ASH 2017

bluebirdbio

December 10, 2017

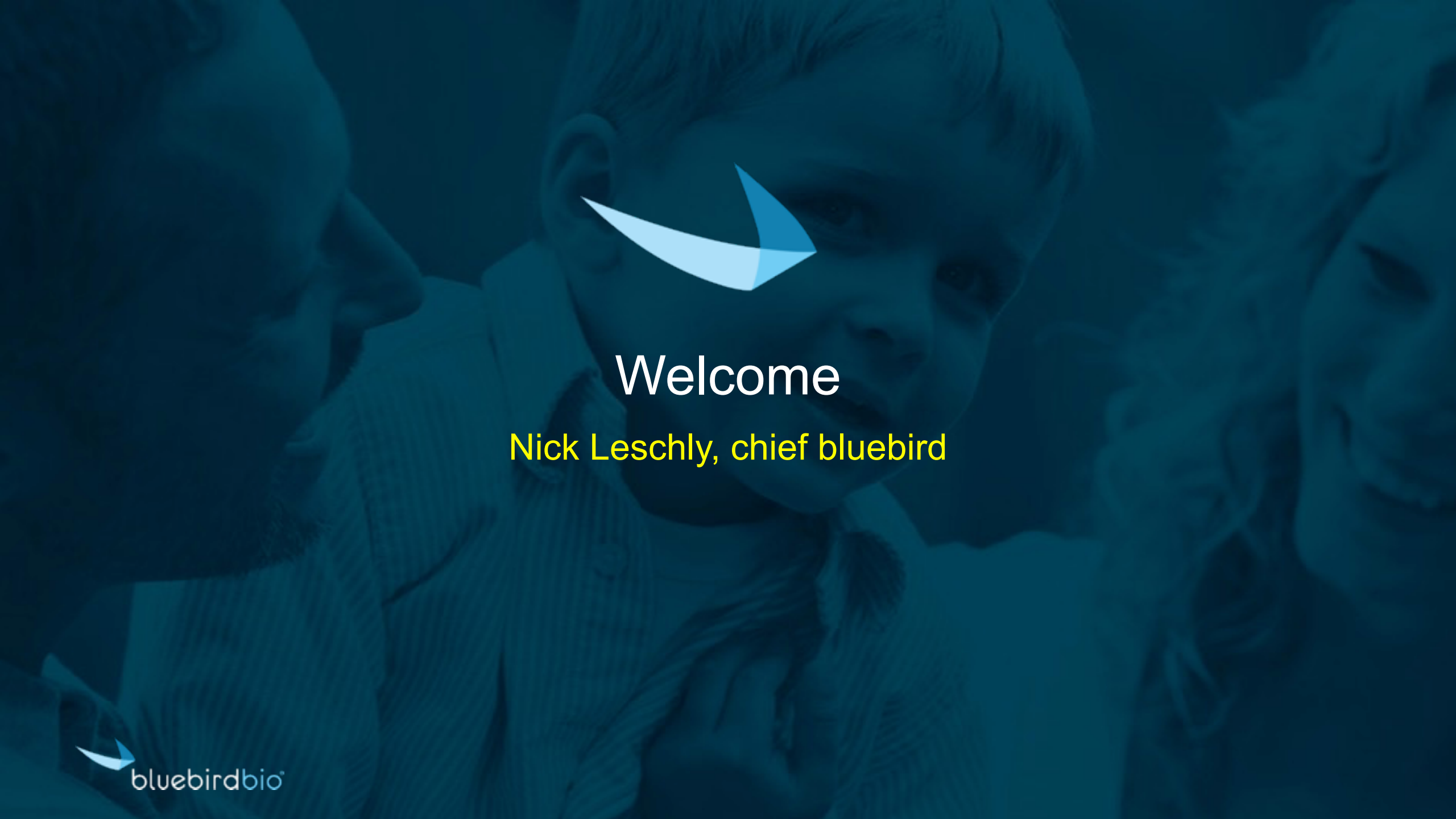
NASDAQ: BLUE

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,** corporate communications, bluebird bio **Nick Leschly,** chief bluebird, bluebird bio
Thalassemia	**David Davidson, M.D.,** chief medical officer, bluebird bio
Sickle Cell Disease	**John Tisdale, M.D.,** National Heart, Lung and Blood Institute (NHLBI), Bethesda, MD
Multiple Myeloma	**Jesus Berdeja, M.D.,** Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN
Closing	**Nick Leschly,** chief bluebird, bluebird bio



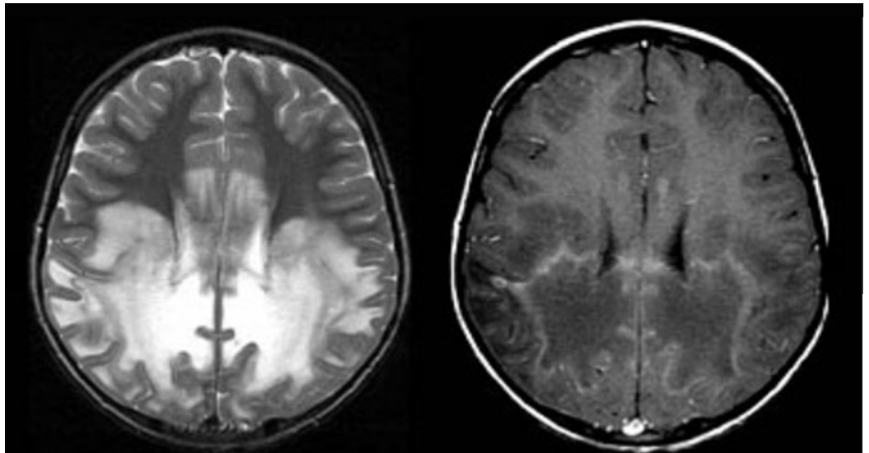
Welcome

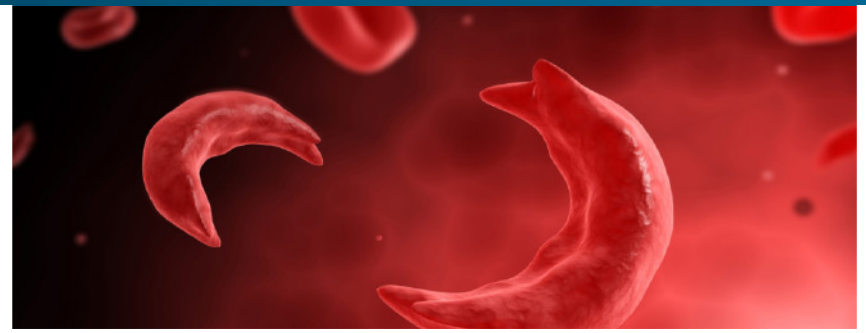
Nick Leschly, chief bluebird

bluebirdbio

Our Vision: Make Hope a Reality

OUR PATIENTS

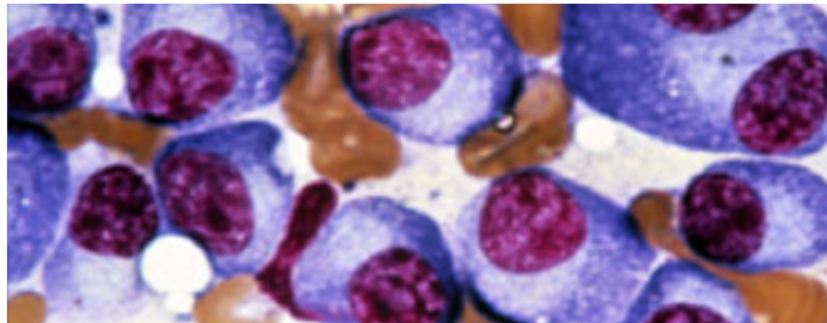




BLUE MOJO

TRUE BLUE

OUR PEOPLE



World-class Gene Therapy Platform and Integrated Global Capabilities

∞ | Patient Impact

2+ Products on the Market

2+ Programs Nearing Commercialization

4+ Additional Programs in the Clinic

Healthy Ecosystem Enabling Transformative Therapies & Innovation

Leading the Way – Recent Developments

The Gene Therapy **Products** Company

In-House Manufacturing

Oncology Pipeline

TC BIOPHARM
medigene
T cells for oncology

Commercial Readiness

apceth BIOPHARMA
Lonza
novasep passion & smart processes
brammer bio
MilliporeSigma

SGD Pipeline

Boston Children's Hospital
Until every child is well™
shmiR for SCD

Pricing & Reimbursement

Duke
MARGOLIS CENTER *for* Health Policy

Regulatory

RMAT (SCD)

BTD + PRIME (BCMA)

2017 – A Breakthrough Year for bluebird

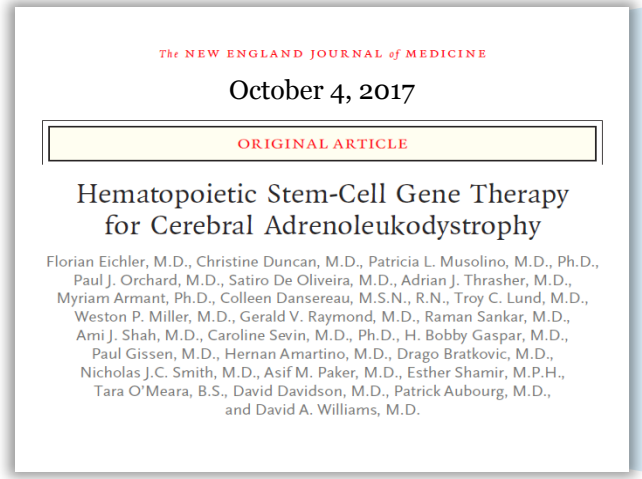
Preparing and investing *in team and infrastructure to bring* ***multiple transformative gene therapies*** *to patients to address the* ***underlying genetic causes of life-threatening diseases***

Cerebral ALD	**15 of 17 patients hit primary endpoint.**
Transfusion-Dependent β-Thalassemia	**Even better. Driving towards filing.**
Severe Sickle Cell Disease	**Big step closer to cracking the SCD code for patients.**
Multiple Myeloma	**94%. 56%. 89%. PFS not yet reached. Going pivotal and beyond.**

Late Stage Programs

Dave Davidson, M.D., chief medical officer, bluebird bio

Lenti-D Treatment Halts CALD Disease Progression


The NEW ENGLAND JOURNAL of MEDICINE

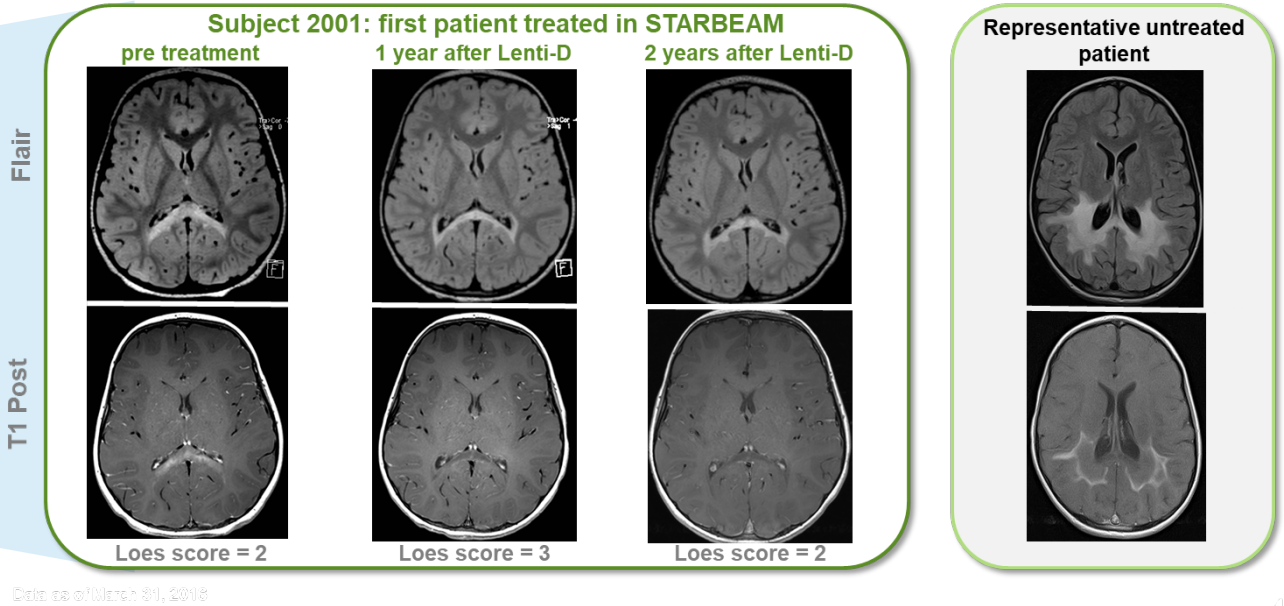
October 4, 2017

ORIGINAL ARTICLE

Hematopoietic Stem-Cell Gene Therapy for Cerebral Adrenoleukodystrophy

Florian Eichler, M.D., Christine Duncan, M.D., Patricia L. Musolino, M.D., Ph.D., Paul J. Orchard, M.D., Satiro De Oliveira, M.D., Adrian J. Thrasher, M.D., Myriam Armant, Ph.D., Colleen Dansereau, M.S.N., R.N., Troy C. Lund, M.D., Weston P. Miller, M.D., Gerald V. Raymond, M.D., Raman Sankar, M.D., Ami J. Shah, M.D., Caroline Sevin, M.D., Ph.D., H. Bobby Gaspar, M.D., Paul Gissen, M.D., Hernan Amartino, M.D., Drago Bratkovic, M.D., Nicholas J.C. Smith, M.D., Asif M. Paker, M.D., Esther Shamir, M.P.H., Tara O'Meara, B.S., David Davidson, M.D., Patrick Aubourg, M.D., and David A. Williams, M.D.

N Engl J Med 2017; 377:1630-1638



Data as of March 31, 2018

4

15/17 patients (88%) alive and MFD-free at 24 months follow-up

- Exceeds pre-determined efficacy benchmark for the study MFD-free survival in 13/15 (76%)

Safety profile consistent with autologous transplantation

- No GvHD, no graft rejection

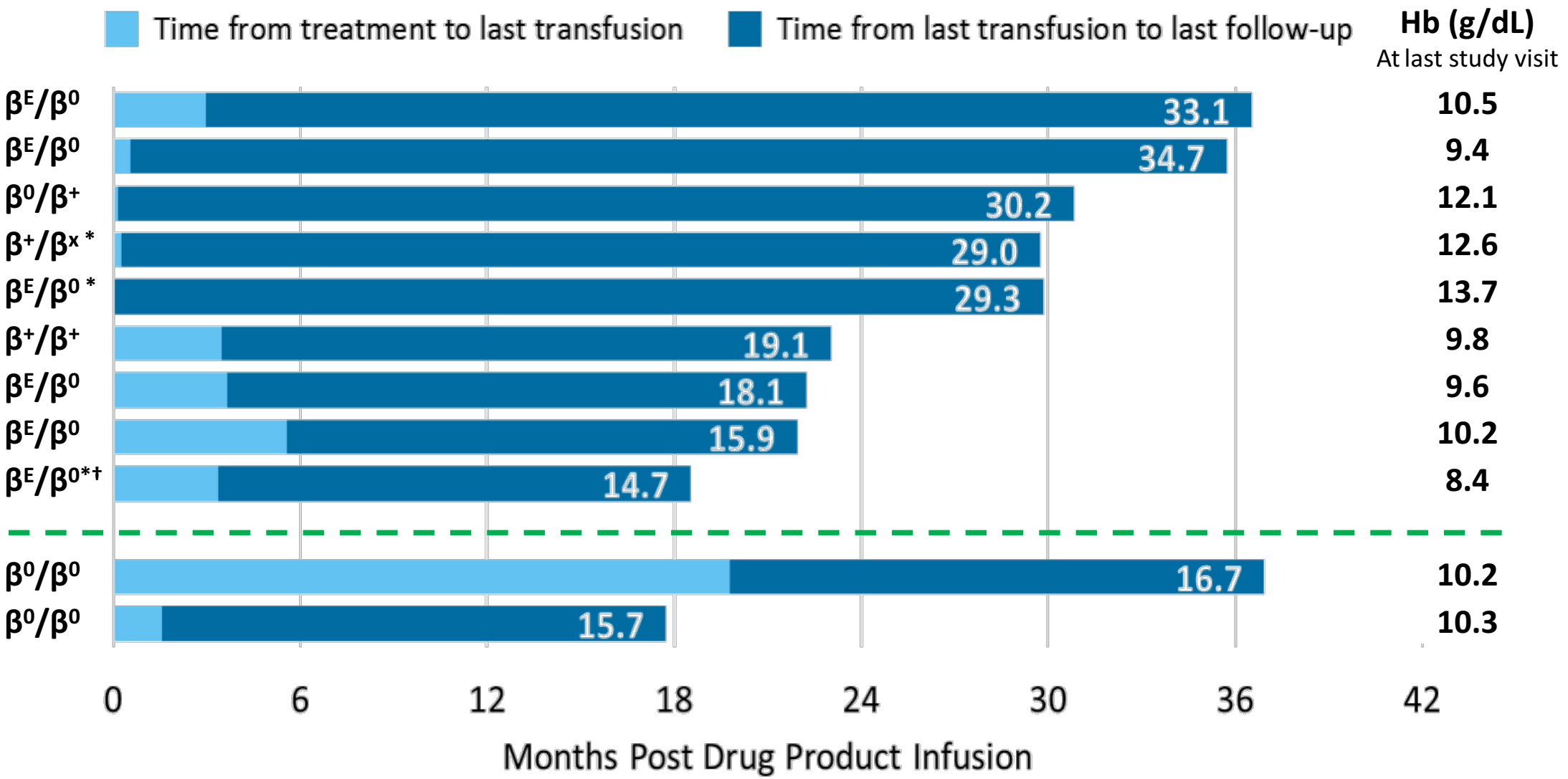
Two patients did not meet primary endpoint:

- Patient 2016: Withdrew due to radiographic progression, later underwent allogeneic transplant; subsequently died from complications of allo
- Patient 2018: Rapid disease progression early in the study; developed severe disabilities from CALD progression; died from complications unrelated to Lenti-D

Transfusion-Dependent Thalassemia Clinical Studies

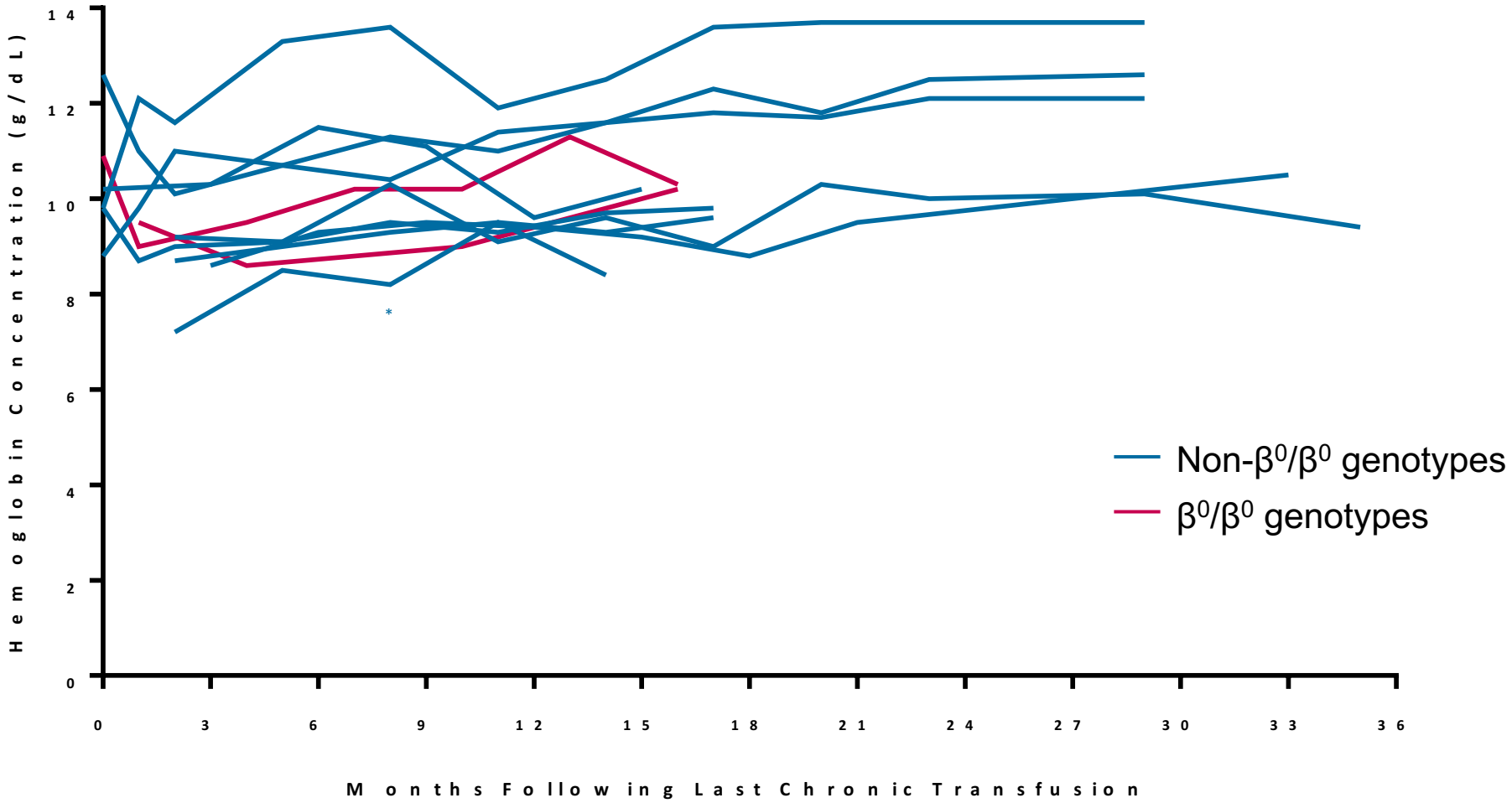
NORTHSTAR STUDY	HGB-204	• Basis of EU filing • Original manufacturing process • All genotypes
HGB-205	HGB-205	• Basis of EU filing (with Northstar) • Original manufacturing process
NORTHSTAR-2 STUDY	HGB-207	• Basis of US filing • Refined manufacturing process • non-β^0/β^0 genotypes
NORTHSTAR-3 STUDY	HGB-212	• β^0/β^0 genotypes • Refined manufacturing process • First patient treated in November 2017

Northstar: 9/10 Patients with non-β^0/β^0 Genotypes and 2/8 with β^0/β^0 Genotypes are Free from Chronic RBC Transfusions



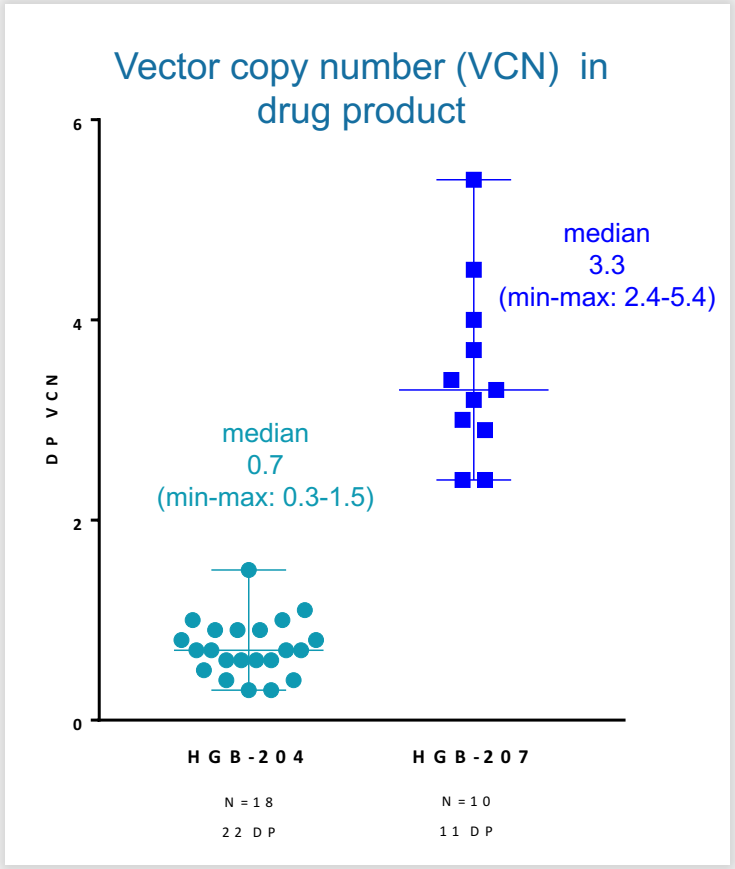
Data as of September 21, 2017

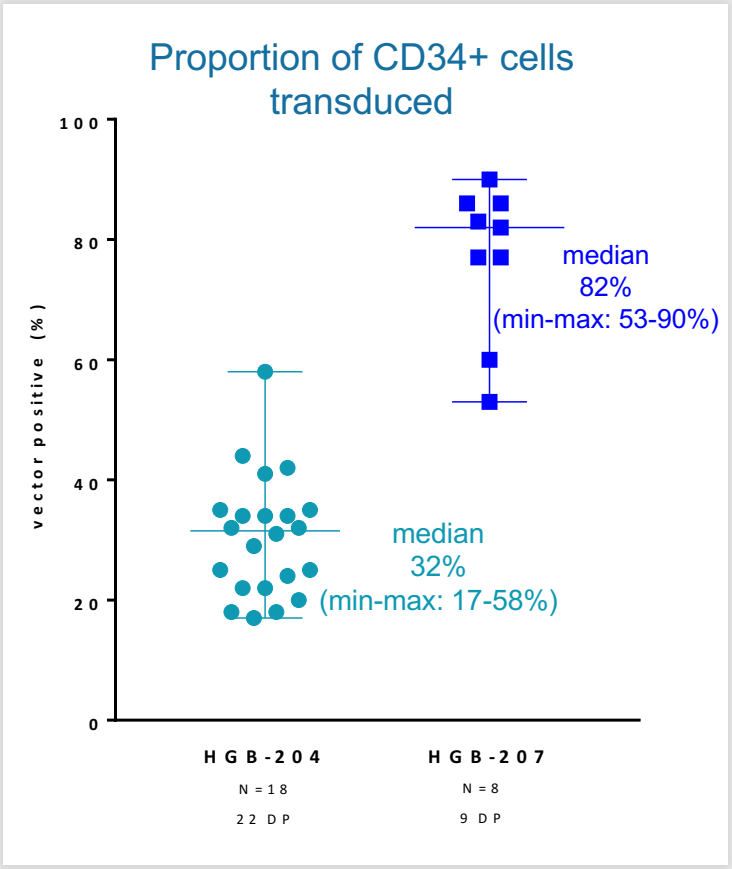
Northstar: Hemoglobin Remains Stable in Patients Free from Chronic Transfusions Up to Three Years

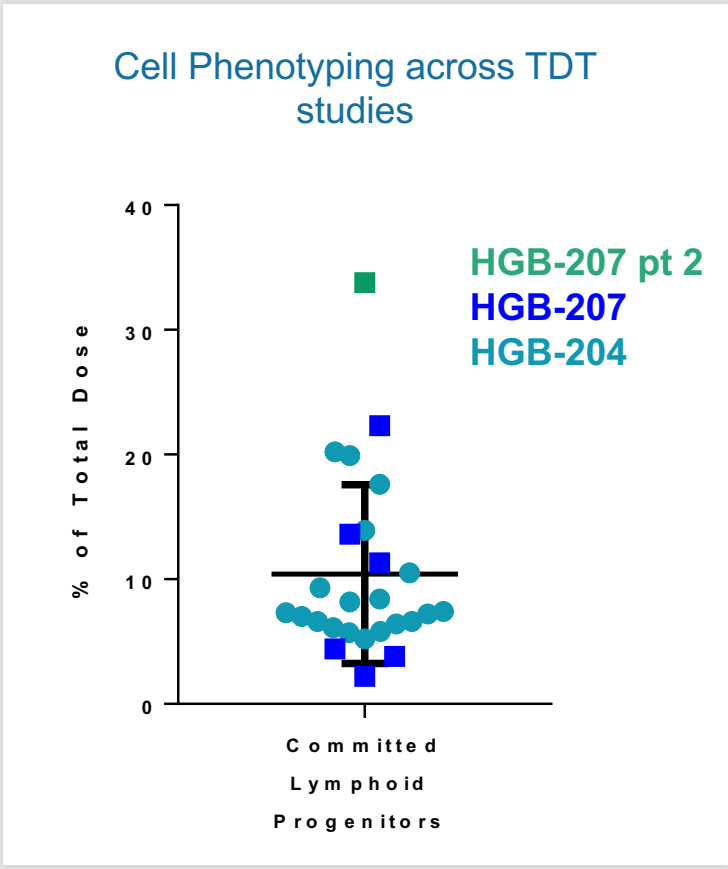


*Patient 1118 is free from chronic RBC transfusions, however received a single transfusion at 13 months post-infusion during an acute viral illness

Refined Manufacturing Process Yields Higher Drug Product Vector Copy Number and Proportion of Transduced Cells

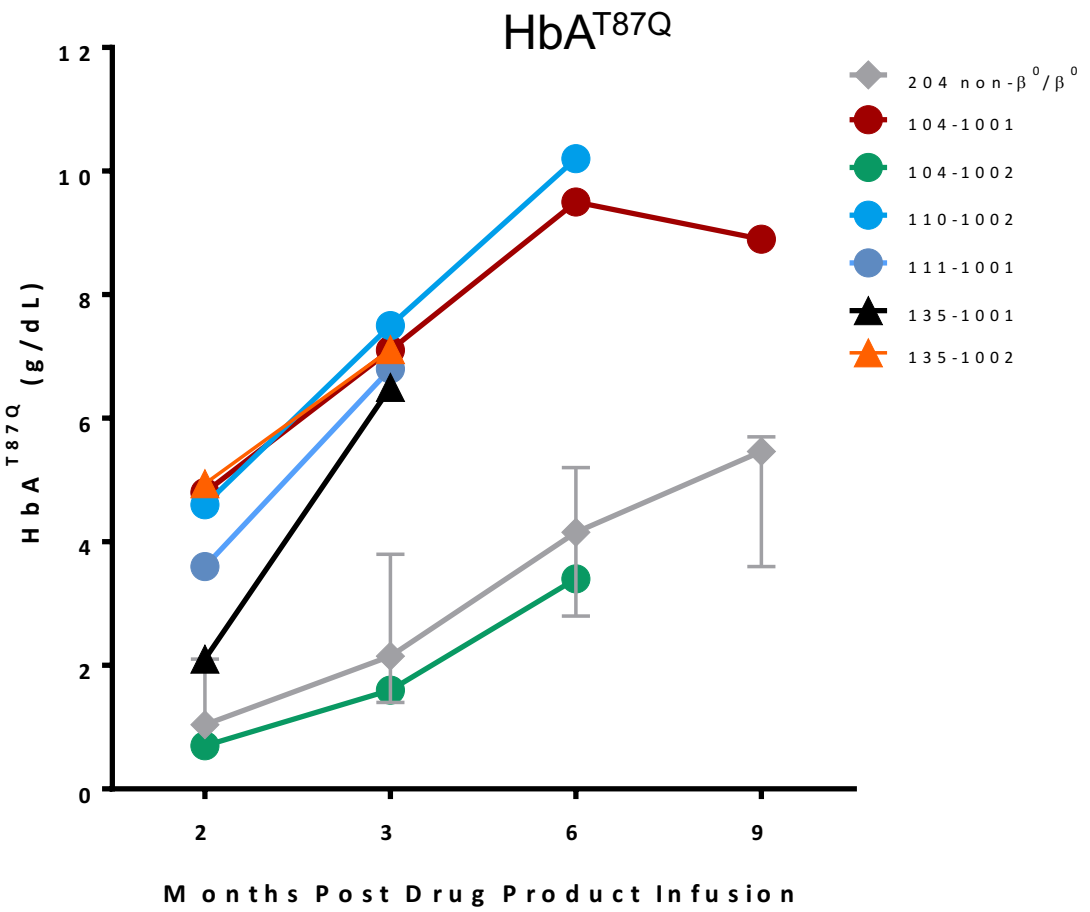




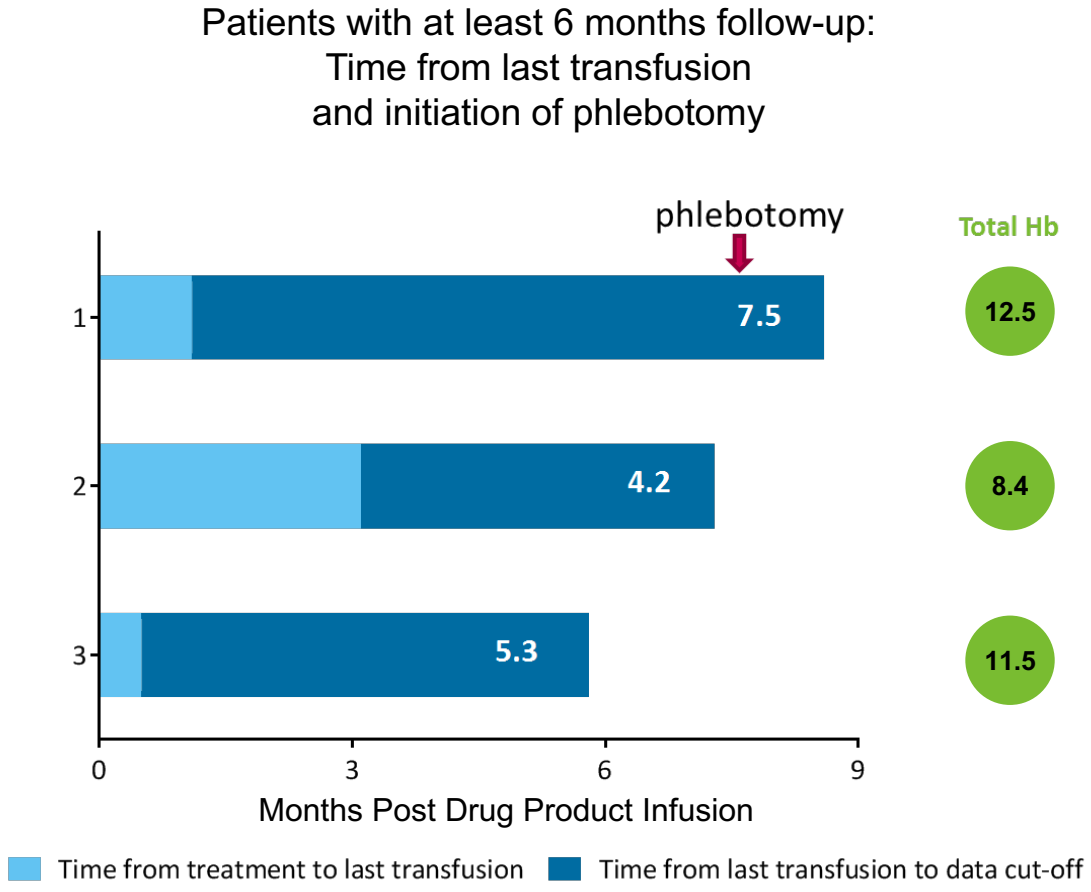


* No of DP exceed number of patients since some patients were mobilized twice
* % LVV not available for 3 patients at time of analyses

Northstar-2: Higher Transduction Efficiency Translates to Robust HbA^{T87Q} with 5 of 6 Patients Producing >6 g/dL HbA^{T87Q} at 3 Months



Circles indicate females



TDT Registration Strategy

General agreement with EU & US regulators on the registration path for LentiGlobin for the treatment of transfusion-dependent β-thalassemia

EU

Pursue **CONDITIONAL APPROVAL** in patients with non-β^0/β^0 genotypes on the basis of data from ongoing Northstar (HGB-204) & HGB-205 studies, as well as available data from Northstar-2 (HGB-207) study

ADAPTIVE PATHWAYS

PRIME

US

Pursue **approval** in adults and adolescents with non-**β^0/β^0** genotypes based on data from ongoing pivotal Northstar-2 (HGB-207) trial

Pediatric population to be included as a cohort of Northstar-2 (HGB-207), rather than separate study

Submission for approval in **β^0/β^0** patients to be based on ongoing Northstar-3 (HGB-212) study

BREAKTHROUGH THERAPY DESIGNATION

ORPHAN DRUG DESIGNATION

Sickle Cell Disease

John Tisdale, M.D., National Heart, Lung and Blood Institute (NHLBI), Bethesda, MD

Why Gene Therapy in SCD?

First disease described at the molecular level; minimal progress in treatment in past 50 years

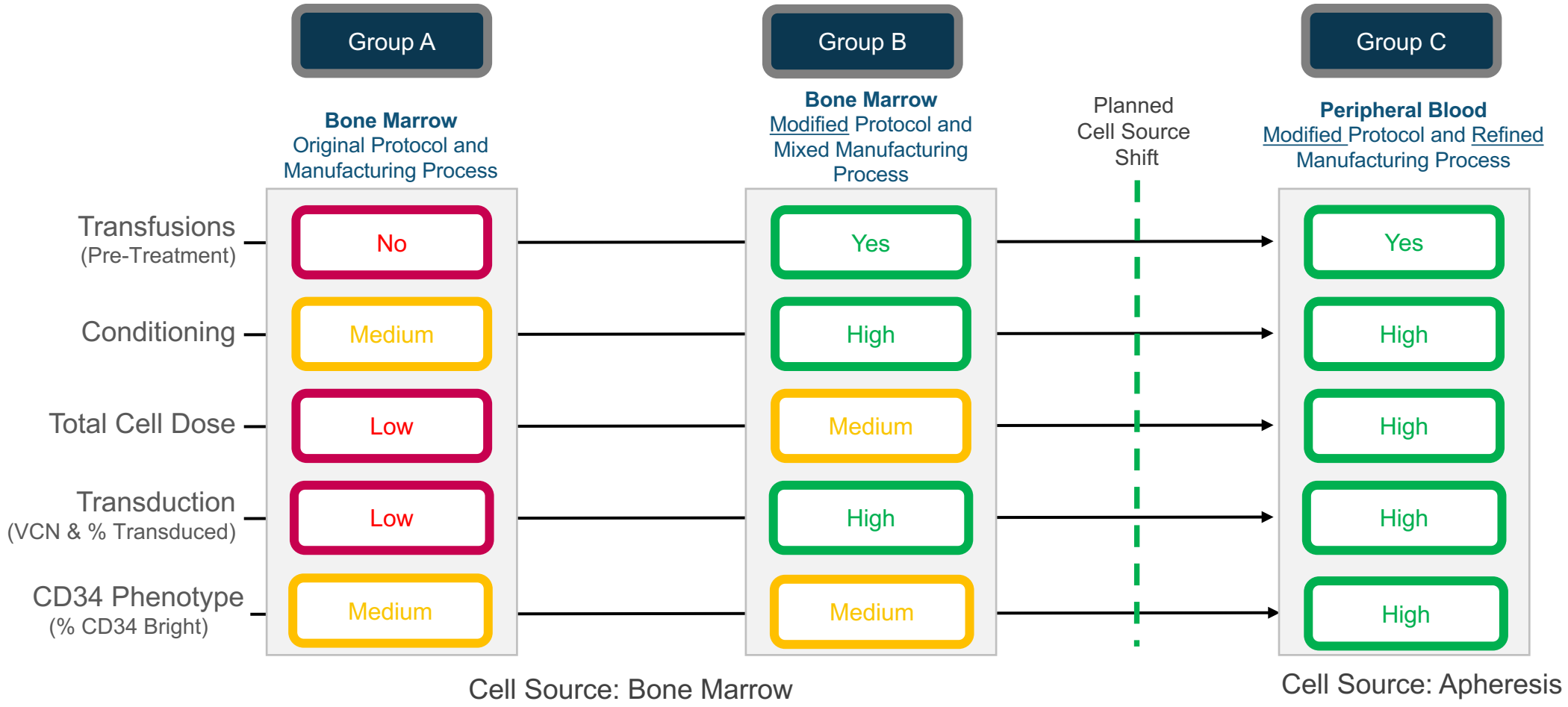
- Greater than 100,000 Americans affected, millions worldwide
- High morbidity and early mortality
  - Mean age of death in US is 44 years*
- Only 2 FDA-approved treatments
  - Symptom reduction only
  - Not universally effective
- Significant health disparity
- HLA-matched bone marrow transplant curative
  - Limited by donor availability to less than 10% of patients

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

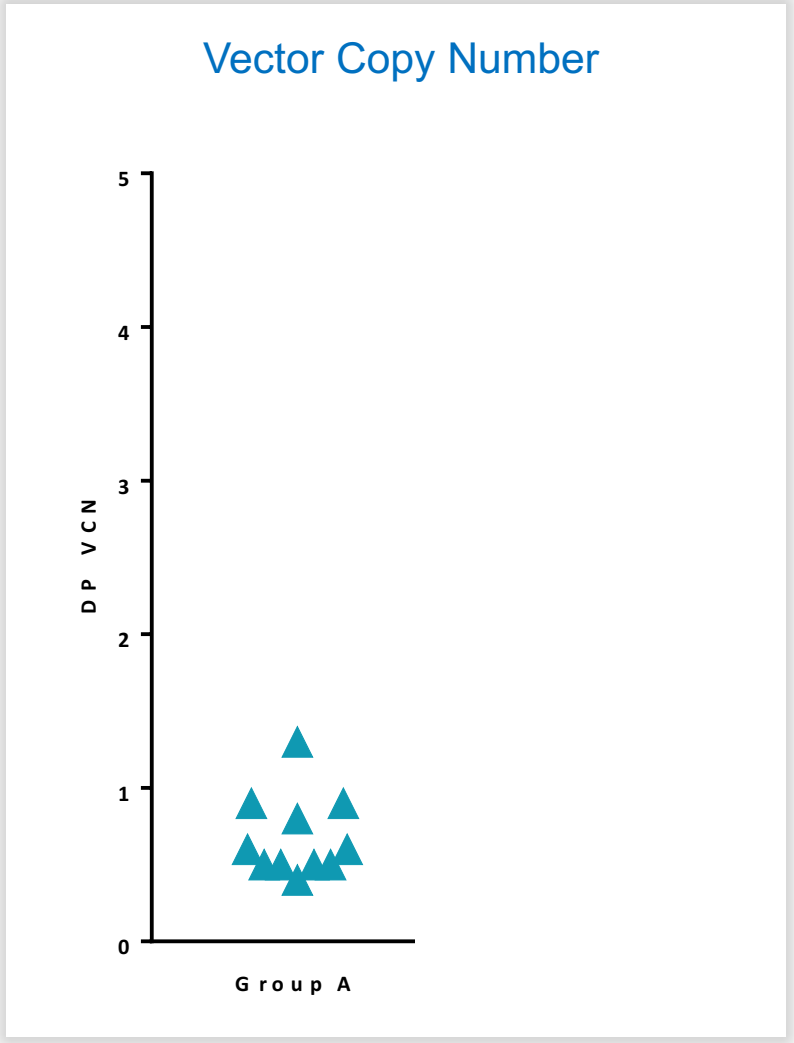
Key Questions on Sickle Cell Disease Gene Therapy Efforts

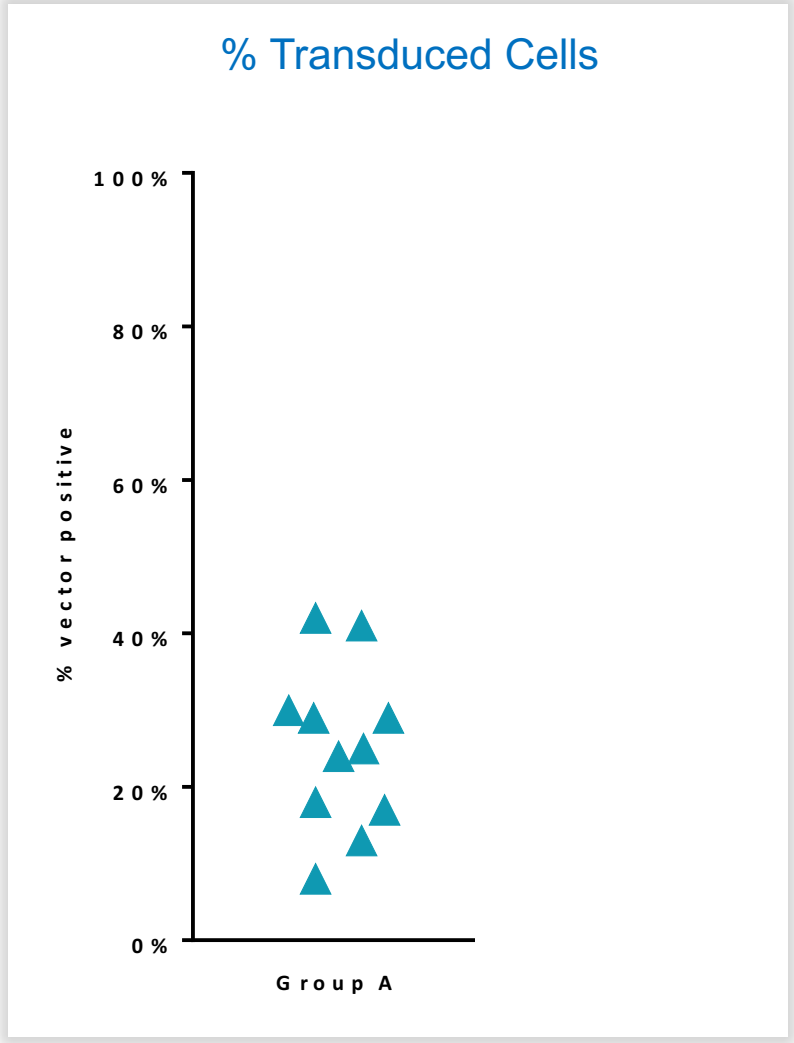
- Have the changes to the process and protocol improved *in vivo* VCN and HbA^{T87Q} production?
- Can we improve patient experience by eliminating the need for bone marrow harvest?
- Can mobilization with plerixafor allow us to yield more and better cells versus bone marrow?
- What impact will the implementation of plerixafor have on clinical outcomes?

HGB-206: Evolution of LentiGlobin in SCD – New Early Data from Patients in Group B and Group C



Enhancements to Manufacturing Lead to Improved Drug Product Characteristics





LentiGlobin manufacturing process

- Original
- Refined

Data as of November 30, 2017

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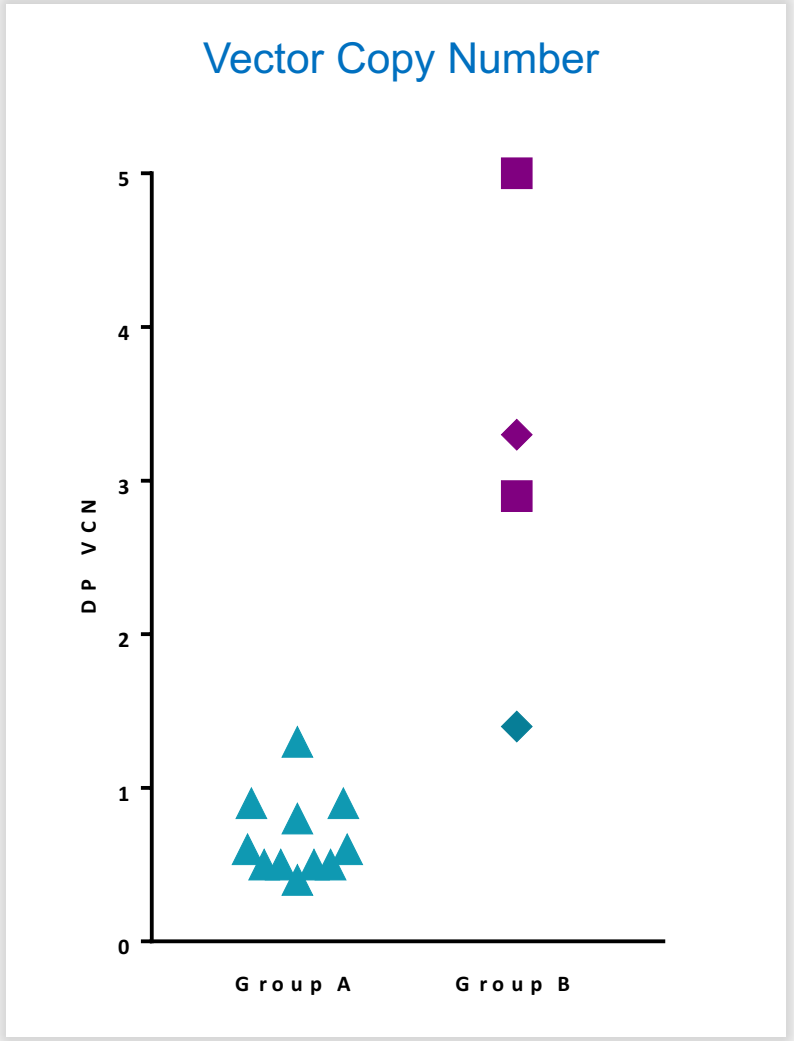

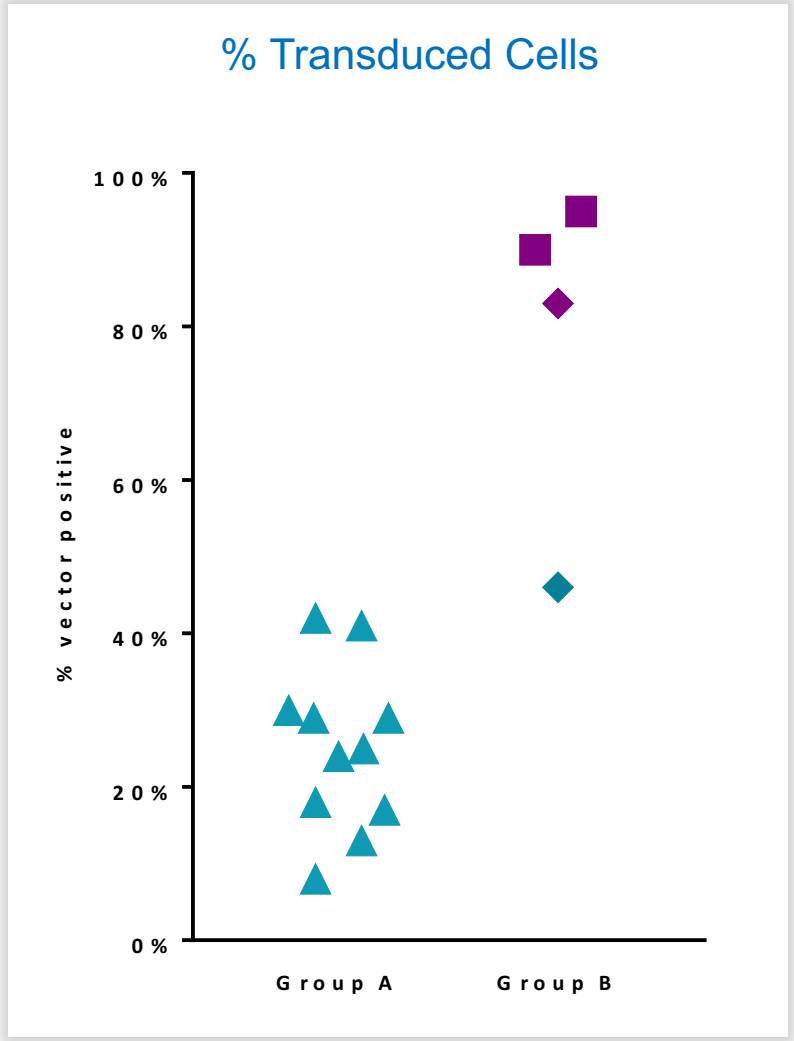

LentiGlobin manufacturing process

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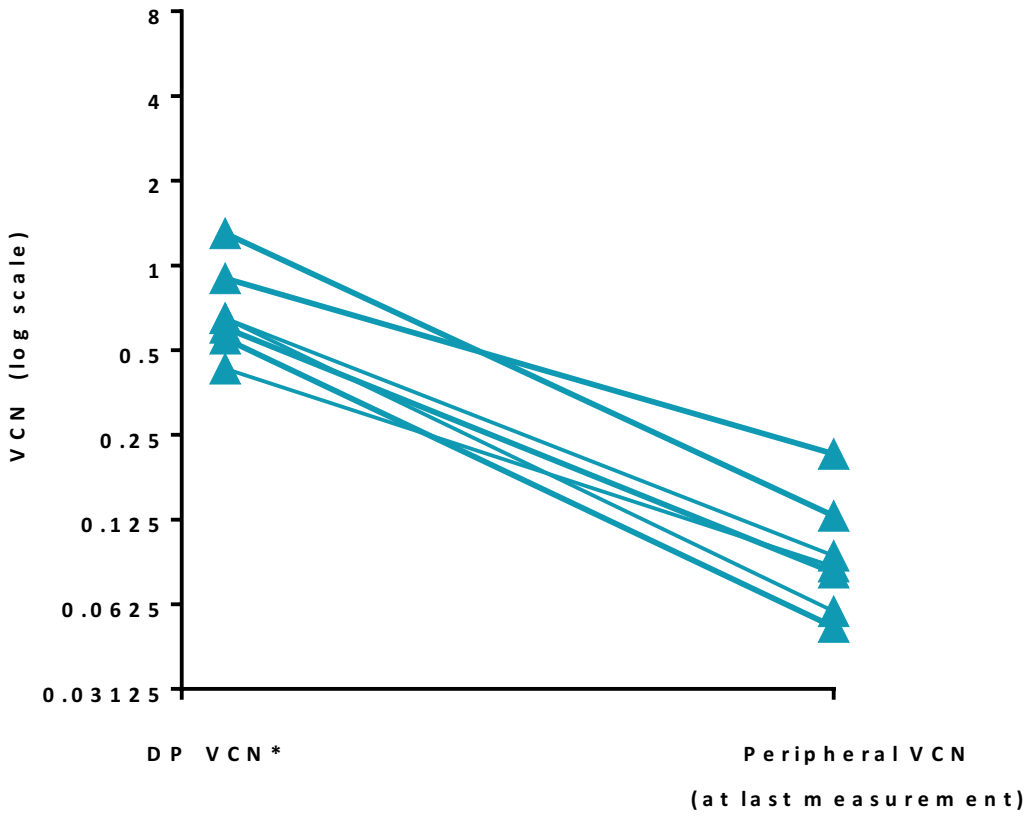
- Refined

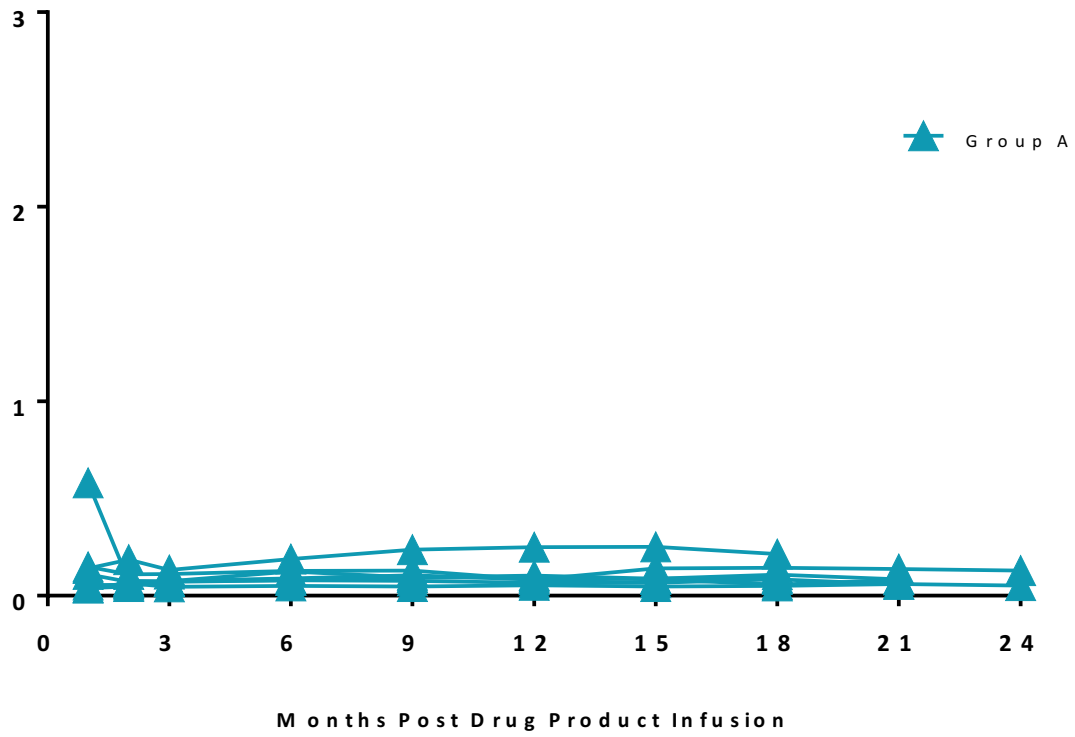
Data as of November 30, 2017

Process and Protocol Changes Lead to Higher Peripheral Blood Vector Copy Number (VCN) After Drug Product Infusion

VCN in drug product and peripheral blood



Peripheral blood VCN over time



*Mean DP VCNs used for patients with >1 DP lot

LentiGlobin manufacturing process

Original
Refined

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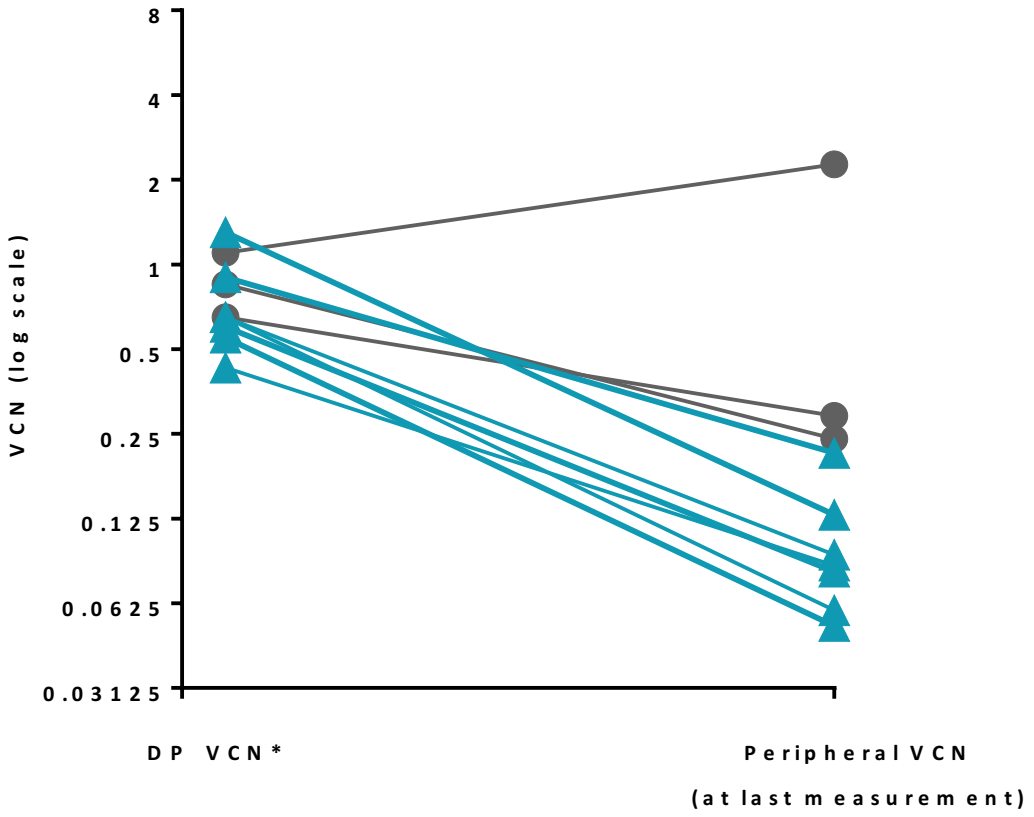

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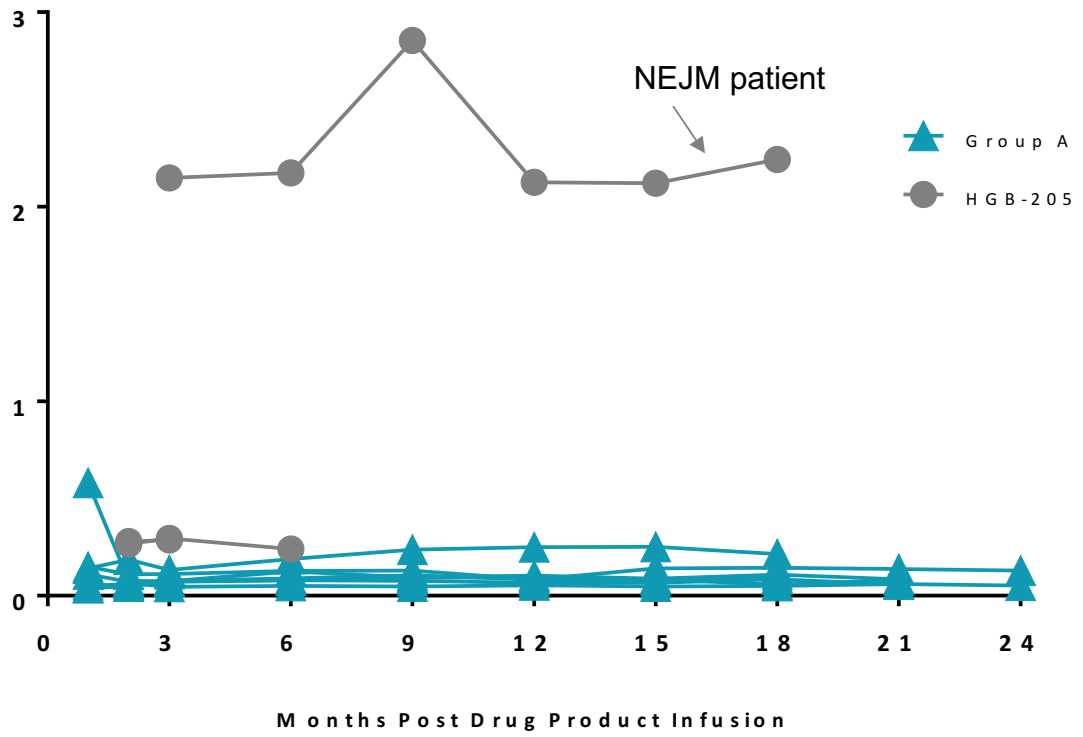

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Original

Refined

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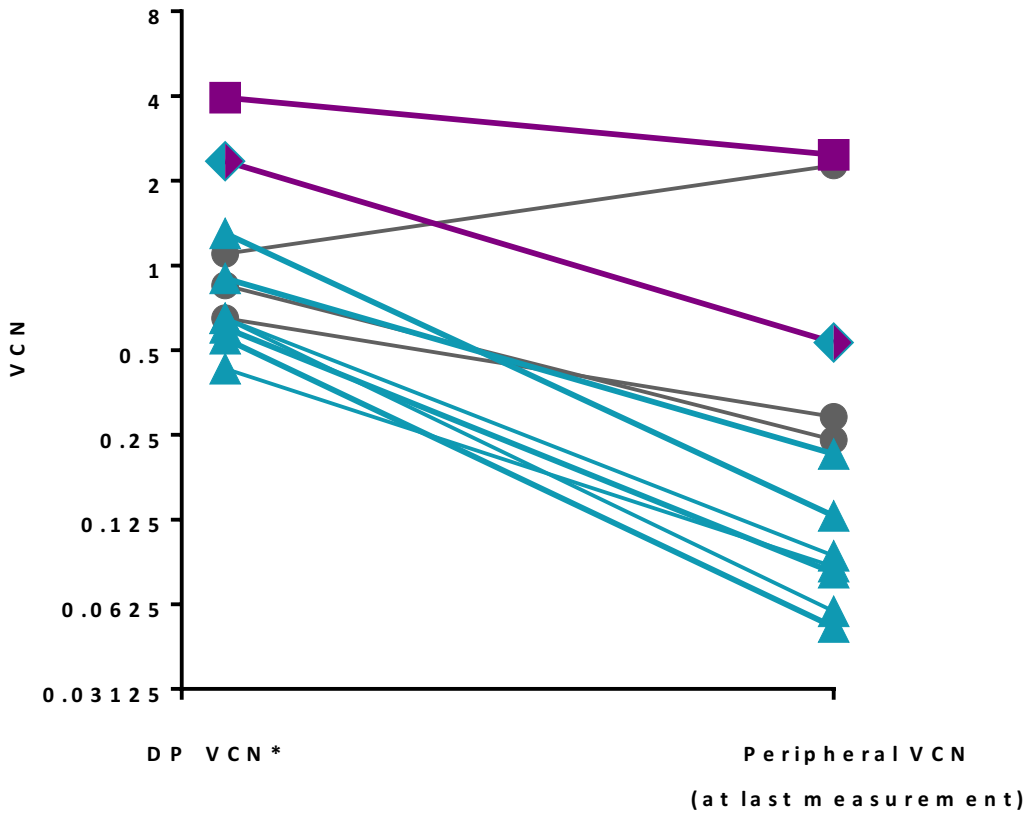

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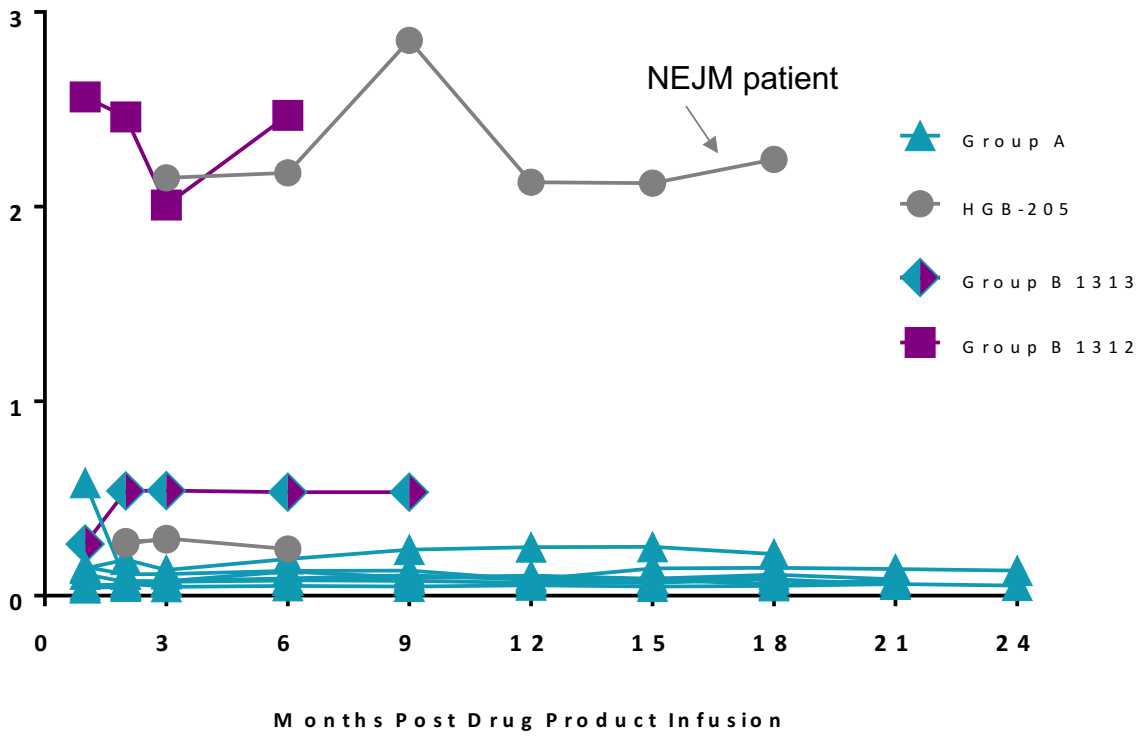

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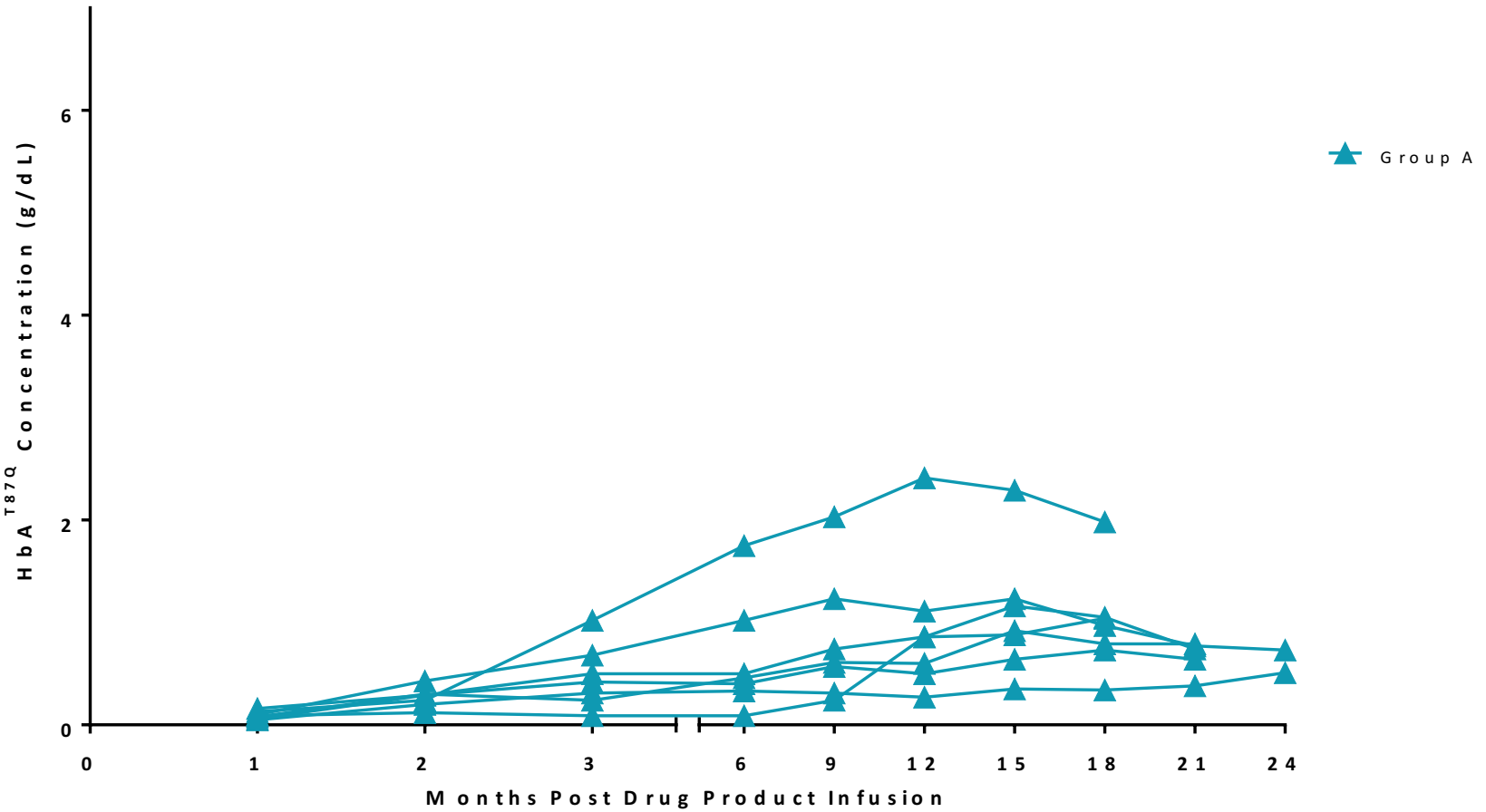
LentiGlobin manufacturing process

Original
Refined

Data as of November 30, 2017

Improvements in Drug Product Characteristics and Protocol Improve HbA^{T87Q} Production



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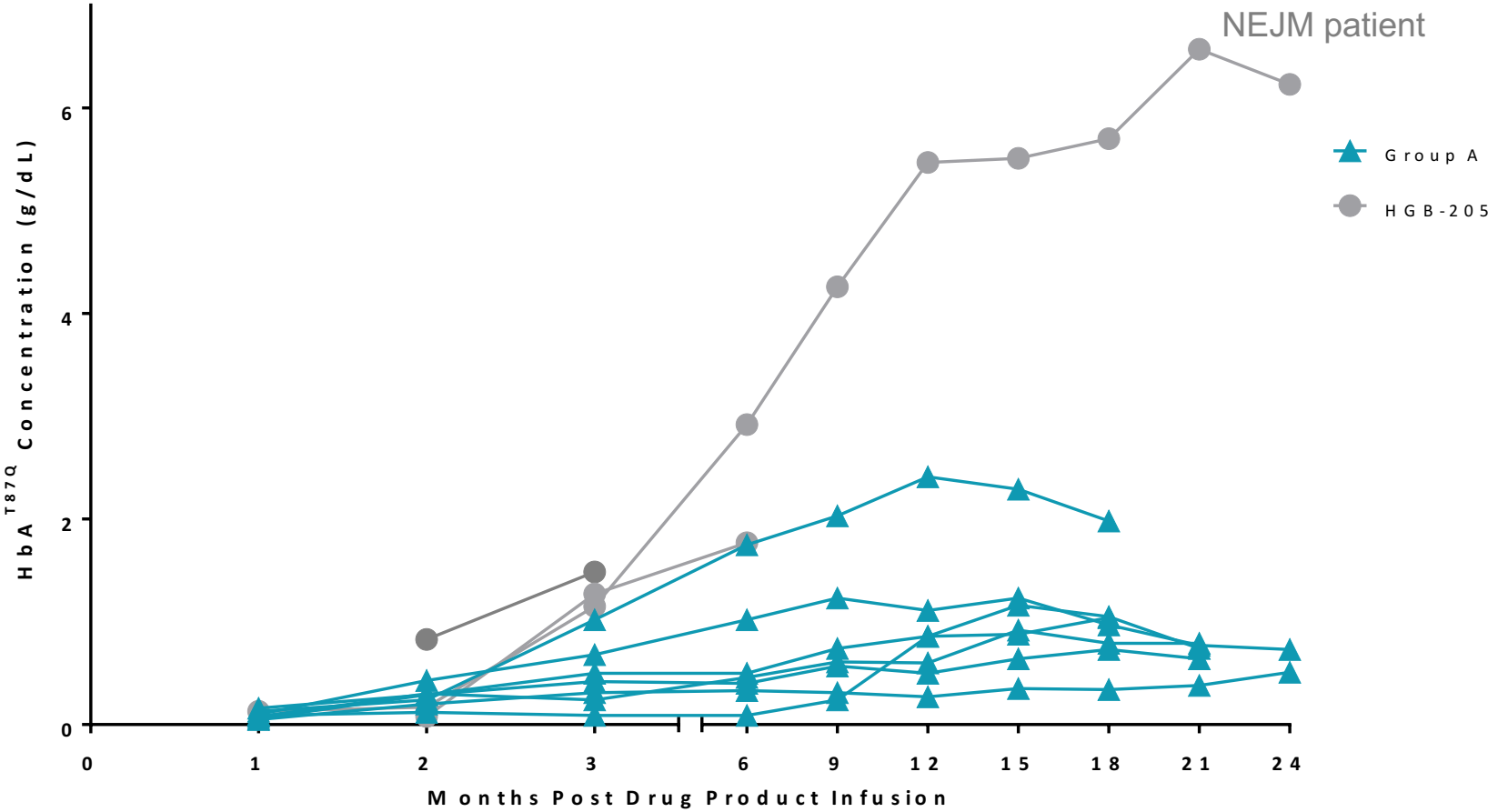

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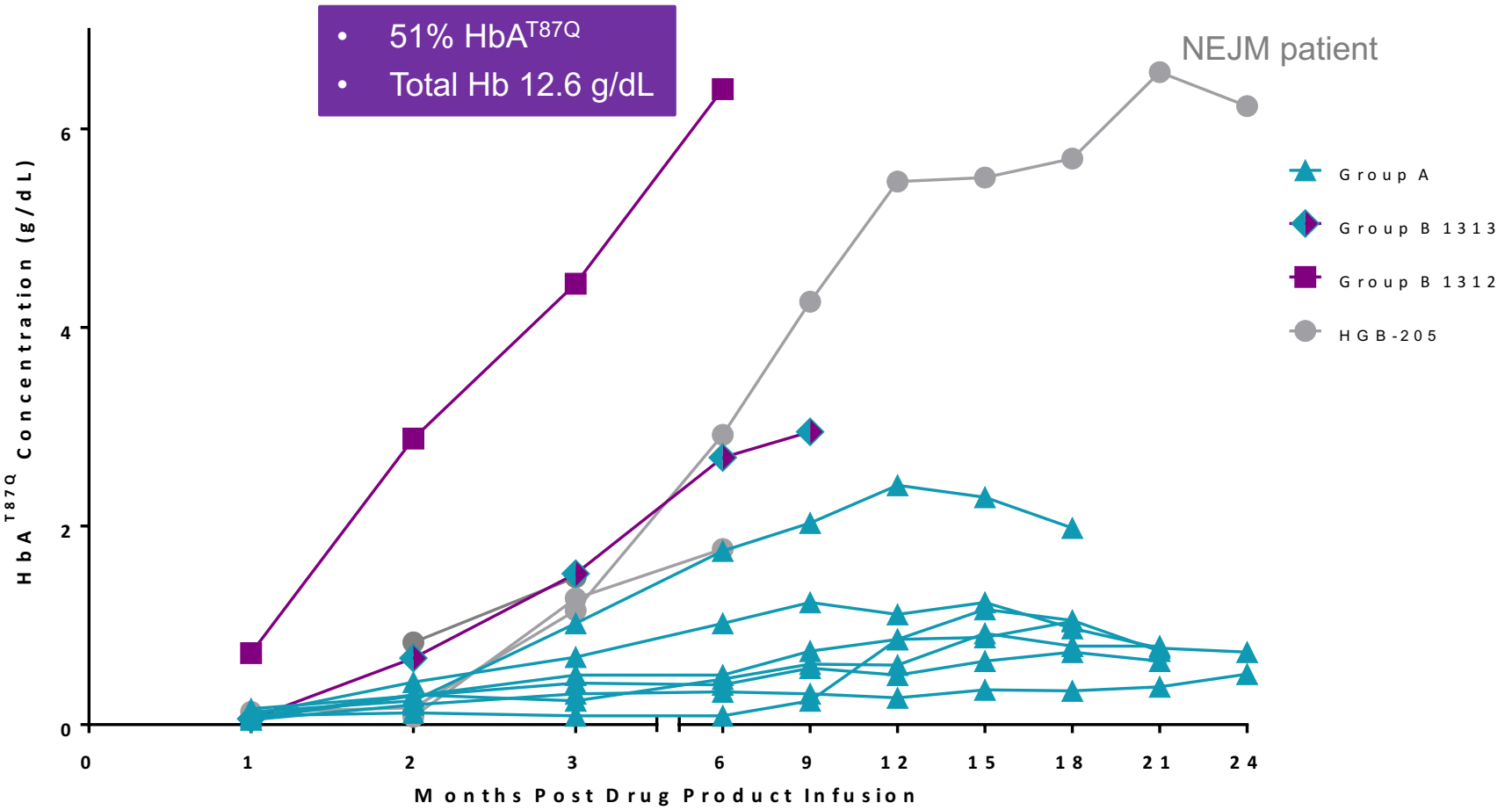


- Higher DP VCN ✓
- Higher *in vivo* VCN ✓
- Higher T87Q ✓

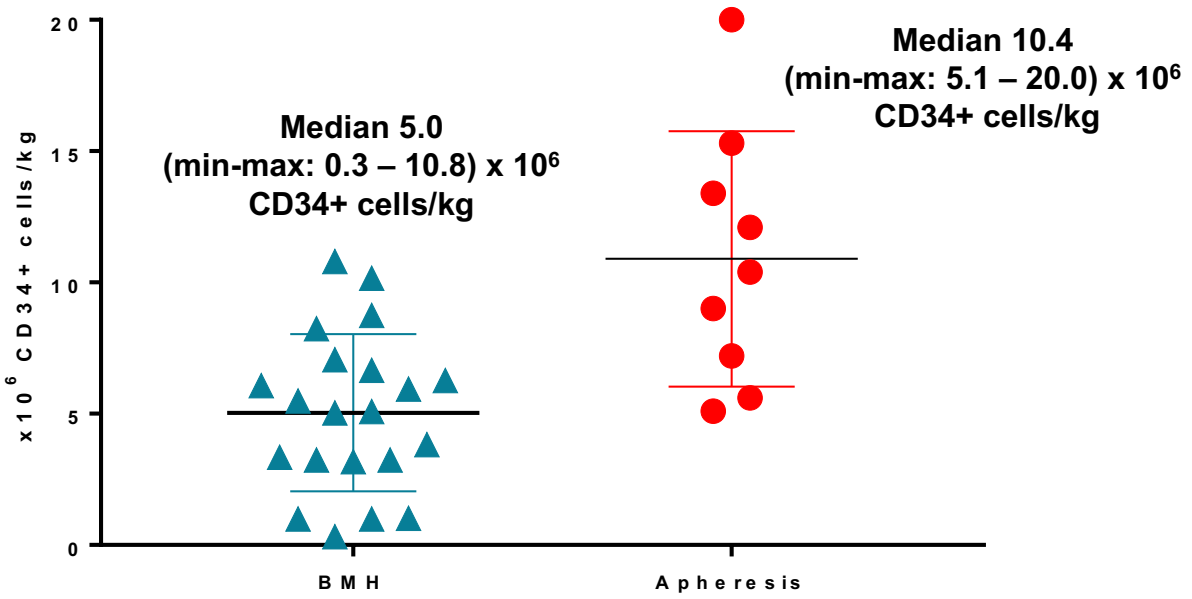
Data as of November 30, 2017

Data with Plerixafor Mobilization and Apheresis Support Using Peripheral Blood for DP Manufacture

Key Findings in 7 Patients

- **ACCEPTABLE SAFETY PROFILE** no dose limiting toxicities observed
- **CELL DOSE** delivered higher than with bone marrow harvest
- **CELL PHENOTYPE** may be more favorable than BMH

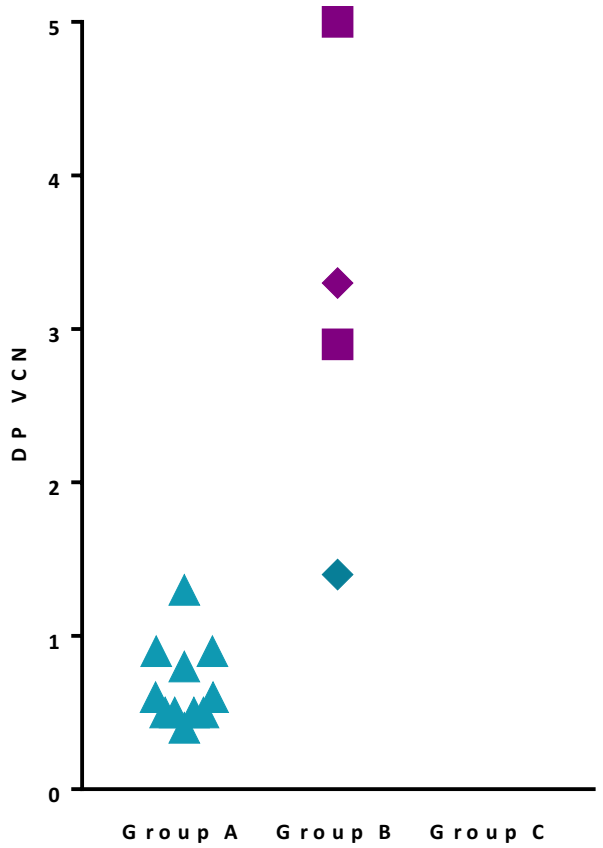
Total CD34 cells collected per collection cycle



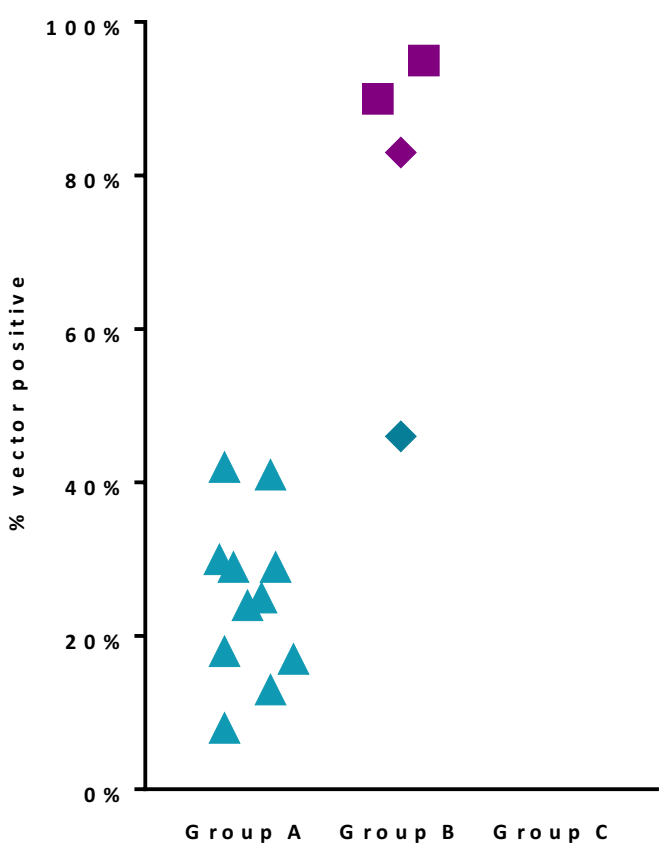
Plerixafor mobilization implemented in HGB-206

Group C: Shift to Apheresis May Further Improve Drug Product Characteristics

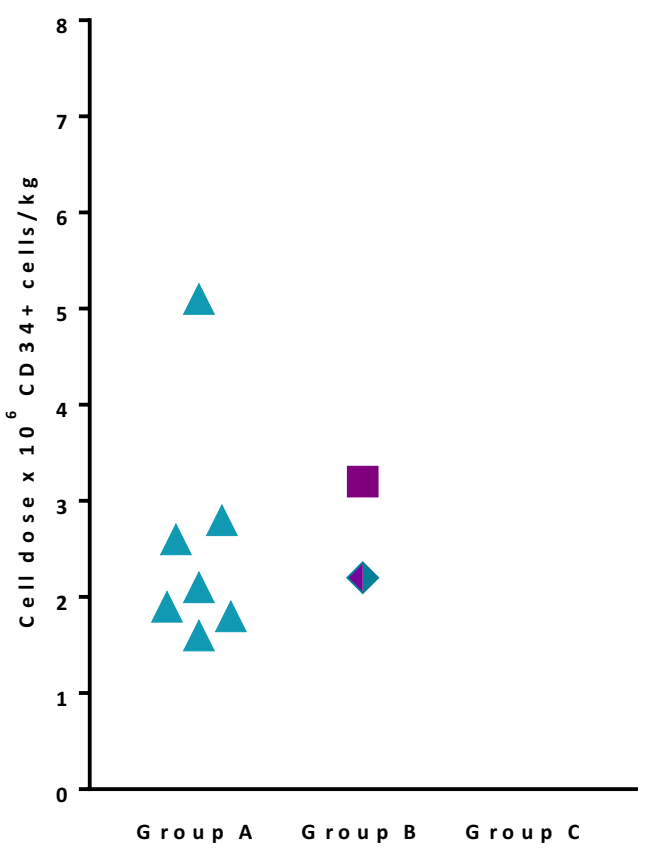
Vector Copy Number



% Transduced Cells



CD34+ cell count in DP



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Group C: Shift to Apheresis May Further Improve Drug Product Characteristics

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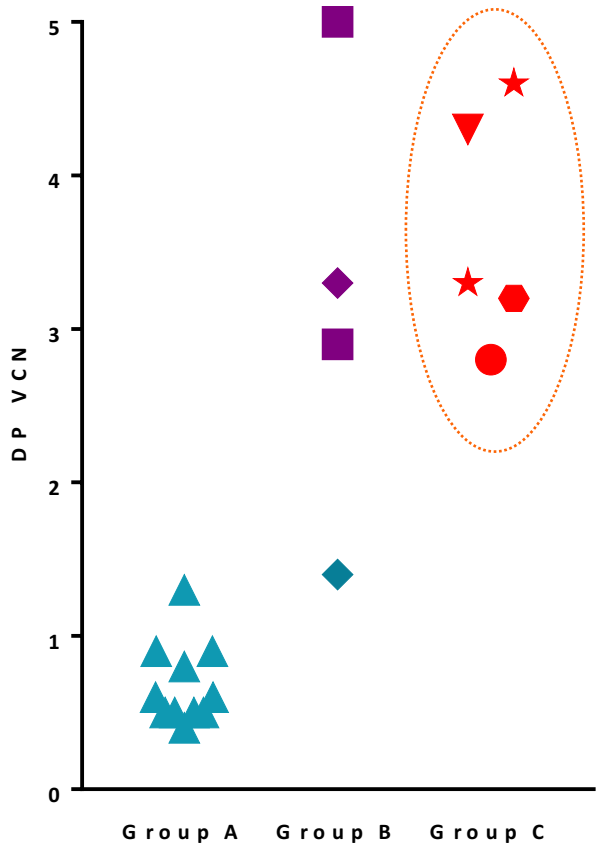

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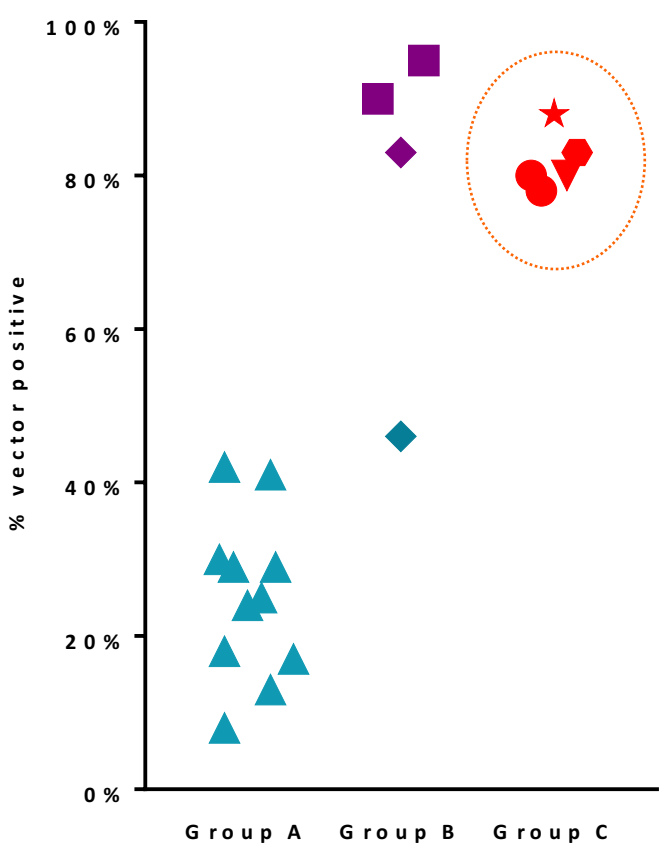

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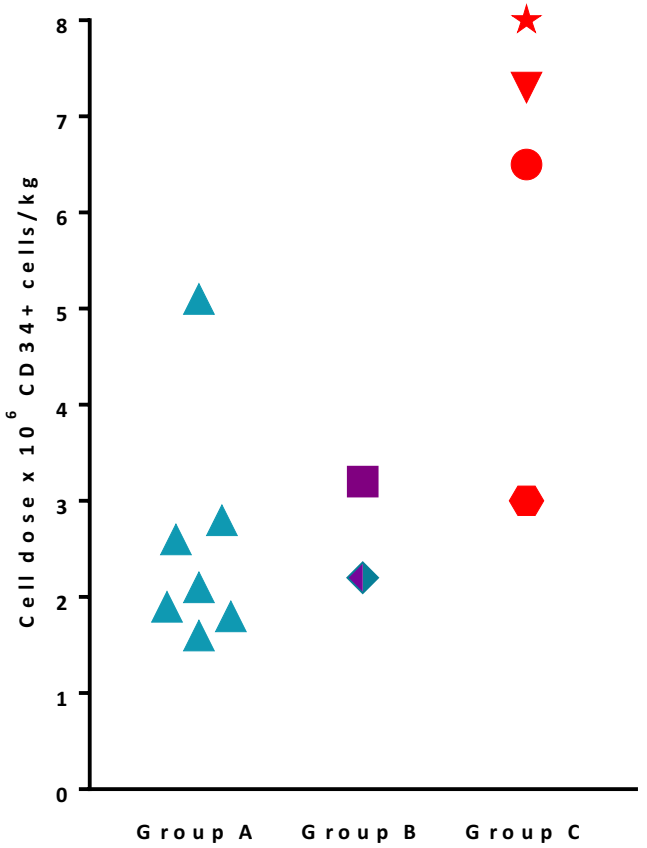

Data as of November 30, 2017

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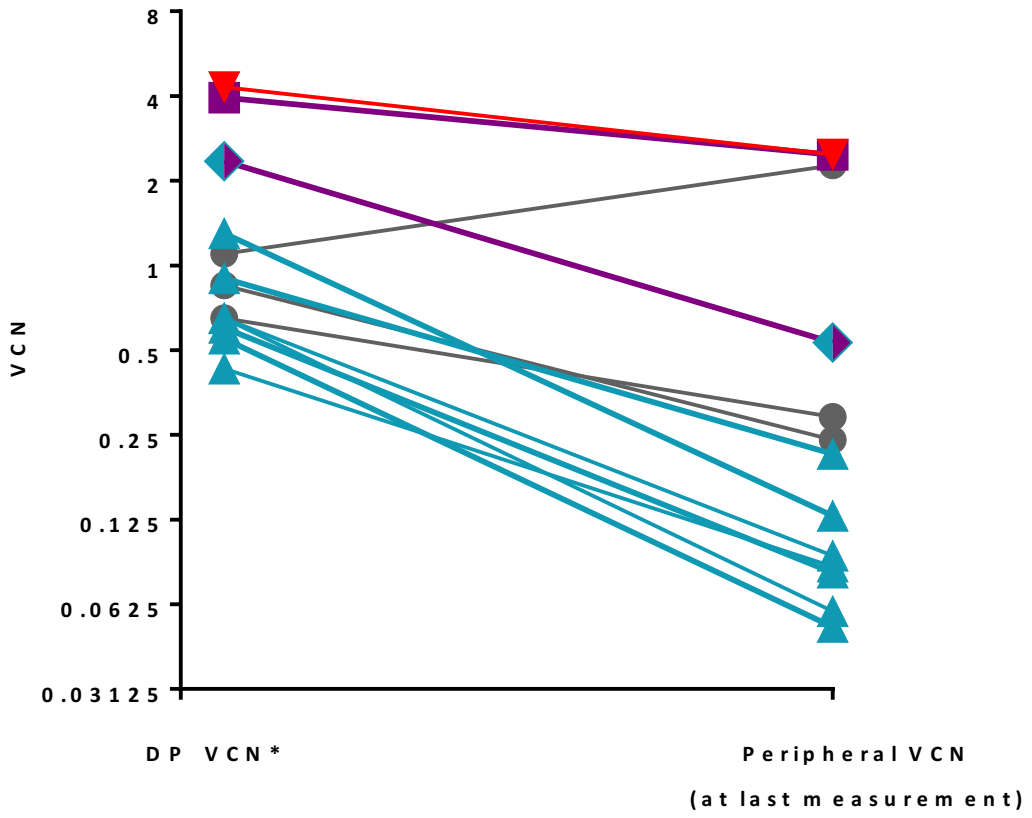
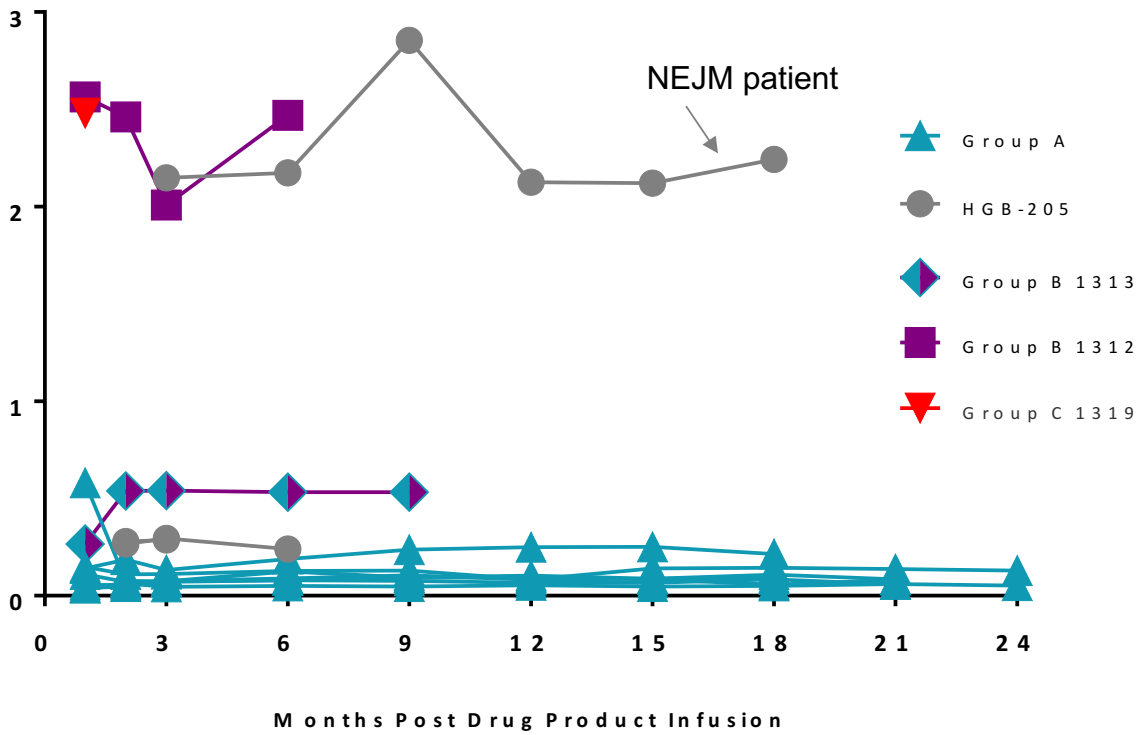
VCN in drug product and peripheral blood



Peripheral blood VCN over time



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Original
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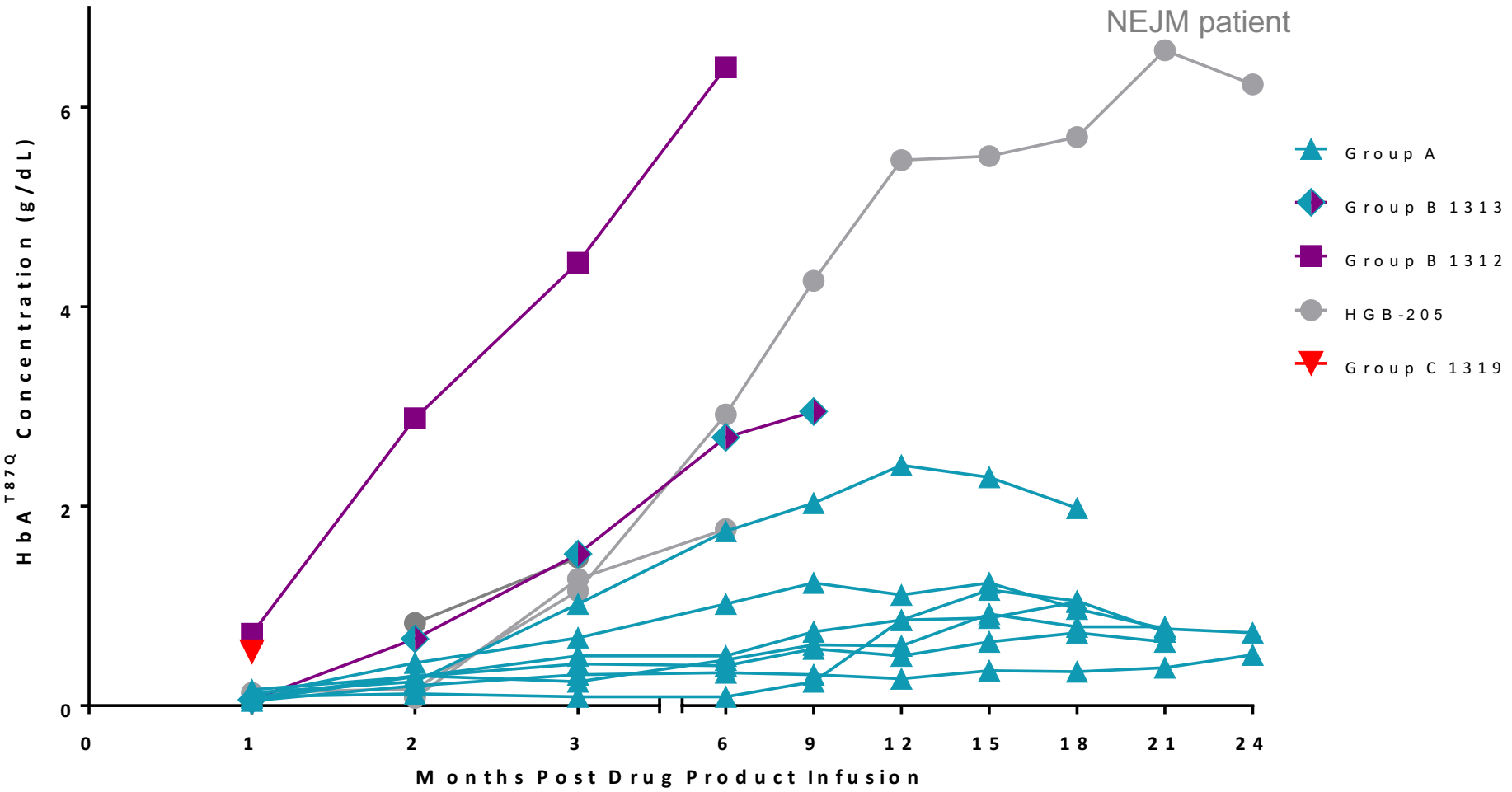
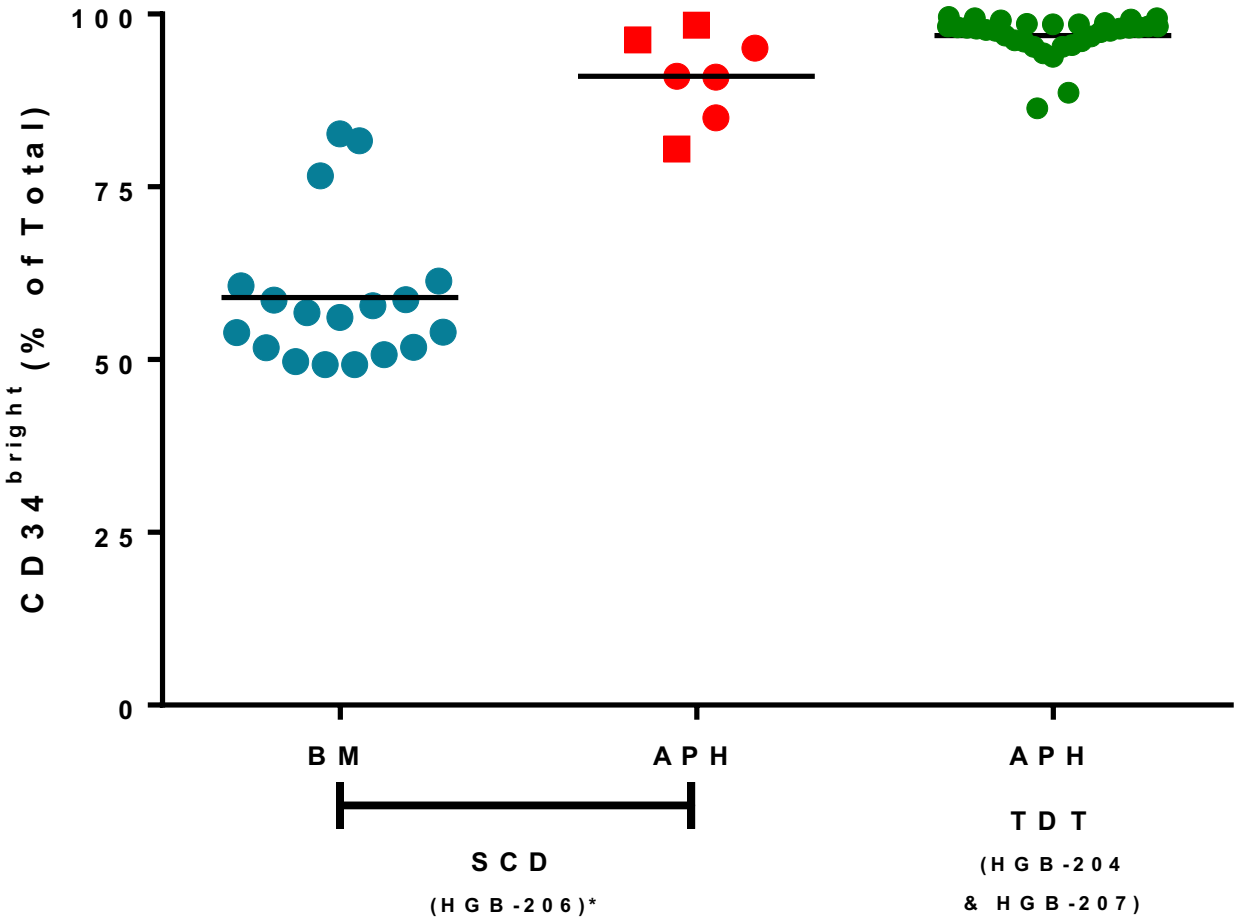


Data as of November 30, 2017

Most CD34+ Cells Collected Through Plerixafor Mobilization and Apheresis Have Desirable “Bright” Phenotype



SCD BM

- Median 56.5, min-max 49.3-82.7

SCD APH

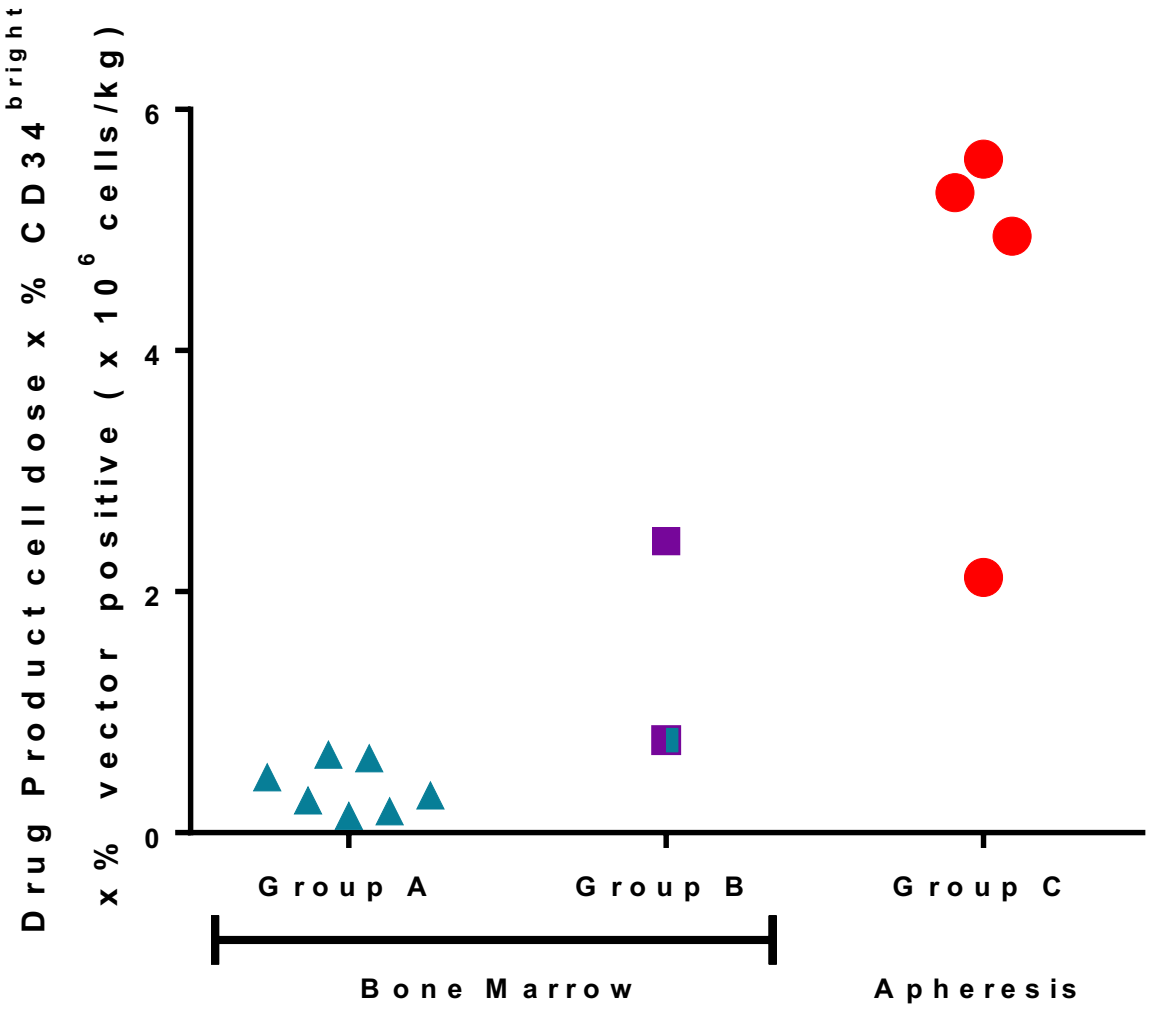
- Median 91.0, min-max 80.5-98.4

TDT APH

- Median 97.9, min-max 86.4-99.6

*squares indicate cells transduced for research only

Mobilization and Apheresis Combined with Improved DP Transduction Raises Dose of Cells that Drive Long-Term Hemoglobin Production



Key Questions

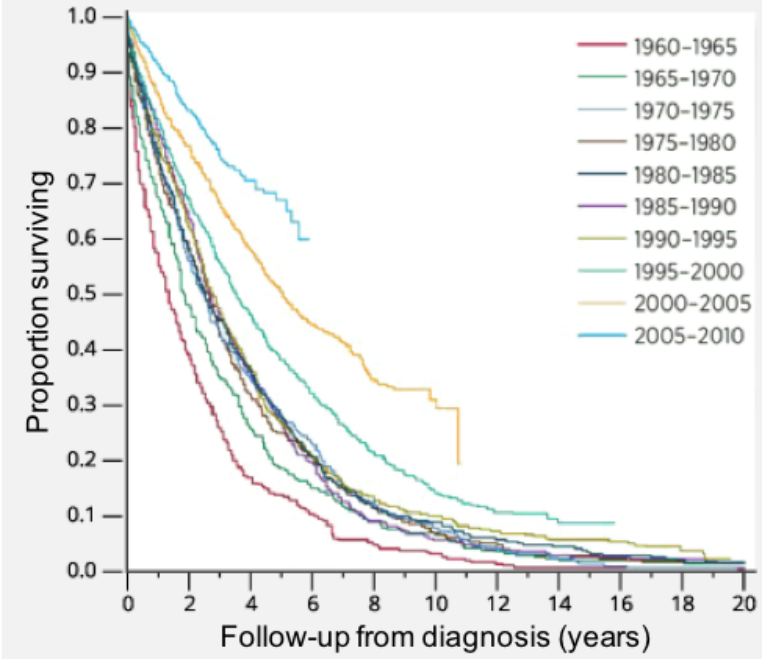
- Have the changes to the process and protocol improved *in vivo* VCN and HbA^{T87Q} production? ✓
- Can we improve patient experience by eliminating the need for bone marrow harvest? ✓
- Can mobilization with plerixafor allow us to yield more and better cells versus bone marrow? ✓
- What impact will the implementation of plerixafor have on clinical outcomes? **2018**

Multiple Myeloma

Jesus Berdeja, M.D., Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN

Despite Progress in Multiple Myeloma, There Remains a Need for New Therapies

Improvement in overall survival from median of 3 to 8-10 years



CCR Focus AACR

Kenneth C. Anderson Clin Cancer Res 2016;22:5419-5427

Clinical efficacy of daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma

Saad Z. Usmani,[1] Brendan M. Weiss,[2] Torben Plesner,[3] Nizar J. Bahlis,[4] Andrew Belch,[5] Sagar Lonial,[6] Henk M. Lokhorst,[7] Peter M. Voorhees,[8] Paul G. Richardson,[9] Ajai Chari,[10] A. Kate Sasser,[11] Amy Axel,[11] Huaibao Feng,[12] Clarissa M. Uhlar,[11] Jianping Wang,[11] Imran Khan,[12] Tahamtan Ahmadi,[11] and Hareth Nahi[13]

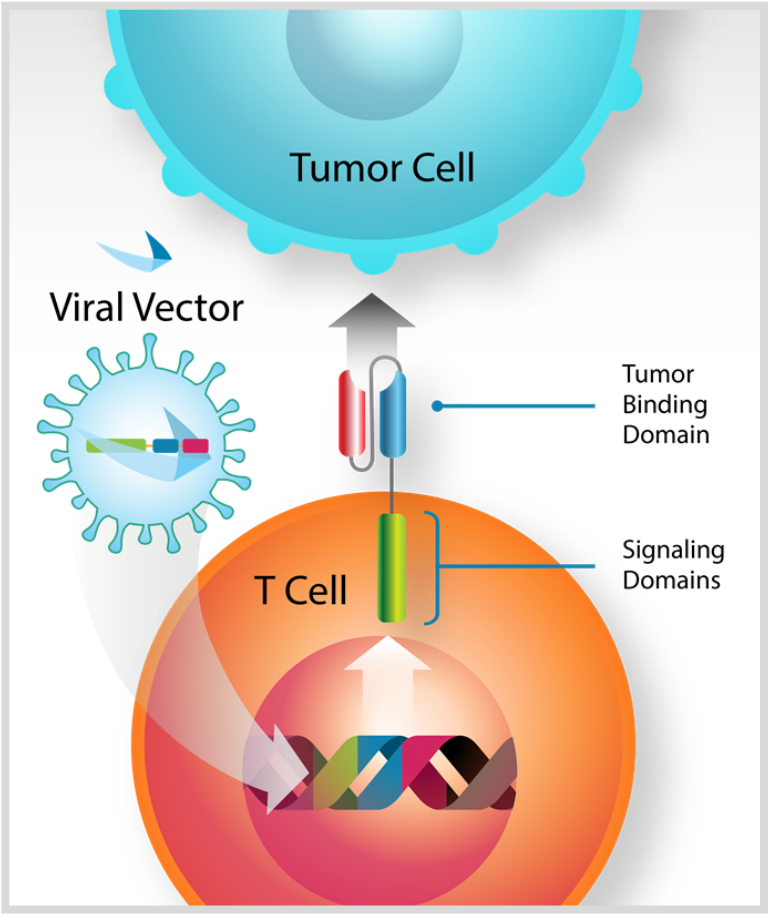
"Despite the availability of these classes of drugs for the treatment of MM, a recent analysis of patients with relapsed and refractory MM (RRMM) who were double refractory to a PI and an IMiD or ***had relapsed after ≥3 prior lines of therapy****, including the novel agents pomalidomide (third-generation IMiD) and carfilzomib (second-generation PI),* ***showed a median overall survival (OS) of 8 months.****"*

Usmani, Blood 2016

Current U.S. Standard of Care in 4th Line Multiple Myeloma

Current U.S. Standards of Care For Multiple Myeloma
4th Line of Therapy

	Pomalyst and dex. (Pomalyst Product Monograph)	Daratumamab (Lancet 2016, Lonial, S)
N	452	106
Inclusion Criteria	• ≥2 prior therapies (including REVLIMID and bortezomib) • Relapsed and refractory multiple myeloma • Disease progression on or within 60 days of last therapy	• Previously treated with at least three lines of therapy (including proteasome inhibitors and immunomodulatory drugs), or were refractory to both proteasome inhibitors and immunomodulatory drugs
Prior Tx	5 (2-14)	5 (2-14)
CR Rate (%)	<1%	~3%
ORR (%)	23.5%	29%
PFS (mos)	3.6 months	3.7 months

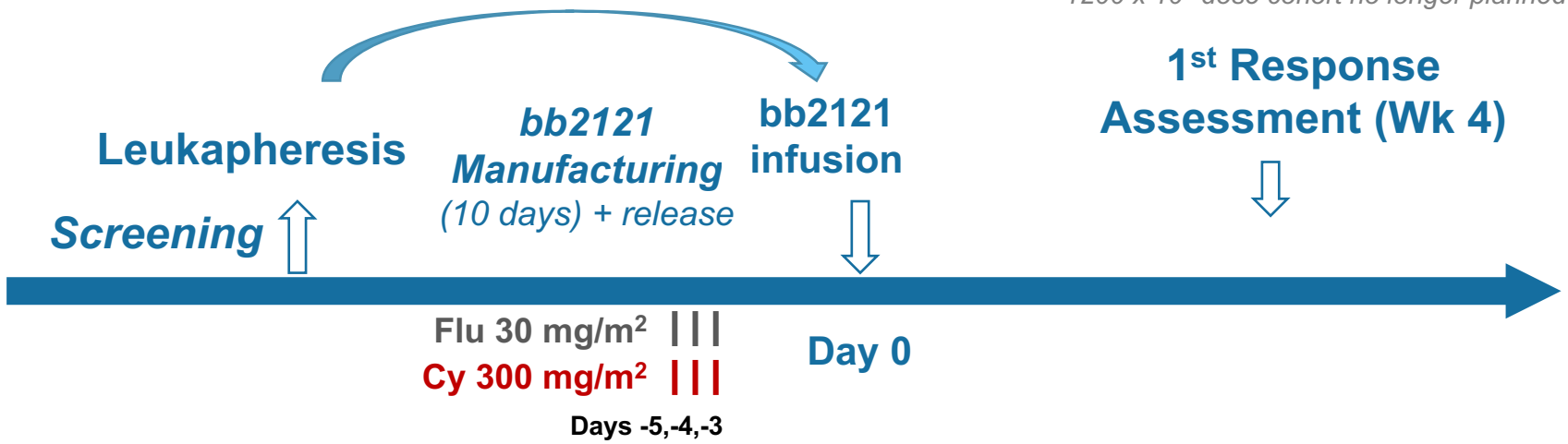


CRB-401 Study Design and Status

3 + 3 Dose Escalation of CAR + T Cells

50×10^6 → 150×10^6 → 450×10^6 → 800×10^6 → $1200 \times 10^{6*}$

*1200×10^6 dose cohort no longer planned



Study Status (Escalation Phase)

Cells Collected N=24

Clinical deterioration prior to infusion n=3

Dosed N=21

Evaluable for Response N=21

Manufacturing success rate of 100%

Expansion Cohort Initiated in August 2017

12 additional patients have been collected and dosed in the Expansion Cohort as of 02 Nov 2017

Baseline Demographics, Clinical Characteristics and Treatment History from Dose Escalation

21 patients have received bb2121 as of the data cut-off of October 2, 2017
Median follow-up is 35 weeks (min, max: 6.6, 69)

Demographics and Clinical Characteristics		
Parameter	**Statistic**	**Dosed Patients (N = 21)**
Age (years)	Median (min, max)	58 (37, 74)
Male	n (%)	13 (62)
Time since diagnosis (years)	Median (min, max)	4 (1.3, 15.8)
ECOG PS[1]		
0	n (%)	10 (48)
1		11 (52)
ISS[2] stage		
I	n (%)	6 (29)
II		11 (52)
III		4 (19)
High-risk cytogenetics		
del17p, t(4;14), t(14;16)	n (%)	9 (43)

[1]ECOG, Eastern Cooperative Oncology Groups Performance Status
[2]ISS, International Staging System
[3]SCT, Stem Cell Transplant

MM Treatment History		
Parameter	**Statistic**	**Dosed Patients (N = 21)**
Prior lines of therapy	Median (range)	7 (3, 14)
Prior autologous SCT[3]	n (%)	21 (100)
Prior Therapies	**Exposed, n (%)**	**Refractory, n (%)**
Bortezomib	21 (100)	14 (67)
Carfilzomib	19 (91)	12 (57)
Lenalidomide	21 (100)	18 (86)
Pomalidomide	19 (91)	15 (71)
Daratumumab	15 (71)	10 (48)
Cumulative Exposure	**Exposed, n (%)**	**Refractory, n(%)**
Bort / Len	21 (100)	14 (67)
Bort / Len / Car	19 (91)	10 (48)
Bort / Len / Pom	19 (91)	12 (57)
Bort / Len / Car / Pom	18 (86)	9 (43)
Bort / Len / Car / Pom / Dara	15 (71)	6 (29)

Dose Escalation Select Treatment Emergent Adverse Events; Generally Well Tolerated

Dose Escalation Patients (N = 21)[1]		
Preferred Term	**Overall n (%)**	**Grade 3 or higher n (%)**
Cytokine release syndrome	15 (71)	2 (10)
Neurotoxicity[2]	5 (24)	0
Neutropenia	18 (86)	18 (86)
Thrombocytopenia	11 (52)	9 (43)
Anemia	14 (67)	12 (57)

[1]Data cut-off of October 2, 2017
[2]Neurotoxicity includes the preferred terms: depressed level of consciousness, confusional state, bradyphrenia, somnolence

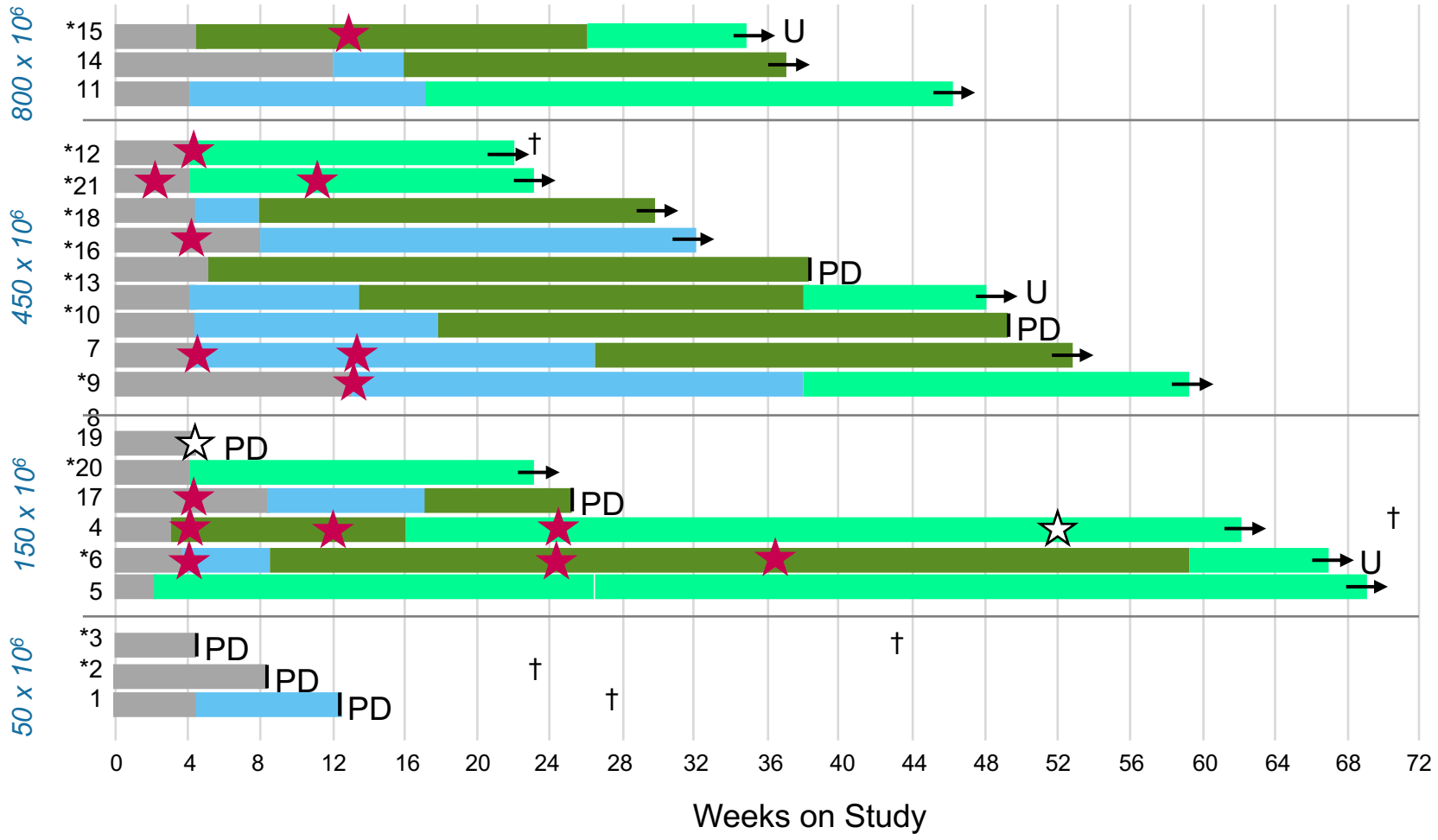
- No dose-limiting toxicities (DLTs) observed in dose escalation
- Cytopenias mostly related to Cy/Flu lymphodepletion
- Mortality: 3 deaths due to disease progression at 50 × 10^6 dose; 2 in patients treated at active doses in CR at the time of death (cardiac arrest, MDS)
- 14 patients experienced 1 or more SAEs: CRS* Grade 1-2 that required hospitalization per protocol (N=4); Pyrexia (N=2)

Reversible Grade 4 neurotoxicity followed by rapid myeloma response in patient from expansion cohort

- 46 y/o female with 11 prior lines of therapy – 450 x 10^6 CAR+ cells
- High tumor burden M spike = 8.03 g/dL, BMPC 90%
- History of subarachnoid hemorrhage prior to enrollment
- Low BCMA expression: BCMA 1% of malignant cells (IHC)

*CRS uniformly graded according to Lee et al., Blood 2014;124:188-195

High Frequency of Deep and Durable Tumor Response in Active Dose Cohorts



- Median follow up of 40 weeks in active dose cohorts; PFS not yet reached
- 17/18 (94%) ORR at active doses
- 56% Complete Response Rate and 89% VGPR or better
- 9/10 evaluable patients MRD negative
- Durable ongoing responses over 1 year
- Responses continue to improve as late as month 15 (VGPR to CR)

CR/sCR
VGPR
PR
Stable Disease
PD
MRD-
† Deceased
U Unconfirmed response
MRD+

* High Tumor Burden (>50% Bone Marrow Involvement)

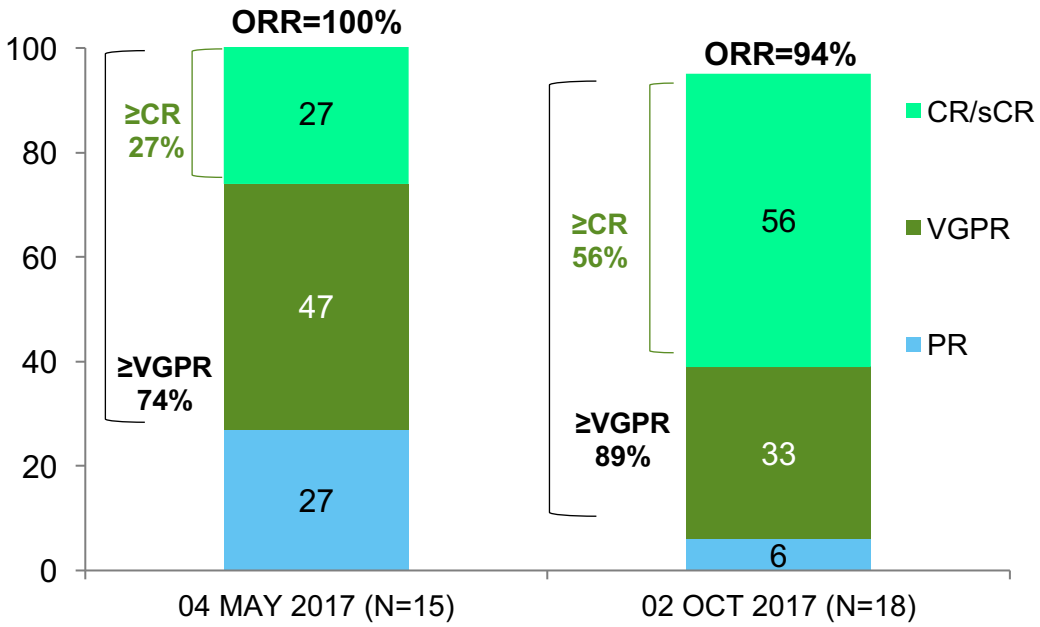
Patient 12 died of cardiopulmonary arrest
Patient 4 died of MDS following discontinuation

56% of Patients Achieved a Complete Response; 94% Overall Response Rate

Dose Escalation: Cohorts ≥150 × 10^6 CAR T Cells (N=18)
Median duration of follow up 40 weeks (min, max: 6.6, 69.1)

- Median Duration of Response not yet reached
- Median Progression Free Survival not yet reached
- 81% Progression Free Survival at 6 months
- 71% Progression Free Survival at 9 months

Objective Response Rate
Subjects Treated in Escalation – Cohorts ≥150 × 10^6



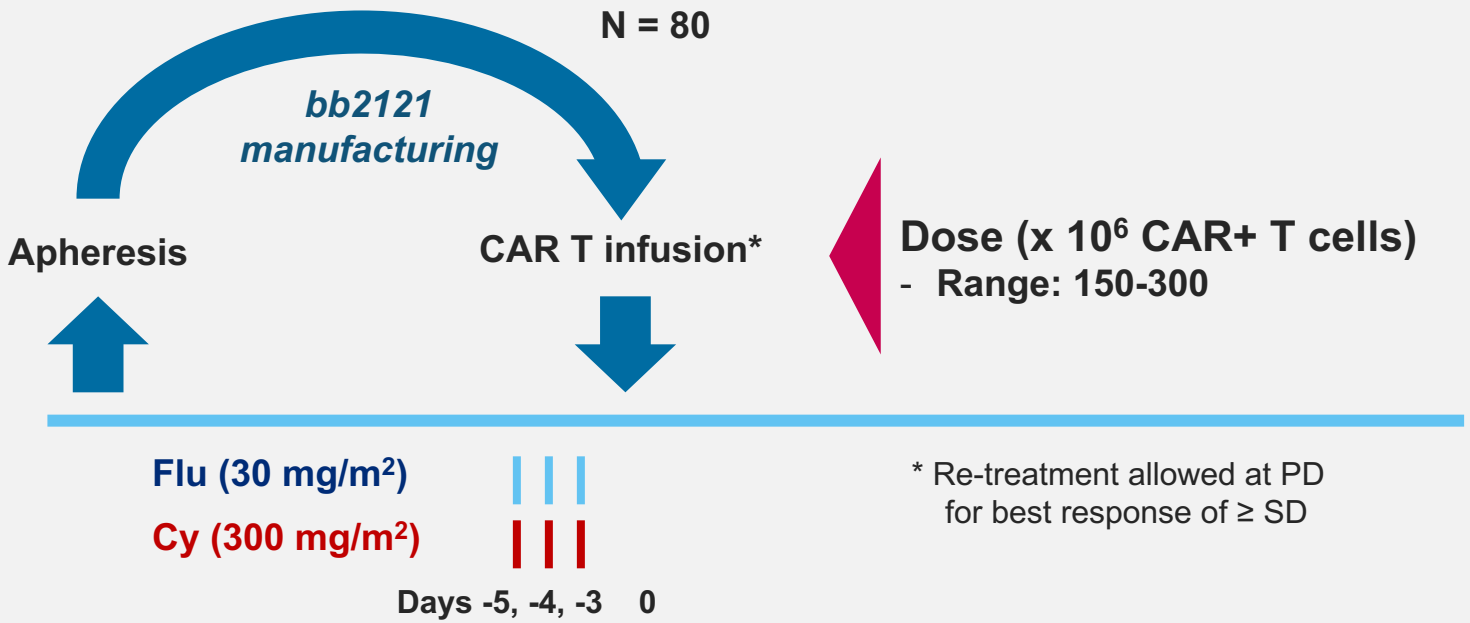
Note: Objective Response defined as attaining Stringent Complete Response, Complete Response, Very Good Partial Response, or Partial Response. Including unconfirmed responses.

BB2121-MM-001: bb2121 Pivotal Trial (KarMMa)

KarMMa

Relapsed and refractory MM

- ≥3 prior treatment regimens with ≥ 2 consecutive cycles each (unless PD was best response)
- Received prior IMiD®, PI and anti-CD38
- Refractory (per IMWG) to last treatment regimen



Endpoints

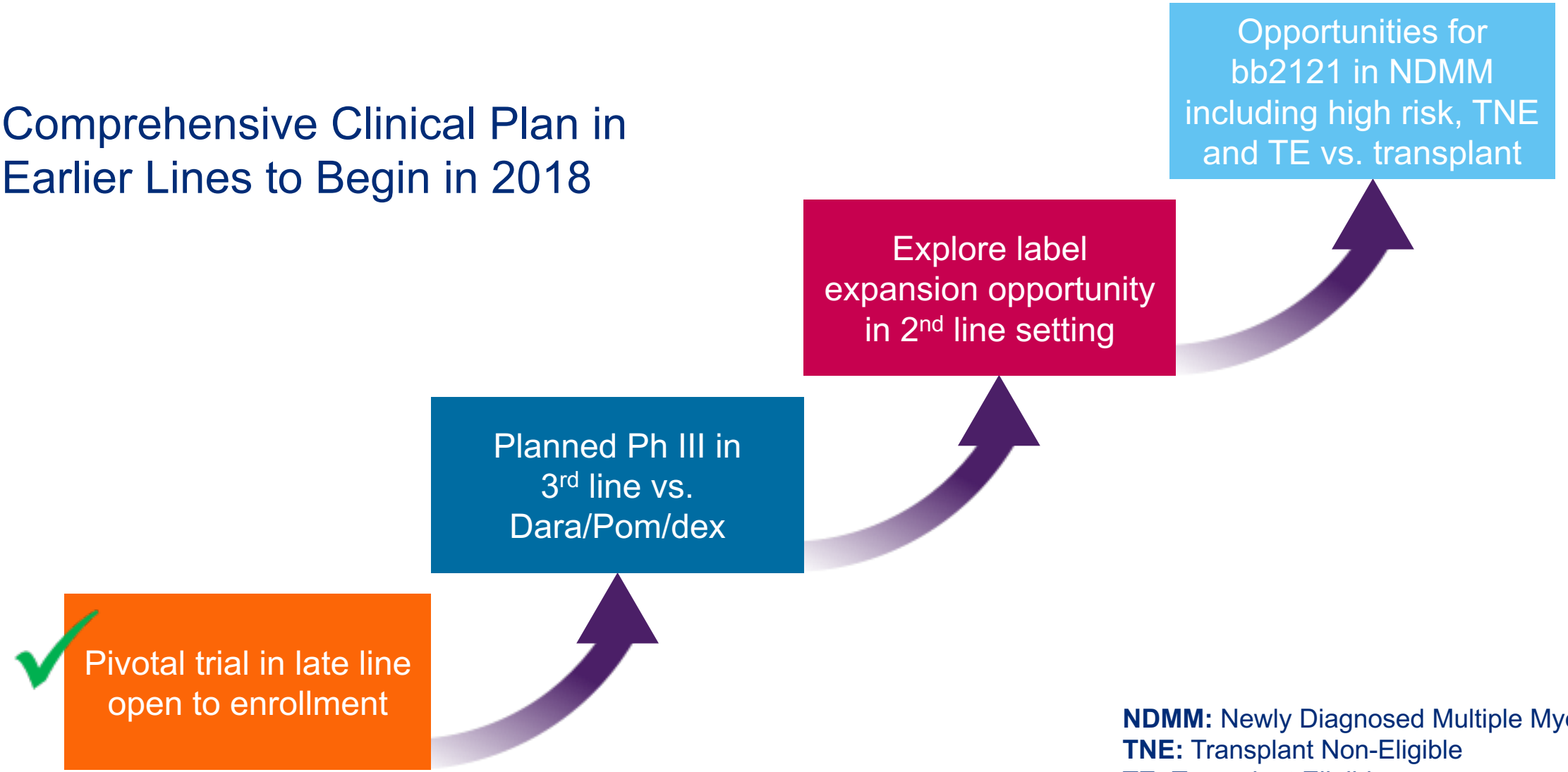
Primary: ORR

Key Secondary: CR, TTR, DOR, PFS, TTP, OS, Safety, bb2121 expansion and persistence, MRD (genomic and flow assays)

Exploratory: BCMA expression/loss, T cell immunophenotype, GEP in BM, HEOR

Advancing bb2121 into Earlier Lines of Multiple Myeloma

Comprehensive Clinical Plan in Earlier Lines to Begin in 2018



NDMM: Newly Diagnosed Multiple Myeloma
TNE: Transplant Non-Eligible
TE: Transplant Eligible

What's Next…

bb2121

- Pivotal KarMMA trial now enrolling in the US, EU and Canada with anticipated launch in 2020
  - Target enrollment: 80
  - Primary endpoint: ORR
  - Dose range of 150 to 300 x 10^6 CAR T cells
- Celgene planning additional clinical studies to explore bb2121 in earlier lines of therapy
- Expansion cohort enrolling rapidly

bb21217

- Second generation anti-BCMA CAR T therapy – study actively enrolling

Closing

Nick Leschly, chief bluebird

bluebirdbio

2017 – A Breakthrough Year for bluebird

Preparing and investing *in team and infrastructure to bring* ***multiple transformative gene therapies*** *to patients to address the* ***underlying genetic causes of life-threatening diseases***

Cerebral ALD

- 15 of 17 patients hit primary endpoint
- Continued strong clinical data support path to registration

Transfusion Dependent β-Thalassemia

- Progressing first filings for EU and US approvals
- Refined manufacturing process delivering near normal or normal levels of Hb production with 3-year data showing sustained benefit

Severe Sickle Cell Disease

- Protocol amendments delivering highest and most rapid anti-sickling Hb production to date
- Shifting to plerixafor mobilization; easier for patients and initial data showing collection of more and better cells

Multiple Myeloma

- Deep response; high ORR and CR rates in heavily pretreated relapsed and refractory patients
- Durability; median PFS not yet reached at 40 weeks
- Rapid and expanding clinical program with Celgene for this potentially groundbreaking therapy


Q & A
bluebirdbio