Oral Testosterone Undecanoate, TU (TLANDO™)

NDA 208088

Bone, Reproductive and Urologic Drugs Advisory Committee Meeting

Jan 10, 2018

Lipocine Inc.

Introduction

Mahesh Patel, PhD

President and CEO

Lipocine Inc.

Oral Testosterone Undecanoate (TU) – TLANDO Indication

- **225 mg TU twice daily**
- **Indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:**
  - Primary hypogonadism (congenital or acquired)
  - Secondary hypogonadism (congenital or acquired)
- **Proposed indication identical to the indication of FDA approved Testosterone Replacement Therapy (TRT) class**
- **Novel delivery option in an established treatment modality**

Testosterone Undecanoate (TU)

- **Ester prodrug of testosterone**
- **Bypass ‘first pass’ liver inactivation**
- **Identical prodrug**
  - Present in Aveed® (injectable TU): US approval 2014
  - Present in Andriol® (oral TU): marketed in numerous ex-US countries, including Canada, Australia, and several EU countries

Key Studies in Original NDA Submission August 2015

- **M12-778 (Phase 2 Dose Finding Study)**
- **14-001 (Food-Fat Effect Study)**
- **13-001 (Phase 3 Dose Titration Study)**
  - Primary efficacy endpoint target evaluated during fixed dosing (Week 3) and post-titration (Week 13)
  - Safety assessed up to 52 weeks exposure

Complete Response Letter
June 2016

- ***Per FDA…***

  … "Approvability of your NDA is dependent upon deriving a dosing algorithm for the label that will provide health care providers and patients with a practical titration scheme, will ensure patients are effectively treated (within the eugonadal range), and will avoid unacceptably high serum testosterone concentrations."…

  … "Use modeling and simulation data from the completed Phase 3 trial to select the titration scheme that you propose for real-world use. Test your selected dose titration scheme in a new Phase 3 trial and show that it leads to acceptable efficacy and safety"

  … "should be able to leverage data from the existing trials to help support safety"

NDA Resubmission with New Studies August 2017

- **Modeled study 13-001 data and conducted simulations**
  - Results supported a 225 mg twice daily fixed (no titration) dose regimen
- **16-002, Phase 3 Fixed Dose Study – 225 mg TU BID**
  - Met pre-specified primary efficacy endpoint target
- **16-003, Phase 3 Fixed Dose Study – 150 mg TU TID**
  - Results support 225 BID mg fixed dose regimen

Five Studies Support Effectiveness and Safety of TLANDO 225 mg BID

- M12-778 (Phase 2 Dose Finding Study)
- 14-001 (Food-Fat Effect Study)
- 13-001 (Phase 3 Dose Titration Study)
- 16-002 (Phase 3 Fixed Dose Study-225 mg BID)
- 16-003 (Phase 3 Fixed Dose Study-150 mg TID)

Sponsor Presentation

Introduction	**Mahesh Patel, PhD** President and CEO, Lipocine
TRT Overview	**Adrian Dobs, MD, MHS** Professor of Medicine, Director, Johns Hopkins Clinical Research Network
Efficacy	**Gary Hoel, RPh, PhD** Clinical Consultant, Lipocine
Safety	**Anthony DelConte, MD** Chief Medical Director, Lipocine
CV Safety	**Peter A. McCullough, MD, MPH** Vice Chief of Medicine and Cardiologist, Baylor University Medical Center
TLANDO in Clinical Practice	**Adrian Dobs, MD, MHS**
Summary	**Anthony DelConte, MD**

Additional Expert

Dr. Culley C. Carson III, MD

Distinguished Professor of Urology, UNC

Sponsor Presentation

Introduction	**Mahesh Patel, PhD** President and CEO, Lipocine
TRT Overview	**Adrian Dobs, MD, MHS** Professor of Medicine, Director, Johns Hopkins Clinical Research Network
Efficacy	**Gary Hoel, RPh, PhD** Clinical Consultant, Lipocine
Safety	**Anthony DelConte, MD** Chief Medical Director, Lipocine
CV Safety	**Peter A. McCullough, MD, MPH** Vice Chief of Medicine and Cardiologist, Baylor University Medical Center
TLANDO in Clinical Practice	**Adrian Dobs, MD, MHS**
Summary	**Anthony DelConte, MD**

Testosterone Replacement Therapy (TRT) Overview

Adrian S. Dobs, MD, MHS

Professor of Medicine and Oncology
The Johns Hopkins University School of Medicine
Division of Endocrinology, Diabetes and Metabolism

Male Hypogonadism

- **Male hypogonadism is an endocrine disorder characterized by:**
  - Absence or deficiency of endogenous testosterone
  - Signs and symptoms of androgen deficiency
- **Causes of hypogonadism:**
  - Testicular defects: primary hypogonadism
  - Hypothalamic-pituitary defects: secondary hypogonadism

Signs and Symptoms of Hypogonadism

Suggestive of Hypogonadism	Less Specific
• Incomplete sexual development • Reduced libido and activity • Decreased spontaneous erections • Infertility • Gynecomastia • Height loss, low trauma fracture, low bone mineral density • Reduced muscle bulk and strength • Hot flushes, sweats	• Decreased energy and vitality • Depressed mood, • Poor concentration and memory • Increased body fat • Diminished physical performance • Mild anemia

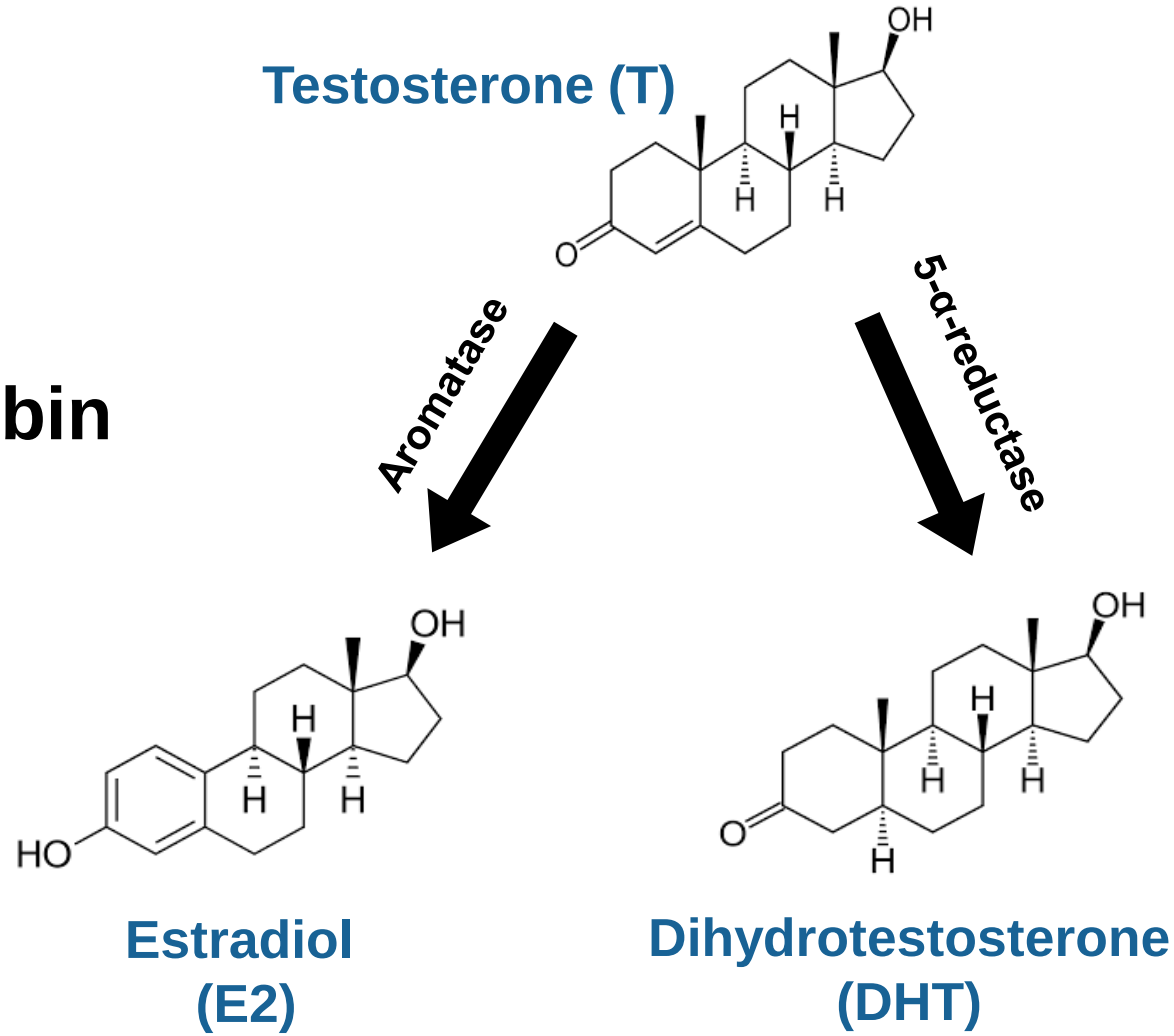
Adapted from Bhasin, et al., 2010 Endocrine Society Guidelines

Need for an Oral TRT Product

- **Improve management of hypogonadism**
  - Current treatments primarily limited to topicals and injectables
  - Oral formulation provides a different treatment option
- **Minimal administration risk**
  - No transference
  - No immediate post dosing reactions, anaphylaxis or pulmonary oil micro-embolism (POME)
  - No supra-physiologic dosing with injectables

Effects of Testosterone Treatment

- Increase in testosterone
  - free and total
- Reduction in SHBG
- Increase in hematocrit/hemoglobin
- Increase in estradiol
- Increase in DHT



Endocrine Society Guidelines: Patient Management

- Confirm testosterone levels in normal range
- Obtain patient feedback on signs and symptoms
- Evaluate for adverse events
- Monitor safety labs (e.g. PSA, HCT, lipids)
- Continued doctor/patient dialogue on risk/benefit

Summary

- **Unmet need for an oral treatment option**
- **Treatment goals for TRT:**
  - Restore testosterone levels to eugonadal range
  - Improve symptoms associated with hypogonadism
- **Increased T levels often associated with changes in hormone and lab parameters**
  - Corresponding increase in estradiol and DHT
  - Androgenic effect of testosterone (e.g. increased HCT, PSA)
- **Standard of care includes monitoring for symptom relief and possible risks associated with TRT**

Sponsor Presentation

Introduction	**Mahesh Patel, PhD** President and CEO, Lipocine
TRT Overview	**Adrian Dobs, MD, MHS** Professor of Medicine, Director, Johns Hopkins Clinical Research Network
Efficacy	**Gary Hoel, RPh, PhD** Clinical Consultant, Lipocine
Safety	**Anthony DelConte, MD** Chief Medical Director, Lipocine
CV Safety	**Peter A. McCullough, MD, MPH** Vice Chief of Medicine and Cardiologist, Baylor University Medical Center
TLANDO in Clinical Practice	**Adrian Dobs, MD, MHS**
Summary	**Anthony DelConte, MD**

Clinical Efficacy

Gary Hoel, RPh, PhD

Clinical Consultant
Lipocine

Key Efficacy Studies

Description	Study
Food-Fat Effect	14-001
Phase 2 Dose Finding	M12-778
Phase 3 Dose Titration	13-001
Phase 3 Fixed Dosing (225 mg two times daily)	16-002
Phase 3 Fixed Dosing (150 mg three times daily)	16-003

Standard TRT Class Study Endpoints

- **Primary endpoint targets:**
  - T $C_{avg,\ 0\text{-}24h}$ in eugonadal range: ≥75% of subjects
  - 95% confidence interval (CI) lower bound: ≥65% of subjects

- **Secondary endpoint targets:**
  - T C_{max} <1500 ng/dL: ≥85% of subjects
  - T C_{max} 1800–2500 ng/dL: ≤5% of subjects
  - T C_{max} >2500 ng/dL: 0% of subjects

Bioanalytical Assay Studies

- **Bioanalytical procedures were established to ensure the reliability of the test results**
- **Bioanalytical testing and method validation was performed by PPD® Laboratories**
  - Stability studies demonstrated TU and T are stable for 24 hours at room temperature and 750 days frozen at -20°C

Bioanalytical Questions

- Does TU to T conversion occur in serum test tubes leading to an overestimation of T levels?
- Are the results of the T measurements reliable?
- Are the sample collection and handling methods applicable to the clinical practice setting?

TU to T Conversion Caused by Solvent-Induced Hemolysis

Dataset	Sample	TU-Spiking Solvent	Results
LaChance, et al.	Serum	100% methanol	T increase
Sponsor evaluation	Plasma	100% acetonitrile	T increase
LaChance, et al.	Plasma	100% methanol	T increase

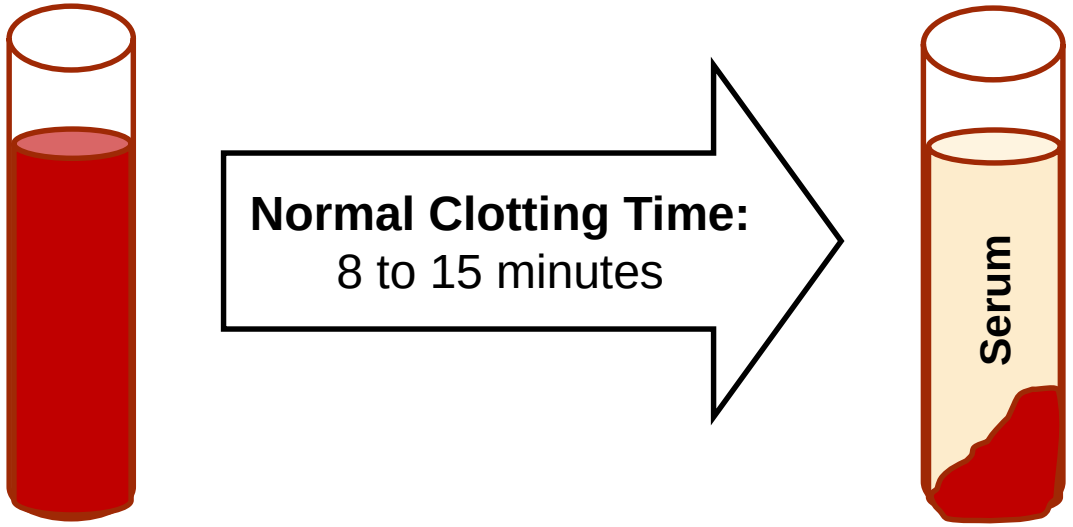
No TU to T Conversion with Biocompatible Solvent

Dataset	Sample	TU-Spiking Solvent	Results
Wang, et al.	Serum	Ethanolic PBS	Stable T levels
LaChance, et al.	Serum	Ethanolic PBS	Stable T levels
Sponsor recent evaluation	Serum	Ethanolic PBS	Stable T levels

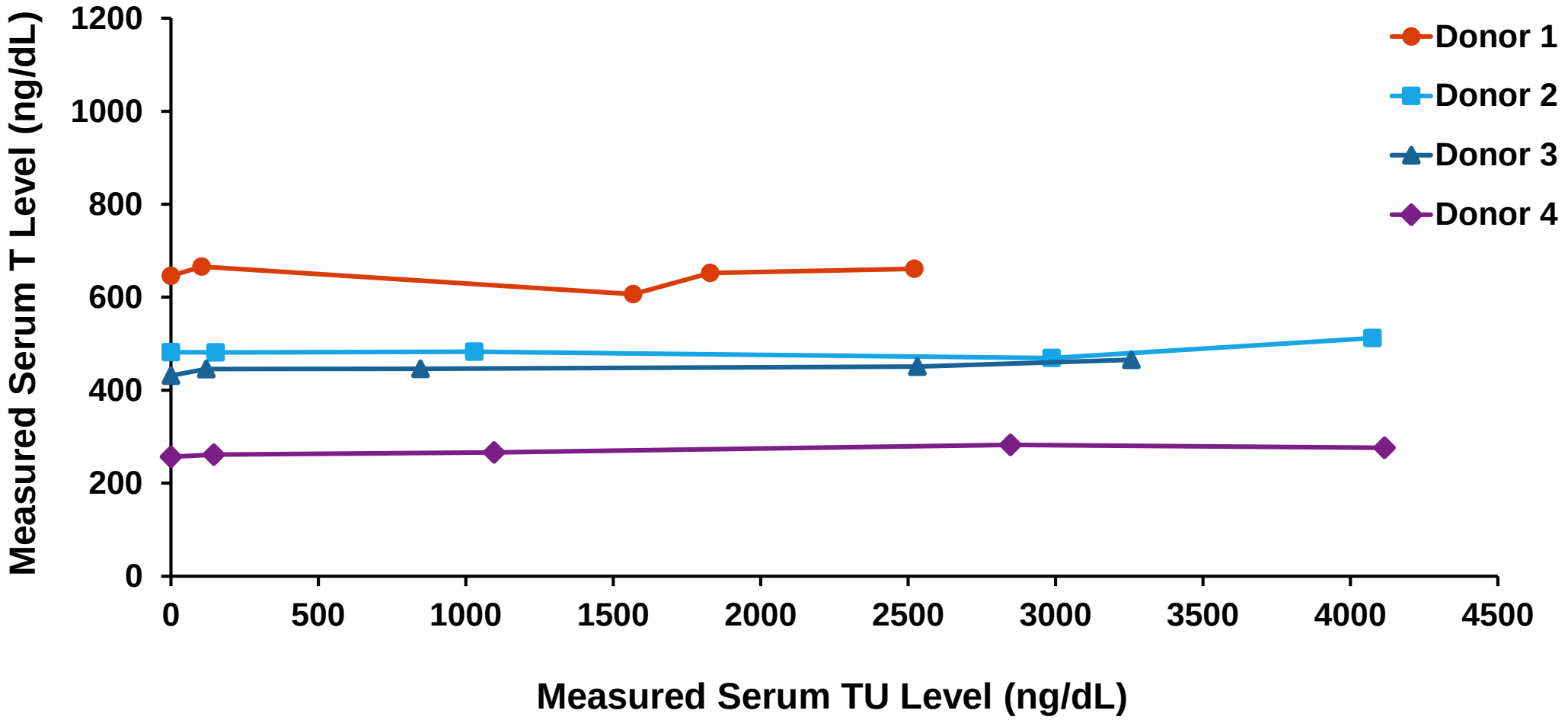
TU and T Evaluation in Blood / Serum Process

- **TU dissolved in ethanolic PBS solution is spiked into freshly collected blood**
- **Allowed to clot for 30 minutes at room temperature**
- **Centrifuged for 15 minutes to harvest serum**
- **TU and T concentrations are measured from the serum samples**

Freshly collected blood in serum tubes (per clinical practice)



TU and T Evaluation in Blood / Serum Process



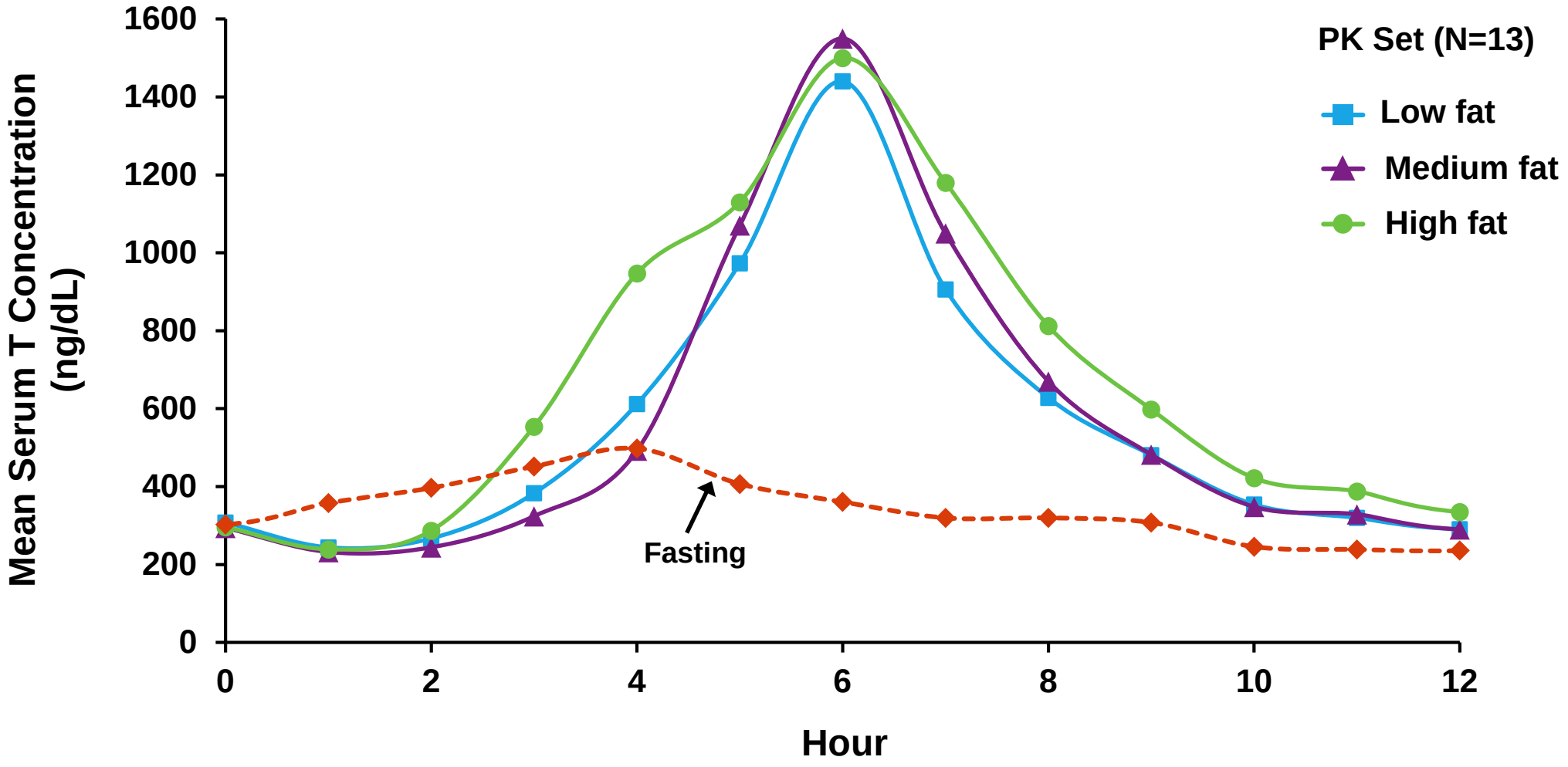
Testosterone Assay Data are Reliable

- **No conversion of TU to T occurs *ex vivo* during blood collection and serum sample processing**
- **Treatment outcomes confirm reliability of T measurements**
  - Pharmacological effects (e.g., LH/FSH suppression)
  - Testosterone metabolite levels (e.g., E2)
- **Standard blood collection procedures can be used in clinical practice to determine testosterone levels**

Study 14-001: Food-Fat Effect Study

- **Randomized, 4-period, crossover, single dose study**
- **N=14 hypogonadal men**
- **Dose: 225 mg**
- **Conditions**
  - Fasting
  - Low fat
  - Medium fat
  - High fat

Study 14-001: Study Results



Study M12-778: Phase 2 Dose Finding

- Randomized, double-blind, placebo-controlled, multiple-fixed dose study
- N=84 hypogonadal men
- Doses: 75 mg, 150 mg, 225 mg, and 300 mg BID or placebo with standard meal
- 24-hour PK profile on Day 15

Study M12-778: Dose Finding Study Results

PK Parameters	Criteria / Targets	Subjects Meeting the Criteria Post-Steady State (Day 15) TU BID Dose 75 mg n=16	150 mg n=15	225 mg n=24	300 mg n=9
Primary Endpoint					
$C_{avg, 0-24h}$ 300–1140[a] ng/dL	≥75%	44%	47%	**83%**	100%
Lower bound 95% CI	≥65%	27%	35%	**69%**	79%
Secondary Endpoints					
C_{max} <1500 ng/dL	≥85%	100%	100%	**88%**	44%
C_{max} 1800–2500 ng/dL	≤5%	0	0	**0**	11%
C_{max} >2500 ng/dL	0%	0	0	**0**	33%

[a] Lab normal range.

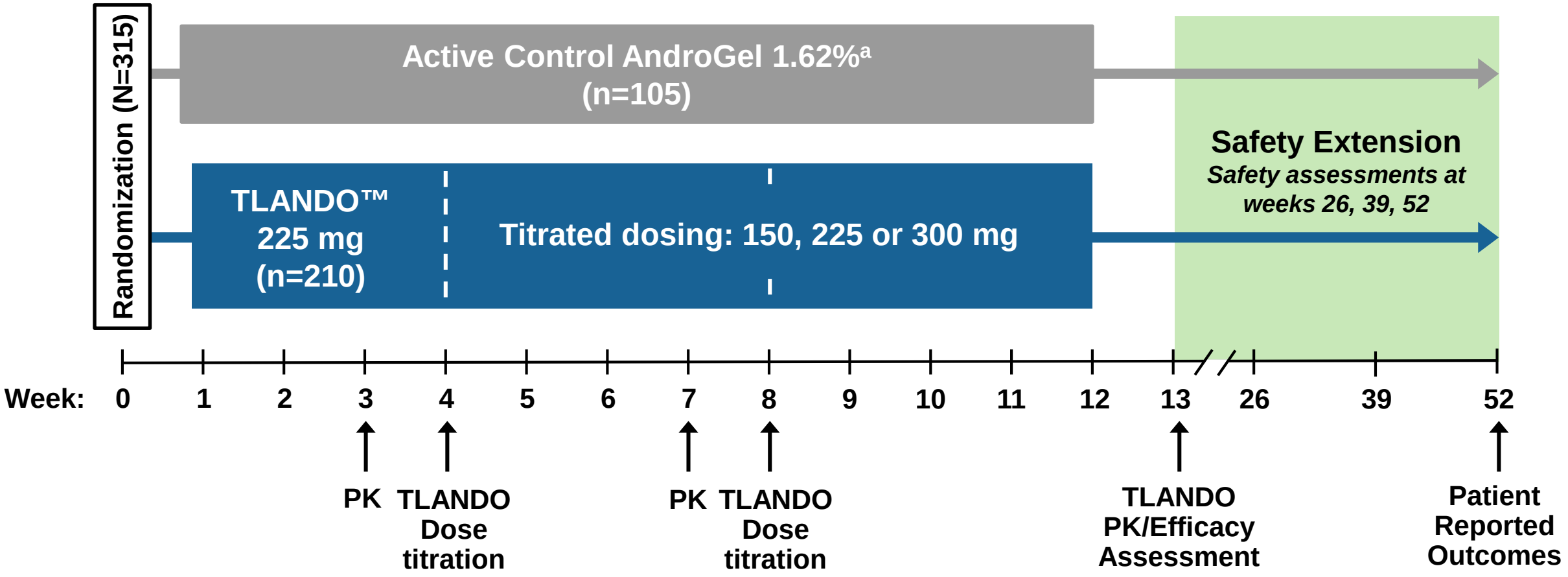
Study 13-001: Phase 3 Dose Titration

- **Randomized (2:1), active-controlled (AndroGel® 1.62%)**
- **52 week treatment duration**
- **N=315 hypogonadal men**
  - n=210 TLANDO
  - n=105 AndroGel

Study 13-001: Dosing and Titration

- **Starting dose**
  - TLANDO: 225 mg BID with standard meal
  - AndroGel: 40 mg QD
- **Titration**
  - TLANDO
    - » At Week 4 and 8 based on C_{avg} and C_{max} values from 24-hour PK profile
    - » 150, 225 or 300 mg BID
  - AndroGel
    - » Per product label instructions

Study 13-001: Study Timeline



[a] AndroGel administered per label; titration based on single T measurement.

Study 13-001: Demographics and Baseline T

Characteristic	Statistics	TLANDO N=210	AndroGel N=105
Age	Mean (SD)	52.6 (10.2)	54.2 (9.4)
≤65 Years	n (%)	190 (90.5)	96 (91.4)
Race			
Black or African American	n (%)	32 (15.2)	10 (9.5)
White		172 (81.9)	92 (87.6)
Body mass index, kg/m²	Mean (SD)	30.8 (3.9)	31.0 (3.9)
Baseline testosterone, ng/dL	Mean (SD)	209 (71.0)	200 (72.6)

Study 13-001: Disposition and Analysis Sets

	All Subjects	TLANDO	AndroGel	Description
Randomized	315	210	105	
Full Analysis Set	–	193	–	Provided at least one PK profile
Completers – Week 13	–	157	–	

Study 13-001: Primary Efficacy Endpoint (T C_{avg})

Measure	Target % Subjects	Full Analysis Set N=192[a]	Full Analysis Set (LOCF) N=192[a]
		Week 3 Pre-Titration[b]	Week 13 Post-Titration
Primary Efficacy Endpoint			
% subjects with T $C_{avg\ 0\text{-}24h}$ 300–1140 ng/dL	≥75%	**86%**	**88%**
95% CI lower bound	≥65%	**81%**	**83%**

[a] FAS has 193 subjects with one subject missing 24-hour C_{avg} data, therefore N is 192 for C_{avg}
[b] At Week 3 all subjects were on 225 mg BID dose of TLANDO.
LOCF, last observation carried forward.

Study 13-001: Secondary Endpoints (T C_{max})

T C_{max} Criteria	Target % Subjects	Subjects in T C_{max} Criteria	
		Full Analysis Set N=193	Full Analysis Set (LOCF) N=193
		Week 3 Pre-Titration	Week 13 Post-Titration
<1500 ng/dL	≥85%	68%	72%
1800–2500 ng/dL	≤5%	11%	11%
>2500 ng/dL	0%	5%	4%

Study 16-002: Phase 3 Fixed Dosing

- **Open-label, single arm**
- **N=95 hypogonadal men**
  - No BMI
  - No dietary fat restrictions
- **Dosing: fixed dose**
  - 225 mg BID with meal
- **24-hr PK profile obtained on Day 24**

Study 16-002: Demographics and Baseline T

Characteristic	Statistic	TLANDO N=95
Age	Mean (SD)	56.0 (8.9)
≤65 years	n (%)	79 (83.2)
Race		
Black or African American	n (%)	15 (15.8)
White		77 (81.1)
Body mass index, kg/m²	Mean (SD)	32.8 (5.5)
Baseline testosterone, ng/dL	Mean (SD)	202 (74.5)

Study 16-002: Subject Disposition

Status	n (%)
Subjects enrolled	95 (100)
Completed the study	94 (99)
Total discontinued early from the study[a]	1 (1)

[a] AE in one subject was gastric ulcer related hemorrhage, classified as not due to study drug.

Study 16-002: Primary Efficacy Endpoint (T C_{avg})

Measure	Target % Subjects	Safety Set BLOCF Analysis[a] N=95
% subjects with $C_{avg\ 0\text{-}24h}$ 300–1080 ng/dL	≥75%	**80%**
95% CI lower bound	≥65%	**72%**

[a] BLOCF: Last observation carried forward including baseline. Subjects randomized into the study and who took at least one dose of the study drug. Missing data was imputed by baseline carried forward (i.e., considered treatment failures).

Study 16-002: Secondary Endpoints (T C_{max})

T C_{max} Criteria	Target % Subjects	T C_{max} (0-24h) N=95
<1500 ng/dL	≥85%	74%
1800–2500 ng/dL	≤5%	14%
>2500 ng/dL	0%	1%[a]

[a] One subject had C_{max} value of 2730 ng/dL (one single measurement >2500 ng/dL).

Study 16-003: Primary Efficacy Endpoint (T C_{avg}) TLANDO 150 TID

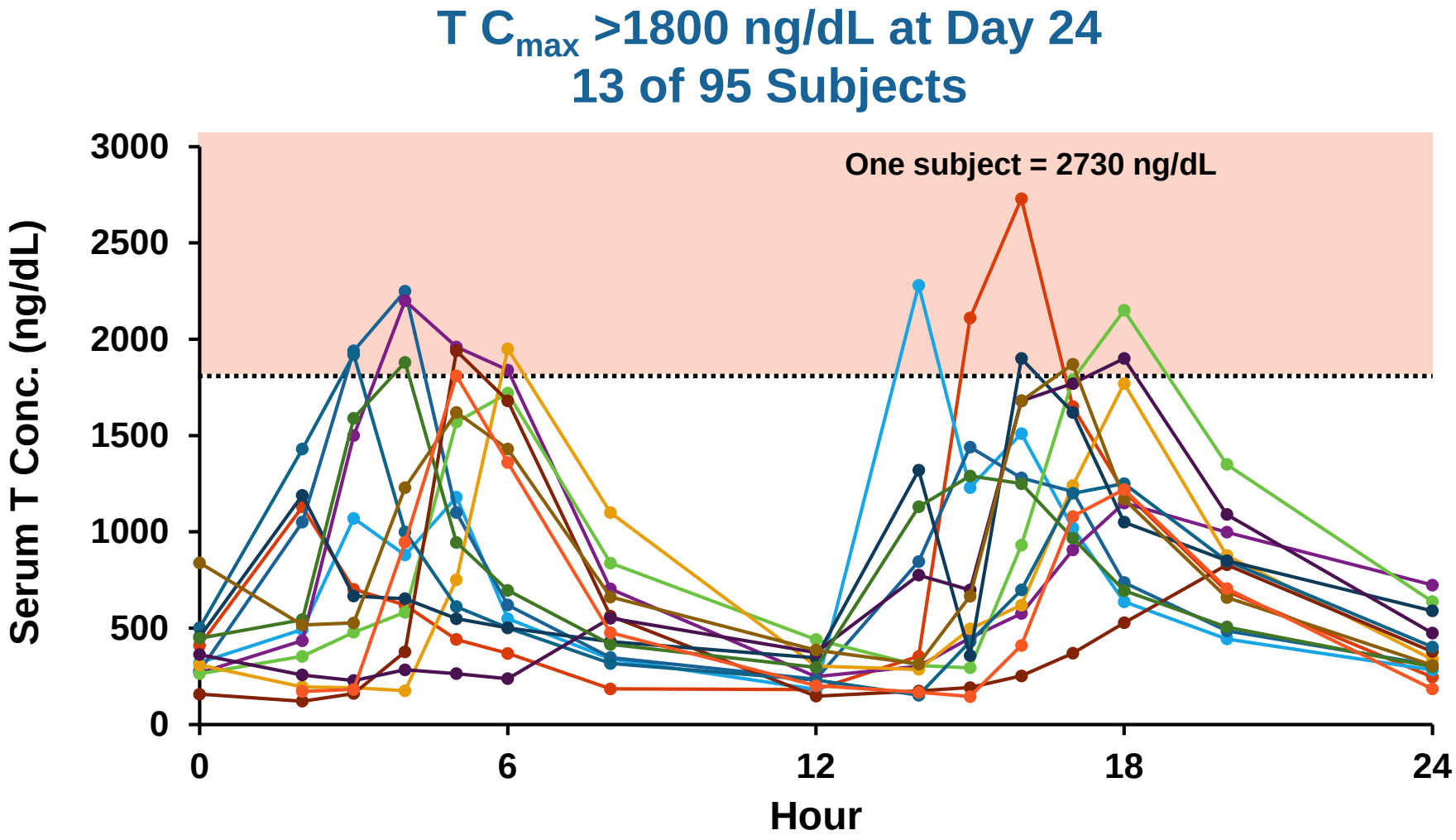
Measure	Target % Subjects	Safety Set BLOCF Analysis[a] N=100
% subjects with $C_{avg\ 0\text{-}24h}$ 300–1080 ng/dL	≥75%	69%
95% CI lower bound	≥65%	60%

[a] BLOCF: Last observation carried forward including baseline. Subjects randomized into the study and who took at least one dose of the study drug. Missing data imputed by baseline carried forward (i.e., considered treatment failures).

Study 16-003: Secondary Endpoints (T C_{max})

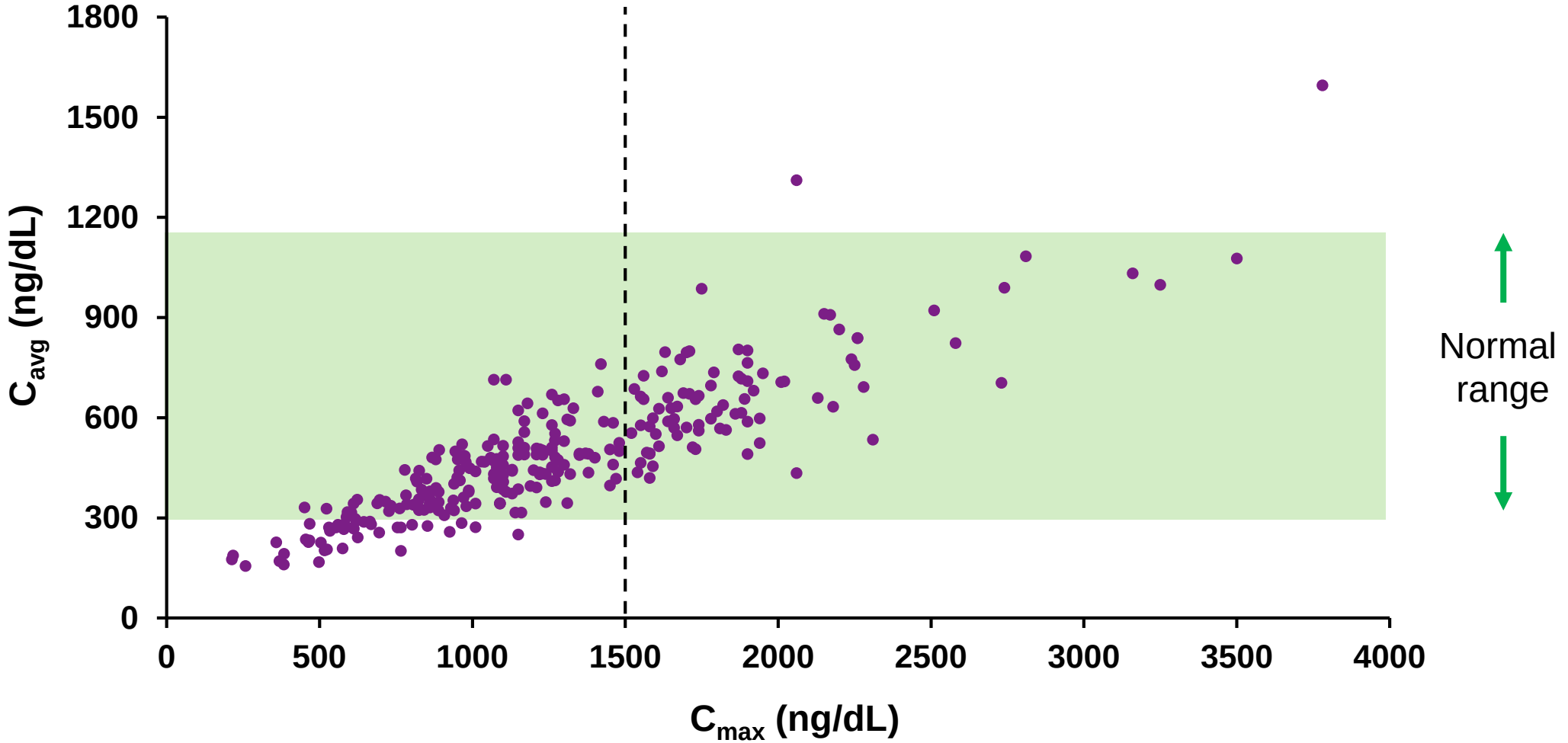
T C_{max} Criteria	Target % Subjects	T C_{max} (0-24h) N=100
<1500 ng/dL	≥85%	95%
1800–2500 ng/dL	≤5%	1%
>2500 ng/dL	0%	0%

C_{max} Excursions Are Transient



Data from Study 16-002.

High C_{max} Does Not Result in Overexposure

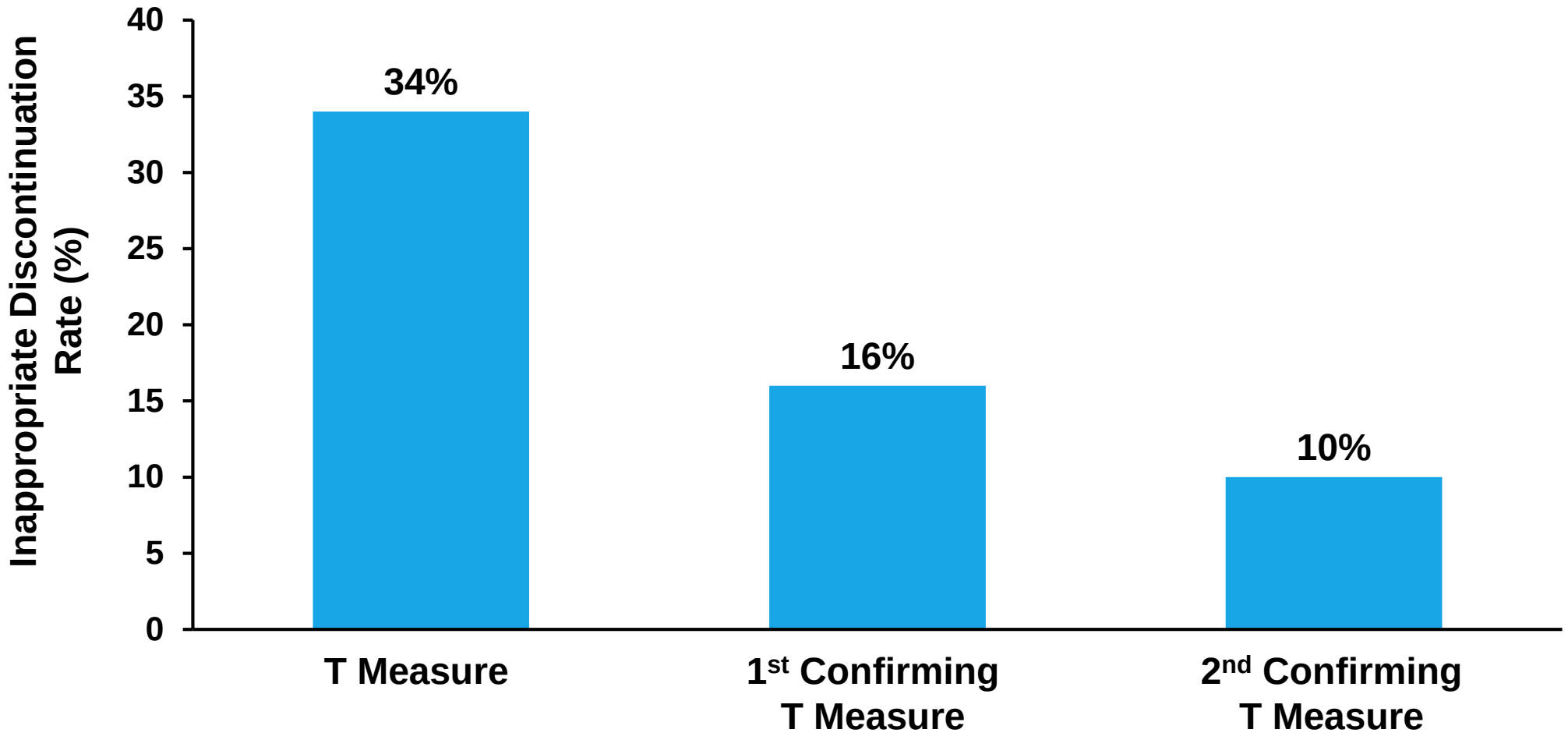


Data from Study 16-002 and 13-001 Week 3 (N=286 for 225 mg BID).

TLANDO: Monitoring and Stopping Criteria

- Check serum T levels 3–4 weeks after starting TLANDO, periodically thereafter
- Sampling should occur 7–9 hours after the morning dose
- If T consistently below 300 ng/dL and symptoms have not improved after 3 months of treatment, alternative treatment should be considered
- If T consistently above normal range, TLANDO should be discontinued

Confirmatory T Measurement Reduces Inappropriate Discontinuation Rate



Based on Study 13-001.

Consistent Efficacy of 225 mg BID Fixed Dose Across Studies

Measure	225 mg BID Fixed Dose		
Study	M12-778 (Day 15)	13-001 (Week 3)	16-002 (Day 24)
N	24	192	95
Primary Efficacy Endpoint (% Subjects)			
T $C_{avg\ 0\text{-}24h}$ 300–1080 ng/dL	83%	86%	80%
95% CI lower bound	69%	81%	72%
Testosterone Concentrations			
Mean (SD) T C_{avg}, ng/dL	446 (162)	494 (193)	476 (174)

Efficacy Conclusions

- TLANDO restored testosterone levels to normal in most subjects
- 225 mg BID fixed dosing with food was proven effective
- Efficacy was consistent across multiple studies

Sponsor Presentation

Introduction	**Mahesh Patel, PhD** President and CEO, Lipocine
TRT Overview	**Adrian Dobs, MD, MHS** Professor of Medicine, Director, Johns Hopkins Clinical Research Network
Efficacy	**Gary Hoel, RPh, PhD** Clinical Consultant, Lipocine
Safety	**Anthony DelConte, MD** Chief Medical Director, Lipocine
CV Safety	**Peter A. McCullough, MD, MPH** Vice Chief of Medicine and Cardiologist, Baylor University Medical Center
TLANDO in Clinical Practice	**Adrian Dobs, MD, MHS**
Summary	**Anthony DelConte, MD**

SAFETY

Anthony DelConte, MD

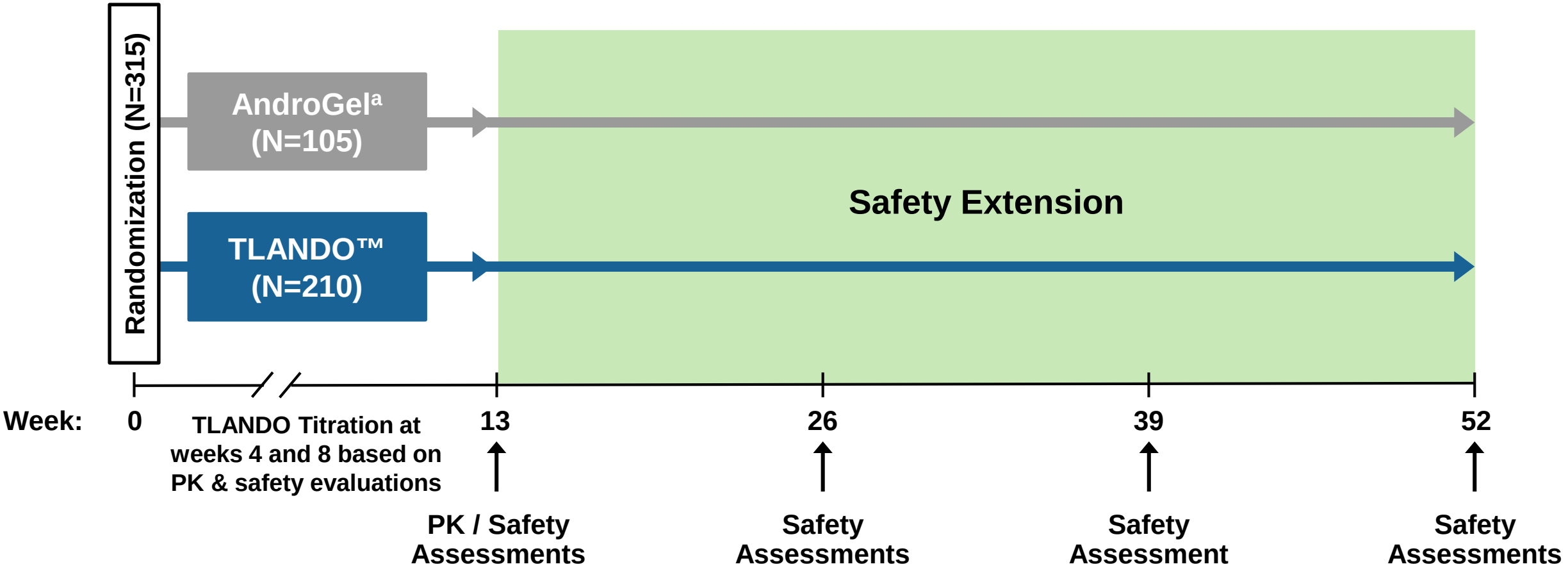
Chief Medical Director, Lipocine

Safety Presentation Outline

- **Study 13-001: TLANDO vs AndroGel**
  - Patient disposition
  - T, DHT, and estradiol
  - FSH, LH
  - Adverse events
  - Vital signs, laboratory findings and C_{max}
- **ACTH (Studies 16-002, 16-003)**
- **Integrated Safety Experience**
- **Summary**

ACTH: AdrenoCorticoTropic Hormone; DHT, Dihydrotestosterone; FSH, Follicle Stimulating Hormone; LH, Luteinizing Hormone; T, Testosterone.

Study 13-001: Study Design



[a] AndroGel 1.62% administered per label; titration based on single T measurement at weeks 2 and 4.

Study 13-001: Patient Characteristics

Parameter	Statistic	TLANDO N=210	AndroGel N=105
Age, yrs	Mean (SD)	52.6 (10.2)	54.2 (9.4)
BMI, kg/m^2	Mean (SD)	30.8 (3.9)	31.0 (3.9)
Baseline testosterone, ng/dL	Mean (SD)	208.6 (71.0)	199.8 (72.6)
Key medical history at baseline			
Hypertension	%	46	45
Diabetes	%	22	35
Lipid disorders	%	47	49

Study 13-001: Patient Disposition

Status	TLANDO n (%)	AndroGel n (%)
Subjects randomized	210	105
Subjects who received treatment	210 (100)	104 (99.0)
Subjects who completed the study	130 (61.9)	71 (67.6)
Subjects who discontinued early from the study	80 (38.1)	34 (32.4)
Reason for Early Discontinuation		
Consent withdrawn due to:		
Confinement or schedule conflict	14 (6.7)	3 (2.9)
Reason other than confinement or schedule conflict	10 (4.8)	2 (1.9)
Abnormal lab parameters, adverse events, or lack of efficacy based on symptoms[a]	22 (10.5)	11 (10.5)
Lost to follow-up	14 (6.7)	12 (11.4)
Other		
Met the stopping criteria for C_{max} or C_{avg}	9 (4.3)	NA
Duplicate subjects[b]	4 (1.9)	3 (2.9)
Protocol deviation	7 (3.3)	3 (2.9)

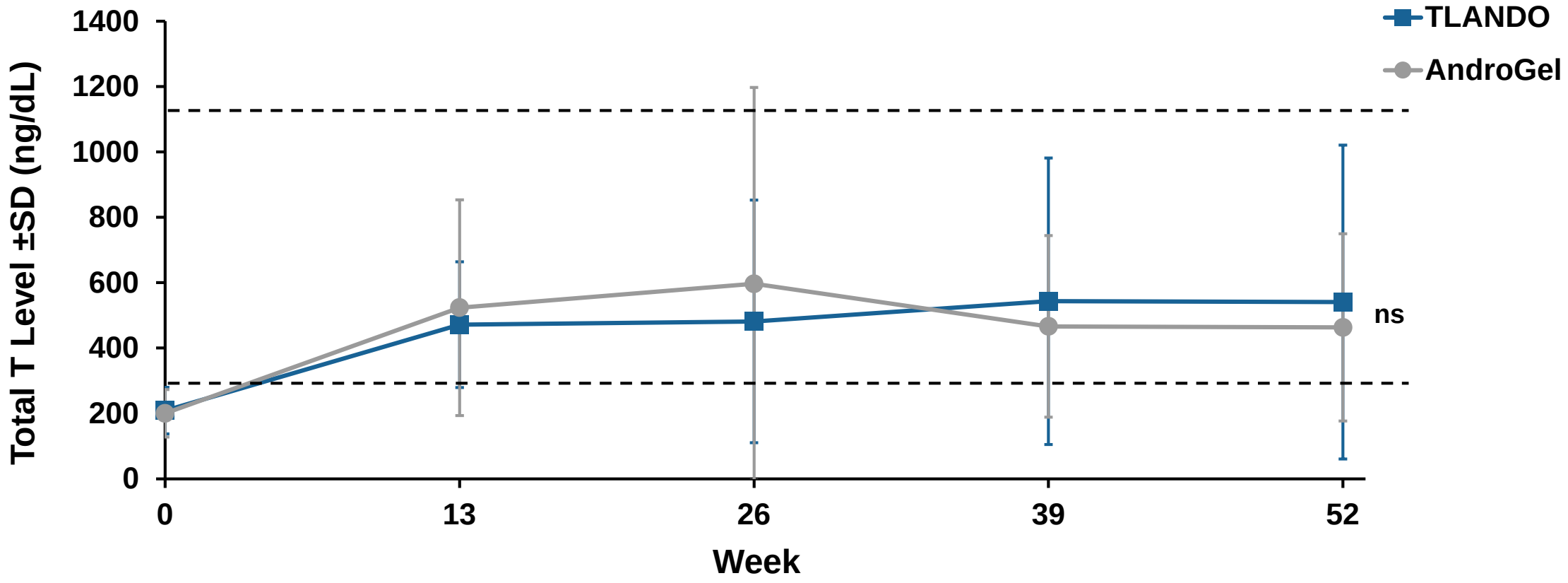
[a]Subset Disposition is shown in next slide.
[b]Subjects who enrolled and/or screened at more than one site. In cases where this occurred, subjects were withdrawn at both study sites.

Study 13-001: Discontinuations Subset

Parameter	TLANDO N=210 n (%)	AndroGel N=105 n (%)
Discontinued due to abnormal lab parameters, any AEs & lack of efficacy	**22 (10.5)**	**11 (10.5)**
Other adverse events	7 (3.3)	5 (4.8)
Lack of efficacy (symptomatic)[a]	5 (2.4)	4 (3.8)
Hematocrit >54%	3 (1.4)	1 (1.0)
Serious adverse events[b]	3 (1.4)	0
Weight gain	3 (1.4)	0
Prostate specific antigen >4 ng/mL	1 (0.5)	1 (1.0)

[a] Patient reported.
[b] SAE not related to study drug: (1) fall out of hammock, (1) spider bite with staphylococcal bacteremia and osteomyelitis, and (1) one day hospitalization due to imbalance and ataxia.

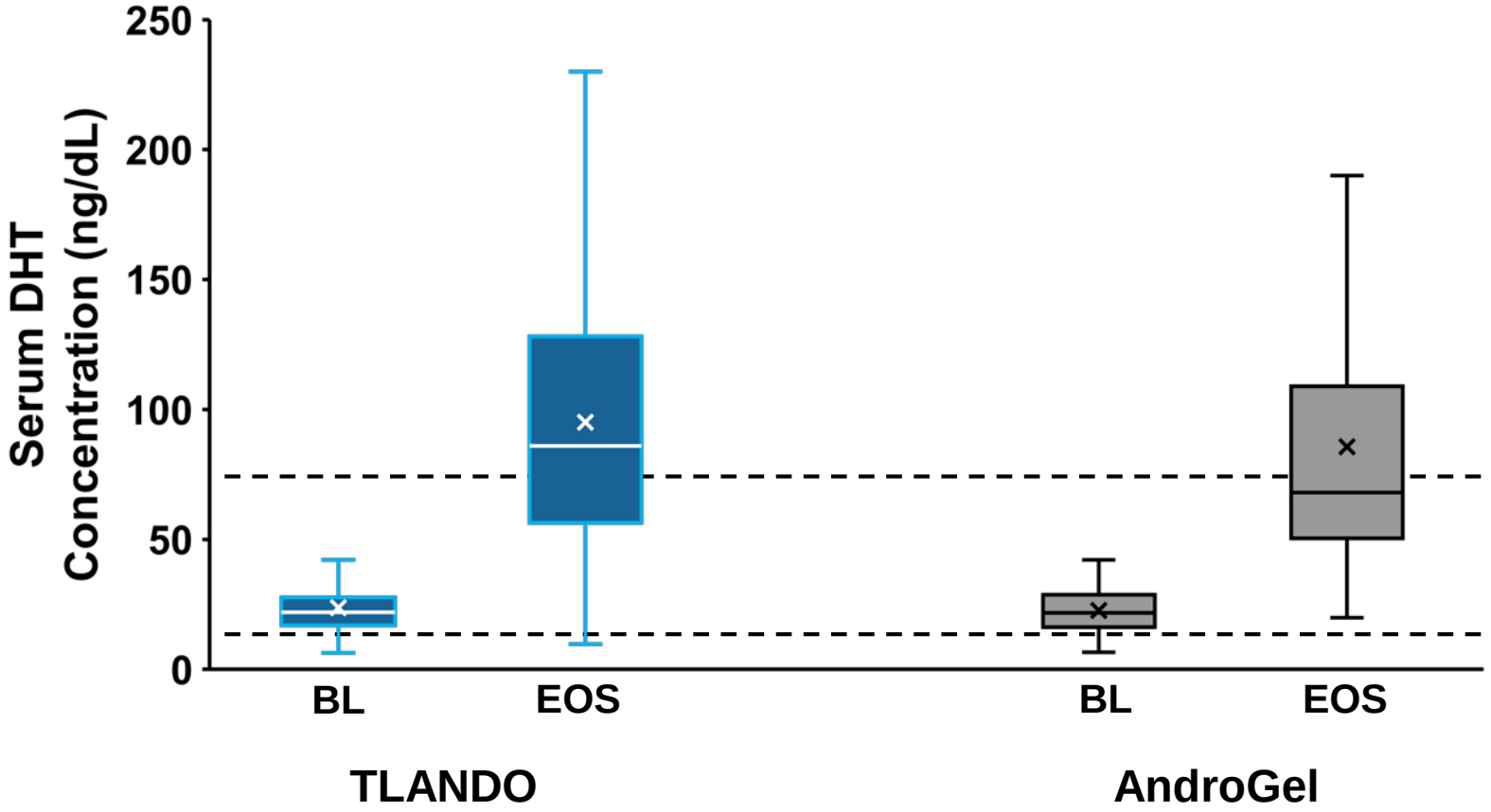
Study 13-001: Total T



TLANDO N=	208	157	143	134	142
AndroGel N=	104	91	80	74	96

Dotted lines indicate Total T normal range (300 – 1140 ng/dL). ns, not significant (p≥0.05); T, testosterone.

Study 13-001: DHT at Baseline and End of Study

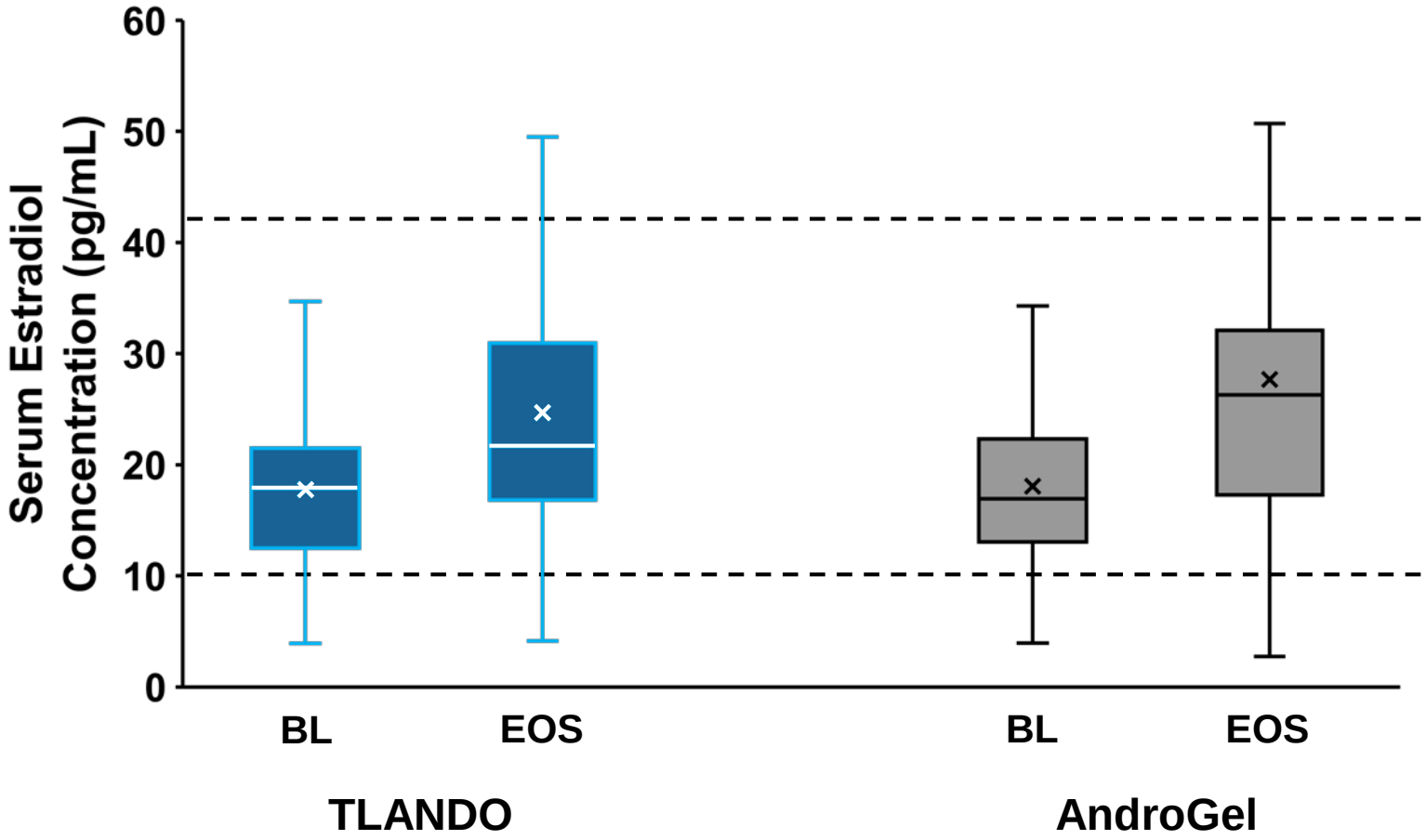


Dotted lines indicate DHT normal range (10.6 – 71.9 ng/dL). BL, baseline; DHT, Dihydrotestosterone; EOS, end of study.

Study 13-001: Treatment-Emergent Adverse Events in >2% of TLANDO-treated Subjects Based on DHT C_{avg} ≤ or >2 x ULN

System Organ Class	Preferred Term	≤2 x ULN N=126 n (%)	>2 x ULN N=31 n (%)
Gastrointestinal disorders	Diarrhea	3 (2.4)	1 (3.2)
	Nausea	2 (1.6)	2 (6.5)
Infections and infestations	Influenza	4 (3.2)	0
	Nasopharyngitis	3 (2.4)	2 (6.5)
	Upper respiratory tract infection	6 (4.8)	2 (6.5)
Investigations	Enzyme level increased	4 (3.2)	0
	Weight increased	5 (4.0)	2 (6.5)
Musculoskeletal and connective tissue disorders	Back pain	3 (2.4)	1 (3.2)
Nervous system disorders	Headache	3 (2.4)	1 (3.2)
Skin and subcutaneous tissue disorders	Acne	4 (3.2)	1 (3.2)
Vascular disorders	Hypertension	4 (3.2)	0

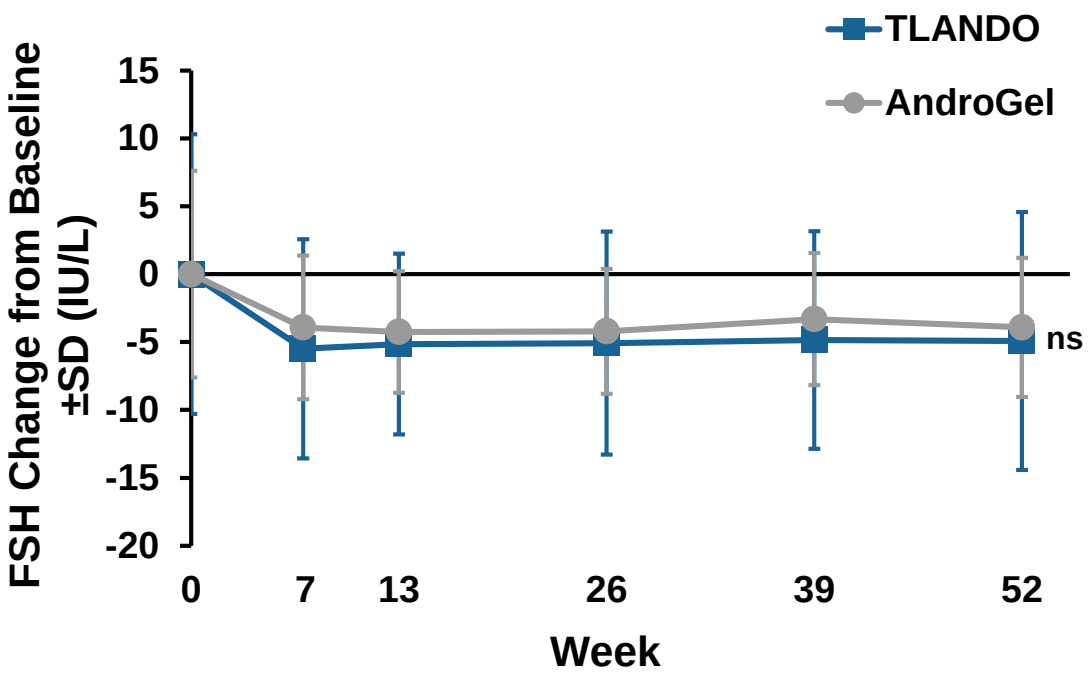
Study 13-001: Estradiol at Baseline and EOS



Dotted lines indicate E2 normal range (10 – 42 pg/mL). BL, baseline; EOS, end of study.

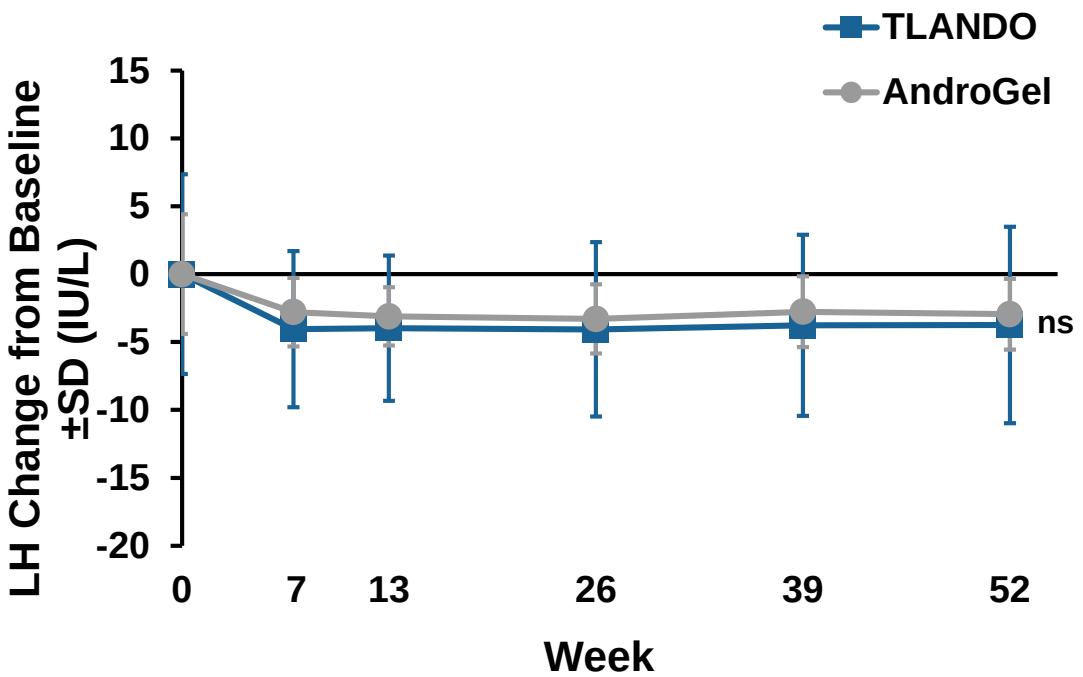
Study 13-001: FSH, LH

FSH



TLANDO N=	207	119	152	144	136	128
AndroGel N=	104	95	89	82	76	69

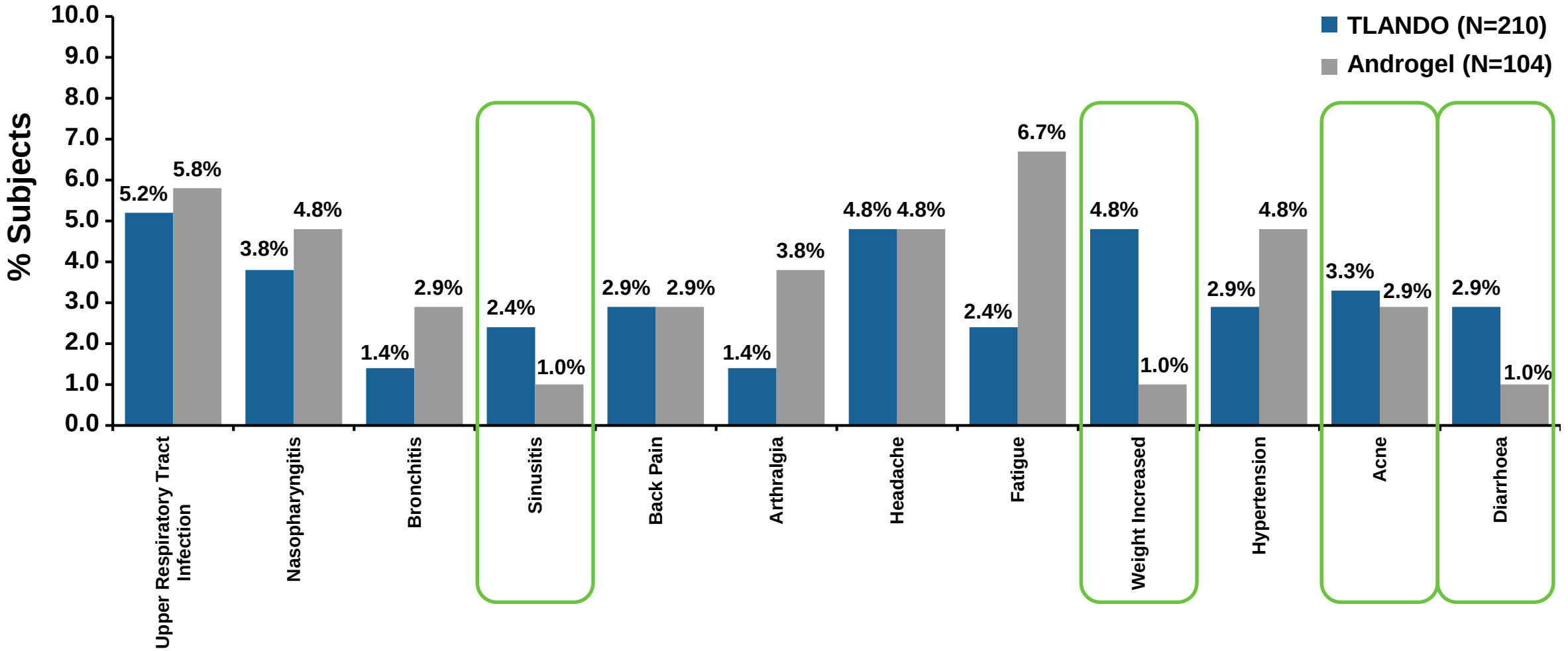
LH



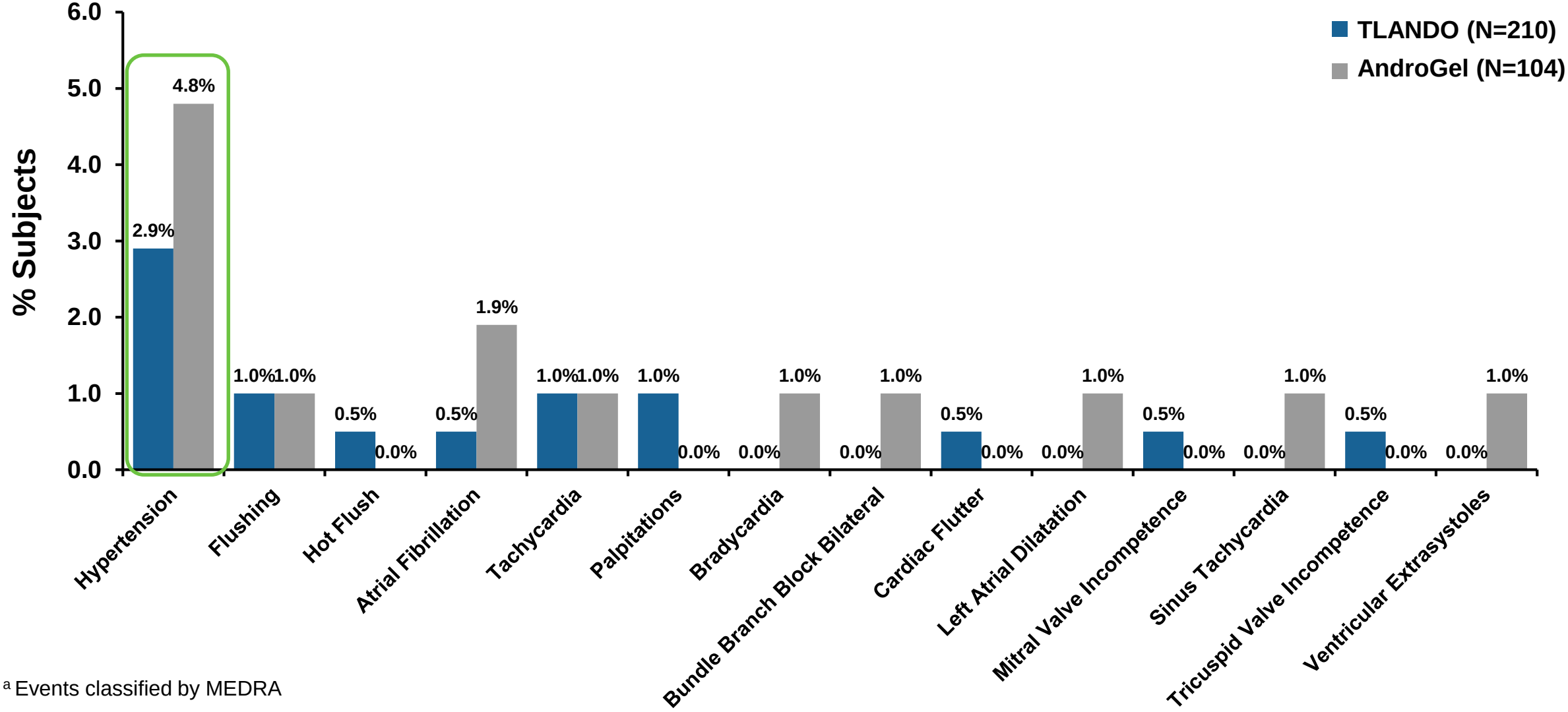
TLANDO N=	207	119	152	144	137	128
AndroGel N=	104	95	89	82	76	69

FSH, follicle stimulating hormone; LH, luteinizing hormone; ns, not significant (p≥0.05).

Study 13-001: Adverse Events in >2% of Subjects



Study 13-001: Non-Serious Cardiovascular Events[a]



[a] Events classified by MEDRA

Study 13-001: Potential Androgenic Adverse Events

Preferred Term	TLANDO N=210 n (%)	AndroGel N=104 n (%)
Acne	7 (3.3)	3 (2.9)
Peripheral edema	3 (1.4)	1 (1.0)
Prostatic symptoms	3 (1.4)	1 (1.0)
Sleep apnea syndrome	3 (1.4)	1 (1.0)
Polycythemia	1 (0.5)	1 (1.0)

Study 13-001: Serious Adverse Events

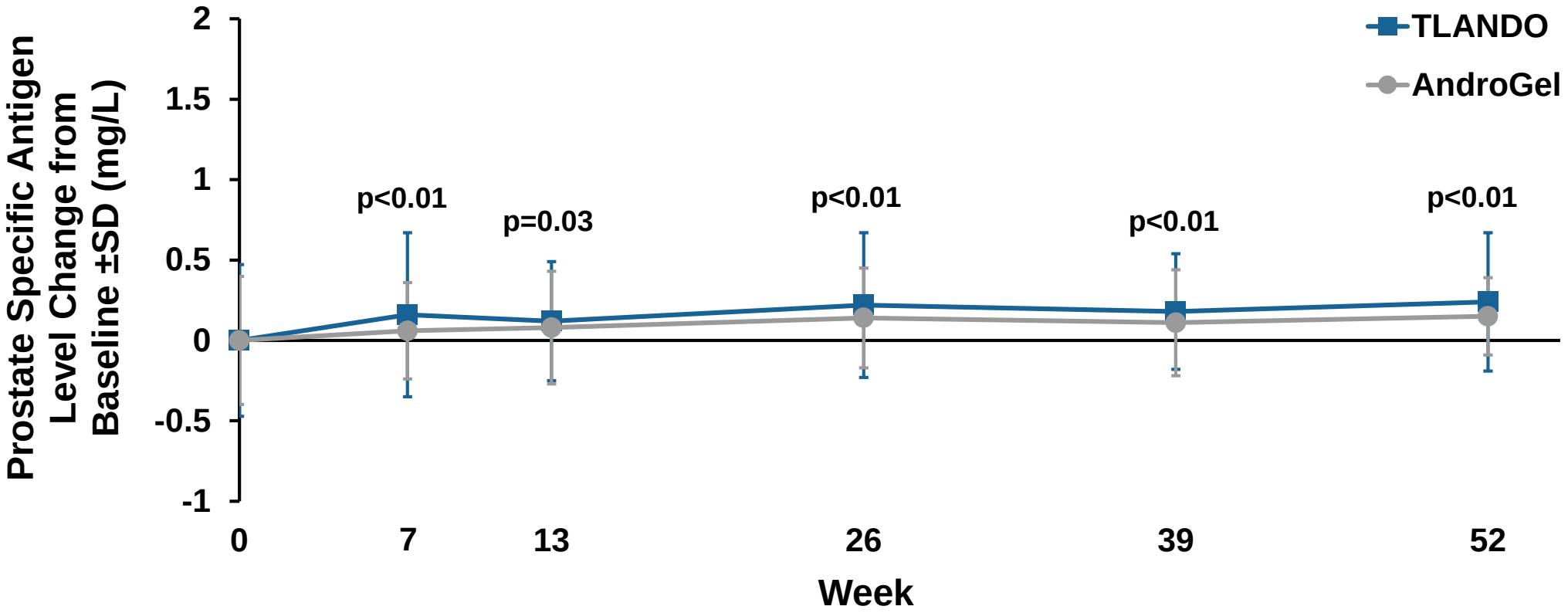
System Organ Classification	TLANDO N=210 n (%)	AndroGel N=104 n (%)
Any SAE	**12 (5.7)**	**2 (1.9)**
Drug-related SAEs	0	0
Infections and infestations	3 (1.4)	1 (1.0)
Musculoskeletal and connective tissue disorders	3 (1.4)	0
Gastrointestinal disorders	2 (1.0)	0
General disorders and administration site conditions	1 (0.5)	1 (1.0)
Injury, poisoning and procedural complications	2 (1.0)	0
Nervous system disorders	2 (1.0)	0

Study 13-001: Vital Signs, Laboratory Findings, C_{max}

- **Vital Signs**
  - Blood pressure*
  - Heart rate*
- **Laboratory Findings and I-PSS**
  - Prostate specific antigen, I-PSS
  - Total cholesterol, triglycerides, HDL, LDL*
  - Hemoglobin/Hematocrit*
  - Serum Electrolytes
- **C_{max} Safety Relevance**

*Will be reviewed in cardiovascular safety presentation.
I-PSS, International Prostate Symptom Questionnaire.

Study 13-001: Prostate Specific Antigen



TLANDO N=	208	182	156	144	137	129
AndroGel N=	104	96	91	82	76	69

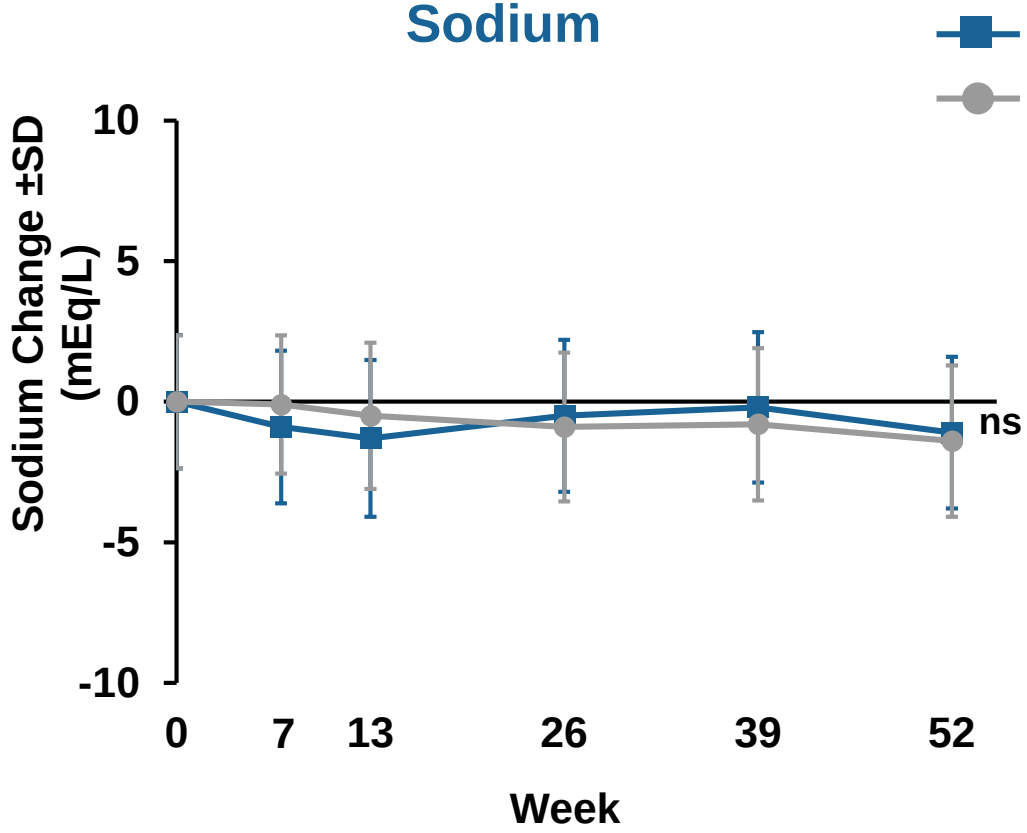
Study 13-001: International Prostate Symptom Questionnaire (I-PSS)[a]

Visit	TLANDO N=210 Mean (SD)	AndroGel N=104 Mean (SD)
I-PSS Total Score		
Baseline	5.6 (4.83)	4.6 (3.93)
End of study/Early termination	6.9 (5.85)	7.0 (6.31)
Change from baseline	1.0 (4.22)	2.3 (5.07)

[a]I-PSS <7: Mild, 7–19: Moderately symptomatic of benign prostatic hyperplasia (BPH).

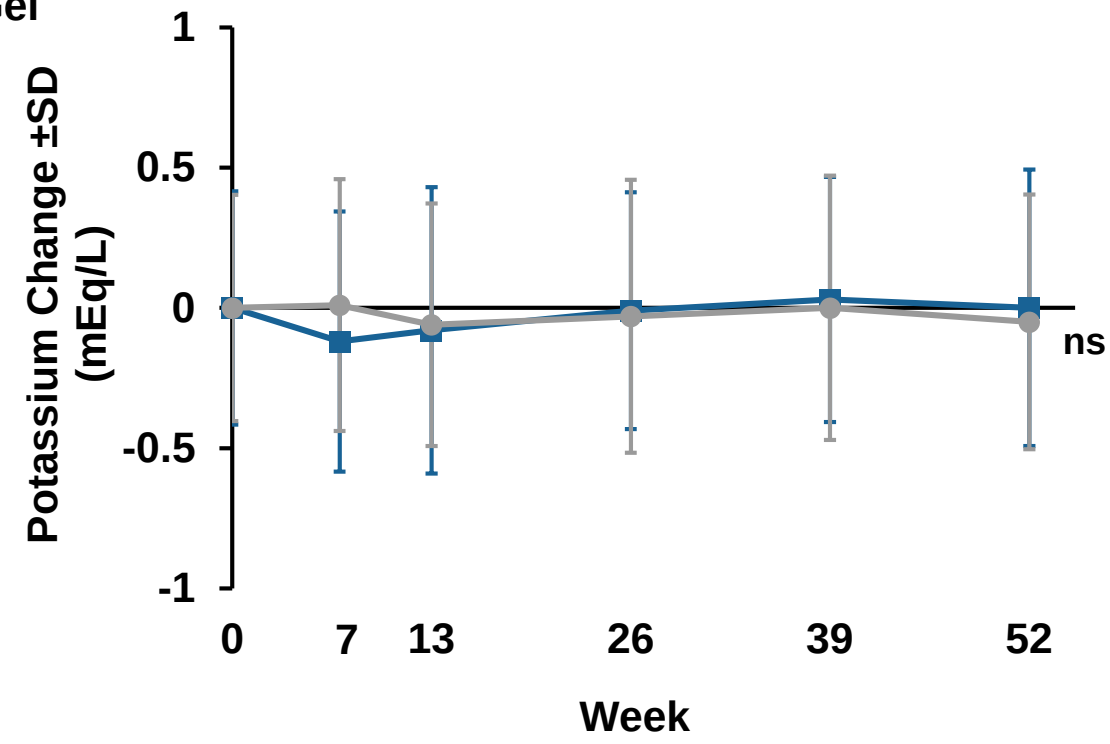
Study 13-001: Sodium and Potassium Levels

Sodium



TLANDO N=	207	179	155	142	135	125
AndroGel N=	104	96	89	82	76	68

Potassium



TLANDO N=	207	175	154	142	134	126
AndroGel N=	104	95	91	82	76	68

ns, not significant (p≥0.05)

T C_{max} and Safety Relevance

- **Time spent with T >1500 ng/dL is brief and often an isolated event**
- **Study 13-001 analyses assessed in TLANDO treated subjects with C_{max} >1500 ng/dL (week 13) vs those with C_{max} ≤1500 ng/dL (week 13)**
  - No impact on the following parameters:
    - » AEs
    - » BP
    - » HDL
    - » Hemoglobin/Hematocrit
    - » PSA

Study 13-001: Results Summary

- **AEs with TLANDO comparable to AndroGel**
- **Cardiovascular events infrequent, balanced between treatment arms**
- **Androgenic events consistent with TRT class**
- **SAEs occurred in 5.7% of TLANDO and 1.9% of AndroGel subjects**
  - None attributed to study drug
- **PSA values with TLANDO within normal range; I-PSS score shows no meaningful change**
- **T C_{max} >1500 ng/dL not associated with an excess of adverse events or excess androgenic effect (HDL, PSA, Hgb/Hct)**

Study 16-002, 16-003: ACTH Stimulation Test

- **68 subjects underwent a ACTH stimulation test at baseline and three weeks after treatment**
  - 62 were normal at baseline and end of study
  - 5 had abnormal ACTH at screening and were uninterpretable
  - 1 was normal at baseline and abnormal at end of study

TLANDO Integrated Safety Experience

- **591 subjects in 12 studies**
  - 66 postmenopausal women
  - 525 hypogonadal men
    - 229 men received TLANDO >4 weeks
    - 130 men received TLANDO for 52 weeks

Integrated Safety Results in 525 Hypogonadal Men

- **Adverse events consistent with class**
- **13 serious adverse events**
  - No drug related SAEs
  - No deaths
  - No DVTs
  - No cardiovascular SAEs (including MACE)
  - No prostate cancer

DVT, deep vein thrombosis; MACE, major adverse cardiac events.

TLANDO™ Safety Summary

- Safety profile well-characterized and demonstrated no unexpected risks
- Overall safety profile comparable to AndroGel
- Changes seen in metabolic parameters consistent with androgenic effects and consistent with that seen with other replacement products
- T C_{max} excursions had no meaningful clinical impact
- Metabolites of testosterone (DHT and E2) were consistent with AndroGel and not associated with safety risks

Sponsor Presentation

Introduction	**Mahesh Patel, PhD** President and CEO, Lipocine
TRT Overview	**Adrian Dobs, MD, MHS** Professor of Medicine, Director, Johns Hopkins Clinical Research Network
Efficacy	**Gary Hoel, RPh, PhD** Clinical Consultant, Lipocine
Safety	**Anthony DelConte, MD** Chief Medical Director, Lipocine
CV Safety	**Peter A. McCullough, MD, MPH** Vice Chief of Medicine and Cardiologist, Baylor University Medical Center
TLANDO in Clinical Practice	**Adrian Dobs, MD, MHS**
Summary	**Anthony DelConte, MD**

Cardiovascular Safety

Peter A. McCullough, MD, MPH

Vice Chief of Medicine and Cardiologist,
Baylor University Medical Center

TRT and Cardiovascular Safety

- **Decades of clinical experience with parenteral, topical, and now oral TRT**
- **Hypogonadal men without TRT have independent increase in CV risk**
- **>600 published articles on hypogonadism, CV risk, TRT**
  - Mixed results demonstrating benefit, neutrality, and harm
- **2014 FDA convened an expert panel and in 2015 reported findings**
  - Possible increased CV risk with TRT
  - Signal is weak
  - Large outcomes trial is needed (currently planned)

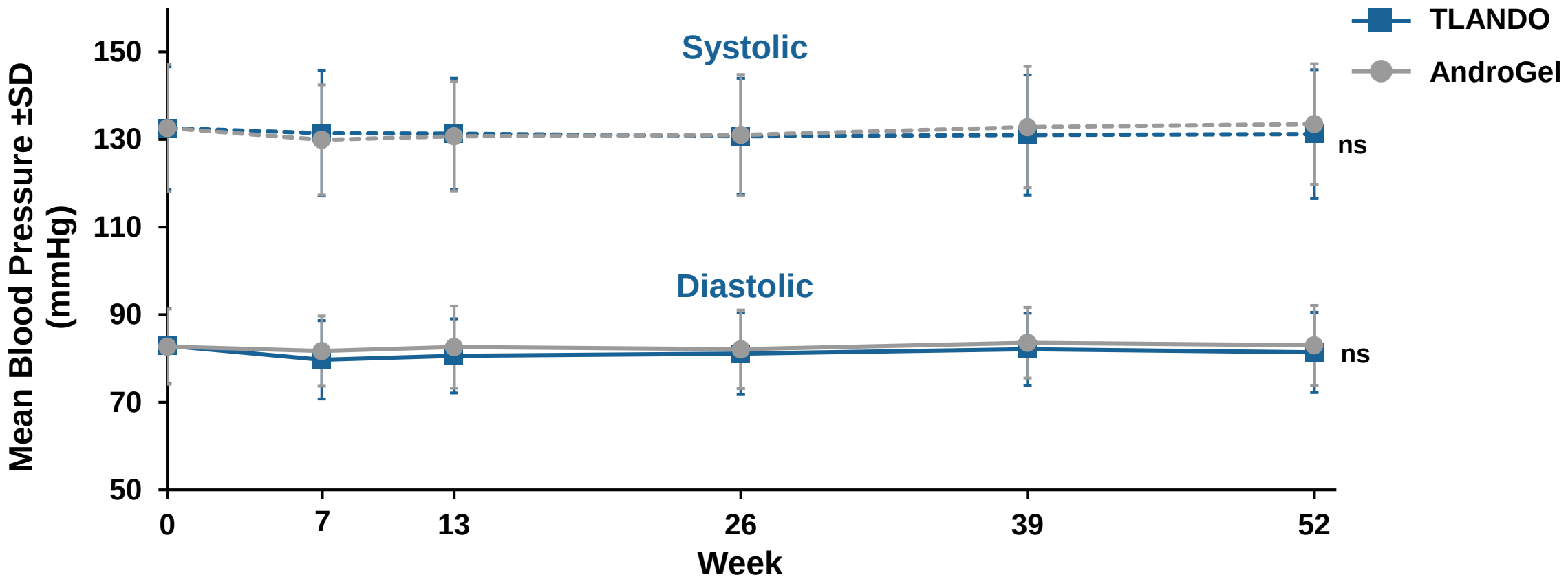
Kloner RA, et al. 3rd. Testosterone and Cardiovascular Disease. *J Am Coll Cardiol*. 2016 Feb 9;67(5):545-57. doi: 10.1016/j.jacc.2015.12.005. Review. PubMed PMID: 26846952.

FDA Evaluating Risk of Stroke, Heart Attack, and Death with FDA-Approved Testosterone Products issued on January 31, 2014. Safety Announcement 03-03-2015

General Overview

- **Recap of cardiovascular (CV) safety events**
  - No deaths
  - No cardiovascular SAEs (no major adverse cardiac events [MACE])
  - No deep venous thromboses or systemic embolism
- **No overall adverse impact on blood pressure**
- **Small, non-significant impact on blood pressure-related medication changes**
- **Expected TRT class changes in lipid values and hemoglobin/hematocrit**
- **No impact on estimated global CV risk (Framingham Score)**

Study 13-001: Mean Group Blood Pressure Baseline to 52 Weeks



TLANDO N=	210	182	157	144	138	130
AndroGel N=	104	97	92	82	76	71

ns, not significant (p≥0.05) between group differences.

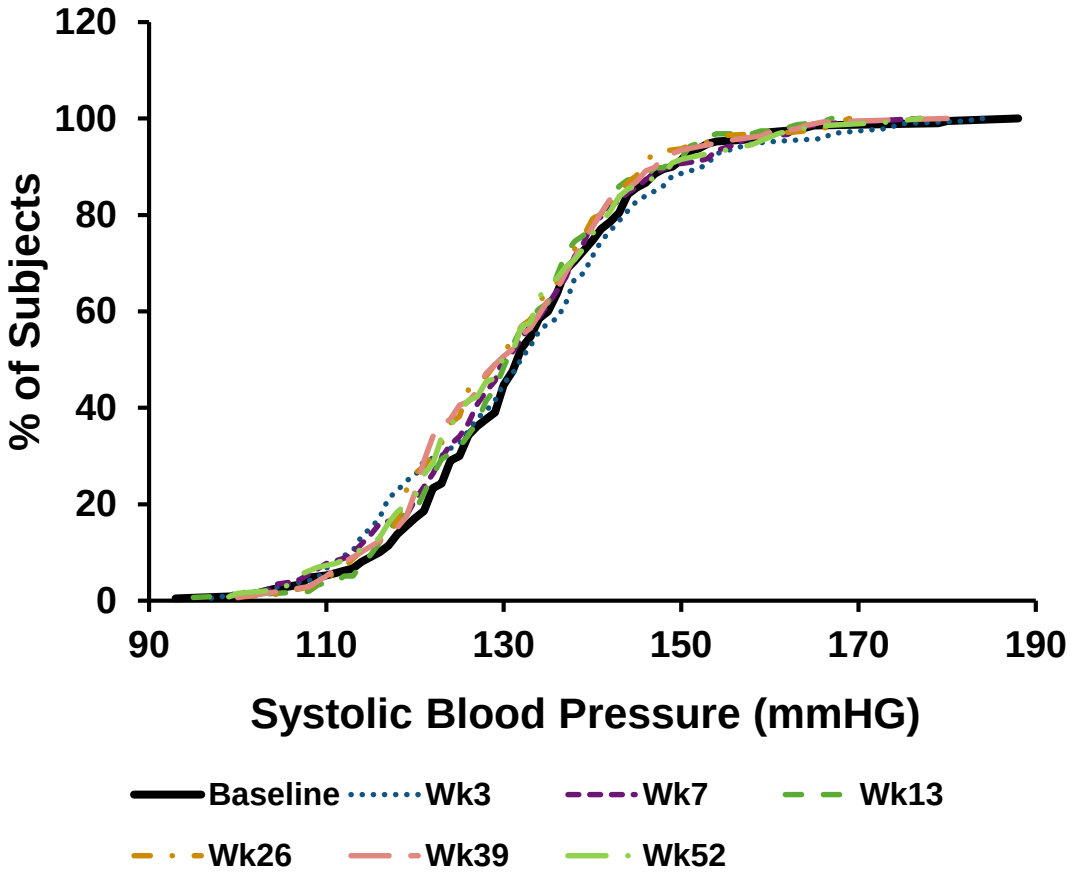
Study 13-001: SBP Within Subject Change from Baseline to End of Study or Early Termination

	TLANDO N=210			AndroGel N=104		
	N	SBP Value Mean ± SD (mmHg)	Intra-individual Change from Baseline Mean ± SD (mmHg)	N	SBP Value Mean ± SD (mmHg)	Intra-individual Change from Baseline Mean ± SD (mmHg)
Baseline	210	133 ± 14		104	133 ± 15	
Week 2				100	132 ± 15	-1.1 ± 12
Week 3	193	133 ± 16	-0.1 ± 13			
Week 4				100	132 ± 14	-0.2 ± 13
Week 7	182	131 ± 14	-0.9 ± 14	97	130 ± 13	-3.1 ± 13[a]
Week 13	157	131 ± 13	-0.8 ± 13	92	131 ± 12	-2.6 ± 12[a]
Week 26	144	131 ± 13	-1.1 ± 13	82	131 ± 14	-2.0 ± 14
Week 39	138	131 ± 14	-0.5 ± 14	76	133 ± 14	-0.7 ± 13
Week 52	130	131 ± 15	-0.3 ± 14	71	134 ± 14	0.0 ± 13
Early Term.	49	130 ± 11	-3.5 ± 12[a]	15	131 ± 12	1.0 ± 15

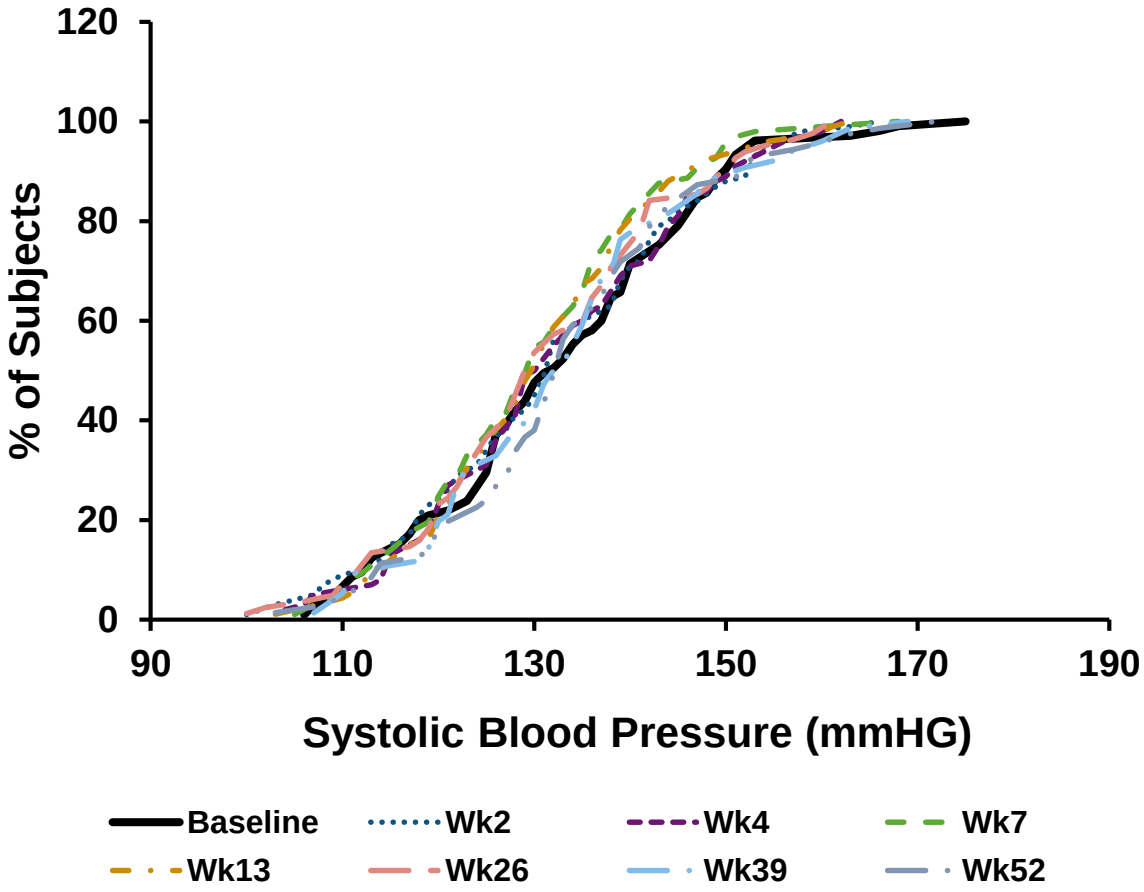
[a]Significant difference within treatment group ($p<0.05$).
No significant differences between treatment groups ($p\geq0.05$).

Study 13-001: SBP Cumulative Frequency Distribution Curves at Each Time Interval of Exposure

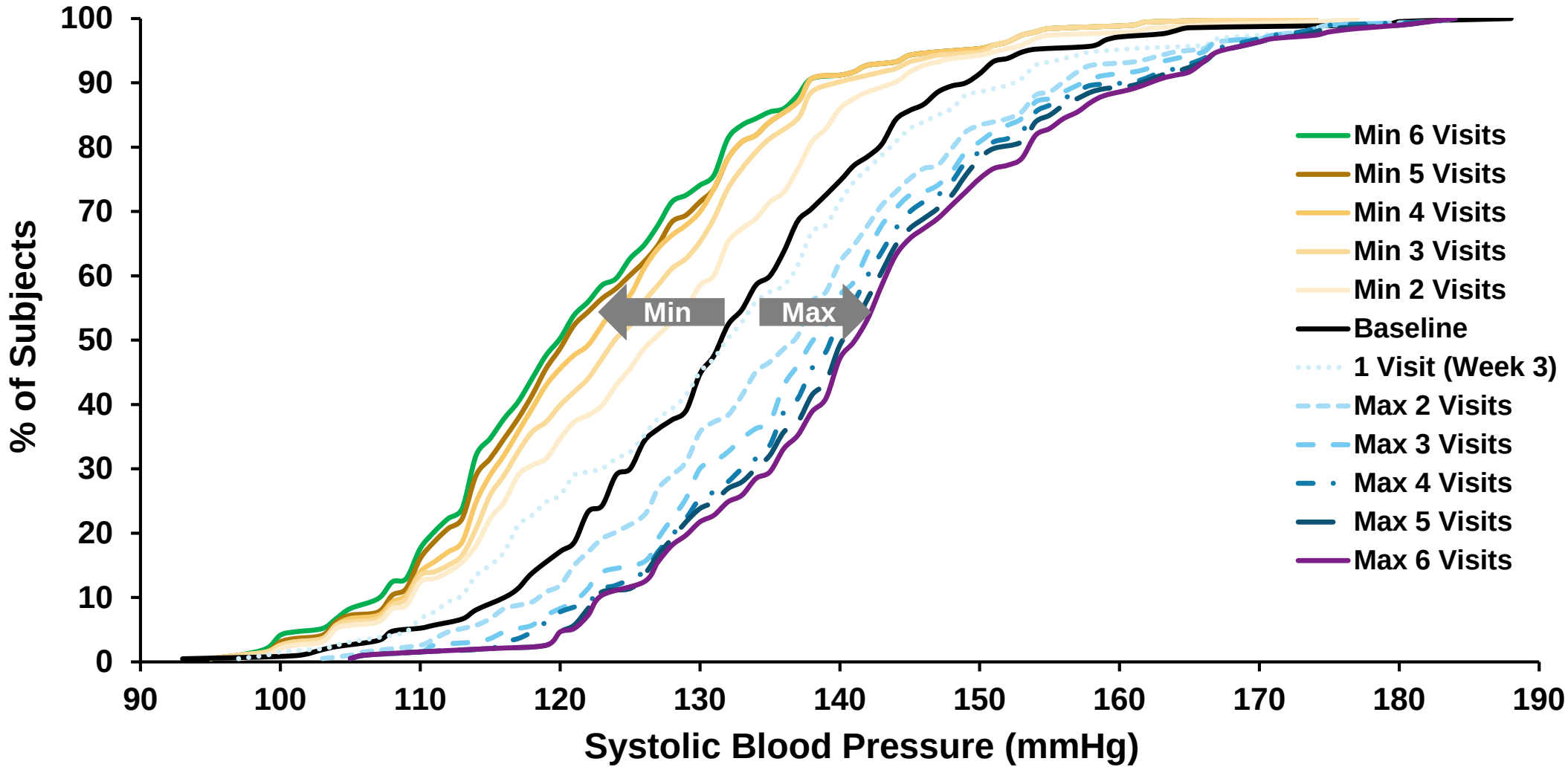
TLANDO



AndroGel



Study 13-001: TLANDO Maximum and Minimum SBP Cumulative Frequency Distribution Curves According to Visits Completed



13-001: Categorical Shift of BP (Baseline to End of Study)

Treatment	End of Study JNC-7 SBP/ DBP Cutoff	Baseline Normal <120 and <80	Prehypertension 120-139 or 80-89	Stage 1 140-159 or 90-99	Stage 2 ≥160 or ≥100
TLANDO (N=179)	**Count**	**20**	**98**	**53**	**8**
	Normal	35 %	20 %	8 %	0 %
	Prehypertension	45 %	58 %	36 %	13 %
	Stage 1 Hypertension	20 %	20 %	53 %	50 %
	Stage 2 Hypertension	0 %	1 %	4 %	38 %
AndroGel 1.62% (N=86)	**Count**	**11**	**44**	**25**	**6**
	Normal	27 %	16 %	0 %	0 %
	Prehypertension	64 %	55 %	40 %	33 %
	Stage 1 Hypertension	9 %	25 %	52 %	33 %
	Stage 2 Hypertension	0 %	5 %	8 %	33 %

Study 13-001: Patients With and Without a History of Hypertension (HTN)

Subjects of Interest	TLANDO N=210 n (%)	AndroGel N=104 n (%)
Baseline diagnosis of HTN or on antihypertensive therapy	100 (47.6)	49 (47.1)
On baseline antihypertensive therapy	86/100 (82.0)	44/49 (89.8)
Increased in antihypertensive dose	2/86 (2.3)	2/44 (4.5)
Without baseline diagnosis of hypertension and not on antihypertensive therapy	110 (52.4)	55 (52.9)
BP >150/90 mmHg ≥2 measurements on study drug[a]	3/110 (2.7)	3/55 (5.5)
Initiation of antihypertensive therapy	0	0

[a]JNC 8 *JAMA*. 2014;311(5):507-520. doi:10.1001/jama.2013.284427 Published online December 18, 2013.

Study 16-002: Systolic and Diastolic Blood Pressure

- **TLANDO 225 mg BID (24 days)**
  - Single arm study
  - Morning blood pressure measurement

Visit	N	Systolic Blood Pressure (mmHg) Mean ± SD		Diastolic Blood Pressure (mmHg) Mean ± SD	
		Value	Intra-individual Change from Baseline	Value	Intra-individual Change from Baseline
Baseline[a]	95	130 ± 14		80 ± 10	
Day 24[b]	94	130 ± 12[c]	-0.5 ± 14	80 ± 9[c]	-1.0 ± 8.0
Day 25[b]	94	130 ± 14[c]	0.2 ± 14	81 ± 9[c]	0.1 ± 8.1

[a]Measured in clinic; [b]Measured during confinement. [c]ns, not significant (p≥0.05)

Study 16-003: Systolic and Diastolic Blood Pressure

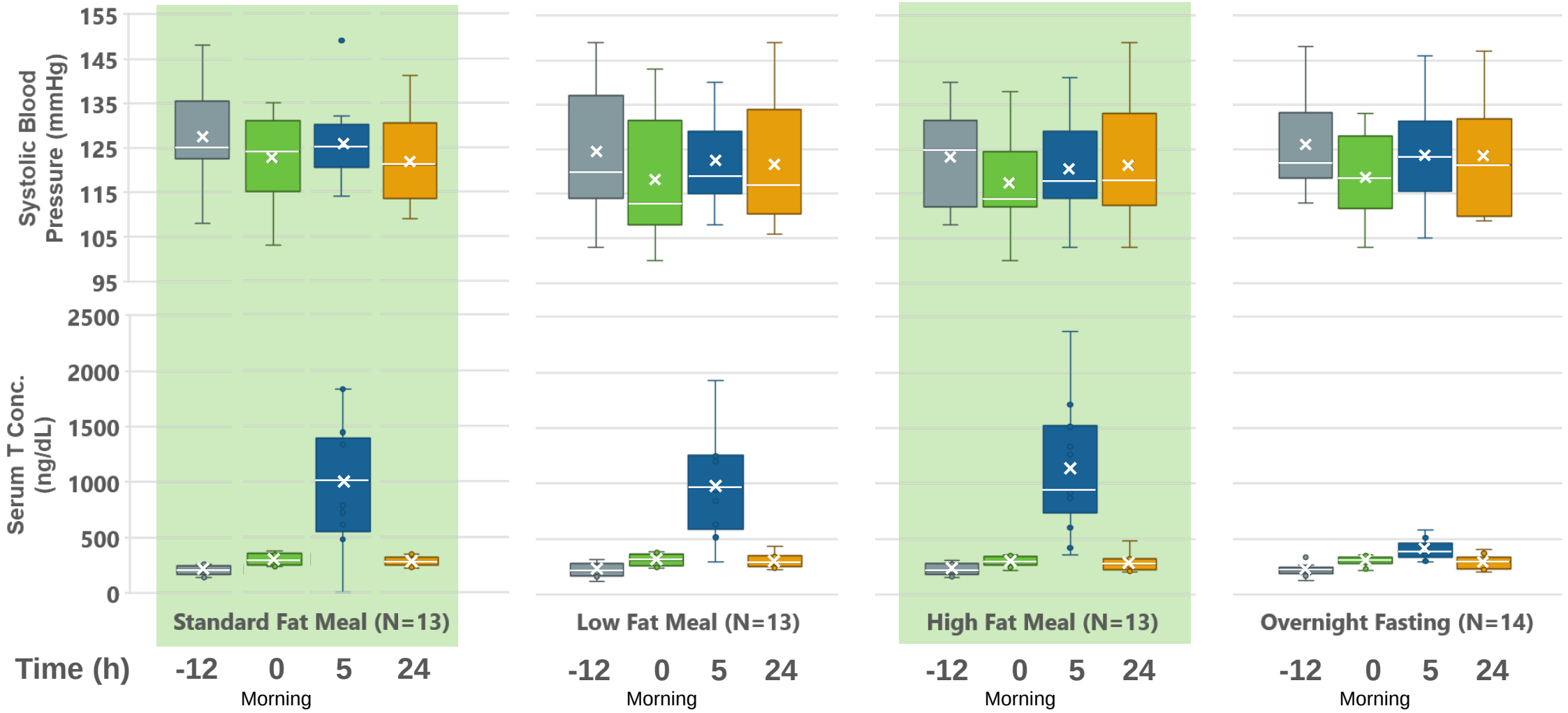
- **TLANDO 150 mg TID (24 days)**
  - Single arm study
  - Baseline blood pressures measured in the morning
  - Day 24 and 25 blood pressures measured mid-day

Visit	N	Systolic Blood Pressure (mmHg) Mean ± SD		Diastolic Blood Pressure (mmHg) Mean ± SD	
		Value	Intra-individual Change from Baseline	Value	Intra-individual Change from Baseline
Baseline[a]	100	129 ± 13		81 ± 9	
Day 24[b]	98	133 ± 14[c]	4.1 ± 13	81 ± 9[d]	-0.3 ± 8
Day 25[b]	98	133 ± 13[c]	4.3 ± 12	81 ± 9[d]	0.0 ± 8

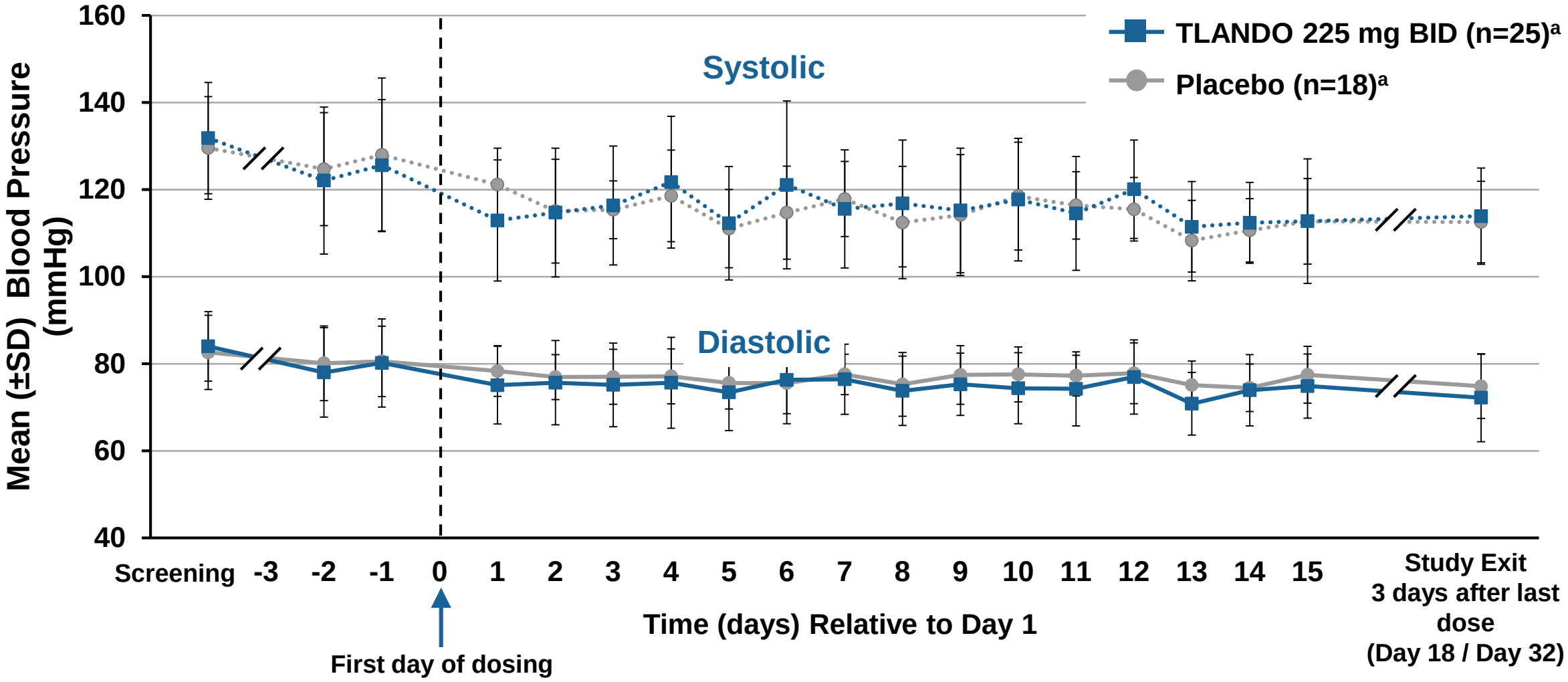
[a]Measured in clinic; [b]Measured during confinement. [c]significant ($p<0.05$); [d]ns, not significant ($p\geq0.05$) .

Study 14-001: Multiple BP Measurements Over 24 Hours after Single Dose TLANDO 225 mg

Randomized crossover trial, hypogonadal men in confinement, study of food-fat effect, 3 day washouts



Double-Blind RCT (M12-778): TLANDO vs Placebo



[a]One subject in placebo discontinued after Day 11 and one subject in TLANDO 225 mg treatment arm discontinued after Day 7.

Key Observations: TLANDO and Blood Pressure

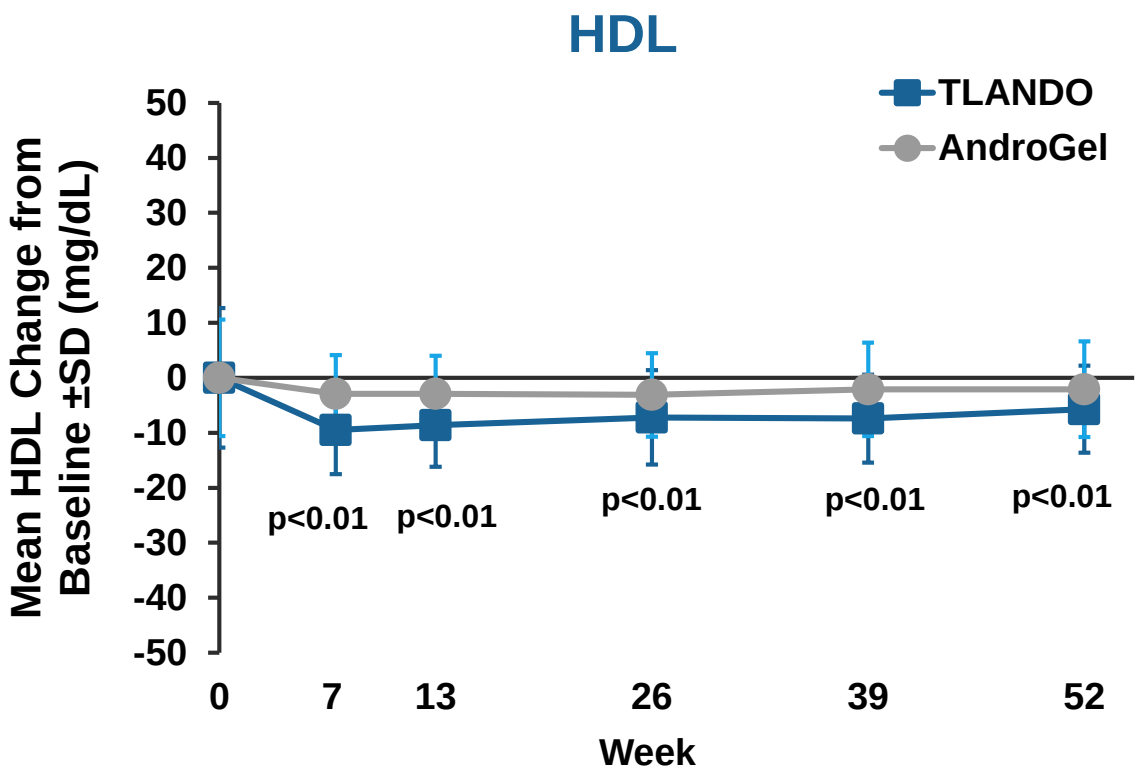
- **Overall, no adverse impact on blood pressure seen with TLANDO up to 52 weeks**
  - Mean, change from baseline, minimum, maximum, cumulative frequency distribution, daily, over 24 hours
  - Single arm, active control AndroGel, and placebo controlled trials
  - No bias due to dropout rate
- **No increase in BP at serum T C_{max} with single dose TLANDO 225 mg over 24 hours**
- **No study discontinuations related to blood pressure/management**
- **Changes in antihypertensive therapy were uncommon**
- **Low rates of new HTN (2.7% TLANDO, 5.5% AndroGel) among subjects without HTN at baseline, no treatment was initiated in either group**
- **From these observations, an ambulatory blood pressure study is not necessary**

Study 13-001: Mean Pulse Rate Change from Baseline to 52 Weeks

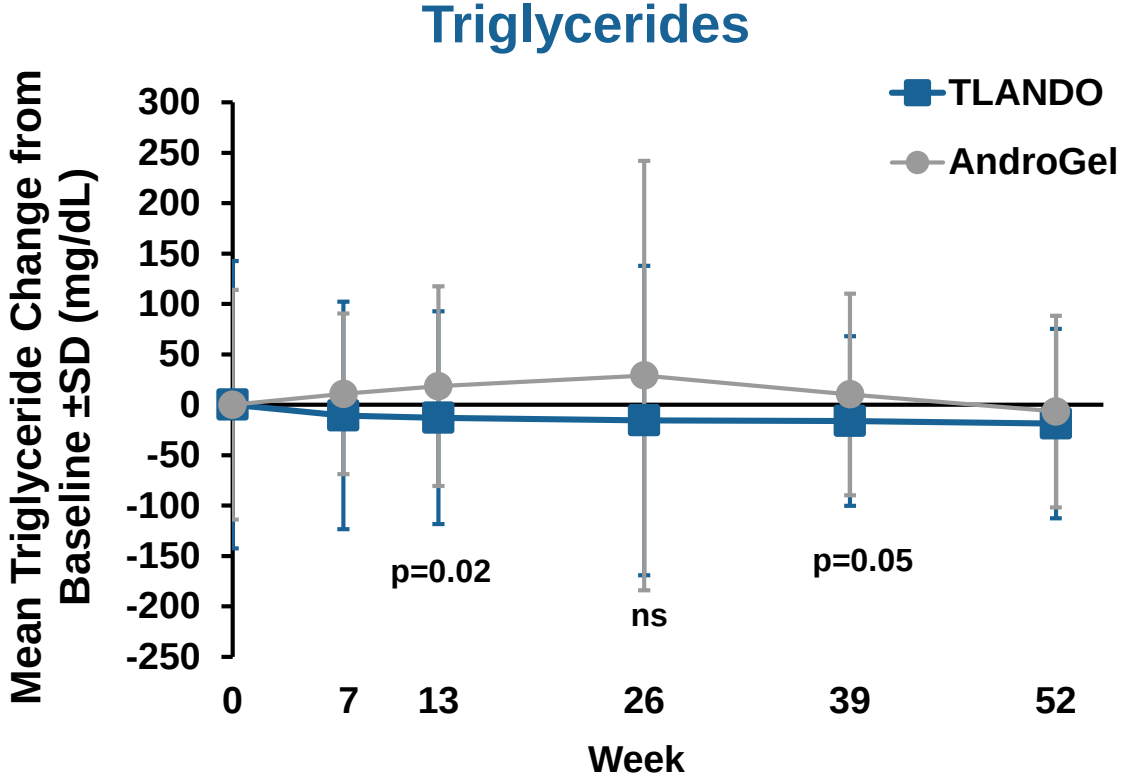
Visit	TLANDO N=210				AndroGel N=104				Between Arms P-value
		Mean ± SD (beats/min)				Mean ± SD (beats/min)			
	N	Pulse Rate	Intra-individual Change from Baseline	P-value for Change	N	Pulse Rate	Intra-individual Change from Baseline	P-value for Change	
Baseline	210	71 ± 10			104	69 ± 11			
Week 2					99	73 ± 11	3.7 ± 9	<0.0001	
Week 3	193	72 ± 10	1.8 ± 9	0.0007					
Week 4					100	73 ± 11	4.1 ± 10	<0.0001	
Week 7	182	73 ± 12	2.0 ± 9	0.0002	97	72 ± 11	3.4 ± 9	<0.0001	ns
Week 13	157	73 ± 12	2.6 ± 10	<0.0001	92	73 ± 11	4.7 ± 12	<0.0001	ns
Week 26	144	73 ± 11	2.6 ± 9	<0.0001	82	72[a] ± 11	3.1 ± 10	0.0011	ns
Week 39	138	74 ± 11	3.3 ± 9	<0.0001	76	71[a] ± 11	3.1 ± 10	0.0016	ns
Week 52	130	73 ± 11	2.1 ± 10	0.0006	71	70[a] ± 9	1.4 ± 9	ns	ns
Early Term.	49	74 ± 9	2.3 ± 8	0.0146	15	72[a] ± 15	1.5 ± 12	ns	ns

[a]ns, not significant (p≥0.05)

Study 13-001: High Density Lipoprotein and Triglycerides



TLANDO N=	207	182	157	144	138	128
AndroGel N=	104	96	91	82	76	68

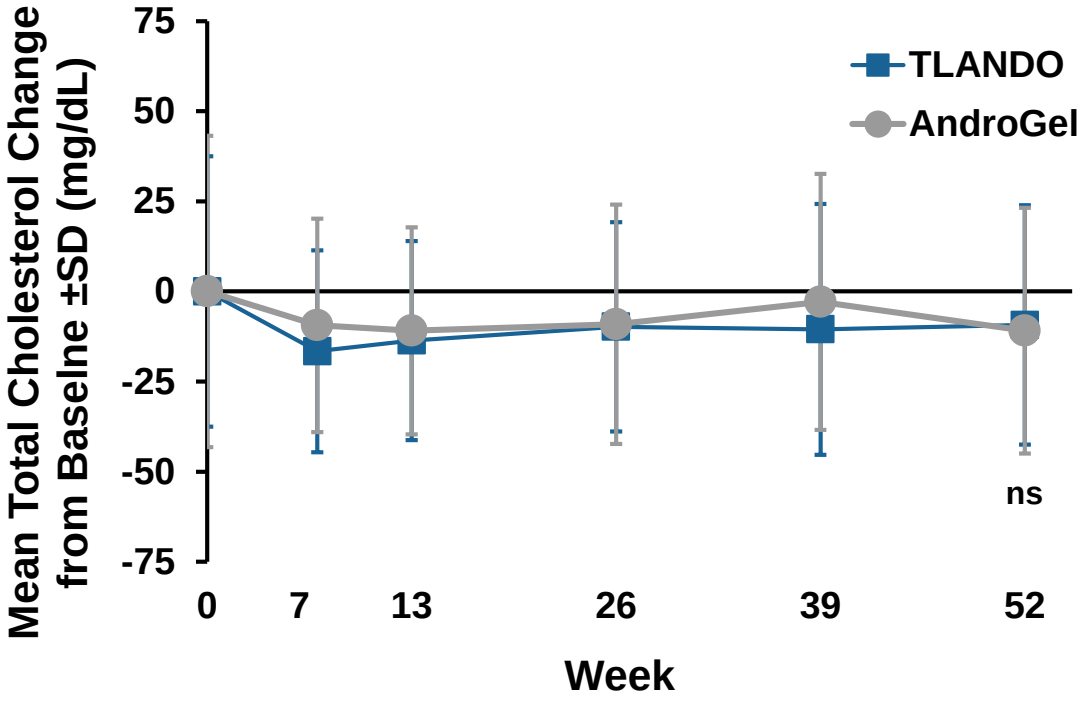


TLANDO N=	207	182	157	144	137	128
AndroGel N=	104	96	91	82	76	68

ns, not significant (p≥0.05) between group differences.

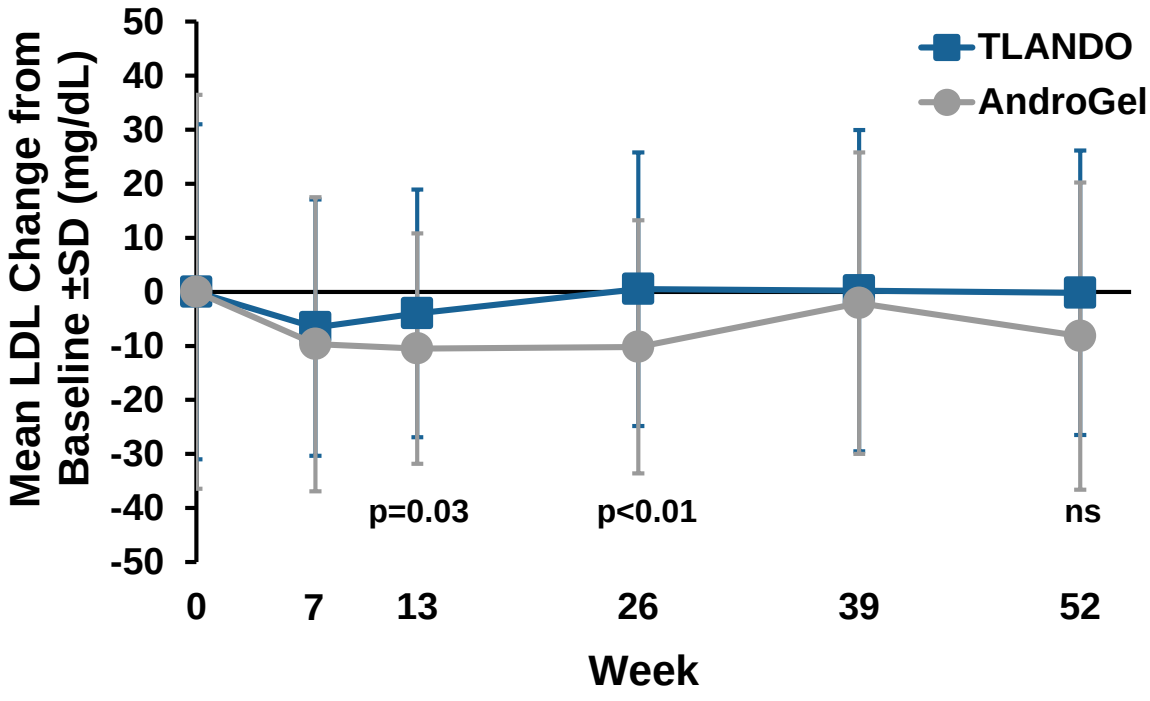
Study 13-001: Total Cholesterol and LDL Cholesterol

Total Cholesterol



TLANDO N=	207	182	157	144	137	129
AndroGel N=	104	96	91	82	76	69

LDL



TLANDO N=	194	175	150	140	134	124
AndroGel N=	97	90	81	77	70	64

ns, not significant (p≥0.05) between group differences.

Study 13-001: Framingham Risk Score (Baseline to End of Study)

	TLANDO			AndroGel		
	Baseline	End of Study	Intra-individual Change from Baseline	Baseline	End of Study	Intra-individual Change from Baseline
N	207	177	175	104	82	82
Mean % ± SD	15.3 ± 10.4	16.0 ± 10.6	0.3 ± 4.5	18.2 ± 12.4	19.4 ± 12.5	-0.1 ± 6.1
Median %	13.4	13.8	0.3	16.1	18.3	-0.2
P-value	ns			ns		

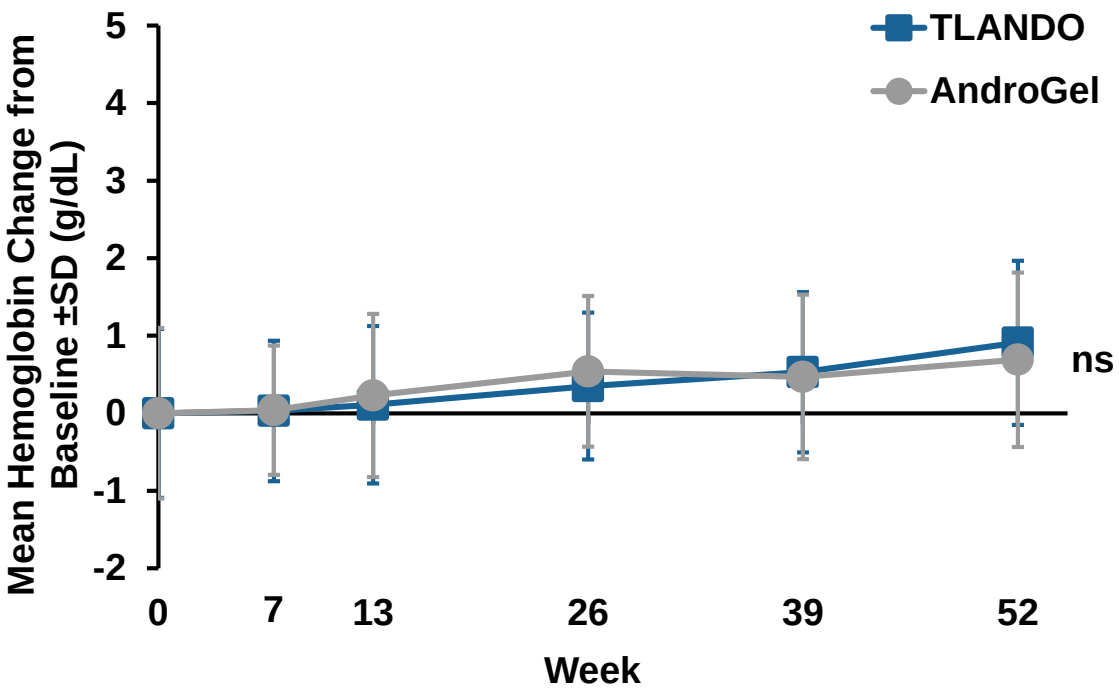
ns, not significant (p≥0.05) within group differences.

- **10 year risk (%) of coronary heart disease event for men based on variables of age, diabetes, smoking, blood pressure, total cholesterol, HDL cholesterol**

Wilson PW, et al, (12 May 1998). Prediction of coronary heart disease using risk factor categories. *Circulation*. 97 (18): 1837–1847.

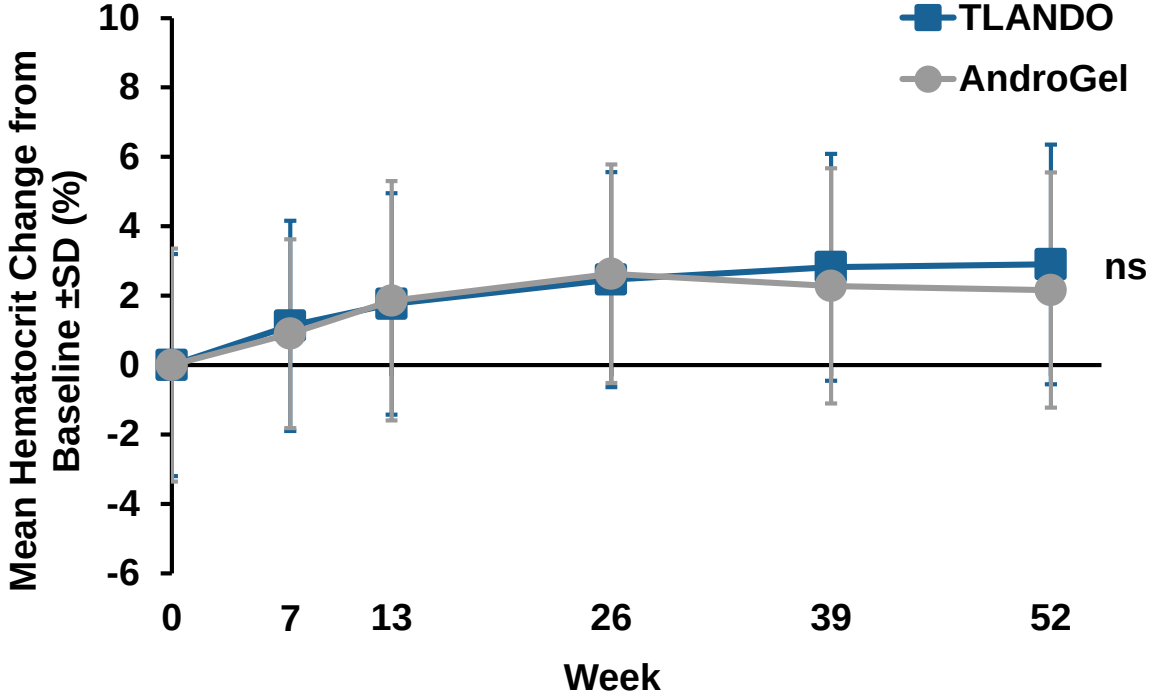
Study 13-001: Hematology Labs

Hemoglobin



TLANDO N=	206	177	155	144	137	128
AndroGel N=	103	96	91	81	76	67

Hematocrit



TLANDO N=	206	177	155	144	137	128
AndroGel N=	103	96	91	81	76	67

ns, not significant (p≥0.05) between group differences.

Study 13-001: Hematocrit Values – Subjects Meeting Various Thresholds

Hematocrit Value	TLANDO N=210 n (%)	AndroGel N=104 n (%)
Anytime During the Study		
≥ 50%	51 (24.3)	28 (26.9)
≥ 51%	37 (17.6)	21 (20.2)
≥ 54%	8[a] (3.8)	1[a] (1.0)

[a]3 TLANDO subjects and 1 AndroGel subject discontinued due to hematocrit elevation.

Summary of TLANDO and Cardiovascular Risk

- No overall adverse impact on blood pressure
- No new cases of hypertension requiring treatment through 52 weeks
- Small increase in pulse in both TLANDO and AndroGel
- Minor expected TRT effects on lipid values – no increase in LDL
- Expected TRT effect on hemoglobin and hematocrit
- No meaningful impact on global CV risk (Framingham)

Sponsor Presentation

Introduction	**Mahesh Patel, PhD** President and CEO, Lipocine
TRT Overview	**Adrian Dobs, MD, MHS** Professor of Medicine, Director, Johns Hopkins Clinical Research Network
Efficacy	**Gary Hoel, RPh, PhD** Clinical Consultant, Lipocine
Safety	**Anthony DelConte, MD** Chief Medical Director, Lipocine
CV Safety	**Peter A. McCullough, MD, MPH** Vice Chief of Medicine and Cardiologist, Baylor University Medical Center
TLANDO in Clinical Practice	**Adrian Dobs, MD, MHS**
Summary	**Anthony DelConte, MD**

TLANDO in Clinical Practice

Adrian S. Dobs, MD, MHS

Professor of Medicine and Oncology
The Johns Hopkins University School of Medicine
Division of Endocrinology, Diabetes and Metabolism

TLANDO: A Clinician's Perspective

- Dose/regimen adequately explored and is efficacy established?
- Safety concerns?
- Easy for patients to take?
- Appropriate monitoring guidelines?
- Benefits outweigh the risks?

TLANDO 225 mg BID
Has efficacy been established?

- **Three trials demonstrate efficacy**
  - Several studies indicating 225 mg BID as a fixed dose
  - C_{avg} within normal range in approximately 80% of patients
  - Symptoms improved – SF-36, PDQ
- **Effects on hormones and other labs are consistent with other TRTs**
  - Hormones – FSH, LH, DHT, E2
  - Lab Parameters – Hgb, Hct, lipids, PSA

SF-36, 36 Item Short Form Survey; PDQ, Psychosexual Daily Questionnaire.

Safety – Estradiol

- **Increases in estradiol occur normally with increases in T**
- **Not correlated with AEs**
- **Serum levels similar to AndroGel and other TRT products (normal: 10-42 pg/mL)**

	TLANDO	AndroGel 1.62%	Aveed[c]	Fortesta[c]	Natesto[c]
Reported Estradiol (pg/mL), mean	29[a] 24.0[b]	27.6[b]	14 – 36	32 – 34	27

[a] E2 C_{avg} obtained from 24-day 16-002 study.
[b] E2 conc. obtained from 52 week end of study in 13-001 study.
[c] E2 conc. values were obtained from NDA of the product.

Safety-Dihydrotestosterone (DHT)

- **Literature findings:**
  - Restoration of T causes increased DHT levels (normal: 10.6–71.9 ng/dL)
  - Intraprostatic concentrations do not correlate with serum levels
  - Administration of DHT gel in Europe showed no safety concerns
- **Serum levels with TLANDO were similar to Androgel and other TRT**
  - No correlation with AEs

	TLANDO	AndroGel 1.62%	Axiron[c] (Day 60 – 120)
Reported DHT (ng/dL), mean	108[a] 92[b]	87[b]	96.2 – 98.7

[a] DHT C_{avg} obtained from 24-day 16-002 study.
[b] DHT conc. obtained from 52 week end of study in 13-001 study
[c] DHT conc. values were obtained from NDA on the product.

Safety – Adrenal Function

- **68 subjects underwent a ACTH stimulation test at baseline and three weeks after treatment (Studies 16-002, 16-003)**
  - 62 were normal at baseline and end of study
  - 5 had abnormal ACTH at screening and were uninterpretable
  - 1 was normal at baseline and abnormal at end of study
- **No AEs suggestive of adrenal insufficiency over 52 weeks exposure (Study 13-001)**
- **Potassium and sodium levels were stable over 52 weeks and there was no evidence of hypotension observed (Study 13-001)**
- **No adrenal concerns have been raised with TRT after decades of use**

Other Safety Parameters

- **Overall AE profile comparable to AndroGel**
- **Hepatic**
  - No hepatic signals seen
- **CV**
  - No CV safety signals seen
- **Lipids**
  - Slightly lower HDL vs AndroGel
- **Hgb/Hct**
  - Increases similar to AndroGel and consistent with the class
- **PSA**
  - PSA changes similar to AndroGel and consistent with the class

Is TLANDO easy for patients to take?

- Oral therapy
- BID dosing
- Fixed dose requires no titration
- Taken with food without regard to fat content

Are the commonly recommended monitoring guidelines appropriate?

- **Standard clinical testosterone measurements used**
- **Monitoring for symptoms and safety labs are consistent with recommended guidelines**
  - Lipids, PSA, Hgb/Hct
- **TLANDO specific recommendation**
  - Testosterone measurement between 7–9 hr post-morning dose
  - If the level is high or low, recommend at least one additional sample to confirm

Do benefits outweigh the risks?

Benefits	Risks
▪ Restoration of testosterone levels ▪ Symptoms improved ▪ Oral administration ▪ No titration required ▪ Avoids risks of injectable and topical TRT	▪ Well established and monitorable class effects • Hgb/Hct • Lipids • PSA

Sponsor Presentation

Introduction	**Mahesh Patel, PhD** President and CEO, Lipocine
TRT Overview	**Adrian Dobs, MD, MHS** Professor of Medicine, Director, Johns Hopkins Clinical Research Network
Efficacy	**Gary Hoel, RPh, PhD** Clinical Consultant, Lipocine
Safety	**Anthony DelConte, MD** Chief Medical Director, Lipocine
CV Safety	**Peter A. McCullough, MD, MPH** Vice Chief of Medicine and Cardiologist, Baylor University Medical Center
TLANDO in Clinical Practice	**Adrian Dobs, MD, MHS**
Summary	**Anthony DelConte, MD**

Summary

Anthony DelConte, MD

Chief Medical Director, Lipocine

TLANDO Program: Key Findings

- **Fixed dose 225 mg BID, no titration required**
- **Standard serum tubes**
- **Safety**
  - No signal for GI concerns
  - No adverse impact on blood pressure
  - No deaths or MACE events
  - HDL lowering, no effect on total cholesterol, LDL, or TG
  - No signal for adrenal insufficiency

TLANDO Summary

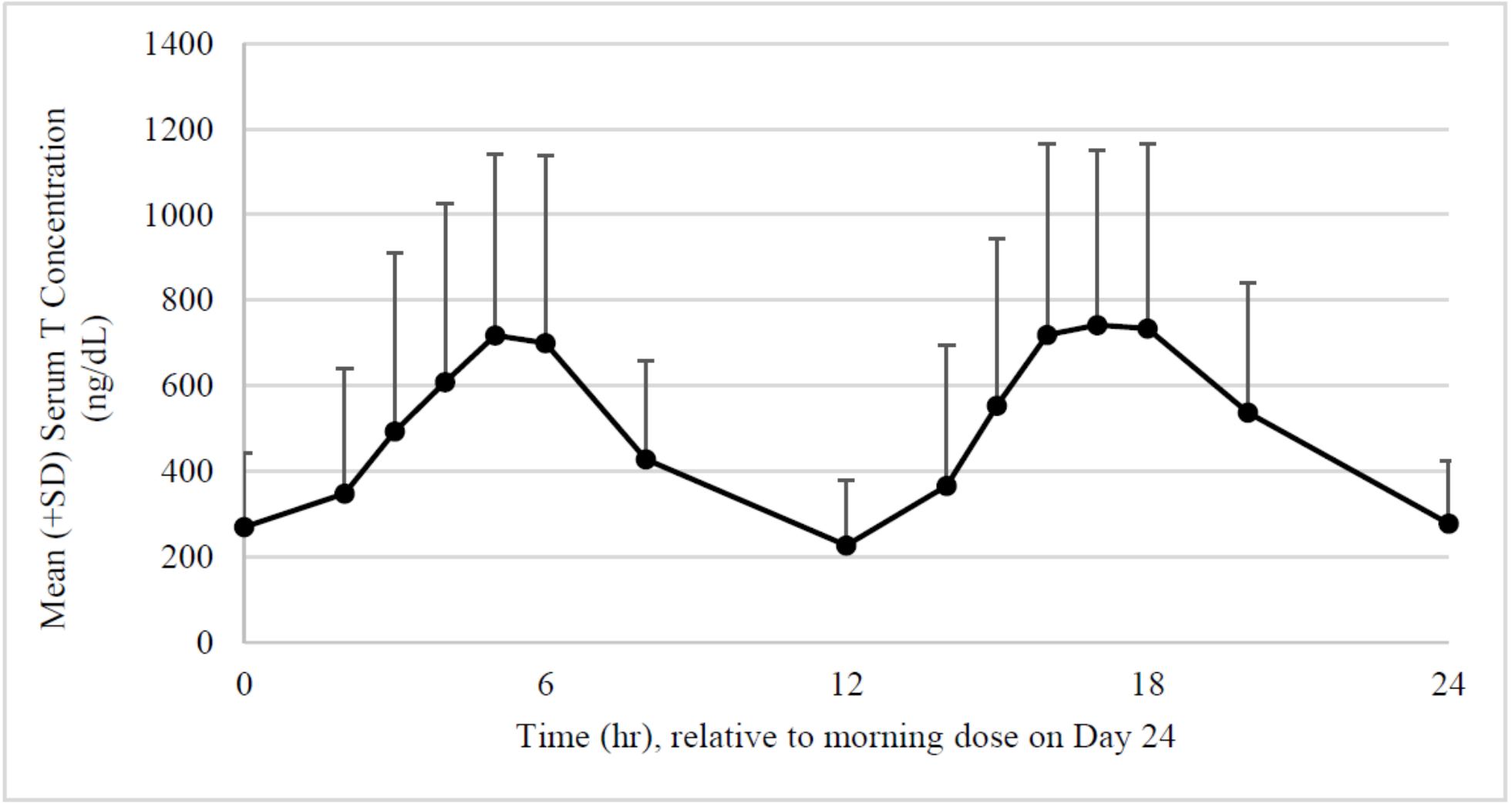
- Clinical program demonstrated efficacy of 225 mg BID fixed dose
- Safety of TLANDO has been adequately characterized
- Monitoring criteria in clinical practice identifies patients who should continue therapy
- Proposed indication follows the class of TRT products
- TLANDO fulfills unmet need for an oral treatment option for hypogonadal patients who require TRT
- Overall benefit/risk profile of TLANDO supports approval

Backups Shown

T10 pg. 34. Dose Distribution of TLANDO

Visit	Number of Subjects			
	150 mg TU twice daily	225 mg TU twice daily	300 mg TU twice daily	Total
Week 3	0	193	0	193
Week 7	51	105	26	182
Week 13	50	82	25	157

F4. pg 48. Mean (SD) Serum T Concentration (ng/mL) over Time on Day 24 – PK Set (N = 90)

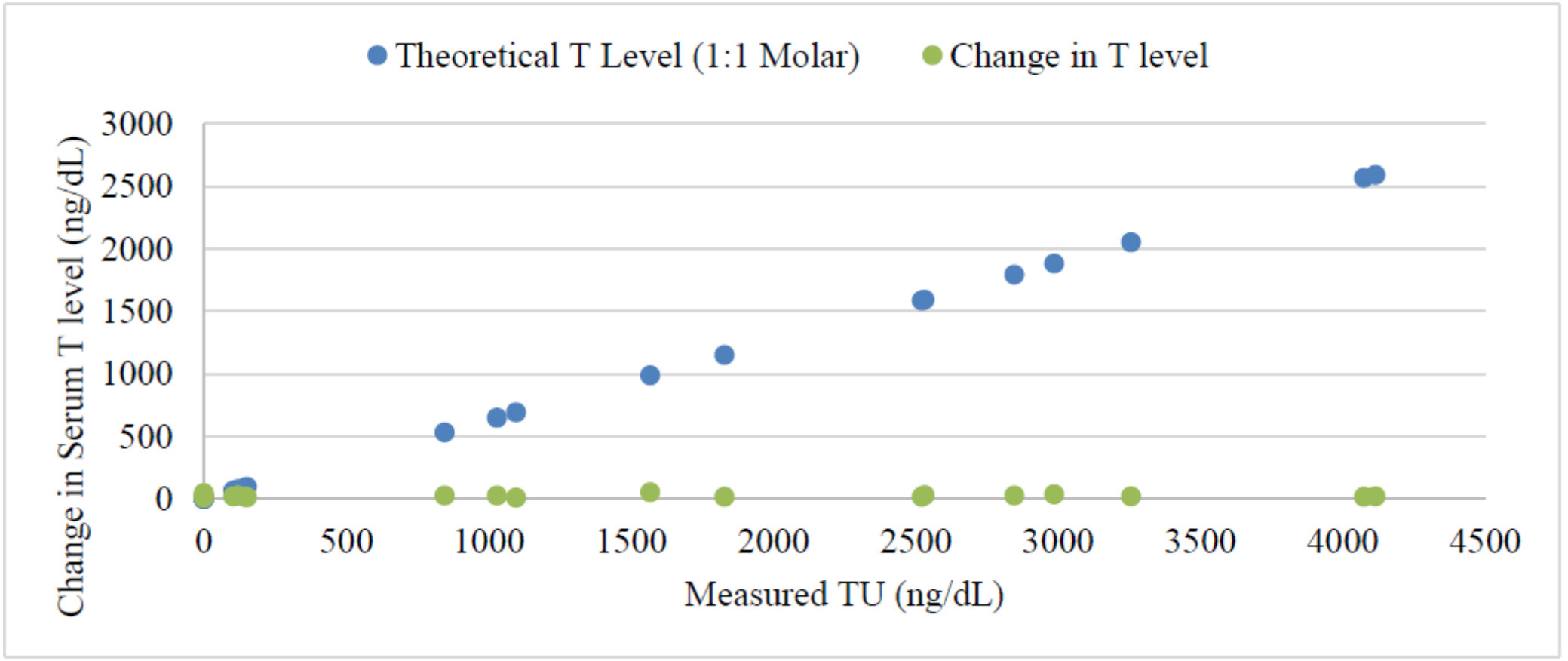


T79. Discontinuation Criteria Applied to Study 16-002 and Study 13-001

	Criteria: 300 – 1080 ng/dL Between 7 and 9 Hrs Post AM Dosing*	
	Study 16-002 Efficacy assessment (225 mg twice daily)	Study 13-001 Week 3 PK data (225 mg twice daily)
Total N	94	193
Total number of subjects with Cavg< 300 ng/dL	18	24
Subjects with Cavg < 300 ng/dL who are identified using proposed criteria	14	20
Total number of subjects with Cavg> 1080 ng/dL	0	4
Subjects with Cavg > 1080 ng/dL who are identified using proposed criteria	-	4

* Results based on 8 hours post AM dosing data.

F17. pg 109. Measured and Theoretical Change in Serum T Levels (ng/dL) as a Function of Increasing TU Levels (ng/dL) (1:1 Molar TU to T)



Recovery of TU From Spiked Whole Blood Samples

Spiked Solution TU Concentration (ng/mL)	Projected Whole Blood TU Concentration* (ng/mL)	Measured TU (ng/mL)			
		Donor 1	Donor 2	Donor 3	Donor 4
0	0	0	0	0	0
100	5	1.04	1.52	1.2	1.45
1,000	50	15.68	10.29	8.46	10.96
3,333	166.5	18.29	29.87	25.31	28.47
8,500	425	25.21	40.75	32.57	41.16

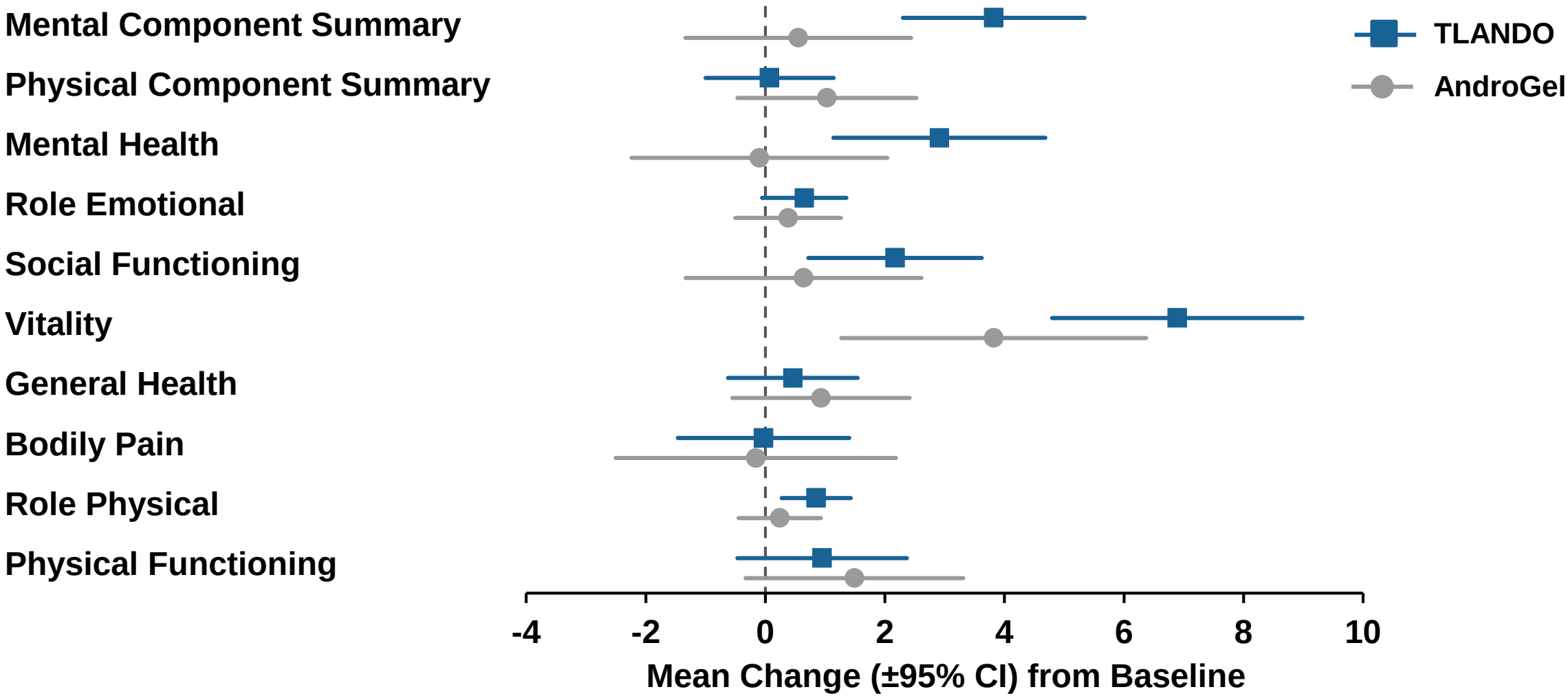
- **Approximately 4 mL of whole blood collected and spiked with about 0.2 mL of PBS/ ethanolic solution of TU**
- **Project whole blood concentration based on the volume of spiking solution and blood.**
- **Projected Serum TU concentration were not estimated due to unknown values of RBC partitioning, clot matrix effects and hematocrit levels in the donors**
- **Solubility and stability in the spiking solution evaluated for up to 6 hours at room temperature**

No Cross-Reactivity of TU in Total T Measurement by Radio Immuno Assay (RIA)

- No cross-reactivity of TU in measurements of serum T in Radio Immuno Assay
- Serum samples fortified with TU (20 to 2000 ng/mL) and DHTU (10 to 1000 ng/dL)
- Fortified and unfortified (control) samples analyzed for T on Siemens Centaur XP

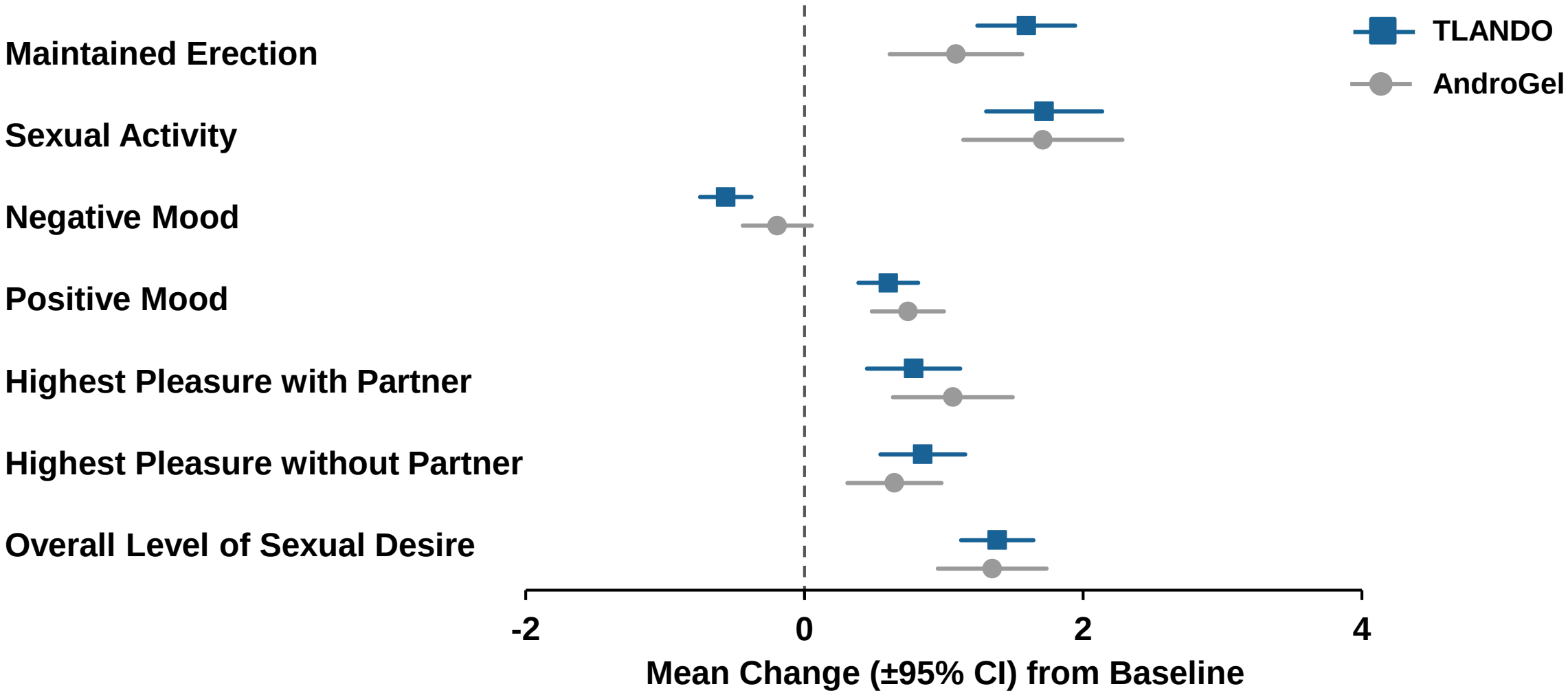
TU Concentration (ng/mL)	20	100	500	1000	2000
DHTU Concentration (ng/mL)	10	50	200	500	1000
	Mean Total Testosterone Concentration (ng/dL)				
Unfortified Sample (N=2)	388.95	377.17	511.95	471.30	307.37
Fortified Sample (N=2)	382.48	413.59	473.70	452.43	322.51
Relative % Difference	-1.68 %	9.21 %	-7.76%	-4.08 %	4.81 %

Study 13-001: SF-36 Score - Change from Baseline to End of Study



SF-36, Short Form-36

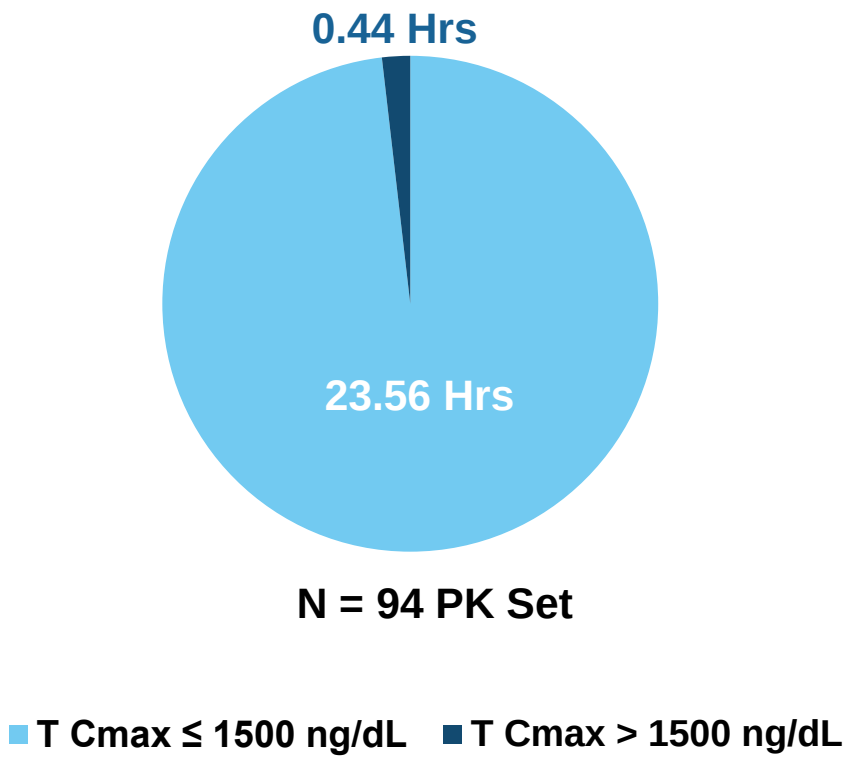
Study 13-001: PDQ Score - Change from Baseline to End of Study



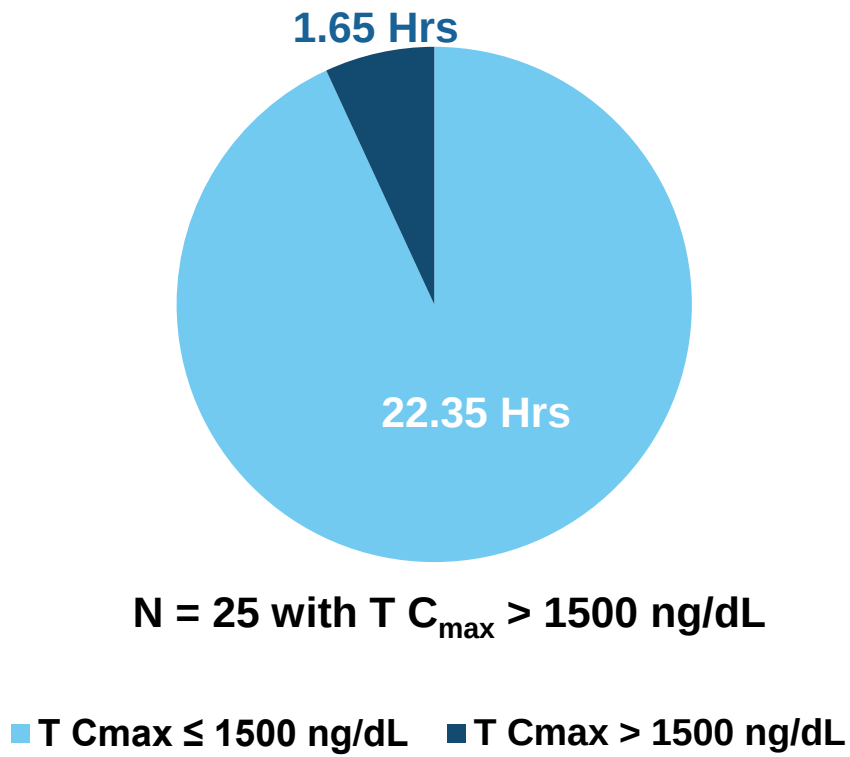
PDQ, Psychosexual Daily Questionnaire

Study 16-002: TLANDO: Exposure Times at Different T Categories

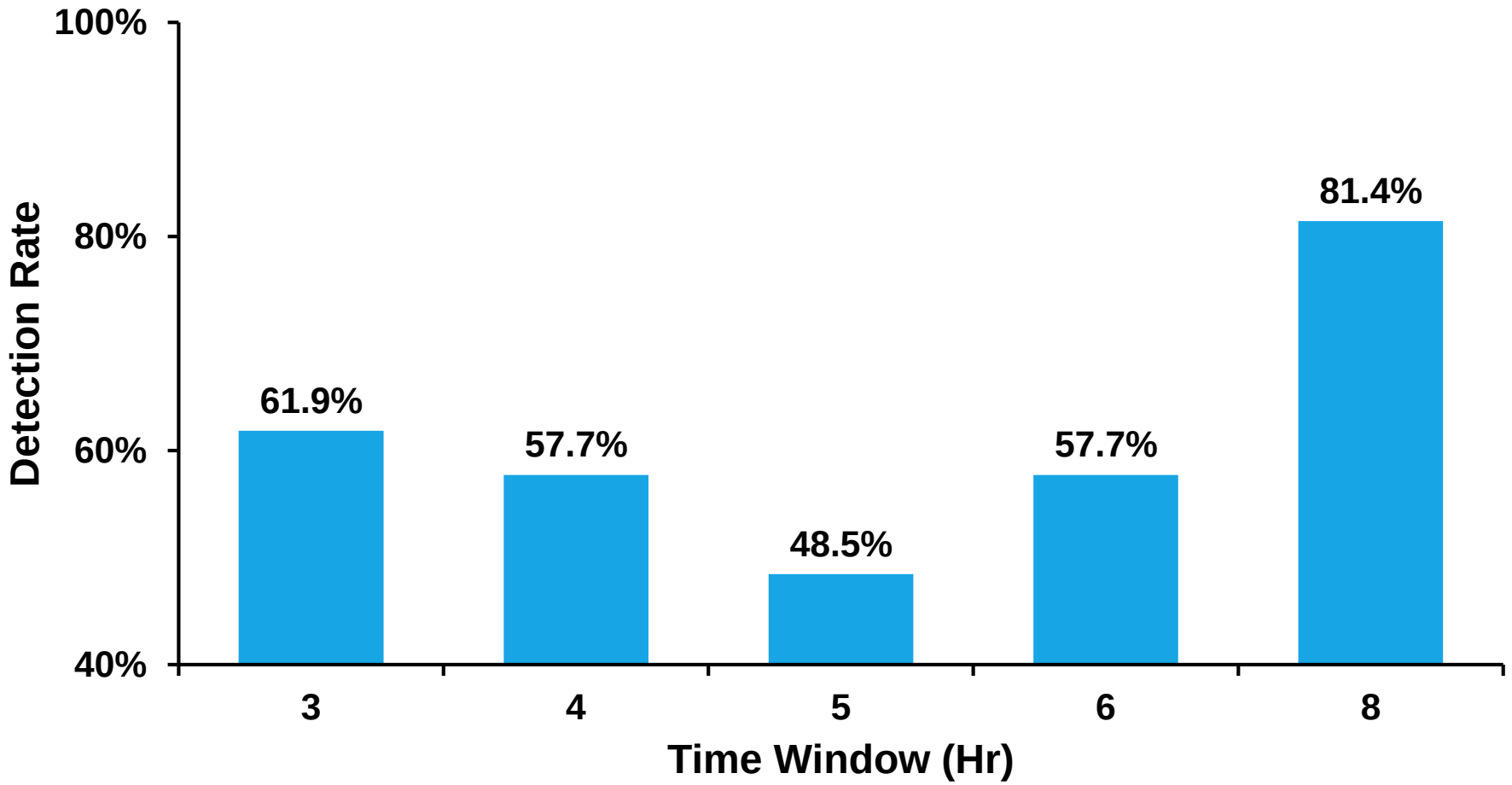
Time Spent a Day by C_{max} Threshold



Time Spent a day by C_{max} Threshold

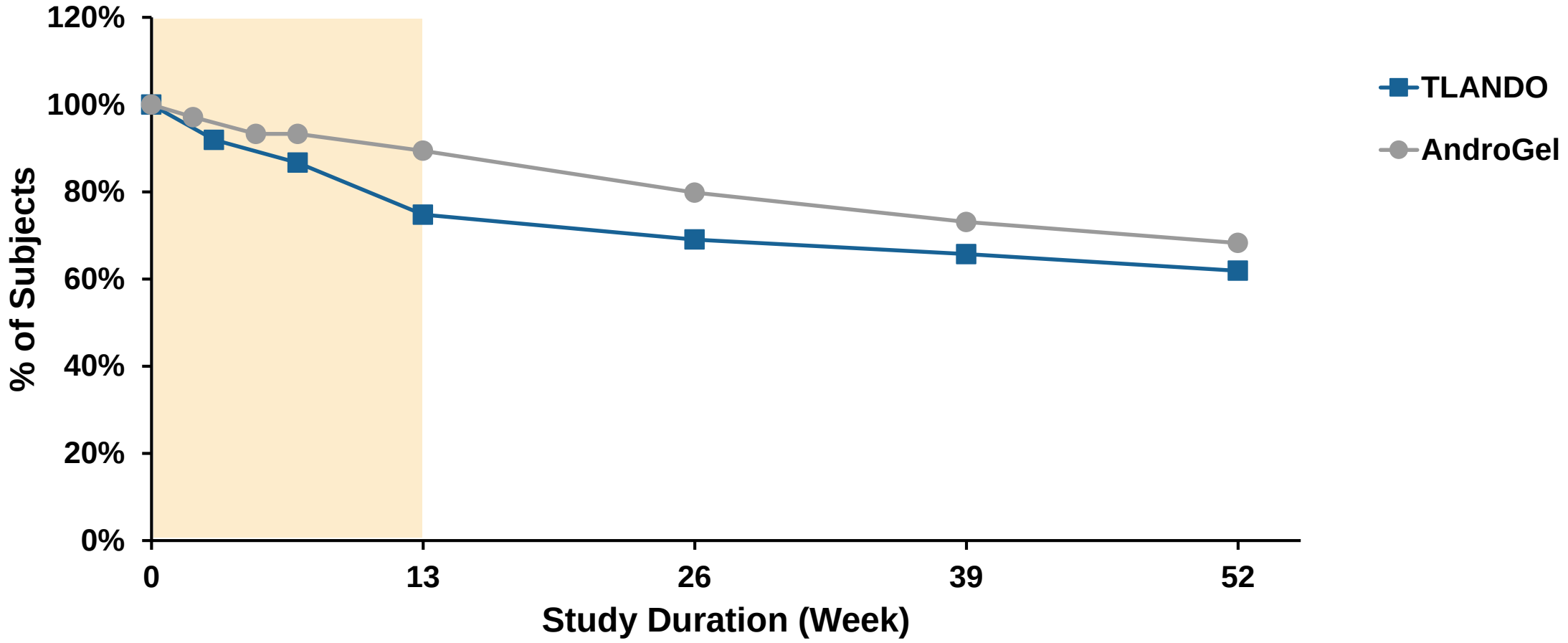


Clinical Identification of Non-Normal Range Patients[a]

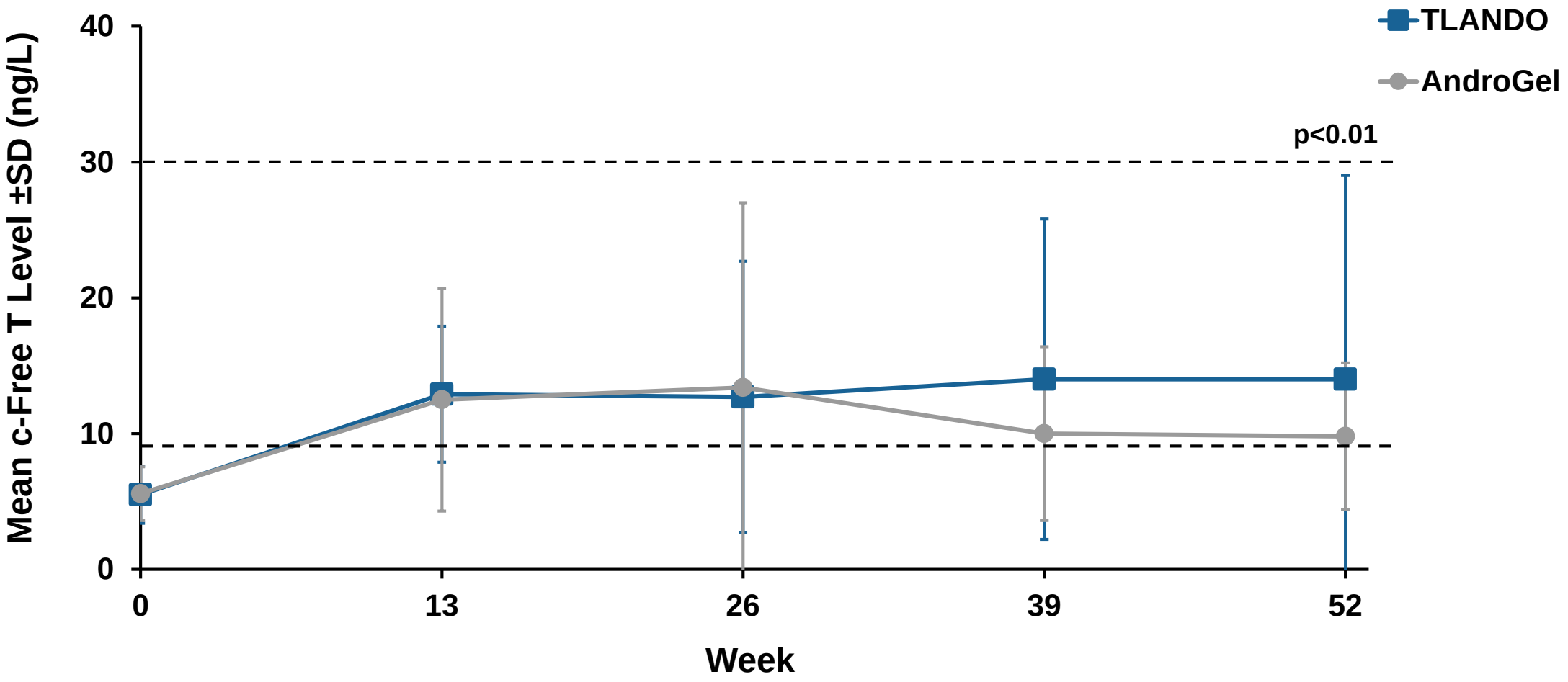


[a]Studies 13-001 and 16-002

Study 13-001: Patient Discontinuation by Time

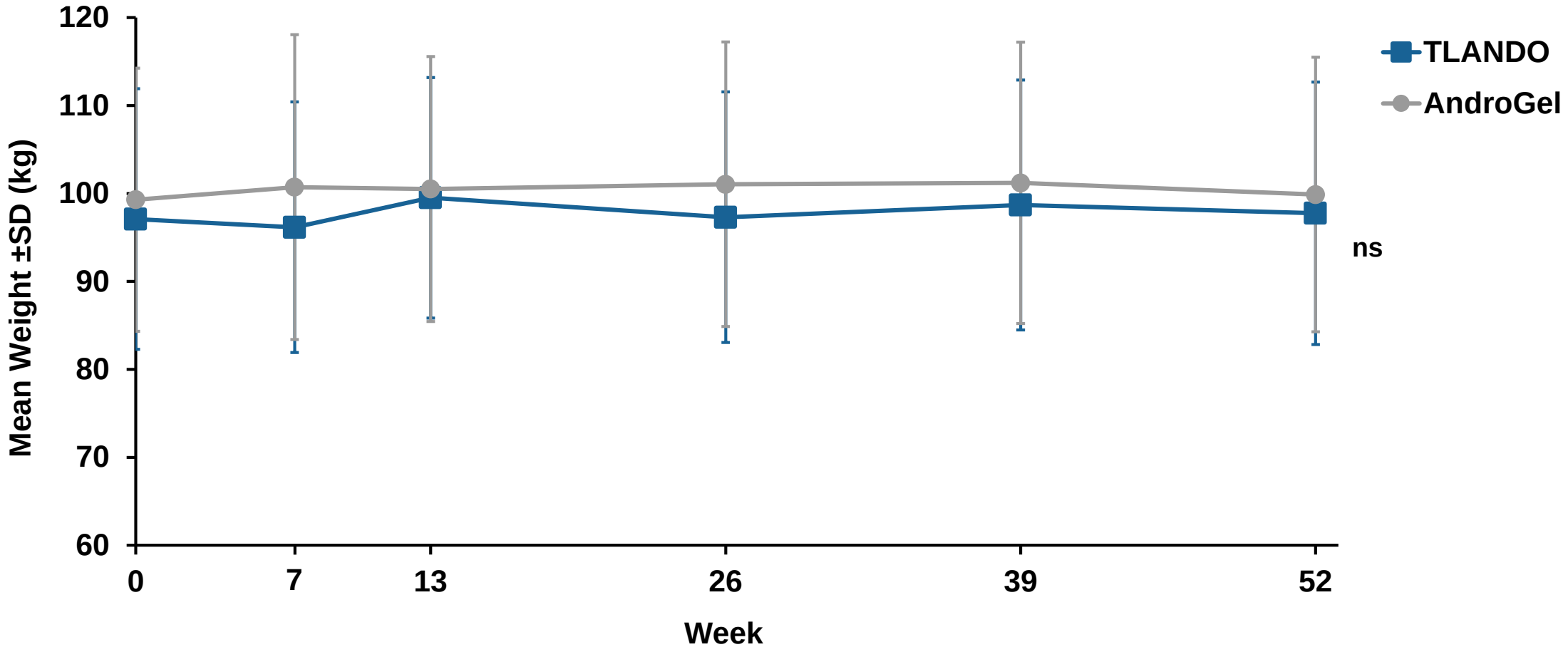


Study 13-001: Calculated Free T



Dotted lines indicate Free T normal range (9 – 30 ng/dL). T, testosterone.

Study 13-001: Weight (kg)



TLANDO N=	210	85	78	96	90	127
AndroGel N=	104	48	49	44	42	66

ns, not significant (p≥0.05)

Study 13-001: LH Values by Primary and Secondary Hypogonadal Patients

			Mean (SD) [IU/L]		
		n (%)	Baseline	End of Study	Change from Baseline
TLANDO	All		5.8 (7.3)	2.9 (4.8)	-2.9 (6.2)
	Primary	54 (26%)	13.4 (11.1)	6.2 (8.1)	-7.2 (10.8)
	Secondary	153 (73%)	3.1 (1.5)	1.7 (1.7)	-1.3 (1.8)
AndroGel	All		4.7 (4.4)	2.3 (4.3)	-2.5 (2.6)
	Primary	26 (25%)	8.9 (6.6)	4.8 (7.5)	-4.1 (3.4)
	Secondary	78 (75%)	3.4 (2.0)	1.4 (1.7)	-1.9 (2.1)

LH (Normal Range= 1.4 to 18.1 IU/L)

Study 13-001: FSH Values by Primary and Secondary Hypogonadal Patients

			Mean (SD) [IU/L]		
		n (%)	Baseline	End of Study	Change from Baseline
TLANDO	All		8.4 (10.3)	4.6 (8.6)	-3.9 (8.8)
	Primary	54 (26%)	20.4 (14.3)	10.9 (14.9)	-9.5 (15.6)
	Secondary	153 (73%)	4.2 (2.0)	2.4 (2.0)	-1.9 (2.1)
AndroGel	All		7.2 (7.6)	4.1 (6.8)	-3.1 (5.6)
	Primary	26 (25%)	17.0 (9.7)	8.9 (10.5)	-8.1 (6.8)
	Secondary	78 (75%)	3.9 (1.9)	2.5 (3.9)	-1.4 (4.0)

FSH Normal Range= 1.7 to 8.6 IU/L