Summary Basis for Regulatory Action

Date:	
From:	Anna Kwilas, PhD, Review Committee Chair, Office of Tissues and Advanced Therapies (OTAT), Division of Cellular and Gene Therapies (DCGT)
BLA STN:	125755/0
Applicant:	bluebird bio, Inc.
Submission Receipt Date:	October 18, 2021
Action Due Date:	September 16, 2022
Proper Name:	elivaldogene autotemcel
Proprietary Name:	SKYSONA
Indication:	Slowing the progression of neurologic dysfunction in boys 4-17 years of age with early, active cerebral adrenoleukodystrophy (CALD).

Recommended Action: The Review Committee recommends accelerated approval of this product.

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Director, Office of Tissues and Advanced Therapies

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Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (OTAT/DCGT and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and OTAT/DCGT) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Anna Kwilas, PhD, CBER/OTAT/DCGT Tal Salz, PhD, CBER/OTAT/DCGT Andrew Timmons, PhD, CBER/OTAT/DCGT Brian Stultz, MS, CBER/OTAT/DCGT Massoud Motamed, PhD, CBER/OTAT/DCGT Carolina Panico, MD, PhD, CBER/OTAT/DCGT Seth Schulte, MS, CBER/OCBQ/DBSQC Esmeralda Alvarado Facundo, PhD, CBER/OCBQ/DBSQC Most (Nahid) Parvin, PhD, CBER/OCBQ/DBSQC/LBVI Tao Pan, PhD, CBER/OCBQ/DBSQC Wei Wang, PhD, CBER/OCBQ/DMPQ
Pre-license Inspection	Wei Wang, PhD, CBER/OCBQ/DMPQ Jakob Reiser, PhD, CBER/OTAT/DCGT Anna Kwilas, PhD, CBER/OTAT/DCGT Christian Lynch, CBER/ORO/DROP
Clinical • Clinical (Product Office) • Post-marketing safety epidemiological review (OBPV/DPV) • BIMO	Shelby Elenburg, CBER/OTAT/DCEPT Leah Crisafi, CBER/OTAT/DCEPT Alisha Thomas, CBER/OBPV Colonius King, CBER/OCBQ/DIS
Statistical • Clinical data (OBPV/DB) • Non-clinical data	Shuya (Joshua) Lu, CBER/OBPV
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	Danielle Brooks, CBER/OTAT/DCEPT
Clinical Pharmacology	Xiaofei Wang, CBER/OTAT/DCEPT
Labeling • Promotional (OCBQ/APLB) • Carton/Containers (OTAT/DRPM and OTAT/DCGT)	Benjamin Cyge, CBER/OCBQ/DCM/APLB Anna Kwilas, PhD, CBER/OTAT/DCGT
Other Review(s) not captured above categories, for example: • Consults • Devices • Software	Naomi Knoble David Reasner Marian Strazzeri Lili Garrard Tianjiao Dai, PhD, CBER/OBPV/DB

• Human Factors • FONSI	
Advisory Committee Summary	Advisory Committee Meeting June 9, 2022

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1. Introduction

On October 18, 2021, bluebird bio, Inc. submitted an original Biologics License Application (BLA), STN BL 125755, for licensure of elivaldogene autotemcel (eli-cel) with the proprietary name of SKYSONA. SKYSONA is an autologous hematopoietic stem cell-based gene therapy. The Applicant proposed the indication, "for the treatment of patients less than 18 years of age with early cerebral adrenoleukodystrophy (CALD) who do not have an available and willing human leukocyte antigen (HLA)-matched sibling hematopoietic stem cell (HSC) donor." Currently, there are no FDA-approved treatments for CALD, but allogeneic hematopoietic stem cell transplant (allo-HSCT) is the standard of care for boys with early, active CALD.[12,26] As allo-HSCT is associated with significant morbidity and mortality, particularly when a suitable HLA- matched donor cannot be found, there is a substantial unmet medical need for patients with CALD.

SKYSONA consists of an autologous CD34+ cell-enriched population, that contains the patient's own hematopoietic stem cells (HSCs), transduced ex vivo with the Lenti-D lentiviral vector (LVV) containing the ATP-binding cassette, sub-family D, member 1 (*ABCD1)* gene encoding the adrenoleukodystrophy protein (ALDP). SKYSONA is supplied frozen in 20 mL fluoro-ethylene-propylene bags as a suspension for intravenous infusion. Each bag contains between 4×10^6 and 30×10^6 cells/mL (3.6 to 30×10^6 CD34+ cells/mL), frozen in approximately 20 mL of cryopreservation solution. The minimum dose is 5.0×10^6 CD34+ cells/kg patient weight.

CALD is an X-linked genetic neurodegenerative disease that affects boys. The genetic mutation leads to impaired expression of ALDP and accumulation of very long chain fatty acids (VLCFAs) that initiate an inflammatory cascade ultimately leading to inflammatory cerebral demyelination. [1-3, 15-18] There is heterogeneity in time to symptom onset from initial early MRI changes and rate of neurologic deterioration. In general, the clinical course in childhood is rapid with progressive cognitive and neurologic deficits leading to major disability including cortical blindness, incontinence, requirement for tube feeding, loss of communication, loss of ambulation, and loss of voluntary movement and ultimately premature death. The literature describes that approximately 30-50% of untreated boys with CALD die within 5 years of diagnosis, and nearly all survivors have severe neurologic dysfunction or disability. [4-6,11,25,31]

In the SKYSONA clinical trials, patients underwent hematopoietic cell mobilization and apheresis followed by full myeloablative and lymphodepleting conditioning. Granulocyte colony stimulating factor (G-CSF) and, in most patients, plerixafor, were used for mobilization, followed by apheresis to harvest the cells. The collected cells were shipped to the manufacturing site where CD34+ cells were selected and then transduced with Lenti-D LVV to manufacture SKYSONA. After return of the transduced cells to the treatment site, subjects underwent conditioning with busulfan for myeloablation and cyclophosphamide or fludarabine for lymphodepletion. SKYSONA was subsequently infused to reconstitute the hematopoietic system with cells containing the integrated *ABCD1* gene that produces functional ALDP.

This document summarizes the basis for accelerated approval of SKYSONA based on an intermediate clinical endpoint reasonably likely to predict benefit. Consistent with 21 USC 355, substantial evidence of effectiveness for SKYSONA for this rare disease with unmet need is based on a single adequate and well controlled investigation with confirmatory evidence. Specifically, we considered pooled data from 2 single-arm, open-label clinical studies, ALD-102 and ALD-104, compared to external controls to comprise a single adequate and well controlled investigation. Studies ALD-102 and ALD-104 enrolled subjects ages 4-17 years of age with early, active CALD, defined by a Neurologic Function Score (NFS) ≤1 and brain magnetic resonance imaging (MRI) with gadolinium enhancement (GdE+) and a Loes Score 0.5-9. Most subjects (58/61, 95%) were asymptomatic at baseline. The external control for the primary efficacy analysis was an untreated natural history population with early, active disease from Study ALD-101, an historical, retrospective study that included untreated CALD subjects. The recommendation for accelerated approval is based primarily on a Kaplan-Meier (KM) time to event analysis in a symptomatic subset of SKYSONA-treated subjects and similar untreated controls. SKYSONA slows the progression of neurologic dysfunction (NFS ≥ 1) assessed by major functional disabilities (MFDs) or death at 24 months from time of symptom onset compared to an untreated natural history population.

The additional confirmatory evidence of efficacy consists of:

1) Trends toward delayed symptom onset in a small number (n=5) of SKYSONA-treated subjects based on disease modeling;
2) Resolution of gadolinium enhancement on brain MRI (i.e., GdE-) at Month 24 following treatment in the majority (33/36, 92%) of SKYSONA-treated subjects;
3) Pharmacodynamic response data for the number of CD14+ %ALDP+ cells (the functional cells) at Month 6 following treatment which showed differences between subjects who did and did not experience an MFD, death or receive rescue allo-HSCT by Month 24 following treatment.
4) Nonclinical data that support a pharmacologic effect on VLCFA metabolism.

The most important risk of treatment with SKYSONA is insertional oncogenesis. Three subjects in the SKYSONA clinical trials developed hematologic malignancy. The first two cases of hematologic malignancy were diagnosed approximately 1 and 2 years after treatment with SKYSONA, before these patients may have experienced any clinical benefit from the SKYSONA. The third case of hematologic malignancy occurred approximately 7.5 years after treatment with SKYSONA and occurred in the first subject to have been treated with SKYSONA, who therefore had the longest timeframe for observation for development of malignancy. The incidence of hematologic malignancy after treatment with SKYSONA is uncertain because of the short period of follow-up for many of the subjects, with 99% of treated subjects having less than 7.5 years of follow-up data. There is concern that additional patients may be diagnosed with hematologic malignancy given that every boy treated with SKYSONA has integration into *MECOM*, the proto-oncogene that appears to be the driver of two of the three cases of hematologic malignancy. Furthermore, many boys treated with SKYSONA have evidence of an expanding clone, including at least four who also are known to have bone marrow dysplasia.

Although the primary evidence of effectiveness is based on a subset of subjects who had mild symptoms, the clinical review team believes it is reasonable to extrapolate efficacy to asymptomatic (i.e., NFS=0) early, active CALD (brain MRI with Loes score 0.5-9 and presence of gadolinium enhancement) in boys 4-17 years of age due to the disease pathophysiology being the same. There are clinical data from patients treated with allo-HSCT to suggest that early replacement of functional ALDP offers increased clinical benefit.[8,13,14,26] Additionally, there is evidence from Studies ALD-102 and ALD-104 of decreased brain inflammation detected by resolution of gadolinium enhancement on brain MRI at Month 24 in 33/36 (92%) of the entire early, active CALD study population treated with SKYSONA who had 24-month MRI data following treatment, indicating that SKYSONA could be favorably altering the disease course for boys with asymptomatic and symptomatic early, active CALD.[11]

Despite this extrapolation of efficacy to the asymptomatic early, active CALD population, there are two populations for whom there is greater uncertainty regarding a favorable benefit-risk determination given the uncertainty of durability of effect and the magnitude of hematologic malignancy risk. Specifically, boys with isolated pyramidal tract pattern of disease on brain MRI and asymptomatic boys with very early radiographic findings (i.e., Loes score 1-2). Boys with the isolated pyramidal tract MRI pattern are known to have a slower progression of radiographic and clinical disease, typically with stable Loes score over time and prolonged duration between radiographic diagnosis and the onset of symptomatic disease (usually adulthood).[10] Boys with very early radiographic and asymptomatic disease are poorly represented in the natural history of disease due to frequent delayed diagnosis at the time the natural history subjects were diagnosed, and thus the time course of expected clinical progression of disease is relatively unknown. Therefore, relative long-term efficacy and benefit-risk assessment in these populations with isolated pyramidal tract disease or very early radiographic and asymptomatic disease could only be determined with a longer duration of follow-up. Because 45 of 61 (74%) of subjects treated with SKYSONA had a baseline Loes score of 1-2 and/or isolated pyramidal tract disease, the magnitude of uncertainty regarding the long-term efficacy of SKYSONA is high in the greater population of boys who are diagnosed and treated for CALD.

The review team recommends accelerated approval of this BLA with three Clinical Post-Marketing Requirements (PMRs). Two Clinical PMRs are to provide confirmatory evidence to demonstrate the long-term efficacy of SKYSONA in boys with early, active CALD through assessments of efficacy outcomes including MFDs, death and NFS changes. One PMR will follow subjects treated in Studies ALD-102 and ALD-104 for at least 10 years and the other PMR will enroll and treat an additional 24 boys with more advanced early, active CALD and assess event-free survival over 5 years. The final Clinical PMR will be a clinical safety study designed to characterize the risk of hematologic malignancy, including incidence, risk factors, prognosis, and outcomes. Insertional oncogenesis through regularly scheduled assessments (combined blood count and integration site analysis) and for-cause bone marrow evaluations will be monitored. Chemistry, Manufacturing, and Control (CMC) Post-marketing Commitments (PMCs) are recommended for lot release assay robustness, drug product sampling, drug product in-use stability, product contact material leachable/extractable evaluation, and

additional final container closure testing as well as PMRs for final product container closure leachable/extractable testing.

2. Background

CALD is a rare neurodegenerative metabolic disorder caused by X-linked mutations in *ABCD1* that lead to impaired peroxisomal expression of ALDP needed to transport VLCFAs into the peroxisome for degradation.[1-3, 15-18] The estimated U.S. prevalence is at most 800 boys based on actuarial estimates from Mosser, 1993 and Moser, 2000.[17,4] The accumulation of VLCFAs are believed to primarily affect the adrenal cortex through direct toxicity and affect the brain white matter by causing perivascular accumulation of cytotoxic T lymphocytes and expression of pro-inflammatory cytokines and chemokines that result in progressive inflammatory demyelination.[3, 19-21] The most concerning symptoms of CALD are neurologic disability and premature death. The disease course is heterogenous and marked by variable rates of progression depending on location, extent of contrast enhancement of lesions on brain magnetic resonance imaging (MRI), age at presentation, and extent of neurologic and neurocognitive symptoms.[4-14] Boys typically present with academic difficulties, inattention or hyperactivity between 4-10 years of age.[4-7] Left untreated, the disease progresses to neurologic dysfunction, disability and ultimately death, usually by the second decade of life from complications of disease.

The NFS, a 25-point composite scale that focuses on 15 domains of neurologic function, is traditionally used to evaluate the clinical status of CALD patients.[4,8] A score of 0 indicates absence of clinical signs of cerebral disease (i.e., asymptomatic), and higher scores correspond to increasing severity of neurological dysfunction. The MFDs as defined in this BLA are a subset of the NFS that most significantly impact daily function. The six MFDs are (1) loss of communication, (2) cortical blindness, (3) requirement for tube feeding, (4) total incontinence, (5) wheelchair dependence, or (6) complete loss of voluntary movement.

Approximately 40% of patients with X-linked adrenoleukodystrophy develop CALD. The diagnosis is made once there is evidence of cerebral demyelination on brain MRI. Lesions are graded according to a Loes score,[9] which assigns a severity score (0-34) based on location and extent of demyelination, as well as presence/ absence of focal and/or global atrophy. A score of 0 indicates a normal MRI (i.e., no cerebral disease), and higher scores indicate increased severity of cerebral lesions.

Patterns of cerebral disease with prognostic implications have been identified,[10] and are as follows:

- Pattern 1: Parieto-occipital white matter
- Pattern 2: Frontal white matter
- Pattern 3: Isolated pyramidal tract
- Pattern 4: Cerebellar white matter
- Pattern 5: Concomitant parieto-occipital and frontal white matter
- Other: Any pattern other than those characterized by patterns 1-5

It was found by Dr. Loes that MRI patterns appear to predict age of presentation, where patients with patterns 1 or 5 disease typically presenting in childhood, with patterns 2 or

4 disease presenting in adolescence, and with isolated pyramidal tract (pattern 3) disease presenting in adulthood.[10] Patients with pattern 1 or 2 disease experience rapid disease progression if the pattern is present at an early age, particularly if gadolinium enhancement is present. Disease progression is generally slower in patients with pattern 3 or 4 disease. Pattern 5 disease is uncommon and is associated with much more rapid progression than other patterns. Additional literature reports the observation that disease is more likely to progress and/or be more rapidly progressive to neurologic dysfunction, disability and death if patients present in childhood with a greater degree of cerebral involvement (i.e., greater Loes scores) and gadolinium enhancement on brain MRI.[4,11,13,14] Gadolinium enhancement on brain MRI has been associated with breakdown of the blood-brain barrier and is thought to represent progressive and active inflammatory demyelination associated with increased risk of rapid disease progression.[11]

There are no FDA-approved treatments for CALD in the United States (US). Allo-HSCT[12] has been the standard of care since approximately 2001 and is the only therapy considered by experts to be disease- modifying, i.e., able to slow or stabilize disease progression.[8,13, 24,26] Retrospective studies have documented more favorable neurologic outcomes when allo-HSCT is performed early in the course of disease, prior to onset of significant neurologic dysfunction or radiographic disease burden.[8,13,14] It has also been observed that allo-HSCT may increase rapidity of disease progression in patients with advanced cerebral disease (Loes score >9), and is no longer recommended for patients who meet this criterion.[8,13,14,] As such, allo-HSCT is performed in the early, active radiographic course of disease (Loes score 0.5-9 with gadolinium enhancement on brain MRI), which often corresponds to a time when patients are asymptomatic or mildly symptomatic (NFS 0 or 1). The goal of treatment in this early, active phase of disease is to treat prior to the onset of significant neurologic dysfunction in an effort to prevent progression to disability and death, which is often rapid and more difficult to stabilize once disease is symptomatic.

Most studies that have demonstrated efficacy of allo-HSCT have assessed MRI and neurocognitive changes and/or progression to disability and death following treatment as compared to the natural history of disease. With increasing identification of X-ALD cases due to newborn screening and genetic testing of family members of affected individuals, routine MRI screening now allows for diagnosis of CALD at some of the earliest stages of cerebral disease, often prior to onset of neurologic dysfunction or neurocognitive changes.[7, 28-30] There is lack of an appropriate natural history (i.e., untreated) population that has been followed from such an early stage of disease to understand the clinical course of asymptomatic early, active cerebral disease if left untreated. Therefore, the long-term efficacy of allo-HSCT as compared to the natural history of disease in the earliest asymptomatic disease stages with minimal radiographic cerebral disease burden is unknown. Additionally, because studies have demonstrated that radiographic and clinical disease progression may occur in the initial 12-24 months following treatment with allo-HSCT before disease stabilization is achieved, allo-HSCT is now routinely performed without delay upon diagnosis of CALD in an effort to prevent neurologic dysfunction, disability and death.[8,9,12-14] Few (if any) patients are expected to go untreated upon diagnosis of CALD unless disease is already advanced, and as a result

there likely will never be an appropriate untreated comparator with very early asymptomatic disease.

The preferred allo-HSCT donor is a HLA-matched unaffected sibling, but these HLA-matched sibling donors are only available for ≤ 30% of patients.[8] Allo-HSCT is associated with known risks, including graft rejection, graft versus host disease, and infection, and these risks are believed to be increased with alternative (HLA- mismatched or non-sibling HLA- matched) donors. Morbidity and mortality following allo-HSCT are significant, with 5-year survival varying between 50-95%, depending on donor type, conditioning regimens and stage of disease at time of treatment, with percentages reflecting death from disease progression and transplant-related causes.[13,14] SKYSONA is a novel one-time autologous gene therapy product intended to slow or stabilize disease progression in CALD. By virtue of its autologous nature, it is designed to mitigate risks observed with allogeneic HSCT, thereby addressing an unmet need for patients with this disease.

Product Description

SKYSONA is a biological product containing genetically modified autologous HSCs transduced with Lenti-D LVV encoding ALDP. Following engraftment into the bone marrow, transduced HSCs differentiate into various cell types, including monocytes, that are capable of producing functional ALDP. The functional ALDP can then locally degrade very long chain fatty acids (VLCFAs), which is thought to slow and possibly prevent further inflammation and demyelination.

The regulatory history of SKYSONA is outlined in Table 1.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Pre-IND meeting	September 3, 2010
2. IND submission	March 27, 2013
3. Orphan Drug designation granted (DRU-2012-3682)	April 19, 2012
4. Breakthrough Therapy designation granted	May 21, 2018
5. Pre-BLA meeting	June 21, 2021
6. Rare Pediatric Disease designation granted (#RPD-2016-79)	August 9, 2017
7. BLA 125755/0 submission	October 18, 2021
8. BLA filed	December 17, 2021
9. Mid-Cycle communication	March 8, 2022
10. Late-Cycle meeting	May 31, 2022
11. Major Amendment	January 13, 2022
12. Advisory Committee Meeting	June 9, 2022
13. Action Due Date	September 16, 2022

3. Chemistry Manufacturing and Controls (CMC)

This BLA includes an adequate description of the manufacturing process and characterization of SKYSONA. The CMC review team concludes that the manufacturing process, along with associated test methods and control measures, is capable of yielding a product with consistent quality characteristics.

a. Product Quality

Manufacturing Summary

To manufacture SKYSONA, autologous hematopoietic progenitor cells obtained by apheresis (HPC-A) are collected from each patient at a Qualified Treatment Center (QTC). The apheresis material is shipped to Lonza-Houston, Inc. (Houston, TX) for drug substance/drug product manufacturing. CD34+ cells are selected using the (b) (4) (b) (4). Briefly, the HPC-A are enriched for cells expressing CD34 by (b) (4) The enriched CD34+ cells are then prepared for transduction (b) (4), enriched CD34+ cells are (b) (4) in the presence of Lenti-D LVV, (b) (4) and growth factors, (b) (4) to transduce the cells. After transduction, the cells are washed (b) (4). The washed transduced cells, (b) (4) (b) (4) To produce the SKYSONA drug product, the drug substance is formulated in (b) (4) cryopreservation solution containing 5% dimethyl sulfoxide (DMSO). The formulated drug product is filled into one or two 20 mL fluoro-ethylene-propylene bags, depending on the number of cells produced. Bags are placed in metal cassettes and cryopreserved at (b) (4) in vapor-phase liquid nitrogen until lot release testing is complete. Once released, SKYSONA is shipped in a vapor-phase liquid nitrogen dry shipper to the QTC for administration back to the same patient.

The Lenti-D LVV is a nonreplicating, self-inactivated lentivirus, based on HIV-1, pseudotyped with the Vesicular Stomatitis Virus glycoprotein (VSV-G). The LVV is manufactured at a contract manufacturing facility via transient transfection of HEK293T cells. A third-generation vector design is utilized in which the necessary viral genes are expressed from four separate plasmids to minimize the risk of generating replication-competent lentivirus. The packaged genomic viral RNA encodes no viral genes and contains less than 25% of the HIV-1 genome. The Lenti-D LVV harvest is purified, (b) (4), formulated, and sterile (b) (4) before being filled into (b) (4) vials and stored at ≤-65°C until required for use in SKYSONA manufacturing.

Manufacturing Control Strategy

The SKYSONA manufacturing control strategy consists of 1) raw material and reagent qualification programs, 2) in-process monitoring, 3) in-process control testing, and 4) lot release and stability testing, (5) manufacturing process validation and continuous process verification, and (6) traceability through chain of identity and chain of custody (COI/COC). The raw material and reagent qualification program consists of source

material risk assessment, vendor qualification, confirmation of the certificate of analysis and material testing. Raw materials derived from animals and humans are controlled to ensure the absence of microbial contaminants and adventitious agents. The manufacturing process has been adequately validated using a combination of healthy donor and patient-derived starting material. Critical process parameters are established for unit operations based on process characterization and risk assessment studies. In-process monitoring and controls are implemented throughout the process to support process consistency. The manufacturing process validation demonstrated removal of process-related impurities, including residuals associated with (b) (4) manufacturing. The Lenti-D LVV manufacturing process was also validated. Additional validation studies, including aseptic process simulation and shipping validation studies were also performed. Lot release test methods are suitably validated or verified, except for robustness studies for some tests, which will be resolved through a PMC. SKYSONA specifications are adequate to ensure product quality and consistency with drug product used in the clinical study. Additional testing of the final filled drug product is also being implemented through a PMC. Manufacturing and testing comply with Current Good Manufacturing Practices. COI/COC are established at the time of apheresis collection and maintained throughout the manufacturing process to administration by conducting label checks at specified times throughout the process to ensure that the patient receives the correct autologous lot.

Comparability Assessments

During the review of the BLA, comparability of products which were manufactured at different manufacturing facilities was assessed to enable pooling of clinical data. Four manufacturing facilities were utilized to manufacture SKYSONA for the ALD-102 and ALD-104 studies; LHI-PL (commercial site), LHI-(b) (4) (reference site), (b) (4), and (b) (4) . Comparability evaluation of (b) (4) was not possible because the methods used to release products manufactured at (b) (4) were not shown to be comparable to the commercial methods. The comparability assessment that was provided in the initial BLA was incomplete and the acceptance criteria were not adequately justified. During the review period, the Applicant provided a supplemental comparability analysis, with consideration of FDA comments. The supplemental comparability analysis demonstrated equivalence for the majority of the SKYSONA critical quality attributes (CQAs), the exceptions being (b) (4) for products manufactured at (b) (4) and LHI-PL and (b) (4) for products manufactured at LHI-PL, relative to products manufactured at the LHI-(b) (4) reference site. However, FDA determined that the observed differences were not biologically or clinically significant, and the clinical product manufactured with the commercial process was considered comparable across LHI-(b) (4), LHI-PL, and (b) (4)

Manufacturing Risks, Potential Safety Concerns, and Management

Product mix-up

SKYSONA is an autologous product manufactured in a multiproduct manufacturing facility; as such, product mix-ups, either of autologous lots or with other stem cell products manufactured at the same facility, would result in potential risks. The COI/COC ensures that the patient receives their autologous lot. COI/COC is established at the point of apheresis collection, checkpoints are indicated throughout the manufacturing process, and patient identifiers are confirmed prior to administration. The COI/COC is

maintained through integrated computer-based programs with human-readable identifiers present on all labels as well. Additionally, (b) (4) manufactured in a production suite at any given time. Prior to transduction, the vector label is confirmed to ensure the correct LVV is used. Lot release testing also confirms product identity and ALDP activity.

Replication Competent Lentivirus (RCL)
RCL is a theoretical concern for the SKYSONA manufacturing process. The likelihood of RCL generation is reduced by the Lenti-D LVV design: (1) the genetic elements are separated across 5 plasmids requiring multiple recombination events to form RCL; (2) HIV-1 accessory genes have been removed from the packaging plasmids and therefore any resulting recombinant would lack sequences necessary for viral replication; (3) *gag/pol*, *rev*, and *VSV-G* genes are not packaged into the Lenti-D LVV. The final Lenti-D LVV and production cells are tested for RCL by co-culture in accordance with current FDA guidance prior to release and use in the SKYSONA manufacturing process. To date, no RCL has been detected in clinical trial lots of either the Lenti-D LVV or transduced cell product.

Insertional Mutagenesis
LVV integration poses a risk for insertional mutagenesis. Activation of proto-oncogenes or disruption of tumor suppressor genes has the potential to cause secondary malignancies. To mitigate the risk of insertional mutagenesis, the vector used for SKYSONA manufacturing was designed to remove any known viral enhancer elements (self-inactivating design). Despite this mitigation strategy, multiple incidences of insertional mutagenesis were observed in the ALD-102 and ALD-104 studies indicating that there is a risk of insertional mutagenesis resulting in a hematological malignancy (MDS) with SKYSONA. The magnitude of risk for MDS is unknown. MDS has been observed at several years after treatment, for example, one of the three subjects who developed MDS, did so 7.5 years after treatment. Most of the subjects treated to date with SKYSONA (66/67, 99%) have been followed for < 7.5 years. For a more comprehensive discussion of insertional mutagenesis, please see section 7.

CMC PMR/PMCs
The following issues were identified but could not be resolved during the review cycle. These issues will be resolved through PMRs/PMCs by March 30, 2024.

Several unresolved issues were present for the final container (b) (4) which is not an approved or cleared cryopreservation bag. To resolve these issues bluebird bio committed to perform (b) (4) testing and (b) (4) testing on the (b) (4) bag to ensure bag integrity in PMCs. Due to potential safety concerns, bluebird bio will also perform additional testing to support the extractable data provided during the review and leachable testing on the final container as PMRs.

Several issues with drug product lot release testing submitted in the BLA also could not be resolved. These included a lack of robustness assessments for multiple assays, such as (b) (4) assays. Additionally, some samples for SKYSONA lot release testing were taken from the drug substance and not the drug product. bluebird

bio committed to add additional drug product sampling for the following tests: (b) (4)

bluebird bio also committed to revise the (b) (4) testing plan.

Additional PMCs include supplemental in-use stability data for the drug product and feasibility of a leachable study on the (b) (4).

b. Testing Specifications

The final SKYSONA lot release specifications are shown in Table 2.

Table 2: Final Commercial SKYSONA Release Specifications

Quality Attribute	Test	Method	Acceptance Criteria
Potency and Strength	Vector Copy Number (VCN)	(b) (4) qPCR	(b) (4)
	% LVV+ Cells	(b) (4)	(b) (4)
	(b) (4)		
	(b) (4)		
	(b) (4)	(b) (4)	(b) (4)
	%ALDP+ Cells	(b) (4)	(b) (4)
Identity	CD34+ Cell Identity	(b) (4)	
Purity and Content	(b) (4)		(b) (4)
	(b) (4)		(b) (4)
	Total Cell Concentration	(b) (4)	4 to 30 x 10^6 total cells/mL
	(b) (4)		(b) (4)
Safety	Sterility	(b) (4)	No Growth
	Endotoxin	(b) (4)	(b) (4)
	(b) (4)	(b) (4)	None Detected
Quality	Appearance	Visual assessment	Colorless to white to red, including shades of white or pink, light yellow, and orange.

SKYSONA lot release analytical methods and their validations and/or verifications were found to be adequate for their intended use except for outstanding assay robustness studies for the following methods: (b) (4) assays and the outstanding issue for (b) (4) testing of the drug product. The Applicant has provided written commitments to resolve these issues as PMCs.

Impurity Profile
The active ingredient in SKYSONA is viable Lenti-D LVV-transduced CD34+ cells. Impurities in SKYSONA can be divided into product-related impurities (b) (4) and process-related impurities (residuals derived from (b) (4) not intended to be in the final product). Impurities were evaluated during SKYSONA process characterization and process validation. The level of all evaluated impurities in SKYSONA was acceptable and the calculated possible impurity per dose was below the maximum permissible single exposure level outlined in literature, as applicable.

Stability
Long-term stability studies have been completed and support a SKYSONA shelf life of 9 months when stored at ≤ -140°C in vapor phase of liquid nitrogen. The stability studies utilized SKYSONA manufactured at-scale from normal healthy donor starting material. Accelerated and stress studies were also performed. In-use stability testing supported a post-thaw expiry of 4 hours.

The shelf life of (b) (4) was supported for Lenti-D LVV when stored at ≤-65°C.

c. CBER Lot Release

An exemption has been granted from CBER Lot Release testing, including no requirement for submission of product samples to CBER. The basis for this decision is that SKYSONA is an autologous product; as such each lot will treat a single patient. Failure of a single lot will have minimal potential impact on public health.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. Inspection histories and activities for facilities involved in the manufacture of SKYSONA are summarized below.

Manufacturing Facilities for SKYSONA

Name/Address	FEI Number	Waiver or Inspection	Justification and Results
(b) (4) *drug substance critical intermediate, BB305 LVV, manufacturing and testing*	(b) (4)	Waived	ORA (b) (4) VAI
Lonza Houston, Inc. 14905 Kirby Drive Houston, TX 77047 USA *beti-cel drug substance and drug product manufacturing and testing*	3013629214	PLI	CBER February 14 -18, 2022 NAI
(b) (4) *Drug product release testing*	(b) (4)	Waiver	ORA (b) (4) VAI
(b) (4) *Drug product release testing*	(b) (4)	Waiver	ORA (b) (4) VAI
(b) (4) *Drug product release testing*	(b) (4)	Waiver	ORA (b) (4) VAI
(b) (4) *Drug product release testing*	(b) (4)	Waiver	ORA (b) (4) NAI

Name/Address	FEI Number	Waiver or Inspection	Justification and Results
(b) (4) *Drug product release testing*	(b) (4)	Waiver	ORA (b) (4) VAI

CBER conducted a pre-license inspection (PLI) of the Lonza Houston, Inc. facility in February 2022. No FDA Form 483 was issued, and the inspection was classified as No Action Indicated (NAI).

Office of Regulatory Affairs (ORA) performed a surveillance inspection of (b) (4) All 483 issues were resolved, and the inspection was classified as voluntary action indicated (VAI).

ORA performed a surveillance inspection of (b) (4). All 483 issues were resolved, and the inspection was classified as VAI.

ORA performed a surveillance inspection of (b) (4) All 483 issues were resolved, and the inspection was classified as VAI.

ORA performed a surveillance inspection of (b) (4). All 483 issues were resolved, and the inspection was classified as VAI.

ORA performed a surveillance inspection of (b) (4). No Form FDA 483 was issued, and the inspection was classified as NAI.

ORA performed a surveillance inspection of (b) (4). All 483 issues were resolved, and the inspection was classified as VAI.

e. Container/Closure System

The container closure system (CCS) for SKYSONA consists of a primary package container (a 20 mL (b) (4) Cryopreservation bag), a secondary package container (a (b) (4) Overwrap bag), and a tertiary metal package container (cryocassette). SKYSONA is filled into (b) (4) bag(s) (e.g., 1 bag for 20 mL DP, or 2 bags for 40 mL DP). The (b) (4) bag is sterile and read-to-use (RTU, manufactured by (b) (4)). The product transfer tubing and sample tubing are sealed by (b) (4). Following visual inspection, a product label is applied to the bag, and the product bag is placed inside of a sterile RTU (b) (4) Overwrap (manufactured by (b) (4)). The overwrap bag is (b) (4). The product bag is inserted into a metal cassette that has been labeled with a label containing both product and patient information. The container-closure integrity (CCI) was tested using (b) (4) method by (b) (4) to determine the primary package container is able to maintain the container integrity under normal use, storage and transportation conditions.

The BLA was missing information about the (b) (4) Cryopreservation bag, which resulted in several PMCs and two PMRs.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31(c). This request and supporting information provided by bluebird bio are acceptable to conclude that SKYSONA poses a negligible risk to the environment or to the general public. There are no significant environmental or public health impacts posed by the product or its manufacturing. Data provided in the BLA indicates that the potential for recombination of the LVV into a replication competent form is low. The potential for SKYSONA to persist in the environment is negligible because these cells have stringent nutritional requirements for survival and therefore are not viable in the environment. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

In vitro pharmacology studies were conducted with healthy human donor CD34+ HSCs, CD34+ HSCs obtained from patients with adrenomyeloneuropathy (AMN), and ALDP-deficient fibroblasts obtained from patients with CALD, transduced using the Lenti-D vector used in eli-cel. These studies demonstrated that vector-driven *ABCD1* transgene expression and ALDP production resulted in improvements in very-long-chain fatty acid metabolism in CALD fibroblasts and AMN patient CD34+ HSCs. In vivo assessment of Lenti-D-transduced healthy donor derived CD34+ HSCs transplanted in myeloablated immunodeficient mice demonstrated bone marrow and brain engraftment that was associated with stable *ABCD1* transgene expression and ALDP production for the 3-month study duration.

A 92-day GLP toxicology study in myeloablated (b) (4) mice evaluated a single administration of $1x10^6$ Lenti-D transduced healthy human CD34+ HSCs/mouse. There were early mortalities in both the test article (Lenti-D transduced CD34+ HSCs) and control (non-transduced CD34+ HSCs) groups. Although the cause of death was undetermined, the early mortalities occurred at a higher frequency in the control group and human cell engraftment was confirmed in both groups. No other test article related toxicities were observed in this study. Although a true no observed adverse effect level (NOAEL) could not be determined, the dose level administered in this study, approximately $5x10^7$ CD34+ cells/kg, represents the maximum feasible dose and a10-fold multiple of the minimum recommended dose level for patients with CALD (≥$5x10^6$ CD34+ cells/kg).

Traditional carcinogenicity studies were not conducted for eli-cel and were not warranted. However, integration site analysis was performed on Lenti-D transduced pre-transplant human CD34+ HSCs and post-transplant engrafted bone marrow cells (BMCs) from animals in the GLP toxicology study harvested at 29 and 92 days. Lenti-D transduced HSCs demonstrated the expected integration profile for self-inactivating lentiviral vectors, with preferred integration in gene-coding regions across the whole genome, no preference for integration in transcriptional start sites, and no bias for the 5'

or 3' end of genes. There were no notable differences between the pre- and post-transplant samples.

An in vitro immortalization assay was conducted with mouse lineage-depleted (hematopoietic non-lineage committed; Lin-) BMCs (the murine equivalent of human CD34+ HSCs) transduced with Lenti-D. There was a reduced potential for immortalization induced by insertional mutagenesis of the clinical vector, Lenti-D, compared to positive control vectors.

Reproductive and developmental toxicity studies were not performed for eli-cel which is acceptable based on the product characteristics and safety profile.

5. Clinical Pharmacology

The clinical pharmacology review team's recommendation for approval of SKYSONA (eli-cel) is based on review of data from clinical studies, Studies ALD-102 (Phase 2/3) and ALD-104 (Phase 3, ongoing), and a long-term follow-up study, Study LTF-304 (ongoing).

Key clinical pharmacology findings are summarized below:

General Pharmacodynamics

- One month after infusion of SKYSONA, lentiviral vector copy was detected in peripheral blood leukocytes (PB VCN) and CD14+ cells (CD14+ VCN), demonstrating the early presence of transduced cells. Levels of PB VCN and CD14+ VCN stabilized by Month 6. Subjects had a Month 6 median (min, max) PB VCN level of 0.38 (0.07, 2.23) c/dg in Study ALD-102 (N=25) and 1.04 (0.03, 3.13) c/dg in Study ALD-104 (N=32). Median CD14+ VCN levels at Month 6 were 0.61 (0.07, 3.96) c/dg (N=29) and 1.41 (0.04, 3.82) c/dg (N=28), for Studies ALD-102 and ALD-104 respectively. VCN levels in peripheral blood and CD14+ cells generally remained stable as of the data cut-off date, although high inter-subject variability of PB VCN and CD14+ VCN kinetic profiles was observed.
- All subjects who received SKYSONA with at least 1 month of follow-up produced ALDP in peripheral blood leukocytes and $CD14^+$ cells, demonstrating early expression of the transgene. The %ALDP+ cell counts stabilized at 6 months after SKYSONA infusion. Subjects had a Month 6 median (min, max) %ALDP+ $CD14^+$ cell count of 16% (2%, 71%) in Study ALD-102 (N=23) and 26% (2%, 86%) in Study ALD-104 (N=25) respectively. The %ALDP+ $CD14^+$ cells generally remained stable through Month 24 with a median (min, max) of 15% (6%, 45%) in Study ALD-102 (N=23) and 28% (2%, 40%) in Study ALD-104 (N=11). As of the data cut-off date of January 07, 2022, ALDP expression in CD14+ cells was detected in 3 of 7 subjects who had the last follow-up through Month 60 in Study ALD-102 (N=7), indicating long-term expression of transgenic ALDP in the progeny of hematopoietic stem cells.
- Subjects with higher PB VCNs generally had higher PB %ALDP+ cells at a given timepoint. There was a positive linear relationship between PB VCN and PB %ALDP+ cells at Month 6.
- ALDP is a peroxisomal membrane protein involved in the transport and metabolism of very long-chain fatty acids (VLCFA). VLFCA levels in fasting serum were variable in

study subjects treated with SKYSONA. There was a decrease in VLCFAs based on decreased median values of C26:0 LysoPC and C26:0/C22:0 ratios from baseline to Month 24 post-administration of SKYSONA.

Dosing Characteristics and Responses

- SKYSONA drug product vector copy number (DP VCN) and the percentage of transduced cells in drug product (DP %LVV+ Cells) measure drug product characteristics related to transduction efficiency. There was a positive correlative relationship observed between DP VCN and DP % LVV+ cells: DP %LVV+ Cells shows a linear relationship with DP VCN up to approximately 60% LVV+ Cells, at which point they appear to plateau at higher DP VCNs.
- There was a positive correlation observed DP VCN and PD parameters (PB VCN and PB %ALDP+ cells): subjects with higher DP VCNs generally had higher stable PB VCNs and PB %ALDP+ cells.
- DP %LVV correlated positively with ALDP expression in both peripheral blood leukocytes and CD14+ cells.
- The median (min, max) of SKYSONA DP VCN in subjects with 24 months follow up period after infusion of SKYSONA was 1.3 (0.5, 3.1) c/dg. The DP VCN values in subjects who experienced an MFD or received allo-HSCT due to disease progression by Month 24 after eli-cel infusion were no more than 1.20 c/dg (median: 0.85 c/dg, range: 0.5 to 1.2 c/dg). were no more than 1.20 c/dg (median: 0.85 c/dg, range: 0.5 to 1.2 c/dg).
- There was no correlation between the total cell dose of SKYSONA and engraftment (neutrophil and platelet).

Pharmacodynamic Responses and Clinical Outcomes

- PD responses and Disease Progression Events: Compared to subjects who did not experience disease progression events (MFD or allo-HSCT for disease progression) at Month 24 after eli-cel infusion, the median levels of the following PD parameters were substantially lower in subjects who developed MFD or underwent allo-HSCT due to disease progression: PB VCN at Month 6; 24-month exposure of PB VCN and CD14+ %ALDP+ Cells at Month 6.
- PD responses and MDS: among subjects with at least 6 months of follow up, the median levels of PB VCN at Month 6 and maximum PB VCN during the observation period were substantially higher in subjects diagnosed with MDS (N=3), compared to subjects who did not have MDS (N=62). All three subjects diagnosed with MDS had maximum PB VCN levels more than 2.0 c/dg (median (range): 3.13 (2.15, 4.82)). The median (min, max) value of maximum PB VCN was 0.96 (0.11, 3.40) c/dg in subjects who did not have MDS, although there were subjects without MDS who had PB VCN levels greater than 2.0 c/dg.

6. Clinical/Statistical

a. Clinical Program

To support licensure of SKYSONA, bluebird bio, Inc. submitted data from one completed Phase 2/3 study, one ongoing Phase 3 study, and one ongoing long-term follow-up study. The clinical review team's recommendation for accelerated approval of SKYSONA

is based on review of a single adequate and well-controlled trial consisting of pooled efficacy data from 61 subjects treated with SKYSONA in the Phase 2/3 study, ALD-102, and the Phase 3 study, ALD-104 as compared to an external control of untreated early, active disease CALD patients (n=7) from the retrospective natural history study, ALD-101. In addition to the 61 subjects evaluated for efficacy of SKYSONA, the safety database included an additional six subjects that were the earliest treated subjects from ALD-102. Comparability to the to-be-marketed product was not demonstrated for the product administered to these six subjects, and thus their clinical outcome data were excluded from the efficacy analysis.

Studies ALD-102 and ALD-104 are open-label, multicenter, single-arm studies evaluating the efficacy and safety of SKYSONA at a dose of ≥ 5 x 10^6 CD34+ cells/kg in boys with early, active CALD. Early, active CALD is defined by NFS ≤ 1, Loes score between 0.5 and 9, and presence of GdE+ on brain MRI. The studies had the same open label design, eligibility criteria and assessment schedule and were conducted in a staggered fashion, with ALD-104 opening for enrollment after ALD-102 was fully enrolled. The studies differ in the mobilization, conditioning, and pre-engraftment medication regimens, but are otherwise similar in the way they were conducted.

The external control data for the assessment of SKYSONA efficacy came from patient medical records of untreated natural history subjects with early, active CALD in a retrospective natural history study, ALD-101.

SKYSONA was additionally compared to 51 subjects with early, active disease who received allo-HSCT as treatment for CALD, subdivided into groups based on donor subtype for purposes of comparing overall survival due to concerns for allo-HSCT-related toxicities. The allo-HSCT population was a pooled group from the retrospective data collection study, ALD-101, and a mixed prospective/retrospective observational study following allo-HSCT, Study ALD-103.

The prespecified primary efficacy endpoint was the number and proportion of subjects in ALD-102 who had none of the 6 MFDs, were alive, did not receive a rescue allo-HSCT or rescue cell administration, and had not withdrawn or been lost to follow-up at Month 24 (i.e., Month 24 MFD-free survival). As none of the study subjects in ALD-104 had reached 24 months of follow-up after treatment with SKYSONA at the time of BLA submission, only ALD-102 subjects were evaluated for the primary efficacy endpoint. The study success criterion was superiority compared to a clinical benchmark of 50%. This benchmark was derived from 2 subpopulations from Study ALD-101. The upper bound of the 95% confidence interval (CI) of Month 24 MFD-free survival for the untreated subpopulation of ALD-101 (the untreated population who had gadolinium-enhancing MRIs and included subjects with early and advanced disease) was 46%. The lower bound of the 95% CI for Month 24 MFD-free survival in the allo-HSCT-treated subpopulation of study ALD-101 with early, active disease was 50%. The 50% benchmark was chosen to demonstrate that SKYSONA was better than no treatment on MFD-free survival at 24 months.

Efficacy Results

Thirty-two subjects with early, active CALD were enrolled in Study ALD-102 and treated with SKYSONA. Data from the 26 subjects who received investigational product deemed comparable to the to-be-marketed product were included in the analysis of the primary efficacy endpoint. All were male and aged between 3 and 13 years at time of consent, and between 4 and 14 years at time of treatment. Of 26 subjects, 31% were White/Caucasian, 38% Hispanic/Latino, 4% Black/African American, 4% Asian, 15% Other race (including mixed races), and 8% did not report race. Twenty-three out of 26 (88%) subjects achieved Month 24 MFD-free survival (95% CI: 70%, 98%). ALD-102 was thus successful on the primary efficacy endpoint.

Although ALD-102 met the success criterion for the primary efficacy endpoint, results were difficult to interpret due to:

1) lack of comparability between the SKYSONA-treated subjects and the populations from ALD-101 that were used to determine the clinical benchmark. Untreated subjects were diagnosed at a time when disease understanding was evolving, contrast was not routinely used for MRI assessments, and delayed diagnosis was common.
2) insufficient length of study to ensure that the results suggesting superiority of treatment (with allo-HSCT or SKYSONA) over lack of treatment were not simply an artifact of early case identification.
3) an imputation strategy that over-estimated the number of failure events (and thus dropped the lower bound of the 95% CI) in the allo-HSCT-treated early, active disease subpopulation from ALD-101.

Given these limitations and because CALD is a rare and devastating disease, the reviewers conducted additional exploratory analyses to assess clinical benefit. The main challenges were that few events (MFDs and deaths) occurred in the allo-HSCT and SKYSONA populations, and subjects treated with allo-HSCT and SKYSONA were generally diagnosed and treated at very early stages of disease. In comparison, event rates were high in the untreated natural history population, but the natural history population was older, with more advanced cerebral disease on MRI, and more likely to present with symptomatic disease at time of diagnosis or shortly after diagnosis. As a result, it was difficult to determine if the lower numbers of MFDs and deaths in the treated populations were due to a treatment effect or due to treatment at an early stage of disease with insufficient duration of follow-up to detect progression to MFD or death. It is unclear what the clinical course would have been in subjects with very early stages of disease had they not been treated. In essence, it was not possible to use all the available efficacy data to compare outcomes following treatment with SKYSONA (and allo-HSCT) to untreated CALD because of the concern for lead-time bias in comparisons of SKYSONA to the natural history of untreated disease.

In an attempt to better understand the natural history of untreated, early active disease, modeling was performed to evaluate the timing of clinical disease progression to MFDs and death from first onset of symptomatic disease. Subpopulations of the natural history, allo-HSCT, and SKYSONA populations who developed 1 or more MFDs during the course of follow-up were evaluated to see if modeling of individual subject progression over time provided insight as to a broader understanding of the time course of

progression and/or demographics or disease features that might predict a more rapid course of progression. Modeling was then extended to evaluate the course of subjects who experienced symptoms (NFS ≥ 1) but had not progressed to MFD or death during the course of follow-up. Finally, the clinical review team asked the Applicant to provide graphical representations of NFS changes over time with individual lines for each subject in the early, active CALD natural history population, allo-HSCT population, and SKYSONA population. These graphics (not shown) demonstrated a rapid trajectory of NFS increase for untreated subjects after first NFS ≥ 1, typically peaking to maximum documented NFS within 24 months. In comparison, lines either stabilized or had a lesser degree of incline for the treated (SKYSONA and allo-HSCT) populations. Although timing of progression from symptomatic disease to disability or death in these early, active disease populations has not specifically been demonstrated in the literature, the literature supports what was seen in the natural history populations that even asymptomatic children with Loes scores >1 and GdE+ on MRI have high rates of progression to neurologic dysfunction, disability and death within 5 years of initial presentation.[4-6,11,25,31] Although the efficacy analysis was complicated by large numbers of SKYSONA- treated subjects who were asymptomatic and with mild cerebral disease (i.e., Loes score 1-2) at time of treatment, this modeling demonstrated a trend of apparent slowing or stabilization of the progression of neurologic dysfunction once disease had become symptomatic in the treated populations (regardless of baseline Loes score) as compared to the natural history of disease.

The review team analyzed datasets to identify a group of patients/ subjects who were expected to already be on a more rapid trajectory of disease progression by virtue of having developed symptomatic disease, based on the modeling just discussed. The strategy was intended to identify a more homogeneous, prognostically enriched subpopulation in the SKYSONA-treated subjects and in the untreated external control population, to allow for an analysis of MFD-free survival (i.e., time to develop an MFD or die) in comparable populations. Allo-HSCT was included in the analysis as an additional comparator to see if similar apparent treatment effects were seen for both SKYSONA and allo-HSCT based on the NFS modeling.

To be included in this analysis, the subjects had to meet the following criteria:

1. meet the criteria for early active disease at time of diagnosis (untreated subjects) or treatment (subjects treated with SKYSONA or allo-HSCT), with the exception that untreated subjects may have a brain MRI with GdE+ at any time during follow-up in the study OR unknown gadolinium status (due to lack of routine use at the time many natural history subjects were diagnosed) with clinical course suggestive of active disease;
2. have had symptomatic disease at some time during the study: either NFS=1 at baseline or development of symptoms (NFS ≥ 1) during the course of follow-up; and
3. have been followed for at least 24 months after onset of symptomatic disease (NFS ≥ 1) or had an MFD or death.

The exploratory MFD-free survival analysis compared subsets of the early active disease natural history population (N=7), allo-HSCT population (N=16), and SKYSONA population (N=11). In this analysis, time zero was date of first NFS ≥1.

The demographics and disease characteristics of these subpopulations are shown in Table 3. Although not identical, these subpopulations have been "homogenized" by selecting subjects/ patients with similar prognostic features. Values for the natural history population are somewhat skewed due to the inclusion of a subject with isolated pyramidal tract disease on brain MRI who was diagnosed later in childhood and did not become symptomatic until approximately 10 years after diagnosis, and the isolated pyramidal tract pattern is described in the literature as being slowly progressive and with typical symptom onset in adulthood.[10] The SKYSONA subpopulation subject who had isolated pyramidal tract disease had an atypical course, with rapidly progressive disease on brain MRI and development of symptoms in childhood, and ultimately died of transplant-related causes following rescue allo-HSCT due to progression of disease. Conservative imputations for time of first NFS ≥1 to an earlier time point in two natural history subjects who presented with first symptoms and MFD at the same time biased against SKYSONA in the analysis.

Although all concerns for lead time bias cannot be eliminated with an enrichment analysis, the confidence in comparability of populations is increased by the fact that the majority of subjects in the natural history and SKYSONA subpopulations were asymptomatic (NFS=0) at baseline, had a total NFS score of 1 at time of first NFS ≥1 and developed symptoms within 24 months of diagnosis (natural history population) or treatment (SKYSONA subpopulation). With these similarities, we can be more confident that any differences between SKYSONA and the natural history populations in the analysis of MFD-free survival are truly treatment effect.

Table 3: Demographics and Disease Characteristics for Symptomatic Subpopulations: SKYSONA, Allo-HSCT, and Natural History

Parameter	SKYSONA (n=11)	Allo-HSCT (n=16)	Natural History (n=7)
Age at CALD Diagnosis; Median (min, max)	6 (1, 10)	7 (2, 13)	9 (5, 15)
Age at Treatment; Median (min, max)	6 (4, 10)	8 (5, 13)	NA
Age at First NFS ≥1; Median (min, max)	7 (4, 10)	8 (5, 14)	10 (5, 17)
Pattern: Parieto-Occipital N (%)	10 (91)	12 (75)	4 (57)
Pattern: Frontal N (%)	0	4 (25)	2 (29)

Parameter	SKYSONA (n=11)	Allo-HSCT (n=16)	Natural History (n=7)
Pattern: Pyramidal Tract N (%)	1 (9)	0	1 (14)
Baseline NFS: 0 N (%)	9 (82)	9 (56)	6 (86)
Baseline NFS: 1 N (%)	2 (18)	7 (44)	1 (14)
NFS Total Score =1 at Time of First NFS ≥1 N (%)	10 (91)	13 (81)	6 (86)
NFS Total Score >1 at Time of First NFS ≥1[a] N(%)	1[a] (9)	3[a] (19)	1[a] (14)
Baseline Loes; Median (min, max)	2.5 (1, 9)	5.8 (1, 9)	5 (2, 9)

Abbrev: allo-HSCT: allogeneic hematopoietic stem cell transplant; CALD: cerebral adrenoleukodystrophy; NFS: Neurologic Function Score; MFD: Major Functional Disability

[a] At time of first NFS ≥1, one SKYSONA subject had a total score of 2, three allo-HSCT subjects had scores of 2,4 and 5, and one natural history subject had a total score of 3.

Source: reviewer analysis of bluebird bio, Inc. BLA 125755 ADSL, ADMRI, and ADEFF3 datasets

Analysis of MFD-free survival:

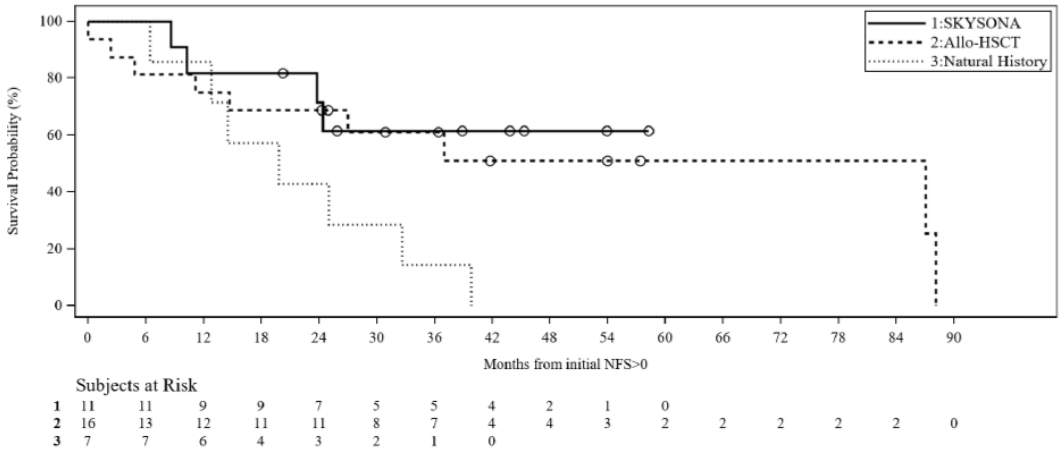
The Applicant, at our request, conducted a Kaplan-Meier (KM) time-to-event analysis that compared estimated time to progression to MFD or death from first NFS ≥ 1 among the untreated and treated subpopulations (Figure 1). The KM curves showed a striking difference between treatment groups (SKYSONA, allo-HSCT) and untreated natural history group.

MFD-free survival KM estimates at the 24-month time point were 43% (95% CI: 10%, 73%), 69% (95% CI: 41%, 86%), and 72% (95% CI: 35%, 90%) for the untreated, allo-HSCT treated and SKYSONA-treated symptomatic subpopulations, respectively. It is notable that 28% of SKYSONA-treated symptomatic subjects experienced an MFD or death within 24 months of first NFS ≥ 1, as compared to 57% of the untreated natural history subpopulation. In essence, twice as many symptomatic natural history subjects progressed to MFD or death within 24 months of symptom onset as compared to a similar SKYSONA subpopulation.

Estimated MFD-free survival at later time points, and the analysis of MFD-free survival comparing the SKYSONA subpopulation to the allo-HSCT and natural history subpopulations using a Cox regression model provide supportive evidence and encouraging trends. However, we are not confident about the analysis of efficacy beyond 24 months due to limited numbers of subjects being followed long-term in this analysis. Supportive evidence from this analysis includes:

1) all untreated natural history subjects who became symptomatic during the course of follow-up in this analysis experienced an MFD or death within 42 months of first NFS ≥ 1. Although the estimated MFD-free survival for SKYSONA at this same time point is encouraging, it is inconclusive due to the small number of subjects available for evaluation of the endpoint at 42 months in the symptomatic SKYSONA subpopulation.
2) the observed nominally statistically significant hazard ratio of 0.27 (95% CI: 0.08, 0.93) for SKYSONA showed that SKYSONA may reduce the risk of MFD or death by 73% as compared to similar subjects in the untreated natural history symptomatic subpopulation, though we are not confident in this statistic for the reasons mentioned about duration of follow-up and because of a wide confidence interval due to small number of events.
3) all SKYSONA subjects who maintained MFD-free survival at Month 24 had a period of NFS stability with no further increase in NFS for at least 24 months. Though numbers are small, the stabilization of NFS with no further increase in score over a period of 24 months further supports a treatment effect of slowed progression of neurologic dysfunction.

Figure 1: Kaplan-Meier Curve of MFD-Free Survival from Time of Initial NFS ≥1 Between SKYSONA, allo-HSCT and Natural History Symptomatic Subpopulations



Abbreviations: MFD, Major Functional Disability; NFS, Neurologic Function Score; allo-HSCT, allogeneic hematopoietic stem cell transplant
Note: One SKYSONA-treated subject is censored at 20 months but is included in the analysis because he had an additional follow-up visit after the January 2022 data cut where no MFD or death was reported (and thus had been followed for more than 24 months with no progression to MFD or death).
Source: bluebird bio, Inc. BLA 125755 Ad hoc analysis Figure 80.56.2.1

Specific subject-level matching of subjects in this analysis provides additional evidence of the treatment effect, particularly in those with higher-risk baseline features. Four subjects were similar at baseline with MRI patterns consistent with parieto-occipital and auditory involvement, a Loes of 8.5-9, and diagnosed in childhood (prior to age 10). Both the SKYSONA subject (b) (6) and the untreated subject (b) (6) were 9 years old at baseline. The other two subjects were treated with allo-HSCT (b) (6)
All 3 treated subjects had a baseline NFS of 1, and the untreated subject had a baseline NFS of 0. The treated subjects were at even higher risk of disease progression due to being symptomatic at baseline compared to the natural history subject (and biasing against SKYSONA). In Figure 1 above, the SKYSONA subject is the one censored at

~44 months following first NFS ≥ 1 with no MFD or death at last follow-up. The other 3 subjects developed MFDs and thus failed MFD-free survival: the untreated subject at 40 months, one allo-HSCT subject at 36 months and the other at ~85 months. Subject (b) (6) treated with SKYSONA with high baseline Loes and NFS 1 at baseline has evidence of slowed progression of disease that would not be expected had he not been treated. Additionally, although he experienced increase of NFS to 3 by his 12-month visit, he has maintained a stable NFS for ~30 months, and his Loes score has remained stable since his Month 24 visit. His disease course provides evidence of stabilization and slowing of disease progression as compared to a matched natural history comparator, and he has also had slower progression than one of the similar allo-HSCT subjects.

Although the analysis was post-hoc, careful matching of subjects provided assurance that the populations were comparable, with early symptomatic disease and high risk of rapid disease progression. There is a chance the populations were inherently different at baseline; however, this analysis provided a comparison of the most similar natural history and SKYSONA populations evaluated throughout the course of the BLA review and included comparison of subject level-matched outcomes that demonstrated a benefit of SKYSONA over the natural history control. The analysis of MFD-free survival at 24 months following first NFS ≥ 1 establishes an effect of SKYSONA on an intermediate clinical endpoint that is reasonably likely to predict long-term clinical benefit on MFD-free survival and slowing of progression of neurologic dysfunction as compared to the natural history of disease in symptomatic subpopulations. Success on this intermediate clinical endpoint forms the basis of accelerated approval, and confirmatory PMR studies will be required to assess long-term efficacy in early, active CALD.

Supportive Evidence of Delayed Symptom Onset and MRI Changes

Delayed Symptom Onset

Individual subject matching of SKYSONA subjects with high-risk prognostic disease features at baseline to similar subjects in the untreated natural history population provided additional evidence of efficacy through comparisons of clinical course. Evidence of delayed symptom onset was present in two subsets of SKYSONA- treated subjects with a baseline NFS of 0 (asymptomatic at time of treatment) who:

1) remained asymptomatic during a period of time when symptomatic disease progression would have been expected in the absence of treatment, or
2) developed neurologic dysfunction at an age and duration of follow-up after treatment that was later than would have been expected when compared to the natural history of disease.

Subjects who were already included in the MFD-free survival analysis are not duplicated here. High risk factors in this evaluation included a parieto-occipital pattern of disease diagnosed in childhood (10 years of age and younger) and followed at least 2 years after treatment. In addition to evidence as compared to untreated natural history subjects with early, active disease from Study ALD-101, rapid radiographic and clinical disease progression in children 10 years of age or younger presenting with parieto-occipital

pattern of disease and gadolinium enhancement on brain MRI is also supported by the literature. [10,11,14, 27]

Five subjects treated in childhood (age 10 years or younger) with a parieto-occipital pattern of disease on brain MRI reached adolescence (11 years of age and older) after at least 24 months of follow-up and remained asymptomatic (NFS=0) at last follow-up. Of these 5 subjects, 2 (40%) had a baseline Loes score of 1-2 and the remaining 3 (60%) had Loes scores between 4-9. Of the 3 subjects in the higher Loes score (4-9) group, 2 (66%) had improved (decreased) Loes score at Month 24 and a stable neurocognitive course. The third higher baseline Loes score subject (Loes 7.5) had an initial worsening (increase) in Loes score at Month 24, after which time it stabilized. The asymptomatic course of the subjects with baseline Loes scores ≥ 4 for 24 months or more following treatment with SKYSONA is unexpected based on the natural history of disease. The two subjects with baseline Loes score of 1-2 had a longer duration of follow-up (approximately 3-6 years following treatment with SKYSONA), though the expected time of progression to symptomatic disease from identification of mild cerebral disease (Loes score 1-2) is unknown, as it is not well-represented in the natural history population or clearly described in the medical literature.

Two subjects treated in childhood with a parieto-occipital pattern of disease on brain MRI developed first symptoms (NFS of 1 or more) more than 24 months following treatment and at an age that would not be expected based on the natural history of disease. One subject, treated at 5 years of age, developed first NFS changes 74 months following treatment at 10 years of age. The other subject was treated at 7 years of age and developed first NFS changes at 11 years of age and 42 months following treatment. These subjects are not represented in the analysis of MFD-free survival because they had not been followed for at least 24 months from time of symptom onset.

Despite evidence of delayed symptom onset in a small number of SKYSONA-treated subjects, there is insufficient evidence to determine if treatment is able to delay symptom onset in the entire population of patients with early, active CALD. Additionally, as numbers are small, it is not clear if these subjects could represent a disease phenotype with slower progression than expected. The analysis is limited by insufficient long-term data beyond 24 months in treated subjects and the large percentage of subjects with very early cerebral lesions (Loes score 1-2) and asymptomatic disease (NFS=0) at baseline for whom the time course of disease progression is relatively unknown due to poor representation in the natural history of disease. Of 61 subjects in the SKYSONA Efficacy Population, 44 (72%) had baseline NFS=0 and Loes score 1-2. Only a longer duration of follow-up could provide more information about delayed symptom onset in the population of early, active CALD with mild cerebral lesions and asymptomatic disease and increase confidence that such a prolonged asymptomatic course would not be expected in the natural history of untreated disease. There are also insufficient data to determine if SKYSONA might prevent onset of neurologic dysfunction in patients treated very early in the disease course.

Resolution of Gadolinium Enhancement at Month 24 Following Treatment

Of 36 subjects with data available for gadolinium enhancement assessment on brain MRI at Month 24 following treatment, 33 (92%) had resolution of enhancement (GdE-). The three subjects who had GdE+ MRIs at Month 24 had resolution of enhancement (GdE-) at the Month 36 visit. In comparison, 27 of 27 (100%) allo-HSCT subjects with Month 24 values for gadolinium assessment had GdE- MRIs. Spontaneous resolution of gadolinium enhancement is not expected to occur in the natural history of disease, though lack of routine and regular use of contrast media for MRI assessments in CALD at the time many of the natural history subjects were diagnosed limits the interpretation of these results in comparison to the natural history population. As gadolinium enhancement of demyelinating lesions is indicative of active inflammatory disease at high risk of progression, the resolution of enhancement (GdE-) in the majority of subjects is supportive evidence of a treatment effect of SKYSONA, with reduced cerebral inflammation that predicts slowing of progressive demyelination.

Extrapolation of Evidence of Effectiveness to the Entire Early, Active CALD Population

The primary evidence of efficacy lies in the outcomes of subjects with parieto-occipital disease, as the pattern was the most common across studies, presents the earliest (in childhood) and is one of the most rapidly progressive if left untreated. Although numbers of subjects are small, there is evidence for efficacy in frontal patterns of disease, as well. The treatment effect of slowed progression of symptomatic disease to MFD or death as compared to the natural history of disease appears similar between allo-HSCT and SKYSONA, regardless of baseline pattern of disease or age at onset of symptoms. Additionally, the CALD literature suggests that, although typical presentation of frontal disease is in adolescence, earlier childhood frontal disease is rapidly progressive,[10] and there is evidence of this in the study populations. Of 10 subjects across study populations (2 untreated, 3 treated with SKYSONA, 5 treated with allo-HSCT) with early, active frontal disease at baseline, all were younger than 13 years at time of diagnosis and/or treatment, and all were expected to experience rapid disease progression. All but 2 subjects (1 subject treated with SKYSONA and 1 treated with allo-HSCT) became symptomatic within 24 months of diagnosis (for the untreated) or treatment (for the populations treated with SKYSONA or allo-HSCT), regardless of baseline Loes score. Therefore, with 80% of subjects with early, active frontal disease presenting in childhood developing symptomatic disease within 24 months of presentation, the asymptomatic course in the one (33%) SKYSONA-treated subject who has remained asymptomatic at 2 years following treatment provides additional supportive evidence of delayed onset of neurologic dysfunction.

Experts in the CALD community stress that early intervention prior to clinical progression is crucial, despite uncertainty regarding expected time to progression if asymptomatic disease is left untreated due to heterogeneity of disease. Allo-HSCT literature suggests disease progression may occur in the 12-24 months following treatment, followed by clinical and radiographic disease stabilization.[14] The trends following treatment with SKYSONA appear to be similar. This variability of clinical course despite early treatment supports early treatment of asymptomatic patients upon first detection of early, active cerebral disease to slow or possibly delay the progression to symptomatic disease,

disability, and death. Although many of the subjects treated with SKYSONA in the clinical trials were treated earlier in the disease course and with lower-risk baseline disease features than the subjects characterized in these analyses, we believe efficacy of SKYSONA can be extrapolated to the entire population with early, active disease, regardless of baseline MRI pattern, Loes score, or NFS. The underlying pathophysiology of disease is believed to be the same and results from pharmacodynamic factor analysis and resolution of gadolinium enhancement on brain MRI for most subjects supports this extrapolation. The clinical review team therefore feels the substantial evidence of efficacy in symptomatic subjects at Month 24 and supportive evidence in asymptomatic high- risk subjects can be extrapolated to the entire asymptomatic or mildly symptomatic population with early, active CALD, regardless of MRI pattern of disease (with the possible exception of those with isolated pyramidal tract disease as discussed below).

Efficacy Concerns in Subjects with Isolated Pyramidal Tract Disease

The small subpopulation of CALD subjects with isolated pyramidal tract disease on brain MRI had worse outcomes following treatment with SKYSONA as compared to the natural history of disease. Because of these findings, patients with isolated pyramidal tract disease, whose disease generally doesn't become symptomatic until adulthood, may need to be considered differently than patients with other MRI patterns of disease as far as timing of intervention. In the untreated natural history population in ALD-101, two (2) subjects met criteria for early, active CALD with isolated pyramidal tract disease at time of diagnosis at 9 and 11 years of age. Despite lack of treatment, both remained asymptomatic for approximately a decade, first developing NFS changes at 19 and 20 years of age, respectively. Adult presentation of symptomatic CALD in patients with isolated pyramidal tract disease is supported by the literature.[10] Ten (16%) subjects treated with SKYSONA had isolated pyramidal tract disease at time of treatment, and 3 (30%) have subsequently received rescue allo-HSCT prior to age 20 years – 2 received allo-HSCT as treatment for MDS, and 1 received allo-HSCT as rescue therapy at the investigator's discretion due to progressive cerebral disease on brain MRI, and subsequently died of transplant-related causes. The remaining 7 subjects with isolated pyramidal tract disease, although stable since treatment with SKYSONA, have not been followed for a sufficient duration to determine their long-term neurofunctional outcomes. Careful consideration as to whether and when to treat boys with isolated pyramidal tract disease is warranted, weighing the benefit-risk profile for individual patients based on baseline disease factors, age, and available HSC donor options.

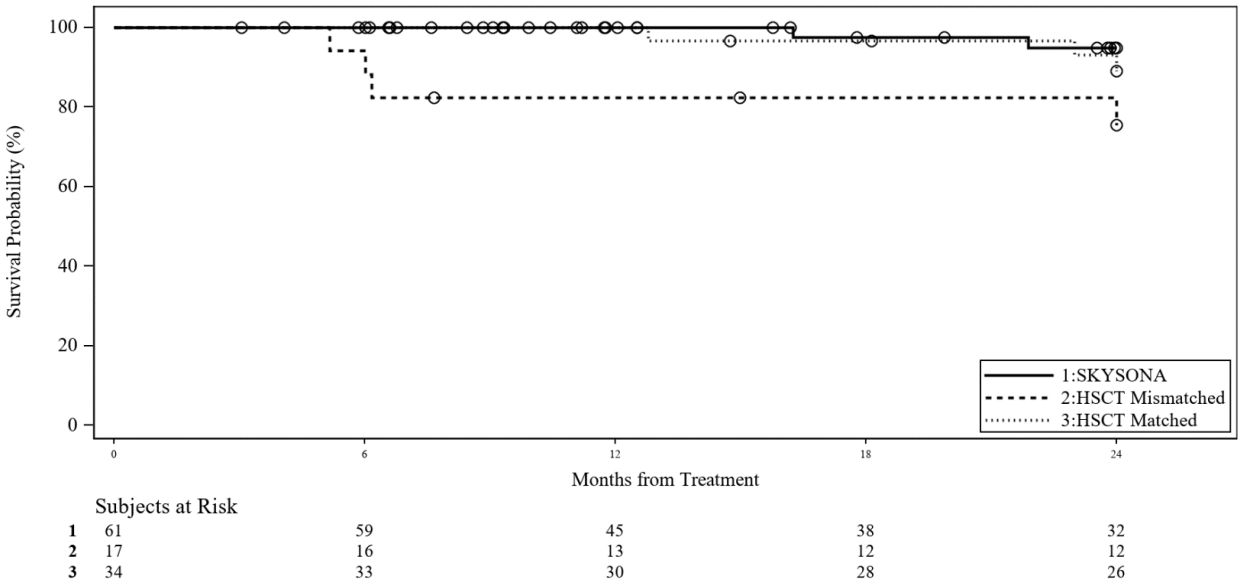
Comparative Analyses of Overall Survival of SKYSONA and Allogeneic Hematopoietic Stem Cell Transplant

There were insufficient data to compare relative efficacy of SKYSONA to the standard of care, allo-HSCT, in the treatment of CALD. However, comparison of SKYSONA with an external early, active disease allo-HSCT control (pooled from Studies ALD-101 and ALD-103) was performed for overall survival (OS). OS was analyzed as time-to-event Kaplan-Meier estimates comparing SKYSONA (entire efficacy population, N=61) to early, active allo-HSCT subpopulations by donor type: HLA-Matched allo-HSCT Subpopulation (N=34) and HLA-Mismatched allo-HSCT Subpopulation (N=17) (Figure 2). There were insufficient long-term data to compare OS beyond Month 24 following treatment.

However, a distinct difference in OS in the first 9 months following treatment was seen for the subpopulation who received allo-HSCT from an HLA-mismatched donor as compared to SKYSONA and allo-HSCT from an HLA-matched donor. While this analysis does not provide evidence of efficacy of SKYSONA, it does demonstrate a survival advantage of SKYSONA as compared to allo-HSCT from an HLA-mismatched donor, with early mortality in the HLA-mismatched allo-HSCT Subpopulation largely attributed to allo-HSCT-related toxicities.

Additionally, no subjects treated with SKYSONA experienced GVHD. SKYSONA therefore appears to offer a survival advantage over allo-HSCT from a mismatched donor by virtue of avoiding certain transplant-related toxicities.

Figure 2: Kaplan-Meier Curve of Overall Survival Between SKYSONA and Allo-HSCT Treated Donor Subpopulations



Subjects at Risk

1	61	59	45	38	32
2	17	16	13	12	12
3	34	33	30	28	26

Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplant
Source: bluebird bio, Inc. BLA 125755 Draft Package Insert

Efficacy Summary

In summary, the clinical review team concludes that there is evidence of effectiveness on an intermediate clinical endpoint for SKYSONA in pediatric patients with early, active CALD from a single adequate and well-controlled trial comprised of pooled data from two clinical studies, compared to external controls, that demonstrate slowed progression to MFDs or death from time of first NFS ≥ 1 to Month 24 in symptomatic subjects who have been treated with SKYSONA as compared to the natural history of disease and confirmatory evidence. Supportive evidence of efficacy is based upon subjects with parieto-occipital or frontal MRI patterns who would have been expected to experience rapid disease progression in childhood in the absence of treatment but had evidence of delayed onset of neurologic dysfunction either with asymptomatic course or onset of symptoms in adolescence and/or at least 24 months of follow-up after treatment. There

is additional supportive evidence of effectiveness from improvement in Loes score in 2 subjects and resolution of gadolinium enhancement in the majority of subjects at Month 24 following treatment with SKYSONA.

There is additional confirmatory evidence of effectiveness from in vitro pharmacology studies wherein fibroblasts from patients with CALD were transduced with the Lenti-D vector demonstrated vector-driven *ABCD1* transgene expression, ALDP production, and improved VLCFA metabolism. In vivo studies of Lenti-D-transduced HSCs from healthy donors transplanted into myeloablated immunodeficient mice demonstrated stable *ABCD1* transgene expression and ALDP production in bone marrow and brain during the study's duration. Clinical pharmacodynamic response data are also supportive. The median (min, max) value of %ALDP+ CD14+ cells at Month 6 in subjects who maintained MFD-free survival at 24 months following infusion of SKYSONA was 23.1 (2.0, 71.4) which was more than twice as high as the median value of %ALDP+ CD14+ cells at Month 6 in subjects who failed MFD-free survival by Month 24, which was 10.9 (10.8, 18.21).

The clinical review team also is of the opinion that evidence of effectiveness can be extrapolated to the entire asymptomatic or early symptomatic (i.e., NFS ≤ 1) population with early, active CALD regardless of baseline Loes score or pattern of disease, with the possible exception of patients with pyramidal tract disease who do not typically have symptom onset until adulthood and who had worse outcomes following treatment with SKYSONA than the natural history of disease. Additionally, there is an early survival benefit of SKYSONA compared to allo-HSCT from HLA-mismatched donors due to avoidance of allo-HSCT-related toxicities in that population.

Despite the limitations of heavy reliance on post-hoc exploratory analyses, the totality of efficacy evidence supports accelerated approval of SKYSONA for the indication of slowing the progression of neurologic dysfunction in boys with early, active CALD, with careful consideration given to timing of treatment based on available HSC donor options, the relative risks of treatment, and the CALD disease phenotype of the patient (including but not limited to MRI pattern of disease, Loes score, and presence or absence of early neurologic dysfunction at time of intended treatment). Significant uncertainty remains about durability of effectiveness, which is of particular concern given the large number of subjects treated with SKYSONA in the clinical studies who had baseline NFS=0 and Loes scores of 1-2, because the time course of disease progression to symptomatic disease, disability and death is poorly understood in patients diagnosed at such an early stage of disease. Given the uncertainties about the benefit-risk assessment in subjects with baseline NFS=0 and Loes scores of 1-2, as well as subjects with isolated pyramidal tract disease, additional time in follow-up is warranted to understand the long-term benefit and durability of effectiveness of SKYSONA. A PMR study will be required to confirm efficacy of SKYSONA, and will evaluate long-term outcomes on MFDs, death, need for rescue allo-HSCT, NFS, MRI findings, neurocognitive outcomes, quality of life measures, %ALDP+ CD14+ cells, and peripheral blood VCN.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring (BIMO) inspections were performed for the Applicant and two clinical investigators (CI) participating in the conduct of Protocols ALD-102 and ALD-104 in support of this original BLA. The inspections did not reveal problems that impact the data submitted in this BLA.

c. Pediatrics

The application does not trigger PREA because SKYSONA received orphan drug designation (ODD) prior to the submission of the BLA. Per the Pediatric Research Equity Act (PREA) and 21 Code of Federal Regulations (CFR) 314.55(d), ODD products are exempt from pediatric study requirements.

The proposed population for SKYSONA is pediatric patients. The clinical data support the safety and effectiveness of SKYSONA in pediatric patients 4 to 17 years of age.

d. Other Special Populations

SKYSONA has not been studied in other special populations.

7. Safety and Pharmacovigilance

The safety population included 67 subjects treated in the Phase 3 studies, ALD-102 and ALD-104. These subjects underwent mobilization and apheresis, myeloablation with busulfan, lymphodepletion with cyclophosphamide or fludarabine, and SKYSONA treatment with a median dose of 12 $x10^6$ CD34+ cells (range 5 – 38.2). The median (min, max) age across studies was 6 (4, 14) years; 100% were male; 54% were White/Caucasian, 4% were Black or African American, 1% were Asian, 10% were of other races including mixed race, and 30% did not report race; 25% were of Hispanic ethnicity. Subjects were followed for a median of 23.5 months (range 1.4 months to 7.3 years). Safety data with a data cutoff of Aug. 18, 2021, were systematically reviewed, and cases of concern for malignancy or diagnosed malignancy that occurred at any time after the data cutoff date were reviewed on an ad hoc basis.

Summary of safety findings:

Insertional oncogenesis is the major safety concern with SKYSONA. Three subjects have been diagnosed with hematologic malignancy that has been attributed to SKYSONA, and more cases may potentially be diagnosed with time. A secondary concern is delayed hematopoietic reconstitution, manifest by opportunistic infections, delayed engraftment, and prolonged cytopenias. These are known risks of HSCT, although their timing and extent after treatment with SKYSONA suggest that the HSC manipulation that is inherent in the production of SKYSONA may have some deleterious effects on HSC function. Aside from the insertional oncogenesis and delayed hematopoietic reconstitution, SKYSONA seems to have a safety profile that reflects the myeloablative and lymphodepletion conditioning agents that are administered prior to SKYSONA.

Two subjects died after treatment with SKYSONA. One underwent allogeneic HSCT due to CALD progression and subsequently died from HSCT complications. The second subject died from multisystem organ failure that was a complication of an adenovirus infection. He also had rapid progression of his CALD. It cannot be ruled out with certainty that his treatment with SKYSONA less than two years earlier may have contributed to the florid adenovirus infection.

There were many serious adverse reactions in the trials, having occurred in in 57% of subjects. The most common non-laboratory, non-cancer serious adverse reactions (≥ 3% incidence) that occurred after treatment with SKYSONA were febrile neutropenia (18%), pyrexia (18%), seizure (7%), pseudomonal bacteremia (3%), pancytopenia (3%), vascular device infection (3%), mucositis (3%), and vomiting (3%). No subjects were diagnosed with graft versus host disease.

Nonlaboratory adverse events (AEs) that occurred after SKYSONA administration in > 20% of subjects included mucositis, febrile neutropenia, alopecia, vomiting, pyrexia, abdominal pain, decreased appetite, diarrhea, and constipation. Severe laboratory-based AEs that occurred after SKYSONA administration in > 40% of subjects included cytopenias (neutropenia, thrombocytopenia, leukopenia, lymphopenia, and anemia) and hypokalemia.

MDS is a rare hematologic malignancy in pediatric patients with no predisposition to development in children with CALD. However, it has been diagnosed in three subjects after treatment with SKYSONA. For all three subjects, the malignancy appears to have been caused by integration of the lentiviral vector into a proto-oncogene. Two of the malignancies were the result of integrations into the proto-oncogene *MECOM.* It is therefore very concerning that *MECOM* integrations are present in every subject who has been treated with eli-cel. Furthermore, some subjects with *MECOM* integrations have evidence of clonal expansion and seem at high risk for developing malignancy.

The two subjects with MDS that is attributed to integration into *MECOM* have several notable similarities in that (1) both subjects had severely impaired hematopoietic system reconstitution following myeloablation and SKYSONA administration, (2) both subjects had evidence of a large clone with an integration site in *MECOM* in their first integration site analysis (ISA), performed at six months, (3) gene expression studies in both subjects demonstrated overexpression the *MECOM*-associated onco-protein, *EVI1,* (4) the clone with *MECOM* had transformed into MDS within two years of SKYSONA administration, and (5) both subjects had the same type of MDS, MDS with single lineage dysplasia affecting megakaryocytes.

In the third subject, the development of MDS was attributed to integration into another proto-oncogene and a paralog of *MECOM*, *PRDM16*. Other distinctions regarding this subject were his relatively normal hematopoietic reconstitution after treatment with SKYSONA, his longer time to development of malignancy, and the absence of a predominant clone that was identified before his cancer diagnosis. In addition, he had a different type of MDS, MDS with excess blasts-2.

In addition to the three subjects with MDS, the clinical review team has a specific concern for the possible development of malignancy in at least nine other subjects.

With the exception of the malignancy cases, the types of AEs observed are expected in the post-myeloablative setting. However, the occurrence of serious infections many months after SKYSONA administration, as well as evidence of delayed hematopoietic reconstitution relative to what would be expected after autologous transplant of peripherally derived HSCTs, illuminated the possibility that the HSCT processing or the presence of vector within the cells interferes with hematopoietic and immune reconstitution. Thus, the safety review focused on the issues of infections, delayed engraftment, and prolonged cytopenias, in addition to the risk of insertional oncogenesis.

Of the 86 reported infections, the most important bacterial infections included several subjects with bacteremia and one central venous catheter infection. Bacteremia was reported in four subjects: one subject had pre-engraftment bacteremia, one subject had pseudomonas and stenotrophomonas bacteremia during the third month post-SKYSONA, one subject had streptococcal bacteremia at ~4 months post-SKYSONA, and another subject had pseudomonas bacteremia at ~8 months post-SKSYONA. Also notable is an atypical mycobacterium infection of a central venous catheter ~6 months after treatment with SKYSONA.

There were also important viral opportunistic infections that occurred after treatment with SKYSONA. These included human herpesvirus 6 viremia in one subject that started ~2.5 months after treatment with SKYSONA and was not resolved during the follow-up period, and cytomegalovirus reactivation in a separate subject at ~3 months. There was Epstein-Barr virus (EBV) reactivation in 2 additional subjects; one infection started ~2.5 months after treatment with SKYSONA and lasted approximately 6 months, and one EVB reactivation started ~1.5 years after SKYSONA in the second subject and was not resolved during the follow-up period. In addition to the occurrence of opportunistic systemic viral infections, there was a separate case of severe BK cystitis ~6 weeks after treatment with SKYSONA.

Delayed hematopoietic reconstitution is evident based on review of the engraftment data. All subjects met the Applicant's criteria for neutrophil engraftment, which was defined as three consecutive absolute neutrophil counts $\geq 0.5 \times 10^9$/L on three different days within 42 days of SKYSONA administration. However, it should be noted that engraftment was hastened by the use of G-CSF in most subjects. Seven of 67 subjects (10%) required G-CSF beyond Day 42, including three subjects who required G-CSF beyond 3 months after treatment with SKYSONA. In addition, four subjects had absolute neutrophil counts of $< 0.5 \times 10^9$/L on at least one assessment beyond 42 days, despite having met engraftment criteria prior to that point.

Platelet engraftment was defined as three consecutive platelet values $\geq 20 \times 10^9$/L on different days and no platelet transfusions administered for 7 days immediately preceding and during the evaluation period. Platelet engraftment was not achieved within 42 days of SKYSONA administration in 13 of 63 patients (21%). The median time to platelet engraftment was 29 days (range, day 14 to 108), and two subjects were treated

with a thrombopoietin receptor agonist at the time engraftment criteria were met until 10 or 14 months after treatment with SKYSONA. Five subjects had severe epistaxis prior to platelet engraftment; no other serious or severe bleeding adverse events were reported.

Delayed hematopoietic recovery is also evident in the evaluation of cytopenias. Grade 3 or higher cytopenias on or after Day 60 occurred in 47% of subjects and included low platelet count (14%), low neutrophil count (22%), low lymphocyte count (27%), and low hemoglobin (2%). Serious adverse reactions of pancytopenia occurred in two patients who required support with blood and platelet transfusions as well as growth factors (G-CSF for up to 6 months and eltrombopag for up to 14 months) after SKYSONA administration.

Another potential risk of SKYSONA, which has occurred in one patient, is failure of the transduced cells to persist after their administration to a patient. Six months after treatment with SKYSONA, the subject had percent ALDP+ cells below the limit of quantitation, gadolinium enhancement on MRI, and an increase in Loes score. He experienced a steep decline in peripheral blood vector copy number below the limit of quantitation within 9 months after treatment with SKYSONA. Subsequent MRIs provided evidence of further progression of CALD, and the subject therefore underwent allogeneic hematopoietic stem cell transplant. This subject is the only patient with a full deletion of the *ABCD1* gene, and an immune response is thought to have caused the failure of vector-containing cells to persist.

A final concern is the potential for generation of RCL due to recombination events. Scheduled assessments during the studies did not reveal any evidence of recombinant lentivirus following treatment with SKYSONA.

In conclusion, the primary safety concern with SKYSONA is hematologic malignancy. Three subjects have been diagnosed with MDS after treatment with SKYSONA, however these cases are not sufficient for understanding the frequency, risk factors, and outcomes of hematologic malignancy after treatment with SKYSONA. To better characterize this known risk and determine mitigating measures, a PMR safety study will be required as a condition of approval.

Pharmacovigilance Plan (PVP)

The PVP (dated September 30, 2021) includes the sponsor's assessment of identified and potential risks and missing information based on the pre-licensure clinical trial data, published literature, known product-class effects, and other relevant sources of safety information. The sponsor's proposed plan for routine pharmacovigilance is consistent with 21 CFR 600.80.

FDA Guidance Long Term Follow-up After Administration of Human Gene Therapy Products (January 2020) available at https://www.fda.gov/media/113768/download recommends 15-year long term follow up for products with integrating vectors. In keeping with this Guidance, the sponsor is also conducting a long-term follow up study for patients receiving the product in the premarket clinical trial setting (study LTF-304, discussed above), and a post-marketing study, REG-502 for patient receiving the

marketed product post-licensure. Due to the serious risk for insertional oncogenesis, there will be a PMR under Section 505(o) of Federal Food, Drug, and Cosmetic Act (FDCA) for a 15-year long term follow up post-marketing safety study to further characterize the serious risk of secondary malignancies (Study REG-502).

Should the BLA be approved, the PMR protocol design and data analysis plan will be finalized with the sponsor post-licensure. Of note, an algorithm for monitoring for insertional oncogenesis, including a schedule for conducting ISAs, will be agreed upon. On August 19, 2022, the clinical review team provided additional recommendations on the REG-502 study design for the PMR, including the need for additional testing for safety outcome assessment monitoring at pre-specified intervals. Additional testing will include bone marrow biopsy, peripheral blood sample with blood smear, integration site analysis, vector copy number, and gene expression studies. FDA will review the final study protocol upon submission to ensure that FDA recommendations on study design were appropriately incorporated.

8. Labeling

The proposed proprietary name, SKYSONA, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on December 2, 2021 and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on December 8, 2021.

APLB reviewed the proposed Prescribing Information, Patient Package Insert, and package and container labels on August 9, 2022, and found them acceptable from a promotional and comprehension perspective.

9. Advisory Committee Meeting

An Advisory Committee (AC) Meeting was convened on June 9, 2022, primarily to discuss the risk of insertional oncogenesis and the cases of hematologic malignancy that have been attributed to this novel product. In addition to presenting CALD data, the presentations included data relevant to the risk of insertional oncogenesis in two related LVV products. The review team also presented concerns about the efficacy data and sought input regarding the benefit-risk calculation for SKYSONA.

The AC agreed that insertional oncogenesis is a serious and important risk of SKYSONA. They recommended very close follow-up of treated subjects to identify those appearing at high risk of malignancy, enabling an early search for a bone marrow donor should HCST be indicated for treating the malignancy. They also recommended closely following the malignancy cases in order to characterize their aggressiveness and responsiveness to treatment, to further inform the benefit-risk analysis. Lastly, they voted unanimously that the data from the two related LVV products does not inform the safety of SKYSONA.

Regarding the benefit-risk of SKYSONA, the AC voted unanimously (with one abstention) that the benefit-risk for SKYSONA is favorable. The population determined by the AC to have a favorable benefit-risk included boys without an available HLA-

matched hematopoietic stem cell donor. However, the AC did not provide a clear consensus about the benefit-risk in boys with a matched non-sibling donor.

10. Other Relevant Regulatory Issues

SKYSONA was granted breakthrough therapy designation, and the BLA was reviewed under priority review. The Applicant was also issued a Rare Pediatric Disease voucher.

The review team considered potential for traditional approval in a limited population; however, given the limitations highlighted earlier and lack of adequate data to support durability, the review team recommends Accelerated Approval. However, the review team was not in agreement on whether the population should be restricted based on availability of an appropriate allo-HSCT donor, as while allo-HSCT is standard of care, it is not an FDA approved therapy. The majority of the clinical team support SKYSONA being approved for the limited early, active CALD population without an available and willing HLA-matched donor. They concluded that the medical literature provided convincing evidence for the effectiveness of allo-HSCT to delay and slow neurologic progression in boys with early, active CALD. While the BLA application did not contain sufficient long-term clinical data to compare SKYSONA to allo-HSCT, it contained historical and contemporaneous natural history data demonstrating a high 1-year mortality due to HSCT complications for boys with early, active CALD who received allo-HSCT for mismatched donor. Given the uncertainties regarding durability of effect and magnitude of risk of hematologic malignancy from SKYSONA they concluded it was only the population who had significant early mortality following allo-HSCT for which there is a favorable benefit/risk profile. The other member of the clinical review team favored a broader indication independent of potential alternative treatment options because of the uncertainty regarding efficacy of allo-HSCT to support regulatory decision making and wanting patients and their families to have options independent of allo-HSCT donor availability.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Applicant provided substantial evidence of effectiveness and reasonable assurance of safety based on a single adequate and well-controlled trial with confirmatory evidence and the clinical review team recommends accelerated approval of SKYSONA for treatment of boys with early, active CALD based on an intermediate clinical endpoint of slowed progression to MFD or death within 24 months of first symptom onset for SKYSONA as compared to the natural history of disease.

b. Benefit/Risk Assessment

SKYSONA administration slowed the progression of neurologic dysfunction (as represented by MFD-free survival at Month 24 following first NFS ≥1) as compared to the natural history of disease. There is supportive evidence that SKYSONA administration

appears to have delayed the onset of symptomatic disease in a few subjects at high risk of symptomatic disease progression as compared to the natural history of disease. There is additional supportive evidence from brain MRI findings: improvement in Loes score for 2 subjects and resolution of gadolinium enhancement for most subjects at Month 24 following treatment with SKYSONA. The clinical review team believes that efficacy can be extrapolated to the entire population of early, active CALD with asymptomatic or mildly symptomatic disease. Additionally, SKYSONA appears to offer an early survival advantage over allo-HSCT from an HLA-mismatched donor due to avoidance of HSCT-related toxicities in that population. Confirmatory evidence of efficacy is provided by in vitro and in vivo pharmacologic studies demonstrating transgene engraftment and production of functional ALDP with resultant metabolism of very long chain fatty acids, as well as a pharmacodynamic correlation between median values of %ALDP+ CD14+ cells at Month- 6 and the Month-24 MFD-free survival rate. The most important and severe risk identified with SKYSONA is hematologic malignancy. While the risk of hematologic malignancy is of significant concern, the overall benefit-risk profile of SKYSONA is favorable due to the substantial benefit of slowed, clinical disease progression in a disease that ultimately leads to disability and premature death if left untreated.

A PMR safety study will be required to assess the long-term risk of hematologic malignancies related to insertional oncogenesis. Furthermore, a boxed warning and a medication guide will help to ensure that patients, their caregivers, and their physicians are able to make well-informed decisions about treatment with SKYSONA and monitoring for malignancy.

The evidence supports accelerated approval of SKYSONA for the indication of slowing the progression of neurologic dysfunction in boys with early, active CALD, with careful consideration given to timing of treatment based on available HSC donor options, the risk of hematologic malignancy, and the CALD disease phenotype of the patient (including but not limited to MRI pattern of disease, Loes score, and presence or absence of neurologic dysfunction at time of intended treatment).

c. Recommendation for Post-marketing Activities

Accelerated approval regulations require that Applicant conduct adequate and well-controlled clinical trials to verify and describe clinical benefit attributable to this product. Applicant agreed to conduct the following studies:

1. Follow all subjects who received elivaldogene autotemcel in Studies ALD-102 and ALD-104 to assess event-free survival (i.e., alive without Major Functional Disability (MFD) or need for hematopoietic stem cell transplant (HSCT)) for a minimum of ten years following administration of elivaldogene autotemcel.

   Final Protocol Submission: January 31, 2023

   Interim Clinical Study Report Submission: July 31, 2027

   Final Study Report Submission: July 31, 2032

2. Investigate event-free survival for at least five years post-treatment in 24 boys with more advanced early active, cerebral adrenoleukodystrophy (CALD) [(based on baseline Loes scores and Neurologic Function Score (NFS)] who will be newly treated with elivaldogene autotemcel (SKYSONA).

   Final Protocol Submission: January 31, 2023

   Study fully enrolled by: June 30, 2033

   Study Completion date: June 30, 2038

   Final Study Report Submission: December 31, 2038

Because of the risk of hematologic malignancy with SKYSONA, the Applicant agreed to conduct the following post-marketing safety study as a PMR:

3. A postmarketing, prospective, multi-center, observational study to assess the long-term safety of elivaldogene autotemcel and the risk of secondary malignancies occurring after treatment with elivaldogene autotemcel. The study will include at least 120 adrenoleukodystrophy patients and the enrolled patients will be followed for 15 years after product administration. The study design will include monitoring at pre-specified intervals for clonal expansion with adequate testing strategies.

   Final protocol submission: December 31, 2022

   Study completion date: April 30, 2047

   Final study report submission: April 30, 2048

The Applicant agreed to the following CMC PMRs:

4. A study to support the extractable data provided for the (b) (4) bag, including the sample processing steps in the (b) (4) and an appropriate identification process used for the extractables.

   We acknowledge the timetable you submitted on August 17, 2022, which states that you will conduct this study according to the following schedule:

   Final Protocol Submission: November 30, 2022

   Study Completion Date: February 28, 2023

   Final Report Submission: April 30, 2023

5. A study to evaluate leachables of the (b) (4) bag over the duration of the shelf-life of elivaldogene autotemcel. This evaluation will also include a full toxicological risk assessment for the identified leachables and extractables.

Final Protocol Submission: November 30, 2022

Study Completion: January 30, 2024

Final Study Report Submission: March 30, 2024

The Applicant agreed to the following CMC PMCs:

6. bluebird bio, Inc., commits to qualify a (b) (4) test of their (b) (4) to provide greater (b) (4) assurance of their final drug product and to submit these qualification results as a supplement to their file on or before March 31 of 2023.

   Final Report Submission: March 31, 2023

7. bluebird bio commits to providing a final report of the qualification results of (b) (4) from the drug product manufacturing facility.

   Final Report Submission: October 31, 2022

8. bluebird bio, Inc., commits to establish the sensitivity of (b) (4) method for the (b) (4) bag.

   Final Report Submission: February 28, 2023

9. bluebird bio, Inc., commits to perform the additional robustness assessments of the (b) (4) assays as described in BLA 125755.

   Final Report Submission: June 30, 2023

10. bluebird bio, Inc., commits to add testing of eli-cel cryopreserved drug product (DP) for (b) (4) as described in BLA 125755.

    Final Report Submission: February 28, 2023

11. bluebird bio, Inc., commits to perform a supplemental in-use stability study of eli-cel assessing the stability of (b) (4) under the intended conditions as described in BLA 125755.

    Final Report Submission: March 31, 2023

12. bluebird bio, Inc., commits to assess the feasibility of detecting (b) (4)

(b) (4) The feasibility assessment will include a proposed path forward for completing a leachable study for the (b) (4), including a date the final leachable study report will be submitted to the FDA.

Final Feasibility Assessment Report Submission: February 28, 2023

13. bluebird bio, Inc., commits to conducting (b) (4) testing following the conditions outlined in (b) (4) and provide justifications for the test method, results, and conclusions as part of a complete test report. Complete test reports for this (b) (4) testing on the (b) (4) bag will be submitted as a final study report by December 31, 2022.

    Final Report Submission: December 31, 2022

14. bluebird bio, Inc., commits to perform a (b) (4) study to evaluate drug product bag integrity following (b) (4) (e.g., (b) (4) The testing will include (b) (4). Complete test reports for this testing will be submitted as a final study report by December 31, 2022.

    Final Report Submission: December 31, 2022

12. References

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13. History

Written/ Revised	Approved By	Approval Date	Version Number	Comment
C. Vincent	N/A	Mar 2, 2022	5	Technical correction and updates made to align with CBER's reorganization
C. Vincent / SBRA WG	D. Martin, RM/BOS Chief	Feb 16, 2021	4	Revisions include new policy and substantive procedural changes for clarity and to facilitate timely review/routing.
Rehkopf	Rehkopf	Aug 9, 2017	3	Technical revision to reorder the sections in order to keep the clinical information together
Dixon	Rehkopf	Oct 21, 2016	2	Revised to remove instructions from the template; created associated job aid
Joneckis	Yetter		1	Developed to meet requirements under FDAAA