Treatment with Investigational LentiGlobin™ Gene Therapy for Sickle Cell Disease (bb1111) Results in Complete Elimination of SCD-Related Severe Vaso-Occlusive Events in Phase 1/2 HGB-206 Clinical Study Presented at 62nd ASH Annual Meeting and Exposition

No severe vaso-occlusive events (VOEs) were reported through 24 months of follow up in Group C patients of the HGB-206 study who had a history of at least four severe VOEs and at least six months of follow-up (n=19)[1]

At up to 30 months follow-up and 32 patients treated, Group C patients continue to produce consistent levels of gene therapy-derived anti-sickling haemoglobin (HbA^{T87Q}), reducing levels of abnormal sickle haemoglobin (HbS) that causes symptoms of sickle cell disease[1]

Patient-reported quality of life outcomes, assessed through validated PROMIS-57, demonstrated clinically meaningful reductions in pain intensity at month 12 post-LentiGlobin for SCD treatment[2]*

ZUG, Switzerland— Dec. 7, 2020— bluebird bio, GmbH. (Nasdaq: BLUE) announced that new data from Group C of its ongoing Phase 1/2 HGB-206 study of investigational LentiGlobin™ gene therapy (bb1111) in adult and adolescent patients with sickle cell disease (SCD) show a complete elimination of severe vaso-occlusive events (VOEs) and VOEs as defined in the study protocol between six and 24 months of follow up. These data are being presented at the 62nd American Society of Hematology (ASH) Annual Meeting and Exposition, taking place virtually from December 5-8, 2020.

"Now with more than two years of data, we continue to observe promising results in our studies of LentiGlobin for SCD that further illustrate its potential for complete resolution of severe VOEs and VOEs as seen between Month 6 and Month 24 follow up. Importantly, our data show the potential for LentiGlobin for SCD to produce fundamentally disease-modifying effects with sustained pancellular distribution of gene therapy-derived anti-sickling HbA^{T87Q} and improvement of key markers of haemolysis that approach near-normal levels in the study," said David Davidson, M.D., chief medical officer, bluebird bio. "In addition to these clinical outcomes, for the first time with a gene therapy we now have patient-reported outcomes through the validated PROMIS-57 tool, showing reduction in pain intensity at 12 months after treatment. These results provide insight into the potential real-life impact gene therapy for SCD may offer patients."

SCD is a serious, progressive and debilitating genetic disease.[3,4,5] In the U.S., the median age of death for someone with sickle cell disease is 43 – 46 years.[6,7] SCD is caused by a mutation in the β-globin gene that leads to the production of abnormal sickle haemoglobin (HbS).[3,4,5,8] HbS causes red blood cells to become sickled and fragile, resulting in chronic haemolytic anaemia, vasculopathy and unpredictable, painful VOEs.[3,4,5,8,9]
In the HGB-206 study, VOEs are defined as episodes of acute pain with no medically determined cause other than a vaso-occlusion, lasting more than two hours and severe enough to require care at

**Defined as the threshold of change that is clinically meaningful for the patient. For the PROMIS, this is generally regarded as at least a 2-point change for the pain Numeric Rating Scale (NRS) and a 5-point change for the other domains.*

a medical facility.[1] This includes acute episodes of pain, acute chest syndrome (ACS), acute hepatic sequestration, and acute splenic sequestration.[1] A severe VOE requires a 24-hour hospital stay or emergency room visit, or at least two visits to a hospital or emergency room over a 72-hour period, with both visits requiring intravenous treatment.[1]

This gene therapy was designed to add functional copies of a modified form of the β-globin gene ($\beta^{A\text{-}T87Q}$-globin gene) into a patient's own haematopoietic (blood) stem cells (HSCs).[10] If the treatment is successful, the patients' red blood cells can produce anti-sickling haemoglobin (HbA^{T87Q}) that decreases the proportion of HbS, with the goal of reducing sickled red blood cells, haemolysis and other complications.[3]

"As a physician, I regularly see the debilitating effects and severe pain that my patients with sickle cell disease experience when they have a VOE," said presenting study author Alexis A. Thompson, M.D., Northwestern University Feinberg School of Medicine. "The results observed with this treatment, including the complete elimination of VOEs after six months, are very encouraging."

As of August 20, 2020, a total of 44 patients have been treated with gene therapy in the HGB-205 (n=3) and HGB-206 (n=41) clinical studies. The HGB-206 total includes: Group A (n=7), B (n=2) and C (n=32).[1]

HGB-206: Group C Updated Efficacy Results

The 32 patients treated with gene therapy in Group C of HGB-206 had up to 30.9 months of follow-up (median of 13.0; min-max: 1.1 – 30.9 months).[1]

In patients with six or more months of follow-up (n=22), median levels of gene therapy-derived anti-sickling haemoglobin, HbA^{T87Q}, were maintained with HbA^{T87Q} contributing at least 40% of total haemoglobin at Month 6.[1] At last visit reported, total haemoglobin ranged from 9.6 – 15.1 g/dL and HbA^{T87Q} levels ranged from 2.7 – 8.9 g/dL. At Month 6, the production of HbA^{T87Q} was associated with a reduction in the proportion of HbS in total haemoglobin; median HbS was 50% and remained less than 60% at all follow up timepoints.[1] All patients in Group C were able to stop regular blood transfusions by three months post treatment and remain off transfusions at the latest data cut-off.

Nineteen patients treated in Group C had a history of severe VOEs, defined as at least four severe VOEs in the 24 months prior to informed consent (annualized rate of severe VOE min-max: 2.0 – 10.5 events) and at least six months follow up after treatment.[1] There have been no reports of severe VOEs in these Group C patients following treatment.[1] In addition, all 19 patients had a complete resolution of VOEs after Month 6.[1]

Haemolysis Markers

In SCD, red blood cells become sickled and fragile, rupturing more easily than healthy red blood cells.[9] The breakdown of red blood cells, called haemolysis, occurs normally in the body. However, in SCD, haemolysis happens too quickly due to the fragility of the red blood cells, which results in haemolytic anaemia.[4]

Patients treated with gene therapy in Group C demonstrated near-normal levels in key markers of haemolysis, which are indicators of the health of red blood cells.[1] Lab results assessing these indicators were available for the majority of the 25 patients with ≥6 months of follow-up.

Pancellularity
As previously reported, assays were developed by bluebird bio to enable the detection of HbA^{T87Q} and HbS protein in individual red blood cells as well as to assess if HbA^{T87Q} was pancellular, i.e. present throughout all of a patient's red blood cells. In 25 patients with at least 6 months of follow up, on average more than 80% of red blood cells contained HbA^{T87Q}, with pancellularity further increasing over time.

HGB-206: Improvements in Health-Related Quality of Life
Health-related quality of life (HRQoL) findings in Group C patients treated in the HGB-206 study were generated using the Patient Reported Outcomes Measurement Information System 57 (PROMIS-57), a validated instrument to measure HRQoL in SCD.[2]

Data assessing pain intensity experienced by nine Group C patients were analyzed according to baseline pain intensity scores relative to the general population normative value: 2.6 on a scale of 0 – 10, where 10 equals the most intense pain. Data were assessed for HGB-206 Group C patients with PROMIS-57 results available at baseline, Month 6 and Month 12.[2]

Of the five patients with baseline scores worse than the population normative value average, four demonstrated clinically meaningful reductions in pain intensity at Month 6 and 12; the group had a mean score of 6.0 at baseline and a mean score of 2.0 at month 6 and 2.4 at Month 12 respectively.[2] Of the four patients with better than or near population normative values at baseline, two reported improvement and two remained stable with a mean score of 2.3 at baseline, 0.3 at month 6 and 0.8 at Month 12.[2]

HGB-206: Group C Safety Results
As of August 20, 2020, the safety data from Group C patients in HGB-206 remains generally consistent with the known side effects of haematopoietic stem cell collection and myeloablative single-agent busulfan conditioning as well as underlying SCD.[1] One non-serious, Grade 2 adverse event (AE) of febrile neutropenia was considered related to gene therapy. There were no serious AEs related to gene therapy treatment.[1]

One patient with significant baseline SCD-related and cardiopulmonary disease died 20 months post-treatment; the treating physician and an independent monitoring committee agreed his death was unlikely related to gene therapy, and that SCD-related cardiacopulmonary disease contributed.[1]

About HGB-206
HGB-206 is an ongoing, Phase 1/2 open-label study designed to evaluate the efficacy and safety of gene therapy for SCD that includes three treatment cohorts: Groups A (n=7), B (n=2) and C (n=32). A refined manufacturing process that was designed to increase vector copy number (VCN) and improve engraftment potential of gene-modified stem cells was used for Group C. Group C patients also received gene therapy for SCD made from HSCs collected from peripheral blood after mobilization with plerixafor, rather than via bone marrow harvest, which was used in Groups A and B of HGB-206.

About LentiGlobin for Sickle Cell Disease
LentiGlobin is an investigational gene therapy being studied as a potential treatment for SCD. bluebird bio's clinical development program for gene therapy for SCD includes the ongoing Phase 1/2 HGB-206 study and the ongoing Phase 3 HGB-210 study.

LentiGlobin for SCD received Orphan Medicinal Product designation from the European Commission for the treatment of SCD, and Priority Medicines (PRIME) eligibility by the European Medicines Agency (EMA) in September 2020. The U.S. Food and Drug Administration (FDA) granted Orphan Drug status, Regenerative Medicine Advanced Therapy (RMAT) designation, and Rare Pediatric Disease designation for LentiGlobin for SCD.

LentiGlobin for SCD is investigational and has not been approved in any geography.

About bluebird bio
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: cerebral adrenoleukodystrophy, sickle cell disease, β-thalassaemia 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; Paris, France; and Athens, Greece.

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