# UNITED STATES
# SECURITIES AND EXCHANGE COMMISSION
**WASHINGTON, D.C. 20549**

# FORM 8-K

**CURRENT REPORT**

**Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934**

**Date of Report (Date of earliest event reported): December 3, 2018**

# bluebird bio, Inc.

**(Exact name of Registrant as Specified in Its Charter)**

| DELAWARE | 001-35966 | 13-3680878 |
|---|---|---|
| (State or Other Jurisdiction of Incorporation) | (Commission File Number) | (IRS Employer Identification No.) |
| 60 Binney Street, Cambridge, MA (Address of Principal Executive Offices) | | 02142 (Zip Code) |

**Registrant's Telephone Number, Including Area Code: (339) 499-9300**

**Not Applicable**
**(Former Name or Former Address, if Changed Since Last Report)**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (see General Instructions A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Indicate by check mark whether the registrant is an emerging growth company as defined in as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

**Item 7.01 Regulation FD Disclosure.**

On December 3, 2018, bluebird bio, Inc. ("bluebird") conducted an investor webcast presenting updated clinical data for the LentiGlobin product candidate in the treatment of patients with transfusion-dependent β-thalassemia (HGB-204, HGB-207, and HGB-212), for the LentiGlobin product candidate in the treatment of patients with sickle cell disease (HGB-206), and for the bb21217 product candidate in the treatment of patients with relapsed-refractory multiple myeloma (CRB-402), as presented at the 60th Annual Meeting of the American Society of Hematology ("ASH") in San Diego, CA. A copy of the presentation is being furnished as Exhibit 99.1 to this Current Report on Form 8-K.

The information in Item 7.01 of this Current Report on Form 8-K and Exhibit 99.1 attached hereto is intended to be furnished and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933 or the Exchange Act, except as expressly set forth by specific reference in such filing.

**Item 8.01 Other Events.**

On December 3, 2018, bluebird issued a press release announcing data presented at ASH from the Phase 3 Northstar-2 (HGB-207) and Phase 3 Northstar-3 (HGB-212) clinical studies of its investigational LentiGlobin product candidate in patients with transfusion-dependent β-thalassemia.

Also on December 3, 2018, bluebird issued a press release announcing data presented at ASH from patients in Group C of its ongoing Phase 1/2 HGB-206 study of its investigational LentiGlobin product candidate in patients with sickle cell disease.

The full text of bluebird's press releases regarding these announcements are filed as Exhibits 99.2 and 99.3 to this Current Report on Form 8-K and are incorporated herein by reference.

**Item 9.01 Financial Statements and Exhibits.**

(d) Exhibits

| Exhibit No. | Description |
|---|---|
| 99.1 | Investor presentation provided by bluebird bio, Inc. on December 3, 2018. |
| 99.2 | Press release issued by bluebird bio, Inc. on December 3, 2018 regarding data from HGB-207 and HGB-212 studies. |
| 99.3 | Press release issued by bluebird bio, Inc. on December 3, 2018 regarding data from Group C HGB-206 study. |

**SIGNATURES**

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Date: December 4, 2018

**bluebird bio, Inc.**

By: /s/ Jason F. Cole
Jason F. Cole
*Chief Legal Officer*

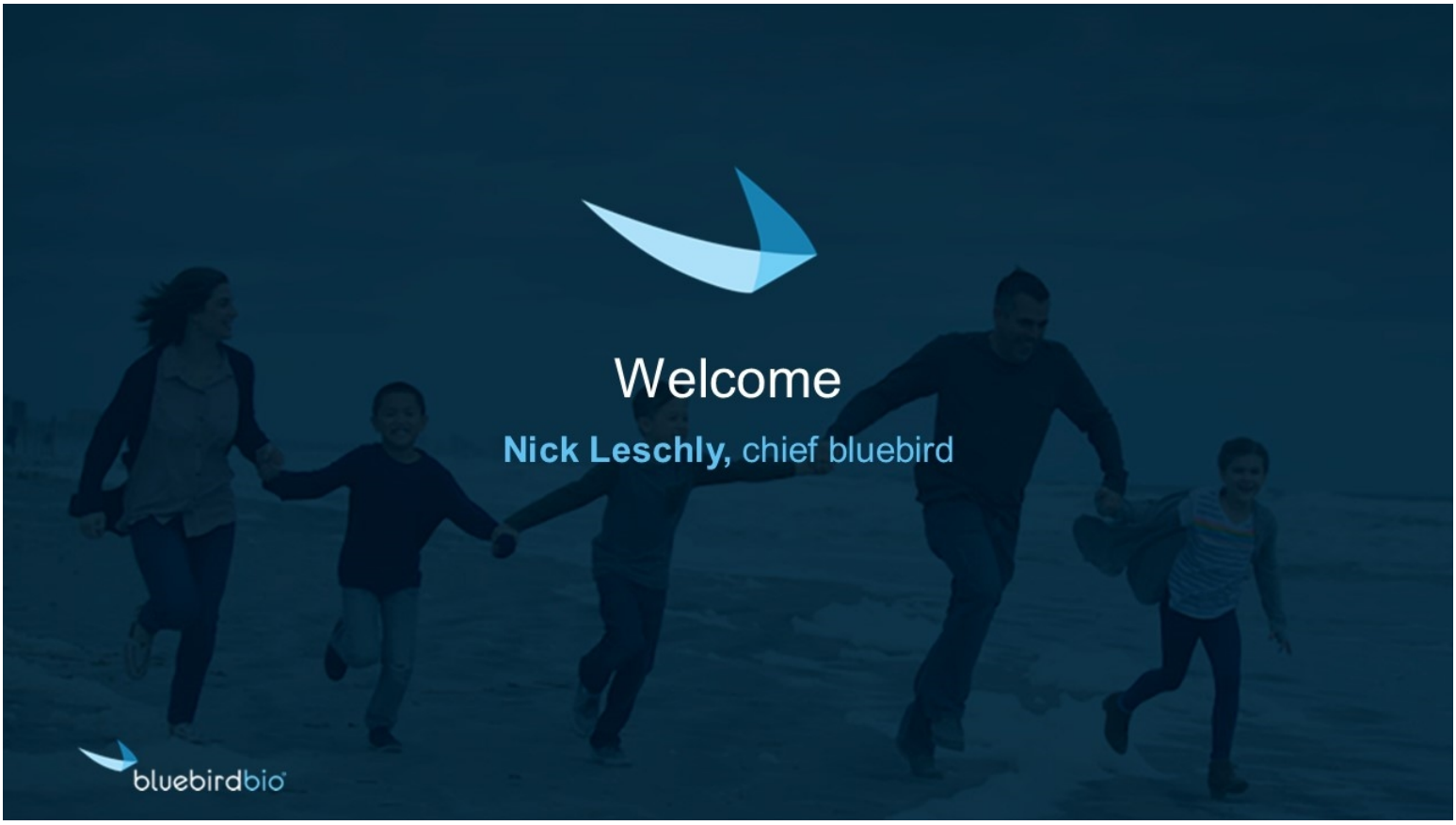
Exhibit 99.1

# Forward-Looking Statements

These slides and the accompanying oral presentation contain forward-looking statements and information. The use of words such as “may,” “might,” “will,” “should,” “expect,” “plan,” “anticipate,” “believe,” “estimate,” “project,” “intend,” “future,” “potential,” or “continue,” and other similar expressions are intended to identify forward-looking statements. For example, all statements we make regarding the initiation, timing, progress and results of our preclinical and clinical studies and our research and development programs, our ability to advance product candidates into, and successfully complete, clinical studies, and the timing or likelihood of regulatory filings and approvals are forward looking. All forward-looking statements are based on estimates and assumptions by our management that, although we believe to be reasonable, are inherently uncertain. All forward-looking statements are subject to risks and uncertainties that may cause actual results to differ materially from those that we expected. These statements are also subject to a number of material risks and uncertainties that are described in our most recent quarterly report on Form 10-Q, as well as our subsequent filings with the Securities and Exchange Commission. Any forward-looking statement speaks only as of the date on which it was made. We undertake no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events or otherwise, except as required by law.

# Agenda

| | |
|---|---|
| Welcome | **Liz Pingpank,** director, investor relations, bluebird bio<br>**Nick Leschly,** chief bluebird, bluebird bio |
| Severe Genetic Diseases | **David Davidson, M.D.,** chief medical officer, bluebird bio<br>**John Tisdale, M.D.,** National Heart, Lung and Blood Institute at the National Institutes of Health (NIH), Bethesda, MD |
| Multiple Myeloma | **Liviu Niculescu, M.D., Ph.D.,** SVP, global medical affairs, bluebird bio<br>**Nina Shah, M.D.,** University of California, San Francisco |
| Closing | **Nick Leschly,** chief bluebird, bluebird bio |


Welcome
Nick Leschly, chief bluebird
bluebirdbio


Making Hope
A Reality


2022 Vision on Track
LentiGlobin TDT
Potential First Approval (2019)
Lenti-D CALD
Potential First Approval (2020)
2022
THE GENE THERAPY PRODUCTS COMPANY
LentiGlobin SCD
Data-Driven Acceleration
∞
Patient Impact
bb2121 Multiple Myeloma
Potential First Approval (2020)
2+ Products on the Market
2+ Programs Nearing Commercialization
4+ Additional Programs in the Clinic

# 2018 – A Year of Tremendous Learning and Growth

***Advancing** the development of our programs and working with regulatory authorities to reach our goal of delivering **transformative therapies to patients** with severe genetic diseases and cancer.*

| | |
|---|---|
| **Transfusion-Dependent β-Thalassemia** | • First Marketing Authorization Application (MAA) filed with EMA with PRIME Designation<br>• 2019 EU launch on track<br>• U.S. registration plan based on Northstar-2 with Breakthrough Designation |
| **Sickle Cell Disease** | • Robust and consistent production of anti-sickling $HbA^{T87Q}$ hemoglobin<br>• Accelerated development path with RMAT Designation |
| **Cerebral Adrenoleukodystrophy** | • General regulatory agreement on Biologics License Application (BLA) and MAA filings<br>• Anticipated 2020 approval on track with Breakthrough Designation |
| **Multiple Myeloma** | • Registration-enabling study enrollment complete; 3rd & 2nd line studies enrolling soon<br>• bb21217 proof-of-concept; dose escalation underway<br>• Anticipated 2020 approval on track with Breakthrough and PRIME Designations |
| **Pipeline & Technology** | • Manufacturing: North Carolina facility build out<br>• Research Engine: Regeneron & Gritstone oncology partnerships<br>• Pipeline Growth:<br>  • SCD next gen BCL11a program with Dana-Farber/Boston Children's Cancer and Blood Disorders Center<br>  • *in vivo* gene editing CAR T preclinical proof of concept (CBL-B) |

# Breadth & Depth of ASH Data Underscores BLUE Potential

| | | |
|---|---|---|
| NORTHSTAR / NORTHSTAR-2 / NORTHSTAR-3 | LentiGlobin TDT | • **Northstar: Outcomes following study completion**<br>• **Northstar-2: Updated results**<br>• **First look: Northstar-3** |
| HGB-206 | LentiGlobin SCD | • **HGB-206 Group C: Updated results**<br>• HGB-206 Group A & B: Updated results<br>• Real world evidence: U.S. population<br>• HGB-205: Analysis of RBC properties in patients |
| CRB-402 | bb21217 MM | • **First look: CRB-402 initial results in R/R multiple myeloma** |
| BCL11a | shRNA$^{miR}$ SCD | • **First look: Initial clinical results in partnership with Dana-Farber/Boston Children's Cancer and Blood Disorders Center** |
| | Preclinical | • **First look: megaTAL engineered CAR T cells**<br>• **NHP-based target validation with gene-edited hematopoietic stem cells** |

**Bold indicates bluebird oral presentations*

# Transfusion-Dependent β-Thalassemia and Sickle Cell Disease

**David Davidson, M.D.**, chief medical officer, bluebird bio

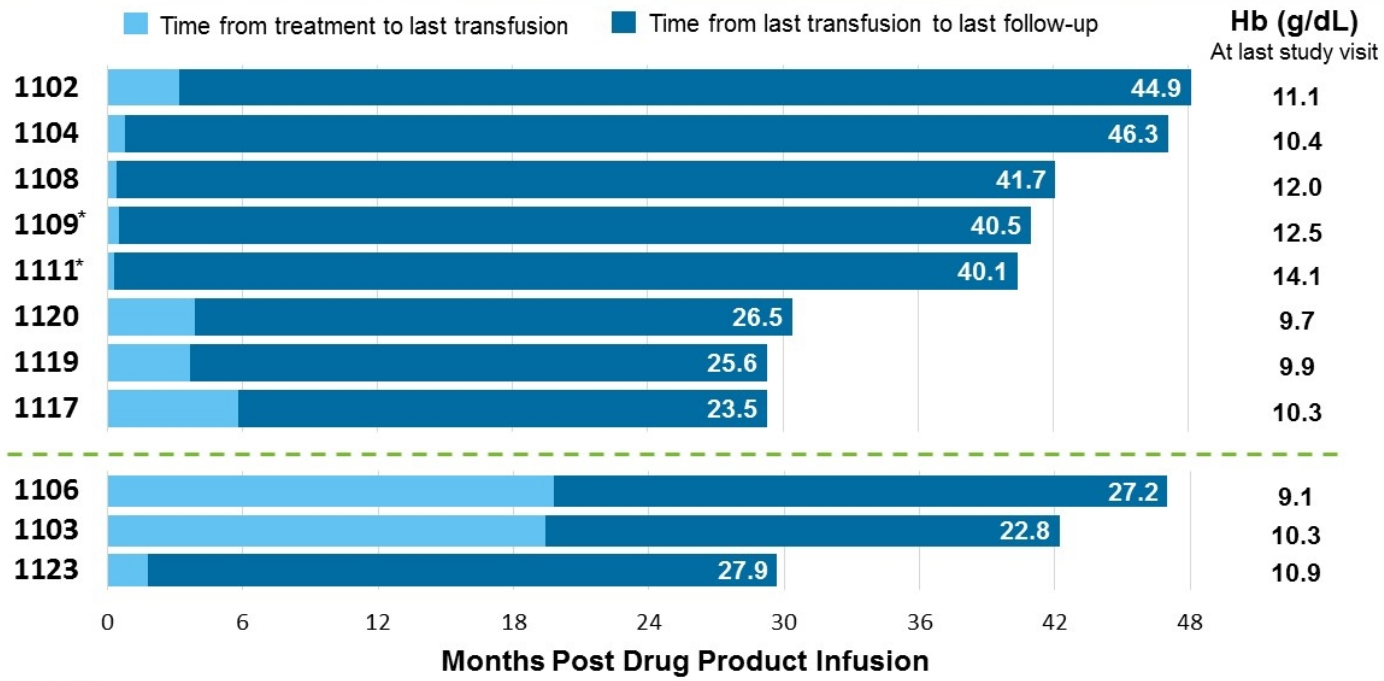
# Transfusion-Dependent β-Thalassemia (TDT)

- Inherited blood disease that requires lifelong, frequent blood transfusions and iron reduction therapy

## PROGRAM OVERVIEW

- Filed MAA with European Medicines Agency
- General regulatory agreement with FDA for BLA filing
- Studies ongoing:
  - Northstar-2 (HGB-207)
  - Northstar-3 (HGB-212)
  - HGB-205
- Long-term follow-up: LTF-303

# 8/10 Patients with Non-$\beta^0/\beta^0$ Genotypes and 3/8 Patients with $\beta^0/\beta^0$ Genotypes are Free from Chronic RBC Transfusions



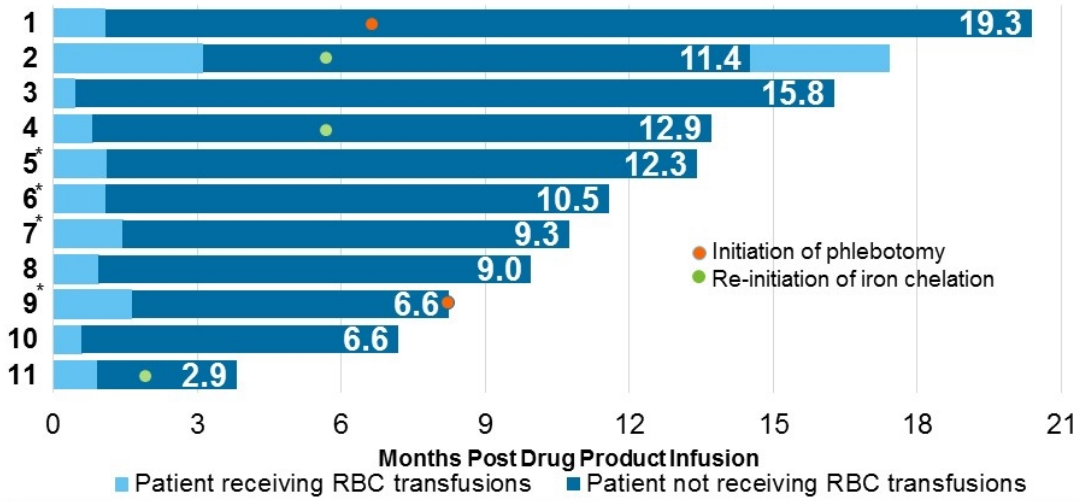



*Indicates male patients. Hb, hemoglobin; TI, transfusion independence (weighted average Hb ≥9 g/dL without any red blood cell transfusions for ≥12 months)

# 10/11 Patients Are Transfusion Free with Hemoglobin >11g/dL

NORTHSTAR-2 STUDY

## Time free from chronic transfusions in patients with ≥3 months follow-up



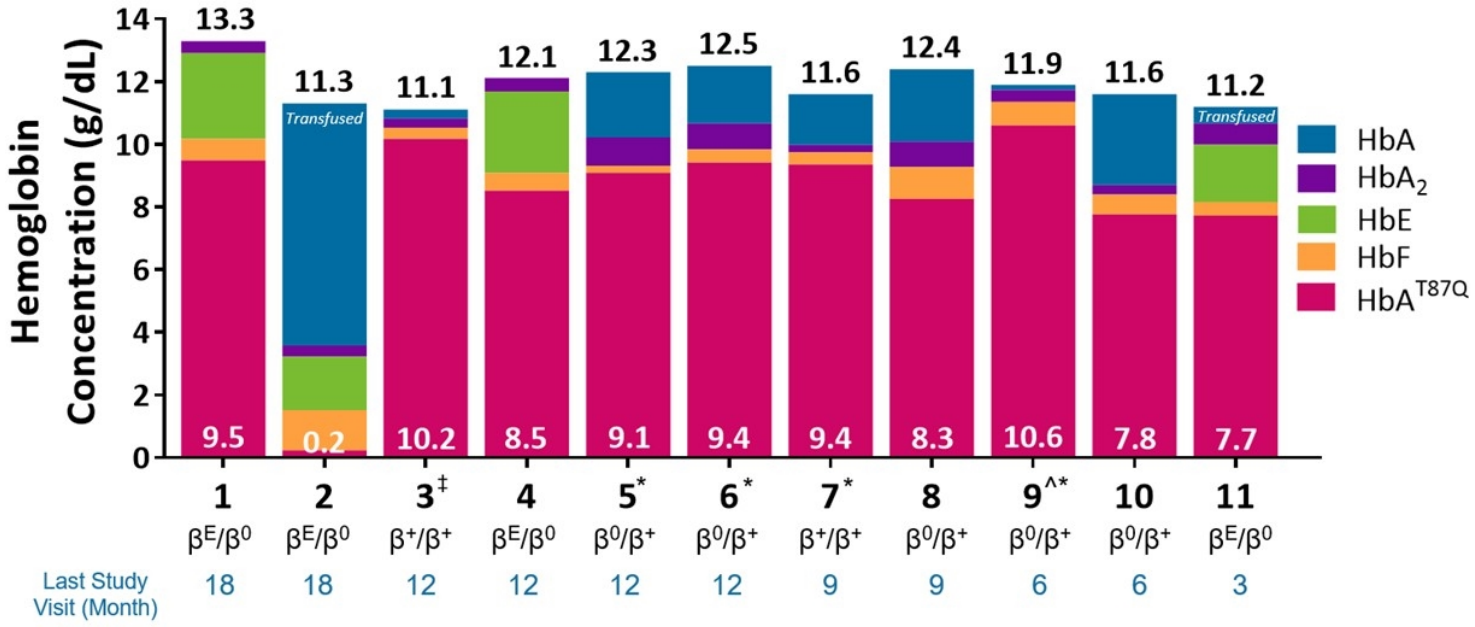

| | Hb (g/dL) At last study visit | Peripheral VCN At last study visit |
|---|---|---|
| 1 | 13.3 | 3.2 |
| 2 | 11.3‡ | 0.4 |
| 3 | 11.1 | 2.2 |
| 4 | 12.1 | 1.7 |
| 5* | 12.3 | 1.7 |
| 6* | 12.5 | 2.9 |
| 7* | 11.6 | 5.6 |
| 8 | 12.4 | 1.1 |
| 9* | 11.9 | 4.9 |
| 10 | 11.6 | 5.4 |
| 11 | 11.2 | 5.6 |

**Safety profile post DP infusion remains consistent with myeloablative conditioning**

**Patients 1 and 3 have achieved the protocol definition of transfusion independence†**

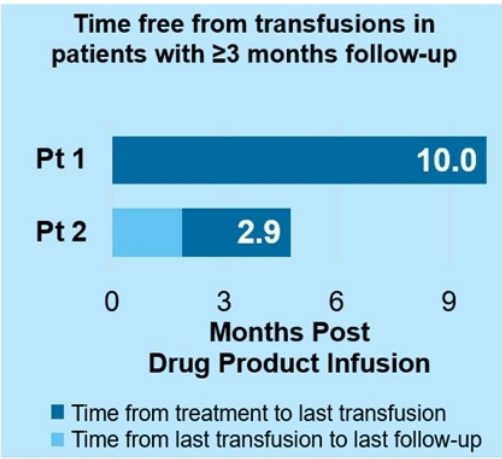
*Male patients; ‡Hb supported by transfusions; †Weighted average Hb ≥9 g/dL without any RBC transfusions for ≥12 months; Hb, hemoglobin; VCN, vector copy number (vector copies/diploid genome)

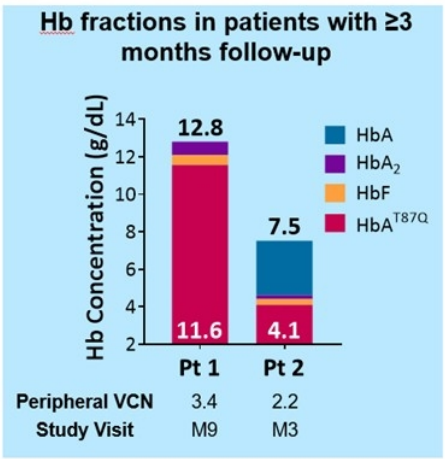
# High Levels of Gene Therapy Derived $HbA^{T87Q}$ in 10/11 Patients

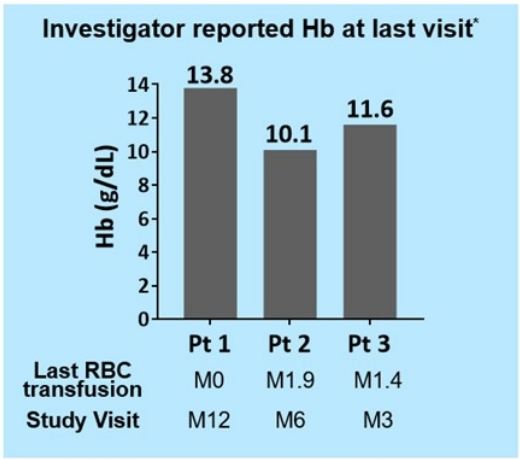



*Male patients; ‡Patient is homozygous for IVS-I-5 β-globin mutation; ^Patient is heterozygous for IVS-I-5 β-globin mutation. Hb, hemoglobin.

# Normal Total Hemoglobin in First Northstar-3 $\beta^0/\beta^0$ Patient




**Safety profile post-drug product infusion remains consistent with myeloablative conditioning**

*Includes investigator reported data as of November 19, 2018, not from programmed statistical outputs

AEs, adverse events; DP, drug product; Hb, hemoglobin; VCN, vector copy number (vector copies/diploid genome)

# TDT Data – Key Takeaways

**Transfusion-Dependent β-Thalassemia**

- **MAA Filed** with EMA; commercial preparation on track
- **Northstar-2:** 10/11 patients with ≥3 months follow-up are transfusion free
- **Northstar-3:** First patient with $\beta^0/\beta^0$ genotype achieving normal total hemoglobin; 2/2 patients with ≥6 months follow-up producing >10g/dL total hemoglobin

**Sickle Cell Disease**

- Accelerated development plan using novel composite primary endpoint based on hemoglobin
- **Group C** patients treated under refined manufacturing protocol show robust production of anti-sickling hemoglobin
- Early indications from biomarker analysis support fundamentally improving RBC physiology

**Multiple Myeloma**

- **bb2121:** KarMMa enrollment complete; clinical program is advancing including planned 2019 studies in front line, in collaboration with Celgene
- **bb21217:** Overall response rate of 83% at first dose level tested (vs. 57% at same dose in CRB-401); early indications of increased persistence using enriched CAR T cells

**Next-generation**

- **shmiR:** At ≥4 months post-gene therapy, ~70% F cells were observed and HbF contributed ~25-30% of total Hb
- **CBL-B:** Further validation underway; taking aim at solid tumors

# Sickle Cell Disease Development Plan

## Sickle Cell Disease (SCD)

- Severe blood disorder that causes anemia, frequent pain crises and shortened lifespan
- Global annual birth incidence ~ 300,000 – 400,000
- Mean age of death in the U.S. is 44 years[1]

### PROGRAM OVERVIEW

- Plan to pursue accelerated development path based on hematological primary endpoint
  - Phase 3 study to begin in 2019
- HGB-206 amended and Group C expanded

[1]Paulukonis et al, California's Sickle Cell Data Collection Cohort, 2005-2015* ASH 2017*

# Increasing Momentum to #ConquerSCD

**2017**

- March 2017, bluebird SCD case study published in *NEJM*
- July 2017, the FDA approved Endari (L-glutamine oral powder) to address acute complications of SCD


**2018**

- February 2018, Admiral Brett Giroir, M.D., appointed as Assistant Secretary for Health, HHS, is shining a spotlight on the toll of SCD and the need for improved treatment options
- March 2018, NHLBI launched "Cure SCD Initiative" spearheaded by Dr. Francis Collins
- October 2018, FDA-ASH Sickle Cell Disease Clinical Endpoints Workshop

"Unfortunately, some treated [SCD] patients will have no reduction of their symptoms and the disease will continue to progress," says Ann T. Farrell, M.D., director of the FDA's Division of Hematology Products, CDER. "***Better therapies are desperately needed***," Farrell explains. "We will continue to work with sponsors as much as possible to help remove roadblocks to new product development. ***It's important for the FDA to help as much as we can***."

FDA

# Accelerated Development Plan Using Novel Composite Primary Endpoint Based on Hemoglobin

**EXPANDED**

Updated Primary Endpoint

Up to add'l 21 patients

Expanded age range

## HGB-206 Group C

**(Sickle Cell Disease, history of VOEs over 24 months)**

**Ongoing Phase 1/2, single arm, multi-center, U.S. study**
**N=41 (Group C)**

- Primary Endpoint: $HbA^{T87Q}$ and Total Hb
- Key Secondary Endpoint:
  - Reduction in severe VOEs
- ≥12 years of age - ≤50 years of age

## HGB-210

**(Sickle Cell Disease, history of VOEs over 24 months)**

**Phase 3, single arm, multi-center, global study**

- Primary Endpoint: $HbA^{T87Q}$ and Total Hb
- Key Secondary Endpoint:
  - Reduction in severe VOEs

**NEW**

Planned for 2019

Additional Clinical Investigation in Other Patient Types and Ages Planned

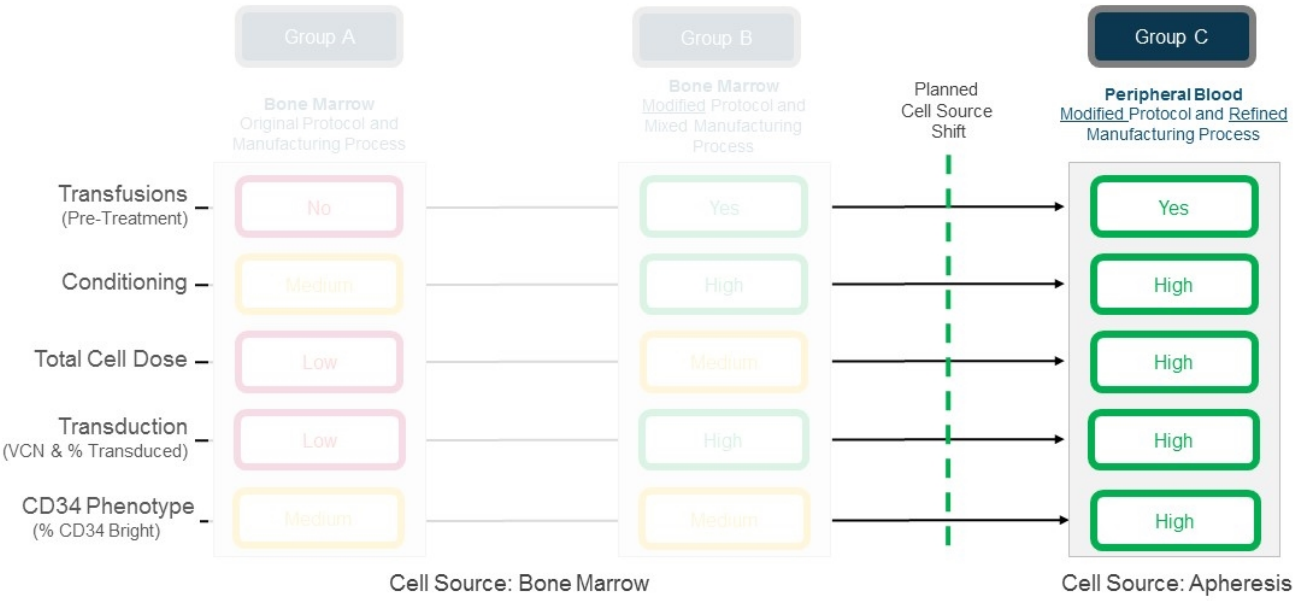
Plans Based on Ongoing Engagement with Regulators

# Sickle Cell Disease

**John Tisdale, M.D.,** National Heart, Lung and Blood Institute at the NIH, Bethesda, MD

# Evolution of LentiGlobin in SCD

HGB-206



# Group C: Patient Characteristics
*N=14 Patients Who Started Cell Collection*

HGB-206

| Parameter | Group C N=14 |
|---|---|
| **Age at consent**<br>median (min – max), years | **25.5**<br>(18 – 36) |
| **Gender** | **6 F 8 M** |
| **Genotype**<br>$\beta^S/\beta^S$ | **14** |
| **Prior SCD History** | |
| **Hydroxyurea use**, n | **8** |
| **Recurrent VOCs**[*], n<br>Annualized no. of events, median (min – max) | **9**<br>**6.5** (3.5 – 14.0) |
| **ACS**[†], n<br>Annualized no. of events, median (min – max) | **2**<br>**1** (1 – 1) |
| **Any history of stroke**, n | **3** |
| **TRJV >2.5 m/s**, n | **0** |

* ≥2 events/year in preceding 2 years; † ≥2 episodes in preceding 2 years, with at least one episode in the past year or in the year prior to the initiation of a regular transfusion program

ACS, acute chest syndrome; F, female; M, male; VOC, vaso-occlusive crisis; pRBC, packed red blood cell; TRJV, tricuspid regurgitant jet velocity

# Group C: Safety Profile Generally Consistent with Myeloablative Busulfan Conditioning

HGB-206

| **Non-hematologic* grade ≥ 3 AEs**<br>Post-DP infusion in ≥2 patient | **n (%)**<br>**N=9** |
|---|---|
| Febrile neutropenia | 6 (67) |
| Stomatitis | 6 (67) |
| **Serious AEs***<br>Post-DP infusion in ≥1 patient | **n (%)**<br>**N=9** |
| Abdominal pain | 1 (11) |
| Depression | 1 (11) |
| Drug withdrawal syndrome | 1 (11) |
| Hallucination | 1 (11) |
| Mucosal inflammation | 1 (11) |
| Nausea | 1 (11) |
| Non-cardiac chest pain | 1 (11) |
| Splenic hematoma | 1 (11) |
| Vomiting | 1 (11) |

*Hematologic AEs commonly observed post-transplant have been excluded

- **No VOEs post-DP infusion in 9 patients**
- SAEs were reported in 4 patients
  - No AE considered related to DP
  - No cases of VOD observed to date
- No vector-mediated RCL detected to date
- Integration site (IS) analysis data available for two patients at 6 month visit
  - Total IS: Showed consistent polyclonality
- One patient in Group A: MDS diagnosed 36 months post-DP infusion: no evidence of LVV integration in dysplastic cells; monosomy 7 mutation identified (associated with sporadic and chemotherapy-related MDS)



AE, adverse event; DP, drug product; RCL, replication competent lentivirus; SAE, serious adverse event; VOD, veno occlusive liver disease; VOE, vaso-occlusive event; LVV, lentiviral vector

# Critical Elements of LentiGlobin Success in SCD
*Fundamentally Improving Red Blood Cell Physiology*

| GOAL | GROUP C RESULTS |
|---|---|
| **High & Stable Levels of $HbA^{T87Q}$ Derived Hemoglobin & Total Hemoglobin** | • 4 out of 4 patients with ≥47% anti-sickling Hb (range: 47% - 62%) at 6 months<br>• Sustained expression of $HbA^{T87Q}$ levels through 9 months follow-up |
| **Correction of Hemolysis** | • Normalization of reticulocyte counts, lactate dehydrogenase and bilirubin levels |
| **Pancellular Expression of $HbA^{T87Q}$ Resulting in Reduction of Sickling** | • Pancellular expression shown in two independent assays of patient cells<br>• Reduction of sickling of patient RBCs at levels consistent with sickle trait cells |
| **Improvement of Clinical Outcomes** | • Increased total hemoglobin and robust $HbA^{T87Q}$ production<br>• No VOEs in early clinical follow up |

# Critical Elements of LentiGlobin Success in SCD
*Fundamentally Improving Red Blood Cell Physiology*

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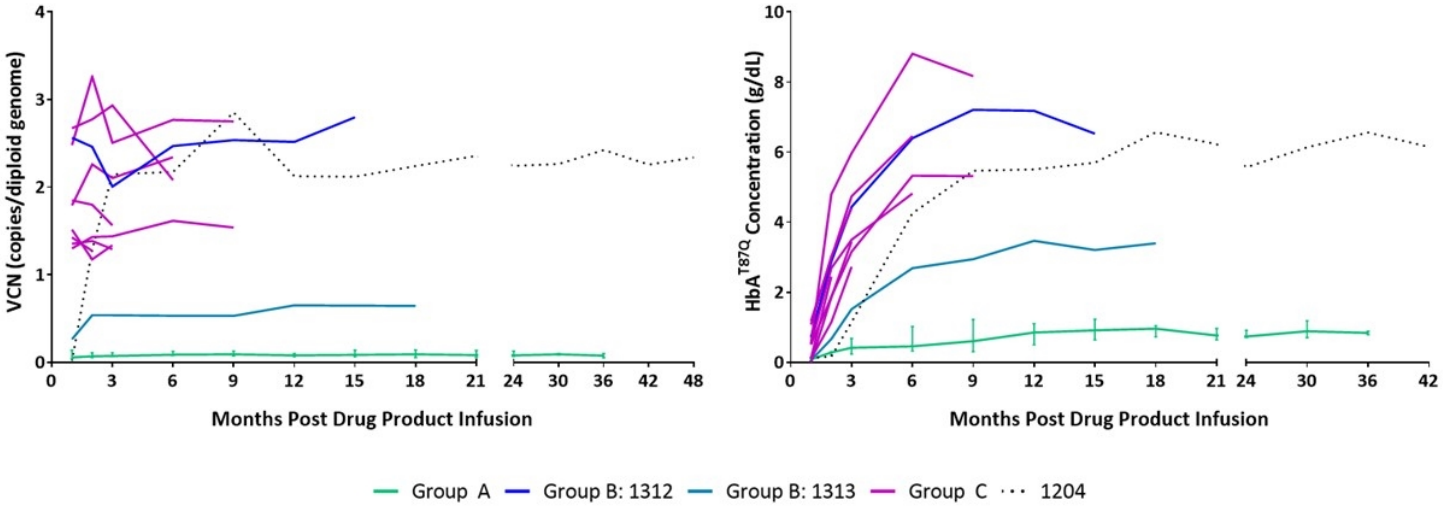
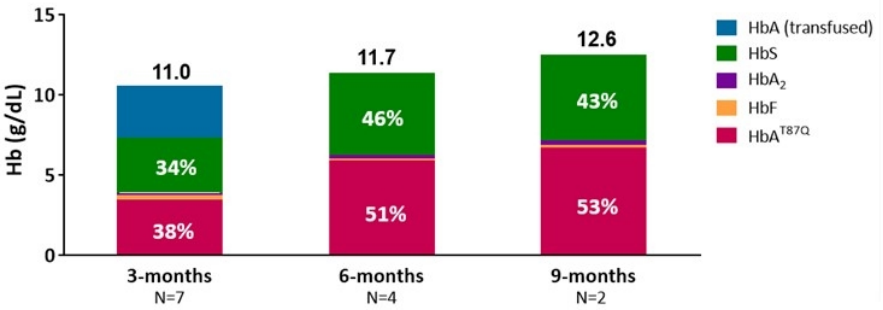
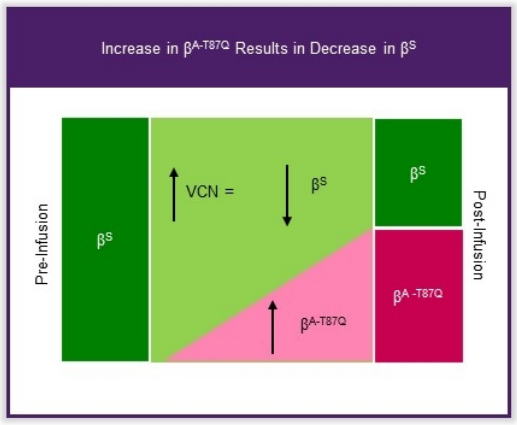
# Group C: Stable Peripheral Blood VCN, $HbA^{T87Q}$ Trajectory Robust and Consistent






For Group A patients, medians (Q1, Q3) depicted; Group A patients with month 36 study visit (N=2)




βS-globin decreasing with increasing HbAT87Q
(average concentration of hemoglobin per cell has not changed post-treatment)

# Critical Elements of LentiGlobin Success in SCD
*Fundamentally Improving Red Blood Cell Physiology*

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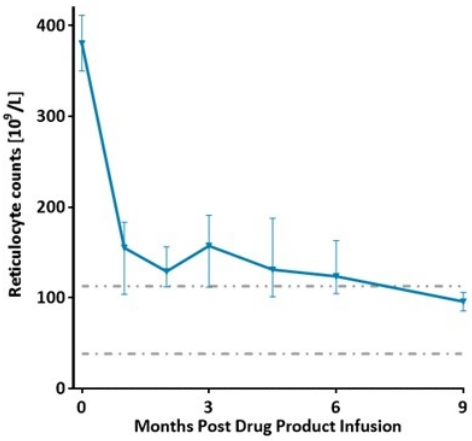
| Improvement of Clinical Outcomes | • Increased total hemoglobin and robust $HbA^{T87Q}$ production<br>• No VOEs in early clinical follow up |

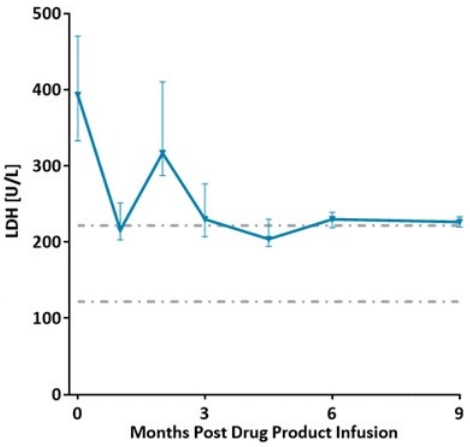
# Impact on Clinical Outcomes of SCD in Group C
## *Normalization of Key Biomarkers of Hemolysis Over Time*

HGB-206

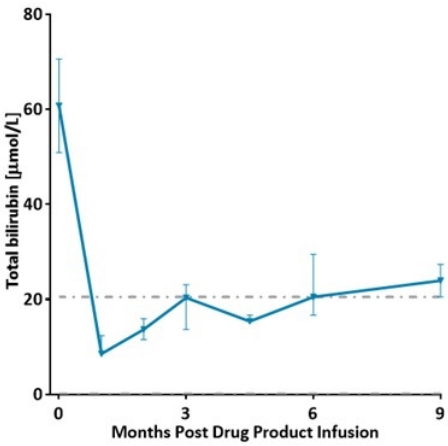
**Reticulocyte Counts**




**Lactate Dehydrogenase**




**Total Bilirubin**




Dot-dash lines denote lower and upper limits of normal values

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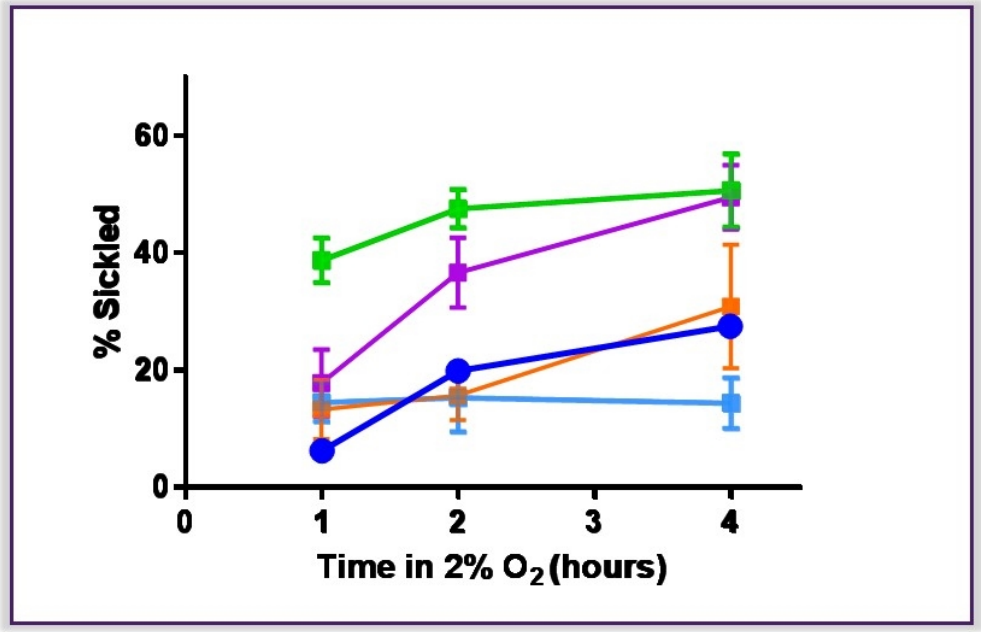
# LentiGlobin has Anti-Sickling Activity Comparable to Sickle Trait

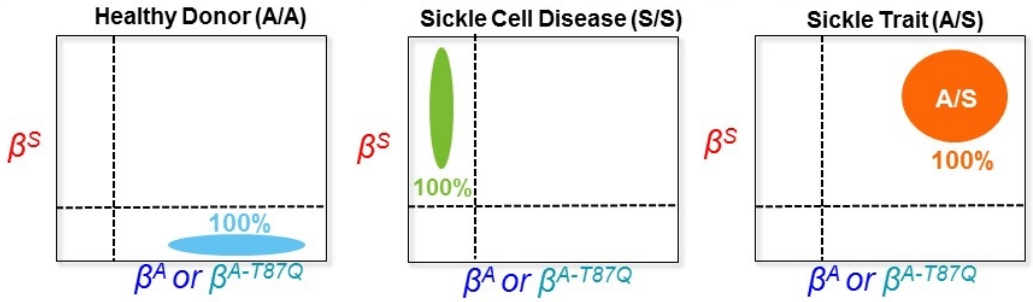
*Reduction in % Sickled and Time to Sickling in Patient RBCs Post-Treatment*




*HbF levels in HPFH donors ranged from 28.1 to 42.3%

# Two Independent Assays Indicate Near Pancellular $\beta^{A\text{-}T87Q}$ Distribution

*Majority of Patient RBCs are Positive for Anti-Sickling Globin*



# Two Independent Assays Reveal Near Pancellular $\beta^{A\text{-}T87Q}$ Distribution

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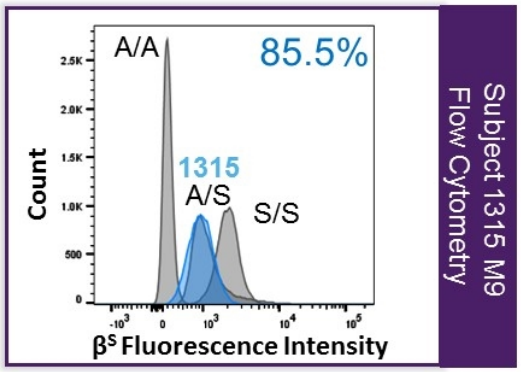


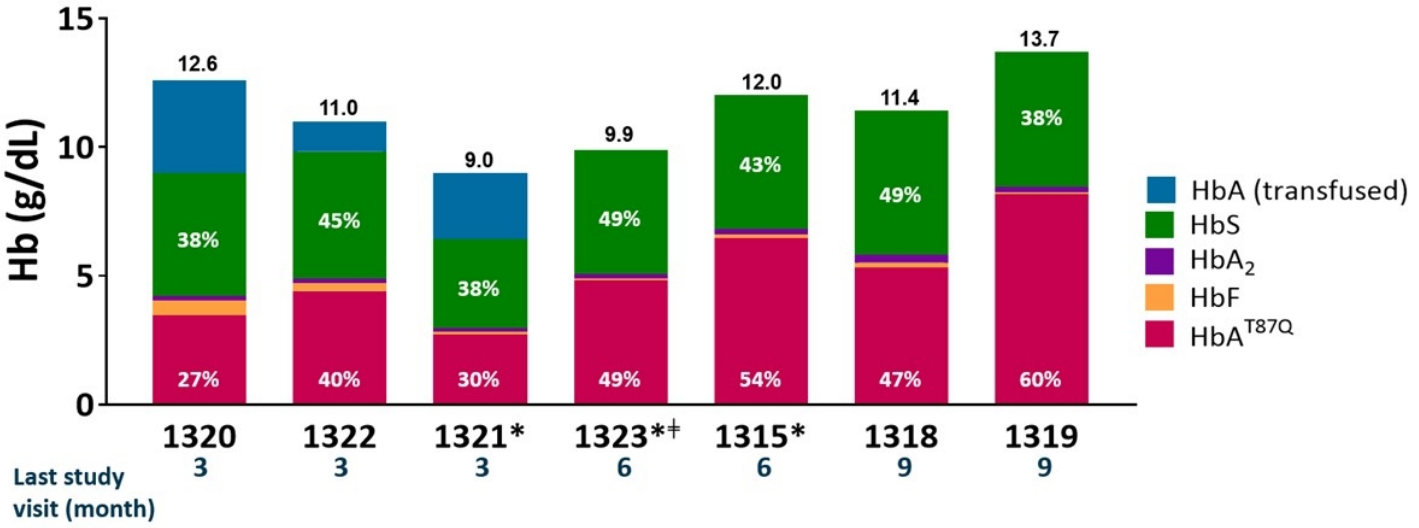
# Critical Elements of LentiGlobin Success in SCD
*Fundamentally Improving Red Blood Cell Physiology*

| GOAL | GROUP C RESULTS |
|---|---|
| **High & Stable Levels of $HbA^{T87Q}$ Derived Hemoglobin & Total Hemoglobin** | • 4 out of 4 patients with ≥47% anti-sickling Hgb (range: 47% - 62%) at 6 months<br>• Sustained expression of $HbA^{T87Q}$ levels through 9 months follow up |
| **Correction of Hemolysis** | • Normalization of reticulocyte counts, lactate dehydrogenase and bilirubin levels |
| **Pancellular Expression of $HbA^{T87Q}$ Resulting in Reduction of Sickling** | • Pancellular expression shown in two independent assays of patient cells<br>• Reduction of sickling of patient RBCs at levels consistent with sickle trait cells |
| **Improvement of Clinical Outcomes** | • Increased total hemoglobin and robust $HbA^{T87Q}$ production<br>• No VOEs in early clinical follow-up |

# Impact on Clinical Outcomes of SCD

## *Resolution of Anemia (and Robust HbA$^{T87Q}$ Levels) in All Patients by 6 Months; No VOEs Since DP Infusion*

HGB-206




Group C: All patients free of VOEs as of data cut-off



* Denotes female patients; ‡ Patient current receiving phlebotomy

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# SCD Data – Key Takeaways

**Transfusion-Dependent β-Thalassemia**

- **MAA Filed** with EMA; commercial preparation on track
- **Northstar-2:** 10/11 patients with ≥3 months follow-up are transfusion free
- **Northstar-3:** First patient with $\beta^0/\beta^0$ genotype achieving normal total hemoglobin; 2/2 patients with ≥6 months follow up producing >10g/dL total hemoglobin

**Sickle Cell Disease**

- Accelerated development plan using novel composite primary endpoint based on hemoglobin
- **Group C** patients treated under refined manufacturing protocol show robust production of anti-sickling hemoglobin
- Early indications from biomarker analysis support fundamentally improving RBC physiology

**Multiple Myeloma**

- **bb2121:** KarMMa enrollment complete; clinical program is advancing including planned 2019 studies in front line, in collaboration with Celgene
- **bb21217:** Overall response rate of 83% at first dose level tested (vs. 57% at same dose in CRB-401); early indications of increased persistence using enriched CAR T cells

**Next-generation**

- **shmiR:** At ≥4 months post-gene therapy, ~70% F cells were observed and HbF contributed ~25-30% of total Hb
- **CBL-B:** Further validation underway; taking aim at solid tumors

# Multiple Myeloma

**Liviu Niculescu, M.D., Ph.D.,** SVP, global medical affairs, bluebird bio

# Multiple Myeloma

- A lethal blood cancer that often infiltrates the bone marrow causing anemia, kidney failure, immune problems and bone fractures

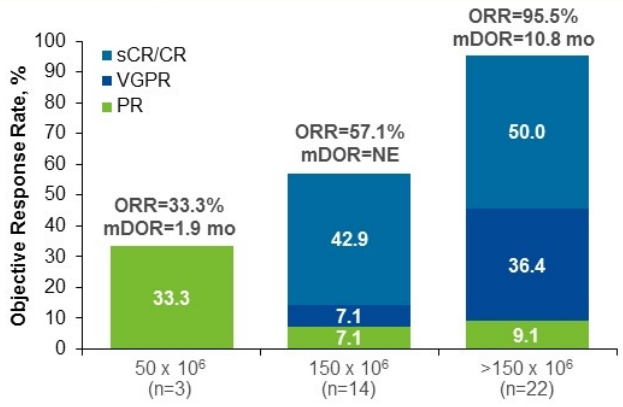
## BCMA PROGRAM OVERVIEW

- bb2121: Enrollment in KarMMa registration-enabling study complete (N=140)
- Additional studies advancing:
  - KarMMa-2 in 2nd line Phase 2 study enrolling soon
  - KarMMa-3 in 3rd line+ Phase 3 study enrolling soon
  - Opportunities for bb2121 in newly diagnosed MM including high risk, transplant ineligible and transplant eligible vs. transplant under evaluation

# CRB-401 Data at ASCO 2018 - Tumor Response and Progression-Free Survival

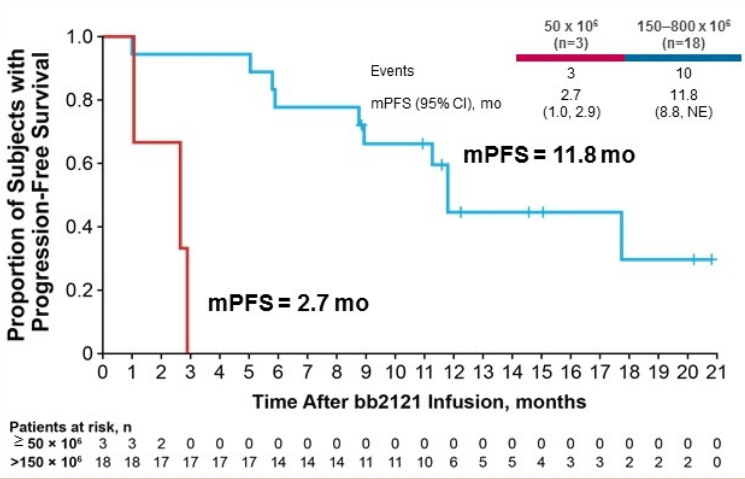
CRB-401

## Tumor Response By Dose[1]




| Median follow-up (min, max), d | 84 (59, 94) | 87 (36, 638) | 194 (46, 556) |
|---|---|---|---|

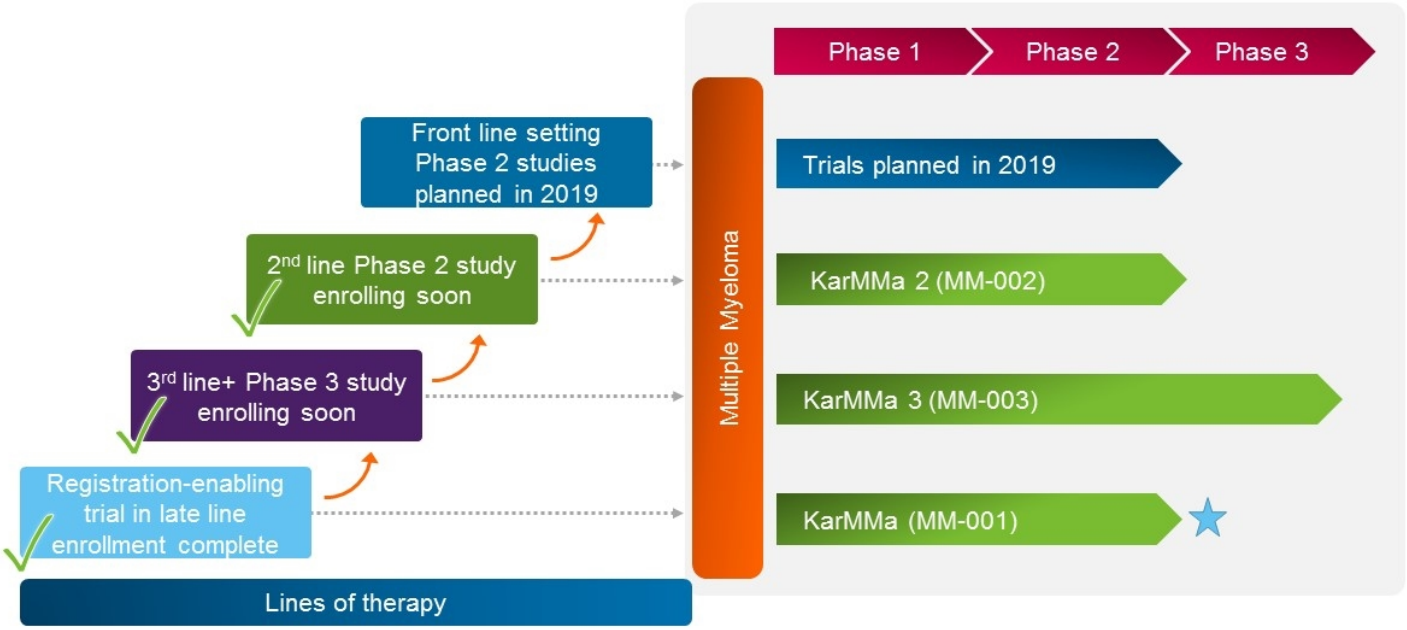
## PFS at Inactive (50 x $10^6$) and Active (150–800 x $10^6$) Dose Levels[2]




- 80.6% ORR across active dose cohorts (150-800 x $10^6$)

CR, complete response; mDOR, median duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; sCR, stringent CR; VGPR, very good partial response. Data cut-off: March 29, 2018. [1]Patients with ≥2 months of response data or PD/death within <2 months. ORR is defined as attaining sCR, CR, VGPR, or PR, including confirmed and unconfirmed responses. Median and 95% CI from Kaplan-Meier estimate. NE, not estimable. [2]PFS in dose escalation cohort.

# Advancing bb2121 into Earlier Lines of Multiple Myeloma



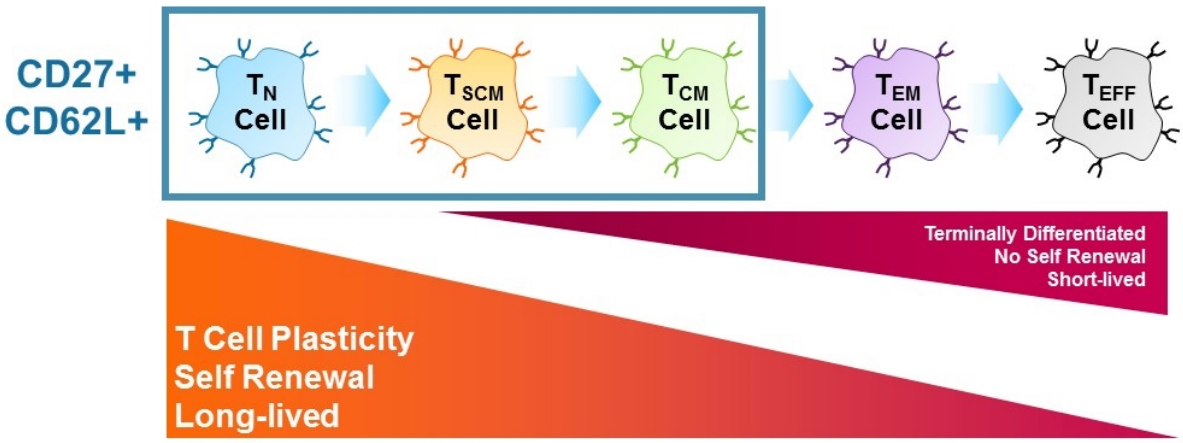

★ *Anticipated Approval in 2020*

# Multiple Myeloma: bb21217

**Nina Shah, M.D.,** University of California, San Francisco

# bb21217: PI3K Inhibition During Manufacturing Drives Increase in Long-lived, Memory-like T Cells

CRB-402

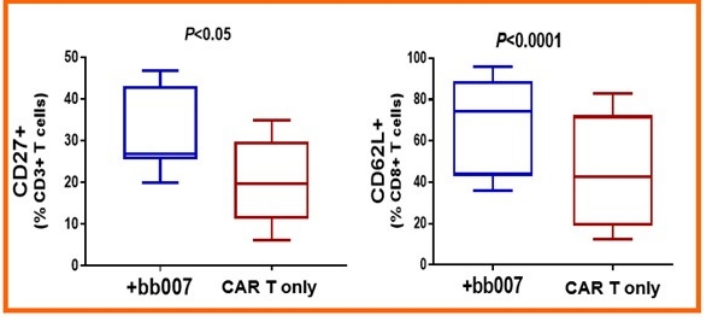



**Hypothesis: Increasing long-lived, memory-like T Cell subsets in the drug product may result in enhanced persistence of functional anti-BCMA CAR T cells *in vivo***

# Preclinical Models: bb21217 is Enriched for Memory-like T Cells Exhibits; Enhanced Persistence of Anti-tumor Effect

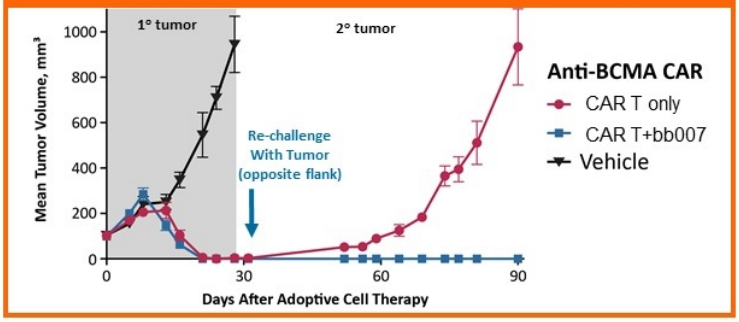
CRB-402

## bb007 enriches for memory-like T Cell phenotype




- CD62L and CD27 are markers of memory-like T cells
- bb21217 is significantly enriched for T cells with this memory-like phenotype

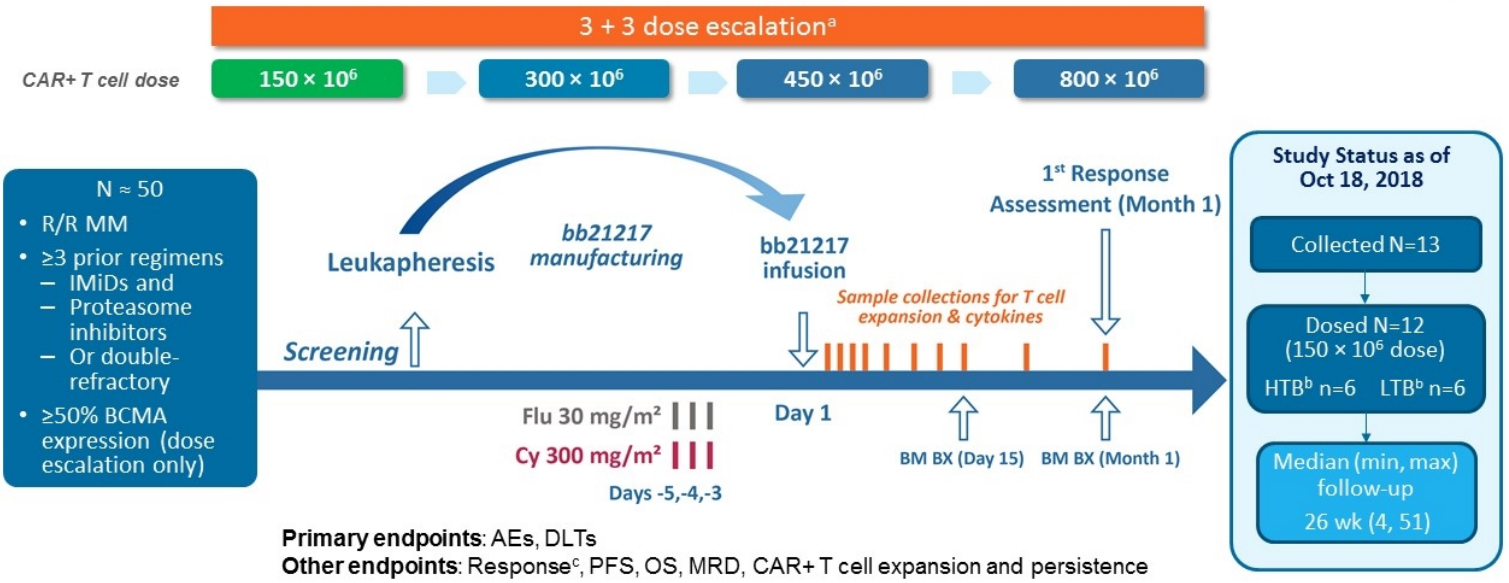
## bb007 enhances anti-tumor effect in mouse models




- ONLY CAR T cells cultured with PI3K inhibitor bb007 (i.e. bb21217) clear a second tumor challenge
- Data are consistent with improved persistence of functional CAR T cells leading to sustained anti-tumor effect

# CRB-402 Phase 1 Study Design and Status

CRB-402




**Primary endpoints**: AEs, DLTs
**Other endpoints**: Response[c], PFS, OS, MRD, CAR+ T cell expansion and persistence

NCT03274219

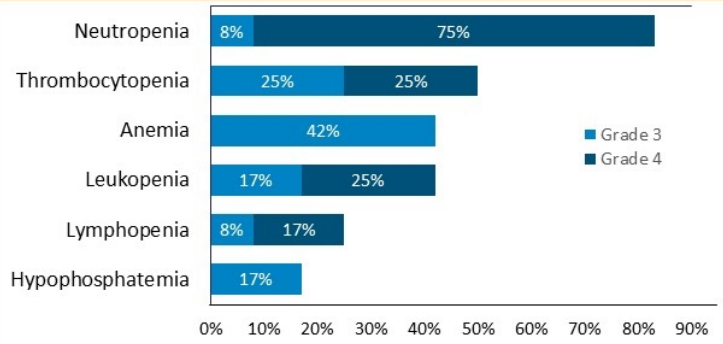
NASDAQ: BLUE

AE, adverse events; BCMA, B-cell maturation antigen; DLT, dose-limiting toxicity; HTB, high tumor burden; IMiD, immunomodulatory imide drugs; LTB, low tumor burden; MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival; R/R MM, relapsed/refractory multiple myeloma. [a]All patients to date received 150 × $10^6$ CAR+ T cells; an intermediate dose of 300 × $10^6$ CAR+ T cells will be the next dose level. [b]HTB defined as ≥50% bone marrow plasma cells pre-infusion; LTB <50%. [c]Per International Myeloma Working Group criteria.

# Early Clinical Safety and Tolerability Consistent with CAR T Experience

CRB-402

## Grade ≥3 AEs in >1 Patient[a]




## AEs of Special Interest[a]

| | Grade, n (%) | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| CRS[b] | 4 (33) | 3 (25) | 1 (8) | – |
| Neurotoxicity[c] | 1 (8) | 1 (8) | – | 1 (8) |

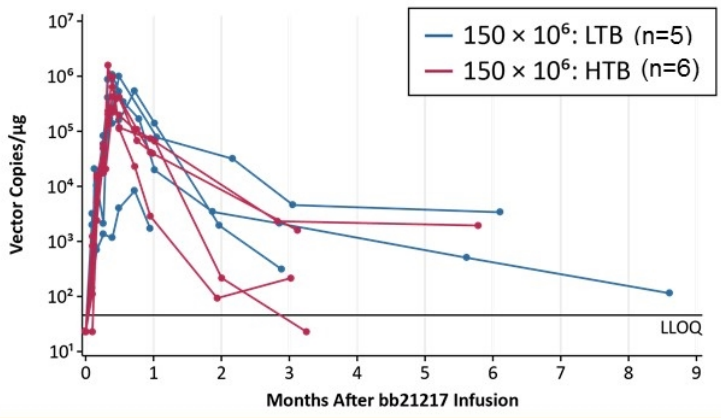
- CRS occurred in 67% of patients
  - Mostly grade 1/2, 1 grade 3, no grade 4
  - Median time to onset of CRS 4.5 days (2,11)
  - Manageable with or without tocilizumab
- 1 patient experienced DLT (grade 4 encephalopathy and grade 3 CRS)
  - Patient had high tumor burden and rapidly accelerating disease at baseline
  - No other DLTs occurred
- 1 grade 3 catheter-related infection; no other severe infections reported to date
- 4 patients experienced 1 or more SAEs
- No deaths on study to date

AE, adverse event; DLT, dose-limiting toxicity; SAE, serious adverse event. [a]AEs occurring between bb21217 infusion and disease progression. [b]Cytokine release syndrome (CRS) uniformly graded according to Lee et al., *Blood* 2014;124:188-195. [c]Events selected as CAR T neurotoxicity on the case report form occurring within 90 days after bb21217 infusion.

# Clinical Data is Early But Consistent with Goal of Enhanced Persistence

CRB-402

**Vector Copy Number Over Time by Baseline Tumor Burden**



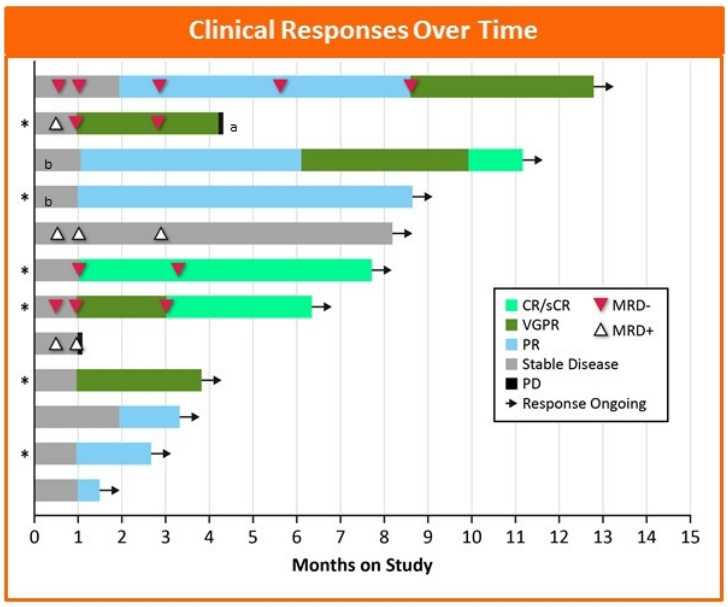

| | Month 1 | Month 3 | Month 6 | Month 9 |
|---|---|---|---|---|
| At risk, n | 9 | 7 | 3 | 1 |
| With detectable vector, n (%) | 9 (100) | 6 (**86**)[a] | 3 (100) | 1 (100) |

- Robust and reliable bb21217 CAR T cell expansion post-infusion observed at first dose
- Early bb21217 clinical data is consistent with robust functional CAR T cell persistence
  - Enrichment for memory-like CAR T cells observed in preclinical studies, and in patients post-infusion
  - Vector detectable up to 9 months post-infusion, and in 3/3 patients at 6-month time point
  - Sustained sBCMA suppression observed, reflecting ongoing plasma cell aplasia

HTB, high tumor burden; LLOQ, lower limit of quantitation; LTB, low tumor burden. [a]One patient with undetectable vector received cyclophosphamide on day 15 for grade 4 encephalopathy.

# Clinical Responses Observed in 10/12 Patients (83%) at First Dose Level Tested (150 x $10^6$ CAR+ T cells)

CRB-402




- 10/12 patients (83%) achieved an objective response at the first tested dose (150 × $10^6$ CAR+ T cells)
- Deepening responses over time; CR achieved as late as month 10
- 100% MRD negativity in 4/4 responders evaluable for MRD status
- Responses are ongoing in all but 1 responder; the first patient dosed continues response >1 year after treatment

CR, complete response; MRD, minimal residual disease; PR, partial response; VGPR, very good partial response. *Patients with high tumor burden. [a]Progression based exclusively on appearance of new bone lesions. [b]MRD status not available.

# High Clinical Response Rate Observed at First Dose Level (150 x $10^6$ CAR+ T cells)

CRB-402

| Clinical Response | |
|---|---|
| | bb21217-Treated (N=12) |
| ORR,[a] n (%) [95% CI] | 10 (83.3) [51.6, 97.9] |
| sCR/CR | 3 (25) |
| ≥VGPR | 6 (50) |
| MRD status in bone marrow, n | |
| MRD-evaluable responders[b] | 4 |
| MRD-neg | 4[c] |
| Median time to first response (min, max), [a,d] mo | 1 (1, 2) |
| Median time to best response (min, max), [a,d] mo | 1 (1, 10) |
| Median follow-up duration (min, max), mo | 5.9 (1.0, 11.8) |

CR, complete response; MRD, minimal residual disease; ORR, objective response rate; PR, partial response; VGPR, very good partial response. *Patients with high tumor burden. [a]Includes unconfirmed responses. [b]Patients with ≥PR and valid MRD assessments. [c]Two MRD-neg. responses at $10^{-6}$ and 2 at $10^{-5}$ sensitivity level by Adaptive next-generation sequencing. [d]Among 10 responders with ≥PR.

# Promising Early Data with Next-Generation Anti-BCMA CAR T

- bb21217 demonstrated promising early clinical activity in heavily pretreated patients with relapsed/refractory multiple myeloma at first dose level tested
  - 83% ORR with 90% of responses ongoing
  - Elimination of MRD in the bone marrow of all 4 evaluable responders
- Early indications of increased persistence using enriched CAR T cells
- Safety profile appears consistent with known toxicities of CAR T cell therapies
- Dose escalation is ongoing

# BCMA Data – Key Takeaways

**Transfusion-Dependent β-Thalassemia**

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**Next-generation**

- **shmiR:** At ≥4 months post-gene therapy, ~70% F cells were observed and HbF contributed ~25-30% of total Hb
- **CBL-B:** Further validation underway; taking aim at solid tumors

# ASH Highlights: Next Generation Programs / Platforms

## First clinical demonstration of the potential to genetically manipulate HbF levels through BCL11a

- Novel LVV expressing a shRNA$^{miR}$ to knock down BCL11a at the level *exclusively* in erythroid cells
- Robust knock down of BCL11a observed in patient cells
- At ≥4 months post-gene therapy, ~70% F cells were observed and HbF contributed ~25-30% of total Hb

**Flipping the Switch: Initial Results of Genetic Targeting of the Fetal to Adult Globin Switch in Sickle Cell Patients**

**Esrick et al. (Abstract #801)**

## Example of bbb's T cell enhancement technologies aimed at delivering transformative outcomes for solid tumors

- bbb megaTAL technology used to efficiently and specifically knockout CBL-B in CAR T cells via gene editing
- Increases cytokine production in response to tumor cells *in vitro*
- Enhances anti-tumor activity of CAR T cells in a mouse xenograft model

**Knockout of CBL-B Greatly Enhances Anti-Tumor Activity of CAR T Cells**

**Hooper et al. (Abstract #338)**

# Ending 2018 Strong: Key Milestones Achieved

## TDT

- ✓ Northstar-2 (HGB-207) Updated Data
- ✓ Northstar (HGB-204) Updated Data
- ✓ MAA Filing in Non-$\beta^0/\beta^0$ Genotypes
- ✓ Northstar-3 (HGB-212) Early Data
- ✓ Northstar-2 Updated Data

## SCD

- ✓ HGB-206 Data
- ✓ Pivotal Registration Plans Update
- ✓ HGB-206 Updated Data

## MM

- ✓ CRB-401 bb2121 Updated Data
- ✓ Earlier Line Studies Advancing*
- ✓ CRB-402 bb21217 Early Data

## CALD

- ✓ Starbeam (ALD-102) Updated Data



*Conducted by Celgene


Q & A
bluebirdbio

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**Exhibit 99.2**

**bluebird bio Presents New Data for LentiGlobin Gene Therapy in Transfusion Dependent β-Thalassemia at 60th Annual Meeting of the American Society of Hematology**

*First presentation of data from patients with a $\beta^0/\beta^0$ genotype and a pediatric patient treated with LentiGlobin in Phase 3 Northstar-3 study both have stopped chronic blood transfusions*

*10 of 11 patients with non-$\beta^0/\beta^0$ genotypes and more than three months follow-up have stopped chronic transfusions in Phase 3 Northstar-2 study*

*Indicators of poor red blood cell production appear corrected in exploratory analysis of bone marrow following treatment with LentiGlobin*

**CAMBRIDGE, Mass. – December 3, 2018** – bluebird bio, Inc. (Nasdaq: BLUE) announced new data from the Phase 3 Northstar-2 (HGB-207) and Northstar-3 (HGB-212) clinical studies of its investigational LentiGlobin™ gene therapy in the treatment of patients with transfusion-dependent β-thalassemia (TDT) at the 60th Annual Meeting of the American Society of Hematology (ASH).

"Our new data for LentiGlobin in transfusion-dependent β-thalassemia includes a broader population of patients with both non-$\beta^0/\beta^0$ and $\beta^0/\beta^0$ genotypes, as well as our first pediatric patients. In all of these patients we observed improved hemoglobin levels and reduced or eliminated requirements for blood transfusions following treatment with LentiGlobin," said David Davidson, M.D., chief medical officer, bluebird bio. "As our clinical studies advance, we continue to gain insight into the therapeutic potential of LentiGlobin across the spectrum of patients affected by TDT."

TDT is an inherited blood disorder caused by a mutation in the β-globin gene, which causes ineffective red blood cell production leading to severe anemia. People with TDT require regular transfusions to maintain hemoglobin (Hb) levels in order to survive, but chronic transfusions carry risks, including iron overload that can result in multi-organ damage and shortened life expectancy.

"In my practice, I see the serious complications of transfusion-dependent β-thalassemia and the everyday toll this disease takes on my patients and their families," said Professor Franco Locatelli, M.D., Ph.D., Full Professor of Pediatrics at the Sapienza University in Rome, Chair of the Department of Pediatric Hematology and Oncology, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy and lead investigator for the Northstar-2 study. "Patients with transfusion-dependent β-thalassemia are not able to make enough hemoglobin to survive, which is why they need regular blood transfusions every two to four weeks. After treatment with LentiGlobin, patients in this Phase 3 study began to produce gene-therapy derived hemoglobin and near-normal hemoglobin levels, which in the majority of patients abrogated the need for blood transfusions."

**Northstar-2 (HGB-207) Efficacy**
After treatment with LentiGlobin, patients are monitored for production of HbA$^{T87Q}$, which is gene therapy derived-hemoglobin. The production of HbA$^{T87Q}$ increases the overall hemoglobin level in patients with the goal of reducing or eliminating the need for transfusions.

Sixteen patients with non-$\beta^0/\beta^0$ genotypes (aged 8 – 34 years); two pediatric and 14 adolescents/adults with TDT have been treated in the Phase 3 Northstar-2 study as of September 14, 2018, the data cut-off date.

Eleven of these patients had at least three months of follow-up available at the data cut-off. Ten of the 11 patients had stopped receiving transfusions and had hemoglobin levels of 11.1 – 13.3 g/dL at the time of the last study visit (3 – 18 months post-treatment). HbA$^{T87Q}$ levels in these 10 patients ranged from 7.7 – 10.6 g/dL and significantly contributed to total hemoglobin (67 – 92 percent).

An exploratory analysis was conducted with bone marrow from six patients with 12 months of follow-up after treatment. The samples were evaluated for cellularity and myeloid to erythroid ratio. A low myeloid to erythroid ratio is a key feature of dyserythropoesis, or abnormal bone marrow red blood cell production, characteristic of patients with TDT. In five patients, all of who had stopped chronic transfusions, an increase in the myeloid to erythroid ratio was observed, suggesting improvement in red blood cell production.

**Northstar-3 (HGB-212) Efficacy**
As of September 14, 2018, three patients with TDT and a $\beta^0/\beta^0$ genotype or an IVS-I-110 mutation had been treated with LentiGlobin in the Phase 3 Northstar-3 study.

All three patients, as of November 19, 2018, had total hemoglobin of greater than 10 g/dL at their last assessment, including a pediatric patient. Patient 1 had no transfusions following LentiGlobin treatment and their last assessment at month 12, Patient 2 had their last transfusion 1.9 months post-treatment and last assessment at month six, Patient 3 had their last transfusion at 1.4 months post-treatment and last assessment at month three.

**Northstar-2 and Northstar-3 Safety**
In the Northstar-2 and Northstar-3 studies the safety profile of LentiGlobin gene therapy remained generally consistent with myeloablative busulfan conditioning, including serious adverse events (SAEs) of vaso-occlusive liver disease. One SAE of grade 3 thrombocytopenia was reported and considered possibly related to LentiGlobin.

As of the data cut-off date, September 14, 2018, a total of 37 pediatric, adolescents and adult patients with TDT and a non-$\beta^0/\beta^0$ or $\beta^0/\beta^0$ genotype, including patients with IVS-I-110 mutations, have been treated with LentiGlobin in the Northstar, Northstar-2 and Northstar-3 studies.

For more information about the ongoing clinical studies of LentiGlobin in TDT visit www.northstarclinicalstudies.com or clinicaltrials.gov and use identifier NCT02906202 for Northstar-2 (HGB-207) and NCT03207009 for Northstar-3 (HGB-212).

**About Transfusion-Dependent β-Thalassemia**
TDT is an inherited blood disorder caused by a mutation in the β-globin gene, which causes ineffective red blood cell production leading to severe anemia. Supportive care for people with TDT consists of a lifelong regimen of chronic blood transfusions to enable survival and suppress symptoms of the disease, and iron chelation therapy to manage iron overload that results from the transfusions.

Despite the availability of supportive care, many people with TDT experience serious complications and organ damage due to underlying disease and iron overload. By eliminating or reducing the need for blood transfusions, the long-term complications associated with TDT may be reduced.

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) has been successfully used to treat TDT and is currently the only available option with the potential to correct the genetic deficiency in TDT. Complications of allo-HSCT include a risk of treatment-related mortality, graft failure, graft-versus-host disease (GvHD) and opportunistic infections, particularly in patients who undergo non-sibling matched allo-HSCT.

**About LentiGlobin**
LentiGlobin is a one-time gene therapy being studied as a potential treatment to address the underlying genetic cause of TDT, which could eliminate or reduce the need for blood transfusions.

bluebird bio's clinical development program for LentiGlobin includes ongoing studies around the world with sites in Australia, Germany, Greece, France, Italy, Thailand, the United Kingdom and the United States. For more information visit: www.northstarclinicalstudies.com or clinicaltrials.gov using identifier NCT01745120.

In addition, bluebird is conducting a long-term safety and efficacy follow-up study (LTF-303) for people who have participated in bluebird bio-sponsored clinical studies of LentiGlobin for TDT and sickle cell disease.

In October 2018, the European Medicines Agency (EMA) accepted the company's marketing authorization application (MAA) for LentiGlobin™ gene therapy for the treatment of adolescents and adults with TDT and a non-$\beta^0/\beta^0$ genotype.

The EMA previously granted Priority Medicines (PRIME) eligibility and Orphan Medicinal Product designation to LentiGlobin for the treatment of TDT. LentiGlobin is also part of the EMA's Adaptive Pathways pilot program, which is part of the EMA's effort to improve timely access for patients to new medicines.

The U.S. Food and Drug Administration (FDA) also granted LentiGlobin Orphan Drug status and Breakthrough Therapy designation for the treatment of TDT.

**About bluebird bio, Inc.**
With its lentiviral-based gene therapies, T cell immunotherapy expertise and gene editing capabilities, bluebird bio has built a pipeline with broad potential application in severe genetic diseases and cancer.

bluebird bio's gene therapy clinical programs include investigational treatments for cerebral adrenoleukodystrophy, transfusion-dependent β-thalassemia and sickle cell disease.

bluebird bio's oncology pipeline is built upon the company's lentiviral gene delivery and T cell engineering, with a focus on developing novel T cell-based immunotherapies, including chimeric antigen receptor (CAR T) and T cell receptor (TCR) therapies. The company's lead oncology programs are anti-BCMA CAR T programs partnered with Celgene.

bluebird bio's discovery research programs include utilizing megaTAL/homing endonuclease gene editing technologies with the potential for use across the company's pipeline.

bluebird bio has operations in Cambridge, Massachusetts; Seattle, Washington; Durham, North Carolina and Zug, Switzerland. For more information, visit bluebirdbio.com.

Follow bluebird bio on social media: @bluebirdbio, LinkedIn, Instagram, YouTube.

LentiGlobin is a trademark of bluebird bio, Inc.

**Forward-Looking Statements**
*This release contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, including statements regarding the Company's views with respect to the potential for its LentiGlobin product candidate to treat transfusion-dependent ß-thalassemia, and the Company's expectations regarding the review, potential regulatory approval and potential commercial launch of its LentiGlobin product candidate in the United States and Europe. Any forward-looking statements are based on management's current expectations of future events and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, the risks that the preliminary positive efficacy and safety results from our prior and ongoing clinical trials of LentiGlobin will not continue or be repeated in our ongoing or planned clinical trials of LentiGlobin, the risks that the changes we have made in the LentiGlobin manufacturing will not result in improved patient outcomes, risks that the current or planned clinical trials of LentiGlobin will be insufficient to support future regulatory submissions or to support marketing approval in the US and EU, and the risk that any one or more of our product candidates, will not be successfully developed, approved or commercialized. For a discussion of other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in our most recent Form 10-Q, as well as discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the Securities and Exchange Commission. All information in this press release is as of the date of the release, and bluebird bio undertakes no duty to update this information unless required by law.*

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**Exhibit 99.3**

**bluebird bio Presents New Data for LentiGlobin Gene Therapy in Sickle Cell Disease at 60th Annual Meeting of the American Society of Hematology**

*LentiGlobin treatment-derived hemoglobin HbA$^{T87Q}$ equals or exceeds sickling hemoglobin (HbS) levels in Group C patients at six months post treatment*

*Total hemoglobin levels stable after month three and reach range of 9.9 – 13.7 g/dL in patients who are at least six months post treatment*

*No reports of vaso-occlusive events in Group C patients at up to nine months post treatment with LentiGlobin*

**CAMBRIDGE, Mass. – December 3, 2018** – bluebird bio, Inc. (Nasdaq: BLUE) announced new data from patients in Group C of its ongoing Phase 1/2 HGB-206 study of the company's investigational LentiGlobin™ gene therapy in patients with sickle cell disease (SCD) today at the 60th Annual Meeting of the American Society of Hematology (ASH).

SCD is a serious, progressively debilitating and life-threatening genetic disease. SCD results from production of abnormal sickle hemoglobin (HbS), which leads to sickled red blood cells (RBCs) and hemolysis.

"After patients with sickle cell disease were treated with LentiGlobin they began to produce gene-therapy derived HbA$^{T87Q}$, which was associated with lower levels of sickling hemoglobin, the type of hemoglobin that damages red blood cells," said David Davidson, M.D., chief medical officer, bluebird bio. "These clinical findings were consistent with results in newly developed exploratory assays used to evaluate patient samples that demonstrated reduction of HbS in most red blood cells, and a reduction in sickling comparable to sickle-trait, suggesting the potential for LentiGlobin to fundamentally improve the underlying red blood cell pathology responsible for the clinical consequences of sickle cell disease."

Many patients with SCD live with severe anemia and vaso-occlusive events which include severe, recurrent pain crises that lead to organ damage and shortened life span.

"Before receiving treatment with LentiGlobin, patients in this study experienced frequent vaso-occlusive events, which is not uncommon for people living with sickle cell disease," said John Tisdale, M.D., National Heart, Lung and Blood Institute, Bethesda, Md. "At nine months post-treatment with LentiGlobin, no vaso-occlusive events had been reported. By understanding the potential correlation between levels of HbA$^{T87Q}$ and clinical outcomes that cause the most significant burden for patients, we will be able to better characterize the potential benefits of LentiGlobin for people living with sickle cell disease."

**HGB-206: Phase 1/2 Study of LentiGlobin for Sickle Cell Disease**
HGB-206 is an ongoing, Phase 1/2 open-label study designed to evaluate the efficacy and safety of LentiGlobin gene therapy for the treatment of adults with SCD. A total of nine patients were treated with LentiGlobin in Group C in HGB-206. As of the data cut-off of September 14, 2018, data was available for seven patients who were at least three months post treatment.

A refined LentiGlobin manufacturing process intended to increase vector copy number (VCN) as well as changes to improve engraftment of gene-modified stem cells, was used for Group C. Group C patients also received LentiGlobin gene therapy made from hematopoietic stem cells (HSCs) collected from peripheral blood after mobilization with plerixafor rather than via bone marrow harvest.

**HGB-206: Group C Efficacy**
In patients who were six months post treatment (n=4), the production of gene therapy-derived hemoglobin, $HbA^{T87Q}$, ranged from 4.8 – 8.8 g/dL and were comparable to or exceeded the levels of sickle hemoglobin, HbS. These patients did not receive a blood transfusion during this time and had total hemoglobin ranging from 9.9 – 13.7 g/dL at their last visit.

No vaso-occlusive events were reported as of the data cut-off (up to nine months post treatment with LentiGlobin). In an exploratory analysis, key markers of hemolysis, including reticulocyte counts, lactate dehydrogenase (LDH) and total bilirubin concentration had decreased compared to baseline.

To help assess the distribution of $HbA^{T87Q}$ in the red blood cells, bluebird bio has developed an antibody that recognizes $\beta^S$, the protein present in HbS.

Using this antibody, the amount of $\beta^S$ was measured in the red blood cells obtained from healthy donors ($\beta^A/\beta^A$), sickle cell trait donors ($\beta^S/\beta^A$) and patients with sickle cell disease ($\beta^S/\beta^S$). Clear and distinct distribution of $\beta^S$ was observed in these control samples, with highest expression in the $\beta^S/\beta^S$ samples, followed by $\beta^S/\beta^A$ and no expression of $\beta^S$ in the healthy donor ($\beta^A/\beta^A$) samples.

Initial results from two patients treated with LentiGlobin gene therapy, who were nine months post treatment, showed that nearly all their red blood cells had lower amounts of $\beta^S$ than the $\beta^S/\beta^S$ and the $\beta^S/\beta^A$ control samples. Given that these patients were no longer receiving any blood transfusions, this suggests $\beta^S$ expression was reduced in these patients due to the production of $HbA^{T87Q}$ following treatment with LentiGlobin.

**HGB-206 Safety**
As of the data cut-off date, the safety profile of LentiGlobin remains generally consistent with underlying SCD and myeloablative conditioning. A serious adverse event (SAE) of myelodysplasia syndrome was reported in a patient who received LentiGlobin approximately three years ago in Group A of the Phase 1/2 HGB-206 study. Analysis of the patient's cells showed no evidence of vector mediated insertional oncogenesis, and the independent data monitoring committees, along with the treating physician, agreed the SAE was unlikely related to LentiGlobin gene therapy.

**About LentiGlobin in Sickle Cell Disease**
LentiGlobin is a one-time gene therapy being studied as a potential treatment to address the underlying genetic cause of sickle cell disease (SCD), which could increase the production of normal hemoglobin.

bluebird bio's clinical development program for LentiGlobin includes ongoing studies around the world with sites in Australia, Germany, Greece, France, Italy, Thailand, the United Kingdom and the United States. For more information visit: https://www.bluebirdbio.com/medical-professionals/our-clinical-trials/.

In addition, bluebird is conducting a long-term safety and efficacy follow-up study (LTF-303) for people who have participated in bluebird bio-sponsored clinical studies of LentiGlobin for transfusion-dependent β-thalassemia (TDT) and SCD.

The European Medicines Agency (EMA) previously granted Orphan Medicinal Product designation to LentiGlobin for the treatment of SCD. LentiGlobin is also part of the EMA's Adaptive Pathways pilot program, which is part of the EMA's effort to improve timely access for patients to new medicines.

The U.S. Food and Drug Administration (FDA) also granted LentiGlobin Orphan Drug status, Fast Track designation and Regenerative Medicine Advanced Therapy Designation for the treatment of patients with SCD.

In 2019, bluebird bio plans to initiate a Phase 3 study of LentiGlobin in SCD. For more information about the ongoing Phase 1/2 HGB-206 clinical study of LentiGlobin in SCD visit clinicaltrials.gov and use identifier NCT02140554.

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