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27th February 2017

Re: Ground Two Appeal against NICE Final Evaluation Determination for Sebelipase alfa

On behalf of the Paediatric Inherited Metabolic Disorders consultants at Birmingham, Manchester, Evelina and Great Ormond Street Children's Hospitals, we are writing formally to appeal the Final Evaluation Determination (FED) of NICE regarding "sebelipase alfa for treating lysosomal acid lipase deficiency" published on 15th February 2017 on the grounds that we believe this recommendation to be unreasonable in the light of the evidence submitted to NICE.

2.1 We believe the severity of the infantile presentation and the significance of its alleviation with this therapy has not been fully recognised and therefore the recommendation at least for infantile patients is unreasonable.

In the document it is acknowledged several times that 'Sebelipase alfa is a potentially life-saving treatment for babies with rapidly progressive LAL deficiency, and there is a compelling clinical need.' This certainly is the case and as clinicians who are currently caring for infants on this treatment in clinical trials and on compassionate provision, we are probably best placed to be able to comment on the clinical benefit from this drug. There is no doubt that the availability of

sebelipase alfa provides a step-change in the approach to treatment of rapidly progressive LAL deficiency and has transformed the condition from one that is uniformly fatal by six months of age into a manageable condition associated with a good quality of life and normal development. There are few currently approved enzyme replacement therapies which can be said to be truly life-saving but sebelipase alfa, at least in the context of rapidly progressive infantile disease, can certainly be said to be life-saving and represents the most effective new enzyme replacement therapy we have seen for many years and arguably have ever seen when considering the infantile cohort.

The magnitude of this improvement does not appear to be reflected in the wording of the recommendations and we would like to draw attention to a number of statements/factual inaccuracies in the FED which we feel demonstrate an underestimation of the true benefit provided by this treatment:

- Section 1.3: "*until they and their NHS clinician consider it appropriate to stop.*" Given that currently no infantile-onset patient has survived without enzyme replacement there can be no position where termination of enzyme replacement therapy is appropriate for a child who is responding to treatment in this population as currently it appears that this will be universally fatal.

- Section 2.3 "*Babies under 6 months who present with LAL deficiency generally have a rapidly progressive condition.*" and Section 5.1 "*symptoms presenting in babies under 6 months was typically rapidly progressive*". These statements are somewhat misleading and could be interpreted as a proportion of babies having a slowly progressive condition. In fact less than 4% of such patients survive to their first birthday, even with supportive treatment (Jones SA *et al.* Genet Med. 2016 May;18(5):452-8.) Indeed as stated in Section 4.8 "*None of the historical control group from LAL-1-NH01 (21 patients with growth failure presenting <1 year)of age) survived past 12 months…..(the median age at death was 3.00 months).*" The severity of disease in infants presenting under six months is therefore universally severe and rapidly progressive and should not be underestimated when considering the dramatic response seen to sebelipase alfa.

2.2 In particular, the degree of systemic inflammation and immune dysfunction which are seen in infantile-onset patients has not been considered in the FED.

In section 4.1 it is not mentioned that the cause of death is ultimately multiorgan failure for patients in infantile-onset LAL deficiency, secondary to a progressive systemic and localized inflammatory response. Liver enlargement is discussed and while the systemic inflammation does engender a degree of hepatomegaly, liver enlargement is not the main clinical hepatic problem, which is ultimately rapidly evolving liver failure. The importance of highlighting the systemic inflammatory response is that it does also compromise haematological and immune function, aspects not mentioned in the FED but which make alternative therapies, including transplantation, impossible for the infantile population at diagnosis.

2.3 The ERG's comment of non compatibility between LAL-1-NH01 and LAL-CL03 cohorts due to the nature of supportive therapy changing is not valid.

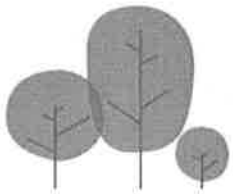
In section 4.26, the ERG states that comparsion between the LAL-1-NH01 and LAL-CL03 cohorts is invalid due to the nature of supportive therapy changing over this time period. The cornerstone of liver failure support is the placement of central lines to give fluid, the use of nutrition and blood products all of which were available through the time period mentioned. However no supportive therapy will ameliorate the lethal progression of this disease and thus any survival can only be due to sebelipase alfa and no other factor.

2.4 We believe it is unreasonable for the committee to make a recommendation against funding based on the uncertainty of long term outcome for the infantile-onset subgroup because all such patients benefit even if their long term response is not maintained.

In the FED one of the stated reservations of the committee is the uncertainty of the long term outcome for this condition and treatment. For a drug that has only been in development for 6 years, that the oldest infant is still alive with a good quality of life at 6 years would suggest that the long term outcome is likely to be very good indeed. For this group of patients the outcome without treatment is uniform and lethal and the experience of the UK clinicians is that the majority of infants respond very favourably to treatment. Clearly as with all therapies, there are some infants who will not respond as well as others. In our experience, which does represent the overwhelming majority of worldwide experience thus far, such patients become quickly identifiable and would then not continue on treatment. However the availability of at least a few months' treatment with enzyme replacement therapy would enable the infant's clinical condition to become somewhat more robust and potentially able to survive other treatment options (such as stem cell or solid organ transplantation) which have historically been unsurvivable before enzyme replacement therapy was available. Therefore we would argue that even if the long term outcomes for these patients are not certain, there is significant clinical benefit obtained even for those whose long term response to sebelipase alfa is not maintained.

2.5 We believe this recommendation goes against previous guidance given by NICE where long term outcome to a treatment was uncertain.

We would also argue that the lack of "real life" long term outcome data is not a reason to decline funding this therapy, but rather a compelling reason to fund it in order to gain this data. Indeed NICE's limited approval of elosulfase alfa for Mucopolysaccharidosis Type IVa for five years subject to a clear managed access agreement designed to obtain further long term functional and quality of life data is a relevant precedent for this. We believe all the UK clinicians would be expecting the long term outcome of infants treated with sebelipase alfa to be overwhelmingly positive compared to the expected outcome without treatment (which is certain).



2.6 We believe this recommendation goes against previous guidance given by NICE where a clear subgroup of infantile patients most at risk exists.

Another relevant precedent for a condition with a clear subgroup of infantile patients at most risk and deriving most benefit would be hypophosphatasia for which NICE concurrently ran an evaluation of asfotase alfa and approved funding for the most severely affected patients. From a clinical standpoint there is little difference between perinatal/infantile hypophosphatasia and infantile lysosomal acid lipase deficiency in terms of severity and potential response to treatment. It therefore appears highly irregular that at least for the infantile patients, there is a difference in approach to funding such an effective treatment.

2.7 We believe that the significance of treatment effect in older children with LAL-deficiency has not been fully appreciated in the guidance.

We acknowledge that patients outside of the infantile age group may show more variability in their disease severity and response to treatment however it is our experience that patients diagnosed with significant liver disease in childhood are more severe than adult patients and more likely to be on a firm trajectory towards endstage chronic liver disease and transplantation in childhood. Whilst the numbers of patients treated so far in this category may be small, experience has suggested that liver fibrosis has regressed somewhat in some patients. Whereas a slowing down of the fibrosis process might be expected to lead to improved outcomes but still potentially require liver transplantation in future, the observation that in some patients fibrosis has *improved* on enzyme treatment suggests that this treatment has the potential to prevent, not just delay, the need for liver transplantation. Again this requires longer term follow-up and outcome data which a clearly designed managed access agreement would provide as has been agreed by NICE for elosulfase alfa. This range of response reflects the heterogeneous nature of genetic diseases and does, as should be aknowldeged, make review difficult.

2.8 We believe it is unreasonable for the group to decline funding for a life-saving treatment based purely on the cost of the treatment when there may be scope for further negotiation with the manufacturer. This leaves clinicians dealing with infantile-onset LAL-deficiency patients in a severe ethical dilemma.

The reservations listed above lead us to conclude that the committee's main reason for not approving this treatment is financial as reflected by the statement "*It was concerned that, even with the company's proposed discount and cost cap, the cost of sebelipase alfa is exceptionally high and is too high to be considered value for money in the context of uncertainties about the potential long-term benefits of treatment.*" It goes without saying that we all understand the financial pressures the NHS currently faces and the high cost of this drug. If the cost of the drug is deemed to be too high then surely a more appropriate approach would be to engage directly in conversations with the manufacturer about a price-point which would be acceptable to NHS England rather than issue a blanket refusal and deny treatment to the patients most at risk. NHS England already commissions a number of expensive enzyme replacement therapies for children which are not as effective as sebelipase alfa has proven in children and this decision places

paediatricians such as us, as well as NHS England, in a precarious ethical state that we can prescribe less effective therapies for some children but must only offer palliative care to infants with rapidly progressive LAL deficiency.

Conclusion: We would urge NICE, in the strongest possible way, to reconsider this decision, which we believe to be unreasonable at least in the case of children with LAL deficiency based on the evidence submitted to NICE and subsequent clinical experience, and approve funding for sebelipase alfa at least for a period of time that will enable the collection of the longer term outcome data needed to justify the long term treatment of these children. I, and/or other consultees from Birmingham, Manchester, Evelina and Great Ormond Street Children's Hospitals, would be willing to be heard at an oral or written appeal.

Yours sincerely

Consultant in Clinical Inherited Metabolic Disorders, Birmingham Children's Hospital

And on behalf of:

Consultant in Clinical Inherited Metabolic Disorders, Birmingham Children's Hospital

Consultant in Clinical Inherited Metabolic Disorders, Birmingham Children's Hospital

Consultant in Clinical Inherited Metabolic Disorders, Royal Manchester Children's Hospital

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