PHARMACOKINETICS AND SAFETY OF NITAZOXANIDE IN SUBJECTS WITH HEPATIC IMPAIRMENT

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BACKGROUND

Nitazoxanide (NTZ) is a broad-spectrum antiparasitic and antiviral drug approved in the U.S. for treatment of diarrhea caused by *Cryptosporidium parvum* or *Giardia lamblia* in adults and children ≥ 12 months of age. Clinical and nonclinical studies suggest that NTZ may also be a potent anti-inflammatory drug, which makes it of interest to be investigated in liver diseases, including acute-on-chronic liver failure (ACLF).

AIMS

This Phase 1, open label, clinical study (NCT05116826) aimed to evaluate the safety and the pharmacokinetics (PK) of NTZ main metabolites tizoxanide (TZ) and tizoxanide glucuronide (TZ-Glu), when NTZ is administered orally 500 mg BID, for 7 days, in subjects with hepatic impairment (HI).

STUDY DESIGN

Study Design and Treatment

- Subjects enrolled were males or females, between 18 and 75 years of age, inclusive.
- Subjects with HI were classified according to Child-Pugh (CP) criteria as moderate, CP B (n=9) or severe, CP C (n=6) and were compared to healthy volunteer controls (HV), (n=10).
- Safety, tolerability, as well as plasma and urine PK of NTZ main metabolites, TZ and TZ-Glu, were assessed following single and 7-day repeated (BID) oral administration of NTZ 500 mg in fed condition.
- Each matched-control HV was enrolled following the enrollment of a subject with moderate and/or severe HI and was matched by age (± 10 years), body mass index (BMI ± 20%), and sex to the enrolled subject(s) with HI.
- Nitazoxanide was supplied as Alinia® 500 mg tablets for oral administration.
- Subjects received 500 mg of nitazoxanide (1 tablet) morning and evening for 6 consecutive days, and the morning of day 7. Drug product was administered 30 minutes following a standardized breakfast and dinner.

Assessments

- Subjects were admitted into the Clinical Research Unit (CRU) on Day -1 and were confined to the CRU until Discharge on Day 9.
- An End of Study (EOS) visit occurred on Day 14.
- PK blood and urine samples for measurement of NTZ metabolites were taken at Day -1 and through Day 9.
- Adverse events (AEs), clinical laboratory evaluations, vital sign assessments, 12-lead electrocardiograms (ECGs), and physical examination (PE) findings were monitored at screening and at specified times during the study (AEs were recorded from signing of the Informed Consent Form until Study Completion).
- An exploratory assessment of pharmacodynamics parameters (PD) was also performed in subjects with HI to evaluate the effect of NTZ and to compare to what has been observed in preclinical models of ACLF.

STATISTICAL ANALYSIS

Safety: All safety assessments were summarized using descriptive statistics. The incidence of AEs for each degree of hepatic function was presented by severity and by relation to the study drug as determined by the Investigator (or designee).

Pharmacokinetics: The primary analyses assessed the PK parameters measured at Day 7 in subjects with moderate or severe HI and subjects with normal hepatic function. PK parameters expressed both in terms of unbound and total concentrations, were analyzed on log-transformed values using mixed ANOVA models including term for group (hepatic impaired stage or control). Ratios of geometric means (GMR) and their 90% Confidence Intervals (CI) were calculated from the back-transformation of the least squares means (LS means) differences between moderate and severe HI and the control groups.

Exploratory Pharmacodynamics: Descriptive statistics were provided for the exploratory PD endpoints in hepatic impaired subjects.

BASELINE CHARACTERISTICS

		Moderate HI (N=9)	Severe HI (N=6)	HV (N=10)
Gender				
	Male	8 (88.9%)	5 (83.3%)	9 (90.0%)
	Female	1 (11.1%)	1 (16.7%)	1 (10.0%)
Age (years)	**n**	**9**	**6**	**10**
	Mean (SD)	60.0 (5.7)	63.5 (7.0)	61.8 (7.1)
BMI (kg/m²)	**n**	**9**	**6**	**10**
	Mean (SD)	30.2 (5.3)	27.1 (4.2)	27.8 (3.8)
MELD-Na Score	**n**	**9**	**5**	**N/A**
	Mean (SD)	9.2 (2.3)	17.6 (2.3)	N/A

SAFETY PROFILE

TEAEs by System Organ Class and Preferred Term

	Moderate HI (N=9)		Severe HI (N=6)		Healthy Volunteers (N=10)	
	n (%)	m	n (%)	m	n (%)	m
At least one treatment emergent adverse event	6 (66.7%)	9	3 (50.0%)	3	3 (30.0%)	4
Nervous system disorders	**3 (33.3%)**	**3**	**2 (33.3%)**	**2**	**0 (0.0%)**	**0**
Headache	3 (33.3%)	3	0 (0.0%)	0	0 (0.0%)	0
Dizziness	0 (0.0%)	0	1 (16.7%)	1	0 (0.0%)	0
Somnolence	0 (0.0%)	0	1 (16.7%)	1	0 (0.0%)	0
Gastrointestinal disorders	**1 (11.1%)**	**1**	**1 (16.7%)**	**1**	**1 (10.0%)**	**1**
Diarrhea	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1
Nausea	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0
Upper gastrointestinal hemorrhage	0 (0.0%)	0	1 (16.7%)	1	0 (0.0%)	0
Renal and urinary disorders	**1 (11.1%)**	**2**	**0 (0.0%)**	**0**	**1 (10.0%)**	**1**
Chromaturia	1 (11.1%)	1	0 (0.0%)	0	1 (10.0%)	1
Pollakiuria	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0
Blood and lymphatic system disorders	**1 (11.1%)**	**1**	**0 (0.0%)**	**0**	**0 (0.0%)**	**0**
Thrombocytopenia	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0
Investigations	**1 (11.1%)**	**1**	**0 (0.0%)**	**0**	**0 (0.0%)**	**0**
Blood creatine phosphokinase increased	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0
Metabolism and nutrition disorders	**0 (0.0%)**	**0**	**0 (0.0%)**	**0**	**1 (10.0%)**	**1**
Hyperglycemia	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1
Psychiatric disorders	**1 (11.1%)**	**1**	**0 (0.0%)**	**0**	**0 (0.0%)**	**0**
Sleep disorder	1 (11.1%)	1	0 (0.0%)	0	0 (0.0%)	0
Skin and subcutaneous tissue disorders	**0 (0.0%)**	**0**	**0 (0.0%)**	**0**	**1 (10.0%)**	**1**
Dermatitis contact	0 (0.0%)	0	0 (0.0%)	0	1 (10.0%)	1

- **NTZ was generally well tolerated in subjects with HI and no safety concerns were raised in this study.**
- **The most common AE recorded was headache and was experienced by 3 subjects with moderate HI.**
- **Incidence of treatment emergent related AEs (TEAEs) was comparable between subjects with HI (26.7%) and HV controls (20.0%).**
- **Only one serious adverse event (SAE) of upper gastrointestinal hemorrhage was reported 14 days after treatment completion in the severe HI group and was considered unrelated to study drug.**

PHARMACOKINETICS OF TZ AND TZ-GLU

TZ and TZ-Glu GMR (90%CI) vs. control group at steady state

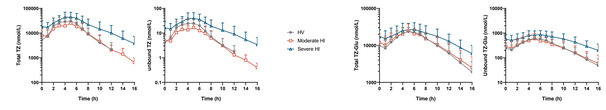
Total TZ	C_{max} (nM)		$AUC_{0\text{-}12}$ (h.nM)		$AUC_{0\text{-}\infty}$ (h.nM)	
	GMR (%)	90% CI	GMR (%)	90% CI	GMR (%)	90% CI
Moderate HI (N=9)	0.8008	(0.5469; 1.1726)	0.8960	(0.6169; 1.3014)	0.9064	(0.6184; 1.3283)
Severe HI (N=6)	1.1921	(0.7871; 1.8056)	1.6353	(1.0805; 2.4748)	1.7940	(1.1739; 2.7417)

Total TZ-GLU	C_{max} (nM)		$AUC_{0\text{-}12}$ (h.nM)		$AUC_{0\text{-}\infty}$ (h.nM)	
	GMR (%)	90% CI	GMR (%)	90% CI	GMR (%)	90% CI
Moderate HI (N=9)	0.9858	(0.7068; 1.3749)	0.9951	(0.6848; 1.4460)	1.0082	(0.6715; 1.5138)
Severe HI (N=6)	0.9287	(0.6465; 1.3341)	1.2180	(0.8109; 1.8296)	1.3917	(0.8941; 2.1664)

Unbound TZ	C_{max} (nM)		$AUC_{0\text{-}12}$ (h.nM)		$AUC_{0\text{-}\infty}$ (h.nM)	
	GMR (%)	90% CI	GMR (%)	90% CI	GMR (%)	90% CI
Moderate HI (N=9)	0.6299	(0.4085; 0.9714)	0.7112	(0.4838; 1.0453)	0.7194	(0.4875; 1.0617)
Severe HI (N=6)	1.1908	(0.7400; 1.9163)	1.6209	(1.0560; 2.4880)	1.7793	(1.1541; 2.7433)

Unbound TZ-GLU	C_{max} (nM)		$AUC_{0\text{-}12}$ (h.nM)		$AUC_{0\text{-}\infty}$ (h.nM)	
	GMR (%)	90% CI	GMR (%)	90% CI	GMR (%)	90% CI
Moderate HI (N=9)	0.8833	(0.6450; 1.2096)	0.8922	(0.6161; 1.2919)	0.9061	(0.6090; 1.3481)
Severe HI (N=6)	1.2061	(0.8532; 1.7050)	1.5824	(1.0533; 2.3772)	1.8071	(1.1726; 2.7851)

C_{max}: Observed maximum plasma concentration, AUC: Area under the plasma concentration-time curve, GMR: Geometric mean ratio



Total and unbound TZ and TZ-Glu plasma concentrations (Mean +SD) vs. time profiles by group at Day 7

- **Formal statistical analyses suggested that moderate hepatic impairment does not affect the PK of total and unbound metabolites TZ and TZ-Glu, except for a decrease by around 37% observed for the C_{max} of unbound TZ.**
- **Severe hepatic impairment appeared to have no impact on C_{max} but increased the overall exposure (AUCs) of total and unbound TZ by approximately 1.6- to 1.8-fold and total and unbound TZ-Glu by around 1.2- to 1.8-fold. These increases in AUCs were statistically significant for all metabolites except total TZ-Glu.**
- **For total and unbound TZ and TZ-Glu, a statistically significant accumulation was evidenced on Day 7 for both peak (C_{max}) and overall exposure, with increases ranging from approximately 1.4- to 1.9-fold compared to Day 1 values.**
- **A correlation analysis showed that for most markers of hepatic function, the correlation with TZ or TZ-Glu PK parameters was poor or weak. For unbound TZ, a moderate linear correlation was identified between C_{max} and bilirubin and between $AUC_{0\text{-}12}$ and international normalized ratio (INR).**

EXPLORATORY PHARMACODYNAMICS AND EFFICACY PARAMETERS

Change from baseline IL-6 and TB during treatment with NTZ

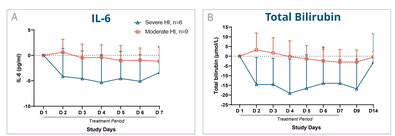


Figure 1: A. Serum IL-6 in subjects with HI during the treatment period (Day 1 to Day 7). **B.** Plasma total bilirubin in subjects with HI during the treatment period (Day 1 to Day 7) and during the washout period (D9 and Day 14). Data are presented as mean ± SD of change from baseline. *IL-6: interleukin 6*.

- **A trend of decrease in IL-6 and total bilirubin in subjects with severe hepatic impairment was observed during the treatment with NTZ. This trend is consistent with what was previously observed in the non-clinical models (data presented in Figure 2).**

Effect of NTZ administration (100 mg/kg) in rodent models of ACLF

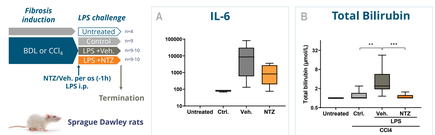


Figure 2: A. Serum IL-6 after LPS injection (1 µg/kg, i.p., 3 hours) in rats with severe liver fibrosis induced by BDL (3 weeks) **B.** Plasma total bilirubin after LPS injection (10 µg/kg, i.p., 24 hours) in rats with severe liver fibrosis induced by CCl4 (10 weeks). Data are presented as mean ± SD, *p<0.05, ***p<0.001 using Mann-Whitney test. i.p.: intraperitoneal injection, BDL: bile duct ligation, LPS: lipopolysaccharides, veh.: vehicle, Ctrl.: control, CCl4: carbon tetrachloride, *IL-6: interleukin 6*.

- **NTZ reduced circulating IL-6 and total bilirubin in rats with severe fibrosis and LPS-induced ACLF.**

CONCLUSION

- NTZ was generally safe and well tolerated in subjects with moderate and severe hepatic impairment when administered orally 500 mg BID for 7 days.
- Severe hepatic impairment augmented the overall exposure of total and unbound TZ and TZ-Glu but did not exceed 2-fold increase.
- A trend of reduction in IL-6 and total bilirubin levels was observed in subjects with severe hepatic impairment during the treatment period. This is in alignment with preclinical studies showing that treatment with NTZ rapidly counteracts systemic inflammation (decrease in serum cytokines, including IL-6, within 3 hours) and improves hepatic function, including total bilirubin, in a rat model of ACLF.
- Safety and pharmacokinetic results, as well as exploratory efficacy data support further development of NTZ in patients with ACLF.

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