WELCOME

BIOMARIN R&D DAY 2018

Hank Fuchs, M.D.
President, Worldwide Research & Development
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.
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<thead>
<tr>
<th>Time</th>
<th>Session Title</th>
<th>Presenter</th>
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<tr>
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<td>Hank Fuchs, M.D., President, Worldwide Research &amp; Development</td>
</tr>
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<td>8:40am – 8:55am</td>
<td>Vosoritide Program and 42-month Update</td>
<td>Jonathan Day, MBBS, PhD, Executive Medical Director, Clinical Science</td>
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<td>8:55am – 9:10am</td>
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<td>Ron Rosenfeld, M.D., Professor and Chair (emeritus) of Pediatrics, Oregon Health &amp; Science University</td>
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<td>Adora Ndu, Pharm.D., J.D., Executive Director and Head of Global Regulatory Policy, Research, and Engagement</td>
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<td>Lunch in Foyer</td>
<td>All</td>
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</table>
## Quick Hits on Programs not Covered Today

### Palynziq
- US launch progress in first quarter since approval
- Update on EU review status
- Extension data

### Tralasinidase alfa (formerly BMN 250) for MPS IIIB
- Re-cap of recent data at SSIEM
- Timelines and next milestones in the program

### Brineura
- Efficacy and safety data out to 5 years continues to persist
- How to think about potential long term treatment
- Update on progress finding children early in the course of CLN2
Palynziq 3Q18 Key Metrics Reflect Strong U.S. Launch

250-300 reimbursed, commercial Palynziq patients expected by year-end

**Commercial Palynziq Patients**
- **Total**: 124
  - Clinical Trial: 81
  - Non-Clinical: 43

**Clinics with 1+ active Palynziq patients**
- 3Q18 Palynziq revenue in millions: $4.1

**Clinics with at least one health care provider REMS certified**
- FY Palynziq Guidance in millions: $10-$14

**Complete Enrollments (non-clinical patients)**
- Total: 111
  - On Therapy in Q3: 43

Data through September 28, 2018
New Data: 36 Month Durability with Palynziq

< 600 μmol/L - EU PKU guideline recommendation
< 360 μmol/L - US guideline recommendation
< 120 μmol/L - physiologically normal

Proportion of Subjects Reaching Blood Phe Threshold over Time
(doses up to 60mg/day) (n=285)

<table>
<thead>
<tr>
<th>Time</th>
<th>≤600 μmol/L</th>
<th>≤360 μmol/L</th>
<th>≤120 μmol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>42%</td>
<td>29%</td>
<td>22%</td>
</tr>
<tr>
<td>12 months</td>
<td>57%</td>
<td>46%</td>
<td>35%</td>
</tr>
<tr>
<td>24 months</td>
<td>71%</td>
<td>63%</td>
<td>54%</td>
</tr>
<tr>
<td>36 months</td>
<td>74%</td>
<td>67%</td>
<td>59%</td>
</tr>
</tbody>
</table>

Subjects reflect general adult PKU population with mean baseline blood Phe 1233μmol/L
Tralesinidase Alfa Treatment Normalizes CSF HS Levels

**Dose Escalation subjects**

- 30 mg QW
- 100 mg QW
- 300 mg QW

**300 mg QW subjects**

- 300 mg QW

- Rapid (1-2 doses) and sustained normalization of CSF HS at 300mg dose
- Demonstrates *in vivo* biochemical activity of tralesinidase alfa

gray bar: median [range: unquantifiable, max] of non-affected

As presented at SSIEM September 6, 2018
MRI Liver Volume Normalizes with Tralesinidase Alfa Treatment

- Patients treated at least 24 weeks
- Liver size normalizes in 9/9 treated patients
- Demonstrates systemic clinical effects of ICV administration

As presented at SSIEM September 6, 2018

Control data: Murry et al (1995), Drug Metab Disp 23(10), pp. 1110-1116
Stabilization with Brineura for CLN2 Sustained for > 3+ years

N=23 at 3 years

Brineura Treated

Natural History
<table>
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THANK YOU
42-Month Data Update with Vosoritide for Achondroplasia

BIOMARIN R&D DAY 2018

Jonathan Day, MBBS, PhD
Executive Medical Director, Clinical Science
Four Pillars Underpin Vosoritide Program

1. Randomised Placebo Controlled Trial
   • 111-301 (5–18 years) pivotal for initial registration
   • “Last Patient Enrolled Today”!

2. Evidence of Sustained Efficacy
   • Biology
   • New Biomarker Data
   • New 42M Phase II Clinical Data

3. Safety Including in Infants and Toddlers
   • 111-206 (0–5 years) for label supplement

4. Natural History Data
Comprehensive Vosoritide Achondroplasia Clinical Program

1. Study 901
   - Baseline Observational Growth Study
   - Age: 0 months to <17 years
   - No study drug
   - N = approx. 350
   - Duration: ≥6 months

2. Study 202 Phase 2
   - Age: 5 to 14 years
   - Open-label
   - N = 35
   - Duration: 24 months

3. Study 301 Phase 3
   - Age: 5 to <18 years
   - Double-blind, randomized, placebo-controlled
   - N = approximately 110
   - Duration: 52 weeks

4. Study 206 Phase 2
   - Age: 0 to <5 years
   - Double-blind, randomized, placebo-controlled
   - N ≥ 70
   - Duration: 52 weeks

5. Study 205 Extension
   - Open-label
   - N = 30
   - Duration: Final Adult Height

6. Study 302 Extension
   - Open-label
   - N = approximately 110
   - Duration: Final Adult Height

7. Study 208 Extension
   - Open-label
   - N = approximately 70
   - Duration: ≤ 4 years

Natural History Data with Final Adult Height
1. Pivotal Phase 3 For Initial Registration

- Now Fully enrolled and all subjects dosed (7th November 2018)
- Top Line Results planned end of 2019
- Primary Endpoint: Change from baseline in AGV at 52 weeks

**Study 901**

- ≥6 months
- No drug administration

**Study 301**

- 52 weeks
- Age: 5 to <18
- Double-blind; 1:1
- N = approximately 110

**Study 302**

- Final Adult Height
- N = approximately 110

**Baseline Observational Growth Study**

- ≥6 months growth data required to enter Study 301

**BMN 111 15 µg/kg**

**Extension Study**

- Open-Label BMN 111
2. Biology Supports Durable Mechanism of Action

Durable effects of *FGFR3* and CNP on skeletal growth

1. Shorter skeletal phenotype in ACH mouse
2. Larger skeletal phenotype in CNP over expressing (NPPC) mouse
3. Normalised skeletal phenotype in crossed NPPC + *Fgfr3* mice

1. *Fgfr3*<sup>ACH</sup> Mouse
2. CNP Mouse
3. CNP reverses *Fgfr3* Mouse

2. Sustained Skeletal Growth Observed in Humans

Human de-novo mutation NPCC gene

- Results in CNP overexpression
- Widespread skeletal overgrowth
- Abnormally tall stature
- Sustained throughout all years of skeletal growth

Activity of the NPR-B/CNP signaling pathway

- Increased signaling activity results in tall stature
- Decreased signaling activity results in short stature
  - Acromesomelic dysplasia Maroteaux type
  - Idiopathic Short Stature

Bocciardi, 2007; Hisado-Oliva, 2018; Moncla, 2007; Tassano, 2013; Ko, 2015; Boudin 2018
2. Targeted Therapy Addressing the Biology

Biology Identifies Biomarkers to Confirm Durable Treatment Effect

---

.Docking Point 1

Collagen X

---

Docking Point 2

Biomarker of Endochondral Bone Formation

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Vosoritide (rhCNP)
2. New Biomarker Collagen Type X

Highly Specific Biomarker of Endochondral Bone Growth

Growth Plate

Collagen Type X biomarker from growth plate chondrocytes is released during long bone growth.

Increased biomarker levels reflect bone growth induced by vosoritide treatment.
2. Collagen Type X Expression Reduced in ACH M

Reduced Hypertrophic Region of Growth Plate and Reduced Collagen X Expression in ACH

- Collagen X shown in growth plate of 3-week-old Ach and WT mice.
- Collagen X protein expression is indicated in by the brown staining in the hypertrophic region of the growth plate (brackets).
2. Sustained Biomarker Response Through 24 Months

Sustained Increase in Serum Collagen X
24 Months

Cohort 3, 15 µg/kg, Mean change from Baseline (SEM)
Primary Objective: Safety and tolerability of daily subcutaneous injections of vosoritide

Study 901
- Baseline Observational Growth Study
  - 6 months growth data required to enter Study 202

Study 202
- Cohort 1 (BMN 111 2.5 µg/kg); n=8
- Cohort 2 (BMN 111 7.5 µg/kg); n=8
- Cohort 3 (BMN 111 15 µg/kg); n=10
- Cohort 4 (BMN 111 30 µg/kg); n=9

Study 205
- Extension Study (n=30)
  - Dose Titration (BMN 111 15 µg/kg); n=12
  - Cohort 3 (BMN 111 15 µg/kg); n=10
  - Cohort 4 (BMN 111 30 µg/kg); n=8

Subjects:
- Subject in C1 voluntarily withdrew after 6/12, Subject in C1 voluntarily withdrew due to anxiety and fear of needles.
- One subject in C2 discontinued study treatment but completed the 24 month study period.
- Subject in C2 discontinued treatment after growth plate closure.
- Subject in C4 withdrew due to Wolf Parkinson White.
2. Durable Growth Sustained through 42 months Cohort 3 at 15 µg/kg

Sustained elevation of AGV shown in sequential 6M time periods

42 Month Additional Height Gained is 5.7 cm
2. Increased Growth Velocity in Cohort 1 and 2 Switchers Through 42 Months

Elevation of AGV after switching shown in sequential 6M time periods

- Cohort 1 and 2 (Baseline and first 6 Months on 2.5 and 7.5 µg/kg) n = 12
- Cohort 1 and 2 (Switching to 15 µg/kg) n = 12
- Cohort 1 and 2 (Switched to 15 µg/kg) n = 12
3. No Correlation of Cardiovascular Effects with Vosoritide Exposure

- Generally well-tolerated across all doses

- BP and HR monitored frequently and all observed blood pressure reductions reported as non-serious, transient (i.e. minutes), and resolved without medical intervention
  - None resulted in study drug interruption or discontinuation

- Over 28,000 injections administered and only one event of symptomatic hypotension
  - Resolved spontaneously within minutes without medical intervention
3. Randomized Placebo Controlled Study in Infants/Toddlers (Study 206)

- Study now enrolling Cohort 1
- Primary Endpoint: Assess the safety and tolerability of daily SC BMN 111 administered to infants and young children with ACH, and evaluate the effect of BMN 111 on height Z-scores
- Safety data only available at time of NDA
4. Large Contemporaneous Natural History Multi-Center Clinical Study

• Multi-center, retrospective, prospective and cross-sectional natural history study, n=1377

• In Collaboration with large US specialist Skeletal Dysplasia Centres
  • Johns Hopkins University
  • AI Dupont Hospital
  • University of Texas
  • University of Wisconsin-Madison

• Comparisons between on treatment final adult height and NH data to support assessment of efficacy over 1 year

• Confirmation of long-term growth effects though ongoing evaluation of 202/205 and Natural History Data
Summary: Sustained Growth Effects of Vosoritide Through 42 Months, Multi-pronged Global Program Progressing Rapidly

Comprehensive global program progressing rapidly
• Well-controlled Pivotal trial
  • 301 fully enrolled and 206 enrolling
• Sustained effect on AGV at 42M
  • Supported by biology and new biomarker – Collagen Type X
• Generally well tolerated
  • Limited symptomatic cardiovascular effects – 1/28,000
• Large contemporaneous Natural History Data
  • Final Adult Height Data

NEXT STEPS: With global study enrolled, Phase 3 data planned end of 2019
THANK YOU
Drug Development Considerations in Achondroplasia

Biomarin R&D Day 2018

Ron Rosenfeld, M.D.
Professor and Chair (emeritus) of Pediatrics, Oregon Health & Science University and Former Sr. VP and Medical Director Lucile Packard Foundation for Children’s Health
Drug Development Considerations in Achondroplasia

Ron Rosenfeld, MD

Professor and Chair of Pediatrics (Emeritus)
Oregon Health and Science University

and

Former Sr. VP and Medical Director
Lucile Packard Foundation for Children’s Health
My Background

- Stanford University: Pediatric endocrinology fellowship 1977-80
- Stanford University: Tenured Professor 1980-1993
- Oregon Health & Science University: Chairman of Pediatrics and Physician-in-Chief of Doernbecher Children’s Hospital 1993-2002
- Senior Vice-President and Medical Director, Lucile Packard Foundation for Children’s Health, Stanford University 2002-2008
- President, STAT5, LLC: Providing consulting service in diagnosis and management of growth disorders
- Published over 600 papers in the field of growth research
Why I Am Enthusiastic About Potential For Vosoritide Rx of Achondroplasia

- Data from “natural experiments” of NPR2 and CNP defects in short stature
- Data from “natural experiments” of overexpression of NPR2 and CNP resulting in tall stature
- Experimental treatment in animal models of ACH
- Failure of alternative therapies in ACH
- Phase 2 data demonstrating sustained normalization of growth velocity in ACH
- Phase 2 growth data corroborated by parallel changes in key biomarkers related to CNP action and skeletal growth
- Therapy directed at underlying pathophysiology
- Durability of treatment effect
- Opportunity for meaningful improvement in height
The Local CNP/GC-B system in growth plate is responsible for physiological endochondral bone growth

Kazumasa Nakao¹, Kenji Osawa¹, Akihiro Yasoda², Shigeki Yamanaka³, Toshihito Fujii²,
Eri Kondo², Noriaki Koyama³, Naotetsu Kanamoto³, Masako Miura³, Koichiro Kuwahara³,
Haruhiko Akiyama³, Kazuhisa Bessho¹ & Kazuwa Nakao⁵

Recent studies revealed C-type natriuretic peptide (CNP) and its receptor, guanylyl cyclase-B (GC-
B) are potent stimulators of endochondral bone growth. As they exist ubiquitously in body, we
investigated the physiological role of the local CNP/GC-B in the growth plate on bone growth
using cartilage-specific knockout mice. Bones were severely shorter in cartilage-specific CNP or
GC-B knockout mice and the extent was almost the same as that in respective systemic knockout
mice. Cartilage-specific GC-B knockout mice were shorter than cartilage-specific CNP knockout
mice. Hypertrophic chondrocyte layer of the growth plate was drastically reduced and proliferative
chondrocyte layer, along with the proliferation of chondrocytes there, was moderately reduced in
either cartilage-specific knockout mice. The survival rate of cartilage-specific CNP knockout mice
was comparable to that of systemic CNP knockout mice. The local CNP/GC-B system in growth plate
Mutations in C-natriuretic peptide (NPPC): a novel cause of autosomal dominant short stature

Alfonso Hisado-Oliva, PhD$^{1,2,3}$, Alba Ruzafa-Martín, MSc$^1$, Lucia Sentchordi, MD, MSc$^{1,3,4}$, Mariana F.A. Funari, MSc$^5$, Carolina Bezanilla-López, MD$^6$, Marta Alonso-Bernáldez, MSc$^1$, Jimena Barraza-García, MD, MSc$^{1,2,3}$, Maria Rodríguez-Zabala, MSc$^1$, Antonio M. Lerario, MD, PhD$^{7,8}$, Sara Benito-Sanz, PhD$^{1,2,3}$, Miriam Aza-Carmona, PhD$^{1,2,3}$, Angel Campos-Barros, PhD$^{1,2}$, Alexander A.L. Jorge, MD, PhD$^{5,7}$ and Karen E. Heath, PhD$^{1,2,3}$
Experiments of Nature Confirm Role of CNP in Human Growth

Research Article

Overexpression of the C-type natriuretic peptide (CNP) is associated with overgrowth and bone anomalies in an individual with balanced t(2;7) translocation*

Renata Bocciardi, Roberto Giorda, Jens Buttgereit, Stefania Gimelli, Maria Teresa Divizia, Silvana Beri, Silvio Garofalo, Sara Tavella, Margherita Lerone, Orsetta Zuffardi, Michael Bader, ... See all authors

First published: 20 March 2007 | https://doi.org/10.1002/humu.20511 | Cited by: 49
Experiments of Nature Confirm Role of CNP in Human Growth

Research Article

Skeletal overgrowth syndrome caused by overexpression of C-type natriuretic peptide in a girl with balanced chromosomal translocation, t(1;2)(q41;q37.1)

Jung Min Ko, Jun-Seok Bae, Jin Sun Choi, Kohji Miura, Hye Ran Lee, Ok-Hwa Kim, Nayoung KD Kim, Sun Kyung Oh, Keiichi Ozono, Choon-Ki Lee, In Ho Choi, Woong-Yang Park, Tae-Joon Cho

First published: 27 February 2015 | https://doi.org/10.1002/ajmg.a.36884
Growth Characteristics in Achondroplasia

Achondroplasia

Average stature


4 cm/yr

6 cm/yr

Failure of Prior Therapies in ACH

- Growth hormone (GH) has been shown to only modestly improve height
  - Only over the short term (12-24 months)
    - No further improvement over a 5-year period
    - Consistent with tachyphylactic pattern seen in studies with hGH
  - Concern over aggravation of body disproportion
  - GH treatment of ACH not approved in the United States or in Europe
  - GH therapy does not address the underlying pathology
- Limb lengthening
  - Controversial with prolonged painful surgery
  - Not used frequently in the United States
Rationale for AGV Endpoint Selection in ACH

• **Objective, non-invasive, practical and reproducible**
  - Change in long bone growth over any timepoint during the active skeletal growth period facilitates measurability of outcome
  - Endpoints based on comorbidities limited by natural history, frequency and practicality

• **Sustained increases in AGV have led to increased adult height in other conditions where there has been no advancement in skeletal maturation**
  - Supported by human mutations, preclinical results, and bone age data

• **Measure of skeletal-wide endochondral bone growth throughout childhood**
  - Endochondral bones: all long bones, spine, base of skull
  - May impact morbidity later, including adulthood

• **Height and functionality are interrelated and impacted by:**
  - Childhood growth
  - Clinical and biological data supporting durability of effect
Regulatory Precedent for Annualized Growth Velocity (AGV) Endpoint

- GH initially approved for GHD using AGV
- Turner Syndrome and Idiopathic Short Stature
  - GH therapy only directed at short stature, rather than underlying pathology
- Prader Willi and Noonan Syndromes and SGA
  - GH therapy only directed at short stature, rather than underlying pathology
  - Approval based largely on AGV, rather than adult height
- IGF-1 for severe primary IGF Deficiency
  - AGV rather than adult height
- High drop-out rate of long-term placebo or observational controls
## Magnitude of Height Deficits in Various Short Statural Conditions

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<thead>
<tr>
<th>DIAGNOSIS</th>
<th>HEIGHT SD (Z-score)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH DEFICIENCY</td>
<td>-2.7</td>
</tr>
<tr>
<td>IDIOPATHIC SHORT STATURE</td>
<td>-2.6</td>
</tr>
<tr>
<td>TURNER SYNDROME</td>
<td>-2.8</td>
</tr>
<tr>
<td>SMALL FOR GESTATIONAL AGE</td>
<td>-2.5</td>
</tr>
<tr>
<td>NOONAN SYNDROME</td>
<td>-2.3</td>
</tr>
<tr>
<td>ACHONDROPLASIA</td>
<td>-6.0</td>
</tr>
</tbody>
</table>

*FDA APPROVED*
Importance of Durability of Effect

- A realistic goal is to allow children with ACH to grow at the same rate as average-statured children.
- During the childhood years, this requires an increase of ~2 cm/year.
- Durability of effect could result in an increase of 20 cm in adult height.
- GH treatment of conditions such as Turner syndrome, Noonan syndrome, SGA has been shown to result in a 7-10 cm increase in adult height, and has justified approval by the FDA.
- Durability can be demonstrated by either:
  - Long-term placebo control trial to adult height (not realistic)
  - Short-term placebo control trial + comparison with natural history
AGV Supported by Highly Relevant Biochemical Data Supporting Durability of Effect

• cGMP: marker of pharmacological activity of Vosoritide
• Bone Collagen: Collagen X is a marker of skeletal growth
• These biochemical data support the durability of CNP as seen in:
  - Naturally occurring mutations of the CNP-NPR2 pathway
  - Phase 2 clinical results of CNP Rx
Rationale for Study Duration and Follow-up in Pivotal Trial in ACH

- 52-week placebo-controlled trials
  - Adequately powered to capture $\Delta$AGV in placebo control setting
  - Logistical limitations of daily injections in longer placebo control trials in children
- Open-label extension on treatment
  - Capture medium and long-term changes in skeletal development
  - Evaluate trends on comorbidities
  - Establish long-term safety
  - Provides prospect of direct benefit to all enrolled subjects
- Post-approval registry
  - Follow patients off-treatment through adulthood
Conclusions: BMRN’s Comprehensive Development Program Achieves these Objectives

• Targeted therapy directed at underlying defect of ACH
  • CNP demonstrates sustained, non-tachyphylactic pattern of consistently increased growth through time

• Clinically meaningful and sustained efficacy seen in 202 | 205
  • Supportive of continued development at 15 µg/kg dose
  • No evidence of adverse impact on proportionality or skeletal maturation

• Clear rationale for selection of AGV over 1 year as primary endpoint
  • Regulatory precedent with growth hormone and IGF-I

• Durability of effect and morbidity will be evaluated
  • Open-label extension studies
  • Modelling with natural history data
THANK YOU

Q&A
Valoctocogene Roxaparvovec Regulatory Path Considerations

Biomarin R&D Day 2018

Geoff Nichol, M.B., Ch.B., M.B.A.
Senior Vice President, Chief Medical Officer and Head of Global Clinical Development
INITIAL VALROX GOAL:
“The prospectively specified primary efficacy goal was a factor VIII activity level of at least 5 IU per deciliter at week 16 after gene transfer.”

FVIII ACTIVITY RESULT:
“After week 20, the factor VIII activity level was consistently more than 50 IU per deciliter in six of seven participants....”

ABR RESULT:
“...the median annualized bleeding rate dropped from 16 events per year before the study to 1 event per year after gene transfer...”

FVIII USE RESULT:
“The median consumption of factor VIII decreased from 5286 to 65 IU per kg/yr.”

104 WEEK UPDATE AT WFH CONFIRMED DURABILITY OF THESE EFFECTS
Steps Forward based on Recent Interactions and Guidelines

1. Key Considerations for Expedited Registration

2. Key Considerations for Full Approval

3. Next Steps toward Approval
Human Gene Therapy for Hemophilia

Draft Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
July 2018
Key Guideline Excerpts Relevant to Valrox Regulatory Filings

IV. CONSIDERATIONS FOR FACTOR VIII/FACTOR IX ACTIVITY MEASUREMENTS ASSESSED BY DIFFERENT CLINICAL LABORATORY ASSAYS
   • Methodology (OC vs. CS)

VI. CONSIDERATIONS FOR CLINICAL TRIALS
   A. Efficacy Endpoints
      1. Traditional Approval
         • Annualized Bleeding Rate (ABR) as a primary endpoint to demonstrate clinical benefit.
      2. Accelerated Approval
         • Factor activity may be considered as a surrogate endpoint for primary efficacy assessment under the accelerated approval pathway.9 (Ref. 12)
           o Resolve discrepancies in factor assay results from various assay methods prior to considering a target factor activity as a surrogate endpoint for primary efficacy assessment.
           o Determine a target factor activity level within the range of factor activity of normal population.

## Key Considerations for Expedited Valrox Registration

<table>
<thead>
<tr>
<th>Key filing elements</th>
<th>Accelerated Approval</th>
</tr>
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<tbody>
<tr>
<td>Choice of Factor VIII Assay</td>
<td>Chromogenic acceptable</td>
</tr>
<tr>
<td>FVIII in normal range</td>
<td>Only stat needed at time of registration</td>
</tr>
<tr>
<td>ABR</td>
<td>FVIII levels predict reduction</td>
</tr>
<tr>
<td>Longer-term data</td>
<td>3.5 years at time of filing</td>
</tr>
<tr>
<td>Comprehensive CMC Package</td>
<td>Must use to-be-commercialized materials in trials</td>
</tr>
</tbody>
</table>
One Stage/Chromogenic Assay Results Differ but are Consistent and Highly Correlated

R-square: 0.951
Slope: 1.651
Specific Activity of ValRox (IU activity/mg protein)

One Stage Assay

Chromogenic Assay

Preliminary data
Specific Activity of ValRox (IU activity/mg protein) Comparable With rBDD FVIII Using CS assay

One Stage Assay

Chromogenic Assay

rBDD Factor VIII Specification Range

Preliminary data
Specific Activity of ValRox (IU activity/mg protein)
Comparable With rBDD FVIII Using CS assay

Preliminary data

One Stage Assay

Chromogenic Assay

rBDD Factor VIII Specification Range

rBDD Factor VIII Specification Range
## Key Considerations for Expedited Valrox Registration

<table>
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<tr>
<th>Key filing elements</th>
<th>Accelerated Approval</th>
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<tr>
<td>Choice of FVIII Assay</td>
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</tr>
</tbody>
</table>
**FVIII Activity Levels in Normal Range with Chromogenic**

*Valrox Phase 1/2 data conforms to regulatory requirements for expedited registration*

Valrox 6e13 vg/kg dose results out to 52 weeks

The upper and lower box bounds represent 25th and 75th percentiles. The whisker lines represent the minimum and maximum values.

Expedited Registration:
Anticipated FVIII activity levels required

The upper and lower box bounds represent 25th and 75th percentiles. The whisker lines represent the minimum and maximum values.
# Key Considerations for Expedited Valrox Registration

<table>
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<td>Choice of FVIII Assay</td>
<td>Chromogenic acceptable</td>
</tr>
<tr>
<td>FVIII in normal range</td>
<td>Only stat needed at time of registration (as demonstrated in Phase 1/2)</td>
</tr>
<tr>
<td>ABR (within 52 weeks)</td>
<td>FVIII levels predict reduction (as demonstrated with Chromogenic in Phase 1/2)</td>
</tr>
<tr>
<td>Longer-term data</td>
<td>3.5 years at time of filing</td>
</tr>
<tr>
<td>Comprehensive CMC Package</td>
<td>Must use to-be-commercialized materials in trials</td>
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</tbody>
</table>
Observed and Predicted number of Bleeding Episodes in 4-Week Interval vs Chromogenic FVIII Activity

Data cutoff date: 16APR2018

Analysis uses 4-Week intervals of Study Day 1 to 28, 29-56, and so on.

Each data point represents the number of bleeding episodes and the average FVIII activity level in a 4-week window of one subject.

Predicted values are based on negative binomial regression.
## Key Considerations for Full Registration

<table>
<thead>
<tr>
<th>Key filing elements</th>
<th>Full Registration</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABR</td>
<td>Non-inferiority/superiority at 1 year</td>
</tr>
<tr>
<td>Longer-term data</td>
<td>4.5 years at time of filing</td>
</tr>
<tr>
<td>Comprehensive CMC Package</td>
<td>Must use to-be-commercialized materials in trials</td>
</tr>
</tbody>
</table>
Substantial Decrease in Annualized Bleed Rates Post Valrox

Valrox 104 week Phase 1/2 ABR data superior to Standard of Care

**ABR results with 6e13 dose through week 104**

97% REDUCTION in MEAN ABR

<table>
<thead>
<tr>
<th></th>
<th>Pre-infusion</th>
<th>Post-infusion (52 weeks)</th>
<th>Post-infusion (104 weeks)</th>
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</thead>
<tbody>
<tr>
<td>ABR (episodes/year)</td>
<td>16.5</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td>16.3</td>
<td>0.9</td>
<td>0.5</td>
</tr>
</tbody>
</table>

**% Patients Bleed Free**

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

*All patients off prophylaxis*

*100% resolution in target joints*

As presented at WFH, May 22, 2018
Valroxcogene Roxaparvovec

Valrox Substantially Improved Quality of Life

Valrox 104 week Phase 1/2 QoL data superior to Standard of Care

![Graph showing QoL improvement](image)

- **QoL improvement observed in all 6 domains:**
  - Consequences of Bleeding
  - Emotional Impact
  - Physical Functioning
  - Role Functioning
  - Treatment Concern
  - Worry

Grey line indicates distribution based on minimally clinically important difference (MCID) at lower threshold

* Pocoski J et al., 2014

As presented at WFH, May 22, 2018
## Summary of Regulatory Paths and Considerations Beyond

### Key filing elements

- ✓ Choice of FVIII Assay
- ✓ FVIII in normal range
- ✓ ABR (within 52 weeks)
- ✓ Longer-term data
- ✓ Comprehensive CMC Package
Accumulated preclinical and clinical data suggest no impact on expression from the following:

- Persistent LFT abnormalities
- Cellular stress due to folded protein response
- Promoter over-expression
- Epigenetic silencing
- Steroid effect
How AAV Vectors Mediate Persistent Expression

1. **Incoming SS DNA delivered to nucleus**
   - Linear SS-DNA
   - Strand annealing
   - Degradation

2. **Expression begins from linear DS genomes**
   - Linear DS-DNA monomer
   - Circular conversion
   - Degradation

3. **Stable expression persists**
   - Circular DS-DNA monomer and concatamers

**The kinetics of expression result from the complex processing of DNA**

Lung, liver, muscle of mice & NHP, vector genomes persist as unintegrated, circular episomes.

Preclinical Observations On Vector Genomes in Mice

Vector catabolism is slow, circular episomes form and persist

![Graph showing relative proportion of duplex DNA over time.](image-url)
Acceptable Safety Profile in Target Population in Phase 1/2

- Generally well tolerated
- No ALT elevations above Grade 2; all transient and resolved
  - All subjects off corticosteroids
  - No association with FVIII activity loss in target population
- No subject developed inhibitors to FVIII
- No subject withdrew
- No evidence of adaptive T-cell response to vector by ELISpot
- Phase 3 protocol now aligned with Phase 1/2 following two ALT elevations from wider inclusion criteria
Increased confidence in our plans to expedite development

- Addressed assay
- Verified efficacy time points
- Target 2H19 decision on filing
- Ongoing Phase 3 study meets criteria for full approval

Increased confidence in durability of valrox persistence

- Slow vector catabolism with persistent circular episomes

Increased confidence in path forward

- Efficacy data aligned with registration guidelines
- Manufacturing expertise and capabilities solidify
# Steps Toward Full Filing

<table>
<thead>
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<td>4.5 years at time of filing</td>
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<tr>
<td>Comprehensive CMC Package</td>
<td>Must use to-be-commercialized materials in trials; make consistent reliable material</td>
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</tbody>
</table>
THANK YOU
CHALLENGES AND CONSIDERATIONS FOR MANUFACTURE OF AN AAV-BASED GENE THERAPY PRODUCT FOR HEMOPHILIA A

BIOMARIN R&D DAY 2018

Robert Baffi, Ph.D., M.B.A.
Executive Vice President Technical Operations
Discussion Topics

- **Regulatory Expectations – Stringent and Rigorous Requirements**
  - Comments From FDA Commissioner Scott Gottlieb
  - Comments From Director of CBER Peter Marks
  - FDA Draft Guidance for Gene Therapy Products
  - Comments From FDA Summary Basis for Regulatory Action

- **Strategic Process Development**
  - Products, Impurities, Process & Equipment (PIPE)
  - Finalize Development of the Process and Facility Prior to Conducting Pivotal Studies

- **In-House Vector Production Capabilities**
  - Drives Process Development Consistent With Regulatory Expectations
  - Allows for Rapid Development, Innovation and Protects Intellectual Property
The more challenging questions relate to product manufacturing and quality, and the impact on the product’s safety or performance.

In contrast to traditional drug review, where 80% of the review is focused on the clinical portion of that process, and 20% is focused on the product issues, I’d say that this general principal is almost completely inverted when it comes to cell and gene therapy.

Pharmaceutical manufacturing paradigm of supporting early-stage development with drug produced through a pilot process before graduating to a commercial process developed for late-stage development and marketing does not fit the realities of gene therapies.

FDA is encouraging sponsors to develop scalable manufacturing processes with inherent quality attributes that can support scale-up and licensure.
Regulatory Expectations – Stringent and Rigorous Requirements

In manufacturing, industry needs to **focus on producing quality products by design in scalable processes**, so that if early clinical trials are promising, they can advance development rapidly.

There is lack of capacity for manufacture of lentiviral and adeno-associated virus (AAV) vectors for limiting clinical development and noted that the process of production in current cell lines is not able to meet demand despite some improvement over the years.

Clinical development is crucial, **but industry needs to have manufacturing under control.**
# Ongoing Evolution of the Regulatory Framework

## Draft Guidance Documents Issued by FDA in July, 2018

### Manufacturing Guidance

- Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy
- Investigational New Drug Applications (INDs)
- Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up)

### Clinical Guidance

- Human Gene Therapy for Hemophilia
- Human Gene Therapy for Rare Diseases
- Human Gene Therapy for Retinal Disorders
- Long Term Follow-up After Administration of Human Gene Therapy Products
It Was Stated In The Summary Basis For Regulatory Action:

- “Validation of the process for manufacturing was conducted by manufacturing one Process Performance Qualification (PPQ) lot for Drug Substance and Drug Product”
- “Typically live viral product cannot undergo orthogonal viral removal steps as the product is a viral particle”.

We Will Submit a More Traditional and Robust CMC Package Including:

- 3 Full Scale PPQ Lots For Drug Substance
- 3 Full Scale PPQ Lots For Drug Product
- Data From 9 Lots Manufactured From 2 Separate Full Scale Campaigns
- Viral Removal Validation - Demonstrating Orthogonal Clearance
- All Data Will Be Generated In The To-Be-Commercial Facility
Holistic approach focused on producing high quality product with scalable processes to enable rapid approval of safe and efficacious therapeutic options for patients.
Proven Capabilities For Manufacturing Complex Biologics

- 5 Approved Biological Products
- 2 Licensed & Approved Biological Facilities
- Conducted 7 PPQ Campaigns for Biologics
- >70 GMP Inspections by FDA, EMA, MHRA, HPRA, AGES, ANVISA, PMDA, TMMDA & Others
Strategic Process Development

PRODUCT

IMPURITIES

PROCESS

EQUIPMENT
Keys to the **PIPE** – Develop the **Process with Quality in Mind**

Empty Capsids Represent a Deleterious Product Related Impurity

**An Empty Capsid**

**A Full Capsid**

![Graph showing relative amounts of full and empty capsids across steps](image_url)
Why Is It Important To Control Product Related Impurities

*Because Empty Capsids Result in Loss of Potency as Determined in a Biomimetic Cell Based Bioassay*
Capsid to Viral Genome Concentration Negatively Impacts Potency

Empty Capsid Impact on Potency of Full Capsids

$R^2 = 0.9927$

Empty Capsids Result in a Linear Decrease in Potency of Full Capsids

Most Likely by Competing for a Limited Amount of Cellular Receptors
Implemented 2000L Suspension Production Process in the to be Commercial Facility

Keys to the PIPE – Develop Commercial Ready Process Early

- Conducting Phase 3 Studies With Material Manufactured at Scale in the to be Commercial Facility:
  - Simplifies Process Validation Efforts
  - Avoids the Need For Conducting Large, Time Consuming, Expensive and Risky Bioequivalence Studies
  - Reduces Regulatory Concerns

- The BMN 270 Phase 3 Material Was Manufactured at Scale in the to be Commercialized Facility

Largest Scale Used For GMP Production of a Gene Therapy Product to Date
In-House Vector Production Capabilities

**FULLY INTEGRATED VECTOR PRODUCTION FACILITY**

- Facility Design Vetted with Health Authorities
- Single Use Technology Throughout
- Multi-Product Production
- Supports Multiple 2000L Bioreactors
- Supports 4000 Patients Per Year at Highest Dose
- ISPE 2018 Facility of the Year – Project Execution

**Biologics Facility**

**Gene Therapy Facility**

**Reduces Risk By Developing Commercial Ready Processes To Support Pivotal Clinical Studies**

BMN 270 Phase 3 Studies Being Conducted With Material Made At Commercial Scale in the to be Commercial Facility

BMN 307 Clinical Studies Will Be Conducted With Material Made At Commercial Scale in the to be Commercial Facility

**Allows Us To Meet Regulatory Expectations - Rapidly Innovate - Protect Intellectual Property**
THANK YOU
Evolving Regulatory Landscape and Significance of Patient Engagement

Biomarin R&D Day 2018

Adora Ndu, Pharm.D., J.D.
Executive Director and Head of Global Regulatory Policy, Research, and Engagement
FDA Delivering on its Promise to Support Innovation and Efficiency of Orphan-drug development

“We’re focused on making the process of generating pre-clinical and clinical evidence required for making risk-based regulatory decisions more modern, more scientifically rigorous, and more efficient”

— FDA Commissioner Scott Gottlieb, 10/15/18
**BioMarin expertise allows us to leverage policies across our programs**

<table>
<thead>
<tr>
<th>Regulatory Developments</th>
<th>Program</th>
<th>Takeaways</th>
</tr>
</thead>
<tbody>
<tr>
<td>Priority Review Voucher</td>
<td>Vimizim, Brineura</td>
<td>Recent vouchers between $80m and $150m</td>
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<tr>
<td><strong>Gene Therapy guidances</strong></td>
<td>Valrox, BMN 307 (PKU)</td>
<td>Accelerated approval path (Valrox) First in human trial as registration enabling (BMN 307-PKU)</td>
</tr>
<tr>
<td>Rare disease guidances</td>
<td>All programs</td>
<td>Flexibility in clinical trial design</td>
</tr>
<tr>
<td>Patient Focused Drug Development</td>
<td>All programs</td>
<td>Incorporates the voice of patients</td>
</tr>
<tr>
<td>FDA reorganization – rare disease office and division</td>
<td>All programs</td>
<td>Improvement in review of all BioMarin products</td>
</tr>
<tr>
<td>Elimination of NIH and FDA dual oversight for GT products</td>
<td>BMN 307 (PKU)</td>
<td>Streamlines several burdensome processes for gene therapy</td>
</tr>
</tbody>
</table>
New FDA Regulatory Framework Provides “Promise” of Gene Therapy to Patients

Recent FDA Draft Guidances on Gene Therapy Applicable to BioMarin

- Human Gene Therapy for Hemophilia
  - Accelerated Approval → 2H19 filing
- Human Gene Therapy for Rare Diseases
- Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)
- Long Term Follow-Up After Administration of Human Gene Therapy Products

Gene Therapy Workshops

- Product Development in Hemophilia Public Workshop – December 2018
- Quantitation of AAV-Based Gene Therapy Products – December 2018

Proactive work through trade associations to influence final guidances
Patient Voice is a “Must-have” in Regulatory Decision-making

“*This is not a vanity issue. This is for my son's physical and psychological health and well-being.*”

- Parent of child with achondroplasia
Patient Voice is a “Must-have” Regulatory Decision-making: Palynziq Case Study

- Disease Burden
- Risk Tolerance
- Patient Experience
- Preference for Treatment
- Desired Outcomes
- Palynziq Approval
Policy and Patient Engagement Will Continue to be a Key Element of Our Overall Strategy

Well positioned to identify and leverage opportunities

Involved in health authority efforts that impact our programs

Influence policies that will impact our programs

Patient voice is a priority \( \rightarrow \) FDA/EMA will continue to improve
Key Regulatory and Policy Takeaways

FDA is delivering on their objectives

Policy advances are supportive of our programs

There is no substitution for patient voice
THANK YOU
Today’s Agenda

1. Our approach to research and innovation

2. Future vision for R&D at BioMarin

3. BMN-307 for PKU: Our next gene therapy program
Our Formula for Rare Disease Drug Development

1. **Approach**
   - Our enriched approach for speed and success

2. **Capabilities**
   - Core enabling capabilities in R&D, regulatory & manufacturing

3. **Technologies**
   - Multiple in-house modalities providing access to a range of targets
Our Enriched Approach for Speed and Success

4 Key Criteria Guide Discovery and Development at BioMarin

1. High unmet need and rapid development
   - IND to approval in 4-6 years for 5 out of 7 products

2. Diseases with genetic mechanisms
   - Hem A, PKU, CLN2, MPS I, IVA, VI, achondroplasia

3. Target epicenters and drive for normalization
   - Gene therapy to restore FVIII expression in Hem A and PAH activity in PKU

4. Discern outcomes through biomarkers
   - Hem A, PKU, MPS: Rapidly gauge efficacy with surrogate endpoints
Capabilities

- **A**: Deep biological expertise spanning multiple therapeutic area domains
- **B**: Leading gene therapy and vector biology capabilities
- **C**: Manufacturing expertise focused on gene therapies and complex biologics
- **D**: Powerful regulatory and clinical development engines
Technologies

Ability to Select the Most Appropriate Tools for Specific Targets

Gene therapy
- Fully integrated gene therapy platform
- One of the world’s largest in-house gene therapy manufacturing facilities

Biologics
- Capabilities spanning: ERTs, modified peptides, PEGylated enzymes, oligonucleotides and antibodies

Small molecules
- Core small molecule discovery and development expertise

- Valoctocogene roxaparvovec for Hemophilia A in Ph3 development
- BMN 307 for PKU
- Several undisclosed programs

- 4 ERT products developed, approved and marketed
- Palynziq approved in 2018
- Additional undisclosed programs

- Firdapse for LEMS
- Kuvan for PKU
- Additional undisclosed programs
*BMN250 is now known as Tralesinidase alfa
Today’s Agenda

1. Our approach to research and innovation
2. Future vision for R&D at BioMarin
3. BMN-307 for PKU: Our next gene therapy program
Future Vision for R&D at BioMarin: 3 Key Priorities

1. Harness genomics for rare disease R&D
2. Leverage our leading gene therapy capabilities
3. Advance early-stage portfolio
1. Harness Genomics to Identify Rare Disease Opportunities

Knowledge of disease genes unlocks 1000s opportunities

- ~3 new rare disease genes discovered weekly

Genomics can transform rare disease R&D

2X Genetically-supported targets can double clinical success rates

10X Approved drugs are up to 10X more likely to target rare genetic variants

Genetic variants targeted by approved drugs

Reference: Adapted from Nelson, M et al. (2015)
Identifying New Targets and Patients

Access to population genetics databases can drive discovery efforts

New genomics partnerships are already having an impact

New CLN2 and PKU patients identified

Reference: Nature, October 11, 2018
Expanding Indications for Existing Portfolio

Using Genomics to Transition from Rare to Less Rare: Lysosomal Storage Disorders as Example

Link between Gaucher disease and Parkinson’s disease

- Gaucher disease mutations in GBA1 also confer a 5-fold higher risk of developing Parkinson’s disease
- External efforts ongoing to treat Parkinson’s disease in this population

Similar links between BMRN LSDs and other diseases

- Genomics and genetics can help identify links between other LSDs and more common diseases
- Potential application of a BMRN ERT in a neuromuscular disorder
Rare Genetic Disorders as Experiments of Nature

- Human genetics can mimic therapeutic dose-response
- Highly attractive for proof of mechanism, efficacy, dose, safety
- Relatively few striking examples; highly sought after
- PCSK9/cardiovascular disease most celebrated
CNP is another Experiment of Nature

1. FGFR3 mutations: Achondroplasia
2. Deletion + translocation of CNP inhibitory region: overgrowth
3. CNP mendelian form: short stature
4. ISS NPR2 mutations: ~100k US individuals*

**Note:** *ISS defined as height less than 2.25 standard deviations below the mean of the general adult population; Olney, R et al. (2006)*
2. Leverage Our Leading Gene Therapy Capabilities

Core gene therapy expertise across 5 domains

1. Tissue tropism
2. Pre-existing immunity
3. Manufacturing
4. Vector optimization
5. Expression

Improved tissue tropism with novel BMRN AAVs – muscle example

Novel BMRN AAVs with less susceptibility to pre-existing immunity

Today’s Agenda

1. Our approach to research and innovation
2. Future vision for R&D at BioMarin
3. BMN-307 for PKU: Our next gene therapy program
BioMarin and PKU: Over a Decade of R&D Innovation

Expanding the Treatable Patient Population Through Innovation

- Synthetic BH4 (PAH cofactor)
- Approved by FDA in 2007 and marketed globally

- Enzyme substitution therapy
- Recombinant PAL
- Approved by FDA in 2018

- AAV5-PAH gene therapy
- Initiated pharmacology in ‘17
- Filing IND in 2H19

Adult PKU Patients in US

Total: 11,400

~1,400
~2,300
~7,500
~200

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.
BMN 307 Program Overview

A  Correction of coat color in PKU model

B  Lifetime Phe correction in mice

C  Vector optimized to drive a 10-fold lower dose

D  Neurotransmitter correction with BMN 307

E  Lack of hypo Phe with BMN 307
BMN 307 and the PKU Model Used for Development

- **BMN 307**: Liver-directed gene therapy (AAV5 PAH)
- **IND filing in 2H19** (Commercial scale material available in 2H19)

- **Validated mouse model of PKU** (the ENU2 model)
  - Mice have no detectable PAH catalytic activity and high Phe levels
- **Model recapitulates many aspects of the human PKU phenotype**, including:
  - High plasma/tissue Phe
  - Reduced neurotransmitters

- **PKU mice also have a light coat color**
- **Acts as a readily detectable biomarker of therapeutic response**

![Image of ENU2 and WT mice]

**Diagram of Phenylalanine Metabolism**
- Phenylalanine $\xrightarrow{BH4}$ Tyrosine $\xrightarrow{Melanin}$ Coat/Skin Color
- ENU2 vs. WT mice
Corrections in Coat Color in ENU2 Mice

ENU2 + vehicle  WT + vehicle  ENU2 + AAVPAH

Pre-dosing  Post-dosing

Lifetime Phe Correction seen in Treated PKU Mice

Phenylalanine reductions seen in ENU2 mice

Phe in µM

- ENU2 vehicle
- ENU2 + AAV5 muPAH
- WT vehicle

- AAV5-PAH normalizes Phe in ENU2 mice
- Levels indistinguishable from WT after 2 weeks
- Efficacy sustained at 80 weeks

Vector Optimized to Drive a 10-fold Lower Dose

Tested a broad range of vector constructs and combinations to optimize the vector and increase potency, resulting in a 10-fold lower dose.

Reference: Data on file, BioMarin (2018); studies used AAV-hPAH.
Neurotransmitter Correction with BMN 307

1. BMN 307 corrects brain Phe, tyrosine and tryptophan

<table>
<thead>
<tr>
<th>Plasma</th>
<th>Phenylalanine</th>
<th>Tyrosine</th>
<th>Tryptophan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Phenylalanine</td>
<td>Tyrosine</td>
<td>Tryptophan</td>
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</table>

Neurotransmitter Correction with BMN 307

BMN 307 normalizes neurotransmitters

**Serotonin**
- Depression, sleep disorders
- Tryptophan
- Serotonin
- 5-HIAA

**Dopamine and Norepinephrine**
- Levels are reduced in patients with inattention, ADHD
- Tyrosine
- Dopamine
- Norepinephrine
- HVA
- MOPEG

Minimal Phe Difference Between Treated and WT Mice

- Similar Phe levels seen between WT mice and ENU2 mice treated with BMN 307
- No hypo-Phe seen with BMN 307 in mice and in NHP studies

References: Data on file, BioMarin (2018); ACMG Practice Guidelines (2014)
BMN 307 PKU Gene Therapy Summary

- **Lifetime Phe normalization** in an established PKU mouse model
- Normalized neurotransmitter levels
- **Vector optimized** to improve potency
- AAV5 program **leverages investments in gene therapy manufacturing and experiences with Valrox**

**Next steps:**
- NHP studies are currently reading out
- All non-clinical studies complete in 1H19
- Leveroni commercial scale material available in 2H19
- IND filing in 2H19
3. Advance Pre-clinical Programs

**Program 1:** Near complete substrate reduction at 7 wks

![Substrate Reduction Graph](image)

-96%

**Program 2:** Biomarker normalization at 2 wks in rare renal disease

![Biomarker Normalization Graph](image)

Small molecule

Genetic MoA

~10k pts

**Program 3:** Muscle protein expression up to ~80% of control

![Muscle Protein Expression Graph](image)

ASO

Genetic MoA

~10k pts

**Program 4:** Near complete storage reversal in rare disease model

![Storage Reversal Graph](image)

Gene therapy

Genetic MoA

~20k pts
THANK YOU

Q&A
Our Enriched Approach for Speed and Success

*4 key criteria guide discovery and development at BioMarin*

1. **High unmet need and rapid development**
   - **Speed to market**
   - IND to approval in 4-6 years for 5 out of 7 products

2. **Diseases with genetic mechanisms**
   - **Probability of success**
   - Hem A, PKU, CLN2, MPS I, IVA, VI, achondroplasia

3. **Target epicenters and drive for normalization**
   - **Medical value**
   - Gene therapy to restore FVIII expression in Hem A and PAH activity in PKU

4. **Discern outcomes through biomarkers**
   - **Productivity**
   - Hem A, PKU, MPS: Rapidly gauge efficacy with surrogate endpoints
## What you learned today

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<thead>
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<th>Continued increased growth through 42-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Development Considerations in Achondroplasia</td>
<td>Program aligns with messages from achondroplasia AdCom</td>
</tr>
<tr>
<td>Valoctocogene Roxaparvovec for Hemophilia A: Regulatory Path Considerations</td>
<td>Health authority alignment on assay choice; ongoing program conforms to regulatory requirements for expedited filing</td>
</tr>
<tr>
<td>Considerations for Manufacture of AAV-Based Gene Therapy Products</td>
<td>Commercial scale material to serve 4000 patients from our facility</td>
</tr>
<tr>
<td>The Evolving Regulatory Landscape and Significance of Patient Engagement</td>
<td>Regulatory policy environment and patient engagement environment favorable to BioMarin</td>
</tr>
<tr>
<td>Genetics, Genomics and the Future of Us; PKU Gene Therapy Preclinical Data Update</td>
<td>Sustainable pipeline and next INDs supported by robust research engine; Lifetime correction of Phe with PKU gene therapy product preclinically</td>
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</tbody>
</table>
Late-stage Product Growth Drivers Next 24 Months

- **Valrox:**
  - Potential AA filing
  - Phase 3 GENER8-1 enrollment completion
  - Potential US/EU Launch if AA
  - Phase 2 three year update

- **BMN 307:**
  - Potential IND filing
  - Potential data readout

- **Vosoritide:**
  - Potential BLA/MAA submissions
  - Full Phase 3 52 week top-line data readout

- **Palynziq:**
  - Potential EU Launch
  - Phase 3 top-line data readout

- **$2 Billion in revenues: FY2020**

- **BMN 307:**
  - Potential data readout
THANK YOU