Discovery and optimization of a novel drug candidate for treatment of late-stage human african trypanosomsiasis

- SCYX 7158 -

Antoine TARRAL

on behalf of

Robert DON

DNDi

Drugs for Neglected Diseases *initiative*

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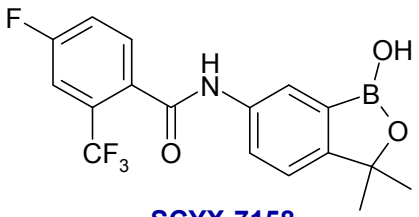
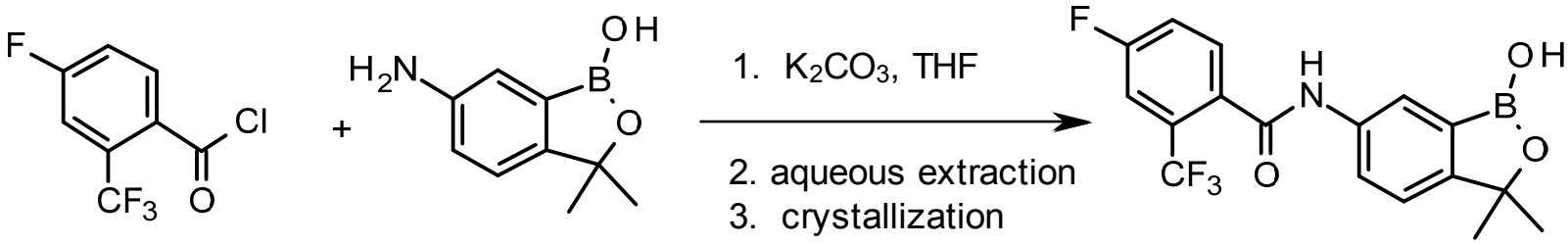
SCYX 7158



SCYX-7158

PM = 367.11 g/mol



SCYX-7158
(016SXS031)

Chemical name: (4-Fluoro-N-(1-hydroxy-3,3-dimethyl-1,3-dihydro-benzo[c] [1,2] oxaborol-6-yl)-2-trifluoromethyl benzamide)

OXABOROLE-6 BENZAMIDE

In Vitro efficacy

***T. brucei* Strain Tested**	**SCYX-7158**
T. b. brucei SBRI 427*	0.267
T. b. rhodesiense STIB 900	0.294
T. b. gambiense 40R	0.363
T. b. gambiense 108R	0.165
T. b. gambiense DAL 1402	0.065
T. b. gambiense ITMAP 141267	0.092
T. b. gambiense Drani	0.129

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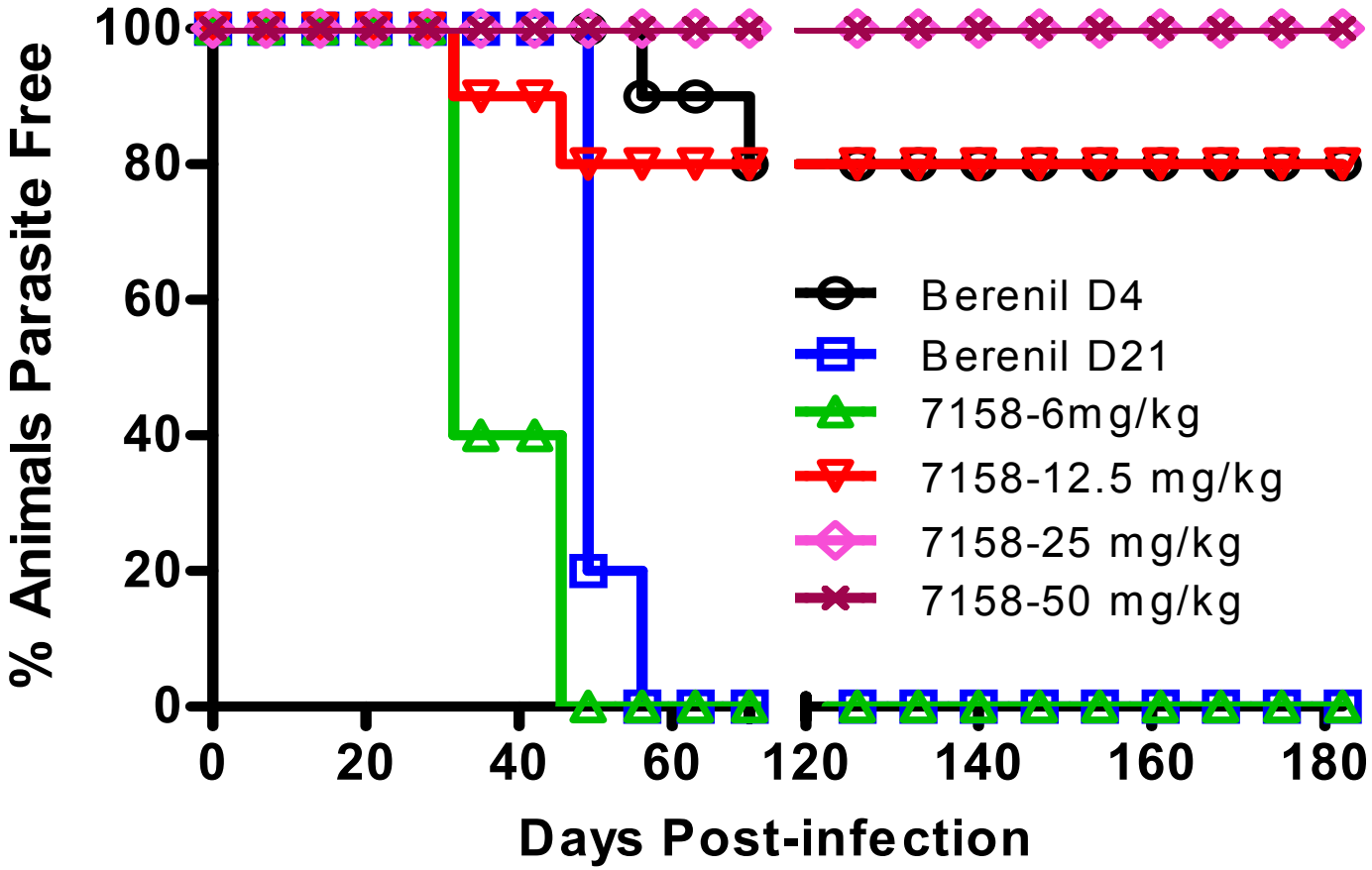
In vivo Efficacy – Stage 2



Safety studies

Safety Pharmacology (GLP)

- Standard genotoxicity battery
  - Ames
  - In vivo micronucleus test
  - In vitro chromosomal aberration
- hERG
- Telemetry (cardiovascular) Dog
- Respiratory in Rat
- Functional Observation Battery in Rat

Toxicokinetics

Safety Pharmacology

- Standard genotoxicity battery
  - Ames — Ames -ve
  - In vivo micronucleus test — negative
  - In vitro chromosomal aberration — negative
- hERG — IC50 >100μM
- Telemetry Dog (5, 15, 40 mpk) — No observations
- Respiratory in Rat (15, 40, 80 mpk) — No observations
- Functional Observation Battery in Rat
  - (15, 40, 80 mpk) — No observations

DMPK

- **Absorption**
  - **In vitro** MDR1-MDCK cells system — High absorption potential; High distribution in brain; No significant effflux
  - **In vivo** Dog ≈ 100% in dog; Monkey ≈ 80%; Rat ,Mouse ≈ 50%
- **Bioavailability** **Tmax** 4.5- 9.5 H in all species; linearity dose proportional
- **Volume of distribution :** ≈ 0.6 – 0.7 l/kg in all species
- **$T_{1/2}$ elimination** ≈ 25H
- **High protein binding** ≈ 95 % in all species

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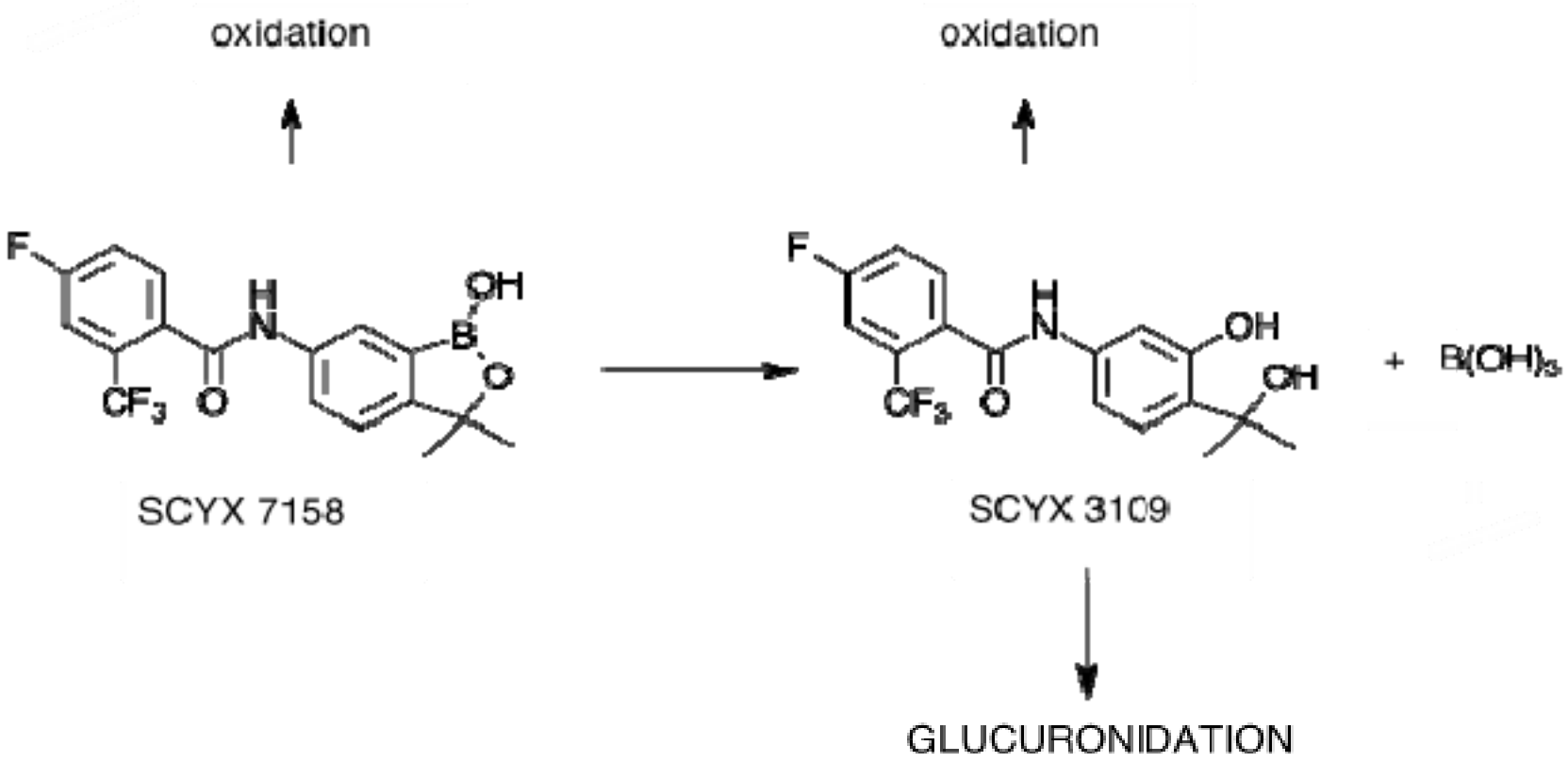
Metabolism



CYP Induction

- Inducer of CYP 2B6 and 3A4

ADME

Mass balance in rats

	Faeces	Urine	F + U	Total measured
Male	66%	20%	86%	89%
Female	73%	14%	87%	90%

Excretion after 14 days

Tissue distribution

- Well distributed in all tissues Brain Rat ≈44% Mouse 38%
- Highest levels in liver kidney and subcutaneous fat
- Lowest levels in eye and brain 1.5 -2 fold lower than blood

Rat Toxicokinetics

Toxicokinetics

- 7 days TK in rat 50, 140, 400mg/kg
  - weight loss and loss of appetite
  - Histopathology : stress related changes
- 28 days TK in rat 5, 15, 40, 80 mg/kg
- Loss of appetite and weight loss at 80 mg/kg
- Main target organ RBC : ↓ RBC:9-11%, ↓Hb 9%,↓Hct 8-10%, ↑ Reticulocyte:75- 80%
- No signs of bleeding nor hemolysis but

↑ Extra medullar hematopoiesis

- Histopath : no signs of bleeding no hemolysis ,
- clinical chemistry: No abnormal signs
  - **NOAEL = 15 mg/kg**

DOG Toxicokinetics

Toxicokinetics

- 7 days study TK in Dog 5, 20, 50 mg/kg
  - weight loss and loss of appetite
  - Histopathology : stress related changes
  - Reduced weight of thymus and spleen
- 28 days TK in dog 5, 15, 40 mg/kg
  - Loss of appetite and weight loss (emesis) at 40 mg/kg
  - Main target findings ; decrease in food consumtion
  - clinical chemistry: - 40 mg/kg/d Hb, Ht, decrease

    -15 and 5 mg/kg: only anecdotic, ancillary variations (Haemato and BC)

NOAEL =15 mg/kg

Clinical Pathology – relevant findings(1)

Gastrointestinal tract,

1. Rat: NAD*
2. Dog: minimal dilated/cystic gland in different segments mainly at 40 mg/kg/d

Possibly relevant, present at high doses

Pancreas,

1. Rat: Acinar cell vacuolation
2. Dog: Acinar cells: decreased basophilia focal acinar cell necrosis-mild 40mg/kg

Possibly relevant

*NAD: No abnormalities detected

Clinical Pathology – relevant findings (2)

Liver:

1. Rat: Hepatocellular hypertrophy in males, Single cell necrosis in females at 40mg/kg, NAD* below.
   Liver function tests are not affected

2 Dog: glycogen depletion in centrilobular hepatocytes and cytoplasmic rarefaction in periportal hepatocytes
Liver function tests are not affected

Relevance ?

Kidney

1 Rat: NAD*

2 Dog: Basophilic tubules, single cell necrosis: 1 male at 15 mg/kg .

-**Renal function (BUN, Creatinin) not affected.**

Relevance ?

*NAD: No abnormalities detected

Clinical Pathology – relevant findings (3)

Adrenals

1. Rat: Cortical hypertrophy both the sexes at 40 mg/kg
2. Dog: Cortical hypertrophy zona fasciculata: minimal to mild

Relevance: stress?

Thyroids

Dog only: follicular epithelial hypertrophy: minimal

Relevance : stress?

Testes Rat: Seminiferous tubule degeneration and epididymides (cellular debris in duct lumen) 40 mg/kg/d

Ovaries Rat: atrophy of interstitial tissue of ovaries, atrophy of uteri and vagina

Relevance : ?

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Summary of DATA

- **New family of drug :** OXABOROLE-6 BENZAMIDE
- **Exhibit a high in vitro potency vs *trypanosoma Brucei***
- ***Good physicochemical properties compatible with brain penetration***
- ***Active in acute and chronic mouse model of HAT model***
- ***Good PK properties compatible with a once a day dosing***
- ***NOAEL in rat 15mg/kg in rat and dog***
- ***Human starting dose in SAD will be 20mg = 0.33 mg/kg***

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Thank you