SCYX-7158 (AN5568): CNS Exposure Predicted from First-in-Human Clinical Studies Indicates a Single Oral Dose Treatment is Possible for Sterile Cures of Stage 2 Human African Trypanosomiasis

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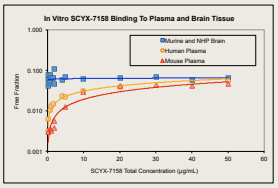
Abstract

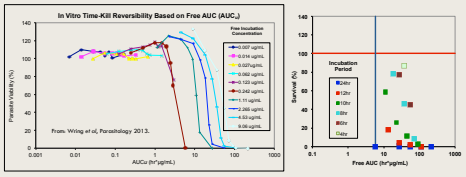
SCYX-7158 (AN5568), an orally bioavailable benzoxaborole for the treatment of Stage 2 (CNS) Human African Trypanosomiasis (HAT), is currently progressing through first-in-human single ascending dose studies in healthy subjects. The purpose of this interim sub-analysis of plasma SCYX-7158 concentration data following single oral doses (20, 40, 80, 120, 160, and 200 mg) is to estimate the likely therapeutic dose required for sterile cures following a single dose treatment, based on maintenance of a target free drug exposure in CNS tissue. In humans, SCYX-7158 has been well-tolerated and demonstrated excellent dose dependent exposure in plasma. The geometric mean value for half-life across all completed treatment groups (20-160mg) is 325 hr / 13.5 days (range, 259-402 hr / 10.8-16.8 days) - consistent with a single dose treatment. A single dose regimen is desirable to mitigate potential treatment failures from poor compliance with multi-day therapy. The efficacy target for free drug exposure in brain tissue is a CNS $AUC_{u,0\text{-}24hr}$ of 5.8 μg.hr/mL for >5 days, as determined by in vitro time-kill and reversibility studies with *T. b. brucei*, and efficacy studies in a murine model of Stage 2 HAT. Values for CNS $AUC_{u,0\text{-}24hr}$ have been calculated from the human concentration versus time data for SCYX-7158 in plasma, using the in vitro ratio of binding to human plasma proteins (concentration dependent fu 1.3-3.0% for 1-10 μg/mL SCYX-7158) and cynomolgus monkey brain tissue (f_u 6.4% for 0.5-10 μg/mL SCYX-7158) in conjunction with free plasma:brain ratio from efficacious doses in murine studies. Predicted CNS $AUC_{u,0\text{-}24hr}$ on the first day of treatment increased proportionally with dose, and exceeded the target exposure following a single 160 mg dose (CNS $AUC_{u,0\text{-}24hr}$ 6.5 μg.hr/mL). Following a 200 mg dose the predicted CNS $AUC_{u,0\text{-}24hr}$ exceeded the target on a daily basis for 3 days, and for 5 days based on average CNS $AUC_{u,0\text{-}24hr}$ measured over 120 hr. The predicted single dose required to exceed the target CNS $AUC_{u,0\text{-}24hr}$ on a daily basis for ≥5 days is ~280 mg.

Free SCYX-7158 in Plasma and Brain Tissue



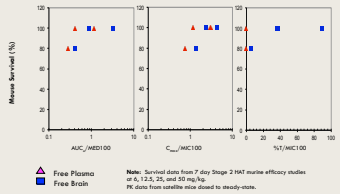
- **Free (unbound) drug levels are considered the pharmacologically active fraction and were used for PK/PD predictions.**
- Binding was measured by equilibrium dialysis in fresh tissue (Wring *et al* 2013).
- Binding of SCYX-7158 to murine and human plasma protein was species dependent, and concentration dependent over the therapeutically relevant range.
- Binding to brain tissue was independent of concentration and species.

In vitro Time-Kill Reversibility

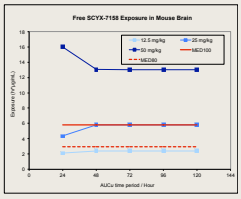


- **Parasitacidal behavior was determined by in vitro Time-Kill Reversibility studies based on free SCYX-7158 concentrations.** (Nare *et al* 2010 and Jacobs *et al* 2011).
- SCYX-7158 demonstrated concentration and time dependent parasitacidal behavior.
- **The MIC_u was 5.808 µg.hr/mL based on 24hr exposure and was set as the target exposure required in CNS tissue for clinical efficacy.**

Exposure Target for Sterile Cures in Stage 2 HAT

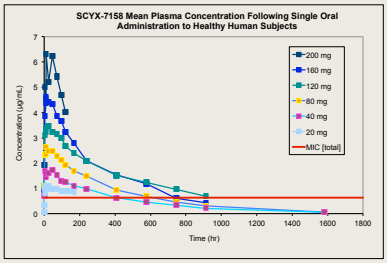


Note: Survival data from 7 day Stage 2 HAT murine efficacy studies at 6, 12.5, 25, and 50 mg/kg. PK data from satellite mice dosed to steady-state.



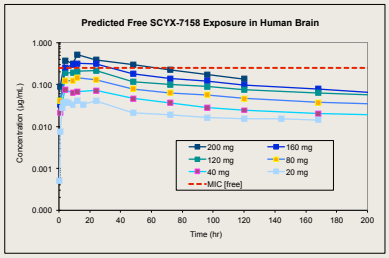
- **In vivo efficacy in a murine model of stage 2 HAT *T. b. brucei* infection (Nare *et al* 2010) was dependent on SCYX-7158 concentration and exposure time i.e. on AUC/MIC, C_{max}/MIC and T(%)/MIC. Consequently, AUC_u/MIC was considerable the most reliable predictor**
- **Sterile cures were associated with maintaining a daily CNS AUC_u target of ≥5.808 µg.hr/mL i.e. an AUC_u/MIC_{100} ≥1 for 5-7 days.**
- 80% cures were achieved when the daily AUC_u was maintained at the *in vitro* MIC_{80} level.
- *In vitro* reversibility studies proved predictive of *in vivo* efficacy.

Interim Pharmacokinetics in Healthy Human Subjects



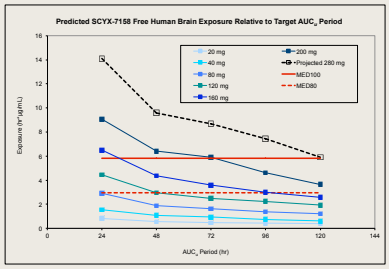
- A single ascending oral dose study was performed in healthy subjects ethnicity-matched to potential patients in sub-Saharan Africa.
- Group size was 6 subjects per dose level, except for the 200mg dose group where data from 3 subjects were available for this analysis.
- SCYX-7158 has been well-tolerated and demonstrated excellent dose dependent exposure.
- SCYX-7158 exposure (AUC and C_{max}) in plasma increased in a generally linear manner with dose.
- **The geometric mean value for half-life across completed treatment groups at time of abstract submission (20-160mg) is 325 hr / 13.5 days (range, 259-402 hr / 10.8-16.8 days).**
- **The prolonged half-life is consistent with a single dose treatment, which is desirable to mitigate against potential treatment failures from poor compliance with multi-day therapy.**

Prediction of Free SCYX-7158 in Brain Tissue



- Predicted values for free SCYX-7158 concentration in brain versus time were calculated from the human concentration versus time data for SCYX-7158 in plasma, using the in vitro ratio of binding to human plasma proteins and cynomolgus monkey brain tissue (calculations described in: Summerfield *et al* 2006), in conjunction with the free plasma:brain ratio determined in efficacious doses in murine stage 2 HAT studies.

Predicted CNS Exposure Achieves Efficacy Target



MED_{80} and MED_{100} minimum effective exposure for 80% or 100% cures

- Predicted CNS $AUC_{u,0\text{-}24hr}$ on the first day of treatment increased proportionally with dose, and exceeded the target exposure (CNS $AUC_{u,0\text{-}24hr}$ 5.8 μg.hr/mL) following a single 160 mg dose (predicted CNS $AUC_{u,0\text{-}24hr}$ 6.5 μg.hr/mL).
- Following a 200 mg dose the predicted CNS $AUC_{u,0\text{-}24hr}$ exceeded the target on a daily basis for 3 days, and for 5 days based on average CNS $AUC_{u,0\text{-}24hr}$ measured over 120 hr.
- **A single 280mg dose of SCYX-7158 is projected to exceed the CNS AUC_u target of 5.8 µg.hr/mL for 5 days, and for >7 days based on average $AUC_{u,0\text{-}24hr}$ measured over 168 hr.**

Conclusions

- **An interim sub-analysis of data from an on-going single ascending oral dose study in healthy subjects ethnicity-matched to potential patients in sub-Saharan Africa has demonstrated that the potency and pharmacokinetics of SCYX-7158 (AN5568) are consistent with a single oral dose treatment for HAT.**
- **A single dose treatment for HAT is desirable to mitigate against potential treatment failures from poor compliance with multi-day therapy.**

In summary:

- SCYX-7158 has been well-tolerated by healthy subjects yielding excellent dose dependent exposure in plasma.
- exposure (AUC and C_{max}) increased in a generally linear manner with dose.
- the geometric mean value for half-life across all completed treatment groups (20-160mg) is 325 hr / 13.5 days (range, 259-402 hr / 10.8-16.8 days) and is consistent with a single dose treatment, which is desirable to mitigate potential treatment failures arising from poor compliance with multi-day therapy.
- an oral dose of 280mg is projected to exceed the CNS AUC_u target of 5.8 µg.hr/mL for 5 days, and for >7 days based on average CNS $AUC_{u,0\text{-}24hr}$ measured over 168 hr.

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