August 2015

BioMarin: Quarterly Update to the Duchenne Community

In an effort to provide regular communication on our DMD programs to the Duchenne community, we are circulating a quarterly update. This update is the first of its kind for BioMarin, and we welcome your feedback to this new communication channel, which you may do by contacting BioMarin Patient Advocacy (contact details below).

Who We Are

BioMarin focuses on developing first-in-class or best-in-class treatments for patients with rare genetic diseases. We are based in Marin County in Northern California and began operations in 1997. Since that time, we have developed and commercialized five products. BioMarin remains steadfast to its original mission—to bring new treatments to market that will make a big impact on small patient populations.

Our acquisition of Prosensa in January 2015 fits strategically with our mission of delivering therapies that address serious unmet medical needs. It is a privilege to collaborate with the Duchenne community, and we look forward to updating you as our programs progress.

Regulatory Updates

We are thrilled by the progress we have made on the regulatory milestones for drisapersen in the short time since we completed our acquisition of Prosensa.

- **New Drug Application (NDA) for drisapersen in the United States**

  Drisapersen is an investigational exon-skipping drug candidate for the treatment of the largest genetically defined subset of DMD, those amenable to skipping exon 51.

  On June 27, 2015 the Food & Drug Administration (FDA) accepted for filing our New Drug Application (NDA) for drisapersen. The Prescription Drug User Fee Act (PDUFA) goal date for a decision is December 27, 2015. The FDA has granted drisapersen Priority Review status, which is designated to drugs that offer major advances in treatment, or provide a treatment where no adequate therapy exists. A Priority Review designation directs FDA's overall attention and resources to the evaluation of applications for treatments that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions. We expect an Advisory Committee panel to convene later in the year to review the drisapersen NDA.

  As the first NDA submitted for a potentially disease modifying therapy for Duchenne, this is an important milestone for the community, and we are grateful for the dedication of the families and their sons who have helped make this possible.

- **Marketing Authorization Application (MAA) for drisapersen in the European Union**

  On June 25, 2015 the European Medicines Agency (EMA) validated the Marketing Authorization Application (MAA) for drisapersen for the treatment of DMD amenable to exon 51 skipping. Validation of the MAA confirms that the submission is complete and starts the EMA's standard review process. This puts drisapersen in line for a potential Committee for Medicinal Products for Human Use (CHMP) opinion in the first half of 2016 and a European Commission Decision by the third quarter of 2016.

Extension Studies of Continued Administration of Drisapersen

Maintenance of dosing for chronic disease through approval has been a hallmark of all BioMarin's programs to date, and we are committed to re-initiate investigational therapy in previously treated boys and young men where possible. There are three separate clinical trials underway for providing extension treatment of drisapersen for those who previously participated in clinical trials. In addition to the standard subcutaneous route of administration, we will be introducing an IV formulation to provide another option for patients in each of these studies.

Study Number	Protocol Highlights	Countries	Eligibility	Study Purpose	Status
DMD115501 (initiated via protocol amendment)	No biopsies; weekly visits with possibility of home dosing option where feasible	United States, Canada	Prior DMD114876 subjects Prior DMD114349 subjects from US & Canada	Assess long-term safety, tolerability and efficacy	Study Ongoing
DMD114673 (initiated via protocol amendment)	No biopsies	Belgium & Sweden	Prior DMD114673 subjects	Assess effect, safety & tolerability of long-term treatment and safety, tolerability & PK of IV administration	Study Ongoing
BMN051-302 (new protocol)	No biopsies	Global	Prior DMD114349 subjects Prior DMD114118 subjects	Assess effect, safety & tolerability of long-term treatment and safety, tolerability & PK of IV administration	Protocol finalized; Regulatory submissions in progress; recruitment to begin in Q3

Additional Studies with drisapersen:

We plan to initiate additional studies for drisapersen, in both younger populations in addition to non-ambulant populations, to begin in the 4th quarter and 1st half of 2016. In order to provide more choice to patients, an IV option may also be available in these studies. The protocols for these studies are being developed, and we will provide updates on timelines as soon as we can.

Additional DMD Programs:

While our priority at the moment is to provide as many patients as possible with access to drisapersen through extension treatment and a potential regulatory approval, we are committed to our follow-on exon skipping compounds and have a team that is actively working on these. Though the chemistries of these compounds are similar to drisapersen, we cannot assume that the same dose, schedule and mode of administration applies to these populations. Therefore, we are working on a development program looking at different dose regimens and schedules for each of these compounds, and are continuing to evaluate the data that are emerging. We will continue to update the community as we make progress on these.

Below is the status of the follow-on exon skipping compounds that are currently in clinical trials:

- **BMN 044** (Enrolling)
  - Extension study from (PRO044-CLINI-01/NCT01037309) was initiated in December 2014 in Europe (Belgium, Italy, Netherlands, Sweden) and is currently ongoing.
  - **Only patients** who previously participated in the dose escalation phase (PRO044-CLIN-01/ NCT01037309) are eligible for this extension study
  - The study is expected to complete in December 2016.
  - We are working on the protocol for a Phase II study of BMN 044, which will include sites in the US. We plan to initiate this in early 2016.

- **BMN 045** (Active, not currently recruiting)
  - This Phase I/II study began in January 2013 with the dose escalation phase and is ongoing in Europe (Belgium, France, Italy, Netherlands, UK)
  - Treatment has been investigated in 15 patients, and boys have been treated for up to 100 weeks.
  - Data are emerging from these first dose finding cohorts, and we are reviewing the data with academic experts to determine the most appropriate next steps. Final conclusions have not been reached and further analysis and interpretation are ongoing. We will make a decision on next steps following the full evaluation.

- **BMN 053** (Active, not currently recruiting)
  - This Phase I/II study began in August 2013 with the dose escalation phase and is ongoing in Europe (Belgium, France, Italy, Netherlands, UK)
  - Data are emerging from these first dose finding cohorts, and we are reviewing the data with academic experts to determine the most appropriate next steps. Final conclusions have not been reached and further analysis and interpretation are ongoing. We will make a decision on next steps following the full evaluation.

- **Natural History Study** (Enrollment Complete)
    - Nearly 270 pediatric patients between the ages of 3-18 were enrolled
    - We recently presented the results from 77 ambulatory boys who have been followed for 12 months.
        - These results further describe the relationship between baseline characteristics (how boys function at the beginning of a study), including age and six-minute walking distance and how the disease progresses. These findings are consistent with that reported in other natural history studies.[1]

We are grateful for the continued support from the Duchenne community and look forward to continuing our work together and fostering our relationships with the patient community as we move forward.

Kind regards,

BioMarin Patient Advocacy

For patient and family group leaders, please contact BioMarin Patient Advocacy at patientadvocacy@bmrn.com or:

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[1] Pane M, et al. *PLOS One* 2014; 9:e109205.