



## **HT-100 Clinical Program Status**

December 23, 2013

Halo's HT-100 clinical program in DMD is temporarily on hold. The active clinical program was placed on hold following a formal action from FDA requiring Halo to stop dosing existing program participants and to not enroll new participants in the program. A more detailed explanation of the reasons for FDA's action and our response to it are contained in the companion Q&A document. Halo's highest priority is to resume the clinical program, and we are working tirelessly to achieve this goal.

The entire Halo team would like to extend our sincere gratitude to our dedicated community of patients, patient families, clinical investigators and site staff, patient foundations, and many allies within the broader DMD community for their commitment to and continued support of the development of HT-100 for DMD.



**Q.** What is the status of the Halo HT-100 clinical program?

**A.** The program is paused. No patients are taking drug, and we are not screening or enrolling new patients. Patients currently in the program are continuing to visit clinical sites for some scheduled visits. As detailed below, however, Halo is working actively with FDA to resume clinical development of HT-100 for DMD.

**Q.** Why is the trial not continuing as planned?

**A.** FDA has placed HT-100 for Duchenne on “clinical hold.” A clinical hold is a legal requirement that no further dosing of patients take place. It is essentially a pause in a clinical program while new data is generated and evaluated, and a decision can be made about the best way to move forward with development. It is not uncommon for products in development to be placed on clinical hold, and many marketed drugs that today are used safely and effectively were at times in their development placed on clinical hold.

**Q.** Why did FDA place HT-100 on clinical hold?

**A.** As part of Halo’s efforts to accelerate HT-100 development, Halo was conducting a toxicology study in dogs in parallel with the clinical program. This toxicology study is a prerequisite for future clinical studies, and we were conducting this study to ensure no delays in future clinical development of HT-100. The study included an evaluation of higher oral doses of halofuginone (the active ingredient in HT-100) than had been used in most earlier toxicology studies; the higher doses were made possible because HT-100, Halo’s proprietary formulation of halofuginone, is better tolerated than previous formulations of the drug candidate. In this study, the dogs got higher exposures (levels of halofuginone in their blood) than in previous studies, and some of the dogs had serious adverse reactions after taking the first or the first few doses. As required by law, Halo quickly reported the available, preliminary findings from this study to FDA. FDA has asked Halo to provide additional information, including the final findings from this toxicology study, to the Agency. Until FDA has a chance to review the relevant data, the Agency has required that we stop dosing patients and therefore placed HT-100 on clinical hold.

**Q.** Have there been safety issues in the HT-100 clinical program?

**A.** No. There have been no results in the on-going clinical trial suggesting a safety concern in patients in the HT-100 clinical program. So far in the clinical program, there have been no significant side effects or laboratory value abnormalities of any kind following treatment with the HT-100 medication. No one has dropped out of the study and no one



has had to be hospitalized for any reason. The clinical hold is based on findings in the dog study and not on findings in the HT-100 clinical program.

**Q.** What was Halo's response to the toxicology study findings? Why didn't you stop the clinical program?

**A.** Halo carefully evaluated the findings from the toxicology study, and considered them in the context of other toxicology and human clinical data generated with HT-100 and halofuginone. Until we had additional data, Halo elected not to escalate to higher repeat doses in the clinical program, but concluded that it was appropriate to continue dosing at the levels that were already being studied in the clinical program. At these doses, patients have been taking HT-100 daily for between 1 and 3 months; been carefully monitored on an ongoing basis by their own physicians, Halo's medical monitor, and a pharmacovigilance (safety review) committee chaired by a clinical investigator; and no data or results in patients were seen indicating a potential safety issue. Therefore, Halo concluded that it was appropriate to continue treatment of patients currently in the study but wait for additional data before escalating to higher doses. FDA, however, has required us to stop dosing all patients.

**Q.** Is FDA working with you to allow the program to move forward?

**A.** Yes. We have engaged in an active dialogue with FDA to clarify their issues and a path to address them, and the Agency provided us with written documentation regarding the clinical hold—a process that often takes 30 days—within a day of their decision. We believe this responsiveness is a reflection of FDA's commitment to work with us to quickly resolve these issues and resume clinical development.

**Q.** Haven't you done other animal studies looking at high-dose toxicity before? Did any of those studies have findings like this?

**A.** Yes, 4-week toxicity studies have previously been conducted with non-coated oral formulations of halofuginone (the HT-100 active ingredient) in other species, including the dog and the rat. As with the current dog study, higher doses were used in the rat and the no-effect-level (NOEL) was much higher in the rat than in this dog study. This tells us that the dog is likely a more sensitive species with respect to adverse effects of this drug. Additional toxicology studies in other species are planned in the near term to further evaluate the effect of the drug on different species, in particular to answer the question of whether the dog is a particularly sensitive species. It would not be unusual for the dog to be a particularly sensitive species. For example, some common anti-inflammatory drugs that are sold over-the-counter cause serious adverse events and even mortality in dogs at the recommended human dose.



**Q.** If you thought that the dog was particularly sensitive to the side effects of the active ingredient in HT-100, why did you do a study with higher doses in that species?

**A.** Halo's HT-100 formulation of halofuginone increases tolerability and allows dosing at higher levels in the dog. The purpose of a toxicology study is to understand the toxicities (negative side effects) of a drug. This allows you to better manage the safety of the drug in humans since you can monitor and manage these known side effects. Once we had addressed the previous dose-limiting toxicity (emesis, or vomiting) of halofuginone with Halo's proprietary HT-100 formulation, the appropriate next step was to identify the toxicities that would emerge at higher doses.

**Q.** Do you plan to restart the clinical program? If so, when?

**A.** Yes, this is our highest priority. We intend to resume clinical development of HT-100 as soon as possible. We are generating additional data from the clinical program and ongoing toxicology studies and will be working with the FDA to lift the clinical hold. Based on current information in this rapidly-evolving situation, our best projection is that we will re-start dosing between six weeks and four months from today (December 23). We will refine this projection as we generate additional data and continue our dialogue with FDA.