bluebird bio Presents New Results from Clinical Development Programme of elivaldogene autotemcel (eli-cel, Lenti-D™) Gene Therapy for Cerebral Adrenoleukodystrophy (CALD), Including Updated Long-Term Data

Long-term results from Phase 2/3 Starbeam (ALD-102/LTF-304) study suggests durability of response post eli-cel with all 20 patients who were free of major functional disabilities (MFDs)[*] at two years (out of 23 evaluable patients) remaining MFD-free through last available follow-up, including all 10 patients who reached at least Year 5 follow-up visit [1]

31 out of 32 patients in ALD-102 had stable neurologic function scores (NFS) following treatment, including 24 patients with a score of zero as of the last available visit[1]

In clinical studies of eli-cel to date, there have been no reports of graft failure, graft rejection or graft-versus-host disease (GvHD), replication competent lentivirus or insertional oncogenesis [1]

Company is on track to submit Marketing Authorisation Application in the EU by year-end 2020, and Biologics License Application in the U.S. in mid-2021

CAMBRIDGE, Mass.--(BUSINESS WIRE)—August 29, 2020—bluebird bio, Inc. (Nasdaq: BLUE) announced updated results from the clinical development programme for its investigational elivaldogene autotemcel (eli-cel, Lenti-D™) gene therapy in patients with cerebral adrenoleukodystrophy (CALD), including long-term results from the Phase 2/3 Starbeam study (ALD-102/LTF-304) and data from the Phase 3 study (ALD-104). These data were presented today at the 46th Annual Meeting of the European Society for Blood and Marrow Transplantation (EBMT).

“CALD is a fatal neurodegenerative disease primarily affecting young boys. Currently, the only treatment available is allogeneic haematopoietic stem cell transplantation (allo-HSCT), which comes with associated, significant risks, including transplant-related mortality, graft failure or rejection, and graft-versus-host disease (GvHD),” said David Davidson, M.D., chief medical officer, bluebird bio. “Eighty-seven percent of patients in our Phase 2/3 Starbeam study are alive and free of MFDs at 24 months or more of follow-up. Importantly, there were no reports of graft failure, graft rejection, or GvHD. It is gratifying to see the consistent outcomes and the durability of the treatment effect demonstrated in the children participating in our long-term follow-up study - including 10 boys who have now reached at least their Year 5 follow-up visit.”

Adrenoleukodystrophy (ALD) is a rare, X-linked metabolic disorder that is estimated to affect one in 21,000 male newborns worldwide.[2,3] 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.[2,3]

[*]Major functional disabilities are defined as loss of communication, cortical blindness, tube feeding dependence, total incontinence, wheelchair dependence, complete loss of voluntary movement, and ultimately death related to neurologic deterioration.

Approximately 40% of boys with adrenoleukodystrophy will develop CALD, the most severe form of ALD.[3,4] CALD is a progressive, neurodegenerative disease that involves breakdown of myelin, the protective sheath of the nerve cells in the brain that are responsible for thinking and muscle control. Symptoms of CALD usually occur in early childhood and progress rapidly, if untreated, leading to severe loss of neurologic function, and eventual death, in most patients.[5,6,7,8] CALD is associated with six MFDs which 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.[6,9,10] Nearly half of boys with CALD who do not receive treatment will die within five years of symptom onset.[5,6]

"Patients with CALD experience a rapid decrease in neurologic function after the initial onset of clinical symptoms, so early diagnosis and treatment are critical in order to stop the disease progression and preserve their neurological function. In the Phase 2/3 Starbeam study, 31 of 32 patients had a stable Neurologic Function Score, suggesting that disease progression had stabilised and minimal neurological function was lost, following eli-cel infusion," said Dr. Jörn-Sven Kühl, Department of Paediatric Oncology, Haematology and Haemostaseology, Centre for Women's and Children's Medicine, University Hospital Leipzig. "These results presented at EBMT 2020 are very encouraging and suggest treatment may prevent neurological decline in boys with CALD."

Eli-cel is a one-time investigational gene therapy designed to address the underlying genetic cause of CALD by adding 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 a functional gene allows patients to produce the ALDP, which is thought to break down the toxic accumulation of VLCFAs in the brain. There is no need for donor HSCs from another person, as is required for allo-HSCT.

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

The ALD-102 study has completed enrollment. All reported data below are as of January 2020 and reflect a total population of 32 patients with a median follow-up time of 30.0 months (9.1 – 70.7 months).[1]

Of the 32 patients treated as of January 2020, 20 have completed ALD-102 and enrolled in a long-term follow-up study (LTF-304). Nine additional patients continue to be followed in ALD-102 and have not reached 24 months post-treatment. 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 death. To date, 104.3 patient-years of follow-up have been reported for ALD-102 and LTF-304.[1]

The primary efficacy endpoint in the study is the proportion of patients who are alive and free of MFDs at Month 24. Of those patients who have or would have reached Month 24, 87% have met the primary endpoint and continue to be alive and MFD-free at more than two years of follow-up (N=20/23). 14 patients have at least four years of follow-up, including 10 patients who have reached at least their Year 5 follow-up visit. The nine patients from ALD-102 who have not reached Month 24, have 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] Of the 32 patients treated, 31 had stable NFS following treatment, defined as NFS ≤4, without a change of >3 from baseline, and twenty-four patients maintained an NFS of 0. An NFS of 0 indicates that there are no concerns with the neurologic functions that are assessed on the 25-point scale. Loes scores generally stabilised within 12–24 months and GdE was no longer seen in most patients following treatment.[1]

The primary safety endpoint is the proportion of patients who experience acute (≥Grade 2) or chronic GvHD by Month 24. GvHD is a condition that may occur after an allo-HSCT, where the donated cells view the recipient's body as foreign and attack. No events of acute or chronic GvHD have been reported post eli-cel treatment. 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. Integration site analysis (ISA) was conducted to determine the pattern of integration post gene therapy infusion and assess whether dominant or expanding clones were present.[1] In one patient, now enrolled in LTF-304 for long-term follow up, a case of benign clonal expansion was observed with three separate integrations in the DNA of the cell at *ACER3*, *RFX3*, and *MECOM*. As of the patient's Month 62 visit in March 2020, the patient remained clinically stable. Bone marrow analyses showed no dysplasia (abnormal cell growth) or molecular abnormalities.[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 the drug product and include one serious AE (SAE), BK viral cystitis (N=1, SAE, Grade 3), and two non-serious AEs, vomiting (N=2, Grade 1). All three AEs resolved using standard measures.[1]

ALD-104 Study

bluebird bio is currently enrolling patients for ALD-104, a Phase 3 study designed to assess the efficacy and safety of eli-cel in patients with CALD after myeloablative conditioning using busulfan and fludarabine, a different chemotherapy conditioning regimen than what is 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 infusion. All reported data below are as of February 2020.[1]

In ALD-104, the 13 patients currently on study have a median of 6.1 months of follow-up to date (min-max: 2.2 – 10.3 months). All 13 patients achieved neutrophil engraftment and 12/13 evaluable patients had platelet engraftment (platelet engraftment pending in one patient as of data cut date). Due to the limited duration of follow-up, only safety data are being presented.[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. In ALD-104, two AEs of pancytopenia were considered possibly related to drug product These two ongoing AEs were deemed as suspected unexpected serious adverse reactions (SUSARs) by

the principal investigator and were diagnosed approximately two months post treatment infusion in two patients (one Grade 2 and one Grade 3). An additional AE was ongoing as of February 2020, a Grade 3 SAE of transverse myelitis that was diagnosed in the presence of viral infection (adenovirus and rhinovirus/enterovirus positivity) approximately six months after eli-cel infusion, and deemed unrelated to treatment.[1]

About elivaldogene autotemcel (eli-cel, formerly Lenti-D™)
In July 2020, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) granted an accelerated assessment to eli-cel gene therapy for cerebral adrenoleukodystrophy (CALD). bluebird bio is currently on track to submit the Marketing Authorisation Application (MAA) in the EU for eli-cel for CALD by year-end 2020, and the Biologics License Application (BLA) in the U.S. in mid-2021.

For information about bluebird bio-sponsored studies visit: **clinicaltrials.gov**.

The European Medicines Agency (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.

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.

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

About ALD Early Diagnosis
Early diagnosis of CALD is important, as the outcome of available treatment varies with the clinical stage of the disease.[6,11,12,13,14] Newborn screening for ALD is a critical enabler of early diagnosis and thus of successful treatment of ALD. Once a patient has been diagnosed with ALD, regular MRI scans are critical to detect white matter changes indicative of progression to CALD.

In the U.S., newborn screening for ALD was added to the Recommended Universal Screening Panel in February 2016 and is currently active in 17 states, accounting for ≥58 percent of U.S. newborns. Outside the U.S., the Minister of Health in the Netherlands has approved the addition of ALD to their newborn screening programme.[15,16,17,18,19] Even though ALD newborn screening has not been implemented in most EU countries, efforts to begin pilot programmes are slowly progressing.[20]

About bluebird bio, Inc.
bluebird bio is pioneering gene therapy with purpose. From our Cambridge, Mass., headquarters, we're developing gene 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 including cerebral adrenoleukodystrophy, sickle cell disease, β-

thalassemia and multiple myeloma, using three gene therapy technologies: gene addition, cell therapy 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; and Paris, France.
For more information, visit **bluebirdbio.co.uk**.

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