

Pharmacokinetic Comparison of Two Fixed-dose Regimens of an Oral Testosterone Replacement Therapy

Jed C. Kaminetsky,¹ Nachiappan Chidambaram,² Anthony DelConte,² Satish Nachaegari,² Chris Welsh,² Mahesh Patel,² Marc Gittelman³

¹Manhattan Medical Research, New York, NY; ²Lipocine, Inc., Salt Lake City, UT; ³South Florida Medical Research, Aventura, FL



Introduction

- The clinical presentation of hypogonadism includes low levels of testosterone (T) and associated symptoms
- Testosterone replacement therapy (TRT) has been shown to restore T levels and improve symptoms
- The most common routes of administration for TRT include intramuscular injections and topical application
- LPCN 1021 is an oral formulation using testosterone undecanoate combined with a novel delivery system to allow efficient absorption and to restore T levels in hypogonadal patients
- A previous 52-week, phase 3 clinical study established the safety and efficacy of LPCN 1021
 - LPCN 1021 restored T levels and improved hypogonadal symptoms with a safety profile comparable to the active comparator used in the study (T gel)

Aim

- To evaluate the pharmacokinetics (PK) of a novel, oral TRT, LPCN 1021 (testosterone undecanoate), using 2 fixed-dose regimens without titration

Methods

- Two multicenter, open-label, single-arm studies were conducted to assess different fixed-dose regimens (no titration) of LPCN 1021
- Both studies were of similar design and included hypogonadal males with low T (<300 ng/dL) who received 24 days of treatment with a 450-mg daily dose of LPCN 1021
- The daily dose was divided into either 2 equal doses (twice daily [BID] study) or 3 equal doses (3 times daily [TID] study) taken with food
- In total, 95 and 100 patients were enrolled into the BID and TID studies, with 94 and 97 patients, completing the studies, respectively
- On day 24, intensive PK sampling was performed using blood samples obtained over a 24-hour period
- The PK of T and other relevant parameters were assessed
- The PK analysis evaluated safety based on the proportion of patients with a maximum T level (C_{max})

Results

- Patient demographics were similar in the 2 studies (**Table 1**)
 - In both studies, the majority of patients were aged ≤65 years and white, with a body mass index of ≥30 kg/m²
- Testosterone PK curves are shown in **Figure 1**
- PK parameters for T (**Table 2**)
 - The average daily T level (C_{avg}) was 476 ng/dL with 37% coefficient of variation (CV) in the BID study and 391 ng/dL with 45% CV in the TID study
 - Mean C_{max} was 1178 ng/dL with 47% CV for BID and 828 ng/dL with 44% CV for TID
 - Median time to maximum concentration (T_{max}) was similar in both studies
- In the BID study C_{max} per dose analysis, 85% of patients had a C_{max} <1500 ng/dL and 7% of patients had a C_{max} between 1800 ng/dL and 2500 ng/dL
 - One patient had a C_{max} level above 2500 ng/dL (2730 ng/dL recorded after the PM dose)
 - This patient was determined to have violated the exclusion criteria (history of gastric surgery/cholecystectomy)
- The TID study met all C_{max} thresholds
- Excursions above the thresholds were transient due to the PK profile of the drug (BID study mean time >1500 ng/dL = 1.7 hours)
- The PK profiles for dihydrotestosterone (**Figure 2**) and estradiol (**Figure 3**) were consistent with previous LPCN 1021 clinical trials
- Adverse events (AEs) were mild and/or moderate in intensity
 - There were no treatment-related serious AEs or deaths in either study (**Table 3**)
 - One patient discontinued the BID study due to an AE that was deemed by the investigator to be unrelated to the study (**Table 3**)
- No correlation between AE or other laboratory parameters and C_{max} levels >1500 ng/dL was found

Table 1. Patient demographics in BID and TID studies

Characteristic	BID study (N = 95)	TID study (N = 100)
Age, mean, years (SD)	56.0 (8.9)	54.1 (8.8)
≤65 years, n (%)	79 (83.2)	91 (91.0)
>65 years, n (%)	16 (16.8)	9 (9.0)
Sex, n (%)		
Male	95 (100)	100 (100)
Race, n (%)		
Asian	1 (1.1)	1 (1.0)
Black or African American	15 (15.8)	13 (13.0)
White	77 (81.1)	84 (84.0)
Multiple	2 (2.1)	2 (2.0)
Body mass index,* mean (SD)	32.8 (5.5)	32.8 (5.5)
<25 kg/m ² , n (%)	3 (3.2)	3 (3.0)
≥25 to <30 kg/m ² , n (%)	26 (27.4)	28 (28.0)
≥30 kg/m ² , n (%)	66 (69.5)	69 (69.0)
Weight, mean, kg (SD)	103.6 (18.7)	106.6 (19.3)

SD, standard deviation. *Calculated as weight (kg)/height (m)²

Figure 1. Testosterone Pharmacokinetics

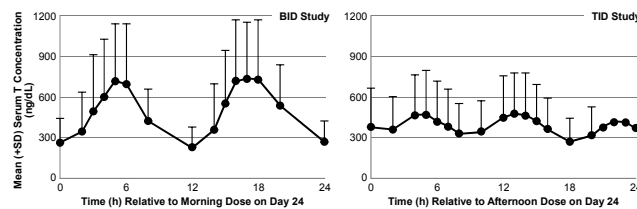


Table 2. Pharmacokinetic parameters for testosterone

Parameter	BID study			TID study			
	24-h post AM dose	12-h post AM dose	12-h post PM dose	24-h post AM dose	8-h post first dose	8-h post second dose	8-h post third dose
T C_{avg} 0-24h, ng/dL	476	—	—	391	—	—	—
Mean (SD)	(174)			(174)			
T C_{max}, ng/dL	1178	979	989	828	633	632	606
Mean (SD)	(484)	(479)	(475)	(363)	(339)	(345)	(317)
T_{max}, h	14.8	5.0	4.8	12.0	4.2	4.8	6.0
Median (min, max)	(2.0, 24.0)	(1.9, 11.9)	(2.0, 12.0)	(2.0, 24.0)	(1.8, 8.0)	(0.0, 8.0)	(0.0, 8.0)

C_{avg} 0-24h = average serum concentration from 0 to 24 hours (area under the curve /24); C_{max} = maximum observed serum concentration post dose; SD = standard deviation; T_{max} = time to maximum observed serum concentration

Figure 2. Dihydrotestosterone Pharmacokinetics

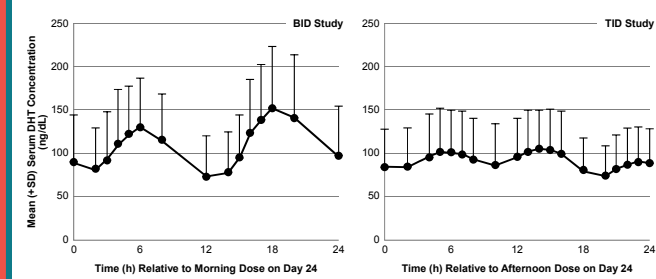


Figure 3. Estradiol Pharmacokinetics

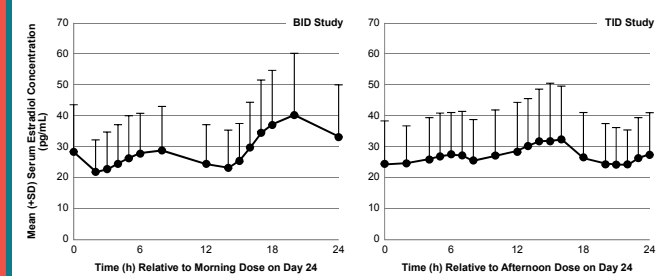


Table 3. Safety summary

Preferred term	BID study (N = 95)		TID study (N = 100)	
	Patients n (%)	Events n	Patients n (%)	Events n
Any TEAE	20 (20.1)	33	9 (9.0)	10
Any treatment-related TEAE	6 (6.3)	9	1 (1.0)	1
Any treatment-related and severe TEAE	0	0	0	0
Any TEAE leading to discontinuation	1 (1.1)	1	0	0
Any treatment-emergent SAE	1 (1.1)	1	0	0
Any treatment-related, treatment-emergent SAE	0	0	0	0
Any TEAE resulting in death	0	0	0	0

AEs were classified into system organ class and preferred term by using Medical Dictionary for Regulatory Activities Version 17.1. AEs were considered as drug reactions if the relationship to study drug was related. Patients were counted only once per system organ class and per preferred term. Percentages are based on N. SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Conclusions

- A BID fixed dose of LPCN 1021 resulted in higher T levels (C_{avg} and C_{max}) compared with TID dosing
- The C_{max} excursions observed in the BID study had no apparent correlation to the overall safety profile
- C_{max} thresholds used in this study were derived from data for topical TRTs and, due to differing PK profiles, the relevance of these measures for an oral TRT is not known
- PK data indicate that a fixed BID dose of LPCN 1021 is an appropriate treatment regimen

**FOR ORGANIZATION
USE ONLY**