Determination of the optimal single dose treatment for acoziborole, a novel drug for the treatment of human African trypanosomiasis: first-in-human study

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Objectives of the study

Primary objectives:

Study Part I

To assess safety and tolerability of single oral ascending doses of SCYX-7158 in healthy male volunteers compared to placebo.

Study Part II and Study Part III

initially planned as food effect and multiple ascending dose study were cancelled, since they were no longer applicable due to single administration and the long half-life of the study drug.

Study Part IV

To evaluate the impact of activated charcoal intake on the PK characteristics of 20 mg SCYX-7158 and determine the most adapted treatment schedule for charcoal to enhance SCYX-7158 elimination while allowing a sustained drug exposure likely to be therapeutically active.

Study Part V

Was initially planned to study the impact of high dose of activated charcoal intake on the PK characteristics of SCYX-7158 but this part was cancelled and included in Study Part VI of the study.

Study Part VI

To compare the relative bioavailability of SCYX-7158 over 96 h of a new tablet formulation of SCYX-7158 versus the capsule formulation and to evaluate the impact of intensive activated charcoal administration.

Secondary objectives:

Study Part I

- To assess PK parameters of SCYX-7158 and its metabolite after single oral ascending doses of SCYX-7158 in healthy male volunteers.
- To evaluate the impact of SCYX-7158 and its related metabolites on the QT interval.
- To determine the free fraction of SCYX-7158 in healthy volunteers.
- To assess concentrations of SCYX-7158 in CSF sample.

Study Part IV

- To assess safety and tolerability of oral 20 mg capsules of SCYX-7158 administered as single oral dose together with activated charcoal according to various activated charcoal dosing schedule.

Study Part VI

- To assess safety and tolerability of a new formulation (tablet) of SCYX-7158 in healthy male volunteers.
- To evaluate the impact of a high dose of activated charcoal intake on the PK characteristics of SCYX-7158

Methodology

Study Part I

A randomized, double-blind, placebo-controlled (except Cohort 9), SAD study of SCYX-7158 with 14 cohorts (Cohort 1: 20 mg, Cohort 2: 40 mg, Cohort 3: 80 mg, Cohort 4: 120 mg, Cohort 5: 160 mg, Cohort 6: 200 mg, Cohort 7: 240 mg, Cohort 8: 320 mg, Cohort 9: previously 320 mg in tablet replaced by 960 mg in tablet and performed after Cohort 13, Cohort 10: 400 mg, Cohort 11: 600 mg, Cohort 12: 800 mg, Cohort 13: 1000 mg and Cohort 14: 1200 mg).

Study Part IV

An open label study to assess impact of co-administration of activated charcoal on both PK and the safety of single oral dose of 20 mg SCYX-7158.

Study Part VI

An open label study:

1) to compare the relative bioavailability of SCYX-7158 over 96 h of a new tablet formulation of SCYX-7158 *vs.* the capsule formulation,

2) to assess impact of co-administration with high dose of activated charcoal 50 g every 4 h after Day 5 to Day 7 and on follow-up visit until complete elimination.

Bioanalysis was performed in open conditions

Duration of treatment

Study Part I

For Cohort 1, capsule of 20 mg strength or matching placebo in one single oral administration without charcoal. Due to the long half-live, from Cohort 2 and followings (except Cohort 9), capsule (s) of 20 and/or 80 mg strength or matching placebo in one single oral administration followed by once daily administration of activated charcoal for 7 days starting from Day 5 (*i.e.*, after collection of the 96 h post-dose PK blood sample). Cohort 9 received 6 tablets of 160 mg without charcoal (no matching tablet placebo).

Study Part IV

Exploration of various charcoal co-administration. One single oral administration of 20 mg SCYX-7158 and once (Cohort 1) or thrice (Cohort 2) daily administration of activated charcoal for 7 days.

Study Part VI

One single administration of SCYX-7158 at 40 or 160 mg tablet and administration of 50 g charcoal every 4 h for 3 days from Day 5 to Day 7.

Dosage regimen

Study Part I

Single oral dose of SCYX-7158 in capsule formulation of 20 or 80 mg or matching placebo on 1 occasion followed by activated charcoal for 7 days from Day 5 to Day 11 once daily and on follow-up visit. Cohort 1 received 20 mg capsule without charcoal and Cohort 9 received 6 tablets of 160 mg without charcoal.

Study Part IV

Single oral dose of 20 mg capsule of SCYX-7158 on 1 occasion followed by activated charcoal for 7 days from 1 to 3 times daily.

Study Part VI

Single oral dose of 40 and 160 mg tablets of SCYX-7158 on 1 occasion followed by 50 g activated charcoal every4 h for 3 days from Day 5 to Day 7 and on follow-up visit until complete elimination.

Criteria for evaluation:

- Efficacy:

Not applicable

- Bioanalytical Assay

Human plasma obtained from blood collected on CPD and acidified with 0.5% of formic acid was used. Acoziborole and the main metabolite SCYX-3109 were analysed on a Supelco Ascentis® Express C18, 2.7 µm, 50 × 4.6 mm I.D. column using a validated liquid chromatography–tandem mass spectrometry

(LCMS/MS) method. The quantification limit of acoziborole and SCYX-3109 was 0.5 and 10 ng/mL, respectively.

- PK:

Study Part I

For each participant of Cohort 1 (20 mg), blood was collected at the following time points: pre dose, and 0.5, 1, 2, 3, 4, 6, 9, 12, 16, 24, 48, 72, 96, 120, 144, and 168 h post-dose.

Due to the long half-live, following changes were made:

For each participant of other cohorts, blood was collected at the following time points: pre dose, and 1, 4, 9, 12, 24, 48, 72, 96, 120, 168, and 240 h post-dose.

Moreover, a maximum of 9 additional PK blood samples were collected during the follow-up visit. The overall duration of follow-up could be reduced if levels of SCYX 7158 below 450 ng/mL were observed before completion of the 6-month period.

Concerning Cohort 9 (administration without charcoal), the follow-up period could be increased if SCYX-7158 blood levels were still above 450 ng/mL after 6 months of follow-up.

For Cohort 2 and for additional cohorts included in Amendment No. 9, 3 additional blood samples were collected at 24, 48, and 72 h post-dosing for determination of the free fraction of the drug.

Urine samples were collected only for Cohort 1 of Study Part I, as no analytical method was available for urine analysis of SCYX 7158 and his metabolite.

One sample of CSF was collected on Day 5 for each cohort included in Amendment No. 9, except Cohort 9 until reaching the concentration target (4 times IC90 determined in the killing curve study).

Study Part IV (20 mg plus exploration of various charcoal co-administration)

Blood was collected at the following time points: pre-dose and 1, 4, 9, 12, 24, 25, 27, 29, 31, 33, 36.5, 38.5, 40.5, 48, 49, 51, 57, 64.5, 72, 96, 120, 144, 168, and 192 h post-dose.

Moreover a maximum of 9 blood samples for PK purpose were drawn during the extra-visits.

Study Part VI (40 and 160 mg tablets plus high dose of charcoal)

For each participant, blood was collected at the following time points: pre-dose, and 1, 4, 9, 12, 24, 48, 72, 96, 120, 144, 168, 192 and 240 h post-dose.

If the concentration at 168 h was below 450 ng/mL, EOS visit was performed 8 days after release from the hospitalization.

If the concentration after charcoal administration was not below 450 ng/mL, then the participant attended extra follow up visits each week to get new PK blood sampling and clinical evaluation and received one dose of 50 g of charcoal. Then as soon as SCYX-7158 plasma concentration was below 450 ng/mL, the participant completed EOS visit.

- PD:

Urinary cortisol and 6-β-hydroxycortisol were measured to determine the ratio of this compound to evaluate if the mRNA *in vitro* inducer expression of the study drug on the CYP3A4 activity is detected in human (Study Part I only).

Fiveplicate ECGs were extracted from 24 h continuous 12-lead ECG Holter recordings and triplicate ECGs were recorded (Baseline D1, D8, D11, V1, V3, V5, V7, V8 for Part I only from Cohort 7 onwards) to evaluate the effect on QT as part of the safety analysis.

Safety:

Monitoring for the occurrence of AEs. Changes in physical examination, vital signs (blood pressure and pulse rate), ECG, and clinical laboratory tests (biochemistry, hematology, and urinalysis).

Safety digitalized 12 leads ECG were performed on D-1; D1 predose, 1, 2, 3, 4, 6, 9, 12, 24 h post-dosing and D8 before discharge for Cohort 1 and D-2, D1 pre-dose ,1,4, 9, 12, 24 h post dosing, D8, D11, V1, V3, V5, V7 and V9 for other cohorts.

Analysis:

- PK:

All plasma concentrations were summarized by dose level or treatment. The derived PK parameters were listed by participant and summarized by dose level or treatment and day where appropriate.

Similar descriptive statistics were presented for SCYX-7158 plasma free fraction concentrations by dose level (participants of Cohort 2 and for cohorts included in Amendment No. 9). Moreover, ratios of each free fraction concentration to the matching plasma concentration were calculated and similar descriptive concentrations were presented by dose level.

Study Part I:

AUC_{0-96} and C_{max} values were analyzed for dose proportionality using analysis of variance techniques except for the first dose level.

SCYX-7158 concentrations in CSF were summarized by dose level.

Study Part IV:

No formal analysis was performed

Study Part VI:

The relative bioavailability between the capsule and the tablet formulation was assessed by comparing the participants of the Study Part VI, receiving the new tablet formulation at doses of 40 and 160 mg, to the participants of the Study Part I receiving the same doses using the capsule formulation.

The comparison was performed on C_{max} and AUC_{0-96}.

- If the analysis of Study Part I indicated that 40 and 160 mg were in the proportional dose range, C_{max} and AUC_{0-96} were dose normalized and analyzed, after log-transformation, using a one-way analysis of variance including a factor for formulation.
- If the analysis of Study Part I indicated that 40 and 160 mg were not in the proportional dose range, the log transformed C_{max} or AUC were analyzed using a 2-way analysis of variance including factors for formulation, dose and their interaction.
- If the analysis of Study Part I indicated that 40 and 160 mg were not in the proportional dose range, the log transformed C_{max} or AUC were analyzed using a 2-way analysis of variance including factors for formulation, dose and their interaction.

- PD (Study Part I only):

Urinary cortisol and 6-β-hydroxycortisol were summarized by dose level and time point.

ECG QTc analysis are included in the safety section.

Safety:

All safety parameters (ECG, vital signs, AEs, etc.) were summarized by dose level or treatment and time point (where appropriate).

Replicate ECG analysis (Part I only)

- 24 h continuous 12-lead ECG Holter recordings:

Time-matched changes from baseline to Day 4 were calculated for each parameter as:

$\Delta Y(\text{time i}) = Y[\text{Day 4, time i}]-Y[\text{Day -1, time i}]$, Y = HR, RR, PR, QRS, QT, QTcF, QTcB, QTcP and QTcI,

All parameters and their time-matched changes from baseline were summarized by dose level and time point. Figure of mean ΔY *vs*. time by dose level was also presented.

Impact of SCYX-7158 doses on the holter ECG parameters was investigated by analyzing the ΔY parameters (Y = QTcF, QTcB, QTcP, QTcI, RR, PR, QRS and QT) using an analysis of variance model including terms for dose level, time and their interaction. The residual matrix was structured in order to take into account the repeated nature of the data.

Estimates of treatments effect and of the difference between active doses and placebo were provided with their 90% CI for each time point. Figures of the difference between active doses and placebo with their 90% CI at each time points were also provided.

Pooling of doses in limited categories of equal size could be performed if the results of the previous analysis suggested that several consecutive doses produce a similar effect. Hence, the analysis was also performed on the pooled doses.

The following additional analyses were carried out:

- Categorical analysis for QTcF, QTcB, QTcI, QTcP, ΔQTcF, ΔQTcB, ΔQTcI and ΔQTcP according to pre defined thresholds,- ECG morphological analysis.

- Digitalized ECG:

Triplicate ECGs were analyzed using the same method than holter extracted replicate.

Online Resource 2 Overview of all treatment-emergent adverse events in Study Parts I, IV and VI

AE	Part I				Part IV		Part VI	
	All (*N*=110)		Placebo (*N*=26)		All (*N*=6)		All (*N*=12)	
	AEs[a]	Participants (%)[b]	AEs	Participants (%)	AEs	Participants (%)	AEs	Participants (%)
NSAEs	85	59 (53.6)	24	17 (65.4)	1	1 (16.6)	40	12 (100)
Related	53	39 (35.5)	12	10 (38.5)	0	0 (0)	39	12 (100)
Not related	32	26 (23.6)	12	8 (30.8)	1	1 (16.6)	1	1 (8.3)
Mild	33	27 (24.5)	13	10 (38.5)	1	1 (16.6)	16	8 (66.7)
Moderate	52	37 (33.6)	11	8 (30.8)	0	0 (0)	24	12 (100)
Severe	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Corrective treatment	39	32 (29.1)	11	8 (30.8)	0	0 (0)	12	10 (83.3)
Treatment discontinuation	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
SAEs	1	1 (0.9)	0	0 (0)	0	0 (0)	0	0 (0)
Related	1	1 (0.9)	0	0 (0)	0	0 (0)	0	0 (0)
Not related	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Corrective treatment	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Treatment discontinuation	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Hospitalization	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Death	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)

AE adverse event, NSAE non-serious AE, SAE serious AE

[a] Number of AEs experienced

[b] Number (percentage) of participants with at least an AE

Online Resource 3 Incidence of study-drug-related adverse events for Study Part I

AE	All		Placebo		acoziborole											
	(*N*=110)		(*N*=26)		20 mg (*N*=6)		40 mg (*N*=6)		80 mg (*N*=6)		120 mg (*N*=6)		160 mg (*N*=6)		200 mg (*N*=6)	
	AEs[a]	Part. (%)[b]	AEs	Part. (%)	AEs	Part. (%)	AEs	Part. (%)	AEs	Part. (%)	AEs	Part. (%)	AEs	Part. (%)	AEs	Part. (%)
Total	54	40 (36.4)	12	10 (38.5)	0	0 (0)	8	5 (83.3)	2	2 (33.3)	1	1 (16.7)	3	2 (33.3)	1	1 (16.7)
Cardiac disorders	2	2 (1.8)	1	1 (3.8)	0	0 (0)	1	1 (16.7)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Palpitations	1	1 (0.9)	1	1 (3.8)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Atrial fibrillation	1	1 (0.9)	0	0 (0)	0	0 (0)	1	1 (16.7)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Endocrine disorders	1	1 (0.9)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Hyperthyroidism	1	1 (0.9)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Gastrointestinal disorders	15	14 (12.7)	5	4 (15.4)	0	0 (0)	2	2 (33.3)	1	1 (16.7)	1	1 (16.7)	0	0 (0)	1	1 (16.7)
Abdominal pain upper	5	5 (4.5)	2	2 (7.7)	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (16.7)	0	0 (0)	0	0 (0)
Nausea	4	4 (3.6)	2	2 (7.7)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (16.7)
Abdominal pain	3	3 (2.7)	1	1 (3.8)	0	0 (0)	0	0 (0)	1	1 (16.7)	0	0 (0)	0	0 (0)	0	0 (0)
Constipation	2	2 (1.8)	0	0 (0)	0	0 (0)	2	2 (33.3)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Abdominal distension	1	1 (0.9)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Investigations	13	13 (11.8)	3	3 (11.5)	0	0 (0)	2	2 (33.3)	0	0 (0)	0	0 (0)	2	2 (33.3)	0	0 (0)
Transaminases increased	6	6 (5.5)	2	2 (7.7)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (16.7)	0	0 (0)
Blood creatine phosphokinase increased	6	6 (5.5)	1	1 (3.8)	0	0 (0)	2	2 (33.3)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Thyroid function test abnormal	1	1 (0.9)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (16.7)	0	0 (0)
Metabolism and nutrition disorders	3	3 (2.7)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (16.7)	0	0 (0)
Decreased appetite	3	3 (2.7)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (16.7)	0	0 (0)
Musculoskeletal and connective tissue disorders	1	1 (0.9)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Back pain	1	1 (0.9)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)

Nervous system disorders	16	14 (12.7)	2	2 (7.7)	0	0 (0)	3	3 (50.0)	1	1 (16.7)	0	0 (0)	0	0 (0)	0	0 (0)
Headache	14	13 (11.8)	2	2 (7.7)	0	0 (0)	3	3 (50.0)	1	1 (16.7)	0	0 (0)	0	0 (0)	0	0 (0)
Dizziness postural	1	1 (0.9)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Loss of consciousness	1	1 (0.9)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Psychiatric disorders	1	1 (0.9)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Insomnia	1	1 (0.9)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Skin and subcutaneous tissue disorders	2	2 (1.8)	1	1 (3.8)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Pruritus	1	1 (0.9)	1	1 (3.8)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Rash pruritic	1	1 (0.9)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)

Online Resource 3 Incidence of study-drug-related adverse events for Study Part I (continued)

AE	acoziborole															
	240 mg (*N*=6)		320 mg (*N*=6)		400 mg (*N*=6)		600 mg (*N*=6)		800 mg (*N*=6)		960 mg (*N*=6)		1,000 mg (*N*=6)		1,200 mg (*N*=6)	
	AEs[a]	Part. (%)[b]	AEs	Part. (%)	AEs	Part. (%)	AEs	Part. (%)	AEs	Part. (%)	AEs	Part. (%)	AEs	Part. (%)	AEs	Part. (%)
Total	1	1 (16.7)	5	3 (50.0)	0	0 (0)	6	5 (83.3)	3	2 (33.3)	6	4 (66.7)	1	1 (16.7)	5	3 (50.0)
Cardiac disorders	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Palpitations	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Atrial fibrillation	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Endocrine disorders	1	1 (16.7)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Hyperthyroidism	1	1 (16.7)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Gastrointestinal disorders	0	0 (0)	3	3 (50.0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	2	2 (33.3)
Abdominal pain upper	0	0 (0)	1	1 (16.7)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (16.7)
Nausea	0	0 (0)	1	1 (16.7)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Abdominal pain	0	0 (0)	1	1 (16.7)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Constipation	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Abdominal distension	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (16.7)

Investigations	0	0 (0)	0	0 (0)	0	0 (0)	3	3 (50.0)	1	1 (16.7)	1	1 (16.7)	1	1 (16.7)	0	0 (0)
Transaminases increased	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (16.7)	1	1 (16.7)	0	0 (0)	1	1 (16.7)	0	0 (0)
Blood creatine phosphokinase increased	0	0 (0)	0	0 (0)	0	0 (0)	2	2 (33.3)	0	0 (0)	1	1 (16.7)	0	0 (0)	0	0 (0)
Thyroid function test abnormal	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Metabolism and nutrition disorders	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (16.7)	0	0 (0)	0	0 (0)	1	1 (16.7)
Decreased appetite	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (16.7)	0	0 (0)	0	0 (0)	1	1 (16.7)
Musculoskeletal and connective tissue disorders	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (16.7)	0	0 (0)	0	0 (0)
Back pain	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (16.7)	0	0 (0)	0	0 (0)
Nervous system disorders	0	0 (0)	2	2 (33.3)	0	0 (0)	3	3 (50.0)	1	1 (16.7)	2	1 (16.7)	0	0 (0)	2	1 (16.7)
Headache	0	0 (0)	2	2 (33.3)	0	0 (0)	3	3 (50.0)	1	1 (16.7)	2	1 (16.7)	0	0 (0)	0	0 (0)
Dizziness postural	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (16.7)
Loss of consciousness	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (16.7)
Psychiatric disorders	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (16.7)	0	0 (0)	0	0 (0)
Insomnia	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (16.7)	0	0 (0)	0	0 (0)
Skin and subcutaneous tissue disorders	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (16.7)	0	0 (0)	0	0 (0)
Pruritus	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)
Rash pruritic	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	0	0 (0)	1	1 (16.7)	0	0 (0)	0	0 (0)

AE = adverse event, Part. = participants

[a] Number of AEs experienced

[b] Number (percentage) of participants with at least an AE

Online Resource 4 Clinical Study Report

CLINICAL STUDY REPORT

Study number:	DNDiOXA001 **PhinC Development reference:** PH11015
EudraCT number:	2011-004639-30
Study title:	Randomized, double-blind, placebo-controlled sequential study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of SCYX-7158 after single oral ascending doses, food effect and multiple oral ascending dose in healthy male volunteers
Drug name:	SCYX-7158 (oxaborole)
Indication / purpose:	Human African Trypanosomiasis (HAT)
Drug development phase:	Phase I
Sponsor:	DNDi 15 chemin Louis Dunant 1202 Geneva (Switzerland)
Sponsor's representative:	Antoine Tarral
Study centers:	SGS aster s.a.s. (closed on July 10th, 2013) 3-5 rue Eugène Millon 75015 Paris (France) Eurofins Optimed 1 rue des Essarts 38610 Gières (France)
Principal Investigator:	Lionel Hovsepian, MD (at SGS Aster) Yves Donazzolo, MD (at Eurofins Optimed)
First patient first visit:	February 6th,2012
Last patient last visit:	March 9th,2015
Report version:	Final version 1.0: August 24th, 2015

This study was conducted in full compliance with applicable Good Clinical Practices and regulations, including archiving.

It was planned to do a single ascending dose (SAD) followed by a food effect and a multiple ascending dose in a single center. After the first dose (20 mg), a longer half-life in human than the predicted one with preclinical data was detected. SAD study was on hold, further *in vitro* (charcoal effect) and dog exploration were performed, strengthening the possibility to use activated charcoal to adsorb SCYX-7158 in the gut and enhancing the possibility of an entero-hepatic recirculation. The protocol was then amended to add Study Part IV exploring in 2 cohorts of 3 subjects the effect of the impact of activated charcoal intake on the elimination rate and thus on the relative bioavailability of SCYX-7158 after single oral dose administration. The more adapted activated charcoal dosing schedule was selected to be administered after SCYX-7158 in order to shorten the follow-up of the subjects. Part V was planned to explore an intensive charcoal administration in the objective to obtain a significant extraction of SCYX-7158 from the body. This part was included in the Part VI. Part VI was planned to asses a comparative PK of new tablet formulation (40 mg and 160 mg) *versus* the same strength of capsule and to evaluate at Day 5, Day 6, and Day 7 the effect of an intensive charcoal administration (50 mg every 4 hours for 3 days) starting on Day 5.

Summary table of study parts

Initial protocol	Part I	SAD	completed
	Part II	Food effect	Cancelled
	Part III	MAD	Cancelled
Amendment No. 6	Part IV	20 mg + charcoal	Completed
Amendment No. 9	Part V	Intensive charcoal administration	Included in Part VI
Amendment No. 10	Part VI	Comparative PK capsules and tablets + intensive charcoal administration	Completed

Furthermore, the study was conducted in 2 sites due to company reorganization and closure of the first study site (January 2014).

The following amendments (13) have been made (see Section 9.8):

- Amendment No. 1 dated November 25th, 2011 was drawn to modify the storage condition of PK samples and to review pharmacovigilance management.
- Amendment No. 2 dated January 5th, 2012 was drawn to adapt the non-inclusion criteria according to Ethics Committee recommendation *i.e.* non-inclusion of G6PD and pyruvate kinase deficient volunteers and sickle cell anemia in the first dose cohort.

- Amendment No. 3 dated March 7th, 2012 was drawn to revise methodology of dose escalation and to add determination of cortisol and hydroxycortisol ratio in urine.
- Amendment No. 4 dated March 21st, 2012 was drawn to extend the time of safety and PK follow-up after results of the 1st cohort and the determination of a long half-life.
- Amendment No. 5 dated May 15th, 2012 was drawn to add supplementary visit.
- Amendment No. 6 dated August 14th, 2012 was drawn to add Study Part IV, to study influence of the co-administration of activated charcoal on the overall exposure and elimination of SCYX-7158 and to suspend Study Part I.
- Amendment No. 7 dated November 29th, 2012 was drawn to include administration of activated charcoal in the SAD and to cancel the food effect (Study Part II) as well as the multiple ascending dose parts (Study Part III) of the study.
- Amendment No. 8 dated February 6th, 2013 was drawn to indicate the opening of a second study center due to the structural reorganization of the first study center.
- Amendment No. 9 dated July 9th, 2013 was drawn to extend the dose progression over 240 mg SCYX-7158 (Cohort 8 to Cohort 11), to add a CSF sampling and to add a part to evaluate the impact of high dose of activated charcoal intake on the PK characteristics of SCYX-7158 (Study Part V).
- Amendment No. 10 dated August 16th, 2013 was drawn to evaluate PK of SCYX-7158 when given as two new SCYX-7158 tablet formulations dosed at 40 and 160 mg (Study Part VI), to shorten the follow-up period once the subjects reached a plasmatic concentration of SCYX-7158 below 200 ng/mL and to remove Study Part V and combine it with Study Part VI.
- Amendment No. 11 dated December 30th, 2013 was drawn to complete the Phase I data with subjects expose to SCYX-7158 administration in same conditions as in the field, that is using the tablet formulation at the therapeutic dose and without charcoal, at the anticipated therapeutic dose (Cohort 9), to shorten the follow-up period once the subjects reached a plasmatic concentration of SCYX-7158 below 450 ng/mL and to adapt the 24-h Holter recording in Cohort 9.
- Amendment No. 12 dated February 24th, 2014 then April 1st, 2014 was drawn to add a non-inclusion criterion on anti-thyroid peroxidase at screening further to observation of suspect thyroid abnormality in a subject.
- Amendment No. 13 dated March 24th, 2014 was drawn to extend the dose progression up to a maximum of 1400 mg, to adapt 24-h Holter recording and to cancel urine collection for the determination of cortisol/hydroxycortisol ratio and extraction of fiveplicate from ECG.

Numbers of cohorts in the study (see description in Section 8.1.1)
Description of cohorts of Study Part I

Cohort	Treatment	Activated charcoal co-administration
1 (8 subjects)*	20 mg SCYX-7158 or placebo (6/2)	**No**
2 (8 subjects)	40 mg SCYX-7158 or placebo (6/2)	Yes
3 (8 subjects)	80 mg SCYX-7158 or placebo (6/2)	Yes
4 (8 subjects)	120 mg SCYX-7158 or placebo (6/2)	Yes
5 (8 subjects)	160 mg SCYX-7158 or placebo (6/2)	Yes
6 (8 subjects)	200 mg SCYX-7158 or placebo (6/2)	Yes
7 (8 subjects)	240 mg SCYX-7158 or placebo (6/2)	Yes
8 (8 subjects)	320 mg SCYX-7158 or placebo (6/2)	Yes
9 (6 subjects)	960 mg SCYX-7158 (6)	**No**
10 (8 subjects)	400 mg SCYX-7158 or placebo (6/2)	Yes
11 (8 subjects)	600 mg SCYX-7158 or placebo (6/2)	Yes
12 (8 subjects)	800 mg SCYX-7158 or placebo (6/2)	Yes
13 (8 subjects)	1000 mg SCYX-7158 or placebo (6/2)	Yes
14 (8 subjects)	1200 mg SCYX-7158 or placebo (6/2)	Yes

*Cohort done in Study Center 1 (SGS aster).

2 SYNOPSIS

Name of Sponsor/Company: DNDi	*Individual Study Table referring to Part of the Dossier*	*(For National Authority Use only)*
Name of Finished Product: Not applicable.	*Volume:*	
Name of Active Ingredient: SCYX-7158	*Page:*	

Title of study: Randomized, double-blind, placebo-controlled sequential study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of SCYX-7158 after single oral ascending doses, food effect and multiple oral ascending dose in healthy male volunteers

Protocol number: DNDiOXA001 **PhinC Development reference:** PH11015

Principal Investigators:

Yves Donazollo, MD, at Eurofins Optimed.

Lionel Hovespian, MD at SGS aster.

Study centers:

Eurofins Optimed, 1 rue des Essarts, 38610 Gières (France)

SGS aster, 3-5 rue Eugène Millon (France) (closed on July 10th, 2013)

Study period:			**Drug Development Phase:**
First subject first visit	:	February 6th, 2012	Phase I
Last subject last visit	:	March 9th, 2015	

Objectives:

Primary objectives:

Study Part I

- To assess safety and tolerability of single oral ascending doses of SCYX-7158 in healthy male volunteers compared to placebo.

Study Part II and Study Part III initially planned as food effect and multiple ascending dose study were cancelled, since they were no longer applicable due to single administration and the long half-life of the study drug.

Study Part IV

- To evaluate the impact of activated charcoal intake on the PK characteristics of 20 mg SCYX-7158 and determine the most adapted treatment schedule for charcoal to enhance SCYX-7158 elimination while allowing a sustained drug exposure likely to be therapeutically active.

Study Part V was initially planned to study the impact of high dose of activated charcoal intake on the PK characteristics of SCYX-7158 but this part was cancelled and included in Study Part VI of the study.

Study Part VI

- To evaluate PK of a new formulation (tablet) of SCYX-7158 in healthy male volunteers.

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Secondary objectives:

Study Part I

- To assess PK parameters of SCYX-7158 and its metabolite after single oral ascending doses of SCYX-7158 in healthy male volunteers.
- To evaluate the impact of SCYX-7158 and its related metabolites on the QT interval.
- To determine the free fraction of SCYX-7158 in healthy volunteers.
- To assess concentrations of SCYX-7158 in CSF sample.

Study Part IV

- To assess safety and tolerability of oral 20 mg capsules of SCYX-7158 administered as single oral dose together with activated charcoal according to various activated charcoal dosing schedule.

Study Part VI

- To assess safety and tolerability of a new formulation (tablet) of SCYX-7158 in healthy male volunteers.
- To evaluate the impact of a high dose of activated charcoal intake on the PK characteristics of SCYX-7158.

Methodology:

The study comprised 3 parts:

- Study Part I was a randomized, double-blind, placebo-controlled (except Cohort 9), SAD study of SCYX-7158 with 14 cohorts (Cohort 1: 20 mg, Cohort 2: 40 mg, Cohort 3: 80 mg, Cohort 4: 120 mg, Cohort 5: 160 mg, Cohort 6: 200 mg, Cohort 7: 240 mg, Cohort 8: 320 mg, Cohort 9: previously 320 mg in tablet replaced by 960 mg in tablet and performed after Cohort 13, Cohort 10: 400 mg, Cohort 11: 600 mg, Cohort 12: 800 mg, Cohort 13: 1000 mg and Cohort 14: 1200 mg).
- Study Part IV was an open label study to assess impact of co-administration of activated charcoal on both PK and the safety of single oral dose of 20 mg SCYX-7158.
- Study Part VI was an open label study:

  1) to compare the relative bioavailability of SCYX-7158 over 96 h of a new tablet formulation of SCYX-7158 *vs.* the capsule formulation,

  2) to assess impact of co-administration with high dose of activated charcoal 50 g every 4 h after Day 5.

Bioanalysis was performed in open conditions.

Number of subjects (planned and analyzed):

	Part I		**Part IV**	**Part VI**	**Total**	
	13 cohorts of 8 and 1 cohort of 6		2 cohorts of 3	2 cohorts of 6	18 cohorts	
	Active	Placebo	Active	Active	Active	Placebo
Planned	84	26	6	12	102	26
Included	84	26	6	12	102	26
Completed the trial	83	26	6	12	101	26
In PK analysis	84	NA	6	12	102	NA
In safety analysis	84	26	6	12	102	26
In ECG analysis	42	12	NA	NA	42	12
In PD analysis	48	16	NA	NA	48	16

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Diagnosis and main criteria for inclusion:

The study was carried out in healthy male African volunteers, aged 18 to 45 years old and with a BMI between 18 and 28 kg/m^2.

Duration of treatment:

Study Part I

For Cohort 1, capsule of 20 mg strength or matching placebo in one single oral administration without charcoal.

Due to the long half-live, from Cohort 2 and followings (except Cohort 9), capsule (s) of 20 and/or 80 mg strength or matching placebo in one single oral administration followed by once daily administration of activated charcoal for 7 days starting from Day 5 (*i.e.*, after collection of the 96 h post-dose PK blood sample).

Cohort 9 received 6 tablets of 160 mg without charcoal (no matching tablet placebo).

Study Part IV: exploration of various charcoal co-administration.

One single oral administration of 20 mg SCYX-7158 and once (Cohort 1) or thrice (Cohort 2) daily administration of activated charcoal for 7 days.

Study Part VI

One single administration of SCYX-7158 at 40 or 160 mg tablet and administration of 50 g charcoal every 4 h for 3 days from Day 5 to Day 7.

Dosage regimen:

Study Part I

Single oral dose of SCYX-7158 in capsule formulation of 20 or 80 mg or matching placebo on 1 occasion followed by activated charcoal for 7 days from Day 5 to Day 11 once daily and on follow-up visit. Cohort 1 received 20 mg capsule without charcoal and Cohort 9 received 6 tablets of 160 mg without charcoal.

Study Part IV

Single oral dose of 20 mg capsule of SCYX-7158 on 1 occasion followed by activated charcoal for 7 days from 1 to 3 times daily.

Study Part VI

Single oral dose of 40 and 160 mg tablets of SCYX-7158 on 1 occasion followed by 50 g activated charcoal every 4 h for 3 days from Day 5 to Day 7 and on follow-up visit until complete elimination.

Test products, dose and mode of administration, batch number:

Product and Formulation:	20 and 80 mg capsule of SCYX-7158 and their respective matching placebo
Batch number:	004286, 004287,004284, 004285
Expiry or retest date:	April 2014, November 2014, April 2014, April 2015
Mode of administration:	*Per os*
Dosage/regimen:	Single oral doses

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Test products, dose and mode of administration, batch number:

Product and Formulation:	40 and 160 mg tablet of SCYX-7158
Batch number:	PD1325 and PD1326
Expiry or retest date:	February 2015
Mode of administration:	*Per os*
Dosage/regimen:	Single oral doses

Criteria for evaluation:

Efficacy:

Not applicable

PK:

Study Part I

For each subject of Cohort 1 (20 mg), blood was collected at the following time points: pre-dose, and 0.5, 1, 2, 3, 4, 6, 9, 12, 16, 24, 48, 72, 96, 120, 144, and 168 h post-dose.

Due to the long half-live, following changes were made:

For each subject of other cohorts, blood was collected at the following time points: pre-dose, and 1, 4, 9, 12, 24, 48, 72, 96, 120, 168, and 240 h post-dose.

Moreover, a maximum of 9 additional PK blood samples were collected during the follow-up visit. The overall duration of follow-up could be reduced if levels of SCYX-7158 below 450 ng/mL were observed before completion of the 6-month period.

Concerning Cohort 9 (administration without charcoal), the follow-up period could be increased if SCYX-7158 blood levels were still above 450 ng/mL after 6 months of follow-up.

For Cohort 2 and for additional cohorts included in Amendment No. 9, 3 additional blood samples were collected at 24, 48, and 72 h post-dosing for determination of the free fraction of the drug.

Urine samples were collected only for Cohort 1 of Study Part I, as no analytical method was available for urine analysis of SCYX-7158 and his metabolite.

One sample of CSF was collected on Day 5 for each cohort included in Amendment No. 9, except Cohort 9 until reaching the concentration target (4 times IC90 determined in the killing curve study).

Study Part IV (20 mg plus exploration of various charcoal co-administration)

Blood was collected at the following time points: pre-dose and 1, 4, 9, 12, 24, 25, 27, 29, 31, 33, 36.5, 38.5, 40.5, 48, 49, 51, 57, 64.5, 72, 96, 120, 144, 168, and 192 h post-dose.

Moreover a maximum of 9 blood samples for PK purpose were drawn during the extra-visits.

Study Part VI (40 and 160 mg tablets plus high dose of charcoal)

For each subject, blood was collected at the following time points: pre-dose, and 1, 4, 9, 12, 24, 48, 72, 96, 120, 144, 168, 192 and 240 h post-dose.

If the concentration at 168 h was below 450 ng/mL, EOS visit was performed 8 days after release from the hospitalization.

If the concentration after charcoal administration was not below 450 ng/mL, then the subject attended extra follow-up visits each week to get new PK blood sampling and clinical evaluation and received one dose of 50 g of charcoal. Then as soon as SCYX-7158 plasma concentration was below 450 ng/mL, the subject completed EOS visit.

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Criteria for evaluation (continued): PD:

Urinary cortisol and 6-β-hydroxycortisol were measured to determine the ratio of this compound to evaluate if the mRNA *in vitro* inducer expression of the study drug on the CYP3A4 activity is detected in human (Study Part I only).

Fiveplicate ECGs were extracted from 24 h continuous 12-lead ECG Holter recordings and triplicate ECGs were recorded (Baseline D1, D8, D11, V1, V3, V5, V7, V8 for Part I only from Cohort 7 onwards) to evaluate the effect on QT.

Safety:

Monitoring for the occurrence of AEs. Changes in physical examination, vital signs (blood pressure and pulse rate), ECG, and clinical laboratory tests (biochemistry, hematology, and urinalysis).

Safety digitalized 12-leads ECG were performed on D-1; D1 predose, 1, 2, 3, 4, 6, 9, 12, 24 h post-dosing and D8 before discharge for Cohort 1 and D-2, D1 pre-dose ,1,4, 9, 12, 24 h post-dosing, D8, D11, V1, V3, V5, V7 and V9 for other cohorts.

Statistical methods:

PK:

All plasma concentrations were summarized by dose level or treatment. The derived PK parameters were listed by subject and summarized by dose level or treatment and day where appropriate.

Similar descriptive statistics were presented for SCYX-7158 plasma free fraction concentrations by dose level (subjects of Cohort 2 and for cohorts included in Amendment No. 9). Moreover, ratios of each free fraction concentration to the matching plasma concentration were calculated and similar descriptive concentrations were presented by dose level.

Study Part I:

AUC_{0-96} and C_{max} values were analyzed for dose proportionality using analysis of variance techniques except for the first dose level.

SCYX-7158 concentrations in CSF were summarized by dose level. Study Part IV:

No formal analysis was performed

Study Part VI:

The relative bioavailability between the capsule and the tablet formulation was assessed by comparing the subjects of the Study Part VI, receiving the new tablet formulation at doses of 40 and 160 mg, to the subjects of the Study Part I receiving the same doses using the capsule formulation.

The comparison was performed on C_{max} and AUC_{0-96}.

- If the analysis of Study Part I indicated that 40 and 160 mg were in the proportional dose range, C_{max} and AUC_{0-96} were dose normalized and analyzed, after log-transformation, using a one-way analysis of variance including a

factor for formulation.

- If the analysis of Study Part I indicated that 40 and 160 mg were not in the proportional dose range, the log transformed C_{max} or AUC were analyzed using a 2-way analysis of variance including factors for formulation, dose and their interaction.

PD (Study Part I only):

Urinary cortisol and 6-β-hydroxycortisol were summarized by dose level and time point.

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Statistical methods (continued): Safety:

All safety parameters (ECG, vital signs, AEs, etc.) were summarized by dose level or treatment and time point (where appropriate).

Replicate ECG analysis (Part I only)

24 h continuous 12-lead ECG Holter recordings:

Time-matched changes from baseline to Day 4 were calculated for each parameter as:

ΔY(time i) = Y[Day 4, time i]-Y[Day -1, time i], Y = HR, RR, PR, QRS, QT, QTcF, QTcB, QTcP and QTcI,

All parameters and their time-matched changes from baseline were summarized by dose level and time point. Figure of mean ΔY *vs*. time by dose level was also presented.

Impact of SCYX-7158 doses on the holter ECG parameters was investigated by analyzing the ΔY parameters (Y = QTcF, QTcB, QTcP, QTcI, RR, PR, QRS and QT) using an analysis of variance model including terms for dose level, time and their interaction. The residual matrix was structured in order to take into account the repeated nature of the data.

Estimates of treatments effect and of the difference between active doses and placebo were provided with their 90% CI for each time point. Figures of the difference between active doses and placebo with their 90% CI at each time points were also provided.

Pooling of doses in limited categories of equal size could be performed if the results of the previous analysis suggested that several consecutive doses produce a similar effect. Hence, the analysis was also performed on the pooled doses.

The following additional analyses were carried out:

- Categorical analysis for QTcF, QTcB, QTcI, QTcP, ΔQTcF, ΔQTcB, ΔQTcI and ΔQTcP according to pre-defined thresholds,
- ECG morphological analysis.

Digitalized ECG:

Triplicate ECGs were analyzed using the same method than holter extracted replicate.

Results:

PK:

PK results showed that SCYX-7158 was quite rapidly absorbed and that levels remained steady for at least 4 days. A lot of rebounds were seen in the plasma profiles suggesting that the drug is subjected to an entero-hepatic recycling. This is the reason why activated charcoal was given to subjects (generally commencing on Day 5) to try to accelerate the clearance of the drug. However, despite the administration of charcoal, SCYX-7158 was very slowly eliminated from the body with a $t_{1/2}$ of about 400 h.

The PK of SCYX-7158 was not linear with dose with a less than dose proportional increase of C_{max} and AUC_{0-96}, in the dose range 40 and 1200 mg. Another important characteristics of the PK of SCYX-7158 was the low inter-subject variability (mean values varying from 8 to about 28% independently of the dose).

Unlike to what observed in animals, the metabolism of SCYX-7158 was very limited as shown by the very low concentrations of SCYX-3109 measured from not detectable in all the subjects of the dose groups 40 and 80 mg, or transiently higher than the LOQ (10 ng/mL) in the other cohorts. This low level of metabolism can be a factor of prolonged $t_{1/2}$ in humans.

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Results (continued):

PK (continued):

Concentrations of SCYX-7158 in ultra-filtrate was determined in order to estimate the free fraction (or unbound fraction) of SCYX-7158 that was available in plasma. The ultra-filtrate to plasma ratio is therefore an estimation of the free fraction. This is an important parameter to investigate as the free fraction supports the activity of the drug since it is able to diffuse in tissue and site of actions. Median free fraction was quite stable over the investigated dose range and the variability between dose groups was independent from SCYX-7158 dose level. Considering the therapeutic dose level, free fraction is 0.9% Stability of the free fraction ratio was stable over the investigated dose range suggested that all the binding sites were not saturated and therefore that there was a very low risk of increased free fraction in patients with low protein levels.

Additionally the concentration of SCYX-7158 was determined in the CSF as a proof that the drug was able to reach the site of action of the drug, this was also an important parameter to investigate before administering the drug to patient. Based on data obtained in the 240 and 320 mg dose levels measured on Day 5 (*i.e.* 96 h post-dose), individual CSF concentrations ranged from 67 to 166 ng/mL (mean of 112 ng/mL) in the 240 mg dose group and 117 to 215 ng/mL (mean of 172 ng/mL) in the 320 mg dose group. The mean CSF to plasma ratios were comparable between the 2 doses groups and were of 2.2 % and 2.6 %, respectively for 240 and 320 mg with a range of 1.8% to 3.2%.

Taking together free fraction results and concentration of unbound SCYX-7158 in CSF indicated that concentration of unbound SCYX-7158 in blood is a reliable indicator of the concentration of unbound drug in the CSF.

A PK modelling was done after the dose of 320 mg in line with the publications of S.Wring et al. (parasitology (2014), 141, 104-118) to simulate the dose progression to reach the pharmacological active concentration AUCu of 5.8µg.h/mL. This concentration was observed in over 90% in all subjects of dose groups from 960 mg SCYX-7158.

Finally, last part of the study investigate the relative bioavailability of two new tablets formulations, one dosed at 40 mg and the second dosed at 160 mg of SCYX-7158. Results showed that the new tablet formulations are bioequivalent to the reference capsules.

PD

At baseline, means of 6-β-hydroxycortisol to cortisol ratios were between 3.54 and 9.55 in the active groups compared to 9.46 in the placebo group.

After dosing, means of 6-β-hydroxycortisol to cortisol concentrations ratio ranged between 4.41 and 8.68 with 40 mg, between 3.97 and 9.43 with 80 mg, between 5.79 and 11.13 with 120 mg, between 3.41 and 8.59 with 160 mg,

between 3.54 and 8.30 with 200 mg, between 5.05 and 8.85 with 240 mg, between 7.03 and 13.29 with 320 mg, between 5.31 and 13.71 with 400 mg and between 4.82 and 8.00 with placebo. Means of 6-β-hydroxycortisol to cortisol concentrations ratio were roughly comparable between doses and between active and placebo groups. No significant changes or trend were observed between the dose levels or between visits, indicating no expression *in vivo* of the mRNA induction activity detected *in vitro*. As compare to rifampicine [20], no CYP 3A4 induction was observed in human with SCYX-7158.

On 24h Holter analysis, as ECG on Day 1 were not collected in a similar way (single reading for Cohorts 5 to 8 and replicate for Cohort 9 and upper) and that several months separated the recording and analysis of the ECG between

them, it was decided to investigate each group of cohorts (5 to 8 on one side, 9 and upper on the other side) respectively to their own placebo subjects (and not pooling all placebo). The analysis showed that the two placebo groups defined by that way were different in terms of change in QTc over time. Therefore, all results and ΔΔ computations were performed regarding to the placebo subject of each group of cohorts.

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Results (continued):

PD (continued):

On Day 1, the largest estimated ΔΔQTcF increase was +5.8 ms (H4, 1200 mg). The largest estimated ΔΔQTcF was negative for all the dose levels except for 320 mg SCYX-7158 with a value of +3.8 ms (90% CI: -4.7; 12.3) at H24, 600 mg SCYX-7158 with a value of +3.0 ms (90% CI: -5.1; 11.1) at H12 and 1000 mg SCYX-7158 with a value of

+4.8 ms (90% CI: -3.3; 13.0) at H24.

3 SCYX-7158 dose levels.

On Day 8, Day 11, Visits 1, 3, 5 and 7, the largest estimated ΔΔQTcF were negative for all the doses.
Similar results were observed for QTcP and QTcI.

Categorical analysis showed some abnormalities mainly PR above 200 ms. No QTc above 450 ms was measured throughout the study with SCYX-7158. No difference was observed in morphological analysis compared to baseline or between active groups and placebo.

Furthermore concentration-response relationship on ΔΔQTcF showed variations of limited extend as experimental data even if values were slightly lower.

Within the limitations of the study, *i.e.,* low subject numbers, the absence of a positive control and methodological differences between groups of doses, the results do not indicate an effect of SCYX-7158 on QTcF.

Safety:

No death, no severe AEs were reported throughout the study. One (1) SAE was reported three (3) months after dosing in 240 mg SCYX-7158 dose group of Part I.

In total, 128 subjects were included, 102 received SCYX-7158 and 26 received placebo. Between Day 1 and the first administration of activated charcoal (when applicable). Fifteen (15/102; 15%) subjects receiving SCYX-7158 reported 20 TEAES and 3/26 (12%) receiving placebo reported 4 TEAES between administration of SCYX-7158 and first administration of activated charcoal. Among these TEAEs, 16/24 (67%) reported by 11 subjects were related to study drug (14/16 (88%) reported by 9 subjects after administration of SCYX-7158 and 2/16 (12%) reported by 1 subject after administration of placebo).

In Study Part I, a total of 85 TEAEs were reported by 59 subjects out of 110 (53.6%). AEs were observed in all the dose levels but dose 20 mg. Among them, 53 AEs reported by 39 subjects were deemed to be related to the study drugs (*i.e*. SCYX-7158 and/or charcoal, when applicable). A total of 32 AEs reported by 26 subjects were not related to any study drugs. It is of interest to note that among these 59 subjects, 17 subjects reported AEs whereas received placebo.

The subjects who received SCYX-7158 without charcoal were subjects of the first 20 mg cohort (6 active, 2 placebo) and the 960 mg cohort (6 active, 0 placebo). Eight (8 out of 85; 9%) AEs were reported by 5/12 subjects and 6 of these AEs were considered related.

In Study Part IV, only 1 TEAE considered as not related to SCYX-7158 was reported by 1 subject.

In Study Part VI (intensive charcoal administration), all the subjects reported at least 1 AE during the study. A total of 40 TEAEs were reported by subjects and all were deemed to be related to the study drugs (*i.e*. SCYX-7158 and/or charcoal, when applicable) but 1. Twenty-four (24) TEAEs were reported by 6 subjects who received 40 mg SCYX-7158 tablet and activated charcoal and 16 AEs were reported by 6 subjects who received 160 mg SCYX-7158 tablet and activated charcoal.

The intensity of TEAEs varied from mild (33 AEs in Part I and 16 AEs in Part VI) to moderate (52 AEs in Part I and 24 AEs in Part VI).

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Results (continued):

Safety (continued)

Overall, the most frequent SCYX-7158 related AEs were gastrointestinal disorders (15 events reported by 14 subjects in Part I and 34 events reported by 12 subjects in Part VI), investigations abnormalities (13 events reported by 13 subjects in Part I and 4 events reported by 4 subjects in Part VI) and nervous system disorders (16 events reported by 13 subjects in Part I).

Gastrointestinal disorders were of various etiologies (abdominal pain, nausea, constipation and vomiting) and were observed either with placebo or different SCYX-7158 dose levels. One could note that use of activated charcoal emphasized the emergence of certain gastrointestinal disorders such as constipation or vomiting.

Nervous system disorders mainly consisted in headache (14 events) but all were unlikely related to SCYX-7158.

One can also note that 7 cases of moderate post-lumbar puncture syndrome were observed out of 16 subjects undergoing this procedure (2 subjects receiving placebo, 2 receiving 240 mg SCYX-7158, and 3 subjects receiving 320 mg SCYX-7158).

Investigation abnormalities consisted of laboratory results. Some individual clinically significant abnormalities were observed: CPK increases (6 events reported by 6 subjects in Part I), transaminases increases (6 events reported by 6 subjects in Part I and 3 events reported by 3 subjects in Part VI) and thyroid hormones fluctuations consisting of irregularly and incomplete sub-clinical variations of TSH, fT3 and fT4 in placebo group as well as in active groups but it could be note that 1 case of hyperthyroidism was reported as SAE after administration of 240 mg SCYX-7158. This case was of mild intensity, sub-clinical, resolved spontaneously and possibly related to SCYX-7158. Most of them could be observed either in subjects who received placebo or subjects who received active drug, regardless of the dose which did not occur in each dose and especially much less variations were observed in the highest dose cohorts, including the therapeutic dose selected. No trends of abnormalities under exposure of SCYX-7158 were detected in the following parameters: bilirubin, pancreatic function (glycaemia, lipase and amylase) lipid profile (triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol), renal function (creatinine, urea, ions), hematology, coagulation test (APTT, INR), reticulocytes, haptoglobin ferritin and coombs test.

Regarding physical examinations, ECG and vital sign no relevant findings were observed.

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Conclusion:

A total of 128 subjects were included (102 active, 26 placebo). PK results showed that SCYX-7158 was quite rapidly absorbed and that levels remained steady for at least 4 days. Mean $t_{1/2}$ was calculated of around 400 h, in cohort with

o.d. without charcoal. Activated charcoal was used to reduce the reabsorption due to enterohepatic circulation and to reduce the long follow-up of the subjects. The PK of SCYX-7158 was not linear with dose with a less than dose proportional increase of C_{max} and AUC_{0-96}, in the dose range 40 and 1200 mg. Furthermore, inter-subject variability was low. The new tablet formulations of 40 or 160 mg are bioequivalent to the reference capsules.

The pharmacologically active exposure was reached with the 960 mg dose which ensure 90% of the future patients to be over this threshold. Therefore, 1200 mg was considered as the safety cohort over the therapeutic dose and was therefore the maximum administered dose of the study.

A relatively high number of abnormalities were recorded throughout the study however the prolonged follow-up and the use of activated charcoal could explain some of these abnormalities. Furthermore, most of these abnormalities were observed either in subjects who received placebo or subjects who received active drug, regardless of the dose. In the highest dose tested (> 600 mg) less AEs were reported by the subjects

Therefore, the data reviewed and analyzed in the present report, suggests that SCYX-7158 was well tolerated in laboratory, vital signs, ECG or physical examination results. The therapeutic dose was fixed to 960 mg with the probability of 90% to reach the active pharmacological free exposure in CSF.

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