

Phase 1 and pre-clinical profiling of ESM-HDAC391, a myeloid-targeted histone deacetylase inhibitor, shows enhanced pharmacology and monocytopenia

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Abstract

AIM: To improve the tolerability and therapeutic application of histone deacetylase inhibitors (HDACi), by application of an esterase-sensitive motif (ESM), to target pharmacological activity directly to mononuclear myeloid cells expressing the processing enzyme carboxylesterase-1 (CES1). **METHODS.** This first-in-human study comprised of single and multiple ascending dose cohorts to determine safety and tolerability. Pharmacodynamic parameters included acetylation, cytokine inhibition and intracellular concentrations of processed acid metabolite in isolated monocytes. Mechanistic work was conducted *in vitro* and in a *CES1/Es1e^{lo}* mouse strain. **RESULTS.** ESM-HDAC391 was well tolerated whilst showing robust targeted mechanistic engagement, as demonstrated by selective retention of compound and increased acetylation in monocytes plus inhibition of *ex vivo* stimulated cytokine production. Importantly, common clinical HDACi toxicities were not observed. ESM-HDAC391 treatment was accompanied by the novel finding of a dose-dependent monocyte depletion that was transient and reversible. In-depth characterisation of monocyte depletion in a transgenic mouse model (*CES1/Es1e^{lo}*) suggested that CSF1R loss on circulating cells contributes to ESM-HDAC-mediated depletion. Further mechanistic investigations using human monocytes *in vitro* demonstrated HDACi-mediated change in myeloid fate through modulation of CSF1R and downstream effects on cell differentiation. **CONCLUSION.** These findings demonstrate selective targeting of monocytes in humans using the ESM approach and identify monocytopenia as a novel outcome of ESM-HDACi treatment, with implications for the potential benefit of these molecules in myeloid-driven diseases.

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