5% expression) led to a phenotypic reversal of disease. It was also noted that “levels of circulating donor neutrophils may not accurately reflect levels of true engraftment, as functional CD18+ cells may preferentially egress the circulation to mediate important beneficial effects at target sites such as the oral mucosa.” Thomas et al. (1995) noted that chimerism is much more variable over time in short-lived granulocytes and monocytes but less so in lymphocytes.

### Canine Models of LAD-I

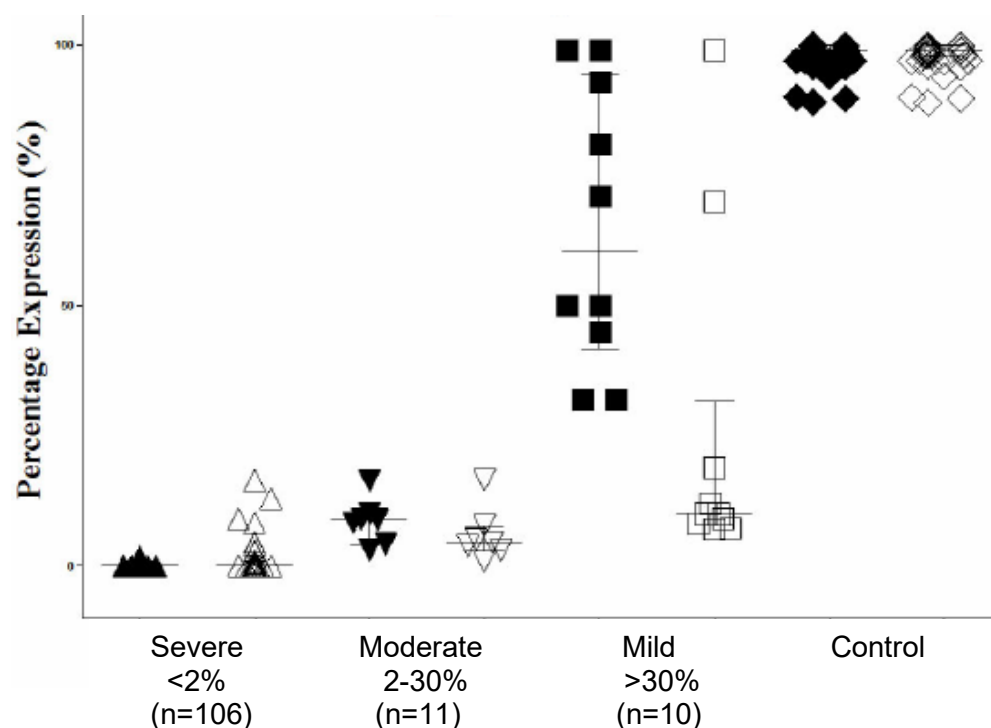
Canine models show that untreated animals with absent CD18 expression typically die from infectious complications at less than 6 months of age. Animals treated with gene-modified cells with resultant CD18 expression in the range of 5-10% were found to have persistent protection against infection for up to 7 years following treatment (Bauer et al. 2008; Bauer et al. 2013). In canine models, selective accumulation of donor neutrophils was seen in the oral mucosa, resulting in significantly higher levels of donor chimerism in saliva as compared to peripheral blood post-transplant (Bauer et al. 2004).

#### APPENDIX D: SUPPLEMENTAL INFORMATION RELATED TO CD11A EXPRESSION

##### Correlation Between CD18 and CD11a Expression in LAD-I

As part of a retrospective review of 127 LAD-I patients from 28 centers in India, Kambli et al. (2020) provided figures plotting CD18 and CD11a expression for patients grouped by severity based on percent CD18 expression on neutrophils, as determined by flow cytometry. Severe LAD-I was defined as CD18 expression <2%, moderate as CD18 2-30%, and mild as CD18 ≥30%. Data was also analyzed by looking at median fluorescence intensity (MFI) and stain index (ratio of intensity of stained/unstained) on different populations of leukocytes (neutrophils, lymphocytes, monocytes). Figure 14 is adapted from Figure S1 of the publication and illustrates percentage expression of CD18 and CD11a on neutrophils. There is a strong correlation between percent expression of CD18 and CD11a, particularly at lower levels of expression. Of note, expression of CD18 was >30% in all cases of mild LAD-I, but CD11a was significantly reduced in 80% of cases. It is the opinion of this reviewer that this may potentially represent expression of a dysfunctional CD18 protein which is incapable of dimerizing with the CD11a subunit, particularly in the setting of similar MFI for CD18 and CD11a (not shown), but this is not explicitly noted in the publication.

**Figure 14: Percentage Expression of CD18 and CD11a on Neutrophils by LAD-I Severity**



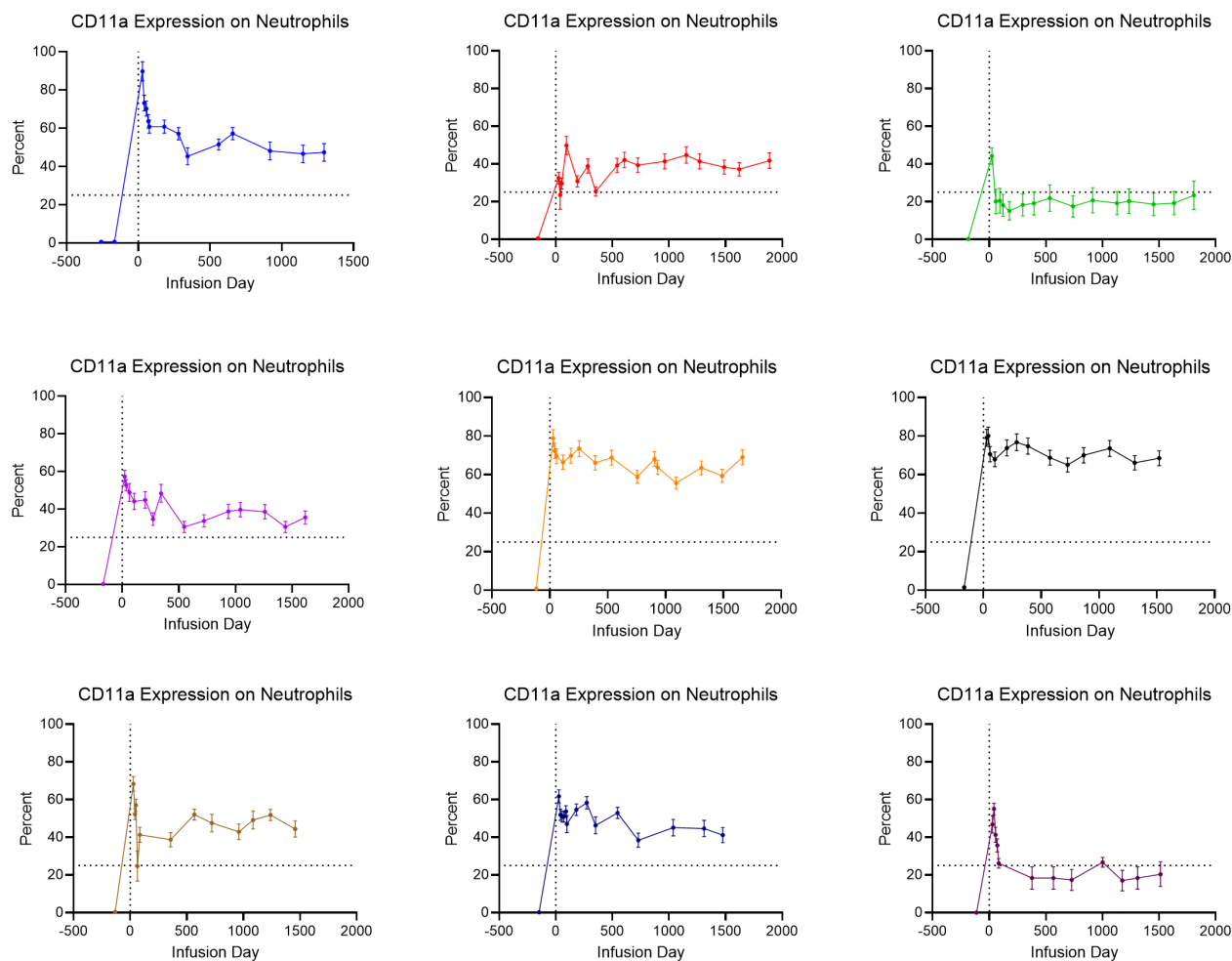
Percentage expression is shown for CD18 (black solid) and CD11a (white hollow) according to LAD-I severity categorization on the x-axis, as determined by percentage of CD18 expression (<2% severe, 2-30% moderate, >30% mild) and as compared to healthy controls.

Source: Adapted from Kambli et al. (2020), Figure S1.  
Abbreviations: LAD-I, leukocyte adhesion deficiency type I.

### CD11a Expression with Analytical Uncertainty

Figure 15 plots CD11a expression over time by subject (arrayed), incorporating the analytical uncertainty of the assay at each value (i.e., including error bars for the CV calculated in Table 4 in [Section 4.2](#)). Of note, for the 2 subjects who did not achieve expression  $\geq 25\%$  (b) (6), none of the error bars fall below 10% expression.

**Figure 15: CD11a Expression with CV for Assay**



(b) (6)

Source: CMC reviewer analysis (A.Timmons).  
Abbreviations: CV, coefficient of variation.

**APPENDIX E: SCHEDULES OF EVENTS (STUDY RP-L201-0318)****Schedule of Events from Screening through Week 1 Post-Infusion – Part 1**

Trial Procedures	Screening & Pre-Treatment Evaluation	Stem Cell Harvest (SCH) (Sequence may be up to 7 days in duration)	Pre-Cond. Day -8 to -6 <sup>1</sup>	Cond. D1 Day -5	Cond. D2 Day -4	Cond. D3 Day -3	Cond. D4 Day -2	Day -1	Day 0	Follow-Up W1 Day 1–7
<b>Consent, history, general eval:</b>	-	-	-	-	-	-	-	-	-	-
Informed consent: trial evaluation and therapy <sup>2</sup>	w/in 2m prior to SCH Day 1	-	-	-	-	-	-	-	-	-
Determination of study eligibility: Inclusion/exclusion criteria	w/in 2w prior to SCH Day 1	-	-	-	-	-	-	-	-	-
Medical history including prior infections <sup>3</sup>	w/in 2w prior to SCH Day 1	-	-	-	-	-	-	-	-	-
Concomitant medications	w/in 2w prior to SCH Day 1	Daily	X	X	X	X	X	X	X	X
Adverse Events	X	Daily	X	X	X	X	X	X	X	X
Vital signs	w/in 1w prior to SCH Day 1	Daily & per Apheresis Prot. <sup>19</sup>	X	X	X	X	X	X	X	X <sup>6</sup>
Weight and Height <sup>4</sup>	w/in 1w prior to SCH Day 1 <sup>4</sup>	SCH Day 1 & each Apheresis Day <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>	X <sup>4</sup>
Physical examination	w/in 1w prior to SCH Day 1	SCH Day 1 & 5; & per Apheresis Prot. <sup>19</sup>	X	X	X	X	X	X	X	X <sup>6</sup>
Lansky Performance (FSS if req.) <sup>5</sup>	w/in 1w prior to SCH Day 1	-	X	-	-	-	-	-	-	-

Source: Adapted from Original BLA 125806; SN0001, Module 5.3.5.2, RP-L201-0318 protocol v3.0, Table 1.

1. Specific evaluation conducted (with additional baseline clinical and laboratory assessments) during 3 days prior to initial conditioning busulfan dose (D-8 to D-6).
2. Authorizes clinical evaluation procedures necessary to determine trial participation, trial therapy, and subsequent follow-up. Determination of LAD-I diagnosis, including percentage CD18 PMN expression, is recommended initial evaluation following informed consent. When initial consent obtained by phone, must be obtained in-person w/in 2 mos prior to Mobilization/SCH sequence.
3. Detailed medical history includes prior hospitalizations with emphasis on diagnosis and treatment of prior infections (both in-hospital and in outpatient settings), prior umbilical cord complications (delayed separation and/or omphalitis), oral/periodontal abnormalities, and other medical complications. Whenever possible, source documentation of infectious complications in mos and years (when applicable) prior to trial enrollment collected. Detailed source documentation of PB flow cytometry CD18/CD11 assays and any prior *ITGB2* mutation analyses, including methods required.
4. Height recorded during initial screening and pre-conditioning evaluations and during post-therapy follow-up. Weight repeated as indicated in table above and per institutional practices.
5. Lansky Play/Performance Score determined as indicated in table. If Lansky Score cannot be obtained (e.g., subject too young), Functional Status Score (FSS) obtained; FSS continued at specified timepoints with Lansky Score obtained in addition to FSS when subject of sufficient age to enable assessment.
6. Follow-up after busulfan conditioning and infusion of IP includes daily assessments until 1) resolution of hematologic nadir; 2) determination that no hematologic nadir likely to occur; or 3) hematologic nadir and determination that no resolution likely to occur (engraftment failure; determination made approximately 42 days post-IP, or earlier if life-threatening complications) and infusion of back-up cells warranted.

## Schedule of Events from Screening through Week 1 Post-Infusion – Part 2

Trial Procedures	Screening & Pre-Treatment Evaluation	Stem Cell Harvest (SCH) (Sequence may be up to 7 days in duration)	Pre-Cond. Day -8 to -6 <sup>1</sup>	Cond. D1 Day -5	Cond. D2 Day -4	Cond. D3 Day -3	Cond. D4 Day -2	Day -1	Day 0	Follow-Up W1 Day 1–7
<b>Clinical laboratory evaluations:</b>	-	-	-	-	-	-	-	-	-	-
Complete blood count & differential <sup>6</sup>	w/in 1w prior to SCH Day 1	Daily	X	X	X	X	X	X	X <sup>6</sup>	X <sup>6</sup>
Chemistry including electrolytes, BUN/Cr, AST/ALT, ALP, LDH, bilirubin, Ca, Mg, Phos	w/in 1w prior to SCH Day 1	SCH D1 & each Apheresis Day	X	X	X	X	X	X	X	X
Coagulation: PT or INR; aPTT <sup>7</sup>	w/in 1w prior to SCH Day 1	As clinically indicated	X	-	-	-	-	-	X	-
Urinalysis <sup>7</sup>	w/in 1w prior to SCH Day 1	As clinically indicated	-	-	-	-	-	-	-	-
Serology incl. HIV, HBV, HCV, other <sup>8</sup>	w/in 1m prior to final SCH Day <sup>8</sup>	-	-	-	-	-	-	-	-	-
PPD skin test or QuantiFERON-TB Gold Plus	w/in 2m prior to SCH Day 1 (& prior to administration of ustekinumab)	-	-	-	-	-	-	-	-	-
Thyroid panel (T4, TSH)	w/in 2m prior to SCH Day 1	-	-	-	-	-	-	-	-	-
Serum immunoglobulins (IgA, IgG, IgM)	w/in 2m prior to SCH Day 1	-	-	-	-	-	-	-	-	-
CD18/CD11a/CD11b expression in PB <sup>9</sup>	w/in 2m prior to SCH Day 1	-	-	-	-	-	-	-	-	-

Source: Adapted from Original BLA 125806; SN0001, Module 5.3.5.2, RP-L201-0318 protocol v3.0, Table 1.

6. Follow-up after busulfan conditioning and infusion of IP includes daily assessments until 1) resolution of hematologic nadir; 2) determination that no hematologic nadir likely to occur; or 3) hematologic nadir and determination that no resolution likely to occur (engraftment failure; determination made approximately 42 days post-IP, or earlier if life-threatening complications) and infusion of back-up cells warranted.
7. Urinalysis and coagulation panel performed as clinically indicated during Mobilization/SCH sequence.
8. For subjects in US, HIV (I and II antibodies), hepatitis B virus panel (HBV surface antigen, HBV surface antibody, HBV core antibody, HBV e-antigen), hepatitis C virus antibodies (anti-HCV Ab), human T-cell lymphotropic virus antibodies (HTLV-I and II Ab), CMV, and Epstein-Barr virus (EBV) required. Serology obtained w/in 3 mos prior to last possible day of apheresis (SCH D7). Screening for human spongiform encephalopathy, including Creutzfeldt-Jakob disease, conducted via by investigator w/doc provided w/collection of serology samples at Screening.  
For subjects in EU, HIV (I and II antibodies), hepatitis B virus panel (HBV surface antigen, HBV core antibody), hepatitis C virus antibodies (anti-HCV Ab), *Treponema pallidum* screening, HTLV-I and II antibodies (HTLV-I and II Ab), CMV, and EBV required. Assessments performed w/in 30 days prior to last possible day of apheresis collection permitted per protocol (SCH D7).
9. Flow cytometry of PB used to determine percentage PMNs expressing CD18 (and CD11a, CD11b). Must be accompanied by sample from unrelated, healthy donor with identical handling, transportation, and storage conditions for both samples.

## Schedule of Events from Screening through Week 1 Post-Infusion – Part 3

Trial Procedures	Screening & Pre-Treatment Evaluation	Stem Cell Harvest (SCH) (Sequence may be up to 7 days induration)	Pre-Cond. Day -8 to -6 <sup>1</sup>	Cond. D1 Day -5	Cond. D2 Day -4	Cond. D3 Day -3	Cond. D4 Day -2	Day -1	Day 0	Follow-Up W1 Day 1-7
<b>Specialized laboratory evaluations:</b>	-	-	-	-	-	-	-	-	-	-
<i>ITGB2</i> mutation analysis <sup>10</sup>	w/in 2m prior to SCH Day 1	-	-	-	-	-	-	-	-	-
Vector copy number (VCN; blood cells) <sup>11</sup>	w/in 2m prior to SCH Day 1 <sup>12</sup>	-	X <sup>11</sup>	-	-	-	-	-	-	-
Integration site analysis (ISA; LV insertional profile; blood cells)	-	-	-	-	-	-	-	-	-	-
Replication competent lentivirus (RCL; blood cells) <sup>12</sup>	-	-	-	-	-	-	-	-	-	-
Antibodies to CD18 (serum) <sup>13</sup>	w/in 2m prior to SCH Day 1 <sup>13</sup>	-	X <sup>13</sup>	-	-	-	-	-	-	-
Blood sample: exploratory assays <sup>14,15</sup>	w/in 2m prior to SCH Day 1 <sup>14, 15</sup>	-	X <sup>14,15</sup>	-	-	-	-	-	-	-
<b>Bone marrow aspirate/biopsy:</b>	-	-	-	-	-	-	-	-	-	-
Histology & cytogenetics <sup>16</sup>	w/in 2m prior to SCH Day 1	-	-	-	-	-	-	-	-	-
CD18/CD11a/CD11b expression in BM cells <sup>16</sup>	w/in 2m prior to SCH Day 1	-	-	-	-	-	-	-	-	-
<b>Other clinical evaluations:</b>	-	-	-	-	-	-	-	-	-	-
12-lead ECG	w/in 2m prior to SCH Day 1	-	-	-	-	-	-	-	-	-
Echocardiogram	w/in 2m prior to SCH Day 1	-	-	-	-	-	-	-	-	-
Skin examination, incl. photography <sup>17</sup>	w/in 2w prior to SCH Day 1	-	X	-	-	-	-	-	-	-
Oral examination, incl. photography <sup>17</sup>	w/in 2w prior to SCH Day 1	-	X	-	-	-	-	-	-	-

Source: Adapted from Original BLA 125806; SN0001, Module 5.3.5.2, RP-L201-0318 protocol v3.0, Table 1.

10. Whole genome sequencing w/subsequent masking of data to only include panel containing *ITGB2* gene to characterize mutation.

11. VCN in PBMCs (including subsets) by qPCR or ddPCR for LV DNA performed according to schedule through M6 assessment. If evidence of LV DNA at M6, further assessments continue according to schedule. Assessments stopped if 3 consecutive values below lower limit of detection (transduced cells not detectable) and evaluation at M6 negative. Additional aliquots of cellular material beyond that required for VCN determination obtained and frozen for assays identified at future timepoints. Collection may occur any time w/in 2 months prior to SCH D1 through pre-conditioning D-8. If PBMCs collected before pre-conditioning period, collection for VCN not required until study timepoints post-IP.

12. Blood cells evaluated for RCL at M3, M6, and M12 following infusion and yearly thereafter. If assessments negative during first year, subsequent yearly evaluations may be discontinued w/ adequate rationale.



13. Serum collected for immunogenicity at specified timepoints and stored for evaluation of anti-CD18/CD11a/CD11b antibodies if clinical events (i.e., reduction in previously detected CD18, absence of CD18 expression despite hematopoietic reconstitution) warrant immunogenicity assessment. Additional aliquots of serum beyond that required for antibody determination obtained and frozen for exploratory assays identified at future timepoints. Collection may occur any time w/in 2 months prior to SCH D1 through pre-conditioning D-8. If serum aliquots collected before pre-conditioning period, collection of serum not required until study timepoints post-IP.
14. Plasma and blood cell pellets cryopreserved for future exploratory assays, which may include evaluation of neutrophil/monocyte arrest/adhesion on endothelial surfaces, and other assays identified at future timepoints. Immortalized cell lines may be created for future research purposes. Collection of samples may occur any time w/in 2 months prior to SCH D1 through pre-conditioning D-8. If samples collected before pre-conditioning period, collection of serum not required until study timepoints post-IP.
15. RNA preparations obtained and frozen.
16. Because BM evaluation not considered standard LAD-I management, conducted at limited timepoints following IP to characterize safety and efficacy of GT. Evaluation involves standard histologic and cytogenetic analysis, and assessments of VCN in BM mononuclear and CD34+ cells (and lineage-specific precursors when feasible). When feasible, BM-derived cells evaluated via flow cytometry for expression of CD18/CD11a/CD11b. At time of pre-treatment evaluation, sample stored when feasible to perform additional analyses in event of hematologic malignancy.
17. Photographic documentation of any skin and/or oral abnormalities (periodontitis, gingivitis) made at timepoints both before and after trial therapy according to table. If no abnormalities identified during pre-treatment evaluation, photographs not required.

## Schedule of Events from Screening through Week 1 Post-Infusion – Part 4

Trial Procedures	Screening & Pre-Treatment Evaluation	Stem Cell Harvest (SCH) (Sequence may be up to 7 days in duration)	Pre-Cond. Day -8 to -6 <sup>1</sup>	Cond. D1 Day -5	Cond. D2 Day -4	Cond. D3 Day -3	Cond. D4 Day -2	Day -1	Day 0	Follow-Up W1 Day 1–7
<b>Investigational therapy &amp; related procedures:</b>	-	-	-	-	-	-	-	-	-	-
Ustekinumab <sup>18</sup>	-	Appx. 2 weeks prior to SCH Day 1 <sup>18</sup>	X <sup>18</sup>	-	-	-	-	-	-	-
<b>HSC collection:</b>	-	-	-	-	-	-	-	-	-	-
Apheresis <sup>19</sup>	-	up to 3 days; starting SCH Day 5	-	-	-	-	-	-	-	-
G-CSF <sup>19</sup>	-	SCH Days 1–6; Day 7 if needed	-	-	-	-	-	-	-	-
Plerixafor <sup>19</sup>	-	SCH Days 5–6; Day 7 if needed	-	-	-	-	-	-	-	-
Peripheral blood CD34+ assessment <sup>19</sup>	-	SCH Days 5–6; Day 7 if needed	-	-	-	-	-	-	-	-
Apheresis product CBC and CD34+ assessment <sup>20</sup>	-	SCH Days 5–6; Day 7 if needed	-	-	-	-	-	-	-	-
Bone marrow HSC collection <sup>21</sup>	-	1 Day	-	-	-	-	-	-	-	-
<b>Conditioning and IP Infusion:</b>	-	-	-	-	-	-	-	-	-	-
Conditioning (busulfan), incl. pre-med <sup>22</sup>	-	-	-	X <sup>22</sup>	X <sup>22</sup>	X <sup>22</sup>	X <sup>22</sup>	-	-	-
Infusion of investigational product	-	-	-	-	-	-	-	-	X	-

Source: Adapted from Original BLA 125806; SN0001, Module 5.3.5.2, RP-L201-0318 protocol v3.0, Table 1.

18. Ustekinumab administered approximately 2w prior to mobilization and 1-2w prior to IP. Admin contingent on vaccination schedule. Live viral or bacterial vaccines must be given at least 15w following last admin. BCG vaccines should not be given for 1y prior or 1y following. In circumstances where admin may conflict w/vaccination guidelines, admin may be withheld. At both timepoints, one dose at 0.75 mg/kg administered SC. Investigator, in consultation with MM, may adjust based on clinical judgement. PPD skin test or QuantiFERON-TB Gold Plus prior to admin.
19. See also Mobilization and SCH sequence, as preferred method of HSC collection for subjects weighing at least 5 kg. G-CSF doses modified (or omitted) in settings of peripheral WBC >50×10<sup>9</sup>/L (reduced dose) or >75×10<sup>9</sup>/L (omitted dose). Apheresis protocol/guidelines at each participating center also guide frequency of clinical evaluations during SCH sequence.
20. CBC including total nucleated cells, WBC, hematocrit, and platelet count performed on each apheresis product.
21. Harvest of HSCs from BM considered only if peripheral CD34+ counts remain less than 10 cells/μL following mobilization procedures on SCH D5–6. BM harvest considered for subjects w/body weight less than 5kg at trial entry or w/contraindications to mobilization or apheresis procedure.
22. Initial busulfan dose(s) 1.6–2.0 mg/kg every 12 h (2-h infusion) on conditioning D1 and 2 (protocol D-5 and -4) with Bu levels (PK) drawn at multiple timepoints following initial dose (conditioning D1; protocol D-5) and at least one subsequent dose. Busulfan dosing on conditioning D3–4 (protocol D-3 and -2, sooner if feasible) calculated to target net busulfan AUC for all 8 (or otherwise) doses of 75,000 ng/ml\*hr. Antiepileptic and anti-emetic prophylaxis (pre-medication) and IV fluids administered per institutional guidelines. Please consult protocol's pharmacy manual for most updated recommendations and requirements.

## Schedule of Events Beyond Week 1 to End-of-Study (Month 24) – Part 1

Trial Procedures	Initial Month (through Day 28 ±5d)	W4 <sup>2</sup> (D28 ±5d)	W6 <sup>2</sup> (D42 ±5d)	W8 <sup>2</sup> (D56 ±7d)	W10 <sup>2</sup> (D70 ±8d)	M3 (±14d)	M4 <sup>2</sup> (±21d)	M5 <sup>2</sup> (±21d)	M6 (±21d)	M9 (±21d)	M12 (±30d)	M18 (±30d)	M24 (±30d)
<b>Consent, history general evaluation:</b>	-	-	-	-	-	-	-	-	-	-	-	-	-
Concomitant medications	Daily <sup>3</sup>	X	X	X	X <sup>2</sup>	X	-	-	X	X	X	X	X
Adverse events*	Daily <sup>3</sup>	X	X	X	X <sup>2</sup>	X	X	X	X	X	X	X	X
Vital signs	Daily <sup>3, 4</sup>	X	X	X	X <sup>2,4</sup>	X	X	X	X	X	X	X	X
Weight and Height <sup>5</sup>	As clinically indicated <sup>3</sup>	X <sup>3</sup>	X	X	X <sup>2</sup>	X <sup>3</sup>	-	-	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>	X <sup>3</sup>
Physical examination	Daily <sup>3</sup>	X	X	X	X <sup>2</sup>	X	-	-	X	X	X	X	X
Lansky Performance (FSS if req.) <sup>6</sup>	-	X	X	X	X <sup>2</sup>	X	-	-	X	X	X	X	X
<b>Clinical laboratory evaluations:</b>	-	-	-	-	-	-	-	-	-	-	-	-	-
Complete blood count & differential <sup>4</sup>	Daily <sup>3, 4</sup>	X	X	X	X <sup>4</sup>	X	X	X	X	X	X	X	X
Chemistry including electrolytes, BUN/Cr, AST/ALT, ALP, LDH, bilirubin, Ca, Mg, Ph <sup>4</sup>	Daily or 3X/week <sup>3, 4, 7</sup>	X	X	X	X <sup>2,4</sup>	X	X	X	X	X	X	X	X
Coagulation: PT or INR; aPTT	Weekly <sup>8</sup>	X	-	-	-	X	-	-	-	-	X	-	X
Urinalysis <sup>9</sup>	W2 (D14 ±5d)	X	X	X	X <sup>4</sup>	X	X	X	X	-	-	-	-
Serology incl. HIV, HBV, HCV	-	-	-	-	-	-	-	-	-	-	-	-	-
Thyroid panel (T4, TSH)	-	X	-	-	-	X	-	-	-	-	-	-	X
Serum immunoglobulins (IgA, IgG, IgM)	-	X	-	-	-	X	-	-	-	-	X	-	X
CD18/CD11a/CD11b expression in PB <sup>10</sup>	Following hematopoietic reconst. <sup>10</sup>	X	X	X	X <sup>2</sup>	X	-	-	X	X	X	X	X
PB smear <sup>4</sup>	W2 (D14 ±5d)	X	X	X	X <sup>4</sup>	X	X	X	X	-	-	-	-
Complement testing – terminal complement complex (C5b-9) <sup>4</sup>	W2 (D14 ±5d)	X	X	X	X <sup>4</sup>	X	X	X	X	-	-	-	-

Source: Adapted from Original BLA 125806; SN0001, Module 5.3.5.2, RP-L201-0318 protocol v3.0, Table 2.

\* Adverse events of special interest (AESI), including evaluation for acute and chronic GVHD following engraftment.

1. LTFU (beyond 2 years post-infusion, to 15 years total) planned w/details provided in LTFU protocol. NOTE: Subjects who have completed ≥ 12 months but <18 months of follow-up post-GT at time of Protocol v3.0 followed at 4-mo intervals between M12 and M24, w/visits occurring at M12, M16, M20, and M24. M16 and M20 visits include all assessments per M18 visit.
2. For subjects w/evidence of hematopoietic recovery, assessments between M1 (D28) and M3 occur approximately every 2w (more frequently if clinically necessary). For subjects clinically stable to travel home between M2 and M3 assessments, W10 assessment may be conducted locally (see footnotes #4 and #18) and otherwise at discretion of Investigator. For subjects who do not reside in proximity of trial center, determination made by Investigator as to whether subject's clinical condition necessitated subject remain in vicinity during intervals between M2 and M3 visits and at monthly visits between the M3 and M6 visits.
3. Follow-up after busulfan conditioning and IP infusion includes daily assessments (height excluded) w/salient abnormal findings recorded in CRF until 1) resolution of hematologic nadir; 2) determination that no hematologic nadir likely to occur; 3) hematologic nadir and determination that no resolution likely to occur (engraftment failure); or 4) as otherwise specified in footnote #4.

If hematopoietic reconstitution identified prior to D28 post-IP infusion, as determined by ANC  $\geq 500$  for 3 consecutive days in absence of life-threatening thrombocytopenia, evaluation occurs at least weekly through D28.

4. Subjects closely monitored for development of thrombotic microangiopathy (TMA) after busulfan conditioning with assessments at least every 2 weeks (or more frequently) up to M3 post-infusion of IP, then monthly (if no clinical concerns) during M4, M5, and M6 post-IP. Assessments include blood pressure; CBC w/differential; renal function (BUN/Cr); liver function (AST/ALT, total bilirubin, and LDH); urinalysis for protein and blood; comprehensive PB smear with evaluation for presence of schistocytes; and complement testing, specifically terminal complement complex (C5b-9). Please refer to [Section 6.1.7.3](#) for further information.
5. Height not required during initial 28 days following IP infusion. Height assessed in addition to weight at M1, M3, M6, M9, M18 and M24 visits.
6. Lansky Play/Performance Score determined as indicated in the table. If Lansky cannot be obtained (e.g., too young), Functional Status Score (FSS) obtained; FSS continued at specified timepoints with Lansky obtained in addition to FSS when subject of sufficient age.
7. During initial 28 days following IP infusion, electrolytes and additional serum chemistries evaluated daily for initial week and then as specified in footnote #4 or otherwise at frequency according to institutional standards for patients receiving autologous HSCT with busulfan conditioning. In absence of institutional guidelines, obtained daily unless Investigator determines subject has not developed (and unlikely to develop) busulfan- or SC-related liver or other metabolic toxicity, in which case should be evaluated 3 times per week through D28/M1.
8. Coagulation assays conducted weekly during initial month after IP infusion (more frequently if clinically indicated).
9. Urinalysis performed as part of TMA monitoring evaluated for protein and blood only; sterile or clean-catch urine samples not required.
10. Flow cytometry of PB used to determine percentage of PMNs expressing CD18 (and CD11a, CD11b). Must be accompanied by sample from unrelated, healthy donor with identical handling, transportation, and storage conditions for both samples. If hematopoietic reconstitution occurs prior to D21 post-IP infusion, then evaluate at time of reconstitution; otherwise, evaluation starting at D28 and according to trial schedule.

## Schedule of Events Beyond Week 1 to End-of-Study (Month 24) – Part 2

Trial Procedures	Initial Month (through Day 28 ±5d)	W4 <sup>2</sup> (D28 ±5d)	W6 <sup>2</sup> (D42 ±5d)	W8 <sup>2</sup> (D56 ±7d)	W10 <sup>2</sup> (D70 ±8d)	M3 (±14d)	M4 <sup>2</sup> (±21d)	M5 <sup>2</sup> (±21d)	M6 (±21d)	M9 (±21d)	M12 (±30d)	M18 (±30d)	M24 (±30d)
<b>Specialized laboratory evaluations:</b>	-	-	-	-	-	-	-	-	-	-	-	-	-
VCN (Blood cells) <sup>11</sup>	-	X	X	X	X <sup>2</sup>	X	-	-	X <sup>11</sup>	X	X	X	X
VCN (Blood myeloid, T & B cell subpopulations) <sup>11</sup>	-	X	-	X	-	-	-	-	X	-	X	-	X
ISA (Blood cells)	-	X	X	X	X	X	-	-	X	X	X	X	X
ISA (Blood myeloid, T & B cell subpopulations)	-	X	-	X	-	-	-	-	X	-	X	-	X
RCL (Blood cells) <sup>12</sup>	-	-	-	-	-	X	-	-	X	-	X	-	X
Serum archive (Antibodies to CD18) <sup>13</sup>	-	X	-	X	-	X	-	-	X	X	X	X	X
Blood sample: exploratory assays <sup>14</sup>	-	X	-	X	-	X <sup>15</sup>	-	-	X <sup>15</sup>	X	X <sup>15</sup>	X	X
<b>Bone marrow aspirate/biopsy:</b>	-	-	-	-	-	-	-	-	-	-	-	-	-
Histology and cytogenetics <sup>16</sup>	-	X	-	-	-	X	-	-	-	-	X	-	X
CD18/CD11a/CD11b expression in BM cells <sup>16</sup>	-	X	-	-	-	X	-	-	-	-	X	-	X
VCN (Total BM cells including CD34+ cells; when feasible) <sup>16</sup>	-	X	-	-	-	X	-	-	-	-	X	-	X
ISA (Total BM cells including CD34+ cells; when feasible) <sup>16</sup>	-	X	-	-	-	X	-	-	-	-	X	-	X
<b>Other clinical evaluations:</b>	-	-	-	-	-	-	-	-	-	-	-	-	-
Skin examination, incl. photography <sup>17</sup>	-	X	X	X	-	X	-	-	X	X	X	X	X
Oral examination, incl. photography <sup>17</sup>	-	X	X	X	-	X	-	-	X	X	X	X	X
12-lead ECG <sup>18</sup>	W2 (D14±5d)	X	X	X	X <sup>18</sup>	X	X	X	X	-	-	-	-
Echocardiogram <sup>18</sup>	-	X	-	X	-	X	X	X	X	-	-	-	-
Decision to administer HSC back-up <sup>19</sup>	-	-	X <sup>19</sup>	-	-	-	-	-	-	-	-	-	-

Source: Adapted from Original BLA 125806; SN0001, Module 5.3.5.2, RP-L201-0318 protocol v3.0, Table 2.

11. VCN in PBMCs (including subsets) by qPCR or ddPCR for LV DNA performed according to schedule through M6 assessment. If evidence of LV DNA at M6, further assessments continue according to schedule. Assessments stopped if 3 consecutive values below lower limit of detection (transduced cells not detectable) and evaluation at M6 negative. Additional aliquots of cellular material beyond that required for VCN determination obtained and frozen for assays identified at future timepoints.
12. Blood cells evaluated for RCL M3, M6, and M12 following infusion and yearly thereafter. If assessments negative during first year, blood specimens processed for analysis collected annually and archived. Subsequent yearly evaluations may be discontinued with adequate rationale.
13. Serum collected for immunogenicity at specified timepoints and stored for evaluation of anti-CD18/CD11a/CD11b antibodies if clinical events (i.e., reduction in previously detected CD18, absence of CD18 expression despite hematopoietic reconstitution) warrant immunogenicity assessment. Additional aliquots of serum beyond that required for antibody determination obtained and frozen for exploratory assays identified at future timepoints.
14. Plasma and blood cell pellets cryopreserved for future exploratory assays, which may include evaluation of neutrophil/monocyte arrest/adhesion on endothelial surfaces, and other assays identified at future timepoints. Immortalized cell lines may be created for future research purposes.

15. RNA preparations obtained and cryopreserved if feasible.
16. Because BM evaluation not considered standard LAD-I management, conducted at limited timepoints following IP to characterize safety and efficacy of GT. Evaluation involves standard histologic and cytogenetic analysis, and assessments of VCN in BM mononuclear and CD34+ cells (and lineage-specific precursors when feasible). When feasible, BM-derived cells evaluated via flow cytometry for expression of CD18/CD11a/CD11b. BM assessment at D28 may be delayed and performed at  $\leq$ W6 at discretion of Investigator. In settings of rapid hematologic reconstitution ( $\leq$ 28 days) and evidence of infection resolution, initial (D28-42) post-IP BM assessment may be withheld at discretion of Investigator. In settings of phenotypic correction where VCN in PB and BM cells comparable and  $>0.1$  at both M3 and 12 assessments, M24 may be cancelled at discretion of Investigator in consult with study Medical Monitor. At all points when BM collected, additional BM collected and stored for future exploratory assays if subject provides consent.
17. Photographic documentation of any skin and/or oral abnormalities (periodontitis, gingivitis) made at timepoints both before and after trial therapy according to table. If no abnormalities identified during pre-treatment evaluation, photographs not required.
18. 12-lead ECG and echocardiogram performed following busulfan conditioning to monitor for development of pulmonary arterial hypertension (PAH). Findings indicative of incipient PAH or which demonstrate PAH warrant additional evaluations, more frequent monitoring, and/or treatment initiation.
19. Dependent on Investigator determination that no evidence of hematologic recovery nor IP engraftment and no or minimal likelihood of recovery or engraftment. Decision made on D42 ( $\pm$ 5 days, approximately 6w) post-IP (earlier/later permitted if life-threatening) and in consultation with IDMC.

**NOTE: Because of the complexity of evaluation in the months subsequent to investigational safety, including the documentation of LAD-I correction at genetic, cellular and phenotypic levels, and documentation regarding potential ongoing product-safety considerations, it is understood that each of the investigational evaluations stipulated above may not be performed at every stipulated timepoint in some instances. It is emphasized that every effort be made to perform these evaluations as comprehensively as possible. Evaluations that are considered essential for optimizing safe care of human subjects (for example, monitoring of blood counts and chemistries) should be prioritized whenever required.**

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