Making Hope A Reality – bluebird style

September 2018
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.
Making Hope A Reality
2022 Vision on Track

LentiGlobin TDT
Potential First Approval (2019)

LentiGlobin SCD
Data-Driven Acceleration

Lenti-D CALD
Potential First Approval (2020)

bb2121 Multiple Myeloma
Potential First Approval (2020)

∞
Patient Impact

2+
Products on the Market

2+
Programs Nearing Commercialization

4+
Additional Programs in the Clinic

THE GENE THERAPY PRODUCTS COMPANY
Leading the Way in Gene & Cell Therapy

**Our Integrated Platforms**
- Gene Therapy
- Cell Therapy
- Gene Editing

**Our Clinical Programs**
- Lenti-D™
- LentiGlobin®

**650+ Global bluebirds**
- Cambridge
- Seattle
- Durham
- Zug

**Regulatory Designations**
- RMAT
  - Regenerative Medicine Advanced Therapy
- ODD
  - Orphan Drug Designation
- BTD
  - Breakthrough Therapy Designation
- PRIME
  - PRotential MEdicines

**Strategic Partnerships**
- 3
  - Potential regulatory approvals by end of 2020

**Manufacturing**
- CRB-401
- KarMMA™
- HGB-205
- HGB-206
- BCL11a**

**Toolbox**
- Lentiviral Gene Delivery
  - Reproducible
  - Scalable
- Genome Editing Platform
  - megaTALs
  - homing endonucleases
Healthy Ecosystem for Transformative Gene Therapy

- Regulatory Atmosphere
- Pricing / Reimbursement & Access
- Industry Validation

- Approvals
  - TDT
  - SCDC
  - BCMA

- Spark Creative Payer Agreements
- Payer Engagement

- PATH TO PATIENTS

- RMAT
- PRIME
- ODD
- Adaptive Pathways

- Breakthrough Designation
- Alex Azar (HHS)
- Scott Gottlieb, M.D. (FDA)

- Novartis KYMRIAHTM
- Gilead/Kite YescartaTM
- bluebird bio

- J&J
- Novartis
- Celgene
- GSK
- Pfizer

- Healthy Ecosystem for Transformative Gene Therapy
- Regulatory Atmosphere
- Approvals
- PATH TO PATIENTS
- Pricing / Reimbursement & Access
- Industry Validation

- CMS Value-Based Payment Talk
- Novartis CMS Agreement
- Alnylam Access Principles
- Gilead
- Juna/Celgene
- Spark LuxturnaTM
- Celgene
Our Focus. Our Imperatives.

1. **Execute & Deliver**: Operate with discipline, urgency and healthy paranoia.
2. **Scale & Reach**: Expand organization and capabilities to bring products to patients globally.
3. **Lead The Way**: Lever product engine, capabilities and resources to solve challenges and unleash opportunities.
4. **Stay BLUE**: Beat the regression odds. Believe in the WHY and act accordingly.
Hopes & Dreams Becoming a Reality

1993
- Genetix Founded

2009/2010
- Science: CALD
- Nature: TDT
- Restart VC Investment
- Changed Name to bluebird bio

2013/2014
- Celgene CAR T partnership
- IPO
- Acquired Genome Editing Company

2015/2016
- TDT: Breakthrough & PRIME Designation
- SCD: RMAT Designation
- NEJM: CALD & SCD
- Acquired Manufacturing Facility

2017
- BCMA: Breakthrough & PRIME Designation

CALD Starbeam (Oct. 2013)
TDT Northstar (March 2014)
SCD HGB-205 (Oct. 2014)
bb2121 for multiple myeloma (Feb. 2016)
Driving the Product Platform to Reality for Patients

- Make & Scale It
- Relentlessly Learn & Innovate
- Deliver It
- Relentlessly Learn & Innovate
- Value It
- Relentlessly Learn & Innovate
- Lever It
- Relentlessly Learn & Innovate
Make & Scale It: Focused on Transitioning from Development to Commercial

**DEVELOPMENT**
- Virus Manufacturing
- Drug Product

**COMMERCIAL**
- Cambridge | Seattle | NC | EU

**SCALE & DEPLOY**
Deliver It: The Best Possible Provider, Payer and Patient Experience

Enabling Patients to Get To Treatment
- Educating Patients and Families on Gene Therapy
- Multi Channel Stakeholder Engagement & Data Dissemination
- Referral Network Development

Supporting Patients Through Treatment
- Providing Patient Support Through Treatment Process
- Cell Traceability & Scheduling
- Drug Product Manufacturing with End to End Supply Chain
- Reimbursement Authorization

Enabling Patients to Complete Treatment
- Allow Patients to Participate in their Ongoing Care and Follow-Up
- Operationalize & Track
- Easy-to-Access Registry

KEY OUTCOME: Treatment Prescribed

KEY OUTCOME: Treatment Delivered & Patient Discharged

Patient Case Management, Navigation, & Services
The value our products bring to patients should stand on its own for all stakeholders.
Value It: Quick Answer is Value Based Payment Over Time

BLUE “VALUE” PRINCIPLES
- Be focused on patient access to innovation
- Be creative and disruptive (if needed)
- Be flexible and share risk
- Be transparent and proactive with stakeholders
- Be proud
- Don’t do stupid short sighted stuff!

CONSTRAINTS & AMBITIONS

UNMET NEED
- Heighten awareness of true unmet need in terms of impact on life expectancy and cost

VALUE EVIDENCE
- Deliver credible and rigorous value platform arguments/data for value

PAYMENT MODELS
- “Free Up” system to recognize value over time
- “Buy time” to prove enduring value
- Fix cost density constraint
- Fix policy constraints (e.g., best price)
- Fix “portability of cure” concern
Lever It: Experience, Capabilities and Partnerships Driving Pipeline Expansion

**Innovation & Capabilities**
- Viral Vector Manufacturing
- Transduction Enhancements
- Plerixafor Mobilization
- PI3ki-based BCMA manufacturing

**New Products & Pipeline**
- bb21217 *Phase 1*
- shmiR *Phase 1*
- CAR Ts and TCRs *Preclinical*
- Gamma Delta T cells *Preclinical*
- MegaTALs *Preclinical*

**Partnerships & Acquisitions**
- TG BIOPHARM
- medigene
- Boston Children’s Hospital
- Celgene
- PREGENEN
Build the CORE… and Build Both RIGHT & LEFT

**Pipeline Build**
- In-house capabilities and expertise
  - Business Development
  - Academic Partnerships

**Infrastructure Build**
- bluebird RTP: LVV manufacturing
  - CMO partnerships
  - Company growth: 650+ birds and funded for success

**Commercial and Launch Build**
- EU presence – Medical, Market Access, Commercial
  - COE network
  - Payer engagement
### Our Quest to Constantly Innovate Continues

<table>
<thead>
<tr>
<th>Product Candidates</th>
<th>Program Area</th>
<th>Preclinical</th>
<th>Phase 1/2</th>
<th>Phase 2/3</th>
<th>Rights/Partner</th>
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</thead>
<tbody>
<tr>
<td>Lenti-D™ Drug Product</td>
<td>Severe Genetic Diseases</td>
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<td>Worldwide</td>
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<tr>
<td></td>
<td>Cerebral ALD</td>
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<tr>
<td>LentiGlobin® Drug Product</td>
<td>Transfusion-Dependent ß-Thalassemia</td>
<td>(Phase 3)</td>
<td></td>
<td></td>
<td>Worldwide</td>
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<tr>
<td></td>
<td>Severe Sickle Cell Disease</td>
<td></td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td>BCL11a shRNA(miR)*</td>
<td>Severe Sickle Cell Disease</td>
<td></td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
<tr>
<td>bb2121</td>
<td>Cancer</td>
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<td></td>
<td>Celgene</td>
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<td></td>
<td>Multiple Myeloma</td>
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<tr>
<td>bb21217</td>
<td>Multiple Myeloma</td>
<td></td>
<td></td>
<td></td>
<td>Celgene</td>
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<tr>
<td>Undisclosed Targets</td>
<td>Various Indications</td>
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<td></td>
<td></td>
<td>Worldwide</td>
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<tr>
<td>Early Research</td>
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<td></td>
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<tr>
<td>Early Pipeline</td>
<td>Undisclosed + Gene Editing</td>
<td></td>
<td></td>
<td></td>
<td>Worldwide</td>
</tr>
</tbody>
</table>

*Development is led by Boston Children’s Hospital
1st Half 2018 Flashback - Path to Patients Full Steam Ahead

**TDT**
- @EHA: 7/8 patients in 207 reaching normal/near normal total hemoglobin by 6 months
- MAA filing on track for 2018 – with Accelerated Assessment

**SCD**
- @EHA: Group C patients showing rapid and consistent anti-sickling HbA^{T87Q} expression
- Anticipated update on development plan by EOY

**CALD**
- @SSIEM: 15/17 patients with 24 months follow up alive and free from MFDs; additional 12 patients treated with no MFDs to date*
- Breakthrough Designation and PRIME

**Multiple Myeloma**
- @ASCO: 95% ORR at doses above 150; 50% CR Rate; Media PFS of 11.8 months
- KarMMa dose range increased (Celgene)

*These patients have not yet reached 24 months of follow up
2018 Milestones

**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
- • Registration Strategy Update
- • HGB-206 Updated Data

**MM**
- ✓ CRB-401 bb2121 ASCO Data
- • Initiate 3^rd Line Study*
- • CRB-402 bb21217 Early Data

**CALD**
- ✓ Starbeam (ALD-102) Updated Data

*Conducted by Celgene*
Transfusion Dependent β-Thalassemia
Transfusion-Dependent β-Thalassemia (TDT)

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

UNMET NEED

- Treatment of underlying disease limited to allo-HSCT, primarily only for pediatric patients with sibling donor matches
- Sometimes severe treatment-related risks and complications
- Requires comprehensive care throughout life

EPIDEMIOLOGY

- Global prevalence ~ 288,000
- Global incidence ~ 60,000

“When I get blood, it is no less than a 14-hour day with transportation included. Getting blood is a lonely job for us thalassemia patients. Transfusion schedules are rigorous and a time consumer. I lose one day every two weeks.” – Laurice
Transfusion-Dependent β-Thalassemia

HGB-204
- Basis of EU filing
- Original manufacturing process
- All genotypes

HGB-205
- Basis of EU filing (with Northstar)
- Original manufacturing process

HGB-207
- Basis of EU and U.S. filings
- Refined manufacturing process
- Non-β^0/β^0 genotypes

HGB-212
- β^0/β^0 genotypes
- Refined manufacturing process
- First patient treated in November 2017
- First pediatric patient treated April 2018
<table>
<thead>
<tr>
<th>EU</th>
<th>Pursue <strong>CONDITIONAL APPROVAL</strong> in patients with non-β^0^/β^0^ genotypes on the basis of data from ongoing Northstar (HGB-204) &amp; HGB-205 studies, as well as available data from Northstar-2 (HGB-207) study</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>Pursue <strong>approval</strong> in adults and adolescents with non-β^0^/β^0^ genotypes based on data from ongoing pivotal Northstar-2 (HGB-207) trial</td>
</tr>
<tr>
<td></td>
<td><strong>Pediatric population</strong> to be included as a cohort of HGB-207, rather than separate study</td>
</tr>
<tr>
<td></td>
<td>Submission for approval in β^0^/β^0^ patients to be based on ongoing Northstar-3 (HGB-212) study</td>
</tr>
</tbody>
</table>

**TDT Registration Strategy**

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

**ADAPTIVE PATHWAYS**

**PRIME**

**BREAKTHROUGH THERAPY DESIGNATION**

**ORPHAN DRUG DESIGNATION**
HGB-207: 7/8 Patients with ≥ 6 Months Follow-up are Transfusion Free

First treated patient achieved transfusion independence and has begun phlebotomy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Phlebotomy Initiated</th>
<th>Hb (g/dL)</th>
<th>Peripheral VCN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>15.1</td>
<td>13.1</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>11.8</td>
<td>11.1</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>8.4</td>
<td>13.3</td>
</tr>
<tr>
<td>5*</td>
<td></td>
<td>8.4</td>
<td>12.2</td>
</tr>
<tr>
<td>6*</td>
<td></td>
<td>7.5</td>
<td>11.6</td>
</tr>
<tr>
<td>7*</td>
<td></td>
<td>5.1</td>
<td>11.9</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>4.7</td>
<td>11.2</td>
</tr>
</tbody>
</table>

- Time from treatment to last transfusion
- Time from last transfusion to last follow-up

- Patient 2 was free from chronic transfusions for 11 months, however received a transfusion following DP infusion due to low Hb; patient had a peripheral VCN of 0.2

*Indicates male patients; Transfusion independence is defined as the weighted average Hb ≥9 g/dL without any RBC transfusions for ≥12 months; Hb, hemoglobin; VCN, vector copy number

Data as of 15 May 2018
HGB-207: 7/8 Patients are Producing ≥ 7.6 g/dL of HbA^{T87Q} by 6 Months

* Indicates male patients; † Patient is homozygous for severe IVS-1-5 β-globin mutation

Data as of 15 May 2018
HGB-207: 7/8 Patients are Producing ≥ 7.6 g/dL of HbA^{T87Q} by 6 Months

†Patient is homozygous for severe IVS-1-5 β-globin mutation  
Data as of 15 May 2018
Peripheral Blood VCN and HbAT87Q Production Over Time

For 204 non-β0/β0 patients, medians (Q1, Q3) depicted

Data as of 15 May 2018 (HGB-207) and 7 Mar 2018 (HGB-204)
HGB-204: 8/10 Patients with Non-β⁰/β⁰ Genotypes Achieve and Maintain Transfusion Independence

Median duration of transfusion independence to date of 33 months in 8/10 patients with non-β⁰/β⁰ genotypes

- **Non-β⁰/β⁰ genotypes (8/10)**
  - 1102: 38.8 g/dL, 9.8
  - 1104: 40.3 g/dL, 9.4
  - 1108: 35.5 g/dL, 12.0
  - 1109†: 35.3 g/dL, 12.5
  - 1111†: 34.7 g/dL, 13.5
  - 1119: 19.4 g/dL, 10.0
  - 1120: 20.3 g/dL, 9.1
  - 1117: 18.4 g/dL, 10.7

- **β⁰/β⁰ genotypes (3/8)**
  - 1116: 21.7 g/dL, 9.3
  - 1103: 16.4 g/dL, 10.3
  - 1123*: 22.1 g/dL, 9.8

**Transfusion Independence**
- Non-β⁰/β⁰ genotypes (8/10): 80% achieved TI for 16+ to 38+ months
- β⁰/β⁰ genotypes (2/8): 25% achieved TI for 14+ and 16+ months

**Reduction in Transfusion Volume**
- Non-β⁰/β⁰ genotypes (2/10): 27% and 82%
- β⁰/β⁰ genotypes (5/8): Median 53% (min – max: 8% – 74%)

*Indicates male patients; Transfusion independence is defined as the weighted average Hb ≥9 g/dL without any RBC transfusions for ≥12 months

Data as of 7 March 2018
LentiGlobin Safety Profile is Generally Consistent with Myeloablative Conditioning

<table>
<thead>
<tr>
<th>HGB-204</th>
<th>HGB-207</th>
</tr>
</thead>
<tbody>
<tr>
<td>• No grade ≥ 3 DP-related AEs</td>
<td>• One grade 1 abdominal pain event was considered possibly related to LentiGlobin</td>
</tr>
<tr>
<td>• One SAE of asymptomatic wild-type HIV infection was reported 23 months after DP infusion and was considered not related to LentiGlobin</td>
<td>• Two SAEs of VOD extended hospitalization following DP infusion</td>
</tr>
<tr>
<td>• Two SAEs of VOD</td>
<td>• Events occurred on Day +23 and Day +34</td>
</tr>
<tr>
<td></td>
<td>• Both patients were treated with defibrotide</td>
</tr>
<tr>
<td></td>
<td>• Both events have resolved</td>
</tr>
</tbody>
</table>

No graft failure  No deaths  No vector-mediated replication competent lentivirus  No early evidence of clonal dominance

AE, adverse event; DP, drug product; HIV, human immunodeficiency virus; SAE, serious adverse event, VOD, veno-occlusive liver disease

Data as of 15 May 2018
Severe Sickle Cell Disease
Sickle Cell Disease (SCD)

- Severe blood disorder that causes anemia, frequent pain crises, and shortened lifespan

UNMET NEED

- High morbidity; early mortality; with median age of death in the 5th decade
- Treatment of underlying disease limited to allo-HSCT, primarily recommended only for pediatric patients with matched sibling donors
- 15-20% of patients with SCD may have HLA-identical sibling donor
- Substantial treatment-related risks and complications

EPIDEMIOLOGY

- U.S. prevalence ~ 100,000; EU prevalence ~ 113,000
- Global annual birth incidence ~ 300,000 – 400,000

“I experienced my first sickle crisis requiring hospitalization at age 5. Since then I’ve endured hundreds of hospitalizations, blood transfusions and surgical procedures. Despite the devastating symptoms of sickle cell, I was determined to complete my educational goals.”- Lakiea

Source: Global Genes
HGB-206: Evolution of LentiGlobin in SCD

**Bone Marrow**

**Group A**
- Original Protocol and Manufacturing Process
- Transfusions (Pre-Treatment): No
- Conditioning: Medium
- Total Cell Dose: Low
- Transduction (VCN & % Transduced): Low
- CD34 Phenotype (% CD34 Bright): Medium

**Group B**
- Modified Protocol and Mixed Manufacturing Process
- Transfusions (Pre-Treatment): Yes
- Conditioning: High
- Total Cell Dose: Medium
- Transduction (VCN & % Transduced): High
- CD34 Phenotype (% CD34 Bright): Medium

**Group C**
- Modified Protocol and Refined Manufacturing Process
- Planned Cell Source Shift
- Transfusions (Pre-Treatment): Yes
- Conditioning: High
- Total Cell Dose: High
- Transduction (VCN & % Transduced): High
- CD34 Phenotype (% CD34 Bright): High

**Cell Source:**
- Bone Marrow (Group A and B)
- Apheresis (Group C)
HGB-206: Study Disposition

Consented
N=29

Ineligible N=4

Pre-treatment Transfusions

Group A
N=9

Bone Marrow Harvest
N=9

Original Manufacturing Process N=7

Discontinued
N=2

LentiGlobin DP Infused
N=7

Long Term Follow-up after 2 years
N=7

Group B
N=2

Bone Marrow Harvest†
N=2

Original → Refined Manufacturing Process N=2

LentiGlobin DP Infused
N=2

Group C
N=14

Plerixafor Mobilization & Apheresis
N=11

Refined Manufacturing Process N=9

LentiGlobin DP Infused
N=6

Cell collection Pending
N=3

Transplant Pending
N=3

DP Manufacture Pending
N=2

Data as of May 15, 2018

* 1 due to insufficient cell collection, 1 withdrew consent; †One patient also received a single mobilization cycle to collect cells for back-up
## HGB-206: Patient Characteristics

### N=22 Patients Who Started Cell Collection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group A N=9</th>
<th>Group B N=2</th>
<th>Group C N=11</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at consent</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (min – max), years</td>
<td>26</td>
<td>24.5</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>(18 – 43)</td>
<td>(22 – 27)</td>
<td>(18 – 35)</td>
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<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 Female</td>
<td>0 Female</td>
<td>5 Female</td>
</tr>
<tr>
<td><strong>Genotype</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>$\beta^S/\beta^S$</td>
<td>9</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td><strong>Prior SCD History</strong></td>
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<tr>
<td>No. of patients</td>
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<tr>
<td>No. of events, median (min – max)</td>
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<tr>
<td><strong>Hydroxyurea use</strong></td>
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<tr>
<td></td>
<td>7</td>
<td>2</td>
<td>6</td>
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<tr>
<td><strong>Recurrent VOCs(^*),†</strong></td>
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<td></td>
<td>4.5 (2.0 – 27.5)</td>
<td>10.0 (2.5 – 17.5)</td>
<td>7.5 (4.0 – 14.0)</td>
</tr>
<tr>
<td><strong>Acute chest syndrome(^*),†</strong></td>
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<tr>
<td></td>
<td>1</td>
<td>1</td>
<td>2</td>
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<tr>
<td><strong>Any history of stroke</strong></td>
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<tr>
<td></td>
<td>2</td>
<td>0</td>
<td>3</td>
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<tr>
<td><strong>Regular pRBC transfusions before study entry</strong></td>
<td></td>
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<tr>
<td></td>
<td>1</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td><strong>TRJV &gt;2.5 m/s(^*)</strong></td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^*\)Within 2 years prior to informed consent, or initiation of regular transfusions in case of VOCs; \(^†\)Median Annualized values in patients with ≥2 events/year (for VOCs), or ≥1 events/year with at least one episode in the year before informed consent or initiation of regular transfusions (for ACS)

ACS, acute chest syndrome; VOC, vaso-occlusive crisis, TRJV, Tricuspid regurgitant jet velocity

Data as of May 15, 2018
Refinements to Manufacturing and Cell Harvest Lead to Improved Drug Product Characteristics

Data as of May 15, 2018

† Number of DP exceeds number of patients since some patients were harvested or mobilized more than once; *% Transduced cells not available for 1 DP at time of analyses; Grey line indicates median

Vector copy number

% Transduced cells

CD34+ cell dose

LentiGlobin manufacturing process (HSC source)

Original (BM)
Refined (BM)
Refined (PB)

BM, bone marrow; HSC, hematopoietic stem cell; Med, median; PB, peripheral blood.

Median

0.6
3.1
4.0

25
87
81

2.1
2.7
7.1

N=7
12 DP†
N=2
4 DP†
N=6
7 DP†
Peripheral Blood VCN is Higher in Patients in Group B and C

For Group A patients, medians (min, max) depicted; Group A patients with month 30 study visit (N=3)

Data as of May 15, 2018 for HGB-206 and Sep 20, 2017 for pt 1204
Patients in Group B and C Demonstrate Higher HbA$^{T87Q}$ Production

- **Group A**: Hb: 14.2 g/dL, HbA$^{T87Q}$: 8.8 g/dL (62%)
- **Group B**: Hb: 12.8 g/dL, HbA$^{T87Q}$: 7.2 g/dL (56%)

Data as of May 15, 2018 for HGB-206 and Sep 20, 2017 for pt 1204

For Group A patients, medians (min, max) depicted; Group A patients with month 30 study visit (N=2)
All Group C Patients Above 30% Anti-Sickling Hemoglobin by 3 Months

At 3 months study visit

- Total Hb (g/dL)
  - Group A: 9.2
  - Group B: 11.1
  - Group C: 10.8

Globin Fractions [g/dL]

- Group A: 57% (HbA transfused), 5% (HbS), 35% (HbA2), 31% (HbA\textsuperscript{T87Q})
- Group B: 35% (HbA transfused), 26% (HbS), 39% (HbA2), 3% (HbA\textsuperscript{T87Q})
- Group C: 31% (HbA transfused), 39% (HbS), 5% (HbA2), 26% (HbA\textsuperscript{T87Q})

At 6 months study visit

- Total Hb (g/dL)
  - Group A: 8.9
  - Group B: 11.5
  - Group C: 14.2

Globin Fractions [g/dL]

- Group A: 74% (HbA transfused), 5% (HbS), 26% (HbA2), 5% (HbA\textsuperscript{T87Q})
- Group B: 53% (HbA transfused), 38% (HbS), 39% (HbA2), 5% (HbA\textsuperscript{T87Q})
- Group C: 62% (HbA transfused), 36% (HbS), 31% (HbA2), 5% (HbA\textsuperscript{T87Q})

- 5 incremental patients since data presented at ASH; no clinically significant new safety events

Median for DP-infused patients depicted, except for Group C at 6 months given N=1

Data as of May 15, 2018 for HGB-206 and Sep 20, 2017 for pt 1204
Multiple Myeloma
Multiple Myeloma (BCMA)

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

UNMET NEED

• Despite the availability of new therapies, remains incurable

EPIDEMIOLOGY

• U.S. incidence: ~30,000
• ~12,000 deaths/year in the U.S.

“When I was diagnosed and realized that there was an empty pipeline... I knew I needed to do something — not only for myself and my family, but for everyone else with this ‘orphan cancer’. I desperately wanted my daughter to remember me and thought that if I lived for five years, maybe she would have memories of her mom.”

- Kathy Giusti, Founder, MMRF
CRB-401 Data at ASCO 2018 - Baseline Demographics and Clinical Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Escalation (N=21)</th>
<th>Expansion (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (min, max) follow-up, d</td>
<td>345 (46, 638)</td>
<td>87 (29, 184)</td>
</tr>
<tr>
<td>Median (min, max) age, y</td>
<td>58 (37, 74)</td>
<td>65 (44, 75)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>13 (62)</td>
<td>16 (73)</td>
</tr>
<tr>
<td>Median (min, max) time since diagnosis, y</td>
<td>4 (1, 16)</td>
<td>6 (1, 36)</td>
</tr>
<tr>
<td>ECOG PS,(^1) n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10 (48)</td>
<td>6 (27)</td>
</tr>
<tr>
<td>1</td>
<td>11 (52)</td>
<td>16 (72)</td>
</tr>
<tr>
<td>High-risk cytogenetics, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>del(17p), t(4;14), t(14;16)</td>
<td>8 (38)</td>
<td>9 (41)</td>
</tr>
</tbody>
</table>

ECOG, Eastern Cooperative Oncology Groups performance status; ISS, international staging system; NA, not available. \(^1\)Data at screening presented. Data cutoff: March 29, 2019
### CRB-401 Data at ASCO 2018 - Heavily Pretreated Patient Population

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Escalation (N=21)</th>
<th>Expansion (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (min, max) prior regimens</td>
<td>7 (3, 14)</td>
<td>8 (3, 23)</td>
</tr>
<tr>
<td>Prior autologous SCT, n (%)</td>
<td>21 (100)</td>
<td>19 (86)</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>3 (14)</td>
</tr>
<tr>
<td>1</td>
<td>15 (71)</td>
<td>14 (64)</td>
</tr>
<tr>
<td>&gt;1</td>
<td>6 (29)</td>
<td>5 (23)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Escalation (N=21)</th>
<th>Expansion (N=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior therapies, n (%)</td>
<td>Exposed</td>
<td>Refractory</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>21 (100)</td>
<td>14 (67)</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>19 (91)</td>
<td>12 (57)</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>21 (100)</td>
<td>19 (91)</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>19 (91)</td>
<td>15 (71)</td>
</tr>
<tr>
<td>Daratumumab</td>
<td>15 (71)</td>
<td>10 (48)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cumulative exposure, n (%)</th>
<th>Exposed</th>
<th>Refractory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bort/Len</td>
<td>21 (100)</td>
<td>14 (67)</td>
</tr>
<tr>
<td>Bort/Len/Car/Pom/Dara</td>
<td>15 (71)</td>
<td>6 (29)</td>
</tr>
</tbody>
</table>

CRB-401 Data at ASCO 2018 - Tumor Response: Dose-related and Independent of Myeloma BCMA Expression Levels

**Tumor Response By Dose**

- **ORR=33.3%**
  - mDOR=1.9 mo
  - Median follow-up (min, max), d: 84 (59, 94)

- **ORR=57.1%**
  - mDOR=NE
  - Median follow-up (min, max), d: 87 (36, 638)

- **ORR=95.5%**
  - mDOR=10.8 mo
  - Median follow-up (min, max), d: 194 (46, 556)

**Tumor Response By BCMA Expression**

- **ORR=100%**
  - Median follow-up (min, max), d: 168 (121, 184)

- **ORR=91%**
  - Median follow-up (min, max), d: 311 (46, 556)

- **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.**
- **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. Low BCMA is <50% bone marrow plasma cells expression of BCMA; high BCMA is defined as ≥50%.**

**• 80.6% ORR across active dose cohorts (150-800 x 10^6)**
CRB-401 Data at ASCO 2018 - Hitting the Mark for Progression Free Survival

- mPFS of 11.8 months at active doses (≥150 x 10⁶ CAR+ T cells) in 18 subjects in dose escalation
- mPFS of 17.7 months in 16 responding subjects from all study cohorts who are MRD-negative

### mPFS at Inactive (50 x 10⁶) and Active (150–800 x 10⁶) Dose Levels¹

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Patients at Risk</th>
<th>mPFS (95% CI)</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 x 10⁶ (n=3)</td>
<td></td>
<td>2.7 (1.0, 2.9)</td>
<td></td>
</tr>
<tr>
<td>150–800 x 10⁶ (n=18)</td>
<td></td>
<td>11.8 (8.8, NE)</td>
<td></td>
</tr>
</tbody>
</table>

**mPFS** = 11.8 mo

### PFS in MRD-Negative Responders Escalation and Expansion Cohorts

- mPFS (95% CI) for 150–800 x 10⁶ (n=16) = 17.7 (5.8, NE)

---

Data cut-off: March 29, 2018. Median and 95% CI from Kaplan-Meier estimate. NE, not estimable.

PFS progression-free survival; MRD, minimal residual disease.

Includes patients treated with <50 x 10⁶ CAR T cells who were MRD-negative at >1 postbaseline time point.
CRB-401 Data at ASCO 2018 - bb2121 Continues to be Generally Well-Tolerated; No New Safety Signals

<table>
<thead>
<tr>
<th>CAR T Treatment-Emergent Adverse Events</th>
<th>All Infused Patients (N=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAE, n (%)</td>
<td>Overall</td>
</tr>
<tr>
<td>Cytokine release syndrome(^1)</td>
<td>27 (63)</td>
</tr>
<tr>
<td>Neurotoxicity(^2)</td>
<td>14 (33)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>35 (81)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>26 (61)</td>
</tr>
<tr>
<td>Anemia</td>
<td>24 (56)</td>
</tr>
<tr>
<td>Infection(^3)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>26 (61)</td>
</tr>
<tr>
<td>First Month</td>
<td>10 (23)</td>
</tr>
</tbody>
</table>

• No grade 4 CRS events
• No fatal CRS or neurotoxicity events

Data cut-off: March 29, 2018. NE, not estimable.\(^1\)CRS uniformly graded per Lee et al., Blood 2014;124:188-195. \(^2\)Events occurring in first 28 d and including dizziness, bradyphrenia, somnolence, confusional state, nystagmus, insomnia, memory impairment, depressed level of consciousness, neurotoxicity, lethargy, tremor and hallucination. \(^3\)Includes the SOC Infections and Infestations. Events observed in >10% include upper respiratory tract infection and pneumonia. \(^4\)Includes patients treated with active doses (150–800 × 10^6 CAR+ T cells; N=40). Median and 95% CI from Kaplan-Meier estimate. \(^5\)Time from first bb2121 infusion to the first grade ≤2 event after day 32.
### Response to Current Standard of Care in Late Line RRMM

**Current standard of care in RRMM after two or more lines of therapy:**

<table>
<thead>
<tr>
<th></th>
<th>Dara</th>
<th>PDd</th>
<th>bb2121</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Phase</strong></td>
<td>II</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>106</td>
<td>103</td>
<td>43</td>
</tr>
<tr>
<td><strong>Eligibility</strong></td>
<td>≥ 3 prior lines Pom allowed Dara-naive</td>
<td>≥ 2 prior lines Pom-naive Dara-naive</td>
<td>≥ 3 prior lines Pom allowed Dara-allowed</td>
</tr>
<tr>
<td><strong>Median prior lines</strong></td>
<td>5</td>
<td>4</td>
<td>7</td>
</tr>
</tbody>
</table>

**PDd** = Pomalidomide + Daratumumab + dexamethasone. Pom = Pomalidomide; Dara = Daratumumab

**Pomalidomide + Daratumumab + dexamethasone (phase I)**
- ORR = 60%
- mPFS = 8.8 mo

**Daratumumab monotherapy (phase II)**
- ORR = 29%
- mPFS = 3.7 mo

- **18%** sCR/Cr
- **25%** VGPR
- **17%** PR
- **9%** SD
- **3%** PD

**Myeloma Response**
bb2121 Patient Case: 21 Months in sCR

General Information

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &amp; Gender</td>
<td>52 year old Male</td>
</tr>
<tr>
<td>Dose group</td>
<td>150x10^6</td>
</tr>
<tr>
<td>Tumor Burden</td>
<td>High</td>
</tr>
<tr>
<td>High Risk Cytogenetics (based on FISH)</td>
<td>No</td>
</tr>
<tr>
<td>Number of prior regimens</td>
<td>6</td>
</tr>
<tr>
<td>Initial diagnosis</td>
<td>May, 2010</td>
</tr>
<tr>
<td>BCMA% (prescreen, baseline)</td>
<td>60, 75</td>
</tr>
</tbody>
</table>

Treatment history

<table>
<thead>
<tr>
<th>Duration/Best Rx</th>
<th>VRD, Doxo</th>
<th>VRD, M, ASCT</th>
<th>K</th>
<th>Pom</th>
<th>VRD</th>
<th>Dara</th>
<th>bb2121</th>
</tr>
</thead>
<tbody>
<tr>
<td>19M</td>
<td>CR</td>
<td>30M</td>
<td>2M</td>
<td>2M</td>
<td>3M</td>
<td>N/A</td>
<td>5M</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

bb2121 Response

minimal residual disease (MRD)-negative

KEY

Advancing bb2121 into Earlier Lines of Multiple Myeloma

Comprehensive Clinical Plan in Earlier Lines to Begin in 2018

- Registration-enabling trial in late line open to enrollment
- Planned Ph III in 3rd line vs. Dara/Pom/dex
- Explore label expansion opportunity in 2nd line setting
- Opportunities for bb2121 in NDMM including high risk, TNE and TE vs. transplant

NDMM: Newly Diagnosed Multiple Myeloma
TNE: Transplant Non-Eligible
TE: Transplant Eligible
| Efficacy? | • 95.5% ORR in doses above 150M cells.  
• 50% CR rate at doses above 150M cells. |
| Durability? | • 11.8 months median PFS in dose-escalation active doses.  
• 17.7 months median PFS in MRD(-) patients with response (escalation and expansion). |
| BCMA? MRD? | • Consistent responses across BCMA expression levels.  
• 16/16 responding, MRD-evaluable patients were MRD negative. |
| Safety? | • No new safety signals (G3/G4 CRS or Neurotox). |
| Path forward? | • KarMMa amendment raised high end of dose range to 450 based on observed dose-response and acceptable safety profile. Potential approval on track for 2020. Earlier line development plan advancing. |
Cerebral Adrenoleukodystrophy
Cerebral Adrenoleukodystrophy

• Severe, often fatal neurological disease in boys

UNMET NEED

• Treatment limited to allo-HSCT
• Sometimes severe treatment-related risks and complications, especially when donor is not a matched sibling

EPIDEMOLOGY

• Global incidence of ALD: 1 in ~21,000 newborns
• Cerebral form develops in ~40% of affected boys

Ethan’s family spent nearly two years trying different medications and meeting with specialists to try and resolve his symptoms. Tragically, during this period, the ravaging effects of ALD were continuing to damage Ethan’s brain and adrenal glands.

Source: Ethan Zakes Foundation


Ethan Zakes 2000 - 2011

Source: Ethan Zakes Foundation
Lenti-D Treatment Halts CALD Disease Progression

15/17 patients (88%) alive and MFD-free at 24 months follow-up; all patients continue to be MFD-free as of April 25, 2018
- Exceeds pre-determined efficacy benchmark for the study MFD-free survival in 13/15 (76%)

12 additional patients treated in Starbeam study
- No MFDs reported as of April 25, 2018; median follow-up for this additional cohort of patients is 4.2 months (0.4 – 11.7 months)

Safety profile consistent with autologous transplantation
- No GvHD, no graft rejection

Two patients did not meet primary endpoint:
- Patient 2016: Withdrew
- Patient 2018: Rapid disease progression early in the study
Recent Collaborations
Science-Driven and Highly Complementary Partnership

**Science**: Best-in-class technology platforms joining forces to crush cancer

**Culture**: Science- and patient-focused companies with a willingness to push boundaries of novel technologies

**Structure**: Aligned and streamlined operating model to enable flexible research and decision making

**Investment**: All-in mindset driving shared and enhanced funding for R&D efforts

**BLUE remains BLUE**: Clear value proposition through product rights, shared funding and capabilities
Engaging the Right Target with the Optimal Target Binder

**VELOCISUITE®**

- target validation at unprecedented pace and precision
- rapid generation of genetically engineered mice
- fully human antibodies through immunization
- rapid identification & preclinical testing of target specific antibodies
- fully human T cell receptors from an engineered mouse
- immunodeficient mouse platform - study of human cells & tumors

**Pick Great Targets**

**Fully Human CARs**

**Identify Human TCRs**

**Better Models**
### Partnership Highlights

#### Research
- Five-year research collaboration
- Refreshable list of **six** targets
- Access to **Regeneron VelociSuite®** Platform technologies
- Leveraging bluebird expertise in cell biology and vector technology
- Brings together two science driven organizations with synergistic technology and expertise

#### Development
- **bluebird** leads R&D managed by a Joint Steering Committee
- **bluebird** retains significant product rights; **Regeneron** receives milestone payments and royalties
- **Regeneron** can opt-in to multiple products to become 50/50 partners
- Joint late-stage development and commercialization allocated between bluebird and Regeneron or future partners on a regional basis

#### Funding
- Share costs equally through pre-IND research and into Phase 1/2 development
- For 50/50 collaboration products, development and commercialization costs (by region) are shared equally
- **bluebird** funds development and commercialization of its wholly-owned products
- **$100 million equity investment** by Regeneron in **bluebird** - 420,000 shares at $238.10 per share or a 59% premium*

---

*Premium of approximately $37 million will be used to cover part of Regeneron’s share of research costs; bluebird intends to use the balance of the proceeds to support its research activities in the collaboration.*
Gritstone Complements bluebird’s Approach to Generating Novel Therapeutics for Oncology

**Patient biopsy**
- **Gritstone**
  - Clinical biopsy

**Tumor targets**
- **Gritstone**
  - Mass spec validation of expressed tumor targets in patients and sequencing of tumor transcriptome
  - **Select patients with target**
  - **Validate 10 targets**

**TCR**
- **Medigen, Regeneron, Gritstone**
  - Identify TCR sequences which bind to validated tumor targets

**Cell therapy**
- **Bluebird**
  - Generate TCR cell therapy targeting validated tumor antigens using patient’s white blood cells

**Patient therapy**
- **Bluebird**
  - Genetically engineered patient cells infused back into patient
Early Pipeline
Good is Never Good Enough for Patients: BLUE Toolbox Strategy

**Transduction**

- v1.0: LentiGlobin
- v2.0: LentiGlobin & Enhancers

**Durability**

- BCMA (bb2121)
- BCMA & PI3Ki (bb21217)

**Product Engine**

- MegaTAL Gene Editing
- Lentivirus
- LNPs
- mRNA

**vFuture**

- LentiGlobin
  - Optimized severe genetic disease products
- BCMA & Solid Tumors
  - New & enhanced oncology products
- Novel areas: autoimmune In vivo gene editing
**Lentiviral Vector Approach to Suppression of BCL11a in SCD**

- Transduced >80% of SCD HSCs \( \rightarrow \) HbF induction of 66-92% (and suppression of HbS to 5-38%)
- Leverage understanding of sickle cell biology and advances to the manufacturing, cell source and patient management now deployed in HGB-206
- Program and IP licensed exclusively from Boston Children’s Hospital
- Clinical study underway
Go TRUE BLUE

We Must Make Hope a Reality