ASH 2018

bluebirdbio

December 3, 2018

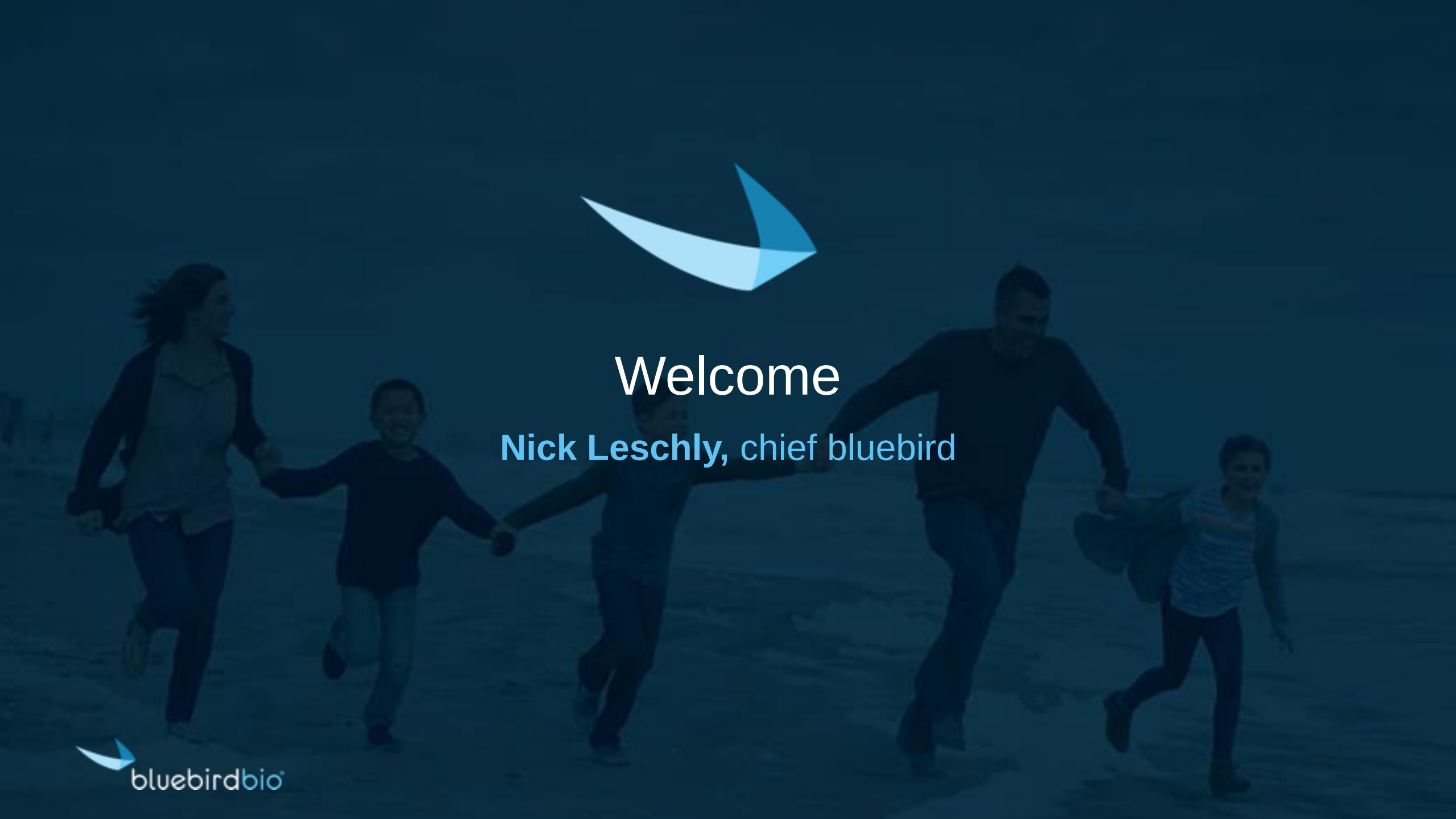
NASDAQ: BLUE

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 **Nick Leschly,** chief bluebird, bluebird bio
Severe Genetic Diseases	**David Davidson, M.D.,** chief medical officer, bluebird bio **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 **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)

LentiGlobin SCD
Data-Driven Acceleration

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 • 2019 EU launch on track • U.S. registration plan based on Northstar-2 with Breakthrough Designation
Sickle Cell Disease	• Robust and consistent production of anti-sickling HbA^{T87Q} hemoglobin • Accelerated development path with RMAT Designation
Cerebral Adrenoleukodystrophy	• General regulatory agreement on Biologics License Application (BLA) and MAA filings • Anticipated 2020 approval on track with Breakthrough Designation
Multiple Myeloma	• Registration-enabling study enrollment complete; 3rd & 2nd line studies enrolling soon • bb21217 proof-of-concept; dose escalation underway • Anticipated 2020 approval on track with Breakthrough and PRIME Designations

Pipeline & Technology	• Manufacturing: North Carolina facility build out
	• Research Engine: Regeneron & Gritstone oncology partnerships
	• Pipeline Growth:
	  • SCD next gen BCL11a program with Dana-Farber/Boston Children's Cancer and Blood Disorders Center
	  • *in vivo* gene editing CAR T preclinical proof of concept (CBL-B)

Breadth & Depth of ASH Data Underscores BLUE Potential

NORTHSTAR STUDY / NORTHSTAR-2 STUDY / NORTHSTAR-3 STUDY	LentiGlobin TDT	• **Northstar: Outcomes following study completion** • **Northstar-2: Updated results** • **First look: Northstar-3**
HGB-206	LentiGlobin SCD	• **HGB-206 Group C: Updated results** • HGB-206 Group A & B: Updated results • Real world evidence: U.S. population • 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** • **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

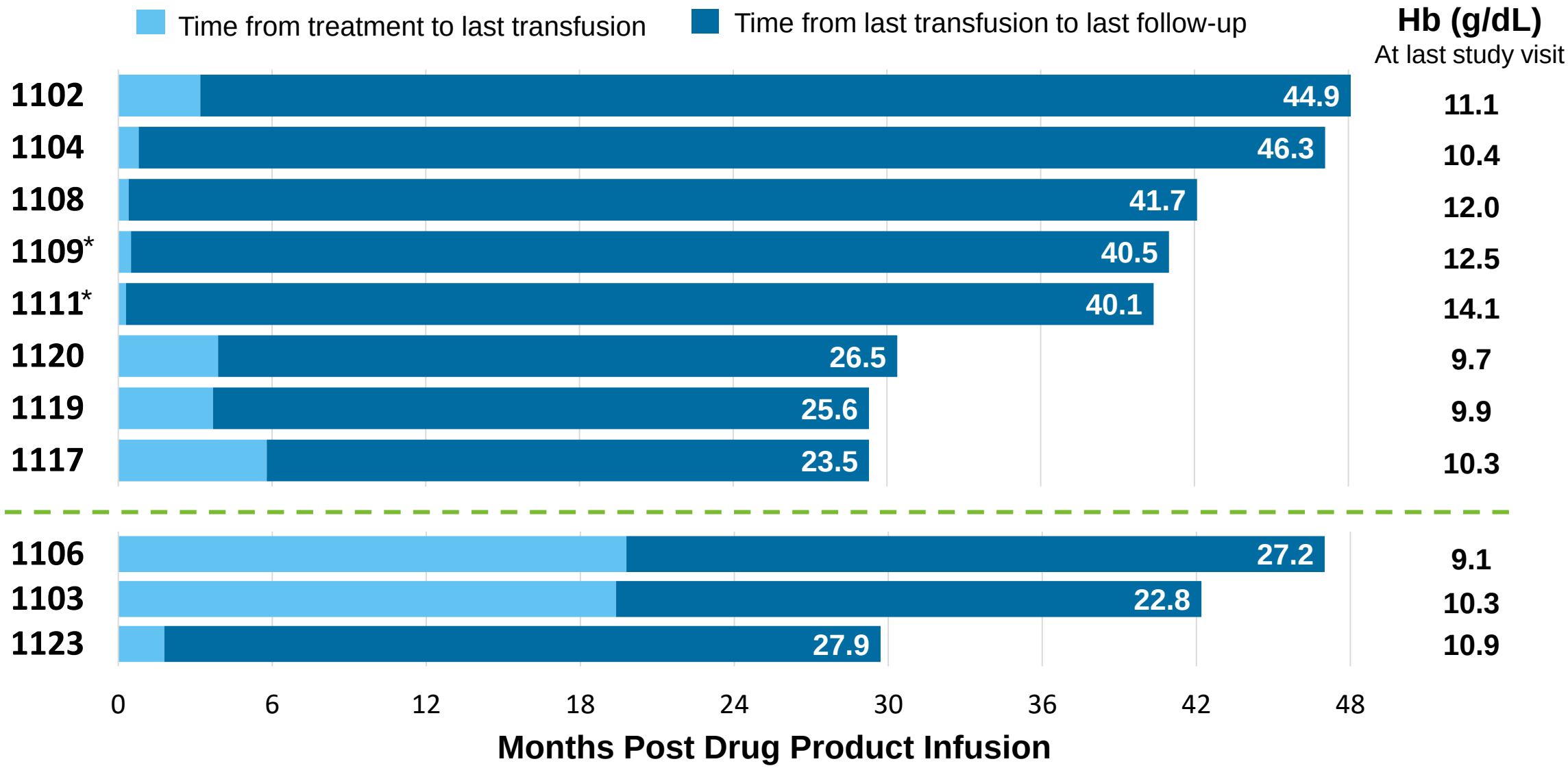
Transfusion-Dependent β-Thalassemia (TDT)

- 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-β^0/β^0 Genotypes and 3/8 Patients with β^0/β^0 Genotypes are Free from Chronic RBC Transfusions



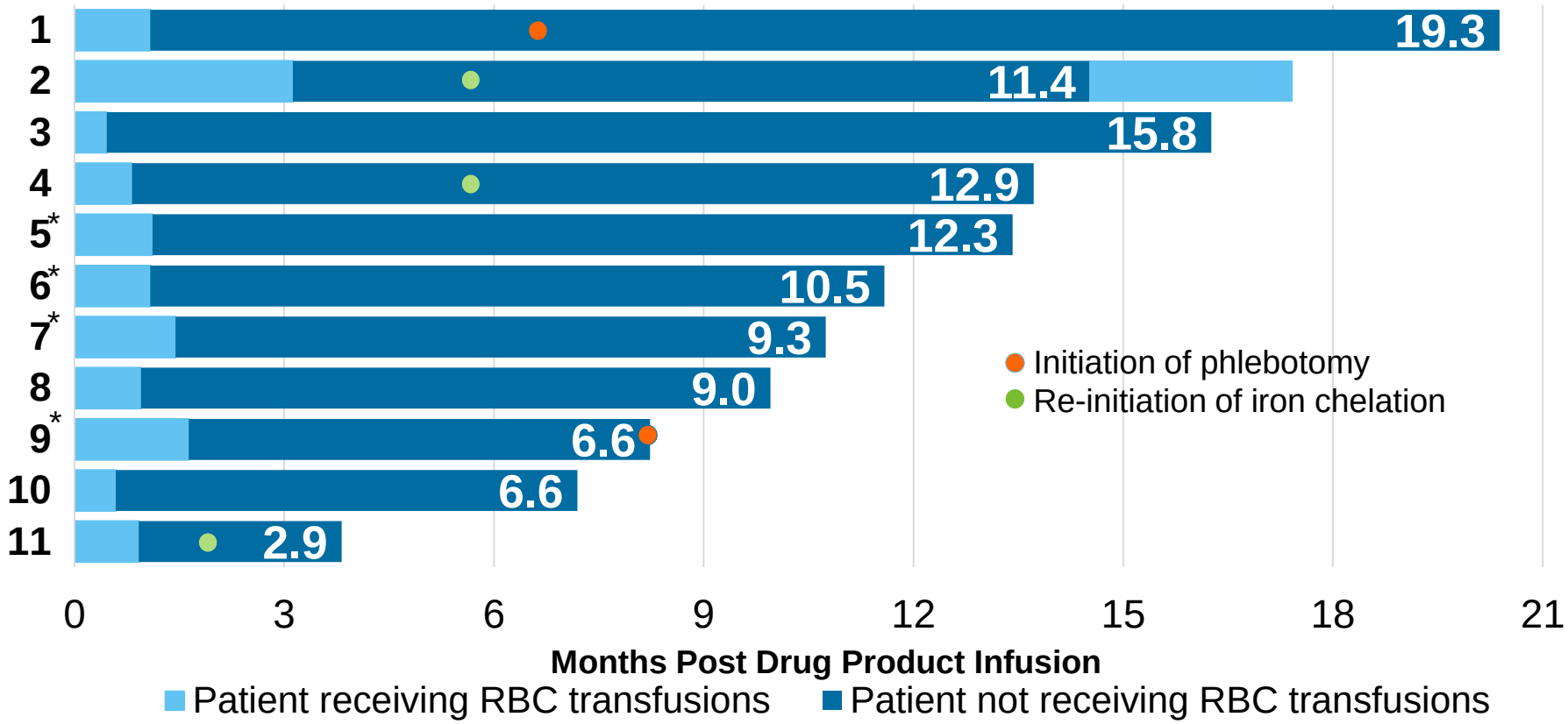
*Indicates male patients. Hb, hemoglobin; TI, transfusion independence (weighted average Hb ≥9 g/dL without any red blood cell transfusions for ≥12 months)

Data as of September 14, 2018

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



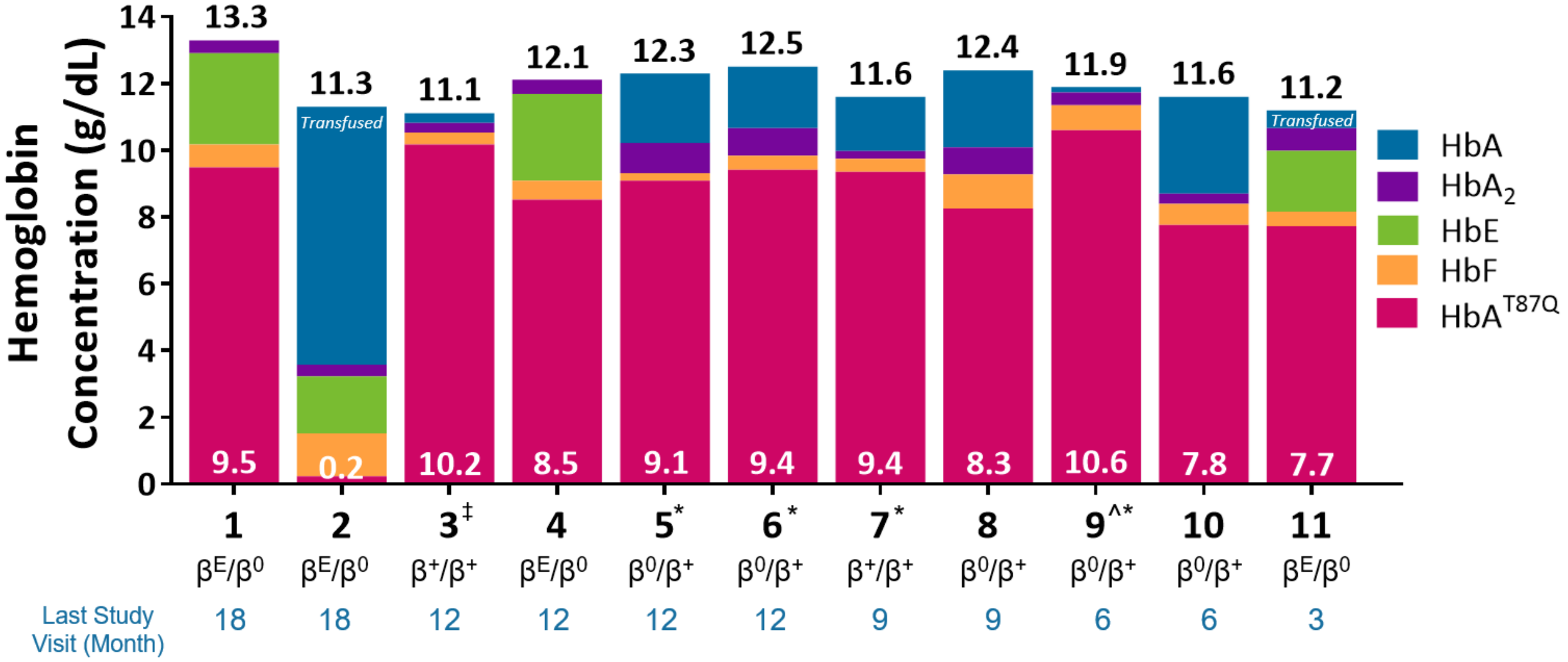
	Hb (g/dL) At last study visit	Peripheral VCN At last study visit
1	13.3	3.2
2	11.3‡	0.4
3	11.1	2.2
4	12.1	1.7
5*	12.3	1.7
6*	12.5	2.9
7*	11.6	5.6
8	12.4	1.1
9*	11.9	4.9
10	11.6	5.4
11	11.2	5.6

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



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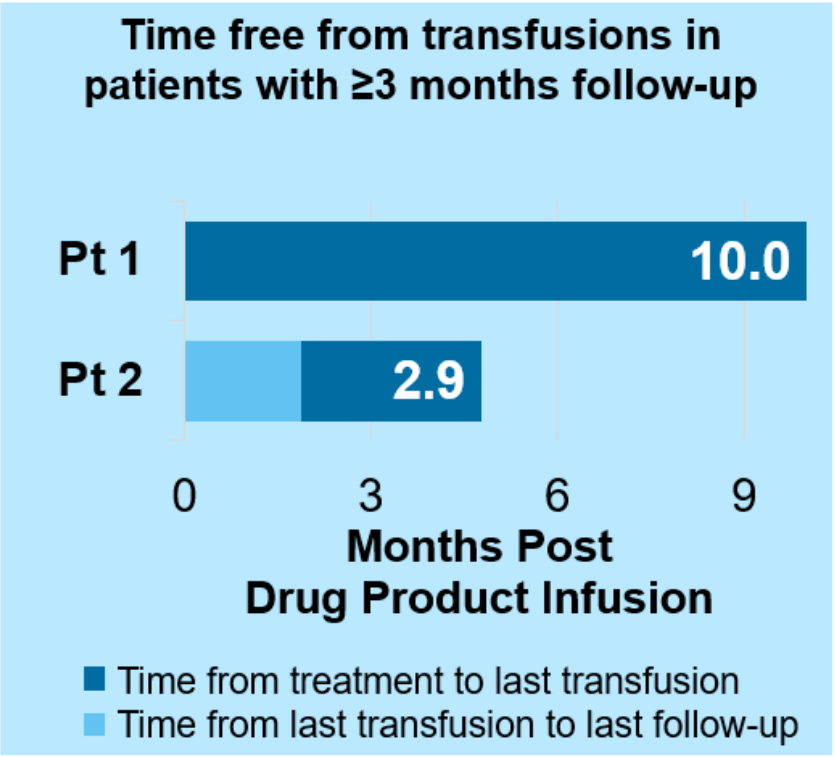
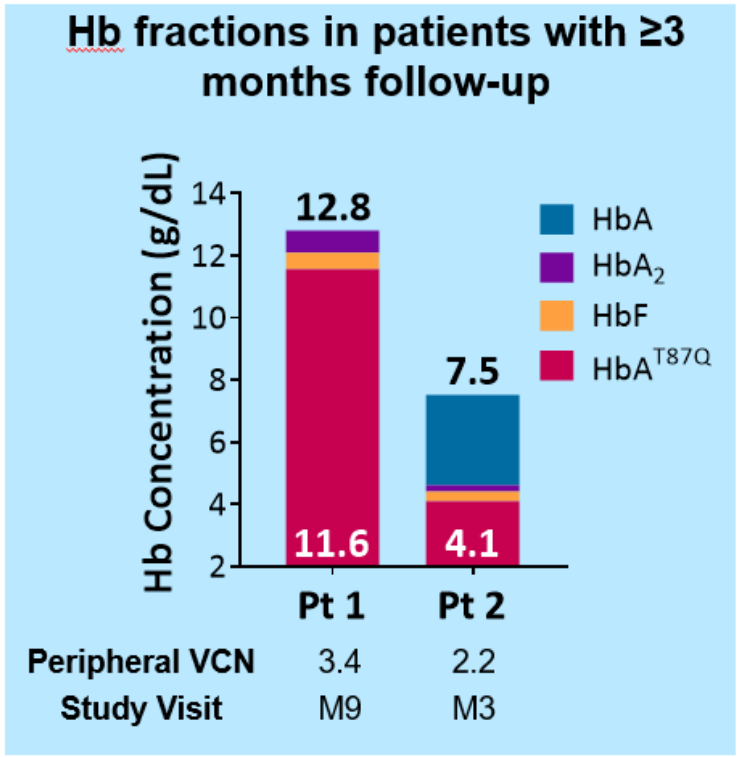
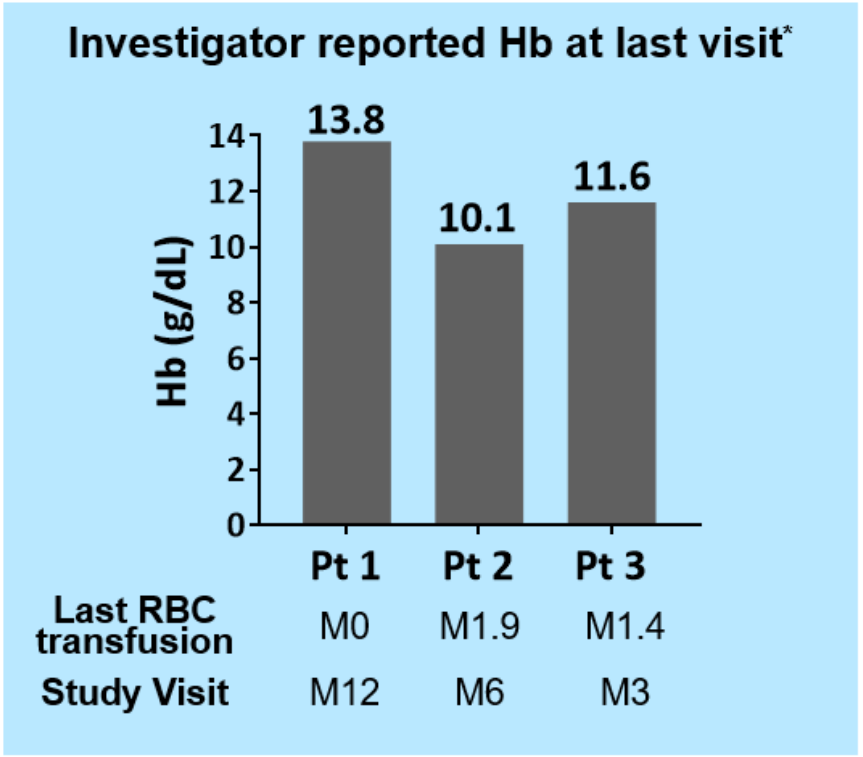
*Male patients; ‡Patient is homozygous for IVS-I-5 β-globin mutation; ^Patient is heterozygous for IVS-I-5 β-globin mutation. Hb, hemoglobin.

Data as of September 14, 2018

Normal Total Hemoglobin in First Northstar-3 β^0/β^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 β^0/β^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

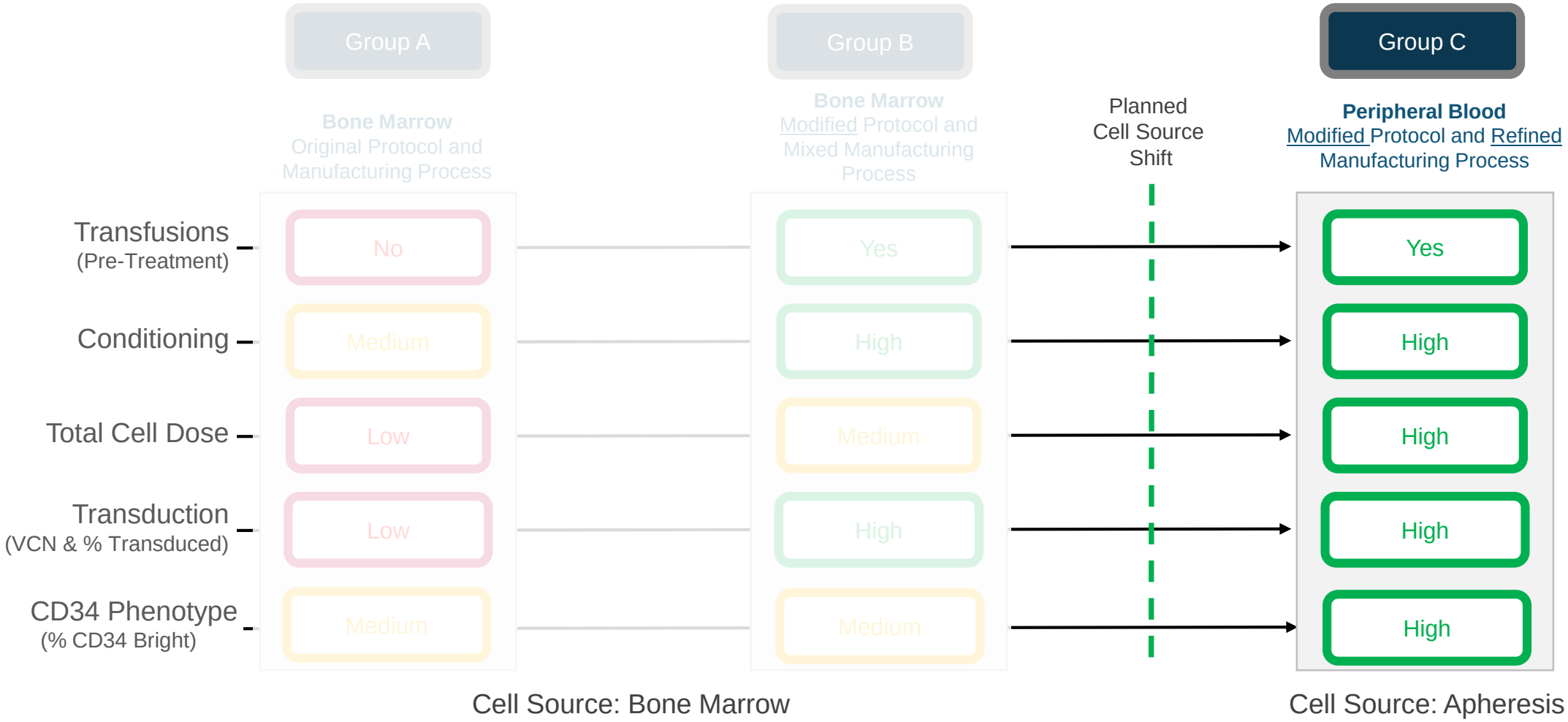
Plans Based on Ongoing Engagement with Regulators

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 median (min – max), years	**25.5** (18 – 36)
Gender	**6 F 8 M**
Genotype β^S/β^S	**14**
Prior SCD History	
Hydroxyurea use, n	**8**
Recurrent VOCs*, n Annualized no. of events, median (min – max)	**9** **6.5** (3.5 – 14.0)
ACS†, n Annualized no. of events, median (min – max)	**2** **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 Post-DP infusion in ≥2 patient	**n (%)** **N=9**
Febrile neutropenia	6 (67)
Stomatitis	6 (67)
Serious AEs* Post-DP infusion in ≥1 patient	**n (%)** **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 • 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 • 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 • No VOEs in early clinical follow up

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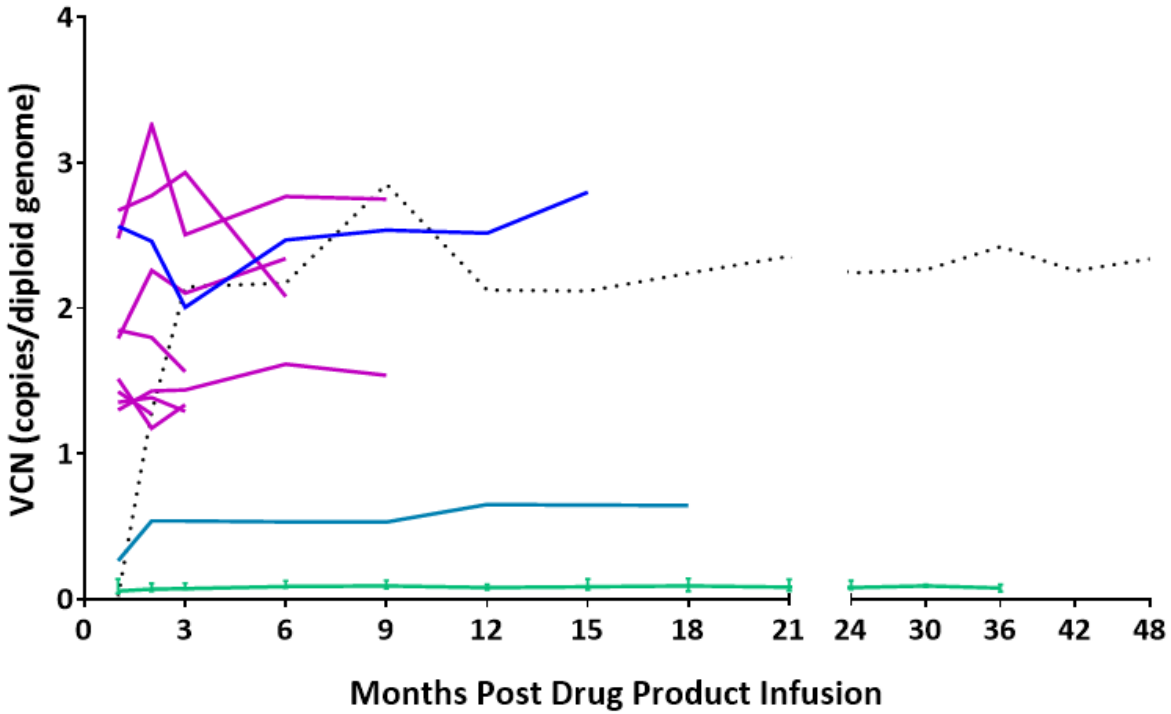
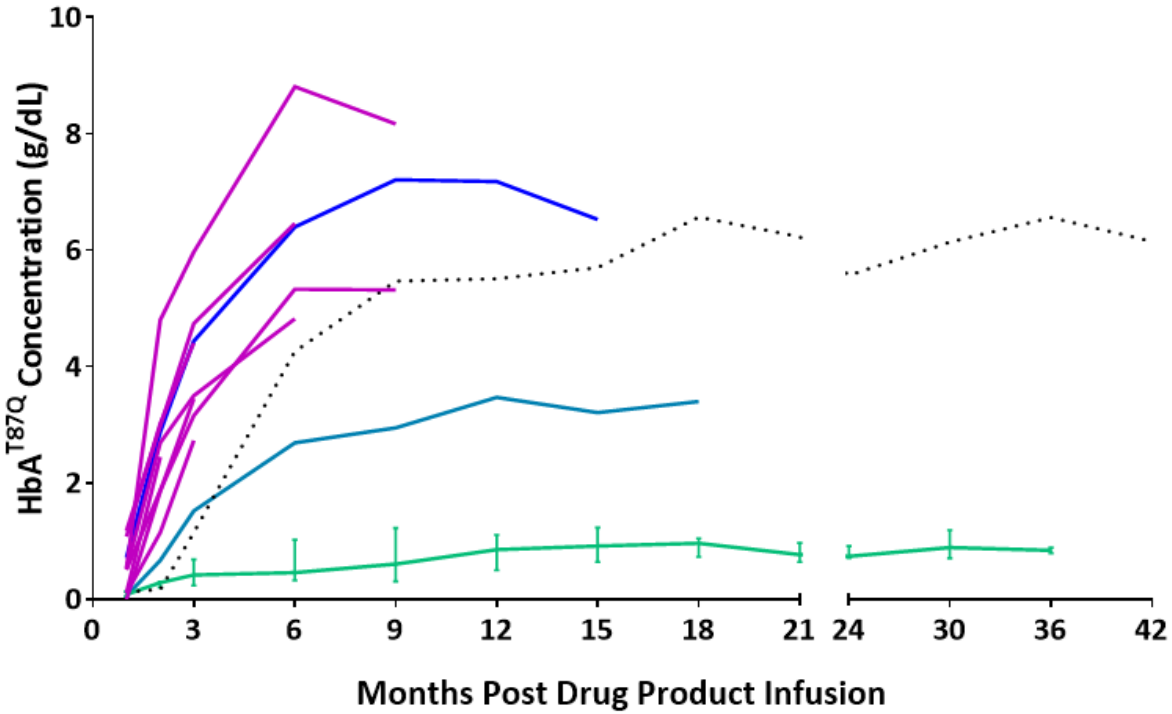
Group C: Stable Peripheral Blood VCN, HbA^{T87Q} Trajectory Robust and Consistent

HGB-206



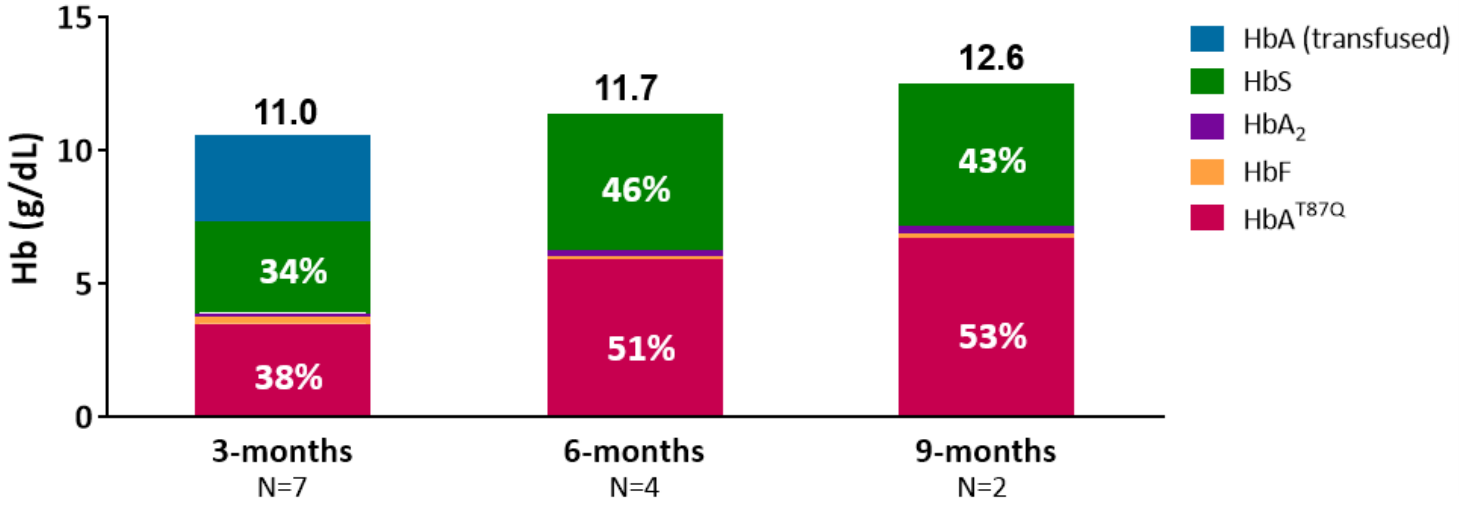


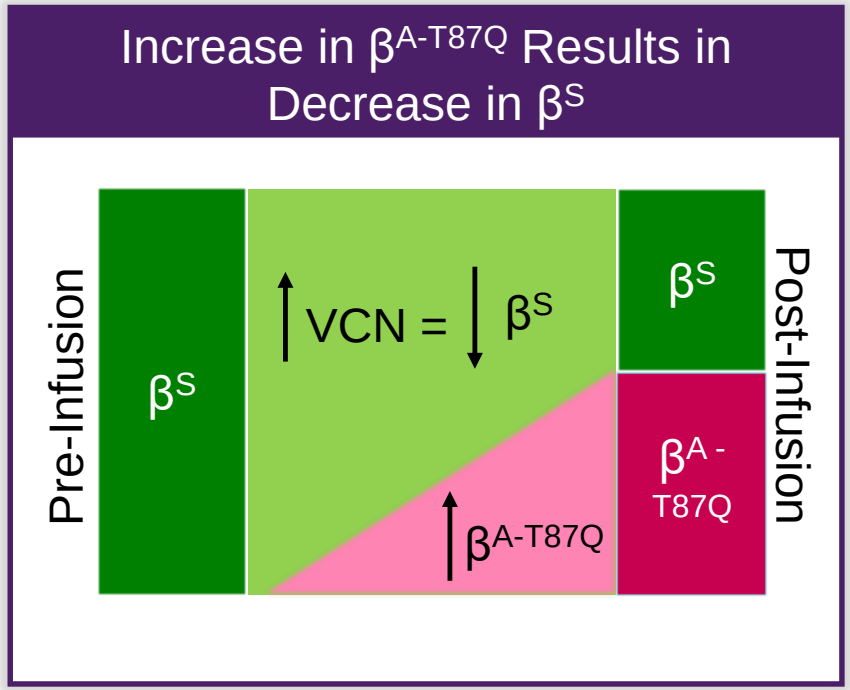
Group A Group B: 1312 Group B: 1313 Group C 1204

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

Group C Patients Achieving Sickle Trait-like Hemoglobin Distribution

HGB-206





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

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Fundamentally Improving Red Blood Cell Physiology

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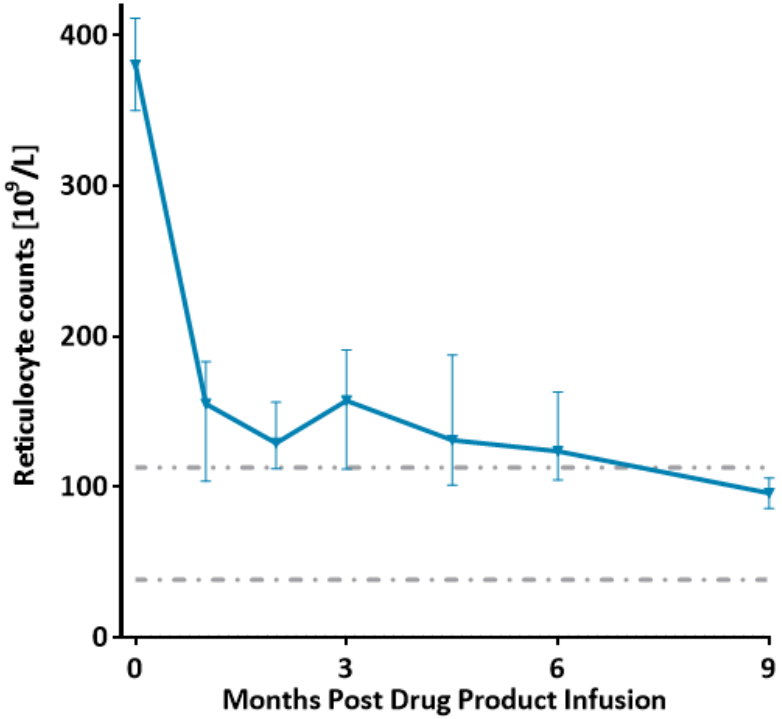
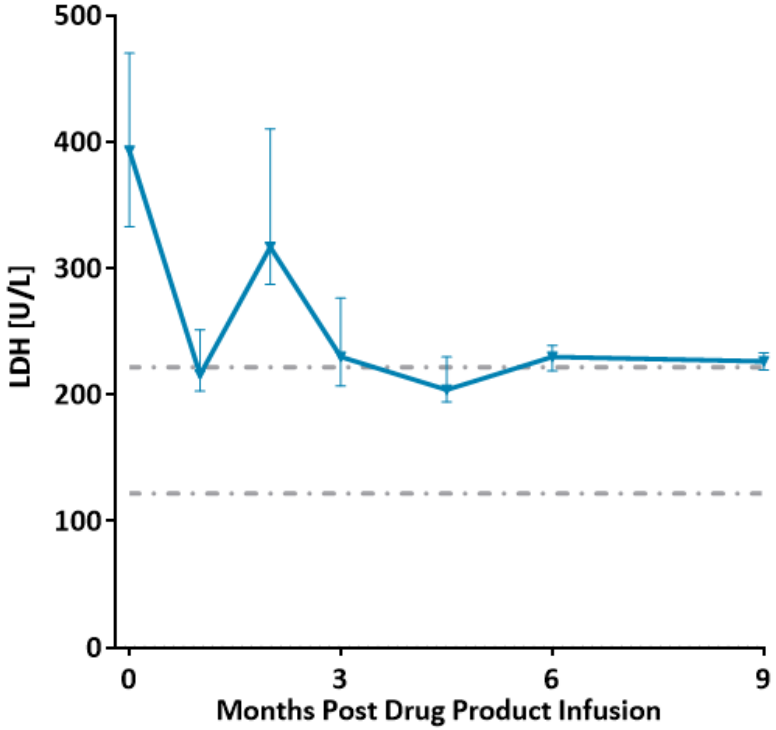
Impact on Clinical Outcomes of SCD in Group C
Normalization of Key Biomarkers of Hemolysis Over Time

HGB-206

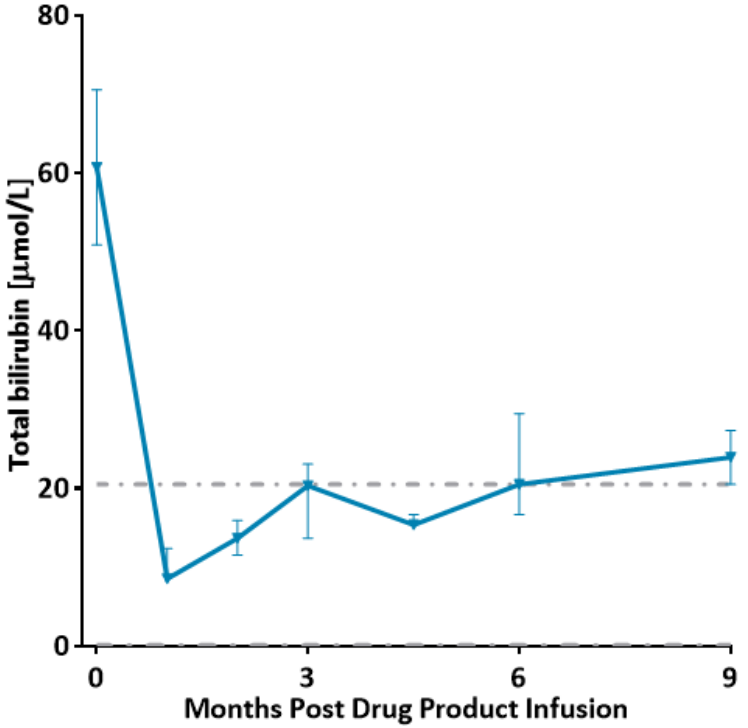
Reticulocyte Counts



Lactate Dehydrogenase



Total Bilirubin



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

Median (Q1, Q3) depicted

Data as of September 14, 2018

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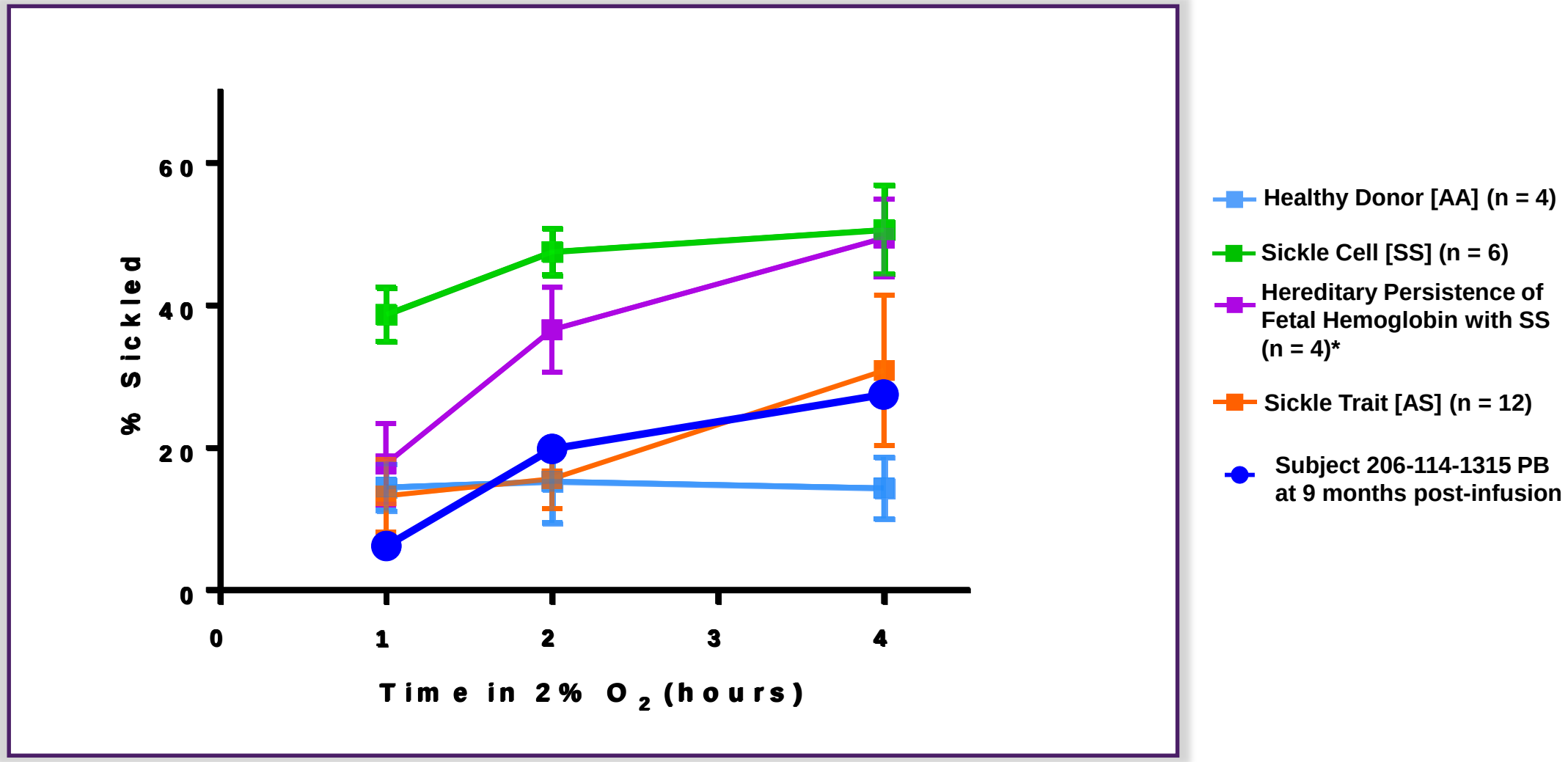
LentiGlobin has Anti-Sickling Activity Comparable to Sickle Trait

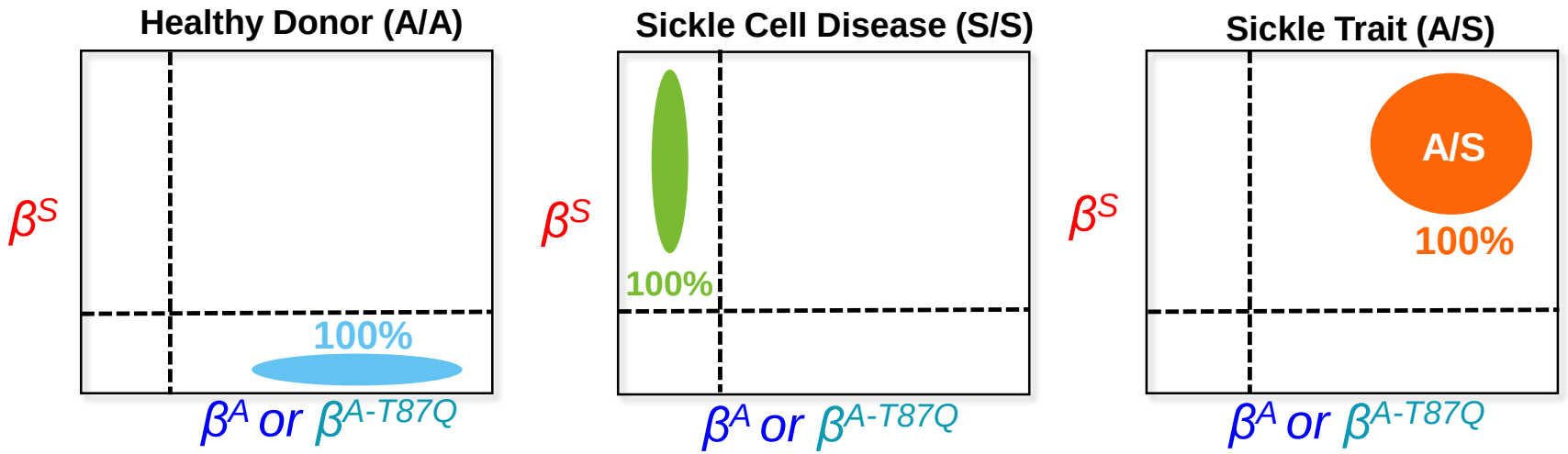
Reduction in % Sickled and Time to Sickling in Patient RBCs Post-Treatment



*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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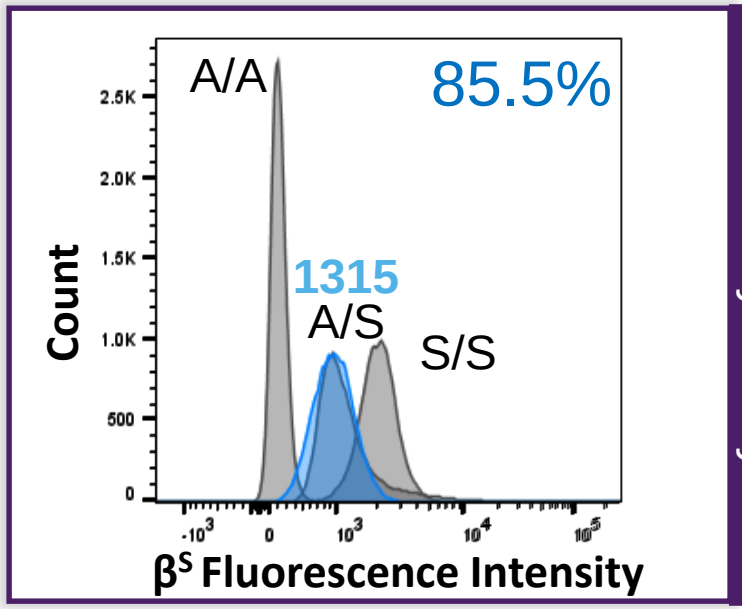
Subject 1315 M9
Single Cell Western



Subject 1315 M9
Flow Cytometry

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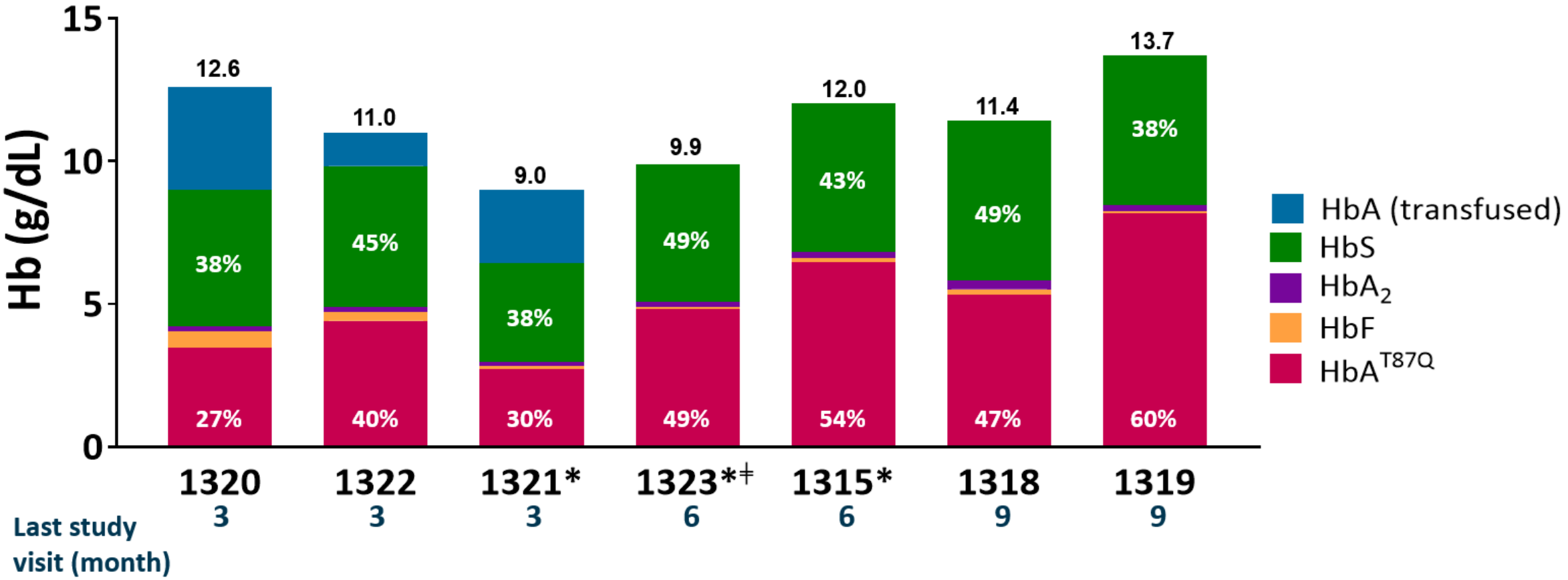
Impact on Clinical Outcomes of SCD

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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- **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

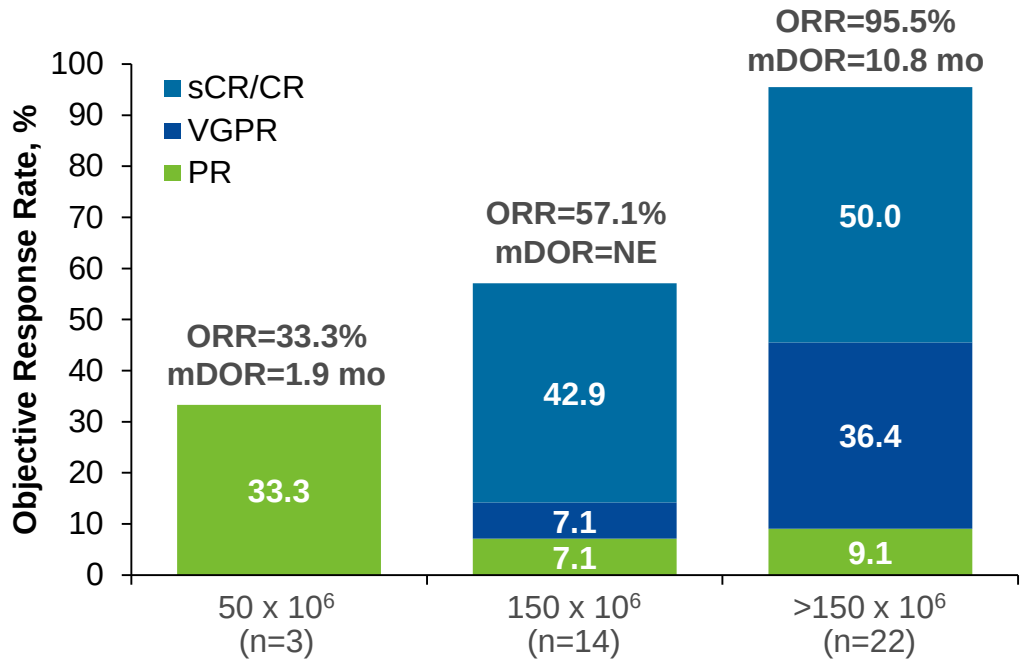
BCMA PROGRAM OVERVIEW

- 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

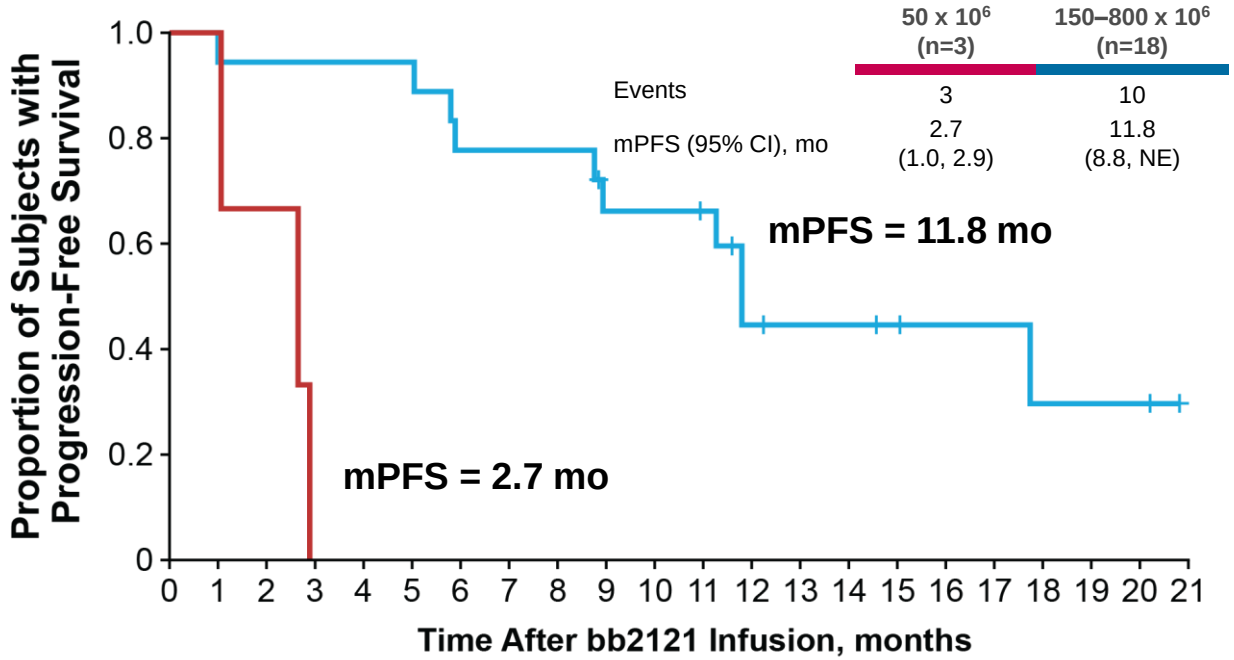
CRB-401

Tumor Response By Dose[1]



	50 x 10^6 (n=3)	150 x 10^6 (n=14)	>150 x 10^6 (n=22)
Median follow-up (min, max), d	84 (59, 94)	87 (36, 638)	194 (46, 556)

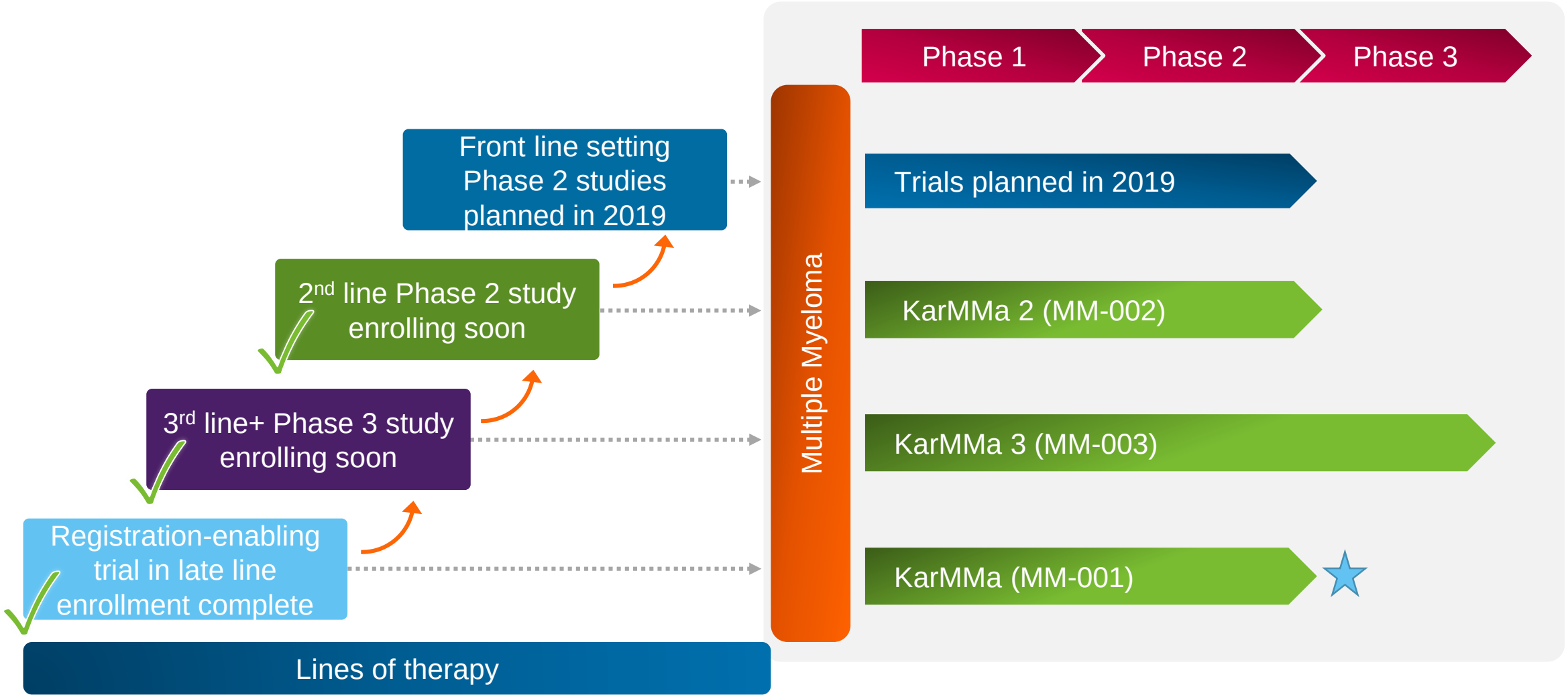
PFS at Inactive (50 x 10^6) and Active (150–800 x 10^6) Dose Levels[2]



- 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



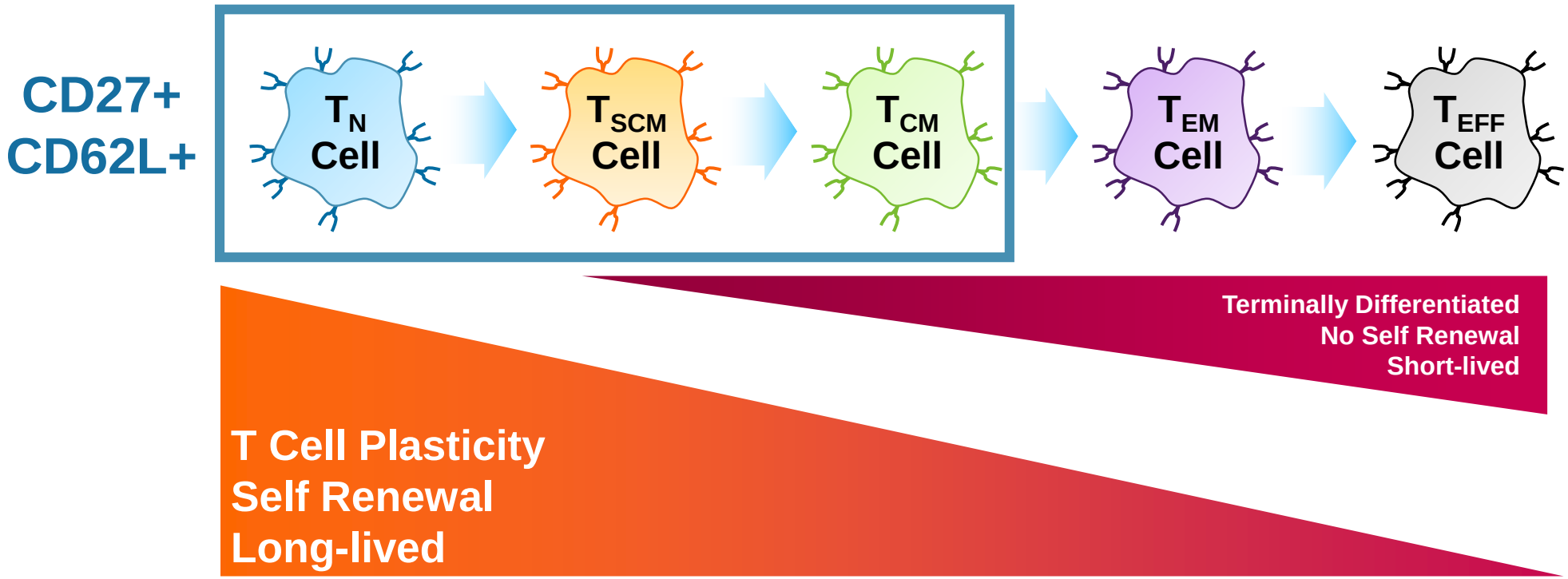
Anticipated Approval in 2020

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

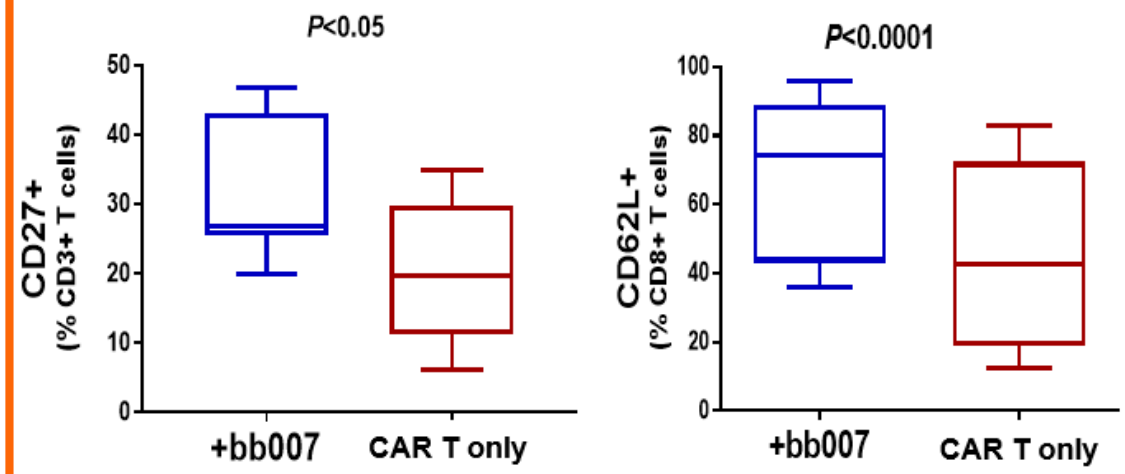


Hypothesis: Increasing long-lived, memory-like T Cell subsets in the drug product may result in enhanced persistence of functional anti-BCMA CAR T cells *in vivo*

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

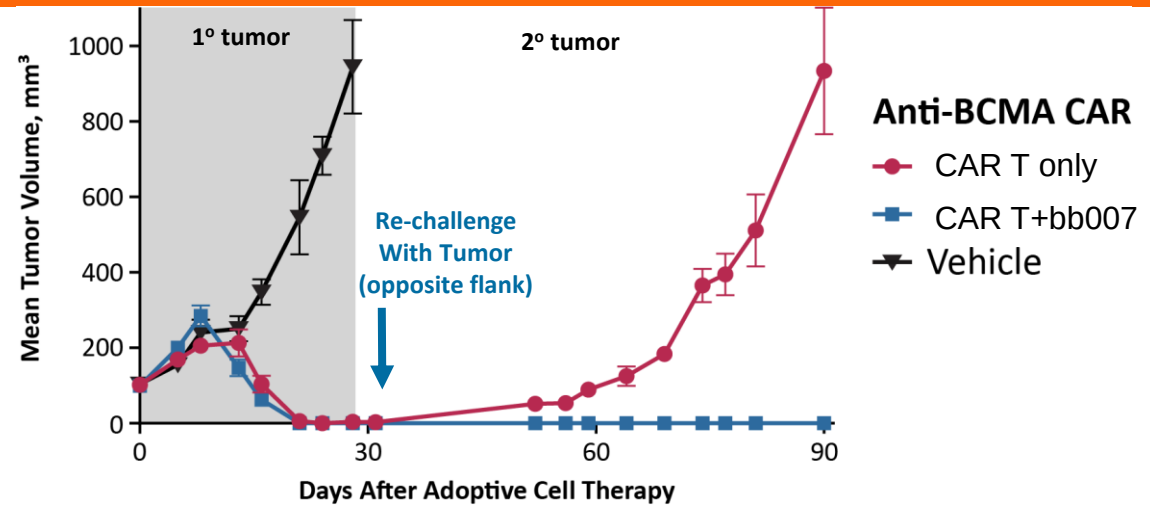
CRB-402

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

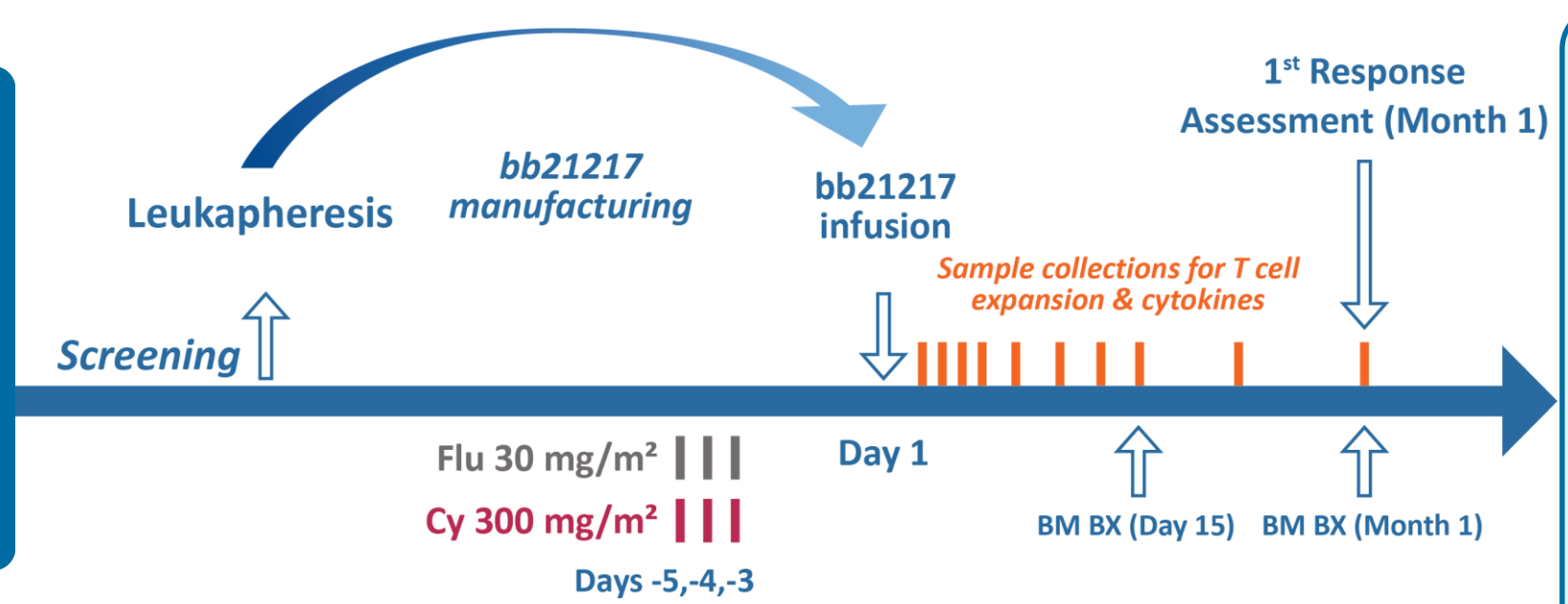
CRB-402

3 + 3 dose escalation[a]

CAR+ T cell dose

150 × 10^6 → 300 × 10^6 → 450 × 10^6 → 800 × 10^6

N ≈ 50
- R/R MM
- ≥3 prior regimens
  - IMiDs and
  - Proteasome inhibitors
  - Or double-refractory
- ≥50% BCMA expression (dose escalation only)



Study Status as of Oct 18, 2018

Collected N=13

Dosed N=12 (150 × 10^6 dose)

HTB[b] n=6 LTB[b] n=6

Median (min, max) follow-up

26 wk (4, 51)

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

NCT03274219

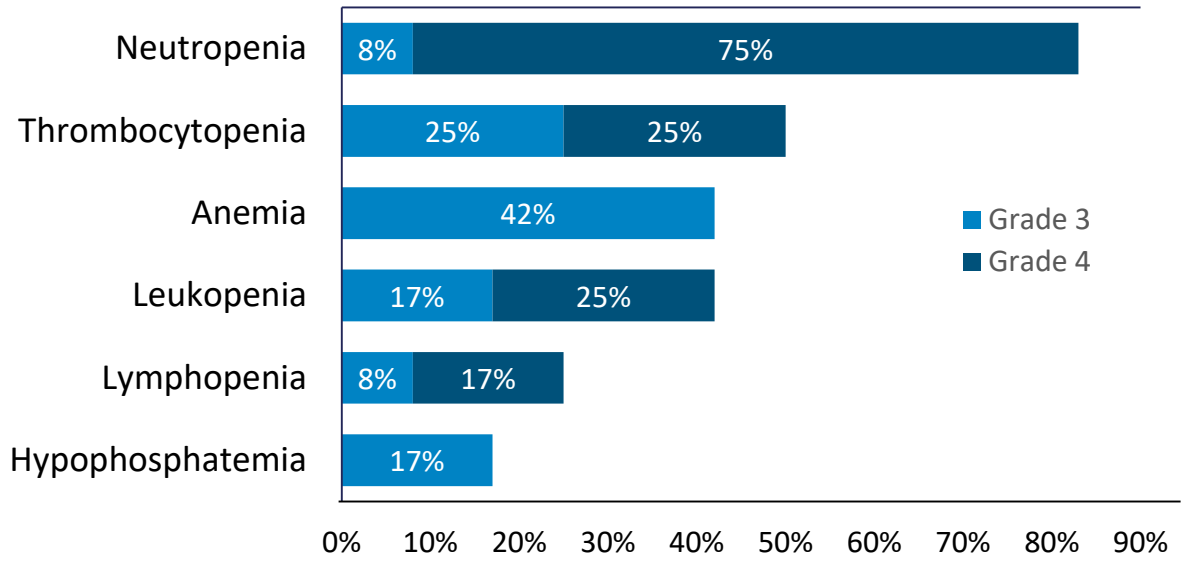
NASDAQ: BLUE

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)

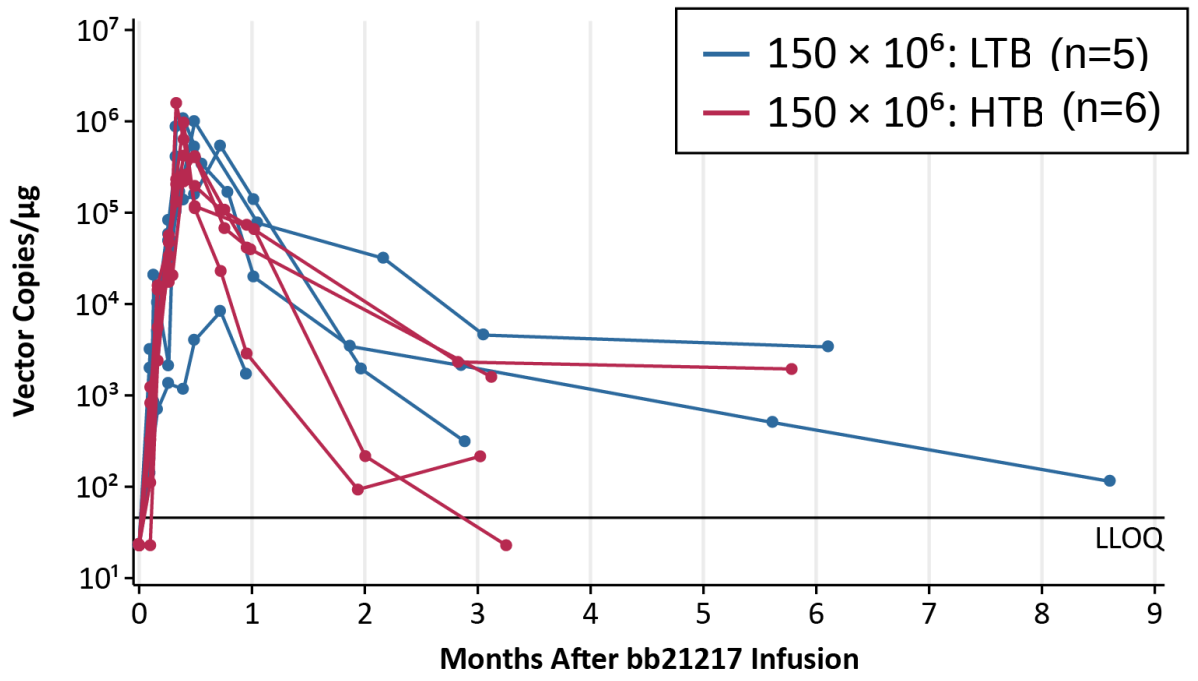
- CRS occurred in 67% of patients
  - Mostly grade 1/2, 1 grade 3, no grade 4
  - Median time to onset of CRS 4.5 days (2,11)
  - Manageable with or without tocilizumab
- 1 patient experienced DLT (grade 4 encephalopathy and grade 3 CRS)
  - Patient had high tumor burden and rapidly accelerating disease 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)

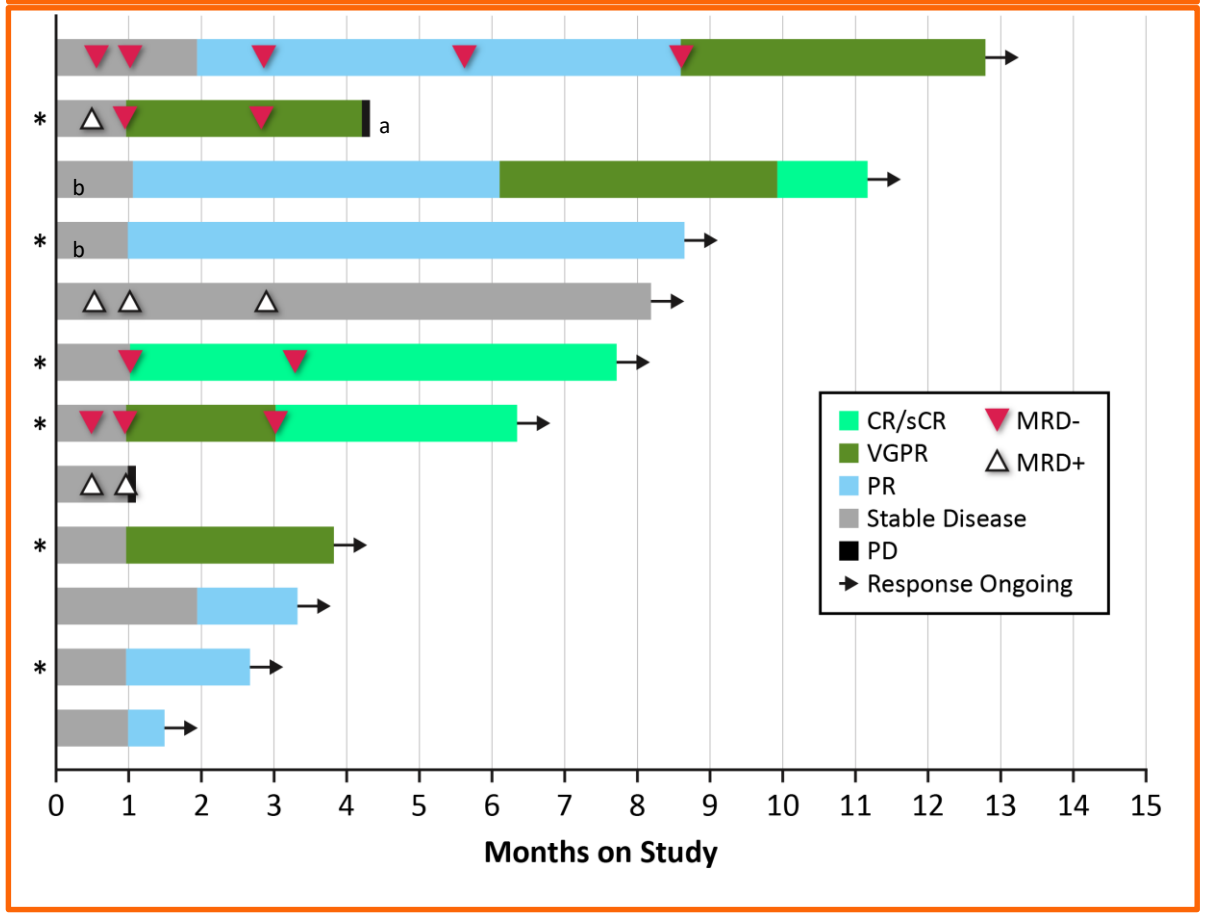
- Robust and reliable bb21217 CAR T cell expansion post-infusion observed at first dose
- Early bb21217 clinical data is consistent with robust functional CAR T cell persistence
  - Enrichment for memory-like CAR T cells observed in preclinical studies, and in patients post-infusion
  - Vector detectable 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

Clinical Responses Over Time



- 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

- **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 β^0/β^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

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-β^0/β^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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