ENHANCED SUPPORT FOR THE DEVELOPMENT OF PROMISING NEW MEDICINES: PRIME ONE YEAR ON

Industry Case study 1 - Gene therapy for the treatment of haemophilia A

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Six Approved Products and a Robust Clinical Portfolio

Commercialized Products

Brineura™ (cerliponase alfa)

Naglazyme® (GALSULFASE)

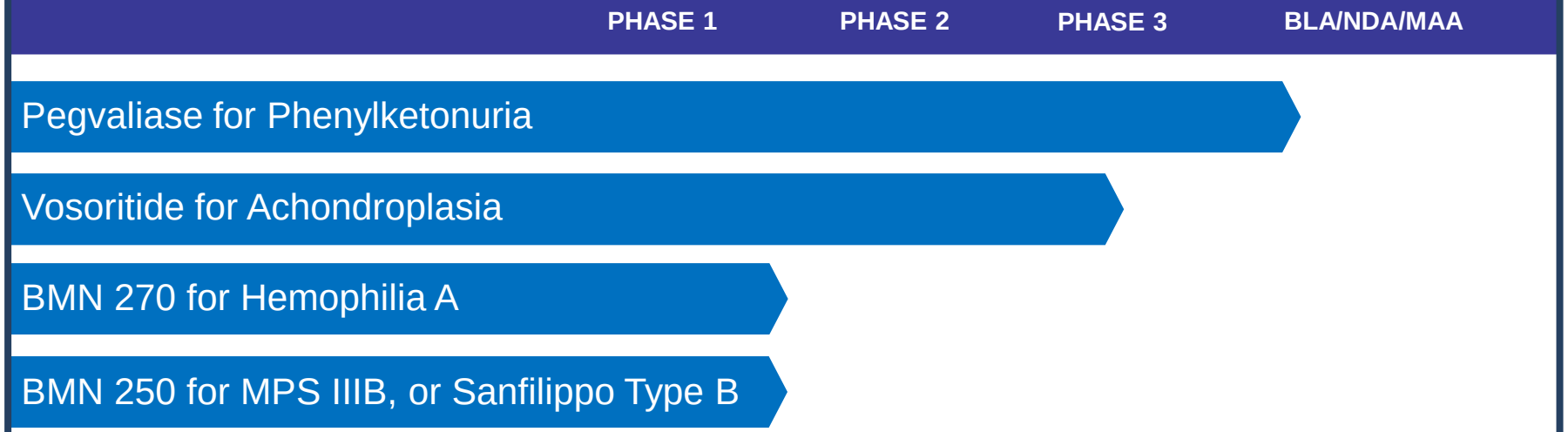
KUVAN® (sapropterin dihydrochloride) Tablets

ALDURAZYME® (LARONIDASE)

VIMIZIM® (elosulfase alfa)

FIRDAPSE™ amifampridine

Late-stage Development Pipeline



Overview of Haemophilia A

- Haemophilia A is a serious X-linked recessive bleeding disorder caused by mutations in the Factor VIII (FVIII) gene that codes for FVIII protein, an essential cofactor in the coagulation cascade.

Severity	FVIII Level	Bleeding Episodes
Severe	< 1 IU/dL or < 1 % of normal	Spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable haemostatic challenge.
Moderate	1-5 IU/dL or 1-5% of normal	Occasional spontaneous bleeding; prolonged bleeding with minor trauma or surgery.
Mild	>5-40 IU/dL or >5-<40% of normal	Severe bleeding with major trauma or surgery. Spontaneous bleeding is rare.

- Clinical manifestations of severe FVIII deficiency are frequent spontaneous bleeding episodes in joints and soft tissues causing permanent disability and occasionally death from haemorrhage when the brain is involved.
- Current treatments consists of intravenous injection of plasma derived or recombinant FVIII protein concentrates at the time of a bleed or prophylactically to prevent bleeding episodes.

Rationale for Development of BMN 270 for the Treatment of Haemophilia A

- Haemophilia A is well suited to a gene therapy approach as clinical manifestations are attributable to the lack of a single gene product (FVIII)
- BMN 270 offers the potential of continuous endogenous production of FVIII at clinically meaningful levels:
  - Significantly alter the bleeding phenotype
  - Eliminate abrupt peaks and troughs which can be seen with exogenous replacement therapy.
  - Eliminate the need for frequent infusions

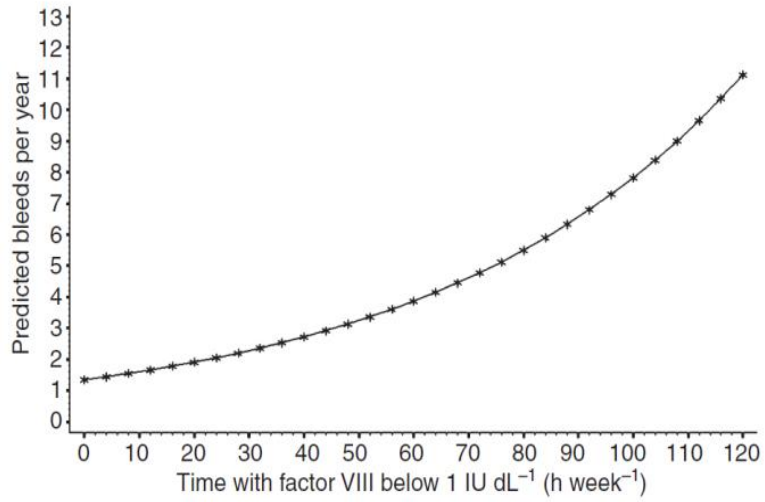
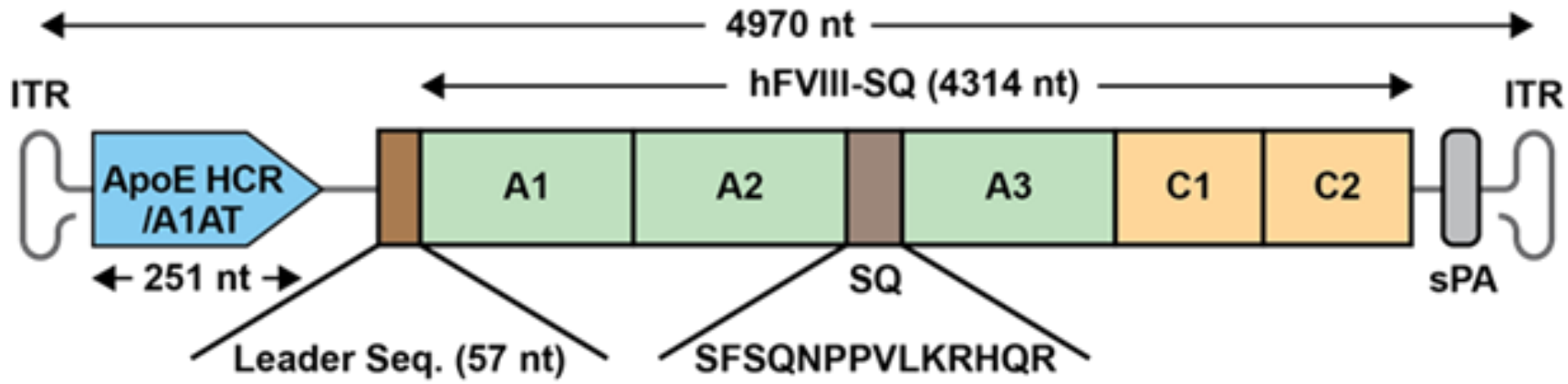


Fig. 3. Predicted bleed count per year dependent on time spent with factor VIII (FVIII) less than 1 IU dL^{-1} for patients aged 10–65 years. The predicted hemarthoses per year (represented with the asterisk, '*') dependent on time per week spent with a FVIII less than 1 IU dL^{-1} are shown for the patients aged 10–65 years.

Collins PW et al; 2009 Journal of Thrombosis and Haemostasis, 7: 413–420

Product Description



- BMN 270 is an AAV5-based gene therapy vector that transduces liver cells resulting in expression of the SQ form of hFVIII under the control of a liver-specific promoter.

- BMN 270 is delivered by single intravenous (IV) dose and is designed to achieve stable, potentially life-long expression of active hFVIII in the plasma.

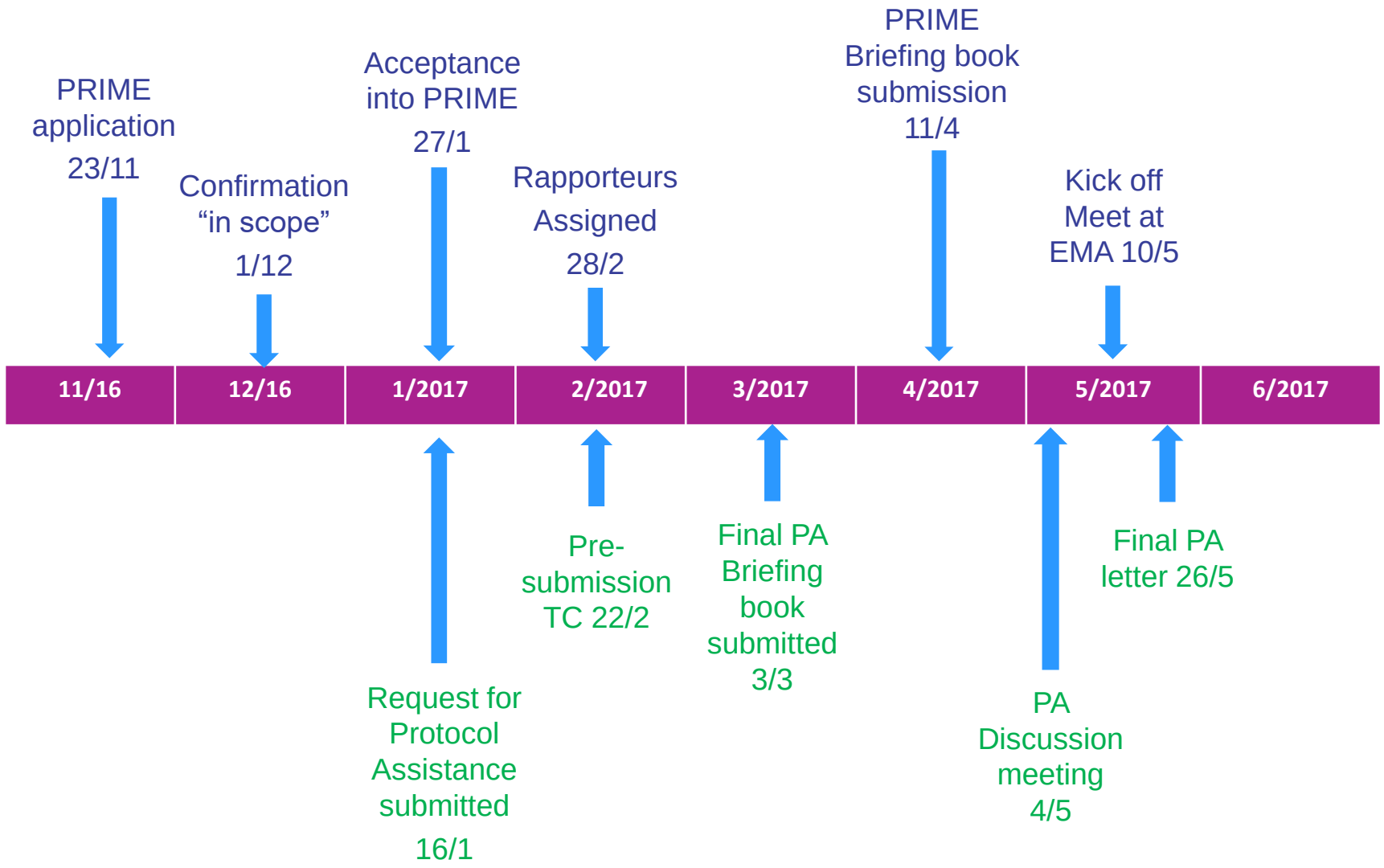
Why PRIME for BMN270?

- Goals of PRIME
  - PRIME aims to bring promising innovative medicines to patients faster by optimising and supporting medicine development
- Benefits of PRIME are important
  - Early Rapporteur Assignment
  - Dedicated contact person at EMA
  - Opportunity for holistic and strategic dialogue on development plan and regulatory strategy with senior regulators at kick off meet
  - Additional support from EMA, SAWP, CHMP, and other committees
  - Possibility of Accelerated assessment *(BMRN experience of revised AA process is very favourable)*

Why did BMN270 Qualify for PRIME

- Eligibility Criteria
  - Medicines eligible for PRIME must address an unmet medical need
  - Preliminary data must be available showing the potential to address this need and bring a major therapeutic advantage to patients
    - “Proof of Concept” data allowed us to meet the requirement for clinical data for PRIME
    - “Proof of Concept” also the enabling data for seeking Scientific Advice (Protocol Assistance) on the development program

BMN270 PRIME timeline and Parallel Protocol Assistance



Experience with PRIME: Kick-Off meet preparation

- Good interaction with assigned contact:
  - very constructive and important to maximizing the value of the PRIME K/O interaction
- Good dialogue and flexibility around the “guiderails” of PRIME:
  - What is considered in scope of PRIME discussion versus Scientific Advice/Protocol Assistance,
- EMA provided draft guidance regarding development of the summary document:

Experience with PRIME: Kick-Off meet

- Wide ranging scope of Kick Off
  - Regulatory (strategy, PDCO/PIP, post-approval plans), CMC (GMP, batch release), non-clinical, HTA…
- Areas in which BioMarin showed awareness/experience in our briefing book were either skipped at Kick-off meet or covered very briefly in the meeting
- In our case, parallel Scientific Advice (protocol assistance) and PRIME (kick off) procedures were ongoing
  - PA discussion meeting identified areas where an EMA “policy” position would be beneficial
  - PRIME K/O held shortly after PA meeting, in a timeframe which allowed prior discussion at SAWP, CAT and CHMP
  - Subsequent PRIME K/O meet was a forum in which the views of senior regulators on the key questions could be shared and discussed with BioMarin
  - Subsequently synthesized into the Final Protocol Assistance letter
  - Final Protocol Assistance advice letter was very clear and actionable

Conclusions

- BioMarin's experience with PRIME has been very positive
  - BioMarin experience with eligibility, planning and logistics, K/O meeting scope etc have been consistent with other industry feedback
  - PRIME K/O interaction allowed a venue for transparent discussion of regulatory strategies
    - Senior level regulators with a high level of expertise and understanding of the "bigger picture"
  - In our case, PRIME and an ongoing Scientific Advice process were extremely complementary
  - No significant gaps/improvement areas that we've seen to date
    - Duration of kick off meet, generation of guidance as experience evolves?

THANK YOU