14<sup>th</sup> November, 2017

Dear Marie-Christine,

Many thanks for your email dated 4<sup>th</sup> November 2017. In response to your questions, please find below the information you have requested regarding clinical trial data and access to SPINRAZA (nusinersen) in Europe.

**Recent publications and presentations**

The EU authorisation of SPINRAZA® (nusinersen) is supported by two pivotal Phase 3 controlled studies for the treatment of spinal muscular atrophy (SMA): ENDEAR (infantile-onset SMA) and CHERISH (later-onset SMA), which demonstrated the clinically meaningful efficacy and favourable benefit-risk profile of nusinersen.

**ENDEAR Study Results**

It is timely to share that *The New England Journal of Medicine (NEJM)*, a peer-reviewed journal, published nusinersen data in their November 2, 2017 edition, and highlighted end of study results from the ENDEAR study.

The two pre-specified ENDEAR primary endpoints were percentage of motor milestone responders, defined as improvements in motor milestone categories in the Hammersmith Infant Neurological Examination (HINE-2), and event-free survival (time to death or the use of permanent assisted ventilation).

- The majority of infants treated with nusinersen in the ENDEAR study achieved motor milestones compared to untreated infants.
  - The final ENDEAR study analysis demonstrated that a greater proportion of infants treated with SPINRAZA were motor milestone responders, compared to untreated infants (51% vs. 0%, P<0.001), including full head control, ability to roll over, and independent sitting and standing.

- Nusinersen significantly increased the likelihood of event-free survival and the likelihood of overall survival. Infants with a shorter disease duration at screening were more likely than those with a longer disease duration to benefit from nusinersen.
  - Nusinersen also met the pre-specified primary endpoint in the end of study analysis, demonstrating a statistically significant 47% reduction in the risk of death or the use of permanent assisted ventilation (P=0.005) and 76% reduction for those with shorter disease duration.

Additionally, a new analysis from ENDEAR was presented at the 22nd International Congress of the World Muscle Society in Saint Malo, France (October 3-7, 2017). The analysis showed infants with SMA who initiated treatment with nusinersen earlier in the disease (shorter disease duration) demonstrated greater benefit and improvement in motor milestones and motor function outcomes.
An interim analysis was also presented from the Phase 2 EMBRACE study which was designed to assess the efficacy and safety of nusinersen in individuals with infantile- and later-onset SMA who were ineligible for the two pivotal studies. The EMBRACE interim analysis showed a larger proportion of infants and children treated with nusinersen were Hammersmith Infant Neurological Examination (HINE) motor milestone responders compared to those who were untreated. Results from the interim analysis also supported the dosing regimen of four loading doses in the first two months, followed by the administration of nusinersen every four months thereafter, for individuals with infantile and later-onset SMA. In the ENDEAR and EMBRACE studies nusinersen demonstrated a favourable benefit-risk profile.

The nusinersen clinical development programme includes over five years of data and is the largest body of evidence for an interventional approach in SMA. Following the positive interim analysis, Biogen ended the ENDEAR study early so that all participants could have the option to receive nusinersen in the SHINE open-label extension study. In addition to SHINE, Biogen continues to collect and evaluate data to provide a deeper understanding of the efficacy and safety of nusinersen across all SMA populations.

For additional detail on these results, we recommend discussing them with your Scientific Advisory Board.

**Early Access Programme**

We continue our commitment to provide nusinersen to patients with infantile-onset SMA free of charge through the Biogen sponsored Early Access Programme (EAP). This is one of the largest, pre-approval EAPs for compassionate use in rare disease allowing SMA patients with the highest unmet medical needs to access the treatment early, rather than waiting for the potentially lengthy reimbursement discussions to conclude. We have established early access through the EAP in countries where the regulatory environment allows us to do this alongside the reimbursement process. Currently, the EAP has led to the initiation and ongoing treatment of more than 500 patients with infantile-onset SMA across 18 countries in Europe.

In some countries that don’t have access to the EAP, we have partnered with national governments to establish separate initiatives. Therefore, there are many patients being treated with nusinersen outside of the Early Access Program via various mechanisms including Named Patient Programs in Greece, Spain, Norway, Sweden, Finland, Croatia, Czech Republic, Turkey, Israel, Kingdom of Saudi Arabia, Qatar, United Arab Emirates, Kuwait and Canada, whilst regulatory and reimbursement decisions are being completed.

**Access to reimbursed treatment**

We fully understand the devastating impact that SMA has on patients, their families and their communities. We are working tirelessly with health care professionals, government agencies, policy makers and patient advocacy groups across Europe to find solutions so that people who could benefit from nusinersen may receive access to this new treatment option as quickly as possible.

In Europe and across the region, significant progress has been made. Patients across all disease types already have access to nusinersen in Germany, Italy, Austria, and Luxembourg and temporary access for all types has been granted in France (post ATU). In Switzerland, Nusinersen is launched and commercially available as a hospital product. Individuals with SMA up to the age of 20 have a right to be
covered via cantonal disability insurance. For individuals with SMA over the age of 20, Biogen will continue negotiations with the Swiss health authorities. In Denmark, we have received reimbursement for pre-symptomatic and Type 1 patients, whilst in Norway, the reimbursement authorities delayed their decision until the end of November. We are disappointed that the Danish and Norwegian agencies did not recognize the same value of treatment for all people with SMA. We will however continue our dialogue with all stakeholders in Denmark and Norway in order to explore the widest access options for all SMA patients.

Additionally, and in the spirit of taking a collaborative approach with payers from across Europe to speed up access, Biogen has participated in MoCa (Mechanism of Co-ordinated Access). MoCA provides a mechanism for European countries to collaborate on coordinated access to orphan medicines in a voluntary, dialogue-based approach, intended to create a fluid set of interactions between key stakeholders, across all aspects of a product.

**Registries**

Biogen’s robust registry strategy is working towards having SMA patients prospectively monitored longitudinally with a common core data set. Collaboration with external registry partners including patient advocacy organisations, SMA expert thought leaders and existing international registry networks (eg TREAT-NMD, ISMAC and other partners), is the basis of Biogen’s strategy.

Finally, in countries where Biogen does not have an affiliate, we are working diligently to find the right partner to represent us in local discussions with appropriate agencies to ensure long-term sustainable access through regulatory approval and reimbursement.

We are incredibly grateful for the collaboration we’ve had with SMA Europe and other patient advocacy organisations, physicians, policy makers and payors who continue to contribute to the overall success of our programme. We will continue to work closely with them to ensure that the community remains informed of developments and that the perspectives of patients and families are taken into account in Biogen’s decision-making process.

Best regards,

The Biogen SMA Team