DNDI-0690: a new promising drug candidate for the treatment of visceral leishmaniasis

Stéphanie Braillard, Béatrice Bonnet, Eric Chatelain

Drugs for Neglected Diseases initiative (DNDI), Geneva, Switzerland

INTRODUCTION

Leishmania donovani / infantum transmitted by sand flies is the causative pathogen responsible for visceral leishmaniasis (VL), a fatal disease present in eastern Africa, India and Latin America. There are between 150,000 and 300,000 cases a year, 50% of which are children. Few treatment options are available and all drugs suffer from significant drawbacks, limiting their use in endemic countries. There is a clear need for novel drugs for VL that are efficacious, affordable, better tolerated and safer than current treatments. We present here DNDI-0690, a 7-substituted nitroimidazoaxazine compound, issued from a DNDI/competitive lead optimization effort which is currently undergoing formal preclinical development before moving to first in human trials in Q1 2018.

SAFETY PROFILE

- No cytotoxicity.
- Genotoxicity: negative in both mini-AMES and in vitro Micronucleus test.
- hERG: IC₅₀ = 30.29 and IC₅₀ = 0.8 µM (whole cell patch clamp, HFL 293 cells at physiological temperature, GUP).
- Off-target activity: no significant activity (>50%) at 10 µM against a wide panel of receptors, channels, transporters and enzymes.
- GLP 14-day toxicity study in rat: NOAEL identified at the highest dose of 250 mg/kg in both male and female, corresponding to an AUCₐₐₜₑₜ of 698 and 619 µg/mL, respectively.

PHARMACODYNAMIC PROFILE

Potency of DNDI-0690 was assessed against various strains/isolates in intra-macrophage assays.

Efficacy was determined in vivo in an acute mouse model where Balb/c were infected with L. donovani HU3 or L. infantum ITFMAP363, while hamsters were infected with ITFMAP263 strain in a chronic model. In both models, treatment duration was 5 days, unless specified.

ADME PROFILE

- Exposure increase less than dose proportional and limited by solubility.
- Absorption limit in rat at AUC ~80000 h·ng/mL.
- No exposure in dog, but suitable exposure in monkey
- Low risk for drug-drug interaction: No CYP inhibition of 1A2, 2C19, 2C9, 2D6, and 3A4, no CYP induction of 1A2 and 2B6, but equi-solubility data on 3A4

PROCESS ROUTE

- 25 convergent steps (Overall yield ~16%).
- Validated up to 4kg scale
- High HPLC and chiral purity material (>99%)

PHYSICO-CHEMICAL PROPERTIES

DNDI-0690

Chirality
One stereocentre (R enantiomer)

Melting point (DSC)
Peak temp ~205°C

pH (measured)
HCl selected among 4 identified (HCl, H₂SO₄, H₃PO₄, and MeSO₄)

Solubility in organic solvents at 20°C
DMSO (64.4 mg/mL)
AcOH, Acetone, 2-butanol, THF: 3.8-9.2 mg/mL

Solubility in other solvents
Water: 6.25 mg/mL
pH 1.2: 128 µg/mL
pH 7.4: 2 µg/mL
Water: 114 µg/mL

Hygroscopicity
Non hygroscopic

PK/PD

Efficacious minimal concentration: 84 to 100 ng/mL Total = 3 to 10.2 nM free

HUMAN DOSE PREDICTION

- Due to a short half-life, DNDI-0690 will need a twice a day administration.
- Predicted range: 2x19 to 2x64 mg/day for a 50 kg human being, based on efficacious free exposure from hamster and mouse studies respectively and predicted human pharmacokinetics based on data from rat and monkey, and human in vitro as well.

CONCLUSION AND PERSPECTIVES

Taken together, these results, emphasized by an encouraging safety margin, lead to the conclusion that DNDI-0690 has the properties of an oral drug candidate for VL. Interestingly, this nitroimidazole compound showed excellent results in two different in vivo cutaneous leishmanial models (see poster C1601). Finally, Mode of Action resolution is under completion.

Following the development of a nanosuspension formulation suitable for rodent and non-rodent species, DNDI-0690 is currently going through a regulatory pre-IND package. First In Human (FIH) study in scheduled for Q1 2018.

WorldLeish 6
16 – 20 May 2017
Poster number C1568
Contact sbraillard@dndi.org