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A new selective HDAC6 inhibitor ameliorates disease phenotype in a Gdap1^{-}/$^{-}$ mouse model.

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GDAP1-related Charcot-Marie-Tooth (CMT) disease can be expressed as an axonal or demyelinating neuropathy, either recessive or dominant. In Spain, GDAP1 mutations are the leading cause of axonal CMT, accounting for approximately 11.5% of clinically diagnosed CMT cases. In recent years, histone deacetylase (HDAC) inhibitors have emerged as promising epigenetic therapeutics, with five currently approved by the FDA. Among these, considerable efforts have focused on developing HDAC6-selective inhibitors, as HDAC6 plays a deacetylase activity–dependent inhibitory role in axonal transport and regeneration, both of which are critical processes affected in axonal CMT. The specific involvement of HDAC6 in axonal dysfunction, along with its selective druggability, makes it an attractive therapeutic target.

Based on the structural properties of the HDAC6 enzyme and Quimatryx S.L. expertise in designing and synthesizing HDAC6-selective inhibitors, a new family of HDAC6 inhibitors that cross the blood-brain barrier was designed. In this sense, a different group from the hydroxamic was chosen as a zinc-chelating group, together with groups that reduce lipophilicity in the rest of the molecule structure.

In this study, we evaluated the therapeutic potential of QTX153, a novel selective HDAC6 inhibitor, in the Gdap1-/- mouse model. Preclinical trials were conducted using a 60 mg/kg dose in both male and female Gdap1-/- mice under two treatment paradigms: a presymptomatic regimen and an intervention initiated after the onset of phenotype. In both approaches, QTX153 administration led to significant improvements in motor function, measured by hind limb angle, severity score, hanging test, and maximum distance on rotarod.

These promising preliminary results demonstrate that QTX153 exerts therapeutic effects even in symptomatic animals, aligning more closely with real-world clinical scenarios and supporting further development of HDAC6-targeted therapies for GDAP1-related CMT.