Preliminary safety and pharmacodynamic response data from a Phase 1/2 study of ICV BMN 250, a novel enzyme replacement therapy for the treatment of Sanfilippo Syndrome Type B (MPS IIIB)

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This presentation contains forward-looking statements about the business prospects of BioMarin Pharmaceutical Inc., including, without limitation, statements about the development plans for BMN 250, the conclusions about BMN 250 based upon the preliminary results presented and expectations regarding the clinical trials for this product candidate. These forward-looking statements are predictions and involve risks and uncertainties such that actual results may differ materially from these statements. These risks and uncertainties include, among others: results and timing of current and planned clinical trials of its product candidates; final analysis of the clinical trial data collected to date, the content and timing of decisions by the FDA, the EMA and other regulatory authorities concerning its product candidates; our ability to manufacture sufficient quantities of BMN 250 for clinical trials, commercial launch and other preapproval requirements; and those other risks detailed from time to time under the caption "Risk Factors" and elsewhere in the Company's Securities and Exchange Commission (SEC) filings, including the Company's Quarterly Report on Form 10-Q for the quarter ended June 30, 2017, and future filings and reports by the Company. The Company undertakes no duty or obligation to update any forward-looking statements contained in this press release as a result of new information, future events or changes in its expectations.
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Sanfilippo Syndrome Type B (MPS IIIB)

- 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

Severe neurological manifestations with mild somatic phenotype

Severe behavioral problems
(ADD, hyperactivity, aggressiveness, anxiety, sleep/wake)
Progressive intellectual decline

Developmental delay
(Speech)
Age (yrs) 1-4 3-4
Severe dementia
Progressive motor retardation
Death
Cause: pneumonia, cachexia

Approximately 13-20
(mean 16.6)
Attenuated phenotype: 40s

References:
Eligible patients transition from 250-901 to 250-201

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

N=20–30

30 mg
N=3

≥4 wks

≥4 wks

≥4 wks

≥4 wks

≥4 wks

≥4 wks

Part 1
N=3

Part 2 = 48 wks

Part 2
N=3 + (20–30)

300 mg

≥4 wks

Treatment Study (250-201)

≥4 wks

*Less if significant DQ decline.
Eligible patients transition from 250-901 to 250-201

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

- 30 mg N=3
  - ≥4 wks
  - ≥4 wks
  - ≥4 wks
  - ≥4 wks
  - Part 1 N=3
- 100 mg ≥4 wks
- 300 mg ≥4 wks
  - Part 2 = 48 wks

Treatment Study (250-201)

- 48 wks N=3 + (20–30)

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

*Less if significant DQ decline.*
Safety and Tolerability

BMN 250-201 Part 1
- Total doses given: 125/128* (3 subjects)
- Treatment-emergent AEs (TEAEs): 90
  - Pyrexia, vomiting, headache, URI most common
- No serious TEAEs
- Device-related AEs: 7
  - ICV infection prior to first BMN 250 infusion (2 AEs, 2 SAEs in 1 subject)
  - Site erythema (1 AE in 1 subject)
  - CSF pleocytosis (1 AE in 1 subject)
  - Blood clot in CSF (1 AE in 1 subject)
- BMN 250-related AEs: 11
  - Pyrexia/fever (9 in 2 subjects)
  - Bradycardia (2 in 1 subject)

Missed doses:  
*Illness (2), IP (1)
**Sedation (1), illness (1), filter clog (1)

BMN 250-201 Part 2 (as of 6/13/17)
- Total doses given: 26/29** (4 subjects)
- TEAEs: 16
  - Pyrexia, vomiting most common
  - No serious TEAEs or device-related AEs
Safety and Tolerability

BMN 250-201 Part 1
• Total doses given: 125/128* (3 subjects)
• Treatment-emergent AEs (TEAEs): 90
  • Pyrexia, vomiting, headache, URI most common
• No serious TEAEs
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• BMN 250-related AEs: 11
  • Pyrexia/fever (9 in 2 subjects)
  • Bradycardia (2 in 1 subject)

BMN 250-201 Part 2 (as of 6/13/17)
• Total doses given: 26/29** (4 subjects)
• TEAEs: 16
  • Pyrexia, vomiting most common
  • No serious TEAEs or device-related AEs

BMN 250-201 Part 2 (current)
• Total doses given: 79/83*** (6 subjects)
• BMN 250-related SAEs: (4 in 2 subjects)
  • Vomiting (2), fluctuating consciousness (1), CSF pleocytosis (1)
• BMN 250-related AEs causing dose change: (4 in 1 subject)
  • Vomiting, headache, fever, CSF pleocytosis)
  • Dosing decreased to 30mg, then titrated back to 300mg over two weeks without further AEs
  • These AEs and SAEs were self-limited

Missed doses:
*Illness (2), IP (1)
**Sedation (1), illness (1), filter clog (1)
***Illness (3), PI concern (1)

Filter clogs (24): 13 full and 11 partial doses

ICV administration of BMN 250 is safe and well-tolerated

No study discontinuations or fatalities in Part 1 or Part 2
CSF Heparan Sulfate Levels

Heparan sulfate (HS)

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

Untreated Sanfilippo B subjects

- Sensi-Pro NRE

Unique structure
Measureable only in Sanfilippo B patients

Common structures
present in unaffected people
Unsaturated (-18 daltons)

Sensi-Pro Total HS

Composition of the glycan – sulfation and quantity

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

Heparan sulfate (HS) non-reducing ends (NRE)

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

Untreated Sanfilippo B subjects

- Sensi-Pro NRE

Unique structure
Measureable only in Sanfilippo B patients

Common structures
present in unaffected people
Unsaturated (-18 daltons)

Sensi-Pro Total HS

Composition of the glycan – sulfation and quantity
CSF Heparan Sulfate Levels

Heparan sulfate (HS)

Untreated Sanfilippo B subjects

gray bar: median [range: unquantifiable, max] of non-affected
CSF Heparan Sulfate Levels

Heparan sulfate (HS)

Untreated Sanfilippo B subjects

30 mg QW 100 mg QW 300 mg QW

HS non-reducing ends (NRE)

gray bar: median [range: unquantifiable, max] of non-affected
CSF Heparan Sulfate Levels

Heparan sulfate (HS)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Untreated Sanfilippo B subjects</th>
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<tbody>
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<td>30 mg QW</td>
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<td></td>
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<tr>
<td>300 mg QW</td>
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</tbody>
</table>

Untreated Sanfilippo B subjects

HS non-reducing ends (NRE)

gray bar: median [range: unquantifiable, max] of non-affected HS non-reducing ends (NRE)

30 mg QW 100 mg QW 300 mg QW

Untreated Sanfilippo B subjects

HS in 3/3 subjects and HS-NRE in 2/3 subjects drop to non-affected range by 300mg dose
MRI Liver Volume/Body Weight: Natural History and Control

- 6 subjects with ≥ 24 weeks of data
- 12.5 – 76 m/o at screening

Liver is large in all subjects
Liver size normalized to body weight increases over time in most subjects

Control data: Murry et al (1995), Drug Metab Disp 23(10), pp. 1110-1116
Liver size decreased ~38-50% in treated subjects over 9-12 months.

Demonstrates systemic clinical effects of ICV administration.

Cognitive DQ Progression by Age: Natural History

- 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 Progression by Age: Natural History and 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
Cognitive DQ Progression by Age: Natural History and Treatment
Summary

• ICV-administered BMN 250 is well-tolerated by Sanfilippo B patients

• Pharmacodynamic results
  • Normalization or near-normalization of CSF HS and HS-NRE in 3/3 BMN 250-treated patients
  • Similar results seen in mouse and dog models: demonstrates translatability of model systems to human
  • Conclusion: BMN 250 has *in vivo* biochemical activity in the CNS

• Liver size
  • Natural history: increased in Sanfilippo B patients
  • Treatment: normalized liver size in 3/3 subjects
  • Similar results seen in mouse model: demonstrates translatability of model systems to human
  • Conclusion: ICV-administered BMN 250 reaches peripheral circulation and has activity in somatic organs

• DQ
  • Natural history: DQ decreased over time in Sanfilippo B patients
  • Treatment: DQ showed improvement from pre-dose baseline in some subjects
  • Conclusion: natural history approximates that seen in Sanfilippo A; robust data set will serve as 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
  • Mitigation steps for filter clogging
Thank you