bluebird bio

Transforming the treatment of Sickle Cell Disease

November 18, 2021

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 our research and development programs, our expectations regarding what the FDA will require for regulatory approval, the timing or likelihood of regulatory filings and approvals, and the timing and likelihood of entering into contracts with qualified treatment centers or payors, and our commercialization plans for approved products 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.

Welcome and sickle cell disease (SCD) overview

Andrew Obenshain,
chief executive officer

bluebirdbio®

The next chapter of bluebird bio begins now

Leadership Team

Experienced team composed of tenured bluebird bio leaders and recent additions

Products that Matter

Core 3 first-in-class transformative gene therapies designed to give patients and their families more bluebird days

Commercial Execution

Laser-focused on launching Core 3 products in the U.S.

Post-separation, **bluebird bio is poised to unlock value** for patients and shareholders

Optimization + Innovation

Strategy in place to optimize existing products and realize next-generation pipeline

Fiscal Discipline

Disciplined capital allocation to immediately and meaningfully improve financial profile

agenda

Welcome and sickle cell disease (SCD) overview
Andrew Obenshain, chief executive officer

Exceptional clinical profile
Richard Colvin, M.D., Ph.D., chief medical officer

De-risked path to BLA
Anne-Virginie Eggimann, chief regulatory officer

Perspectives from a treating physician
Wally Smith, M.D., Director, VCU Health, Adult Sickle Cell Program

Poised to unlock significant commercial opportunity
Tom Klima, chief commercial officer

Closing remarks
Andrew Obenshain, chief executive officer

Q&A

bluebirdbio
recode for life™

bluebird bio: Setting the industry standard for gene therapy

~485 patient-years of experience with bluebird bio's gene therapies

170+ PATIENTS studied across 8 clinical trials

Up to **10 years** of patient follow-up

Target 3 approvals by the end of 2023

200+ drug product lots manufactured across Core 3 programs

Up to **22,000** patients in the U.S. addressable with Core 3 programs[1]

10+ years since inception

~520 employees

bluebirdbio recode for life

1. Hassell KL. Population estimates of sickle cell disease in the U.S. Am J Prev Med. 2010;38(4 Suppl):S512 521; Jul '21 bbb analysis of Komodo patient-level claims data (Apr '20 – Mar '21), IQVIA patient-level claims data (Aug '18 – Jul '19); Hulihan, Mary M., et al. State-based surveillance for selected hemoglobinopathies. Genetics in Medicine 17.2 (2015): 125-130.; Bezman L, et al. Adrenoleukodystrophy: Incidence, new mutation rate, and results of extended family screening. Ann Neurol. 2001;49:512–517; Moser HW, Mahmood A, Raymond GV. X-linked adrenoleukodystrophy. Nature Clin Pract Neurol. 2007;3(3):140-51

Perspective from a sickle cell warrior

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Sickle cell disease is a complex and debilitating disease that has long been misunderstood and underserved

It's More Than Just Pain

- Stroke (1 in 4 patients have a stroke by age 45[1])
- Acute chest syndrome, blocked vessels in the lungs
- Widespread organ damage or organ failure
- Frequent hospitalizations
- >50% of patients with SCD die before 50 years of age[2]

Substantial Health Disparities Persist

- SCD is most prevalent in a population that faces societal and health system barriers
  - 1 in 13 Black Americans are carriers of the sickle cell trait[3]
  - 1 out of every 365 Black children born in the U.S. has sickle cell disease[3]
  - 96% of sickle cell patients in the U.S. are Black[3]
- Historically under-funded area of research and development
  - NIH investment in cystic fibrosis is 3.5x the investment in SCD[4]

SCD is a natural target for gene therapy

1. Kato GJ, Piel FB, Reid CD, et al. Sickle cell disease. Nat Rev Dis Primers. 2018;4:18010.
2. De Baun et al. 2019 Blood 133(6): 615-617
3. Centers for Disease Control. Data & Statistics on Sickle Cell Disease
4. Farooq,F, Mogayzel, P, lLanzkron, S. et al. Comparison of US Federal and Foundation Funding of Research for Sickle Cell Disease and Cystic Fibrosis and Factors Associated with Research Productivity. JAMA Network Open. March 27, 2020.

Exceptional clinical profile

Richard Colvin, M.D., Ph.D.
chief medical officer

bluebirdbio®

Lovo-cel: Potentially first-in-class lentiviral vector gene therapy for SCD

100+ patient-years of experience with bluebird bio's gene therapy for SCD

Sickle Cell Disease*

Lovo-cel

49 patients treated in clinical trials

Up to **6 years** of patient follow-up

ZERO severe vaso-occlusive events following treatment in our HGB-206 Group C cohort

Safety profile remains generally consistent with the risks of autologous stem cell transplant, myeloablative single-agent busulfan conditioning, and underlying SCD

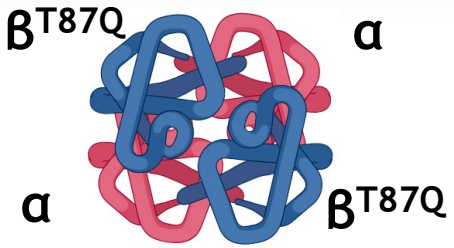
*Real patients pictured, but they have not used our products

Our technology is transformative and backed by clinical data

bluebird bio's lentiviral vector (LVV) gene therapy introduces functional copies of a gene to the patient's stem cells to address the underlying genetic cause of disease

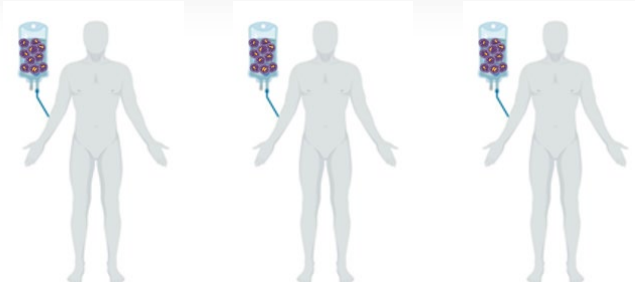
Custom-Designed

LVV and manufacturing process for lovo-cel specifically designed to produce consistent levels of an anti-sickling HbA and reduce HbS below symptomatic levels



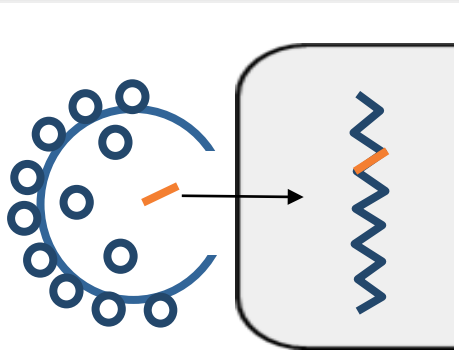
Deeply Studied

Lovo-cel reflects more than 100 patient-years of experience, more than any other gene therapy in development for SCD

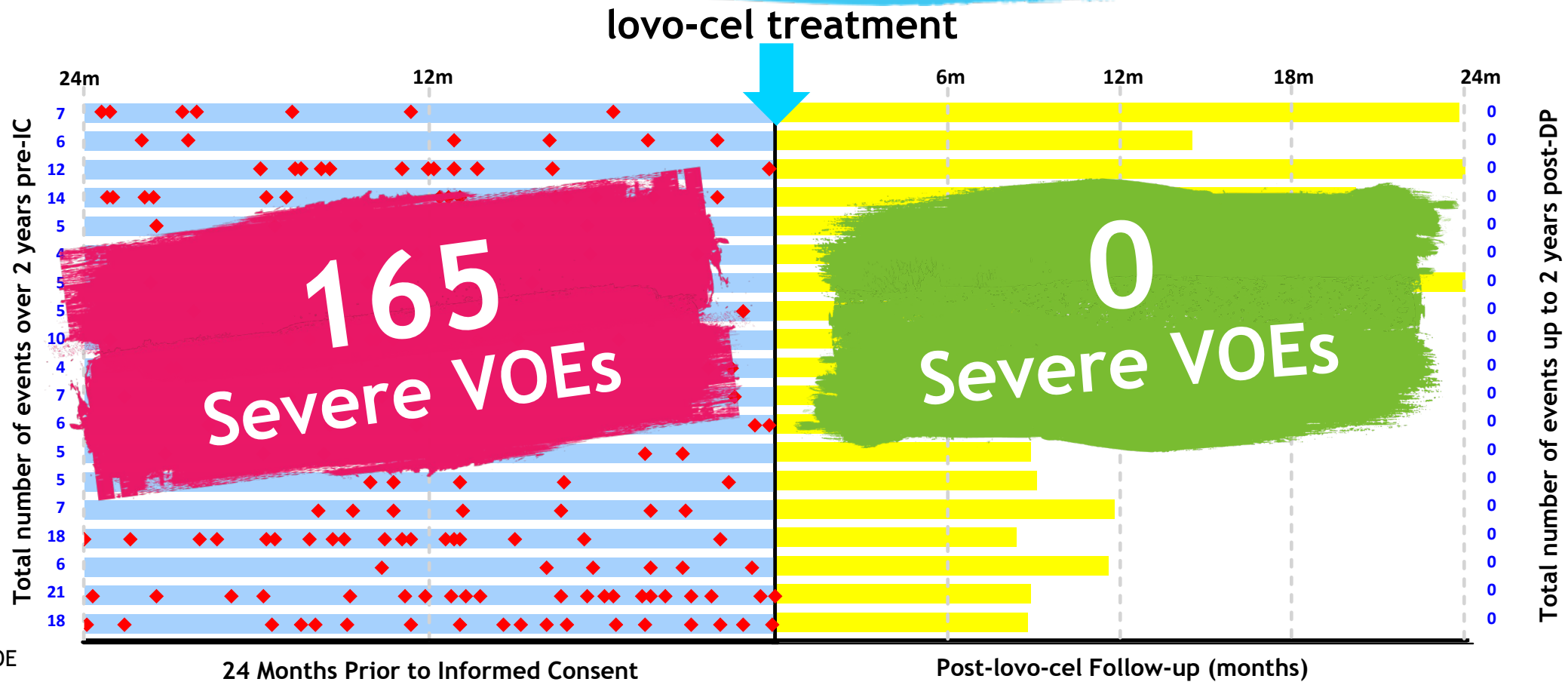


Traceable

Insertion site traceability is a unique differentiator from other modalities; in-depth and effective analytical methods allow for comprehensive safety monitoring



Complete resolution of severe VOEs post-lovo-cel treatment in HGB-206 Group C clinical study



The safety data profile remains generally consistent with the risks of autologous stem cell transplantation and myeloablative single-agent busulfan conditioning, as well as underlying SCD.

In the initial cohort (Group A) of the HGB-206 study, two patients treated with LentiGlobin for SCD developed acute myeloid leukemia (AML). After thorough investigations into the cases, bluebird bio determined that these were unlikely related to the insertion of bluebird's lentiviral vector (LVV) gene therapy for SCD.
In the Group C cohort of the HGB-206 study, there were no serious AEs related to LentiGlobin for SCD. One non-serious, Grade 2 adverse event (AE) of febrile neutropenia was considered related to LentiGlobin for SCD
DP, drug product; ER, emergency room; IC, informed consent; max, maximum; min, minimum; sVOEs, severe VOEs; VOE, vaso-occlusive event; VOC, vaso-occlusive crises.
Protocol sVOEs are shown; Patients with ≥ 4 sVOE at baseline before IC and with ≥ 6 months of follow-up post-DP infusion are included. A severe VOE is as an event with no medically determined cause other than a vaso-occlusion, requiring a ≥24-hour hospital or emergency room observation unit visit or at least 2 visits to a day unit or ER over 72 hours with both visits requiring intravenous treatment for the following: acute episodes of pain, acute chest syndrome, acute hepatic sequestration, and acute splenic sequestration; †HbA^{T87Q} stabilizes within 6 months; *One death, unlikely related to lovo-cel, > 18 months post treatment in a patient with significant baseline SCD-related cardiopulmonary disease.
Note: In the last datacut, one patient had a non-serious VOC expression at Day 107. This event is recorded as an investigator reported VOE but does not meet the definition of a protocol VOE.

Data as of 20 August 2020

ASH 2021: Building on impressive sickle cell disease data set

Poster Presentation

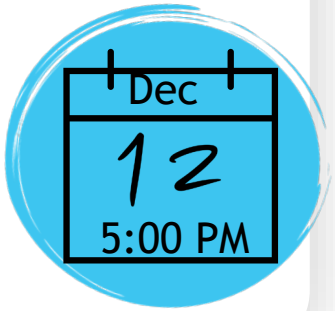
Natural History Studies Highlight Ongoing Unmet Need for Effective Disease Modifying or Curative Therapies

Raffaella Colombatti, M.D., PhD, *Pediatric Hematologist, University of Padova, Padua, Italy*

Oral Presentation

Polyclonality Strongly Correlates with Biological Outcomes and is Significantly Increased Following Improvements to the Phase 1/2 HGB-206 Protocol and Manufacturing of LentiGlobin for Sickle Cell Disease (SCD; bb1111) Gene Therapy

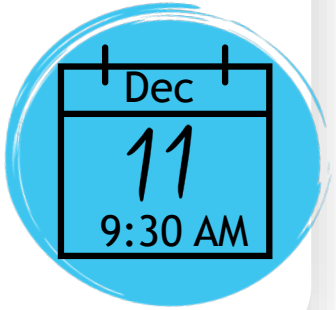
John F. Tisdale, M.D., *Chief, Cellular and Molecular Therapeutics Branch, NHLBI, Bethesda, MD*



Oral Presentation

Sustained Improvements in Patient Reported Quality of Life up to 24 Months Post-treatment with LentiGlobin for Sickle Cell Disease (bb1111) Gene Therapy

Mark C. Walters, M.D., *Medical Director, Jordan Family Center for BMT & Cellular Therapies Research, UCSF Benioff Children's Hospital Oakland, Oakland, CA*



De-risked path to BLA

Anne-Virginie Eggimann,
chief regulatory officer

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De-risked path to BLA submission

Aligned on robust clinical data package with FDA

BLA will include:

- ✓ At least 50 patients treated with up to 7 years of follow-up
- ✓ HGB-206 Group C as primary basis of effectiveness with approximately 30 patients with ≥ 18 mo. of follow up.
- ✓ Pivotal study HGB-206; largest gene therapy study in SCD to date w/ clinically meaningful primary endpoint

All patients in Group C evaluable for primary endpoint have been treated

Clarified and confirmed detailed CMC path to BLA

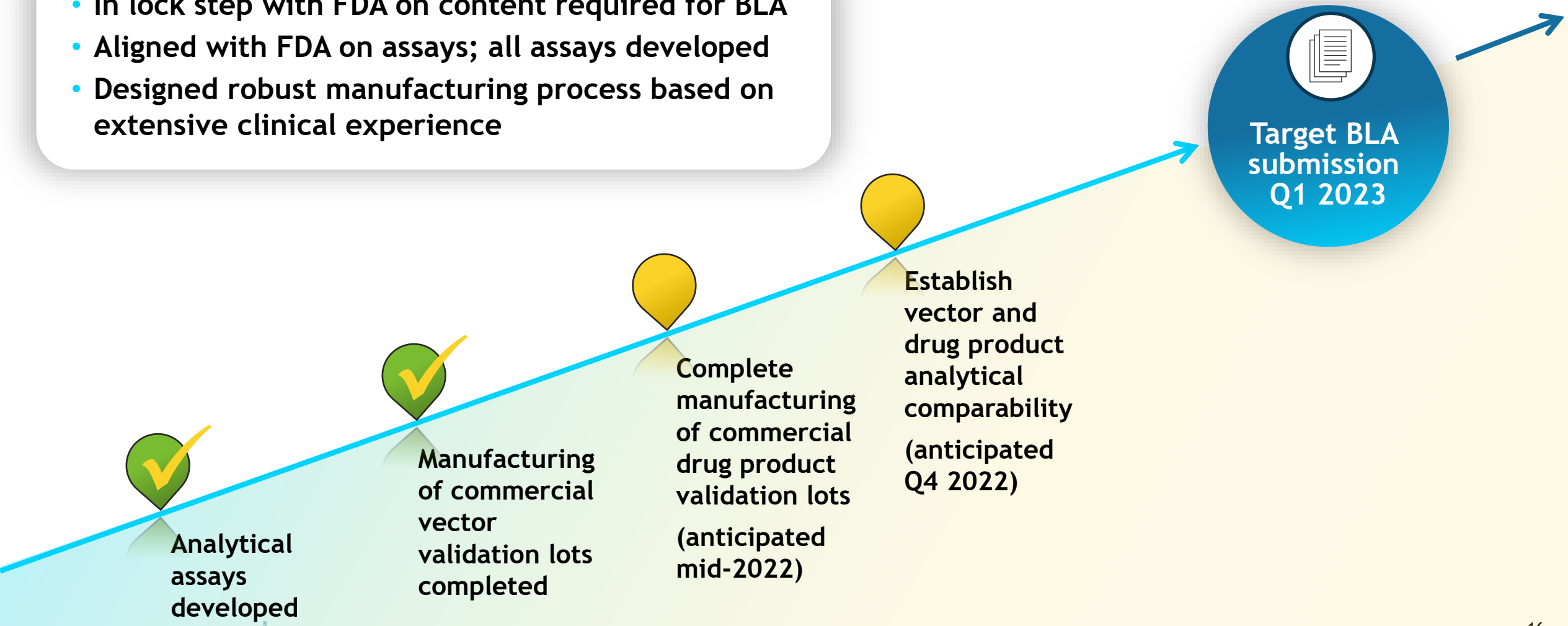
- ✓ Aligned with FDA on reg-CMC road map to BLA submission
- ✓ Aligned with FDA on fastest scientifically-justified steps for analytical comparability requirements
- ✓ Re-initiating Phase 3 HGB-210 with drug product (DP) manufacturing in commercial facility

De-risking CMC path to BLA was critical as FDA spends approximately 80% of their review time on CMC

Based on these key achievements, expect lovo-cel BLA submission Q1 2023

Plan to launch lovo-cel with scalable process to meet commercial demand

- In lock step with FDA on content required for BLA
- Aligned with FDA on assays; all assays developed
- Designed robust manufacturing process based on extensive clinical experience



Perspectives from a treating physician

Dr. Wally Smith

Director, Virginia Commonwealth University Health, Adult Sickle Cell Program

Dr. Smith is an independent treating physician and is not an investigator in bluebird bio's ongoing clinical trials.

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Poised to unlock significant commercial opportunity

Tom Klima,

chief commercial officer

bluebirdbio®

Prepared to deliver blockbuster opportunity by focusing on three key areas

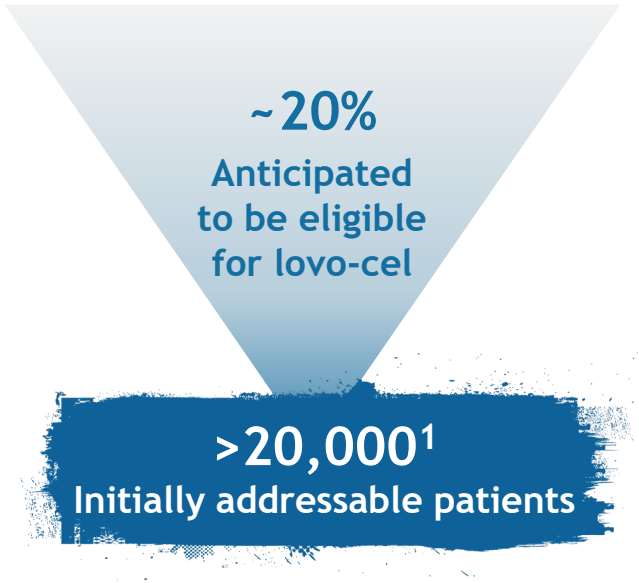
Bringing a potentially curative therapy to patients in need

1. More than a decade of commitment to education, partnership and support with the SCD community
2. Confidence that the value of lovo-cel will be recognized in the US market, leading to coverage and reimbursement
3. Synergies across QTC network from anticipated beti-cel launch and deep understanding of patient treatment dynamics

Significant opportunity to benefit patients with a therapy that treats the underlying cause of sickle cell disease

Large addressable patient population

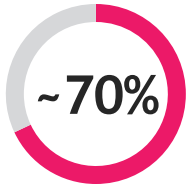
Patients with SCD in the US
>100,000[1]



High burden of disease & unmet need

Among patients with SCD in the US[2]:

…state that the **disease severely impacts** their life



…are **dissatisfied with the current treatments** available

…are **concerned about the future & long-term effects** of their disease

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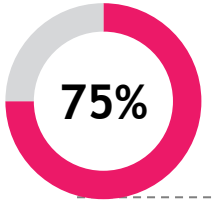
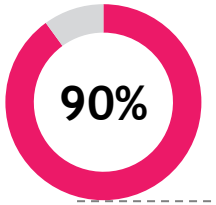
1. Komodo claims data (Apr '20 – Mar '21)
2. 2020 SCD Patient Research data on file

Enthusiasm for gene therapy is high among SCD patients, caregivers, treaters & transplanters

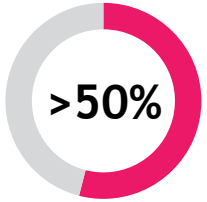
Patients and Caregivers[1]



…believe it is critical that new treatments reduce (or eliminate) the pain associated with SCD



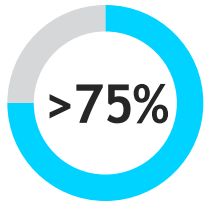
…would initiate a treatment conversation with their managing physician to discuss gene therapy after viewing lovo-cel profile



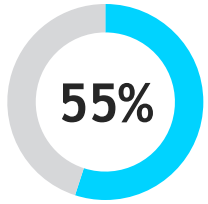
…would immediately accept a referral to a transplant specialist & undergo gene therapy if eligible

&

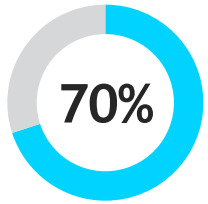
Treaters and Transplanters[2]



…view **lowering VOE risk, reducing hospitalizations & protecting organ health as paramount** for new therapies



…believe **gene therapy can provide a safer alternative to HSCT with matched sibling donor**[1]



…report a **high likelihood of using gene therapy in their patients**, and **>50% would try lovo-cel within 6 months of launch**

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1. 2020 SCD Patient Research data on file
2. 2021 SCD HCP Research data on file

bluebird bio has been committed to meaningful change for people with SCD and their families for more than a decade

Activating Patient Org-Driven Education

- Active engagement with >75 SCD patient organizations
- National, regional and local efforts on awareness, advocacy and understanding disease progression

Supporting Patient/Caregiver Engagement

- Convened multi-stakeholder coalition to improve care for people with SCD.
- Participants include Black Women's Health Imperative, National Medical Association and Black Nurses Association

Advancing policies that increase access

- Established first and only SCD diversity advisory council
- Focused on identifying health disparities and barriers to care

Education, support and advocacy are essential to adoption of gene therapy

An integrated payer-provider approach for robust access at anticipated launch

CUSTOMER	APPROACH	VALUE DELIVERED
Payer	1 Tailored approach to risk-sharing 2 Solutions integrated with customer financial dynamics, leveraging prior launches	
Provider	1 Optionality in distribution model addresses providers' variable payer mix 2 Deep, 3+ year partnership w/ QTCs to understand and mitigate access barriers experienced with CAR-Ts	

Integrated payer-provider approach

- ✓ **ACCESS:** rapid coverage consistent with label
- ✓ **REIMBURSEMENT:** access hurdles removed at provider level
- ✓ **PRICING:** net price aligned with the value of curative* therapy
- ✓ **EXECUTION:** payer satisfaction with contracting

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*bluebird bio therapies intended to provide a potential functional cure to our patients

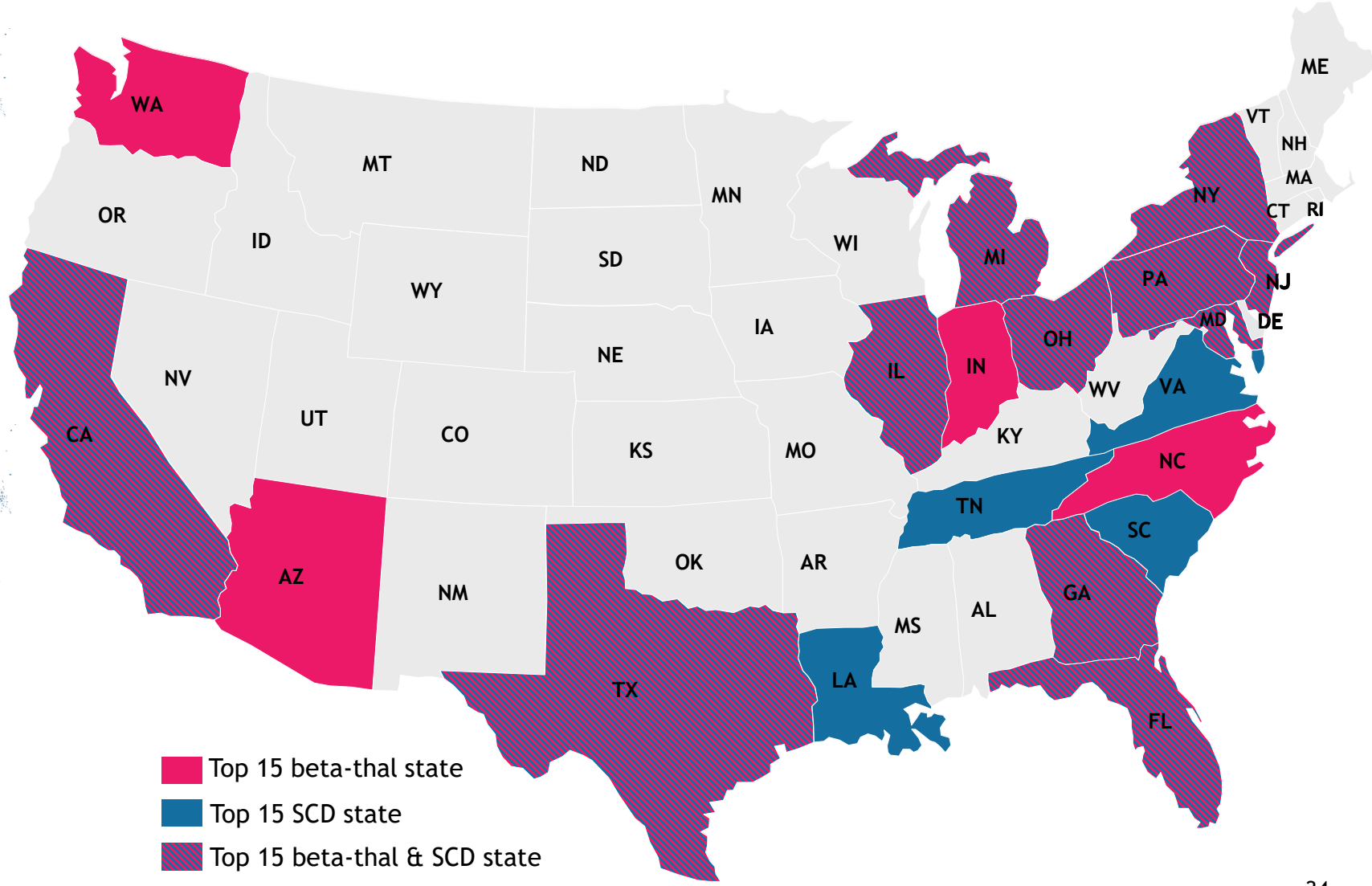
Extensive experience with QTCs and synergies with anticipated U.S. beti-cel launch set lovo-cel up for success

Promotional and operational synergies between beta-thal and SCD give us an advantage

- 100% of QTCs onboarded for beti-cel overlap with planned SCD QTCs
- 67% of beti-cel community HCP targets also treat severe SCD

Maximize proximity to patients

- >90% of SCD patients live within 200-mi. of a planned bbb QTC
- ~70% live within 50-mi.



Source: Komodo claims data (Apr '20 – Mar '21)

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Closing remarks

Andrew Obenshain,
chief executive officer

bluebirdbio®

bluebird bio is poised to deliver for sickle cell disease patients and shareholders

bluebird bio has:

The largest and deepest ex-vivo gene therapy data set	**~100 patient-years of experience** with bluebird's gene therapy for SCD	**49 PATIENTS** treated in clinical trials	Up to **6 years** of patient follow-up
A clear path to BLA submission	**Aligned with FDA** on BLA clinical data package	Confirmed detailed **CMC plan of action** with FDA	Prepared to launch at **commercial scale**
Poised to unlock blockbuster commercial opportunity	**~20,000** Addressable patients with SCD in the U.S.[1]	Leveraging **synergies across QTC network**	**Growing enthusiasm** for gene therapy among patients, caregivers, treaters, and transplanters

Uniquely positioned to deliver transformative therapy for SCD in 2023 and beyond

bluebirdbio®

1. *Hassell KL. Population estimates of sickle cell disease in the U.S. Am J Prev Med. 2010;38(4 Suppl):S512 521; Jul '21 bbb analysis of Komodo patient-level claims data (Apr '20 - Mar '21), IQVIA patient-level claims data (Aug '18 - Jul '19)*

Q&A

Andrew Obenshain
chief executive officer

Richard Colvin
chief medical officer

Anne-Virginie Eggimann
chief regulatory officer

Tom Klima
chief commercial officer

Gina Consylman
chief financial officer

Kasra Kasraian
SVP, technical development and operations

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thank you

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