

Title: Severe persistent injection site reactions after subcutaneous 2'-O-methyl phosphorothioate

oligonucleotide therapy for Duchenne muscular dystrophy

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We present a 13 years 6 months old boy with Duchenne muscular dystrophy due to a deletion of exon 50 of the dystrophin gene. He was diagnosed at the age of 3 and started corticosteroid therapy (prednisolone daily regime) at the age of 4 years 10 months. At the age of 7 years and 4 months he was enrolled in the randomized double blind placebo controlled trial for exon 51 skipping and later in the open label phase II study with the same compound – a 2'-O-methyl phosphorothioate oligonucleotide to induce exon 51 skipping (drisapersen) - that required weekly subcutaneous injections (either in the arms, thighs or abdomen; between 1.2 and 1.5ml per injection). This study was originally sponsored by GSK, and subsequently by Biomarín. He was treated for approximately 2 years and 3 months (between February 2011 and July 2013). Six months after starting the trial, a local reaction was noticed at the site of the subcutaneous injections (worse in the thighs) with localised erythema followed by a bruise-like appearance of the skin that persisted for several weeks. After 14 months of treatment he started to experience pruritus at the site. The lesions progressed and after 18 months into the study he had several areas of marked induration and erythema in both thighs and upper arms (worse lesions measuring 10x15cm). Following further instructions from the sponsor, the abdominal area was used as an alternative injection area. Twenty months into the study he had developed similar lesions in that area with a yellow discoloration. A topical emollient was started shortly after and he was referred to the Dermatology team who documented “morphea-like” skin lesions. Thermography after 23 months of treatment with drisapersen showed hyperthermic areas at the injection sites with a mild and a diffuse rise in temperature on the anterior aspect of both thighs and more significant hyperthermia at the centre of each injection area on the upper limbs. After another 6 months the trial was discontinued by the sponsor. After 1 year from the last injection (July 2014) his skin lesions progressed and started to become painful. He was reviewed in September 2014. A skin biopsy taken at that time showed fibrosis with loss of elastic tissue and some calcification, without inflammation.

The lesions continue to progress both in terms of subjective symptoms (painful to touch and pruritic) and also appearance (as illustrated by figure 1 C – photograph from December 2015).

Due to progressive changes at the injection sites an additional skin biopsy was performed in December 2016. This demonstrated calcification and bone formation in the skin (as illustrated

by figure 1 A&B). These lesions have been reported as Severe Adverse Events to the 2 sponsors.

Although skin reactions with the subcutaneous administration of drisapersen and other antisense oligonucleotides of related chemistries have been previously reported [1-4] most of

them were classified as mild to moderate adverse events. In fact, the full spectrum of severity,

long-term follow up and in particular pathophysiology of these lesions remains poorly documented and understood.

Further efforts are needed to document the severity and to understand the pathophysiology of

these severe skin lesions. This knowledge will be critical both for the use of this group of

compounds in the future but also to help find appropriate treatment options for the skin

lesions which in some cases, such as the one reported by us, appear to be progressive despite

the discontinuation of the treatment.

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Figure

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