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bluebird bio Presents Long-Term Data for elivaldogene autotemcel (eli-cel, Lenti-D™) Gene Therapy for Cerebral Adrenoleukodystrophy (CALD)

90% of evaluable patients (27/30) alive and free of major functional disabilities (MFDs) at two years follow-up in Phase 2/3 Starbeam study (ALD-102)[1]*

Patients in long-term follow-up study (LTF-304) continue to remain alive and MFD-free through up to nearly seven years of follow-up, suggesting eli-cel stabilises the progression of disease[1]

No reports of graft failure, graft rejection, graft-versus-host disease, replication-competent lentivirus or insertional oncogenesis in the 51 patients treated with eli-cel in clinical studies (ALD-102/LTF-304 and ALD-104)[1]

Data presented in oral session during Presidential Symposium at the 47th Annual Meeting of the EBMT

ZUG, Switzerland — 15 March, 2021— bluebird bio, Inc. (Nasdaq: BLUE) announced new data from the clinical development programme for its investigational elivaldogene autotemcel (eli-cel, Lenti-D™) gene therapy in patients with cerebral adrenoleukodystrophy (CALD), including updated results from the pivotal Phase 2/3 Starbeam study (ALD-102) and the long-term follow-up study LTF-304, as well as safety outcomes from the Phase 3 ALD-104 study. These data were presented today in an oral presentation during the Presidential Symposium at the 47th Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT 2021), taking place virtually from March 14–17, 2021.

"The progression of CALD may occur rapidly, leading to severe neurological decline, and often death, of boys with this disease. The results presented today show that at 24 months of follow-up, 90% of patients (27/30) in our pivotal study of eli-cel (ALD-102) were alive and free of major functional disabilities (MFDs). As we continue the long-term follow-up of these patients, we are encouraged that there are now 14 boys who have reached at least their Year 5 follow-up visit and continue to be living without MFDs, demonstrating the potential for a prolonged treatment effect," said Richard Colvin, M.D., Ph.D., VP, head of severe genetic diseases clinical research and development, bluebird bio. "There is a great need for alternative treatment options that reduce the risk of the serious immune complications associated with allogeneic stem cell transplantation, the current standard of care for CALD. Today's presentation continues to illustrate the potential of eli-cel as a one-time, durable treatment option for this devastating disease."

Adrenoleukodystrophy (ALD) is a rare, X-linked metabolic disorder[2,3] that is estimated to affect one in 21,000 male newborns worldwide.[3,4] ALD is caused by mutations in the *ABCD1* gene that affect the production of adrenoleukodystrophy protein (ALDP) and subsequently cause toxic accumulation of very long-chain fatty acids (VLCFAs) primarily in the adrenal cortex and white matter of the brain and spinal cord.[3]

Approximately 40% of boys with adrenoleukodystrophy will develop CALD, the most severe form of ALD[3], which is progressive and neurodegenerative, involving the breakdown of the nerve cells in the brain that are responsible for thinking and muscle control.[5,6] CALD is associated with six MFDs, which

*MFDs are defined as loss of communication, cortical blindness, need for tube feeding, total incontinence, wheelchair dependence, and complete loss of voluntary movement.

severely compromise a patient's ability to function independently: loss of communication, cortical blindness, need for tube feeding, total incontinence, wheelchair dependence, and complete loss of voluntary movement.[7,8,9] CALD usually occurs in early childhood and progresses rapidly, if untreated, leading to severe loss of neurologic function, and eventual death, in most patients.[5]

Eli-cel is a one-time investigational gene therapy designed to add functional copies of the *ABCD1* gene into a patient's own haematopoietic (blood) stem cells (HSCs) that have been transduced *ex vivo* with the Lenti-D lentiviral vector (LVV). The addition of the functional *ABCD1* gene allows patients to produce the adrenoleukodystrophy protein (ALDP), which is thought to activate the breakdown of VLCFAs. The goal of treatment with eli-cel is to stabilise the progression of CALD and consequently preserve as much neurological function as possible. Importantly, with eli-cel, there is no need for donor HSCs from another person.[8]

"CALD is a terrible disease that occurs in early childhood and, if left untreated, often leads to eventual death for these boys, a difficult fact for any clinician to bear. These data from the Phase 2/3 Starbeam study show some potentially promising evidence with up to almost seven years of follow-up and nearly all patients have a stable neurologic function score (n=31/32), indicating that minimal neurologic function was lost following eli-cel infusion. In addition, there were no reports of graft failure, graft rejection, or graft-versus-host disease," said Dr. Jörn-Sven Kühl, Department of Pediatric Oncology, Hematology and Hemostaseology, Center for Women's and Children's Medicine, University Hospital Leipzig. "These long-term results therefore suggest treatment with eli-cel may durably stabilise disease progression and consequently preserve as much neurological function as possible in boys with CALD."

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BACKGROUND INFORMATION

About Starbeam Study (ALD-102)/Long-Term Follow-Up Study (LTF-304)

The ALD-102 study has completed enrollment. All reported data below from ALD-102 are as of October 2020 and all reported data below from LTF-304 are as of November 2020.[1] These data reflect a total population of 32 patients with a median follow-up time of 38.6 months (13.4 – 82.7 months).[1]

Of the 32 patients who have received eli-cel in ALD-102, 27 have completed the study and enrolled in a long-term follow-up study (LTF-304).[1] Two additional patients continue to be followed in ALD-102 and have not reached 24 months post-treatment.[1] As previously reported, two patients withdrew from the study at investigator discretion, and one experienced rapid disease progression early on-study resulting in MFDs and subsequent death.[1] To date, 124 patient-years of follow-up have been collected for ALD-102 and LTF-304.

The primary efficacy endpoint in the study is the proportion of patients who are alive and free of MFDs at Month 24.[1] Of those patients who have reached Month 24, 90% (n=27/30) have met the primary endpoint and continue to be alive and MFD-free at two years of follow-up.[1] There is no evidence of MFDs through nearly seven years (up to 82.7 months) of follow-up in the 27 patients who completed ALD-102.[1] Fourteen patients in LTF-304 have reached at least their Year 5 follow-up visit, including 7 patients who have reached at least their Year 6 follow-up visit. The two patients from ALD-102 who have not reached Month 24 have also shown no evidence of MFDs.[1]

Data on several secondary and exploratory efficacy outcomes are reported, including changes in neurologic function score (NFS), a 25-point score used to evaluate the severity of gross neurologic

dysfunction across 15 symptoms in six categories; resolution of gadolinium enhancement (GdE), an indicator of active inflammation in the brain; and change in Loes score, an MRI measurement of white matter changes in CALD.[1] Stable NFS at last assessment is defined as maintaining an NFS ≤4 without an increase of >3 points from baseline.[1] Of the 32 patients treated, 31 had stable NFS at last available visit following treatment with eli-cel, and 23 patients maintained an NFS of 0.[1] An NFS of 0 indicates that there is no observed impairment in the neurologic functions that are assessed on the 25-point scale. As of available last visit, 26 of 32 patients had stable Loes scores (≤9 or change from baseline ≤6) and 28/32 were GdE-negative.[1]

The primary safety endpoint is the proportion of patients who experience acute (≥Grade 2) or chronic graft-versus-host disease (GvHD) by Month 24.[1] GvHD is a condition that may occur after an allo-HSCT, where the donated cells view the recipient's body as foreign and attack the body. No events of acute or chronic GvHD have been reported post eli-cel treatment.[1] There have been no reports of graft failure or graft rejection.[1] In addition, there have been no cases of replication-competent lentivirus or insertional oncogenesis to date.[1]

The treatment regimen, comprising mobilisation/apheresis, conditioning, and eli-cel infusion, had a safety and tolerability profile primarily reflective of the known effects of mobilisation/apheresis and conditioning. In ALD-102, as previously reported, three adverse events (AE) were considered possibly related to drug product and include one serious AE (SAE), BK viral cystitis (n=1, SAE), and two non-serious AEs, vomiting (n=2). All three AEs resolved with standard measures.[1]

About ALD-104 Study

ALD-104 is a Phase 3 study assessing the efficacy and safety of eli-cel in patients with CALD after myeloablative conditioning using busulfan and fludarabine, a different chemotherapy conditioning regimen than that used in ALD-102 (busulfan and cyclophosphamide). The primary efficacy endpoint is the proportion of patients who are alive and free of MFDs at Month 24, and the primary safety endpoint is the proportion of patients with neutrophil engraftment after eli-cel infusion. All reported data below are as of October 2020.[1]

In ALD-104, the 19 patients currently treated with eli-cel have a median follow-up of 8.6 months (min-max: 0.1 – 16.8 months) to date.[1] Due to the limited duration of follow-up, only safety data are being presented.[1] Efficacy data will be presented in a future scientific forum when sufficient follow-up is reached.

Seventeen of 19 evaluable patients achieved neutrophil engraftment (pending in two patients as of data cut-off date) and 15/19 evaluable patients had platelet engraftment (pending in two patients who are awaiting neutrophil engraftment and in two additional patients as of data cut-off date).[1] All patients with pending neutrophil or platelet engraftment had 35 or fewer days of follow-up.[1]

No events of acute or chronic GvHD have been reported and there have been no reports of graft failure, graft rejection, cases of insertional oncogenesis, or replication-competent lentivirus.[1]

The treatment regimen, comprising mobilisation/apheresis, conditioning, and eli-cel infusion had a safety and tolerability profile primarily reflective of the known effects of mobilisation/apheresis and conditioning. As previously reported, two serious AEs of pancytopaenia were considered possibly related to eli-cel.[1] These two ongoing SAEs were diagnosed approximately two months post eli-cel

infusion and following neutrophil engraftment in two patients.[1] Both patients achieved platelet engraftment (Day 104 and 108) and as of last visit (~13 months post eli-cel infusion) were clinically stable.[1]

An additional previously reported SAE of transverse myelitis was ongoing as of the data cut-off date.[1] The SAE was diagnosed in the presence of viral infection (adenovirus and rhinovirus/enterovirus positivity) approximately six months after eli-cel infusion and assessed as unrelated to eli-cel. As of the data cut-off, the patient was partially responsive to steroids and plasmapheresis and was experiencing incontinence and ambulation issues.[1]

About elivaldogene autotemcel (eli-cel, formerly Lenti-D™ gene therapy)

In October 2020, the European Medicines Agency (EMA) accepted bluebird bio's marketing authorization application (MAA) for its investigational eli-cel gene therapy for the treatment of patients with cerebral adrenoleukodystrophy (CALD). The EMA accepted eli-cel gene therapy for the treatment of CALD into its Priorities Medicines scheme (PRIME) in July 2018, and previously granted Orphan Medicinal Product designation to eli-cel.

The U.S. Food and Drug Administration (FDA) granted eli-cel Orphan Drug status, Rare Pediatric Disease designation, and Breakthrough Therapy designation for the treatment of CALD. bluebird bio is currently on track to submit the Biologics License Application (BLA) in the U.S. in mid-2021.

Eli-cel is not approved for any indication in any geography.

About CALD Early Diagnosis

Early diagnosis of CALD is important, as the outcome of available treatment varies with the clinical stage of the disease.[7,10,11,12,13,14,15] Newborn screening for ALD is a critical enabler of early diagnosis and thus of successful treatment of ALD.[16,17,18] Once a patient has been diagnosed with ALD, regular MRI scans are critical to detect white matter changes indicative of progression to CALD.[11,19]

In the U.S., newborn screening for ALD was added to the Recommended Universal Screening Panel in February 2016 and is currently active in 19 states and the District of Columbia, accounting for ≥60 percent of U.S. newborns.[20] Even though ALD newborn screening has not been implemented in most EU countries, efforts to begin pilot programmes are slowly progressing. The Minister of Health in the Netherlands has approved the addition of ALD to their newborn screening programme.[20,21]

About bluebird bio, Inc.

bluebird bio is pioneering gene therapy with purpose. From our Cambridge, Mass., headquarters, we're developing gene and cell therapies for severe genetic diseases and cancer, with the goal that people facing potentially fatal conditions with limited treatment options can live their lives fully. Beyond our labs, we're working to positively disrupt the healthcare system to create access, transparency and education so that gene therapy can become available to all those who can benefit.

bluebird bio is a human company powered by human stories. We're putting our care and expertise to work across a spectrum of disorders: cerebral adrenoleukodystrophy, sickle cell disease, β-thalassemia

and multiple myeloma, using gene and cell therapy technologies including gene addition, and (megaTAL-enabled) gene editing.

bluebird bio has additional nests in Seattle, Wash.; Durham, N.C.; Zug, Switzerland; Munich, Germany; Milan, Italy; Utrecht, the Netherlands; Hampshire, United Kingdom; Paris, France; and Athens, Greece.

For more information, visit bluebirdbio.eu.

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