WELCOME

Our 20-Year History of Drug Development as a Leading Indicator of our Future

Hank Fuchs, M.D.
President, Worldwide Research & Development

November 14, 2019
Safe Harbor Statement

This non-confidential presentation contains ‘forward-looking statements’ about the business prospects of BioMarin Pharmaceutical Inc., including potential future products in different areas of therapeutic research and development. Results may differ materially depending on the progress of BioMarin’s product programs, actions of regulatory authorities, availability of capital, future actions in the pharmaceutical market and developments by competitors, and those factors detailed in BioMarin’s filings with the Securities and Exchange Commission such as 10-Q, 10-K and 8-K reports.
Establishing a Track Record of Success Developing Innovative Products

**Twenty Years, Seven Approved Treatments...**

- **1997**: BioMarin is Incorporated
- **1999**: First clinical trial for Aldurazyme initiated
- **2001**: Aldurazyme approved by the FDA & EMA, becoming the first treatment for an MPS condition in the world
- **2003**: Acquires Glyko Biomedical
- **2005**: First clinical trial for Naglazyme initiated
- **2007**: Naglazyme (GALNS) IND filed
- **2009**: Naglazyme approved by the FDA
- **2011**: Firdapse launched in the EU
- **2013**: Kuvan approved in the EU
- **2015**: Brineura clinical program announced
- **2017**: Vimizim approved by the FDA
- **2019**: Palynziq approved

**...Thousands of Lives Improved**

- **2020**: $2B in Revenue expected
- **2020**: Phase 3 data readout for vosoritide
- **2019**: First patient enrolled in Phase 1/2 clinical trial for BMN250 in MPS IIIB
- **2017**: First patient enrolled in Valrox Phase 1/2
- **2015**: Vosoritide first clinical trial initiated
- **2013**: Firdapse Phase 1/2 initiated
- **2011**: Brineura approved
- **2009**: Palynziq clinical trial initiated
- **2007**: Aldurazyme approved by the FDA
- **2003**: Naglazyme approved by the FDA
- **2001**: First clinical trial for Naglazyme initiated
- **1999**: Listed on NASDAQ
- **1997**: BioMarin is Incorporated
New Updates Today…

Vosoritide for Achondroplasia: Transforming lives at the genetic level

- Multi-pronged global development program designed to address needs of full pediatric age range
  - Global Phase 3 (5-14 year-olds) to read-out by year-end; approval submissions in 2020
  - Phase 2 (5-14 year-olds) 54-month data; Phase 2 (0-5 year-olds) cohorts enrolled or enrolling
  - Natural History data confirm sustained treatment benefit with vosoritide

Early-stage R&D Engine: Genetics, genomics and what’s next

- Leveraging R&D productivity to build out early pipeline
  - Multiple new IND candidates

Valoctocogene Roxaparvovec for Hemophilia A

- Patient level data supports FVIII levels sufficient to abrogate bleeding risk and eliminate FVIII use
  - PPQ Manufacturing campaigns complete
  - Additional in vivo results and corticosteroid management update
  - Full, 52-week Phase 3 GENER8-1 study enrolled; U.S. and EU regulatory submissions imminent
Esteemed Guests and BioMarin Speakers Presenting Today

**Ravi Savarirayan, M.D., Ph.D.**
Research Fellow, Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, Australia
*The Promise of Impacting Health, not just Height, with Vosoritide for Achondroplasia*

**Andrew Dauber, M.D.**
Chief of Endocrinology, Children's National Hospital, Washington, D.C.
*Vosoritide has the Potential to Address a Range of Statural Deficiencies*

**Jonathan Day, M.B.B.S., Ph.D.**
Executive Medical Director, Clinical Science, BioMarin
*Vosoritide Development Program is Powered for Success; 54-Month Data Update*

**Lon Cardon, Ph.D.**
Chief Scientific Strategy Officer, BioMarin
*An R&D Engine that Leverages our Past to Build and Sustain our Early-Stage Pipeline*

**Robert Baffi, Ph.D.**
President of Global Manufacturing and Technical Operations, BioMarin
*Valrox Manufacturing Readiness and BMN 307 Synergies*

**Wing Yen Wong, M.D.**
Vice President, Clinical Science, BioMarin
*Our Confidence in Valoctocogene Roxaparvovec Continues to Build*
THANK YOU

Let’s get started...
Vosoritide Development Program is Powered for Success; 54-Month Data Update

Jonathan Day, M.B.B.S. Ph.D.
Executive Medical Director, BioMarin Pharmaceutical

November 14, 2019
Our Next Phase 3 Readout for Potential Blockbuster: Vosoritide for Achondroplasia

- Global Phase 3 fully enrolled
  - Top-Line Data expected YE 2019
- 0–5 year-old study underway
  - Cohort 1 (24–60 month olds) – enrollment complete
  - Cohort 2 (6–24 month olds) – enrollment expected complete YE 2019
  - Cohort 3 (newborn–6 month olds) – all sentinels enrolled
Four Pillars Underpin Vosoritide Program

**Phase 3 (301, 302)**
Studies: Powered for Success, Top-line Data by YE
- N=121, (5–18 years) pivotal for initial registration
- Randomized, placebo-controlled and stratified by age group and puberty

**Natural History Data**
- Comparative analyses by age and gender matched (N≥600) against trial data
- Ready for NDA / MAA filings in 2020

**Phase 2 (202, 205)**
Studies: 4.5 Years of Sustained Efficacy and Counting!
- 42-month data now published in NEJM
- 54-month Phase 2 Clinical Data and Natural History Analyses

**Phase 2 (206, 208)**
Studies: Infants and Toddlers, 0–5 years
- 3 cohorts: C1 (2–5 years) enrolled; C2 (6mo–2years) enrolled by YE; C3 (0–6mos) enrolling
- First Cohort 3 sentinels now enrolled – aged <6M
Phase 3 (301, 302) Studies: Powered for Success, Top-line Data by Year-End

- Last Patient Last Visit Complete (30th October 2019)
  - Total of 121 enrolled into 301
  - 119 of 121 patients have rolled over into 302 Extension Study (October 31st)
- Regulatory Filings / Publish in Major Journal all planned in 2020

<table>
<thead>
<tr>
<th>Study 901</th>
<th>Study 301</th>
<th>Study 302</th>
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<tbody>
<tr>
<td>≥6 Months No drug administration</td>
<td>52 Weeks</td>
<td>Final Adult Height N = approximately 119</td>
</tr>
<tr>
<td>Baseline Observational Growth Study</td>
<td>Vosoritide µg/kg</td>
<td>Extension Study</td>
</tr>
<tr>
<td>≥6 months growth data required to enter Study 301</td>
<td></td>
<td>Open-Label Vosoritide</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
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Phase 3 and Phase 2 study have similar populations; P3 powered for success

Phase 3 and Phase 2 have similar patient populations:
• Phase 3 baseline parameters comparable to Phase 2

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<thead>
<tr>
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<th>Phase 2 C3 (5–14 years eligible)</th>
<th>Phase 3 (5–18 years eligible)</th>
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<tbody>
<tr>
<td>Baseline AGV</td>
<td>4.0 cm/yr</td>
<td>4.2 cm/yr</td>
</tr>
<tr>
<td>Mean Age (Range Enrolled)</td>
<td>8.0 (6–11)</td>
<td>8.7 (5–14)</td>
</tr>
<tr>
<td>Tanner 1 vs &gt;1</td>
<td>100% vs 0.0%</td>
<td>79.3% vs 20.7%</td>
</tr>
<tr>
<td>Male vs Female</td>
<td>40.0% vs 60.0%</td>
<td>52.9% vs 47.1%</td>
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Original Phase 3 powering assumptions
• 90% powered with 110 patients to observe ΔAGV of 1.75 cm/year assuming (2.8 SD)

Now with 121 patients and lower variability (~2.0 SD) observed
• >95% powered to detect ΔAGV of 1.75 cm from baseline for each subject
• Well powered for pre-specified endpoints including height Z-score and proportionality
Phase 2 (202) Study: 42-month Data Published in *NEJM*

5.7cm Cumulative Additional Height Gained vs. Baseline over 42 Months

Sustained elevation of AGV shown in sequential 6M time periods
Published Achondroplasia Natural History Data

*AGV Highest in Infancy Then Gradually Declines with Age*

- **6 cm/year**
- **4 cm/year**
- **No pubertal growth spurt**

Hoover Fong 2008; Merker 2018

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**Achondroplasia**

**Average Stature**
Published Achondroplasia Natural History Data

Baseline AGV Continues to Decline

Gradual decline in AGV with age with cumulative effect over time
Contemporaneous Natural History Data

- **In Collaboration with four large U.S. specialist Skeletal Dysplasia Centres**
  - Large, multi-center, natural history study, n=1,377
  - Dr. Hoover-Fong et al. I Johns Hopkins University

- **Designed to serve as comparator population**
  - Protocol with well-defined statistical analysis plan and outcome measures
  - Contemporaneous and High Density growth data in boys and girls (>13,000 measurements)
  - Patient level data that spans across entire pediatric age range

- **Next steps**
  - Perform comparative analyses with 5 year Phase 2 data to underpin duration of effect
  - Ten major publications planned for submission in 2019 / 2020

> Sometimes rigorous natural history models can help inform development programs, and even serve as comparator arms for studies where it may be impractical to randomize patients to placebo

– Scott Gottlieb, Former FDA Commissioner
Phase 2 (202) Study: Sustained Elevation of AGV Over 42 Months

6.8cm Cumulative Additional Height Gained vs. Natural History over 42 Months

- Preliminary Analysis vs. Natural History
- Phase 2 C3 n=10 subjects matched to NH data at baseline and at 42M by age and gender (n=603)
- Cross Sectional Analysis comparing standing height at baseline vs. standing height at 42M
Phase 2 (202) Study: 54-month Data Compared to Natural History

9.0cm Cumulative Additional Height Gained vs. Natural History over 54 Months

2.2cm Additional Height Gained over Last Year

- Preliminary Analysis vs. Natural History
- Phase 2 C3 n=10 subjects matched to NH data at baseline and at 54M by age and gender (n=619)
- Cross Sectional Analysis comparing standing height at baseline vs. standing height at 54M
Phase 2 (206) Study: Infants and Toddlers Ages 0–5 Years

3 Cohorts: C1 (2–5 Years) Enrolled; C2 (6mo–2years) Enrolled by YE; C3 (0–6mos) Enrolling

- Sentinels enrolled to evaluate PK – likely impacted by age / weight
- Trial designed to evaluate dose adjustments required as children get older
- Short acting once-daily avoids risk of drug accumulation / overdose
  - Cohort 1 (aged 2–5yrs) – dosed at 15 µ/kg
  - Cohort 2 (aged 6M–2yrs) – dosed at 30 µ/kg
  - Cohort 3 (aged <6M) – currently under evaluation
- Safety and tolerability in infants and children remains consistent with what has been observed in Phase 2
- Well tolerated to date, delineation of dose in infants expected in December; randomization beginning in December
Phase 2 (206) Study:
Safety Profile in Infants and Toddlers and Phase 2 Safety Update

• Continues to be generally well-tolerated across all studies and at all doses – including in children <6M of age
  • No correlation between Cmax of drug and event

• Last year 28,000 daily doses – symptomatic hypotension 0.0035%

• Now over 57,000 injections administered and still 0.0035%
  • None resulted in study drug interruption or discontinuation
  • Resolved spontaneously within minutes without medical intervention

• Comparison with Placebo to facilitate further evaluation
Vosoritide Pen in Development

**Pen in development to follow after launch**
- Applied experiences from Palynziq
- Support lifecycle of vosoritide

**Delivery Features**
- Single use disposable cartridge
  - Lock out to prevent cartridge re-use or second dose
  - Twist to reconstitute dual chamber cartridge
  - Viewing window to confirm reconstitution
  - Adjustable dose
  - Low injection force and 31G needle
Summary: Sustained Growth Effects of Vosoritide Through 54 Months, Multi-pronged Global Program Progressing Rapidly

Comprehensive Global Program Progressing Rapidly

- Phase 3 powered for success, top-line data by year-end
- Large contemporaneous Natural History Dataset to support NDA/MAA
- Sustained drug effect at 54M (4.5 years)
- Additional height gained of 9.0cm at 54M compared to NH data
- Now dosing infants <6M to evaluate PK / safe dosing
- Cardiovascular effects remain limited – 0.0035%

NEXT STEPS: With Global Study Enrolled, Top-line Phase 3 Results Planned End of Year!!
THANK YOU
The Promise of Impacting Health, not just Height, with Vosoritide for Achondroplasia

Ravi Savarirayan, M.D. Ph.D.
Research Fellow, Murdoch Children’s Research Institute, Royal Children’s Hospital, Melbourne, Australia

Lead Investigator, Vosoritide Phase 2 and Phase 3 Studies

November 14, 2019
Achondroplasia

- Commonest cause of disproportionate short stature ("dwarfism")
- Adult height ~ 4 feet
- Relatively common “rare” condition
- 1 in 20,000 live births
- Medical/functional complications caused by abnormal *endochondral ossification*

Twin boys, one with achondroplasia
Achondroplasia: Life long complications impacting morbidity and mortality
Management priorities: the consequences of disordered endochondral bone formation
1. Foramen Magnum

- Major management and treatment issue
- No consensus on evaluation/management/markers
- Likely cause of higher infant mortality
- Major medical unmet need
2. The Spine

- Thoraco-lumbar kyphosis
- Spinal stenosis (all levels)
- Chronic back pain
- Impaired function
- Treatment/management options limited
3. Long Bones

- Bowing
- Pain
- Deformity
- Functional consequences
4. Sleep Disordered Breathing

- Related to infant mortality with FM
- Obstructive versus central versus combined
- Relationship to symptoms

Original Articles

Distinct patterns of respiratory difficulty in young children with achondroplasia: a clinical, sleep, and lung function study

Robert C Tasker, Isobel Dundas, Aidan Laverty, Margaret Fletcher, Roderick Lane, Janet Stocks
Pain

- Pain and fatigue in achondroplasia impact function and mobility
- Hoover-Fong et al., studied 361 people over 10 years with SD (cross sectional online survey via LPA)
- Chronic pain prevalence was 70.3%, highest in Achondroplasia
- Abnormal anatomy leads to pain, abnormal function and surgeries compound this (a vicious cycle)
Development

- Delays in motor, speech and other developmental milestones prevalent in achondroplasia (Ireland et al.)

- Improved growth might impact these milestones improving function and aiding in activities of daily living such as feeding and toileting
Virtue and value of early diagnosis, intervention

- Early diagnosis is crucial to establish care pathways, counseling, family support and treatment
- Accuracy of diagnosis imperative
- Allows natural history to be explained to family and surveillance/treatment options offered

Expert Reviews

*Best practice guidelines regarding prenatal evaluation and delivery of patients with skeletal dysplasia*

Ravi Savarirayan, MD; Judith P. Rossiter, MD; Julie E. Hoover-Fong, MD; Melita Irving, MD; Viviana Bompadre, PhD; Michael J. Goldberg, MD; Michael B. Bober, MD; Tae-Joon Cho, MD; Shawn E. Kamps, MD; William G. Mackenzie, MD; Cathleen Raggio, MD; Samantha S. Spencer, MD; Klane K. White, MD, MSc; on behalf of the Skeletal Dysplasia Management Consortium
Why height is important?

- Marker of other disease-relevant co-morbidities
  - Is a measurable outcome
  - Likely to correlate with endochondral bone growth beyond AGV (i.e. spine, foramen magnum)

- Has practical, functional value in itself for individuals with achondroplasia
What really matters............
Strong external interest in vosoritide for additional indications: Recent NEJM letter

TO THE EDITOR: Savarirayan et al. (July 4 issue) report increased skeletal growth in patients with achondroplasia (a common type of dwarfism caused by activating mutations in the tyrosine kinase fibroblast growth factor receptor 3 gene FGF3) who received vosoritide, a stable analogue of C-type natriuretic peptide. Their study is a breakthrough in treatment for achondroplasia, and it offers an intriguing possibility of broader clinical applications.

FGF3 is a negative regulator of growth, as evidenced by skeletal overgrowth in mice with deleted fgr3 and tal1 stature in humans with loss-of-function mutations in FGR3. In contrast, C-type natriuretic peptide increases growth and functions mainly through mechanistic inhibition of the FGR3 pathway. Because FGR3 and C-type natriuretic peptide are both endocrine regulators, therapeutic manipulation of the interaction between FGR3 and C-type natriuretic peptide may be associated with increased skeletal growth in conditions involving short stature, such as idiopathic short stature. These conditions constitute approximately 60% of all forms of dwarfism in developed countries and have unknown genetic causes, and patients with these conditions have a limited response to growth hormone therapy.

Pavel Krejčí, Ph.D.
Vosoritide has the Potential to Address a Range of Statural Deficiencies

Andrew Dauber, M.D.
Chief of Endocrinology, Children’s National Hospital, Washington, D.C.
To-be Lead Investigator, vosoritide Phase 2 study in dominantly inherited short stature

November 14, 2019
TAKING THE “IDIOPATHIC” OUT OF SHORT STATURE: GENETIC DISORDERS OF THE GROWTH PLATE

Andrew Dauber, MD MMSc
Chief of Endocrinology
Children’s National Health System
Traditional Endocrinologist View of Growth

Growth hormone

Pituitary gland

IGF-1

IGFBP-3 ALS
Diagnostic and Therapeutic Approach in the Growth Hormone Era
Genomics Shines a Light on Growth Biology

- N≈700,000
- 3,290 variants at genome-wide significance
- 712 loci
- 24.6% of height variance

Thousands of genes are involved in growth!

New Focus on the Growth Plate

Pathways Involved in Growth
- Collagen/extracellular matrix
- IGF/GH signaling
- TGF-beta signaling
- BMP/Noggin
- Hedgehog signaling
- Chromatin
- FGF signaling
- WNT signaling
- Osteoglycin
- TWIST/RUNX2
- NPR2/NPPC
- Bone/cartilage development

Sequence variants in growth plate genes and height

- **Gain-of-function**
  - Tall stature
- **Normal sequence**
  - Normal stature
- **Mild polymorphisms**
  - Modulate function/expression
  - Low-normal stature
- **Less severe**
  - Less critical genes / impair function / heterozygous
  - Isolated short stature
- **Severe loss-of-function mutations**
  - Critical genes / disrupt function / homozygous
  - Skeletal dysplasias

BMP, bone morphogenetic protein; FGF, fibroblast growth factor; IGF, insulin-like growth factor; NPPC, natriuretic peptide precursor C; NPR2, natriuretic peptide receptor-B; TGF, tumor growth factor.

Mutations in *NPR2* Cause Acromesomelic Dysplasia Maroteaux Type
Heterozygous variants in NPR2 cause ISS

Heterozygous Mutations in Natriuretic Peptide Receptor-B (NPR2) Gene as a Cause of Short Stature in Patients Initially Classified as Idiopathic Short Stature


Identification and Functional Characterization of Two Novel NPR2 Mutations in Japanese Patients With Short Stature

Naoko Amano, Tokuo Mukai, Yoshiya Ito, Satoshi Narumi, Toshiaki Tanaka, Susumu Yokoya, Tsutomu Ogata, and Tomonobu Hasegawa

Heterozygous NPR2 mutations cause disproportionate short stature, similar to Léri-Weill dyschondrosteosis

Alfonso Hisado-Oliva1,2,3, Ana I. Garre-Vázquez1, Fabiola Santaolalia-Caballero1, Albert Belinchón1,2,3, Ana C. Barreda-Bonis3,4, Gabriela A Vasques3, Joaquín Ramírez6, Cristina Luzuriaga7, Gianni Carlone8, Isabel González-Casado3,4, Sara Benito-Sanz1,2,3, Alexander A. Jorge5, Angel Campos-Barros1,2, Karen E. Heath1,2,3


What percentage of patients with familial short stature have mutations in NPR2?

• Boston ISS study
  – 99 children with ISS with parental height available
  – 22 (21%) with familial short stature
• 3/22 (13.6%) with NPR2 mutations

• Czech Short Stature Study
  – 917 children with short stature
  – 112 (12%) with familial short stature
• 6/112 (5.4%) with NPR2 mutations

Increased CNP signaling leads to tall stature in humans!

An Overgrowth Disorder Associated with Excessive Production of cGMP Due to a Gain-of-Function Mutation of the Natriuretic Peptide Receptor 2 Gene

PLoS ONE 7(8): e42180. doi:10.1371/journal.pone.0042180

Overgrowth Syndrome Associated With a Gain-of-Function Mutation of the Natriuretic Peptide Receptor 2 (NPR2) Gene


An Activating Mutation in the Kinase Homology Domain of the Natriuretic Peptide Receptor-2 Causes Extremely Tall Stature Without Skeletal Deformities


Height 7’3’’
Idiopathic Short Stature

ACAN  NPR2  FGFR3  NPPC  IHH  SHOX  Noonan (PTPN11 etc.)

And Many Others!

Mutations present with a range of short stature and associated medical co-morbidities.
Clinical relevance of systemic phenotyping and exome sequencing in patients with short stature

• Genetic testing identified a cause in 33% of patients
• Heterozygous carriers of recessive skeletal dysplasia genes represented 3.5% of cases
• In patients who underwent exome:
  – ACAN – 2.5%
  – NPR2 – 1.5%
  – 65% of variants found by exome were dominant inheritance pattern

Hauer et al. Genetics in Medicine, June 2018.
High Rate of Growth Plate Mutations in Familial Short Stature

- 33 patients with severe familial short stature
  - Height < -2.5 SD
- Genetic cause found in 17/33 (52%)
- 9/17 had mutations in growth plate related genes
Idiopathic Short Stature

Dominantly Inherited Short Stature
Trial of Vosoritide for Dominantly Inherited Short Stature

- Patients with high likelihood of growth plate pathology
- Easy to define clinical entity
- Will give rapid signal about potential for use of Vosoritide in this patient population
- Allows for post-hoc genetic analysis
- Plan to launch in 2020
Conclusions

• “Idiopathic” short stature consists of many different genetic disorders.
• Many of these are primary growth plate disorders.
• Patients with dominantly inherited short stature are enriched for growth plate disorders.
• These patients could benefit from a therapy targeted at the growth plate.
• CNP may be beneficial for many of these disorders.
Q&A
An R&D Engine that Leverages our Past to Build and Sustain our Early-Stage Pipeline

Lon Cardon, Ph.D.
Senior Vice President and Chief Scientific Strategy Officer

November 14, 2019
Today’s Key Messages

**Strategy:** R&D focused on leveraging investments and expertise in specific diseases and gene therapy platform

**2019 IND:** BMN 307, AAV5 gene therapy for PKU

**New Gene Therapy IND:** BMN 331, AAV5 gene therapy for HAE

**Sustainability:** 1 Program, multiple indications (DISS); Preclinical programs providing IND optionality for next 2 years+
To Drive Sustainable Growth, We Transitioned Our Pipeline

- **We have been Transitioning the Pipeline**
  - Larger rare: achondroplasia, hemophilia A, PKU
  - Licensing agreement for Tralesinidase Alfa for MPS IIIB

- **While maintaining BioMarin Core Approach**
  
  1. Diseases with high unmet needs
  2. Genetics/known disease mechanisms
  3. Large effect sizes
  4. Proximal endpoints/biomarkers

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Current state

- **Ultra-rare diseases**
  - MPS I
  - MPS IIIB
  - MPS IVA
  - MPS VI
  - CLN2

Future state

- **Harnessing genetics** to identify new opportunities in less rare diseases

- **Less rare diseases**
  - Achondroplasia
  - Hemophilia A
  - PKU
How to Effect the Transition?
Leverage Investments to Enable Expansion

Gene Therapy Leverage

1 Disease, Multiple Programs

1 Program, Multiple Diseases

1 Program, Multiple Diseases
How to Effect the Transition?
Leverage Investments to Enable Expansion

Gene Therapy Leverage

1 Disease, Multiple Programs

1 Program, Multiple Diseases

PKU Franchise – BMN 307; Gene Therapy for PKU – Program Update
BMN 307: Gene Therapy for PKU to Normalize Phe

Recap of Preclinical Data

1. Lifetime Phe Correction in Treated PKU Mice

Phenylalanine reductions seen in ENU2 mice

- Phe in μM

- ENU2 vehicle
- ENU2 + AAV5 muPAH
- WT vehicle

2. Phe Correction in Male and Female PKU mice

- Phe reductions in male PKU mice
- Phe reductions in female PKU mice

3. Neurotransmitter Correction

- Correction of brain Phe, tyrosine and tryptophan
- Normalization of neurotransmitters

Reference: BioMarin (R&D Day 2018)
BMN 307: Gene Therapy for PKU to Normalize Phe

Key Regulatory, Payer and Manufacturing Activities Completed

**Regulatory and Payer Interactions**

- Positive pre-IND and EMA/HTA Scientific Advice meetings
- Supportive of proposed Ph1/2 trial design
- Supportive of potential for registration-enabling Ph1/2 study
- Supportive of therapeutic goal of Phe normalization with normal diet (potential differentiator)

**Manufacturing**

- Building on gene therapy platform established by Valrox
  - Completed successful commercial scale manufacturing campaign
  - Drug product produced for initial clinical study and beyond
  - Commercial scale manufacturing provides key competitive advantage
BMN 307 Clinical Development Plan

902 PHEnom
Observational Study in Patients with PKU
Measure markers of disease and clinical outcomes over time in PKU patients

201 PHEarless
Gene Therapy Interventional Study
Determine the safety, efficacy and tolerability of a single administration of BMN 307 in PKU patients
Phase 1/2 BMN 307 Study:
• Part A: dose selection
• Part B: dose expansion
BMN 307 Key Development Activities and Next Steps

NHP and mouse GLP toxicity studies complete

GMP manufacturing campaign complete (commercial scale)

Completed successful regulatory interactions with MHRA, EMA and FDA
Held Parallel Consultation with EMA and EUnetHTA (European Network for Health Technology Assessment)

UK CTA submitted, and favorable initial responses received Oct 2019
IND submission expected by year-end
Ph1/2 dosing to start in 1Q20
How to Effect the Transition? Leverage Investments to Enable Expansion

Gene Therapy Leverage

1. New Program – BMN 331; Gene Therapy for HAE

2. 1 Program, Multiple Diseases

3. 1 Disease, Multiple Programs
BMN 331 for Hereditary Angioedema: Our Next Gene Therapy IND

AAV5 gene therapy to restore C1-INH expression

Therapeutic goal of reducing frequency and severity of edema attacks

Leverages key learnings and expertise from Valrox and BMN 307
BMN 331 Gene Therapy for Hereditary Angioedema (HAE)

Rare Genetic Disorder Causing Life-threatening Edema Attacks

- Mutations in SERPING1 gene result in insufficient levels of C1 esterase inhibitor, inadequate control of contact system
  - Potentially life-threatening edema attacks

SERPING1 Mutation
autosomal dominant

C1-INH Deficiency
quantity or function

Edema Attacks

Unpredictable severity; attacks occur “at worst times”; psychiatric comorbidities; lifestyle restrictions

- Unmet need for further reducing attack frequency and severity
  - Current SOC reduces attacks to 1 every 2–4 months
  - Patients still experience and fear serious breakthrough attacks

- Therapeutic goal of restoring C1-INH expression to reduce frequency and severity of edema attacks

- ~35,000 diagnosed patients in BioMarin territories

Required Amounts of AAV-Expressed Proteins: FVIII, FIX vs. C1-INH

Normal Levels of C1 Inhibitor Relative to Other Plasma Proteins (mg/dL)

- Required amount of C1-INH is significantly higher than AAV vector-expressed proteins used to treat hemophilia A and B

<table>
<thead>
<tr>
<th>Protein</th>
<th>Half Life</th>
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<tr>
<td>FVIII</td>
<td>8–12 hrs</td>
</tr>
<tr>
<td>FIX</td>
<td>18–34 hrs</td>
</tr>
<tr>
<td>C1inh</td>
<td>~64 hrs</td>
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BMN 331 Gene Therapy for HAE

Gene Therapy to Restore C1-INH Expression

- Program leveraged key gene therapy learnings from Valrox and BMN 307:
  - Promoter & enhancer properties
  - Codon optimization
  - Vector optimization to improve potency

- Compelling initial data and profile:
  - Peak human C1-INH expression at 2 weeks in mice and sustained for study period
  - NHP studies underway
  - IND-enabling studies starting early/mid-2020

Optimized Vector Achieved High Levels of Human C1-INH Activity in Mice 6 Weeks Post Dose

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<thead>
<tr>
<th>Off prophylaxis*</th>
<th>On prophylaxis*</th>
<th>Original vector</th>
<th>Optimized vector</th>
<th>Optimized vector (3x dose)</th>
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<td>Human C1-INH functional activity (mean IU/mL)</td>
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<tr>
<td>0.10</td>
<td>1.00</td>
<td>10.00</td>
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<td>Lower limit of normal (70%)</td>
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<tr>
<td>Min. therapeutic levels (40%)</td>
<td></td>
<td></td>
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</tbody>
</table>

HAE patients

Rag2 KO mice

Reference: BioMarin (data on file, 2019). *Predicted values at steady-state troughs; N Engl J Med 2017;376:1131-40. Original vector: C1-INH levels too low to measure functional activity; Optimized vector low dose: 6 wks timepoint, but was maintained 2-12 wks on similar levels; Optimized vector 3x dose: 6 wks timepoint, but was maintained 2-12 wks on similar levels
How to Effect the Transition?
Leverage Investments to Enable Expansion

1. Gene Therapy Leverage
2. 1 Program, Multiple Diseases
   - New Programs
     - Vosoritide for Dominantly Inherited Short Stature (DISS)
3. 1 Disease, Multiple Programs
From Ultra-Rare to Larger Genetic Diseases

Ultra-Rare

Larger Rare

Larger Genetic Diseases

Our Goal: Target Genetic Components of Larger Diseases

Common Diseases

Not in focus

Mechanistic / Genetic Clarity

Size of Diseases
Vosoritide for DISS: Attractive Indication Expansion Opportunity

Human Genetics Data

- CNP (NPR2, NPPC) mutations:
  - Loss of function
  - Gain of function

Adding Exogenous CNP Rescues cGMP Readout in NPR2 +/- Cell Model

- cGMP EC50 = 257 nM

Reference: BioMarin (data on file, 2019)
**Exploratory Research: Antisense Oligonucleotide for DMD**

- **Muscle Protein Expression in Quadriceps with ASO**
  - Bar chart showing dystrophin expression (%hDMD) across different groups.
  - Groups: VEH, Prog 1, Animal model.

- **No Negative Body Weight Effects Across Multiple Doses**
  - Line chart showing body weight progression over weeks for different groups.
  - Groups: WT Veh, Animal Model Veh, Prog 1.

- **Normalizes Hypertransaminasemia**
  - Scatter plot showing ALT (UL) levels across different groups.
  - Groups: WT, VEH, Prog 1.

**Next Steps for Project: NHP Studies**

Reference: BioMarin (data on file, 2019)
Exploratory Research: Next Generation AAV Capsids

Phylogenetically Distinct Capsids

- AAV-5
- Capsid 1
- AAV_go.1
- Capsid 2
- Capsid 3
- Capsid 4
- AAV-4
- Capsid 6
- AAV-11
- Capsid 7
- AAV-12
- Capsid 8
- Capsid 9
- Capsid 10
- Capsid 11
- AAV-7
- AAV-8
- AAV_rh.10
- AAV_rh.74j
- AAV-1
- AAV-6
- AAV-2
- AAV-3b
- AAV_LK03

Less Susceptibility to Pre-Existing Immunity

BMRN next generation capsids

BioMarin Valrox & BMN 307

Further Assessment and Characterization of BMRN AAVs Underway to Assess Translatability to NHPs, Inter-species Dose Scalability, Safety, Among Others

Reference: BioMarin (data on file, 2019)
Exploratory Research: Re-dosing

Re-dosing AAV5-treated Mice with BMRN AAV

Dose 1: AAV5

Dose 2: AAV5
or
Dose 2: BMRN AAV

Neutralizing Antibody (Preceeding 2nd dose)

Transgene Expression

Low NAb Titers to BMRN AAV Post-AAV5 Indicate Limited Cross-neutralizing Activity

Neutralizing titers to BMRN AAV in Patients from Valrox Clinical Studies

Note: Mice re-dosed at 4 weeks post-first-dose; * Normalized to the expression level resulting from a single dose of a respective capsid
Reference: BioMarin (data on file, 2019)
Today’s Key Messages

**Strategy:** R&D focused on leveraging investments and expertise in specific diseases and gene therapy platform

**2019 IND:** BMN 307, AAV5 gene therapy for PKU

**New Gene Therapy IND:** BMN 331, AAV5 gene therapy for HAE

**Sustainability:** 1 Program, multiple indications (DISS); Preclinical programs providing IND optionality for next 2 years+
THANK YOU
Q&A
Valrox Manufacturing Readiness and BMN 307 Synergies

Robert Baffi, Ph.D., M.B.A.
President of Global Manufacturing and Technical Operations

November 14, 2019
Mastering Complexity By Leveraging Experience

**Small Molecule**
- Kuvan
  - Mw 314 Daltons

**Large Molecule**
- Vosoritide
  - Mw 4,102 Daltons
- Vimizim
  - Mw ~ 110,000 Daltons
- Palynziq
  - Mw ~1,200,000 Daltons

**Large Biologic**
- Mw ~ 110,000 Daltons
- Mw ~5,200,000 Daltons
- Mw 4,102 Daltons
- Mw ~ 1,200,000 Daltons

**Pegylated Protein**
- Mw ~1,200,000 Daltons

**Gene Therapy**
- Valrox
  - Mw ~5,200,000 Daltons

---

**Size**

**Complexity**
- Bicycle
- Automobile
- Jet Fighter
- Air Force One (747)
- International Space Station
Cautioned that manufacturing technology is lagging behind the science of gene therapy.

He highlighted that manufacturing issues continue to be of concern for the field; and made note of the following concerns:

- Low production scale of viral vectors in current generation of cell lines
- Purification processes not standardized
- There is need for international collaboration on advancing methods of production of vectors
Cautioned that manufacturing technology is lagging behind the science of gene therapy. He highlighted that manufacturing issues continue to be of concern for the field; and made note of the following concerns:

- Low production scale of viral vectors in current generation of cell lines
- Purification processes not standardized
- There is need for international collaboration on advancing methods of production of vectors

Valrox CMC Development Strategy and Progress

|------|------|------|------|------|------|------|

Met several times over the years with FDA and EMA to seek endorsement of:
- Facility design, control and validation
- Analytical strategy used for product characterization, specifications and process controls

- Developed and validated 50 orthogonal analytical methods to support comparability testing
- Started Phase 3 studies with the commercial process de-risking the program significantly
- Produced 34 lots to support non-clinical and clinical requirements and to build launch inventory
- Unchanged throughout development: Capsid, Transgene, Host Cell or Formulation
### Quality & Comparability Considerations

<table>
<thead>
<tr>
<th>Desired Product</th>
<th>Product-Related Impurities</th>
<th>Process-Related Impurities</th>
<th>Contaminants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Sequence &amp; Ratio of Capsid Proteins</td>
<td>N-Term Heterogeneity</td>
<td>Host Cell Proteins</td>
<td>Adventitious Virus</td>
</tr>
<tr>
<td>Transgene Sequence</td>
<td>Aggregated</td>
<td>Host Cell DNA</td>
<td>Mycoplasma</td>
</tr>
<tr>
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<td>Deamidated</td>
<td>Media Components</td>
<td>Bioburden</td>
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<tr>
<td></td>
<td>Oxidized</td>
<td>Resin Extractable</td>
<td>Endotoxin</td>
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<tr>
<td></td>
<td>C-Term Heterogeneity</td>
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<td></td>
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<td></td>
<td>Sequence Variants</td>
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<td>Adducts</td>
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<td></td>
<td>Misfolded</td>
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<tr>
<td></td>
<td>Glycoform Variants</td>
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<tr>
<td></td>
<td>DNA Truncation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Empty Capsids</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Non-Functional Capsids</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ICH Q8:**
Critical quality attributes linked to patient safety & efficacy

**TRANSLATION:**
“Something that needs to be controlled to ensure safety & efficacy”

**Analytical Characterization & Clinical Data Establishes**
- Comparability of clinical and commercial product
- No statistical difference in factor expression between clinical and commercial product
- Health authorities reviewed data prior to starting Phase 3 study
- Data presented at pre BLA/MAA meetings led to agreement to file based on the interim Phase 3 results
Patient Factor Expression Varies When Treated with a Single Valrox Product Lot

The data demonstrates patient factor expression levels vary even when treated with the same lot of product.

Notwithstanding variability in factor expression clinical benefit is durable and consistent.

**TRANSLATION:** It is not the material that results in variable levels of factor expression!
Investments in Manufacturing Facility Enables Efficient Development of Gene Therapy Platform

Leveraged experience facilitates compliant development
• 20 years of biologics manufacturing experience
• Inspection vetted quality systems

Empowered the largest gene therapy program ever conducted
• Facility designed to support 5000 patients/year

Enables rapid development & expansion, risk reduction, & IP protection
• Production of Valrox Phase 3 material utilizing commercial process
• BMN 307 clinical material produced utilizing commercial process
• Leveraging learnings to support IND enabling activities for HAE GT
• Expanding capacity – GMP pilot facility under construction
• 2nd commercial gene therapy facility designed for rapid construction
## Regulatory Documentation Ready to Submit!

### Common Technical Document for the registration of pharmaceuticals for human use
- Module 2 – Quality Overall Summary
- Module 3 – Quality
- Clear rational linking science and compliance
- Prospectively defined PPQ validation criteria met
- Robustness and consistency demonstrated over multiple commercial scale campaigns
- Comprehensive data integrity checks integrated into the review process to assure compliance with cGMP

### Checklist Supporting Registration, Approval & Launch

<table>
<thead>
<tr>
<th>Task</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Build, commission and validate facility</td>
<td>✔️</td>
</tr>
<tr>
<td>Establish stability data to support expiry</td>
<td>✔️</td>
</tr>
<tr>
<td>Develop and validate the process</td>
<td>✔️</td>
</tr>
<tr>
<td>Develop and validate frozen shipping logistics</td>
<td>✔️</td>
</tr>
<tr>
<td>Develop and validate the analytical control system</td>
<td>✔️</td>
</tr>
<tr>
<td>Produce commercial launch material</td>
<td>✔️</td>
</tr>
<tr>
<td>Determine the Critical Process Parameters (CPP)</td>
<td>✔️</td>
</tr>
<tr>
<td>Prepare MAA &amp; BLA (Content Lock &amp; Publication)</td>
<td>✔️</td>
</tr>
<tr>
<td>Determine the Critical Quality Attributes (CQA)</td>
<td>✔️</td>
</tr>
<tr>
<td>Pre-Approval Inspections</td>
<td>To be scheduled</td>
</tr>
<tr>
<td>Conducted Process Performance Qualification (PPQ)</td>
<td>✔️</td>
</tr>
</tbody>
</table>
On the Launching Pad

Ready for:
• Submitting Marketing Applications in the U.S. & EU in Q4 2019
• Inspections in H1 2020
• Launching Soon After Approval

Manufacturing product on an unprecedented scale

Setting industry & health authority standards for CMC requirements

Developing a platform technology that will increase the number, speed and productivity of subsequent gene therapy products
Our Confidence in Valoctocogene Roxaparvovec Continues to Build

Wing Yen Wong, M.D.
Vice President, Clinical Science

November 14, 2019
Experienced Hematologist with Proven Track Record in Drug Development for Hemophilia

Vice President, Clinical Science, BioMarin

Investigational gene therapies

Vice President, Global Medical Sciences, Hematology/Immunology, Biogen

Over 10 years experience in drug development for hemophilia spanning clinical research to global medical affairs to support approved therapeutic agents

Head Clinical Research, Hemophilia/Hematology, Baxter

Global Senior Medical Director, Hemophilia/Hematology, Baxter

Supervising Physician, Hematology/Oncology, Children’s Hospital LA

Attending Physician, Pediatric Hematology/Oncology; LAC+USC Medical Center

M.D. from USC Keck School of Medicine

Board Certified in Pediatric Hematology/Oncology

Hematologist; USC Excellence in Teaching Award

Board Certified Hematologist
Physiologic restoration of hemostasis is the desired outcome with gene therapy

- Valrox Gene therapy (2020)
- Non-factor therapies (emicizumab) (2017)
- EHL clotting factors (2014)
- SHL clotting factors (1990s)
- Plasma-derived clotting factors (1969)

Evolution of Products

1. Based on BMRN Q4’ 2019 filing and potential US FDA approval in 2020
Valrox Program Continues to Drive Confidence as Data Accumulate

Confidence in Our Path to Regulatory Success

- Patient level data supports FVIII levels reasonably likely to reduce bleeding
- Submissions on-track in 4Q19
- EMA Accelerated Assessment reflects unmet need

Phase 3 (301) Study: Confidence in Annualized Bleed Rate Outcomes

- Study data support statistical power to demonstrate the reduction in bleeding
- Enhanced steroid management may improve 52-week ABR
- 130 patients dosed! Data expected 4Q 2020/1Q 2021

Phase 1/2 (201) Study: Confidence in Long-term Efficacy and Durability

- *In vivo* biopsy data demonstrate vector expression years after transfer
- *In vivo* data demonstrate comparable blood cell vector DNA in P2 and P3
- 4-year update with 6e13 vg/kg dose expected mid-2020
Phase 3 Study Interim Results: Substantial Reduction in ABR and FVIII Usage

Dramatic Reductions in ABR and FVIII Usage post-Valrox vs. Baseline on Prophylaxis Standard of Care

6e13 vg/kg Dose Interim Analysis cohort, N=16

<table>
<thead>
<tr>
<th></th>
<th>Pre-infusion</th>
<th>Post-infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABR (Episodes/Year)</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Median</td>
<td>Median</td>
<td>Mean</td>
</tr>
<tr>
<td>Mean</td>
<td>Mean</td>
<td>Mean</td>
</tr>
</tbody>
</table>

85% reduction in mean ABR vs. baseline

Annualized FVIII Usage (Infusions/Year)

<table>
<thead>
<tr>
<th></th>
<th>Pre-infusion</th>
<th>Post-infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>132.7</td>
<td>146.1</td>
</tr>
<tr>
<td>Mean</td>
<td>1.2</td>
<td>6.8</td>
</tr>
</tbody>
</table>

95% reduction in mean FVIII usage after week 5 vs. baseline
Phase 3 Interim Analysis FVIII Activity Levels Met Criteria for Submissions

Phase 3 Initial Cohort Data Supports Marketing Authorization Applications in Both the US and EU

- Pre-specified primary endpoint for US registration was the proportion of patients whose FVIII levels were ≥ 40 IU/dL
- 8* of 17 subjects who had reached 26 weeks, had median factor VIII levels ≥ 40 IU/dL during weeks 23-26

* 8th subject achieved pre-specified FVIII level > 40 IU/dL during weeks 23-26, shortly after April 30 data cut

Results through 26 week results with Chromogenic Assay
Phase 3 Results: Hemostasis Achieved Despite Eliminating Prophylactic FVIII Infusions

### FVIII Infusions

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>High</th>
<th>Post-Valrox</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>116.7</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>49.3</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>213.2</td>
<td>1.2</td>
</tr>
<tr>
<td>4</td>
<td>154.7</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>90.4</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>87.7</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>328.6</td>
<td>3.5</td>
</tr>
<tr>
<td>8</td>
<td>147.1</td>
<td>1.2</td>
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<tr>
<td>9</td>
<td>97.1</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>82.7</td>
<td>0.4</td>
</tr>
<tr>
<td>11</td>
<td>180.7</td>
<td>1.2</td>
</tr>
<tr>
<td>12</td>
<td>188.1</td>
<td>0.9</td>
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<tr>
<td>13</td>
<td>105.7</td>
<td>13.5</td>
</tr>
<tr>
<td>14</td>
<td>93.2</td>
<td>2.5</td>
</tr>
<tr>
<td>15</td>
<td>145.7</td>
<td>43</td>
</tr>
</tbody>
</table>

### Treated Bleeds

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>High</th>
<th>Post-Valrox</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
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<tr>
<td>15</td>
<td>0.9</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- FVIII Expression Level
  - High
  - Low
- FVIII Infusions
  - Baseline (left) vs. Week 5 and beyond (right)
- Treated Bleeds
  - Baseline (left) vs. Week 5 and beyond (right)
Phase 3 Results: Hemostasis Achieved Despite Eliminating Prophylactic FVIII Infusions

### FVIII Infusions

<table>
<thead>
<tr>
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</tr>
<tr>
<td>16</td>
<td>145.7</td>
<td>43</td>
</tr>
</tbody>
</table>

### Hemophilic Range Severity

#### Chromogenic

- Subject ID 1
- Subject ID 2
- Subject ID 3
- Subject ID 4
- Subject ID 5
- Subject ID 6
- Subject ID 7
- Subject ID 8
- Subject ID 9
- Subject ID 10
- Subject ID 11
- Subject ID 12
- Subject ID 13
- Subject ID 14
- Subject ID 15
- Subject ID 16

#### One-Stage

- Subject ID 1
- Subject ID 2
- Subject ID 3
- Subject ID 4
- Subject ID 5
- Subject ID 6
- Subject ID 7
- Subject ID 8
- Subject ID 9
- Subject ID 10
- Subject ID 11
- Subject ID 12
- Subject ID 13
- Subject ID 14
- Subject ID 15
- Subject ID 16

### Treated Bleeds

- Subject ID 1
- Subject ID 2
- Subject ID 3
- Subject ID 4
- Subject ID 5
- Subject ID 6
- Subject ID 7
- Subject ID 8
- Subject ID 9
- Subject ID 10
- Subject ID 11
- Subject ID 12
- Subject ID 13
- Subject ID 14
- Subject ID 15
- Subject ID 16

(23–26 Weeks)
# Phase 3 Study: Powered to Demonstrate Superiority in ABR

<table>
<thead>
<tr>
<th>Assumptions Before the 301 Study Start</th>
<th>Mean ABR at Baseline</th>
<th>Mean ABR Post Valrox Treatment</th>
<th>Statistical Power to Demonstrate Superiority in ABR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.5</td>
<td>1.0</td>
<td>90%</td>
</tr>
<tr>
<td>Assumptions Based on Available Data</td>
<td>6.5</td>
<td>1.5</td>
<td>&gt;95%</td>
</tr>
</tbody>
</table>

*Baseline ABR derived from preliminary results of 270-902 run-in study; post-valrox treatment ABR derived from interim analysis of Phase 3 study*
Closer monitoring of ALT Resulting in Decreased Time from Dosing to Corticosteroid Initiation:

<table>
<thead>
<tr>
<th>Time from Dosing to Corticosteroid Initiation</th>
<th>Mean/Median (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1/2</td>
<td>3.0/3.1</td>
</tr>
<tr>
<td>Phase 3 Before May 30, 2019</td>
<td>10.9/10.0</td>
</tr>
<tr>
<td>Phase 3 after May 30, 2019 – Present*</td>
<td>5.0/5.7</td>
</tr>
</tbody>
</table>

*As of October 25, 2019
Phase 1/2: 6e13 vg/kg and 4e vg/kg Demonstrates Durable Factor VIII Expression

6e13 vg/kg Three Year Results with Chromogenic Assay

4e13 vg/kg Two Year Results with Chromogenic Assay
Phase 1/2: Substantial Reduction in Treated ABR and FVIII Use Through Year Three

6e13 vg/kg Dose Cohort at Years 1, 2 & 3; N=6*

<table>
<thead>
<tr>
<th>ABR (Episodes/Year)</th>
<th>Median</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-infusion</td>
<td>16.5</td>
<td>16.3</td>
</tr>
<tr>
<td>Y1 Post</td>
<td>0.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Y2 Post</td>
<td>0.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Y3 Post</td>
<td>0.0</td>
<td>0.7</td>
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</tbody>
</table>

96% Reduction in Mean ABR

6e13 vg/kg Dose Cohort FVIII Usage in Years 1, 2 & 3; N=6*

<table>
<thead>
<tr>
<th>Annualized FVIII Usage (Infusions/Year)</th>
<th>Median</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-infusion</td>
<td>138.5</td>
<td>136.7</td>
</tr>
<tr>
<td>Y1 Post</td>
<td>0.0</td>
<td>2.1</td>
</tr>
<tr>
<td>Y2 Post</td>
<td>0.0</td>
<td>8.8</td>
</tr>
<tr>
<td>Y3 Post</td>
<td>0.0</td>
<td>5.5</td>
</tr>
</tbody>
</table>

96% Reduction in Mean FVIII Usage

% Patients Bleed Free**

<table>
<thead>
<tr>
<th>Year</th>
<th>Baseline</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>14%</td>
<td>71%</td>
<td>86%</td>
<td>86%</td>
</tr>
</tbody>
</table>

Reduction in FVIII Usage Post Valrox 6e13 Dose

<table>
<thead>
<tr>
<th>Year</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>98%</td>
<td>94%</td>
<td>96%</td>
</tr>
<tr>
<td>Median</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

* The one subject treated with on demand rFVIII pre-infusion was excluded
** N=7 and includes the one subject treated with on demand rFVIII pre-infusion
Phase 3 Expected to Confirm Long-term Efficacy and Durability Seen in Phase 1/2

LOESS Curves of Chromogenic FVIII Activity Over Time; Analysis Population: Phase 2 (201) Study and Phase 3 (301) Study mITT
Persistence of Stable, Circularized DNA Supports Long-Term Expression

*PBMCs Model the Fate of Transgene DNA in Long-Lived Cells*

- PBMCs represent a relatively long-lived, nucleated cell that is easily accessible.
- As a proxy for hepatocytes, whole blood and PBMC fractions were analyzed:
  - Linear forms of FVIII DNA associated with RBCs predominate for 4-6 months.
  - ITR-fused (presumed circular) FVIII DNA persists in longer-lived PBMCs.
- Formation of durable, circularized vectors promotes FVIII expression for durations governed by host cell turnover rates.
Liver Biopsies: Dose-dependent Valrox DNA, Detected at >2.5 Years

High FVIII Expressors Have Detectable Vector and Low FVIII Expressors Have Very Few Detectable Vectors

1.3% of Hepatocytes had detectable vector DNA (201 weeks after dosing)

Subject A: 6e12 vg/kg

BMN 270 Vector DNA

FVIII activity undetectable at year 2

32% of Hepatocytes had detectable vector DNA (140 weeks after dosing)

Subject B: 4e13 vg/kg

FVIII activity (OS) 30% at year 2!
Similar Vector DNA Levels Detected in PBMCs in Phase 3 and Phase 2

Peripheral Blood Mononuclear Cells (PBMCs) Measured Below in Both Phase 3 and Phase 2 Studies by Weeks After Infusion
Confidence in Near-term Steps Toward Potential Approvals

Path to Regulatory Success

• Robust evidence of effectiveness across patients; criteria for expedited assessment met
• FVIII expression reasonably likely to predict favorable bleeding outcomes
• On track to submit applications in US and EU; EMA granted Accelerated Assessment in October
• Assuming expedited timelines, potential launch expected in less than a year

Phase 3 (301) Study

• Study adequately powered for ABR to demonstrate superiority over Standard of Care
• Steroid management improved
• 130 patients dosed!

Phase 2 (201) Study

• Durability demonstrated out to 3 years with 6e13 vg/kg dose and 2 years with 4e13 vg/kg dose
• 4 year 6e13 vg/kg dose, 3 year 4e13 vg/kg dose update expected mid-year 2020
• Liver biopsy confirms diffuse and otherwise healthy liver transduction at 2.5 years
• PBMC data support comparability of Phase 2 and Phase 3 product
THANK YOU
Q&A
Key Drivers of the Next Stage of Significant Growth

Dan Spiegelman
Executive Vice President and Chief Financial Officer

Jean-Jacques Bienaimé
Chairman and Chief Executive Officer
Continually Improving our Financial Performance

*GAAP loss in 2016 was ($630.1M) due to a one-time write-off of Prosensa
Leveraging our Deep Foundation in Ultra-rare Product Development and Commercialization to Expand into Larger Genetic Conditions

Our legacy business has contributed over $10 billion in cumulative revenue to date; valrox and vosoritide each represent $1 billion + opportunities

Enzyme Replacement Therapies have contributed $7.6 billion cumulative revenue to date

PKU franchise has contributed $2.7 billion cumulative revenue to date

Transformative therapies in new disease states with high unmet need in multiple $B markets
Patients in the U.S. Being Treated or Awaiting Treatment with Palynziq as of 3Q19

- 3Q18: 235 Palynziq Treated Patients, 111 Not yet dosed or reimbursed
- 4Q18: 409 Palynziq Treated Patients, 157 Not yet dosed or reimbursed
- 1Q19: 554 Palynziq Treated Patients, 140 Not yet dosed or reimbursed
- 2Q19: 709 Palynziq Treated Patients, 158 Not yet dosed or reimbursed
- 3Q19: 823 Palynziq Treated Patients, 153 Not yet dosed or reimbursed

U.S. and EUMEA Addressable Adult PKU Patients*

- Total: ~30,000
- On Kuvan: ~1,900
- On Palynziq: ~8,000
- In Clinic: ~19,200
- Out-of-Clinic: ~670

Significant growth opportunity for Palynziq: ~800/30,000 people treated to date

Palynziq and Kuvan are the only approved products to treat PKU

*Patients addressable for Palynziq include people with PKU ≥ 16 y/o in EUMEA and ≥ 18 y/o in U.S. PKU patients defined as patients diagnosed through newborn screening. Out-of-clinic patients are those who have been diagnosed, but have not returned to clinic in at least 2 years.
Updates Shared Today set us up for Significant Growth and Profitability

**Vosoritide: Achondroplasia**
- **9.0cm** of additional height gained compared to Natural History age/gender matched controls at 54-months
- 2.1cm height gain in the last 12 months
- Phase 3 data by YE, MAA/BLA 2020; Phase 2 (0-5 year olds) enrolling well and has consistent safety profile

**Valrox: Hemophilia A**
- In vivo biopsies show that FVIII expressors have detectable vector in the liver years after gene transfer
- Time from dose to steroid start dramatically reduced as a result of closer monitoring
- Submissions to both U.S. and EU health authorities imminent, potential approvals 2020

**Commercial/Financial**
- With valrox launch in 2H20, our 2020 guidance will be **GAAP Net Income break-even or better**
- Executed transition to larger genetic conditions
- Manufacturing capabilities and commercial breadth to support new products and platforms

**R&D Engine**
- Building on our gene therapy capabilities with new INDs: BMN 307 for PKU and BMN 331 for HAE
- Harnessing genetics to expand indications in existing programs, vosoritide for DISS
- Unlocking opportunities with NextGen AAVs to drive further **program innovation and efficiencies**
THANK YOU