Title: Severe persistent injection site reactions after subcutaneous 2'-O-methyl phosphorothioate
oligonucleotide therapy for Duchenne muscular dystrophy

Authors: Joana Domingos[a], Valeria Ricotti, Anna E. Martinez[b] and Francesco Muntoni[a*]
[a] Dubowitz Neuromuscular Centre, UCL Great Ormond Street Institute of Child Health and Great Ormond
Street Hospital, 30 Guilford Street, London, WC1N 1EH, UK
j.domingos@ucl.ac.uk; 02079052639
v.ricotti@ucl.ac.uk

f.muntoni@ucl.ac.uk; 02079052639
*Corresponding author
[b] Great Ormond Street Hospital for Children NHS foundation Trust, Department of Dermatology, Great
Ormond St, London, WC1N 3JH, UK
Anna.Martinez@gosh.nhs.uk

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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 Biomarin. 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 tights 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
2
tights 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.

References

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Figure
4