Tamoxifen Q&A

What is tamoxifen?

Tamoxifen is a selective estrogen receptor regulator and acts as an agonist or antagonist of estrogen in a tissue-dependent manner. Its use is well established in patients with breast cancer, for which it's been approved since the 1970s. In the breast tissue, Tamoxifen competes with estrogen for binding to the estrogen receptor, which results in a decrease in estrogen receptor signaling-dependent growth in breast tissue. It is theorised that tamoxifen would have a beneficial effect in DMD due to its antioxidant action and regulatory role in calcium homeostasis in muscle tissue.

What pre-clinical evidence is there that tamoxifen would be effective in DMD?

Pre-clinical data from the DMD mouse model, have shown that tamoxifen (TAM), given orally for periods of 2 or 15 months at doses as low as 0.3mg/kg/day, result in almost full recovery of force and structure of muscles. TAM is one of the most efficacious drugs ever investigated in an animal model of DMD.

- TAM was able to increase levels of pro-inflammatory cytokines and growth factors involved in muscle regeneration and fibrosis (transforming growth factor-β (TGFβ), insulin-like growth factor 1 (IGF1) and osteopontin) and to an increased capacity of muscle-purified mitochondria to buffer cytosolic calcium.[1]

- Oral TAM was also found to stabilise the membrane of myofibers, significantly improved muscle strength, reduced muscle fatigue, and slowed phenotype. Furthermore, it could reduce fibrosis of the heart muscle and diaphragm by about 50%.[2]

How was the TAMDMD trial set up?

The TAM DMD trial is a randomised double-blind placebo-controlled 48-week clinical trial with a core population (group A) of 79 ambulant 6.5 to 12 years old DMD patients that are on a stable treatment with glucocorticoids. 16-20 non-ambulant patients age 10 to 16 years who did not receive glucocorticoids were also included, (parallel group B) to obtain efficacy and safety in a broader DMD-population.

All patients received 20mg of TAM or placebo once daily over 48 weeks.

Following completion of the trial, participants were able to enter into an additional 48 week open label extension study.

What were the results of the trial?

Data from the TAMDMD trial, which compared disease progression in a group of boys receiving tamoxifen to that in a group receiving a placebo has now been analysed following completion of the initial stages of the trial. This analysis found that over the 48 week trial period, patients in both the tamoxifen and placebo group showed mild disease progression against all clinical and MRI endpoints. While there was a trend for less disease progression in the tamoxifen group, the differences between the two groups were not large enough to determine if tamoxifen was effective in delaying disease progression.

The data has however shown that across this trial and the follow-on open label extension, there have been no safety concerns so far and the drug has been generally well tolerated.

[1] Trials volume 20, Article number: 637 (2019)

[2] Am J Pathol 2013 Feb;182(2):485-504. doi: 10.1016/j.ajpath.2012.10.018.

What is statistical significance?

Data from clinical trials is analysed by statisticians, who will determine if a result is likely or unlikely to have happened by chance.

In the case of the TAMDMD trial, while there was less disease progression in participants who had received TAM, the differences between the TAM and placebo group were not big enough to conclude that these differences were not down to chance rather than the action of the drug**.**

Will the open label extension arm of the trial now be paused?

Further analysis of the clinical data is currently ongoing to help us to better understand these preliminary results and to better understand the effectiveness of tamoxifen in DMD.

The clinical team is currently working to assess the best next steps for boys currently enrolled in the open label extension study based on all available clinical data. Further information will be provided to trial participants from their sites in due course.