BioMarin Europe Ltd.

Friday 6 March 2015

Mr James Palmer
Clinical Director Specialised Commissioning for NHS England

Mr Richard Jeavons
Director of Specialised Commissioning- Operations Directorate, NHS England

Dear Mr Palmer
Dear Mr Jeavons

Your Letter of 2 March 2015

Thank you for your letter of 2 March 2015. As a point of context, BioMarin's concern is that England is the sole country which participated in the multi-national elosulfase alfa (VIMIZIM®▼) Phase 3 Clinical Trial, that has failed to make a provision for treating patients post trial conclusion and 54 weeks post EMA approval. The actions of BioMarin are based on the following:-

Since EMA approval of elosulfase alfa (VIMZIM®) on 28 April 2014, BioMarin has continued to provide free product to trial patients. However, there are several points you should be made aware of:-

a. Some patients have been taken off treatment by the hospital treating them, claiming that the trial was ended so the trial patients were no longer entitled to treatment. This was despite financial support being made available by BioMarin but due, as far as BioMarin can ascertain, to a reluctance by the NHS Trust in question to continue covering the cost of infusions;
b. BioMarin has provided grant funding for: (i) nursing services to be provided (where it was advised that, due to budgetary constraints, treatment would be ceased without such funding); and (ii) patients to receive travel grants to get to treatment centres for treatment (which would not be necessary if home infusion could be provided, which would be the case if interim funding or reimbursement could be agreed. This would significantly reduce the onus on patients and improve the standard of care). In addition, BioMarin has continued to provide home infusion services at its own cost for the very limited number of clinical trial patients already receiving home infusions. This has all been provided without there being a legal obligation for BioMarin to do so;
c. The NHS position does not consider the patients who did not participate in the trial but are eligible and wish to receive treatment. There are approximately another 40 individuals who suffer from Morquio A syndrome in England who want treatment but did not (or could not) take part in the trial. BioMarin cannot take a course of action that prevents or precludes patients who need and want treatment from having access to elosulfase alfa (VIMIZIM®) simply on the basis that they were not part of the trial. Interim funding should be agreed and put in place to ensure equitable access for all Morquio A sufferers. If NHS England believes in "high quality care for all, now and for future generations", then limiting your concerns - and BioMarin's ability - to provide treatment solely to those who participate(d) in trials would appear to run contrary to that ethos.

BioMarin Europe Ltd.

Please note the following in response to the points and questions raised in your letter:-

Commissioning of elosulfase alfa (VIMIZIM®) generally

As stated in our letter of 23 January, 2015, BioMarin had been engaged with AGNSS (and latterly NHS England) in discussions relating to interim funding for elosulfase alfa (VIMIZIM®) since 2012. In late 2013 as the change from AGNSS was significantly delayed there was a recommendation to clinicians to follow an interim funding route. As such Dr. Hendriksz submitted the complete clinical CRG package to the NHS England CRG representative on 20 February 2014. NHS England delayed until July 2014 to submit the materials to the CRG. Under pressure from clinicians and patients, the CRG approved progression of the funding request on 3 July 2014. It was during August 2014 that Mr Qualie contacted BioMarin, to the effect that in order for any decision to be considered, it had to take into account ongoing treatment in the event of a negative decision by NICE. This was the basis for BioMarin making the revised, without prejudice, 5 year discount offer, to which no response has been received. The only timing point made was that, if the offer had been approved, it would not have taken effect until the new financial year (6 April, 2015). If the Company had been informed at any point that such a decision would have been taken and come into effect in May 2015 (as you suggest in your letter) then BioMarin would have waited for such a decision to be made. BioMarin's primary concern is that, under the revised timetable, even if interim funding were to be approved mid-summer 2015, hospitals would not have any budget available to purchase VIMIZIM® for patients until the new budget year April 2016.

BioMarin assumes that the formal letter before legal action you refer to in the first full paragraph of page 2 of your letter was the threat of judicial review issued by the UK MPS Society. BioMarin further assumes that your withdrawal and amendment of your procedures immediately following receipt of the letter before action was undertaken because you accepted that the new procedures that replaced the old AGNSS system were indeed unfairly biased against orphan diseases. You accepted at a meeting on 10 February 2015, convened by the ABPI, that this was known in October 2014 and the NHS England board were concerned about its fitness for purpose. In practice, you have failed to put in place a fair and equitable process.

Availability of treatment to patients who participated in the clinical trial

BioMarin notes your concern raised in the first paragraph entitled "Availability of treatment to patients who participated in the clinical trial". Whilst BioMarin is not privy to all NHS England policies could you please provide us with a copy of the policy(ies) that state that "NHS England would not normally pay for post-trial treatment in relation to a clinical trial which was not established or funded by NHS England itself or for which payment of post-trial costs was not agreed with NHS England at the outset". Could you please also provide us with figures showing how many companies you agreed post-trial funding with prior to clinical trials commencing and for what period of time such post-trial funding is provided? Furthermore, can you please also confirm that all companies undertaking clinical trials in the UK are aware that, in the absence of such pre-trial agreements being reached, that no post-trial funding will be agreed?

You state in the subsequent paragraph to the one referred to above that NHS policies are firmly based on the principles set out in the Declaration of Helsinki. You state that "unless otherwise agreed in advance with NHS England, those [post-trial treatment] arrangements would be fulfilled by the company or other organisation establishing the trial and would be their on-going responsibility". Please provide the reference in the Declaration of Helsinki (or other legally binding instrument) that states that in the absence of any pre-trial agreement the onus of any and all post-trial treatment must be borne solely by the company or organisation establishing the trial.

You reference paragraphs 22 and 34 of the latest version of the Declaration of Helsinki and state that "these requirements are transferred into the UK law on clinical trials through the Medicines for Human Use (Clinical Trials) Regulations 2004….".

That is incorrect. The version of the Declaration of Helsinki with which sponsors of clinical trials in the UK must comply is the 1996 version, which does not include the requirements you cite.[1] The Medicines for Human Use (Clinical Trials) Regulations 2004 ("the Regulations") make clear at Schedule 1, Part 1, Section 2(1) that the relevant version of the Declaration is the "Declaration of Helsinki adopted by the World Medical Assembly in June 1964, as amended by the General Assembly of the Association in October 1975, October 1983, September 1989 and October 1996." Thus, when the Regulations go on to state that "Clinical trials shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki…" (Schedule 1, Part 2, Section 1), they refer only to the 1996 version.

This is not accidental, nor does it merely reflect the passage of time. The Regulations and Article 3 of EU Directive 2005/28/EC, which both post-date the 2000 version of the Declaration, both specify that the 1996 version is the standard for clinical trials in the EU. This reflects a deliberate decision by the European Commission and the EU member states not to adopt the 2000 version because of concerns with a number of its provisions, such as the suggestion that all study drug must be supplied post-study and the provision questioning the ethics of placebo-controlled clinical trials.[2] As the Medicines and Healthcare Products Regulatory Agency itself stated at the GCP Consultative Committee 29 May 2009:

> "The GCP Directive stated that the Declaration of Helsinki 1996 was the standard for GCP. The Directive did not state that later versions would be automatically adopted by Europe. The Commission has in the past commented that Europe cannot be legally bound to documents over which it has no control. Hence, fixing the version of the Declaration of Helsinki to be followed is consistent with the Commission's previously stated view."

In response to your question as to the basis on which BioMarin considers it appropriate to cease the free provision of elosulfase alfa (VIMIZIM®) in the future please note the following:-

BioMarin is not under any legal obligation to continue to provide free elosulfase alfa (VIMIZIM®) for an indeterminate period. The Company has never, either explicitly or implicitly, agreed or promised to continue providing free product to patients formerly on the clinical trial. In the UK, a sponsor must include in its application for ethics committee approval "the plan for treatment or care of subjects once their participation in the trial has ended" (the Regulations, Schedule 3, Part 1, 1, (m) (iii)). It typically does so in the study protocol and ICF, which the ethics committee considers and approves. As per previous correspondence, the approved protocol and the ICFs signed by patients clearly stipulate that the provision of elosulfase alfa can end concomitant with the patient exiting the trial at either BioMarin or the Investigator's discretion (which is also reflected in the trial protocol). Furthermore, as stated above, the October 2013 version of the Declaration of Helsinki to which you refer has not been incorporated into either UK or EU law and therefore Article 34 is not applicable. Notwithstanding that, the language in Article 34 to which you refer makes it clear that any responsibility for the provision of post-trial access is not only with the sponsor, but also with the host country's government. This is reflected in guidance from the Health Research Authority (HRA):

---

[1] The World Medical Association only included provisions relating to post-trial access to the investigational drug in its 2000 version, but that is not the version that is reflected on EU and UK law.

[2] The EU is not alone in its unwillingness to accept recent versions of the Declaration of Helsinki. The U.S. Food & Drug Administration FDA will accept a foreign clinical study not conducted under an IND only if the study conforms to the ethical principles contained in the **1989** version of the Declaration of Helsinki (see http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm124939.pdf).

BioMarin Europe Ltd.

> "The nature of care after research depends on many factors, including whether the study intervention is available locally on the NHS. In the UK, arranging aftercare will usually mean referring participants to the NHS, where they will continue taking the study intervention (when available), start a different intervention or return to their pre-study intervention. Sometimes study staff will refer participants to another study. In fewer cases, which raise the hardest issues, the sponsor supplies the study intervention, usually when the intervention is unlicensed. The intervention may be supplied in various settings, and may or may not be sponsor-funded."[3]

Nowhere in the law or any guidance from the HRA does it state that, in the absence of any prior agreement, this burden remains solely with the sponsor of the trial.

In addition to the above, it is BioMarin's opinion that the intention behind the Declaration of Helsinki is to ensure, where a benefit is observed, that treatment continues post–trial to the point at which the investigational medicine becomes approved and commercially available. The EU legislation in the Transparency Directive clearly states pricing and reimbursement should be settled within one year of product approval. In this case BioMarin has made every effort to achieve this with no decisions being forthcoming from you. It should be noted that no other country which participated in the elosulfase alfa (VIMIZIM®) Phase 3 Clinical Trial has even attempted to apply your interpretation of the Declaration or request or demand that BioMarin continue to supply free product.

We remain open to discuss matters with you.

Yours sincerely

DocuSigned by:
4663A00AD01141A...

James Lennertz
Group Vice President and Managing Director
BioMarin Europe Ltd

cc: Dr Edmund Jessop
Mr Malcolm Qualie
Mr Iain Mellis
Mr Nick Seddon
Mr Jeremy Hunt, MP
Mr Greg Mulholland, MP
Mr George Freeman, MP
Ms Christine Lavery, MBE

[3] See www.hra.nhs.uk/documents/2013/08/care-after-research.pdf