WELCOME

BIOMARIN R&D DAY 2017

Hank Fuchs, M.D.
President, Worldwide Research & Development
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.
BioMarin R&D Engine is the Foundation of our Success

**BMRN products generated over 10x revenue growth over last 10 years**
- 2007 FY top-line results of $122 million to 2017 FY guidance of between $1.285B - $1.355B
- Buoyed by two new approved products in the last 3 years, including Vimizim and Brineura
- Contributions from continued growth of legacy products, including Naglazyme and Kuvan
- Supported by successful submission of product reimbursement dossiers worldwide

**Successful execution of global clinical development programs**
- Clinical programs large enough for global approval yet small enough to execute in rare disease indications
- Start anywhere finish contemporaneously

**Strong track record within US, EU and other global health authorities**
- PRIME designation, tied for first-ever EU accelerated assessment approval (Brineura)
- Nearly concurrent approvals of Brineura and Vimizim
- 5th potential approval through DGIEP at FDA with current pegvaliase BLA
The R&D Organization Evolves in Step with our Growth

**Adrian Quartel, M.D.**
Group Vice President, Head of Global Medical Affairs
- More than 10 years at BioMarin
- Led EU medical effort of Naglazyme

**Brad Glasscock, Pharm.D.**
Group Vice President, Head of Global Regulatory Affairs
- Previously Director, Regulatory Affairs at Amgen
- Reviewer at FDA (Aldurazyme)
- Regulatory project Manager at FDA

**Camilla Simpson, B.Sc. (Hons), M.Sc.**
Senior Vice President, Head of Product Portfolio Development
- Led regulatory approval of Brineura
- Previously Vice President of Early Development and Business Development
- Regulatory Affairs at Shire
- Regulatory Affairs at Abbott

**Geoffrey Nichol, M.B., Ch.B., M.B.A**
Senior Vice President, Chief Medical Officer and Head of Global Clinical Development
- Previously EVP, Head of R&D at Sangamo Therapeutics, Inc.
- Oversaw development of Opdivo, Yervoy and various others

**Lon Cardon, Ph.D.**
Senior Vice President and Chief Scientific Officer
- Previously, SVP of Alternative Discovery and Development, and Head of Target Sciences at GlaxoSmithKline; Head of Development for Rare Disease programs
- Former academic in the US and UK in bioinformatics and biostatistics

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Welcome Guest Speakers

**Maureen Cleary, M.D., F.R.C.P.C.H.**
Consultant in Inherited Metabolic Disease and Senior Lecturer at Institute of Child Health at Great Ormond Street Hospital for Children
- Focused on Metabolic Disorders including Lysosomal Storage Disorders and has led many clinical research trials
- Member of the clinical expert advisory group for the Highly Specialised LSD NCG service and, following the NHS reforms, represents North London on the Inherited Metabolic Diseases Clinical Reference Group
- Clinical trial investigator on BMN 250 for MPS IIIB program

**Nicola Longo, M.D., Ph.D.**
Professor of Pediatrics and Chief, Division of Medical Genetics, University of Utah
- Chief of the Division of Medical Genetics, Director of the Metabolic Service in the Department of Pediatrics, Director of the Training Program in Clinical Biochemical Genetics and Medical co-Director of the Biochemical Genetics and Newborn Screening Laboratories at ARUP Laboratories in Salt Lake City
- Clinical trial investigator on pegvaliase program

**Steven Pipe, M.D.**
Laurence A. Boxer Research Professor of Pediatrics and Communicable Disease, as well as Professor of Pathology at the University of Michigan, Ann Arbor, Michigan
- Medical director of the Pediatric Hemophilia and Coagulation Disorders Program and of the Special Coagulation Laboratory at the University of Michigan
- Focused on coagulation factor VIII and the molecular mechanisms of hemophilia A

**Massimo Pandolfo, M.D., Ph.D.**
Professor and Chief of Neurology and Director Laboratory of Experimental Neurology, Universite Libre Bruxelles, Hospital Erasme, Brussels, Belgium
- Global expert in the clinical manifestations of Friedreich’s ataxia (FA)
- Clinical investigator on numerous studies focused on neurodegenerative diseases
What Will You Learn Today?

BioMarin Development Portfolio

**Pegvaliase for PKU:** BLA filed June 30; Priority Review received

*Updated data included in Phase 3 BLA & EU status*

**Vosoritide for achondroplasia:** Enrolling Phase 3

*Long-term extension data*

**Valoctocogene roxaparvovec (BMN 270);**

*IND and CTA Active!!!*

**BMN 250 for MPS IIIB:** Phase 1/2 ongoing

*GAG data and clinical data*

**BMN 290:** New IND for Friedreich’s ataxia

Chromatin Modulation Therapy
THANK YOU
MASSIMO PANDOLFO, M.D., Ph.D.
PROFESSOR AND CHIEF OF NEUROLOGY AND DIRECTOR
LABORATORY OF EXPERIMENTAL NEUROLOGY, UNIVERSITE
LIBRE BRUXELLES, HOSPITAL ERASME
**Friedreich Ataxia: Development Biosketch**

| Population          | • Most common inherited ataxia  
|                     | • Autosomal recessive inheritance  
|                     | • FA is a disease of frataxin (FXN) deficiency  
| Clinical            | • Typical onset 7-15 yo with loss of balance, clumsiness  
|                     | • Progressive cerebellar ataxia  
|                     | • Progressive motor, speech, hearing, vision impairment  
|                     | • Premature death cardiomyopathy  
|                     | • Skeletal abnormalities, diabetes  
|                     | • Atypical, late-onset cases  
| Treatment           | • Only supportive therapy  
|                     | • No disease-modifying treatment  
| Pipeline            | • Focus on overcoming frataxin (FXN) deficiency or supplementing mitochondrial deficits  

**Clinical Manifestations of Friedreich Ataxia**

<table>
<thead>
<tr>
<th>&lt;10 y</th>
<th>35 y</th>
</tr>
</thead>
</table>
| • First symptom: **ATAXIA**  
  • Dysarthria, instability of fixation, truncal and gait ataxia, weakness: **PROGRESSIVE NEUROLOGIC IMPAIRMENT**  
  • Scoliosis, foot deformity  
  • ASSISTED GAIT then WHEELCHAIR in 10-15 years  
  • Hearing and vision impairment  
  • Hypertrophic changes in heart in 90%, 20-25% develop **HEART FAILURE**  
  • Risk of early (<30 yo) cardiac mortality  
  • 20% progress to diabetes  
  • Relatively cognitively intact: **LOCKED-IN** |

**Typical, severe cases with profound FXN deficiency (10% of CT)**

- Most common inherited ataxia, prevalence 2-3:100,000
- No disease-modifying therapy
- Limited development pipeline
- Progressive multi-system disease
Clinical Manifestations of Friedreich Ataxia

- First symptom: ATAXIA
- Dysarthria, instability of fixation, truncal and gait ataxia, weakness: SLOWLY PROGRESSIVE NEUROLOGIC IMPAIRMENT
- MILD or NO Scoliosis, foot deformity
- PRESERVED GAIT until late in life
- NO or MILD hearing and vision impairment
- NO or MILD hypertrophic changes in heart, NO HEART FAILURE
- Normal lifespan

Late-onset, mild cases expressing more FXN (30% of CT)

- Most common inherited ataxia, prevalence 2-3:100,000
- No disease-modifying therapy
- Limited development pipeline
- Progressive multi-system disease
Pathology of Friedreich’s Ataxia: Peripheral and Central Targets

A. Atrophy of dorsal root ganglia from lumbar spine compared to normal
B. Atrophy and loss of deep cerebellar nuclei loss in patient (FA) compared to control
C. Hypertrophic cardiomyopathy with sclerosis
D. Cervical spinal cord with loss of dorsal columns, lateral corticospinal and spinocerebellar tracts
FA Caused by Deficiency in Normal Expression of Frataxin

I. Normal Allele

Exon 1 → Exon 2 → Exons 3-5 → FXN

Transcription

FXN pleotropic cell functions

Normal Expression

II. FA Mutation

Exon 1 → Exon 2 → Exons 3-5 → FXN

(GAA)_{650}

Transcription

FXN deficiency impacts multiple pathways in cell bioenergetics

Expression Repressed

GAA expansion causes formation of condensed chromatin repressing normal transcription read-through
Repression of FXN Due to Abnormally Condensed Chromatin

I. Chromatin State Modulated by Epigenetics

![Diagram showing the interaction between Histone Acetyl Transferase (HAT) and Histone Deacetylase (HDAC)]

II. FA Cells Have Specific Epigenetic Markers of Heterochromatin

![Graph comparing normal and mutant intron 1 expression levels for FXN genes](image)

III. FXN Expression Reduced in Patients

![Image showing FXN expression levels in normal and FA cells](image)

IV. FXN Deficiency Detected in Surrogate Tissues (PBMCs)

![Graph showing frataxin protein levels over weeks](image)
Chromatin Modulation Therapy Increases FXN in FA Patients
Soragni E et al., Annals Neurology 2014

Turin, Italy; Luca Durelli, PI

4 cohorts, 5 patients per cohort

Cohorts 1 and 2
  Open label
  Cohort 1 = 30 or 60 mg / patient
  Cohort 2 = 120 mg / patient

Cohorts 3 and 4
  Double-blind, cross-over design
  Dose level dependent upon safety & PK data from previous cohort
    Cohort 3 dose: 180mg/patient
    Cohort 4 dose: 120mg x 2 (separated by 4 hours)

Biomarker measures
  Frataxin mRNA in blood and PBMC
  Frataxin protein in PBMC and cheek swab
  HDAC inhibition and histone acetylation in PBMC

PK and PD data generated for all cohorts

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**TABLE 1. Demographic and Clinical Characteristics of Study Subjects**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
</tr>
<tr>
<td>Age, yr(^a)</td>
<td>30.0 ± 8.1</td>
</tr>
<tr>
<td>Sex, No. (%)</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>9 (40.9)</td>
</tr>
<tr>
<td>F</td>
<td>13 (59.1)</td>
</tr>
<tr>
<td><strong>Disease data</strong></td>
<td></td>
</tr>
<tr>
<td>GAA•TTC triplet expansion on shortest allele(^a)</td>
<td>1,084.8 ± 784.5</td>
</tr>
<tr>
<td>Age of onset, yr(^a)</td>
<td>10.7 ± 4.6</td>
</tr>
<tr>
<td>FARS(^b) score at screening(^a)</td>
<td>59.7 ± 23.2</td>
</tr>
<tr>
<td>Cardiac function, ejection fraction (^a)</td>
<td>63.0 ± 6.9</td>
</tr>
</tbody>
</table>

\(^a\)Data are shown as the mean ± standard deviation.

\(^b\)See Beconi et al.\(^{45}\)

F = female; FARS = Friedreich Ataxia Rating Scale; M = male.
Histone Re-Acetylation Allows FXN Expression in FA Patients

Cohort 3: Quantitative Increase in Full Length FXN mRNA in A Patient PBMCs Compared to Placebo

Safety:
- All doses tolerated
- No observed treatment associated AEs
- No clinically significant telemetry/ECG findings

Biomarker analysis:
- FXN histone re-acetylation at FXN in RG2833-02 FXN mRNA (mean +/- SE)

Graph showing the change in FXN mRNA levels over time for different doses compared to placebos.
Clinical Consortia in Friedreich’s Ataxia

<table>
<thead>
<tr>
<th>CCRN</th>
<th>EFACTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Experienced clinical trial centers in US, Canada, Brazil, Australia</td>
<td>• Experienced clinical trial centers in Europe (13)</td>
</tr>
<tr>
<td>• Extensive natural history database &gt; 1000 FA patients</td>
<td>• Enrolled natural history cohort &gt; 850 FA patients</td>
</tr>
<tr>
<td>• Biomarker development and biobank</td>
<td>• Endpoint and biomarker development complementary to CCRN</td>
</tr>
<tr>
<td>• ‘CRO’-like clinical trial support</td>
<td></td>
</tr>
</tbody>
</table>

FA clinical development objectives enhanced by existing clinical trial infrastructure, long term natural history data and biomarker development
Friedreich’s Ataxia: Clinical and Development Summary

- Rare, autosomal recessive inherited ataxia
- Prevalence estimated 5,000 US; 15,000 worldwide
- Expanded triplet repeat in first intron of frataxin (FXN) gene
  - Mitochondrial protein, involved in Fe utilization, enzyme synthesis, energy signaling
- GAA expansion results in repression of FXN
  - Heterochromatin forms around intron 1 that arrests transcriptional read-through
- Primary therapeutic option is to increase FXN
  - Compensatory strategies unlikely to work
- Chromatin modulation shows promise as therapeutic agents
  - Re-acetylation of histones at FXN locus up to 2-fold increase mRNA after single dose
THANK YOU
NEW IND! BMN 290, CHROMATIN MODULATION THERAPY FOR FRIEDREICH'S ATAXIA

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Dave Jacoby, M.D., Ph.D.
Executive Group Medical Director, BioMarin
Repression of FXN Due to Abnormally Condensed Chromatin

I. Chromatin State Modulated by Epigenetics

II. FA Cells Have Specific Epigenetic Markers of Heterochromatin

III. FXN Expression Reduced in Patients

IV. FXN Deficiency Detected in Surrogate Tissues (PBMCs)
Chromatin Modulation Therapy for Friedreich’s Ataxia

- BMN290 has drug characteristics more compatible for chronic therapy
  - Selected for potency on the mutant FXN locus
  - Acts preferentially on selective subset of acetylation enzymes
  - Less global activity
  - → more FXN expression at lower doses
- BMN290 is more tissue (heart/brain) penetrant
  - → more release of FXN repression in affected tissues
- Direct Mechanism to Restore Expression
  - Selective release of single gene repression, not ‘reprogramming’ gene expression
  - Heterochromatin mechanism also active in patient PBMCs → increased expression monitorable in clinic
  - FXN protein long-lived, supporting alternative dosing paradigms to mitigate potential off-target effects
  - Off target effects predictable and can be monitored in clinic
Screening Demonstrated Selectivity for Mutant FXN Locus

**Lead Molecule**

- **Vorinostat**

**Graphs showing changes in Ac-H3 and FXN protein levels**

**Moderate increase in Ac-H3, maintained after wash-out**

**Increased FXN protein**

**Greater acute increase in Ac-H3, lost immediately after wash-out**

**No FXN protein increase**

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*Cited Reference*

Pimelic Diphenylamide 106 Is a Slow, Tight-binding Inhibitor of Class I Histone Deacetylases.

Received for publication, September 10, 2008, and in revised form, October 23, 2008. Published, JBC Papers in Press, October 24, 2008. DOI: 10.1074/jbc.M803043200

C. James Chou, David Herman, and Joel M. Gottsfeld

From the Department of Molecular Biology, The Scripps Research Institute, La Jolla, California 92037
BMN 290: Improved Qualities for Treating FA

Limitations in metabolism, PK and tissue penetration of in-licensed molecule 109 have been substantially improved in BMN 290, a promising candidate for FA

- Preserves selectivity of lead molecule
- Improved drug qualities
- Tissue penetration greater than plasma in all target tissues for FA
- Improved metabolic profile and PK
- Safe single dose dog cardiovascular study for parent and metabolites
- Predicted limiting safety event (myelosuppression) monitored in clinical setting

- Safe dose in nonclinical studies > 10-fold than the concentration required to increase FXN 2-fold
BMN 290: Tissue Penetration Highly Desirable for FA

I. Oral PK Comparison (Rat)

Properties of BMN 290 highly desirable for treatment of FA

- Tissue distribution > 2 for all affected tissues
- PK predictability supports reproducibility in clinic
- Exposure at levels expected to increase FXN

II. Oral Tissue Distribution (Rat)

III. Exposure Across Species
BMN 290 is Selective for Subset of Acetylation Enzymes

Inhibition of Deacetylase Isoforms (uM)

<table>
<thead>
<tr>
<th>Compound</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMN290</td>
<td>2.11</td>
<td>0.78</td>
<td>0.12</td>
<td>&gt;100</td>
<td>&gt;100</td>
<td>&gt;100</td>
</tr>
<tr>
<td>TSA</td>
<td>0.018</td>
<td>0.018</td>
<td>0.017</td>
<td>-</td>
<td>-</td>
<td>0.001</td>
</tr>
</tbody>
</table>

- Selective molecule: Isoform 3 selective
- Long-standing benefit: slow ‘off’-rate specific for isoform 3
  - Off-rate is up to 12 hours
- Less affinity for HDAC 1,2 and faster off-rates for these isoforms
- Class I safety events seen most prominently in HDAC 1,2 potent molecules
BMN 290 Improved Potency for FXN Increase

mRNA induction in iPSC (RT-PCR) (Gottesfeld Lab)

I. mRNA induction in human neurons differentiated from patient iPSCs

II. mRNA induction in Ex vivo treated patient PBMCs

III. FXN protein in human neurons after BMN 290 treatment
FXN Level is Highly Likely to Predict Clinical Response

An increase of frataxin protein by > 2-fold in target tissues of heart, cerebellum and spinal cord will result in clinical benefit

- Asymptomatic carriers express 40-60% wt FWN from several tissue sources
  - Goal of therapy to express at carrier levels in cells of affected tissues
- FXN-knockdown or tissue specific (heart, neurons) FXN-knockout mouse models develop a severe phenotype:
  - Inducible repression of FXN develop CNS, PNS, cardiac phenotype. Rescued by release of repression (Chandon and Geschwind, 2017)
  - Tissue FXN specific ‘knock-out’ in heart and neurons develop severe phenotype. Reversed by FXN gene therapy (Puccio 2014, 2017)
- BMN 290 is able to restore FXN levels > 2-fold in human neurons (cell culture) and primary patient tissue (PBMCs ex vivo)
BMN 290 Promising Treatment for Friedreich’s Ataxia

- Tissue penetrant molecule that restores FXN expression in model systems
- FA results from GAA repeats (98%) that induce heterochromatin and repress FXN expression by abnormal epigenetic regulation
- BMN 290 allows histone re-acetylation which restores chromatin conformation and re-establishes FXN expression
- Mechanism based development plan
  - 2-fold increase of FXN as target
  - Pathway steps can be directly interrogated in clinical studies
  - Cardiac and neurologic outcomes of studies are readily clinically relevant
- Fit in BioMarin pipeline
  - Severe disease with no disease modifying therapy
  - Strong scientific rationale for treatment
  - Defined development path
THANK YOU

Q&A
PEGVALIASE FOR PKU

BIOMARIN R&D DAY 2017

Geoff Nichol, M.B., Ch.B., M.B.A
Senior Vice President, Chief Medical Officer and Head of Global Clinical Development
Pegvaliase BLA Guided by Ongoing FDA Collaboration

- Treats causative deficiency; profound Phenylalanine (Phe) reductions in adults with Phenylketonuria (PKU)
- Consistent correlations with long-term neurocognitive outcomes
- Fully elucidated immunology from largest clinical program in adult PKU
  - Immunologic profile explains dosing, efficacy, and safety
- Pronounced efficacy and generally well-tolerated safety profile promotes long-term patient retention
Pegvaliase Treats Causative Deficiency to Address Unmet Need in PKU

- Phenylalanine
- Cofactor BH$_4$
- Trans-cinnamic acid
- Ammonia
- Tyrosine
- Supplemental Tyrosine
- Rapid metabolic clearance

Pegvaliase

PAH Enzyme
Correcting High Phe in PKU Mice with Gene Therapy Leads to Normalization of Neurotransmitters

*PKU mice have high plasma Phe and low brain 5-Hydroxyindolacetic acid (5-HIAA) which are both corrected with high dose treatment*
Pegvaliase: Extensive Clinical Development Program

Phase 2
- Low Weekly Dosing
- Daily Dosing
- Induction, Titration, Maintenance

Long Term Extension

Phase 3
- Induction, Titration, Maintenance

Placebo-Controlled, Randomized Discontinuation Trial (RDT)
Long Term Extension (OLE)

Phase 3 efficacy endpoints
- Primary: change in blood Phe
- Secondary: change in attention and mood
Safety and Efficacy Well Characterized in PKU Program

• BLA data in subjects with PKU:
  • Up to 85 months of exposure
  • Over 200 patients currently receiving pegvaliase
  • ~700 patient-years of exposure

• Participants reflect general adult PKU population
  • Baseline blood Phe 1233 µmol/L
Phe reduction in the Face of Unchanged Protein Intake

- Blood Phe Concentration (µmol/L)
- Time Since Initiation of Pegvaliase (months)
- Total Daily Dietary Protein Intake (g)

Legend:
- Red line: Blood Phe Concentration
- Blue circles: Total Daily Dietary Protein Intake
Majority of Subjects Achieved Blood Phe Reduction to Treatment Guidelines

Cumulative Proportion of Subjects Reaching Blood Phe Reduction (%) during each time interval

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Cumulative Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months</td>
<td>28.7%</td>
</tr>
<tr>
<td>12 months</td>
<td>46.1%</td>
</tr>
<tr>
<td>24 months</td>
<td>62.0%</td>
</tr>
</tbody>
</table>

- ≤360 umol/L US guidelines
- ≤120 umol/L upper limits or normal
Consistent Correlation with Blood Phe and ADHD-RS Inattention Score with Long-Term Treatment

Change from Naïve Baseline in Blood Phe at Last Observation of Last Enrolled Study (µmol/L)
Safety Profile Well Characterized

*Individual Exposure up to 7 years, cumulative exposure ~700 patient years*

- Most common AEs
  - Arthralgia (69.5%)
  - Injection site reaction (65.1%)
  - Injection site erythema (52.5%)
  - Headache (51.9%)
  - Nasopharyngitis (41.1%)
  - Rash (40.2%)
- Most AEs (>99%) were mild or moderate in severity
- 8.5% of subjects reported AE’s leading to study withdrawal
- No end organ damage
  - Immune complexes being cleared physiologically
Hypersensitivity AEs (HAEs) Mainly Occur in first 6 Months of Treatment

- With prolonged exposure, AE rates declined for almost all categories
- AE incidences/event rates highest during first 6 months of treatment
- Acute systemic hypersensitivity rate 4.6% (independent adjudication)
Acute Systemic Hypersensitivity NOT IgE-Mediated Anaphylaxis

• Hypersensitivity reactions appear to be correlated with PEG IgM which declines after 6 months
• Reflects Type III hypersensitivity
• Anti-drug IgE undetected in acute systemic events
  • High-sensitivity assays confirm absence of IgE
• 8 of 13 subjects were re-dosed and 6/8 continued therapy
Patient Retention Improved with Tolerability Interventions

Interventions introduced in Ph 3 program included:

- Pre-medications during Induction/ Titration
- Allowance for slower dose titration
- Trained observer for first 16 weeks
- Clinical site and subject education

No severe anaphylaxis events (by Brown’s criteria) after interventions implemented.
BLA Highlights

• Maintained Phe reduction and correlated neurocognitive improvement 3+ years

• Minimized hypersensitivity type reactions through practiced induction/titration and pre-meds

• Conducted detailed review of hypersensitivity reactions, rates similar to other ERT

• Characterized mechanism of hypersensitivity as non IgE-mediated
Pegvaliase – the Path to Approval

Status

- BLA file accepted
- Priority review granted
- Advisory Committee meeting not anticipated

Next Steps

- Submit FDA requested CMC information
  - PDUFA February 28, 2018; expect May 25, 2018 with CMC amendment
- Patient engagement meeting with FDA scheduled for later this year
- Align hypersensitivity characterization with EU guidelines; expect submission 1Q 18
THANK YOU
Disclaimer: Pegvaliaise has not been approved for any indication and this video is not to be used for any promotional purpose. The testimonials in this video are from an advisory board organized by BioMarin with patients that are doing well on Pegvaliaise, all of whom were paid a stipend for their participation and reimbursed their travel costs. Since the advisory board only included patients that did well on therapy, it does not represent the complete range of patient experiences. For instance, it does not represent the experiences of those patients that did not experience a greater than 20% reduction in Phe levels or who discontinued therapy for any reason including the time and burden of the dose titration period or the 8.5% of patients that discontinued due to an adverse reaction to Pegvaliaise, which included 7 patients who discontinued therapy following an anaphylaxis event. Additionally, while the neurocognitive and behavioral statements made here are generally consistent with the correlation of lower blood fee and improved ADHD-RS inattention score BioMarin observed in the Phase 3 trial, the randomized portion of the Phase 3 did not show a neurocognitive benefit of Pegvaliaise.
NICOLA LONGO, M.D., PH.D.
PROFESSOR OF PEDIATRICS AND CHIEF, DIVISION OF MEDICAL GENETICS, UNIVERSITY OF UTAH

PAST PRESIDENT SIMD

CLINICAL TRIAL INVESTIGATOR ON PEGVALIASE PROGRAM
Current therapy consists in Medical Nutritional Therapy (MNT) low in phenylalanine, and sapropterin as adjunct to MNT for subgroup of responsive individuals with PKU.

Adult patients have defects in executive functions, inattention, and psychiatric symptoms¹².

Defects are related to inability to maintain phenylalanine levels within the recommended therapeutic range of 120-360 µmol/L³.

Interventional studies of Phe restriction and supplementation have shown improvements in neuropsychiatric and executive function suggesting deficits are reversible¹².

---

Compliance with Medical Nutritional Therapy (MNT) Decreases with Age

These results include patients who attend clinic

Jurecki et al Mol Genet Metab 2017; 120:190-197
What is the diet in phenylketonuria (PKU)?

Classical PKU:
Can only tolerate ~ 250–300 mg of phenylalanine (5–6 g protein per day)

Steak dinner: 2300 mg phe or 45 grams protein, Enough phe for 9 days
Compliance With Medical Nutritional Therapy (MNT) Decreases With Age

- Medical nutrition therapy requires special foods
- There is less adherence to MNT and blood Phe levels increase as patients get older
- Adults tend to abandon diet with concomitant increase in Phe levels

Adults with PKU report significant comorbidity with high variability/heterogeneity across individual patients.

- Higher prevalence of neuropsychiatric symptoms of inattention, hyperactivity, anxiety, and depression.
- Significant deficits in executive function domains of attention, cognitive flexibility, and inhibitory control.

Adult PKU: Lower blood Phe levels are associated with better neuropsychiatric outcomes

An increase in Phe levels from 709±322 to 1,209±332 µmol/L (p<0.01) had a negative effect on sustained attention as well as on the mood of the patients.

Fig. 2 Mean ± SE of POMSr scale scores as function of treatment, mood type and observer. Patient self report (—), Significant other report (—): ***p ≤ 0.01, **p ≤ 0.05, *p < 0.10

Lower Phe levels Associated with better Executive Function in Adults

Z-scores calculated with data from matching group of healthy controls

*Figure 1.* Comparison of cognitive abilities in lower- and higher-Phe phenylketonuria groups. Results are in z scores from the control group. Higher z scores always indicate worse performance. The asterisks on the lower-Phe group indicate a significant difference with controls; the asterisks on the higher-Phe group refer to a significant difference with the lower-Phe groups. RT = reaction time. *p < 0.05. **p < 0.01. See the online article for the color version of this figure.
Kaplan-Meier Analysis: 53% of subjects were able to normalize their blood Phe within 24 months on Pegvaliase

Cumulative Proportion of Subjects Reaching Blood Phe Reduction (%) during each time interval

- **6 months**: 28.7% ≤ 360 umol/L US guidelines
- **12 months**: 46.1% ≤ 360 umol/L US guidelines, 34.6% ≤ 120 umol/L upper limits or normal
- **24 months**: 62.0% ≤ 360 umol/L US guidelines, 53.4% ≤ 120 umol/L upper limits or normal
Pegvaliase Immunogenicity is Type III
Acute systemic Hypersensitivity events observed in Phase 3 are non-IgE mediated

- Program Data support complement mediated Type III, non-IgE etiology
  - All externally adjudicated 13 subjects tested negative for drug-specific IgE at or near the time of event

- All events managed successfully and resolved without sequelae

- 61.5% (8/13) with an adjudicated event were re-dosed and 75% (6/8) continued therapy

- Incidence of events categorized as severe anaphylaxis events (using Brown criteria), reduced with pre-medications and time on drug.
My Experience

- Treated 28 patients in phase I-III studies (20 patients >1 year)
- In patients receiving significant amounts of Pegvaliase, observed clinical improvements in most patients
- 2 patients treated for >7 years
- Adverse events: reactions at the injection site that decreased with subsequent injections, arthralgia in 2 patients also improving with time. Easily managed clinically.
- 5/25 patients were discontinued before 40 weeks of therapy
- 17/20 treated for > 1 year maintained blood Phe levels within the therapeutic/normal range
- Healthy balanced, nutritional intake improved in all patients
- Reduced blood Phe levels resulted in more clear thinking, success in school (completion of college and master programs), mood (and job) stability
THANK YOU

Q&A
VOSORITIDE FOR ACHONDROPLASIA

BIOMARIN R&D DAY 2017

Adam Shaywitz, M.D., Ph.D.
Executive Medical Director, Clinical Science, BioMarin
Achondroplasia – Disease Background

- Most common form of human disproportionate short stature
  - 1 in 15,000 to 25,000 births with ~ 200 new cases/year in the US

- Autosomal dominant activating mutation in the fibroblast growth factor receptor 3 (FGFR3) gene

- FGFR3 normally functions as an inhibitor of proliferation and terminal differentiation of growth plate chondrocytes
Vosoritide for Achondroplasia

- CNP + receptor both expressed in growth plate
- Modified recombinant human C-type natriuretic peptide (CNP)
- Mimics CNP pharmacologic activity on bone growth
- Longer half-life than native CNP (resistant to neutral endopeptidase)

Horton, 2007
Activation of the CNP Pathway Corrects Growth Defects in Mouse Models of Achondroplasia

- CNP transgenic mice rescue growth defects
- Vosoritide administration rescues growth defects
- Vosoritide administration expands growth plates of long bones
- No evidence of tachyphylaxis
Genetics Supports Important Role for CNP/NPR-B Pathway in Regulating Linear Growth in Man

**Loss-of-Function**

- **CNP loss-of-function**: short stature
- **NPR-B loss-of-function**: acromesomelic dysplasia, Maroteaux type (AMDM), a skeletal dysplasia associated with severe short stature

**Gain-of-Function**

- **CNP overexpression**: abnormally tall stature
- **NPR-B gain-of-function**: abnormally tall stature

_Bartels 2004_  

_Miura 2012_
Vosoritide Achondroplasia Clinical Program

111-901
Baseline Observation
0 months to 17 years
(No Intervention)

111-202
5 to 14 years
Phase 2, Open Label

Open-Label Extension
(111-205)

111-301
5 to <18 years
Phase 3, Placebo Controlled

Open-Label Extension

111-206
0 to <5 years
Phase 2, Placebo Controlled

Open-Label Extension

LPO* Oct 2017
LPI* mid-2018
FPI* 1H 2018

*FPI=First Patient In
*LPI=Last Patient In
*LPO=Last Patient Out
**BMN 111-202**

A Phase 2, Open-label, Sequential Cohort Dose-Escalation Study of BMN 111 in Children with Achondroplasia

- *Updated with 30 month data at pivotal dose (15 ug/kg)*
Durable Growth Effects in Children with Achondroplasia Treated with 15 ug/kg Vosoritide for 30 Months

<table>
<thead>
<tr>
<th>N=10</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGV (cm/yr)</td>
<td>4.0 (2.28)</td>
</tr>
</tbody>
</table>

**Additional AGV Gained Post-Treatment:**

<table>
<thead>
<tr>
<th></th>
<th>6 mos Δ</th>
<th>12 mos Δ</th>
<th>18 mos Δ</th>
<th>24 mos Δ</th>
<th>30 mos Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+2.0 (2.00)</td>
<td>+1.9 (2.02)</td>
<td>+1.6 (1.97)</td>
<td>+1.7 (1.80)</td>
<td>+1.6 (1.87)</td>
</tr>
</tbody>
</table>

Suggests treatment provides additional 4 cm of growth at 30 months

Data reported = mean (SD)
Z Scores – Metric to Gauge Growth vs Population Norms

Children with achondroplasia
Durable Growth Effects in Children with Achondroplasia Treated with 15 ug/kg Vosoritide for 30 Months

<table>
<thead>
<tr>
<th>N=10</th>
<th>Baseline</th>
<th>6 mos Δ</th>
<th>12 mos Δ</th>
<th>18 mos Δ</th>
<th>24 mos Δ</th>
<th>30 mos Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z-score (SDS)</td>
<td>-4.6 (1.14)</td>
<td>0.2 (0.15)</td>
<td>0.4 (0.07)</td>
<td>0.6 (0.19)</td>
<td>0.8 (0.28)</td>
<td>0.9 (0.37)</td>
</tr>
</tbody>
</table>

Table date = mean (SD)

*Whisker bars represent one standard deviation above and below mean*
Durable Growth Effects in Children with Achondroplasia Treated with 15 ug/kg Vosoritide for 30 Months

Data reported = mean (SD)

<table>
<thead>
<tr>
<th>N=10</th>
<th>Baseline</th>
<th>6 mos Δ</th>
<th>12 mos Δ</th>
<th>18 mos Δ</th>
<th>24 mos Δ</th>
<th>30 mos Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>U/L (ratio)</td>
<td>1.9 (0.23)</td>
<td>-0.02 (0.04)</td>
<td>-0.03 (0.04)</td>
<td>-0.04 (0.06)</td>
<td>-0.07 (0.05)</td>
<td>-0.08 (0.05)</td>
</tr>
</tbody>
</table>

Consistent with Best-Case Scenarios for Impact of Treatment on Proportionality of Added Height
Data Suggest Importance of Early Intervention: BMN 111-206 Infant/Toddler Study – Preliminary Design

- New study, anticipated start (FPI) 1H 2018
- Infant/Toddler (0-5 years old), n=60
- 3 Cohorts:
  - Cohort 1: 2-5 years
  - Cohort 2: 6 months – 2 years
  - Cohort 3: 0-6 months
- Key Endpoints
  - Safety/tolerability
  - Growth
  - ADLs/QoL
  - PK
  - Biomarkers
Durable Pharmacodynamic Response Over 30 Months of Treatment Anticipates Continued Effects on Growth

Figure shows mean Urine cGMP/Cr at pre-dose, 1 hr and 2 hr post-dose for cohort 3 (15 ug/kg)

(Whisker bars represent standard error of the mean)
Vosoritide Has Been Generally Well Tolerated Out to 30 Months of Treatment

- Generally well-tolerated across all doses
- No SAEs related to study drug
- No discontinuations from study drug due to AEs related to hypotension or bone related AE’s.
- Injection site reactions (ISRs, 91% of subjects)
  - Mild, transient and majority resolved in 30-60 minutes
- Hypotension (46% of subjects)
  - Majority= asymptomatic, grade 1, reported in the setting of routine BP checks
  - 5 total symptomatic events in 4 subjects
  - All were transient and resolved without medical intervention.
No Clear Correlation Between Dose and HR/BP

Shallow positive slope suggests no or minimal correlation between plasma exposure and decrease in blood pressure or increase in heart rate at exposure range obtained with daily doses between 2.5 and 30 µg/kg BMN 111.
Summary: Sustained Growth Effects of Vosoritide Through 30 Months, Program Progressing Rapidly

- Vosoritide demonstrates durable efficacy out to 30 months at pivotal dose (15 ug/kg):
  - Sustained increases in AGV compared to baseline AGV
  - Continued improvement over time in height z-score
  - Continued improvement over time in proportionality
  - No evidence of tachyphylaxis observed in pharmacodynamic response
- Generally well-tolerated across all doses
- Pivotal trial continues to enroll with anticipated enrolment completion mid-2018
- Infant/toddler study design being finalized, anticipate enrolment to begin 1H 2018
THANK YOU

Q&A
BMN 250 FOR MPS IIIB

BIOMARIN R&D DAY 2017

Maureen Cleary, M.D., F.R.C.P.C.H.
Consultant in Inherited Metabolic Disease and Senior Lecturer at Institute of Child Health at Great Ormond Street Hospital for Children
MUCOPOLYSACCHARIDOSIS (MPS)

Intracerebroventricular Enzyme Replacement Therapy

Dr. Maureen Cleary
Consultant Metabolic Paediatrician
Great Ormond St Hospital NHS Trust, London, UK
October 2017
Outline

• Lysosomes: function and dysfunction

• Mucopolysaccharidosis IIIB (Sanfilippo Syndrome Type IIIB)

• Overview of symptoms & complications

• Rationale for potential therapies

• BMN 250 programme
Lysosomal disorders

- Chronic progressive multisystem disorders
- Usually individuals appear normal at birth
- Phenotype evolves with time
- Enzymes involved in the degradation of
  - Sphingolipids
  - Glycoproteins
  - Glycosaminoglycans
Glycosaminoglycans

• Connective tissues:
  – Proteoglycans
    • protein core
    • complex sugars (glycosaminoglycans GAGs)
      • Dermatan sulfate
      • Heparan sulfate
      • Keratan sulfate
      • Chondroitin sulfate
Glycosaminoglycans & MPS sub-types

Heparan sulfate

MPS II (Hunter)

MPS I (Hurler, Scheie)

MPS III (Sanfilippo)
Symptoms & Complications predominance in MPS sub-types
# MPS Sub-types

<table>
<thead>
<tr>
<th>Type</th>
<th>Disease</th>
<th>Enzyme</th>
<th>Gene</th>
<th>BioMarin approved or in-clinic* therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Hurler/Scheie</td>
<td>α-L-iduronidase</td>
<td>IDUA</td>
<td>Aldurazyme</td>
</tr>
<tr>
<td>II</td>
<td>Hunter</td>
<td>Iduronate 2-sulfatase</td>
<td>IDS</td>
<td></td>
</tr>
<tr>
<td>III-A</td>
<td>Sanfilippo A</td>
<td>Sulfamidase</td>
<td>SGSH</td>
<td></td>
</tr>
<tr>
<td>III-B</td>
<td>Sanfilippo B</td>
<td>α-N-acetylglcosaminidase</td>
<td>NAGLU</td>
<td>BMN 250*</td>
</tr>
<tr>
<td>III-C</td>
<td>Sanfilippo C</td>
<td>Acetyl-CoA α glucosaminidie N-acetyltransferase</td>
<td>MPS3C</td>
<td></td>
</tr>
<tr>
<td>III-D</td>
<td>Sanfilippo D</td>
<td>N-acetylgalactosamine 6-sulfatase</td>
<td>GNS</td>
<td></td>
</tr>
<tr>
<td>IV-A</td>
<td>Morquio A</td>
<td>Galactose-6-sulfatase</td>
<td>GALNS</td>
<td>Vimizim</td>
</tr>
<tr>
<td>IV-B</td>
<td>Morquio B</td>
<td>β-galactosidase</td>
<td>GLB1</td>
<td></td>
</tr>
<tr>
<td>VI</td>
<td>Maroteaux-Lamy</td>
<td>N-acetylgalactosamine 4-sulfatase</td>
<td>ARSB</td>
<td>Naglazyme</td>
</tr>
<tr>
<td>VII</td>
<td>Sly</td>
<td>β-glucuronidase</td>
<td>GUSB</td>
<td></td>
</tr>
<tr>
<td>IX</td>
<td></td>
<td>Hyaluronidase</td>
<td>HYAL1</td>
<td></td>
</tr>
</tbody>
</table>
Sanfilippo Syndrome Type B Overview

- Lysosomal storage disorder caused by deficiency of α-N-acetylglucosaminidase (NAGLU)
- Leads to accumulation of heparan sulfate in the central nervous system (CNS) and peripheral organs

Somatic phenotype with severe neurological manifestations

Developmental delay
- (Speech)
- Age (yrs): 1-4

Severe behavioral problems
- (ADD, hyperactivity, aggressiveness, anxiety, sleep/wake)

Severe dementia
- Progressive intellectual decline
- Progressive motor retardation
- Age (yrs): 3-4

Death
- Cause: pneumonia, cachexia
- Age (yrs): ~13-20 (mean 16.6)

Attenuated phenotype: 40s

References:
Sanfilippo Syndrome Type B Pathology

- Intracellular Heparan Sulfate accumulation
  - Global neuronal loss and atrophy
  - Dilatation of lateral ventricles
  - White matter abnormalities
Cognitive Development Quotient (DQ): Natural History in Sanfilippo A

- DQ declines at similar rates in Sanfilippo A and B patients

Sanfilippo A data: Shapiro et al (2016), J Peds 170, pp. 278-287
Sanfilippo Syndrome Type B Outside of the Brain

- Hepatomegaly and splenomegaly
- Gut
  - Autonomic nerve supply
  - Mucosal involvement
  - Gut dysmotility
  - Tendency to diarrhoea/constipation
LSD and Treatments for the Brain

• Best way to access
  – Direct injection
  – Intrathecal
  – Intravenous
  – Intracerebroventricular (ICV)
    • Brineura via ICV successful in delivering enzyme into hard to reach tissues in the brain for Batten disease; approved 2017
What Measures Indicate a Treatment Effect?

• Biochemical change
  – Heparan sulfate especially in CSF
• Change in Brain structure
  – MRI brain volume
• Functional tests
  – Cognitive tests
• Somatic Effects
  – Hepatomegaly and splenomegaly
Summary of Sanfilippo Syndrome Type B Indication

• Sanfilippo B is a severe neurodegenerative disorder
• No current treatment
• Needs brain directed treatment
• Somatic manifestations also need attention
• Early experience of BMN 250 trial positive
THANK YOU
BMN 250 FOR MPS IIIB

BIOMARIN R&D DAY 2017

Steve Maricich, M.D., Ph.D.
Medical Director, Clinical Science, BioMarin
Study Design (3 Studies)

Baseline Observational Study (250-901) (1-10 y/o; DQ ≥ 50)

- ≥48 wks*
- N=20–30
- Eligible patients transition from 250-901 to 250-201
- 300 mg
  - ≥4 wks
  - Part 2 = 48 wks

- 100 mg
  - ≥4 wks
  - Part 1
    - ≥4 wks
    - ≥4 wks
    - Part 1
      - N=3

- 30 mg
  - ≥4 wks
  - Part 1
    - N=3

Treatment Study (250-201)

- 48 wks
  - Part 2
    - N=3 + (20–30)

Natural History Study (250-902) (0-18 y/o; no DQ requirement)

- Up to 192 wks

*Less if significant DQ decline.
Study Design (3 Studies)

Baseline Observational Study (250-901) (1-10 y/o; DQ ≥ 50)
- Eligible patients transition from 250-901 to 250-201
- Part 1: 30 mg, ≥4 wks, N=3
- Part 2: 100 mg, ≥4 wks, N=30
- 300 mg, ≥4 wks
- ≥48 wks
- Treatment Study (250-201)
  - Part 1: N=3
  - Part 2: N=3 + (20–30)
  - 48 wks

Natural History Study (250-902) (0-18 y/o; no DQ requirement)
- Up to 192 wks

- Safety/tolerability
- CSF heparan sulfate
- MRI liver
- Cognitive DQ

* Less if significant DQ decline.
Intracerebroventricular (ICV) Administration

Leveraging our Brineura Experience for Sanfilippo B

- Bypasses the blood-brain barrier
- 300mg ICV weekly
- Infusion time 5-10 minutes
BMN 250 is Generally Safe and Well-tolerated

<table>
<thead>
<tr>
<th>Event</th>
<th># of occurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doses administered/scheduled</td>
<td>230/240 (96%)</td>
</tr>
<tr>
<td>Treatment-emergent AEs</td>
<td>106 (0 serious)</td>
</tr>
<tr>
<td>Device-related AEs/SAEs</td>
<td>5 AEs</td>
</tr>
<tr>
<td></td>
<td>2 SAEs</td>
</tr>
<tr>
<td>BMN 250-related AEs/SAEs</td>
<td>11 AEs</td>
</tr>
<tr>
<td></td>
<td>4 SAEs</td>
</tr>
<tr>
<td>Study discontinuations</td>
<td>0</td>
</tr>
</tbody>
</table>

*Filter clogs (24): 13 full and 11 partial doses*
CSF HS levels normalize with BMN 250 treatment

Heparan sulfate (HS)

Untreated Sanfilippo B subjects

gray bar: median [range: unquantifiable, max] of non-affected
CSF HS levels normalize with BMN 250 treatment

- HS drops to non-affected range in 3/3 subjects after 1-2 30mg doses
- HS is maintained in the non-affected range in 3/3 subjects at 300mg dose
- Demonstrates *in vivo* biochemical activity of BMN 250

**Heparan sulfate (HS)**

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

**Gray bar:** median [range: unquantifiable, max] of non-affected
MRI liver volume normalizes with BMN 250 treatment

- Liver size normalized in treated subjects over 9-12 months
- Demonstrates systemic clinical effects of ICV administration

Control data: Murry et al (1995), Drug Metab Disp 23(10), pp. 1110-1116
Primary endpoint: cognitive developmental quotient (DQ)

Stable DQ = gaining skills over time

- Developmental quotient (DQ) = cognitive age/actual age * 100
  Example: 4 y/o child whose cognitive age equivalent is 2 y/o
  \[ DQ = \frac{2}{4} \times 100 = 50 \]

- Normal DQ = 100
Cognitive DQ declines in Sanfilippo B patients

- DQ declines over time in Sanfilippo B patients
- Progression over short time periods can be misleading

- 9 subjects with ≥ 12 weeks of data
- 12.5 – 97 m/o at screening
Cognitive DQ trends on BMN 250 treatment

- Developmental Quotient (DQ)
- Age (months)

- Normal

- 9001
- 9002
- 9003
BMN 250 Summary and Next Steps

• ICV-administered BMN 250 is well-tolerated by Sanfilippo B patients
• Early data is encouraging
  • Normalization of CSF HS in 3/3 BMN 250-treated subjects demonstrates that BMN 250 has in vivo biochemical activity in the CNS
  • Normalization of liver size in 3/3 BMN 250-treated subjects demonstrates that ICV-administered BMN 250 reaches peripheral circulation and has activity in somatic organs
  • Preliminary data suggest that DQ stabilized in 2/3 BMN 250-treated subjects
  • BioMarin’s studies are generating a robust data set that will serve as a comparator to assess treatment effects in BMN 250-201 Part 2

• Next steps
  • Ongoing intrasubject endpoint comparison with accruing longitudinal pre- and post-treatment data to determine natural history course and therapeutic efficacy of BMN 250
  • Mitigation steps for filter clogging
THANK YOU

Q&A
BMN 270 FOR HEMOPHILIA A

BIOMARIN R&D DAY 2017

Benjamin Kim, M.D., M.Phil.
Senior Medical Director, Clinical Science
Standard of Care for Severe Hemophilia A Has Significant Limitations

Quality of life impacted by breakthrough bleeds, need for long-term compliance with FVIII prophylaxis, and limits on physical activity

- FVIII prophylaxis has been efficacious in reducing spontaneous bleeds but not eliminating risk of bleeds
  - Peaks & troughs
  - Need to be administered prior to strenuous activity, surgery/procedure

- Compliance challenges
  - IV 2-3x (or more)/week
  - Venous access issues (CVCs: thrombosis infection/sepsis)

- Limitations on physical activities
  - Consider bleeding risks for each activity
  - Overall, physical activity may be decreased compared to general population
Gene Therapy with AAV is Ideal Candidate for Hemophilia A

Potential one-time treatment that replaces a defective gene with a normal one

• Intent of gene transfer therapy
  • Restore absent/defective FVIII by transferring functioning FVIII gene into liver cells
  • Enable continuous FVIII production and abrogates risk of bleeds

• Efficacy easy to assess
  • Clinical (use of replacement FVIII concentrates, bleed rates)
  • Laboratory (consistency of factor levels—no peaks & troughs)

• Over 180 AAV gene therapy clinical trials as of April 2017*
  • 20+ years of accumulated safety data with recombinant AAV
  • Vector shedding generally self-limited
  • Very low integration frequency, no neoplasms

• No concerns regarding compliance, potential to improve joint health and quality of life

*http://www.wiley.com//legacy/wileychi/genmed/clinical/
BMN 270: AAV5-hFVIII-SQ

In vivo transfer of a functional FVIII gene into hepatocytes

- Recombinant, replication-incompetent AAV5 vector
- Hybrid liver-specific promoter
- Codon-optimized human B domain-deleted (BDD) coagulation factor VIII with 14 amino acid “SQ” linker sequence
BMN 270: Proof of Concept with First-in-Human Study

Phase 1/2 Study Design

• Subjects enrolled sequentially into one of up to four cohorts based on FVIII activity at 3 weeks:
  1. 6E12 vg/kg given as a single IV dose
  2. 2E13 vg/kg
  3. 6E13 vg/kg
  4. 4E13 vg/kg

• Dose escalation occurred in cohorts 1-3 if the resulting FVIII activity at the Week 3 visit was < 5 IU/dL and gated by safety assessment

• Endpoints
  • Safety of a single IV administration of a recombinant AAV5-human FVIII vector
  • Change from baseline FVIII activity level
  • Annualized FVIII replacement therapy infusion rate
  • Annualized bleed rate
  • Change in health-related quality of life
BMN 270: Studied in Severe Hemophilia A Patients

**Broad Eligibility Criteria**

**KEY INCLUSION CRITERIA**

- Males that are 18 years or older with established severe hemophilia A (FVIII level <1 IU/dL)
- Treated/exposed to FVIII concentrates or cryoprecipitate for a minimum of 150 exposure days
- Greater or equal to 12 bleeding episodes therapy over the previous 12 months (on-demand subjects)
- No current or prior history of FVIII inhibitors

**KEY EXCLUSION CRITERIA**

- Detectable pre-existing immunity to the AAV5 capsid as measured by AAV5 transduction inhibition or AAV5 total antibodies (<10% screened with pre-existing AAV5 total antibodies)
- Significant liver dysfunction
  - ALT or TBili or ALP >3 fold ULN
  - INR > 1.4
  - Liver fibrosis on biopsy if performed
  - Liver cirrhosis by US
- Hepatitis B if surface antigen positive
- Hepatitis C if RNA is positive
BMN 270: Well-tolerated Across All Doses

Phase 1/2 Summary of Safety

- No subject developed inhibitors to FVIII
- No subject withdrew from the study
- 2 SAEs
  - Grade 2 pyrexia with myalgia and headache at time of infusion, resolved overnight
  - Planned total knee replacement for chronic arthropathy
- AEs of ALT elevation reported in 10/15 subjects:
  - Maximum ALT 119 U/dL
  - All events non-serious, transient (<7 weeks), mild
  - Use of corticosteroids well–tolerated; all 6E13 subjects off steroids
- Vector shedding detected in semen, usually below limit of quantification by Week 24
  - In minority of subjects, persistence in seminal fluid, not sperm (no vertical transmission risk)
  - Negligible horizontal transmission risk
Baseline FVIII activity for all subjects at study start was ≤1% of normal level

Results from 4E13 vg/kg cohort
(Sepetember 14, 2017 data cut)

Factor VIII Activity (IU/dL)

- Mean
- Median

Normal FVIII Range: 50-150 IU/dL
BMN 270: FVIII Levels Sustainably Normalized After 52 Weeks

Baseline FVIII activity for all subjects at study start was ≤1% of normal level

Results from 6E13 vg/kg cohort
(May 31, 2017 datacut)

Normal FVIII Range: 50-150 IU/dL
# BMN 270: Reduces Bleeds and Factor VIII Use

*Median annualized bleed and factor VIII use rates for 4E13 and 6E13 vg/kg were zero*

### 4E13 vg/kg (September 14, 2017 data cut)

<table>
<thead>
<tr>
<th></th>
<th>FVIII Prophylaxis Median (Mean, SD)</th>
<th>After BMN 270 Median (Mean, SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized Bleed Rate*</td>
<td>8.0 (12.2, 15.4)</td>
<td>0.0 (0.8, 1.9)</td>
</tr>
<tr>
<td>Annualized FVIII Use Rate*</td>
<td>155.5 (146.5, 41.6)</td>
<td>0.0 (2.7, 6.7)</td>
</tr>
</tbody>
</table>

### 6E13 vg/kg (After 52 weeks)

<table>
<thead>
<tr>
<th></th>
<th>FVIII Prophylaxis Median (Mean, SD)</th>
<th>After BMN 270** Median (Mean, SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized Bleed Rate*</td>
<td>16.5 (16.3, 15.7)</td>
<td>0.0 (0.7, 1.7)</td>
</tr>
<tr>
<td>Annualized FVIII Use Rate*</td>
<td>138.5 (136.7, 22.4)</td>
<td>0.0 (8.5, 20.9)</td>
</tr>
</tbody>
</table>

*Post-infusion data were based on data after Week 4

**4 of 6 patients had 0 bleeds requiring Factor VIII infusions after Week 4
AAV5-negative patients (>90% screened) experienced clinically meaningful benefit with BMN 270

- **4E13 vg/kg**
  - Targets lower end of normal FVIII activity range
  - Eliminates occurrence of spontaneous bleeds and minimizes FVIII use

- **6E13 vg/kg**
  - Targets middle of normal FVIII activity range
  - Eliminates occurrence of spontaneous bleeds and minimizes FVIII use

- AAV5-FVIII gene therapy well-tolerated
  - Mild elevations in liver enzymes were transient
  - No sequelae related to short-term steroid use
  - No FVIII inhibitors detected
Next Steps: Three Clinical Studies Planned in Near-Term

Two Phase 3 studies and one Phase 1/2 study in AAV5+ patients

BMN 270 Clinical Development Goals

- Obtain global registration in adult hemophilia A patients who received FVIII prophylaxis
- Maximize choice with flexible dosing
- Maximize population that can be treated
BMN 270: Two Separate Registrational Studies Planned

6E13 vg/kg (Phase 3 Study 270-301)
- N ≈ 40; 52-week study with 4-year long-term follow-up
- Patients as their own control
- First patient enrolled by YE 2017; target last patient in by YE 2018

4E13 vg/kg (Phase 3 Study 270-302)
- N ≈ 40; 52-week study with 4-year long-term follow-up
- Patients as their own control
- First patient enrolled by YE 2017/start 2018

**Key inclusion criteria:** Males ≥ 18 years with severe hemophilia A (FVIII ≤1 IU/dL) on FVIII prophylaxis; AAV5 Ab (-)

**Endpoints:** Change from baseline FVIII activity level; annualized FVIII replacement therapy infusion rate, annualized bleed rate (non-inferiority comparison)
BMN 270: Phase 1/2 Study in AAV5+ Patients Planned

Pre-clinical studies demonstrate efficacious gene transfer in monkeys with low-titer AAV5 antibodies

Phase 1/2 Study (270-203) in AAV5+ with 6E13kg/vg dose

- N ≈ 10
- Two cohorts with 5 patients each
  - Cohort 1: Titer ≤ 500
  - Cohort 2: Titer > 500
- First patient enrolled in 1H18

Key inclusion criteria: Males ≥ 18 years with severe hemophilia A (FVIII ≤ 1 IU/dL) on FVIII prophylaxis; AAV5 Ab (+)

Endpoints: Change from baseline FVIII activity level; annualized FVIII replacement therapy infusion rate, annualized bleed rate
Summary: Health Authorities Aligned on Clear Path to Registration

*BMN 270 IND & CTA active, BioMarin poised to start*

**All potential participants enthusiastic and ready to get started**
- ~40 sites identified globally
- No anticipated challenges finding patients
- First patient enrolled by YE 2017

**Supply in-hand from CMO to start Phase 3 studies by YE 2017**
- Construction of BMRN clinical/commercial supply facility completed
- BMRN facility to supply Phase 3 studies in early 2018
  - Eliminates risk of moving supply after Phase 3 and for commercialization
  - Robert Baffi, EVP Technical Operations, to provide more information
THANK YOU
STEVEN PIPE, M.D.
LAURENCE A. BOXER RESEARCH PROFESSOR OF PEDIATRICS AND COMMUNICABLE DISEASE, AS WELL AS PROFESSOR OF PATHOLOGY AT THE UNIVERSITY OF MICHIGAN

FOCUSED ON COAGULATION FACTOR VIII AND THE MOLECULAR MECHANISMS OF HEMOPHILIA A
PRODUCTION CAPABILITIES FOR BMN 270

BIOMARIN R&D DAY 2017

Robert Baffi, Ph.D., M.B.A.
Executive Vice President Technical Operations
Production Capabilities for BMN 270

BioMarin’s Vector Production Facility
Proven Capabilities For Biologic Production

• Strategic Process Development

• Vector Production Considerations:
  • Viral Safety
  • Cell Line Selection Criteria: Insect vs Human
  • Purity: Full vs Empty Capsids

• Conclusions: Production Capabilities for BMN 270
Proven Capabilities For Biologic Production

6 Approved Products

Distributed in 70 Countries

2 Licensed Biologic Facilities

Generating $1.5B in Worldwide Sales

IND to Approval is Less than Half the Industry Average

65 GMP/GLP/GCP Inspections by
FDA, EMA, MHRA, HPRA, ANVISA, MHW, HPB and TMMDA
Size = Complexity

**Small Molecule Drug**
- Aspirin
  - 21 atoms
  - (Mw 180)

**Large Molecule Drug**
- hGH
  - ~ 3000 atoms
  - (Mw 22,000)

**Large Biologic**
- Enzymes
  - ~ 25,000 atoms
  - (Mw 150,000)

**Pegylated Proteins**
- ~ 150,000 atoms
  - (Mw 1,200,000)

**Size**
- Kuvan, Kuvan PFOS
- Firdapse
- Vosoritide
- Aldurazyme, Naglazyme
- Vimizim, Brineura
- Pegvaliase

**Complexity**
- Bike
  - ~ 20 lbs
- Car
  - ~ 3000 lbs
- F16 Jet
  - ~ 25,000 lbs
  - (without fuel)
- Air Force One (Boeing 747)
  - ~ 1,200,000 lbs
  - (Maximum take-off weight)
Size = Complexity

**AAV**
3 Coat Proteins + DNA Gene Coding for Factor VIII
~ 600,000 atoms
(Mw ~ 4,000,000)

**Mastering Technology**

**API** - **rDNA** - **Vector Biology**

- Chemical Synthesis
- Bacterial Fermentation
- Cell Culture Fed-Batch
- Cell Culture Perfusion
- Vector Production

**Drug Product**

- Tablets
- Capsules
- Sachets
- Aseptic Fill Finish
- Vials
- Cartridges
- Drug Combination Devices

**BMN 270**
International Space Station
(Weightless)
Strategic Process Development

Great Surfers Know How to Handle Being in the PIPE

It’s Scary
Looks Easy When Someone Knows How to Do It
The Wipeouts Are Spectacular
Great Companies Know How to Handle Being in the PIPE

Looks Scary
Looks Easy When Someone Knows How to Do It
The Wipeouts Are Spectacular
Strategic Process Development

Keys to the PIPE

Know the Product
Crystall Structure for N-acetylgalactosamine-6-sulfatase (Vimizim)

Characterized the Impurities

Develop the Process

Validate the Equipment
Galli Facility – Flexible and Adaptable

Approved Multi-Product Production
800 people on site in Novato

Contains 3 Independent Production Suites
Perfusion
Fed Batch
Fermentation

Currently Produces 7 Different Proteins

Commercial Products
Vimizim
Brineura
Naglazyme
Aldurazyme

Clinical Products
Pegvaliase
Vosoritide
BMN 250 (Naglu)

Location For Global Functions
Quality
Logistics
Engineering
Process Sciences

Media Preparation Incorporating HTST Viral Inactivation Technology

Optimized For Multi-Product Production
Shanbally Facility – Additional Capacity and Capabilities
Shanbally Facility – Additional Capacity and Capabilities

Approved Multi-Product Production
300 people on site at Shanbally

Two Independent Production Suites
Perfusion
Fed Batch

Two Products Successfully Transferred
GALNS (Perfusion)
TPP1 (Fed Batch)

Media Preparation Incorporating
HTST Viral Inactivation Technology

Licensed Activities
Bulk Production
QC and QA Release
Packaging
Distribution

Expansion Plans Under Review
Bulk Biologics
Gene Therapy
Fill Finish
Vector Production Considerations

• Gene therapy today shares many similarities with recombinant protein products circa 1985
  
  • Production requirements as measured by actual DNA quantities are small but extremely difficult to produce
  
  • Multiple production systems developing for a nascent industry
    • Human, insect cell lines in development
    • Various serotypes being evaluated
    • Purification by centrifugation vs chromatography, or both
  
  • Regulatory PIPE concerns that need to be addressed:
    • Viral Safety
    • Facility and Process Design
    • Validation Strategies
    • Characterization of Complex Products
    • Quality Systems, Purity Levels and Specifications
# PIPE WIPEOUTS – Viral Contamination

## Reported Major Viral Contamination Events in Biopharmaceutical Manufacturing

<table>
<thead>
<tr>
<th>Virus</th>
<th>Cell</th>
<th>Year</th>
<th>Company</th>
<th>Reported by</th>
</tr>
</thead>
<tbody>
<tr>
<td>EHDV</td>
<td>CHO</td>
<td>1988</td>
<td>Bioferon GmbH</td>
<td>Bioferon GmbH</td>
</tr>
<tr>
<td>MVM</td>
<td>CHO</td>
<td>1993</td>
<td>Genentech</td>
<td>Genentech</td>
</tr>
<tr>
<td>MVM</td>
<td>CHO</td>
<td>1994</td>
<td>Genentech</td>
<td>Genentech</td>
</tr>
<tr>
<td>Reovirus</td>
<td>Homo 1 Kidney</td>
<td>1999</td>
<td>Abbott Labs</td>
<td>FDA</td>
</tr>
<tr>
<td>Reovirus</td>
<td>CHO</td>
<td>Not Disclosed</td>
<td>Not Disclosed</td>
<td>BioReliance</td>
</tr>
<tr>
<td>Cache Valley</td>
<td>CHO</td>
<td>1999</td>
<td>Amgen/CMO</td>
<td>Amgen</td>
</tr>
<tr>
<td>Cache Valley</td>
<td>CHO</td>
<td>2000</td>
<td>Not Disclosed</td>
<td>BioReliance</td>
</tr>
<tr>
<td>Vesivirus 2117</td>
<td>CHO</td>
<td>2003</td>
<td>Boehringer-Ingelheim</td>
<td>Boehringer-Ingelheim</td>
</tr>
<tr>
<td>Cache Valley</td>
<td>CHO</td>
<td>2003</td>
<td>Not Disclosed</td>
<td>BioReliance</td>
</tr>
<tr>
<td>Cache Valley</td>
<td>CHO</td>
<td>2004</td>
<td>Not Disclosed</td>
<td>BioReliance</td>
</tr>
<tr>
<td>Human Adenovirus</td>
<td>HEK 293</td>
<td>2010</td>
<td>Eli Lilly</td>
<td>Eli Lilly</td>
</tr>
<tr>
<td>MVM</td>
<td>CHO</td>
<td>2006</td>
<td>Amgen</td>
<td>Amgen</td>
</tr>
<tr>
<td>Vesivirus 2117</td>
<td>CHO</td>
<td>2008</td>
<td>Genzyme, Belgium</td>
<td>Genzyme</td>
</tr>
<tr>
<td>Vesivirus 2117</td>
<td>CHO</td>
<td>2008</td>
<td>Genzyme, USA</td>
<td>Genzyme</td>
</tr>
<tr>
<td>Vesivirus 2117</td>
<td>CHO</td>
<td>2009</td>
<td>Genzyme, USA</td>
<td>Genzyme</td>
</tr>
<tr>
<td>MVM</td>
<td>CHO</td>
<td>2009</td>
<td>Merrimack</td>
<td>Merrimack</td>
</tr>
<tr>
<td>PCV-1</td>
<td>Vero</td>
<td>2010</td>
<td>GlaxoSmithKline</td>
<td>GlaxoSmithKline</td>
</tr>
</tbody>
</table>

Presentation at the PDA Annual Meeting in Phoenix, April 15-18, 2012
The MIT Consortium on Adventitious Agent Contamination in Biomanufacturing; Mike Wiebe, Ph.D. Quantum Consulting Co
PIPE WIPEOUTS – Viral Contamination

These contaminations have resulted in the following:

• Plants Shutdown for Months at a Time

• Delay to Approvals for Products in Development

• Extensive Costs to Remediate (>\$300M)

• Loss Revenues (>\$1B)

• Product Shortages and Rationing of Product to Patients

• Regulatory Scrutiny: Warning Letters and Consent Decrees
PIPE WIPEOUTS – Viral Contamination

Genzyme Market Cap Before and After 2008 Viral Contamination

Lost $5.5B (28%) in Market Cap Post Contamination
Acquired By Sanofi in 2011 For Virtually No Premium Over Pre-Contamination Market Cap

![Market Cap Chart]

- 2008: $15B
- 2009: $10B
- 2010: $10B
### Production Cell Lines Selection Criteria

**TABLE I**

<table>
<thead>
<tr>
<th>Family</th>
<th>Virus</th>
<th>Reference for Growth in HEK293</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adenoviridae</strong></td>
<td>Adenovirus type 5*</td>
<td><em>J. Virol. 1998</em>, 72 (4), 2975–2982</td>
</tr>
<tr>
<td></td>
<td>Adenovirus types 40 &amp; 41</td>
<td>Enteric adenoviruses V. Maurer <em>et al.</em></td>
</tr>
<tr>
<td></td>
<td>Bovine Adenovirus type 5</td>
<td></td>
</tr>
<tr>
<td><strong>Parvoviridae</strong></td>
<td>AAV (adeno associated virus)</td>
<td><em>J. Virol. 1998</em>, 72 (7), 5472–5480</td>
</tr>
<tr>
<td></td>
<td>Human Parvovirus B19</td>
<td><em>J. Virol. 1995</em>, 60 (12), 8096–8101</td>
</tr>
<tr>
<td><strong>Reoviridae</strong></td>
<td>Bluetongue Virus</td>
<td></td>
</tr>
<tr>
<td><strong>Paramyxoviridae</strong></td>
<td>Bovine Parainfluenza Virus type 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bovine Respiratory Syncytial Virus</td>
<td></td>
</tr>
<tr>
<td><strong>Coronaviridae</strong></td>
<td>Coronavirus</td>
<td><em>American Journal of Epidemiology 1972</em>, 96 (2), 94–106</td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Journal of Infectious Diseases 1988</em>, 158 (1), 182–185</td>
</tr>
<tr>
<td><strong>Herpesviridae</strong></td>
<td>EBV</td>
<td><em>J. Virol. 1999</em>, 73 (3), 2115–2125</td>
</tr>
<tr>
<td></td>
<td>Human Herpes Virus type 1</td>
<td><em>J. Virol. 1996</em>, 70 (2), 1132–1136</td>
</tr>
<tr>
<td></td>
<td>Human Herpes Virus type 8 (KSHV)</td>
<td><em>J. Virol. 1998</em>, 72 (6), 5182–5188</td>
</tr>
<tr>
<td></td>
<td>Infectious Bovine Rhinotracheitis virus</td>
<td></td>
</tr>
<tr>
<td><strong>Retroviridae</strong></td>
<td>Porcine Type C Retrovirus</td>
<td><em>J. Virol. 1998</em>, 72 (4), 3082–3087</td>
</tr>
<tr>
<td><strong>Picornaviridae</strong></td>
<td>Rhinovirus</td>
<td><em>The Lancet 1962</em>, 280 (7251), 320–321</td>
</tr>
</tbody>
</table>
Production Cell Lines Selection Criteria

Advantages of Baculo/Sf9 Manufacturing System

Similar potency between vectors produced in Sf9/Baculovirus system or HEK 293

- Several AAV5-FVIII constructs were developed and tested side by side
- In vivo animal studies demonstrated comparability in efficacy of vectors produced in Sf9/Baculovirus vs HEK 293 expression systems
- Sf9 cells can be grown to high titers (30-fold greater than HEK 293)
- Sf9 cells are easier to scale-up for production (2000L or higher)
- Sf9 cells have a much lower risk of infection with human adventitious viruses than HEK 293 cells
- Sf9 cells are not known to carry oncogenes as does HEK 293

Comparison of Sf9/baculovirus (Baculo)- and HEK293 (293)-produced AAV5 vectors in RAG2−/− mice (n=10/group). Plasma human FVIII (hFVIII) protein levels were assessed in mouse plasma 5 or 10 weeks following a single tail vein administration of vehicle or AAV5-SQ or AAV5-V321 at 2e13 vg/kg. Results are mean ± SEM.
Process Development is Tuned to Health Authority Concerns

Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origins (Q5A)

1. Selecting and testing cell lines and other raw materials, including media components, for the absence of viruses which may be infectious and/or pathogenic for humans; Selected Sf9 cell line as it has lower risk for infection with virus pathogenic for humans

2. Assessing the capacity of the production processes to clear infectious viruses; See Table

<table>
<thead>
<tr>
<th>Virus</th>
<th>Description</th>
<th>Family</th>
<th>Genome</th>
<th>Size (nm)</th>
<th>Enveloped</th>
<th>Viral Reduction Log 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-MuLV</td>
<td>Xenotropic Murine Leukemia Virus</td>
<td>Retroviridae</td>
<td>RNA</td>
<td>80-130</td>
<td>Yes</td>
<td>&gt;15.4</td>
</tr>
<tr>
<td>VSV</td>
<td>Vesicular stomatitis virus</td>
<td>Rhabdoviridae</td>
<td>RNA</td>
<td>75 x 180</td>
<td>Yes</td>
<td>&gt;18.7</td>
</tr>
<tr>
<td>AcNPV</td>
<td>Autographa californica nucleopolyhedrovirus</td>
<td>Baculoviridae</td>
<td>DNA</td>
<td>450 x 100</td>
<td>Yes</td>
<td>&gt;15.7</td>
</tr>
<tr>
<td>Reo-3</td>
<td>Reovirus type 3</td>
<td>Reoviridae</td>
<td>RNA</td>
<td>60-80</td>
<td>No</td>
<td>&gt;12.1</td>
</tr>
<tr>
<td>PPV</td>
<td>Porcine parvovirus</td>
<td>Parvoviridae</td>
<td>DNA</td>
<td>18-26</td>
<td>No</td>
<td>&gt;10.3</td>
</tr>
</tbody>
</table>

3. Testing the product at appropriate steps of production for absence of contaminating infectious viruses.

All lots are tested for virus at time of harvest as it has highest chance of detection

http://www.ich.org
Process Development is Tuned to Health Authority Concerns

Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (Q6B)

Product-related impurities are molecular variants arising during manufacturing and/or storage, which do not have properties comparable to those of the desired product with respect to activity, efficacy and safety.

Electron Microscopy of Full Capsids

We Have Developed A Purification Process That Virtually Eliminates the Co-Purification of Empty Capsids

http://www.ich.org
Removal of Empty Capsids from Type 1 Adeno-Associated Virus Vector Stocks by Anion-Exchange Chromatography Potentiates Transgene Expression, Masashi et al., Molecular Therapy, Volume 13, Issue 4, April 2006, Pages 823-828
Leveroni Facility – Vector Production

- **Fully Integrated Vector Production Facility**
- **Facility Design Vetted with Health Authorities**
- **Single Use Technology Throughout**
- **Supports Multi-Host Production**
- **Designed for Multiple 2000L Bioreactors**

**Ballroom Design to Maximize Flexibility**

**Isolator System Used For Fill Finish**
Conclusion: Production Capabilities for BMN 270

We Have Had Positive & Ongoing Communication With Health Authorities
And Have A Thorough Understanding of CMC Regulatory Expectations

Process
- We Have Developed a Robust Vector Manufacturing Process
- Consistent With ICH Guidance Facilitating World Wide Registration

Scale
- Fermentation, Purification & Filling Operations Performed at Full Scale

Facility
- Completed a Facility Intended for Commercial Production and it is Operational
- Material Generated Will Support Clinical and Commercial Demand
- Capable of Supporting ~2,000 Patients Per Year
THANK YOU
CLOSING STATEMENTS

BIOMARIN R&D DAY 2017

Jean-Jacques Bienaimé
Chairman and Chief Executive Officer
Thank You Guest Speakers

**Maureen Cleary, M.D., F.R.C.P.C.H.**
Consultant in Inherited Metabolic Disease and Senior Lecturer at Institute of Child Health at Great Ormond Street Hospital for Children
- Focused on Metabolic Disorders including Lysosomal Storage Disorders and has led many clinical research trials
- Member of the clinical expert advisory group for the Highly Specialised LSD NCG service and, following the NHS reforms, represents North London on the Inherited Metabolic Diseases Clinical Reference Group
- Clinical trial investigator on BMN 250 for MPS IIIB program

**Nicola Longo, M.D., Ph.D.**
Professor of Pediatrics and Chief, Division of Medical Genetics, University of Utah
- Chief of the Division of Medical Genetics, Director of the Metabolic Service in the Department of Pediatrics, Director of the Training Program in Clinical Biochemical Genetics and Medical co-Director of the Biochemical Genetics and Newborn Screening Laboratories at ARUP Laboratories in Salt Lake City
- Clinical trial investigator on pegvaliase program

**Steven Pipe, M.D.**
Laurence A. Boxer Research Professor of Pediatrics and Communicable Disease, as well as Professor of Pathology at the University of Michigan, Ann Arbor, Michigan
- Medical director of the Pediatric Hemophilia and Coagulation Disorders Program and of the Special Coagulation Laboratory at the University of Michigan
- Focused on coagulation factor VIII and the molecular mechanisms of hemophilia A

**Massimo Pandolfo, M.D., Ph.D.**
Professor and Chief of Neurology and Director Laboratory of Experimental Neurology, Universite Libre Bruxelles, Hospital Erasme, Brussels, Belgium
- Global expert in the clinical manifestations of Friedreich’s ataxia (FA)
- Clinical investigator on numerous studies focused on neurodegenerative diseases
BioMarin’s Diverse and Unparalleled Rare Disease Portfolio

**Pegvaliase for PKU:**
Great patient retention; hypersensitivity diminishing;
over 700 patient years/up to 7 years experience;
PATIENTS GET BETTER!

**Vosoritide for Achondroplasia:**
Durable GV and biomarker response; continued improvement in proportionality;
Phase 3 on track; initiating infant/toddler study

**Valrox (BMN 270) for Hemophilia A:**
2 doses normalizing FVIII expression; efficacy maintaining;
Global health authority endorsement; Phase 3 enrollment on track by YE

**BMN 250 for MPS IIIB:**
Normalization of substrate; normalization of organ size;
Encouraging DQ results

**BMN 290 for Friedrich’s Ataxia:**
Devastating orphan indication;
no current treatments; disease modifying approach
BMN 270: Hematologists Support Higher Sustained FVIII Levels*

* Source: LEK research

".....Efficacy is what counts and BMN 270 is not only aimed at reducing bleeding, but also freeing the patient completely...."

- Hematologist, Denmark

"..... BMN 270 is much more attractive than [the furthest along competitor] because it achieves higher FVIII levels...."

- Hematologist, U.S.

"..... I don’t see the reason for [the competitor] if BMN 270 exists. FVIII levels are lower meaning patients will need to be treated with supplemental FVIII which will not be the case with BMN 270...."

- Hematologist, U.S.
Physicians Anticipate that Vosoritide could Positively Impact Achondroplasia Disease Burden and Quality of Life*

“... I would look for a product to restore the proportions and final height of patient which would prevent neurological complications and spinal cord compression. Restoring height may reduce the severity or even eliminate these comorbidities ...” - Clinical Geneticist, U.S.

“... These patients have day to day living issues. They can’t drive, it’s hard to reach countertops, it’s challenging to get clothing - they require special adaptations for those sorts of day to day activities. It would be nice to see a change in their size ...” - Pediatric Endocrinologist, U.S.

“... Assuming no impact on morbidities, the choice for [vosoritide] will depend on the patient, their parent and the goals for their child. Particularly, how important 4” is for their child without knowing the long term side effects ...” - Pediatric Endocrinologist, U.S.

* Source: LEK research
Numerous Anticipated Catalysts on the Horizon

Significant events expected over the next 12 months

- BMN 270: Global Registralional Studies to begin by year-end
- Pegvaliase: MAA filing in EU
- Vosoritide infant and toddler study start
- BMN 290 for Friedreich's Ataxia: Phase 1/2 study start
- Pegvaliase approval decision in the US
- Vosoritide: Phase 3 enrollment completion
- Financial: Increasing non-GAAP Profitability

4Q17 — 2018
Our Path Forward: Strategies for Growth

- Non-GAAP Profitability FY 2017
- Continue to Grow Top-line ~15% to 2020
- Accelerated Growth 2020 and beyond
- Operating Expenses Increasing less than Revenue
- Increasing non-GAAP Profitability
Please join us in the foyer for lunch and informal Mix & Mingle with BioMarin management and speakers.

THANK YOU