

FEXINIDAZOLE A NEW ORAL DRUG FOR THE TREATMENT OF HUMAN AFRICAN TRYPANOSOMIASIS

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Fexinidazole, currently in phase I clinical study for human African trypanosomiasis (HAT, also known as sleeping sickness), is the first success of DNDi's compound mining efforts for nitroimidazoles initiated in 2005. The project aimed to identify promising drug candidates among new and old nitroheterocycles, a class known to have broad spectrum of anti-infective activities against many pathogens including trypanosomes. By the end of 2006, over 500 nitroheterocycle compounds, from more than 15 different sources in both academia and the pharmaceutical industry, were identified, collected, and evaluated *in vitro*. Fexinidazole (Hoe 239), a 2-substituted 5-nitroimidazole, was rediscovered. Fexinidazole has been shown to be moderately active *in vitro* against African trypanosomes, and oral administration of fexinidazole cures mice with both acute and chronic infection, the latter a model for the advanced and fatal form of the disease when parasites have disseminated into the brain. In laboratory animals, fexinidazole is well absorbed after oral administration and readily distributes throughout the body, including the brain. Furthermore, fexinidazole is rapidly metabolized *in vivo* to at least two biologically active metabolites that are likely to account for a significant portion of the therapeutic effect.

Toxicology studies (including safety pharmacology and 4-week repeated-dose toxicokinetics in rat and dog) have shown that fexinidazole is well tolerated, with no issues of concern identified. While fexinidazole, like many nitroheterocycles, is mutagenic in the Ames test due to bacterial specific metabolism, it is not genotoxic to mammalian cells *in vitro* or *in vivo*.

Fexinidazole entered into phase I first-in-human clinical studies in September 2009. It is the only new drug candidate in clinical development for sleeping sickness. DNDi has recently completed the single ascending dose study without observable toxicity concerns. The phase I study is continuing.