DNDI-VL-2098: a nitroimidazooxazole as clinical candidate to treat visceral leishmaniasis

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ABSTRACT

DNDI (Drugs for Neglected Diseases initiative) is a collaborative, patients’ needs-driven, not-for-profit organization whose mission is to develop new drugs for the most neglected tropical diseases, including visceral leishmaniasis (VL). The nitroimidazole class, well known for its anti-infective properties, became the focus of our research effort and quickly led to the identification of DNDI-VL-2098 as a potential candidate for VL. This compound is expected to fulfill DNDI’s Target Product Profile, including:  
a. effectiveness against L. donovani in East Africa and India (including drug resistant strains)  
b. 95% clinical efficacy  
c. no contraindications  
d. oral formulation  
e. dosing once a day for a maximum of 10 days  
f. cost under $10 per course.

INTRODUCTION

Screening of a representative selection of nitroimidazoles quickly led to the identification of DNDI-VL-2001 as a lead compound. Further investigation of this ramecine and its 2 enantiomers showed superiority of the R enantiomer: DNDI-VL-2098. DNDI therefore decided to develop the latter as a candidate for Visceral Leishmaniasis. We describe here the synthesis of DNDI-VL-2098, its main in vitro and in vivo characteristics and early safety profile.

SYNTHESIS

A process chiral route was developed for synthesis of DNDI-VL-2098, in order to improve yields of the synthetic route and limit the use of purifications. 2-Bromo-4-nitroimidazole 3 and the curative derivative 8 were identified as key building blocks that, upon condensation and cyclisation, lead to DNDI-VL-2098 in 2 steps, with 44% yield and 99.5% chiral purity.

IN VITRO PROFILE

Potency against Leishmania strains (IC50 in μM)

<table>
<thead>
<tr>
<th>VL strains</th>
<th>DNDI-VL-2098</th>
<th>Amphotericin B</th>
<th>Miltefosine</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. donovani</td>
<td>0.03</td>
<td>0.023</td>
<td>2.5</td>
</tr>
<tr>
<td>L. donovani HUJ</td>
<td>0.09</td>
<td>0.05</td>
<td>2.05</td>
</tr>
<tr>
<td>L. donovani BHU91</td>
<td>0.29</td>
<td>&gt;150</td>
<td>0.2</td>
</tr>
<tr>
<td>L. donovani SULAD</td>
<td>&lt;0.74</td>
<td>10.6</td>
<td>0.053</td>
</tr>
<tr>
<td>CL strains</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L. major LV39</td>
<td>0.83</td>
<td>&gt;50</td>
<td>0.01</td>
</tr>
<tr>
<td>L. tropica L62</td>
<td>1.34</td>
<td></td>
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<tr>
<td>L. braziliensis M2903</td>
<td>0.63</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L. mexicana B379</td>
<td>6.67</td>
<td></td>
<td>6.55</td>
</tr>
</tbody>
</table>

*Pentavalent Antimonials; **5% resistant strain, ***recent clinical isolate

DNDI-VL-2098 shows broad-spectrum in vitro activity against a range of standard visceral (VL) and cutaneous (CL) Leishmania strains, comparing favourably with currently used drugs (SBV, Amphotericin B and Miltefosine). The compound did not have any toxic effect on the host cells and the selectivity index was very high (>100).

ADMET profile

- High permeability in Caco-2 cells - not a substrate for efflux transporters
- Stable in recombinant human CYPs, human liver microsomes and hepatocytes - projected to have low intrinsic clearance and long elimination half-life in humans
- Among all CYPs, inhibitor of CYP2C19 only (IC50 = 0.5 μM) - considered to have a limited potential for drug-drug interactions
- Moderate to high plasma protein binding (94.4% in human, 96.6% in mouse), uniform blood/plasma distribution (blood-to-plasma ratio: 0.5 in human, 1.4 in mouse)

Overall, the in vitro data generated indicate that DNDI-VL-2098 is a stable, high permeability and low clearance molecule with limited potential for drug-drug interactions.

IN VIVO PROFILE

Pharmacokinetics

The pharmacokinetic profile of DNDI-VL-2098 was assessed in four different species.

- In all rodent species, the compound exhibited low (26 mL/min/kg in hamster) to moderate (2 mL/min/kg in mouse) clearance and excellent oral bioavailability (70% in rat to 100% in mouse and hamster). In the dog, clearance was low (5 mL/min/kg) and oral bioavailability was moderate/variable.

Efficacy

- In the BALB/c mouse - L. donovani model of the disease, experiments conducted at 3.125, 6.25, 12.5, 25 and 50 mg/kg once a day for 5 days led to an average ED50 value of 2 mg/kg.
- In the Golden Syrian hamster – L. donovani model of the disease, ED50 was evaluated to be 9.9 mg/kg at Day 12 after beginning of treatment. No sign of relapse was observed up to Day 50 after treatment at doses as low as 25 mg/kg qd for 5 days.
- Additional in vivo efficacy studies conducted on L. infantum hamster model and followed by promastigote transformation assay suggested the compound induces full parasitological cure when dosed at 50 mg/kg qd for 5 days.

SAFETY PROFILE

- DNDI-VL-2098 moderately inhibited the hERG channel (in transfected Chinese Hamster Ovary cells), with an IC50 of 10.5 μM. A telemetry study in male Beagle dogs showed no modification of QTc up to the highest dose tested (250 mg/kg).
- DNDI-VL-2098 was shown to be neither clastogenic in vitro nor mutagenic both in vitro and in vivo.
- DNDI-VL-2098 did not induce any effect on CNS and respiratory functions up to highest dose tested (600 mg/kg).
- In mice and rats, after single dose oral administration, the No-Oberved-Effect Level (NOEL) was > 2000 mg/kg.

According to allometric scaling predictions for human PK, the minimum efficacious dose in human beings (50 kg) is expected to be in the range of 200 to 350 mg, with a once a day oral administration (estimated long human elimination half-life).

SUMMARY

Nitromidazooxazole DNDI-VL-2098 was extensively studied as a drug candidate for Visceral Leishmaniasis and results showed it had:  
- Potent anti-leishmanial activity against a range of strains in vitro
- Significant reproducible activity following oral administration in vivo: the minimally effective dose in the mouse model was 6.25 mg/kg, and 25 mg/kg in the hamster model for a treatment duration of 5 consecutive days
- Advantages PK and safety profile

The compound is currently in the final stages of preclinical development at DNDI.

In conclusion, DNDI-VL-2098 shows promise for development as a clinical candidate to treat visceral leishmaniasis.

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