



PHARMACOKINETICS OF TWO ORAL FORMULATIONS OF LIVER-DIRECTED, NONSTEROIDAL FARNESOID X-RECEPTOR AGONIST TERN-101 IN HEALTHY VOLUNTEERS

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1 INTRODUCTION

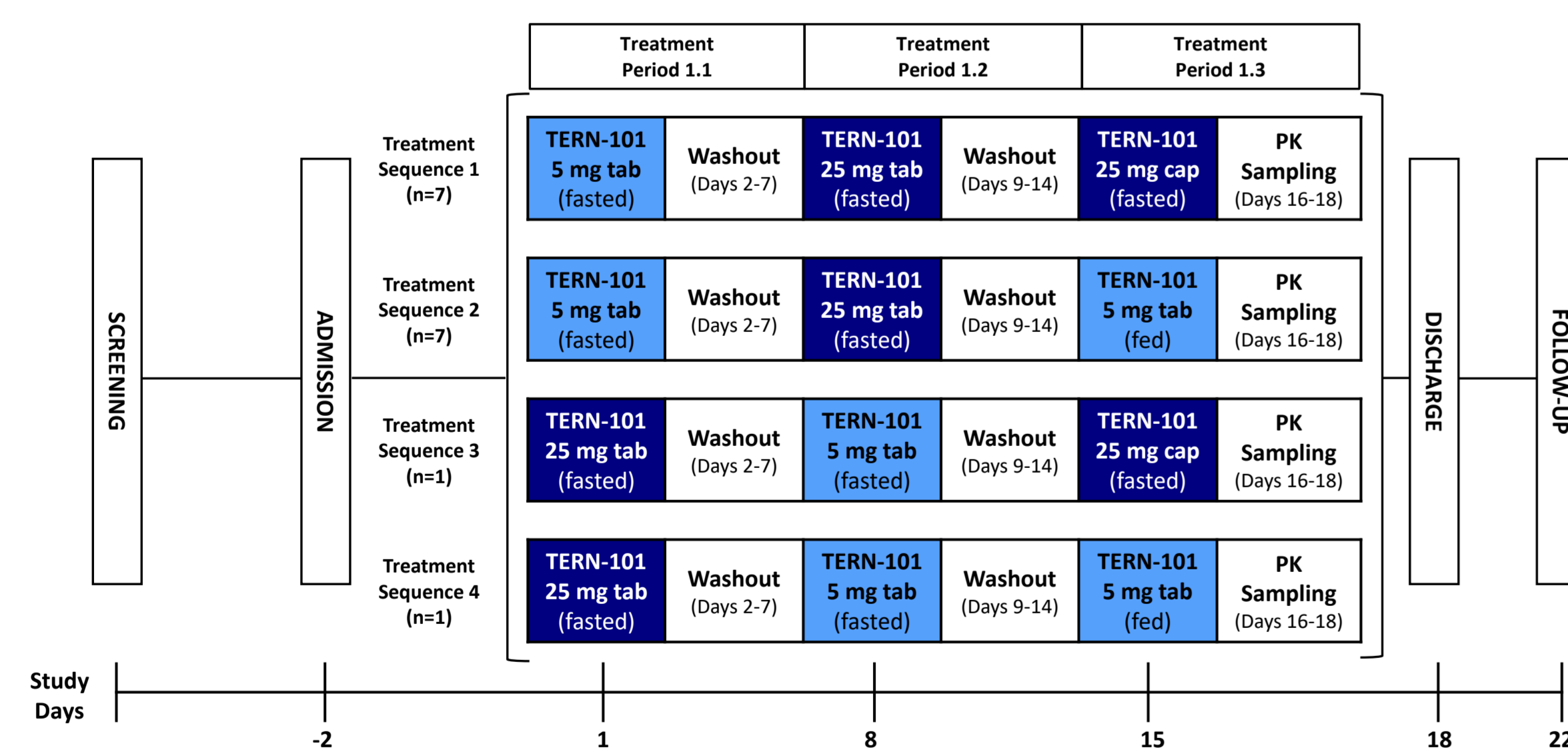
- The farnesoid X receptor (FXR) is a nuclear hormone receptor that regulates metabolic activity in the liver, affecting bile acid, lipid, and glucose homeostasis¹.
- In advanced phase clinical studies, FXR agonism has been shown to improve liver fibrosis². However, benefit-to-risk profile of FXR agonists in development has yet to be fully established in patients with NASH.
- TERN-101 is a potent, nonsteroidal FXR agonist with enhanced liver distribution³ and is currently being assessed in Phase 2 clinical trial in NASH patients (NCT04328077).
- FXR target engagement by TERN-101 has been studied in a 7-day PK/PD study using the capsule formulation. Sustained suppression of 7 α -C4 was seen after multiple doses, and by Day 7 plasma levels of 7 α -C4 were reduced from baseline by 74%, 82%, and 91% in the 25, 75, and 150 mg dose groups, respectively⁴.

2 OBJECTIVES

The crystalline capsule formulation of TERN-101 showed potent target engagement but variable PK and limited absorption in Phase 1 clinical trials. The primary objective of the current study was to compare single dose PK of this formulation with a new TERN-101 amorphous form tablet (designed to improve absorption) and evaluate food effect. Safety was assessed as a secondary objective.

3 METHODS

Figure 1: TERN101-US A401 Study Design



- 16 healthy subjects randomized to one of four treatment sequences across three dosing periods
 - Period 1.1 and 1.2: 5 or 25 mg single dose of TERN-101 tablet fasted
 - Period 1.3: 25 mg TERN-101 capsule fasted or 5 mg TERN-101 tablet fed
- Plasma PK parameters were determined by non-compartmental analysis
- Safety was assessed during dosing and for 7 (\pm 1) days after dosing.

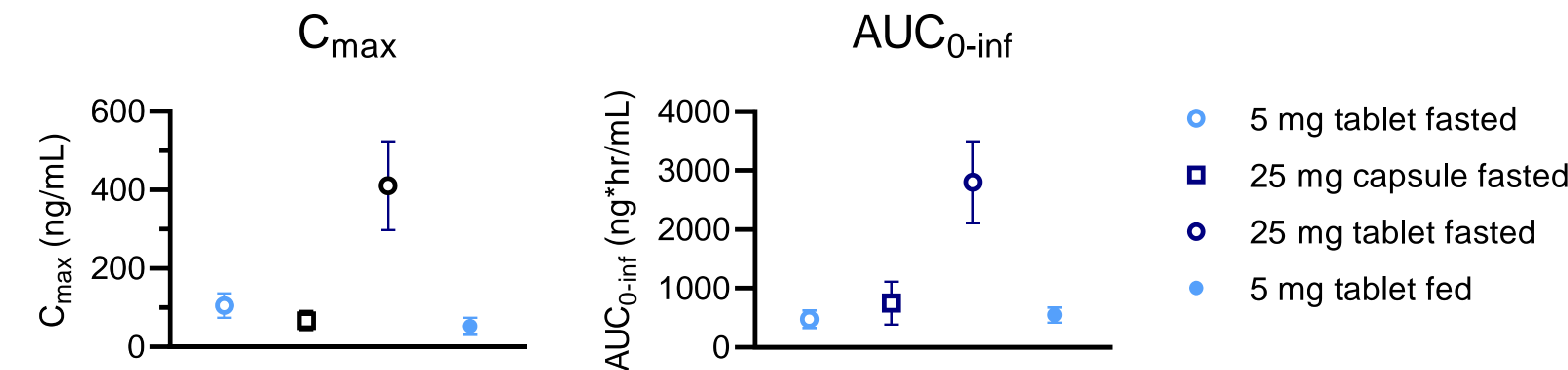
4 RESULTS

Table 1: Safety and Tolerability of TERN-101 Formulations

Adverse events (AE) reported	TERN-101	TERN-101	TERN-101	TERN-101
	5 mg tablet Fasted (n=16)	25 mg tablet Fasted (n=16)	25 mg capsule Fasted (n=8)	5 mg tablet Fed (n=8)
Overall subject AE incidence, n (%)	4 (25)	2 (12.5)	2 (25)	1 (12.5)
AE diagnosis and frequency, n (%)				
Blepharospasm	0	1 (6.3)	0	0
Dizziness	0	0	1 (12.5)	0
Dysmenorrhea	1 (6.3)	0	0	0
Dyspnea	1 (6.3)	0	0	0
Eye lid function disorder	1 (6.3)	0	0	0
Headache	2 (12.5)	0	1 (12.5)	0
Nausea	0	0	1 (12.5)	0
Oropharyngeal pain	0	1 (6.3)	0	0
Pharyngitis	0	0	1 (12.5)	1 (12.5)
Rash	0	1 (6.3)	0	0

- All AEs reported were Grade 1 (mild)
- One event (non-pruritic rash) was considered possibly related to study drug; all others were considered not related to study drug
- Laboratory, vital signs, ECG, and other safety assessments did not show any notable changes
- No subject prematurely discontinued study medication
- No pruritus was reported

Figure 2: TERN-101 tablet and capsule PK comparison



C_{max} and AUC_{0-inf} PK parameters represented as mean (\pm SD). AUC_{0-inf} = area under the plasma concentration-time curve from time 0h to infinity; C_{max} = observed maximum plasma concentration following drug administration

Table 2: Summary of TERN-101 PK parameters following single oral dose of tablet and capsule formulations

Dosage form	Dose (mg)	Fed or Fasted	n	C _{max} (ng/mL)	AUC _{0-inf} (ng*hr/mL)	T _{max} (h)	t _{1/2} (h)	CL/F (L/h)
Tablet	5	Fasted	16	105 (30.4; 28.9%)	474 (153; 32.3%)	0.75 (0.5, 1)	10.9 (4.76, 19)	11.5 (3.32)
				101 (28.7%)	453 (31.3%)			
Tablet	25	Fasted	16	410 (113; 27.7%)	2800 (691; 24.7%)	1.52 (0.5, 4.03)	11.9 (6.39, 16.4)	9.45 (2.4)
				395 (28.8%)	2720 (25.2%)			
Capsule	25	Fasted	8	66.7 (24.6; 36.9%)	751 (366; 48.7%)	3.03 (1.05, 4.05)	25.9 (10.7, 53.4)	38.9 (13.8)
				62.9 (37.7%)	689 (45%)			
Tablet	5	Fed	8	52.2 (21.1; 40.4%)	548 (130; 23.8%)	4 (2, 8)	8.74 (4.88, 12.7)	9.69 (2.76)
				48.5 (43.5%)	533 (26.5%)			

AUC_{0-inf} = area under the plasma concentration-time curve from time 0 to infinity; C_{max} = observed maximum plasma concentration following drug administration; T_{max} = time to reach maximum plasma concentration; t_{1/2} = terminal elimination half-life; CL/F = apparent systemic (or total body) clearance from plasma following extravascular administration. AUC_{0-inf} and C_{max} parameters presented as mean (\pm SD; CV%) and geo mean (geo CV%), CL/F as mean (\pm SD), and T_{max} and t_{1/2} values are represented as median (min, max).

Table 3: Statistical analysis of relative bioavailability of tablet and capsule and the effect of food on the PK of TERN-101 tablet

Test	Reference	PK Parameter	Geometric LS Mean Test		Geometric LS Mean Reference		Geometric LS Mean Ratio (Test/Reference)	
			Subjects (n)	Result	Subjects (n)	Result	Estimate	90% CI
25 mg Tablet Fasted	25 mg Capsule Fasted	C _{max} (ng/mL)	16	382	8	60.8	6.29	(5.21, 7.58)
		AUC _{0-inf} (ng*hr/mL)	16	2720	7	730	3.73	(3.36, 4.15)
5 mg Tablet Fed	5 mg Tablet Fasted	C _{max} (ng/mL)	8	47.1	16	98.2	0.479	(0.398, 0.578)
		AUC _{0-inf} (ng*hr/mL)	8	507	16	454	1.12	(1.01, 1.23)

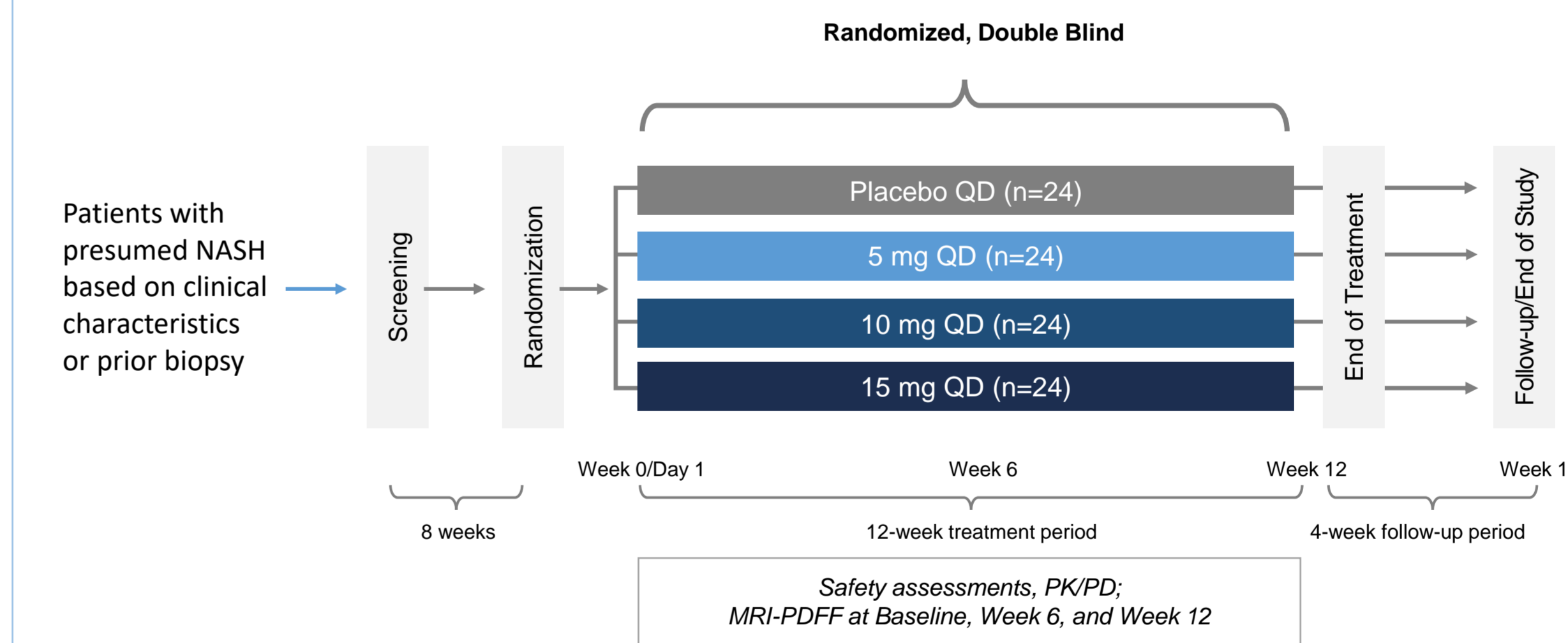
AUC_{0-inf} = area under the plasma concentration-time curve from time 0h to infinity; C_{max} = observed maximum plasma concentration following drug administration; CI = confidence interval

- TERN-101 25 mg tablet provided increased C_{max} and AUC_{0-inf} relative to the 25 mg capsule, indicating improved absorption with the TERN-101 tablet formulation
- TERN-101 exposures were comparable when the tablet (5 mg) was administered under fed and fasted conditions

5 CONCLUSIONS

- TERN-101 tablet formulation achieved faster absorption and higher systemic exposure with less PK variability compared to capsule and can be administered without regard to food.
- TERN-101 was safe and well tolerated with no reports of pruritus across all studies completed to-date.
- TERN-101 tablet formulation is currently being evaluated in a Phase 2a LIFT study in NASH patients.

Phase 2a LIFT Study (NCT04328077) Design for TERN-101 in NASH Patients



The 5 mg, 10 mg, and 15 mg TERN-101 tablet doses selected for the ongoing Phase 2a LIFT study are projected to achieve plasma exposures within the range of exposures achieved with the TERN-101 capsules in the dose range of 25 mg to 150 mg.

6 REFERENCES

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