TIDEGLUSIB (NP031112) DOES NOT SHOW MUTAGENIC POTENTIAL IN A BATTERY OF IN VITRO AND IN VIVO MODELS FOR GENOTOXIC ASSESSMENT

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Introduction: Tideglusib (NP031112) is an ATP-non competitive inhibitor of GSK-3 developed by Noscira S.A., Spain, which is being studied in patients with neurodegenerative disorders such as Alzheimer’s Disease (AD) and Progressive Supranuclear Palsy (PSP) (Phase IIb clinical trials in Europe and the USA).

Aims: To evaluate the safety profile of NP031112 related to genotoxicity potential under investigative (screening) and regulatory (ICH compliant) studies.

Methods: Assays with NP031112, its main metabolite (NP041113) and main impurity (NP060126) divided in the following steps: Screening phase represented by a SOS/umu test and in vitro micronucleus; Regulatory compliant phase (ICH Battery) consisted in in vitro (Ames assay, Mouse Lymphoma assay, Micronucleus assay) and in vivo (Micronucleus assay in mice).

Results: When NP031112 was evaluated in in vitro models, results showed clearly no mutagenic effect. However, in the in vitro Mouse Lymphoma assay, higher cytotoxicity was obtained (although without genotoxicity) and an in vivo confirmatory Micronucleus assay was conducted, confirming the lack of genotoxicity.

In addition, the main metabolite did not result genotoxic in any of the assays performed.

The main production impurity resulted in a non conclusive Ames assay although both the SOS/umu assay and the in vitro Micronucleus were negative. A confirmatory in vivo Micronucleus assay was conducted and no genotoxicity was observed.

Conclusions: Altogether, these demonstrated that neither NP031112 nor its main metabolite nor its main impurity possess mutagenic potential, and support the safety of tideglusib to continue its clinical development.