

Clarus Therapeutics

**Presentation to the
Bone, Reproductive and Urologic Drugs Advisory Committee
January 9th, 2018**

Introduction

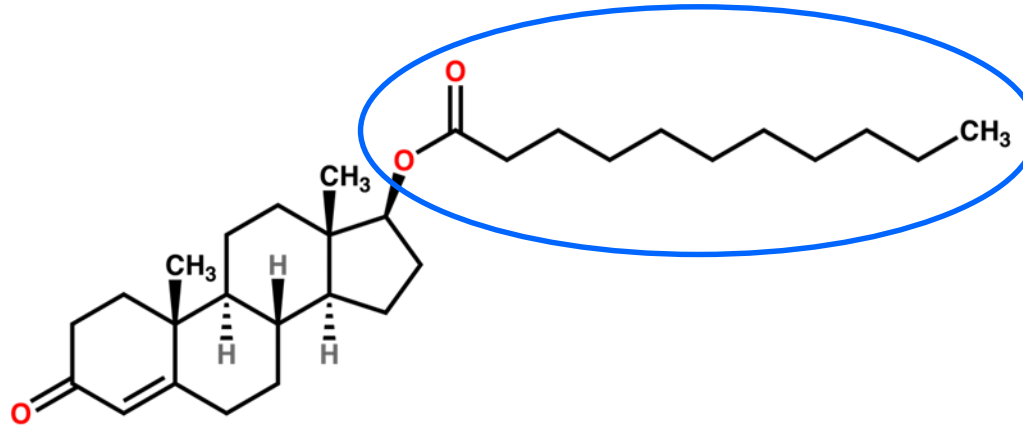
Robert Dudley, PhD, DABT

*Pharmacologist/Toxicologist and President & CEO
Clarus Therapeutics*

Proposed JATENZO Indication Consistent With Class of Approved Testosterone Replacement Therapies (TRT)

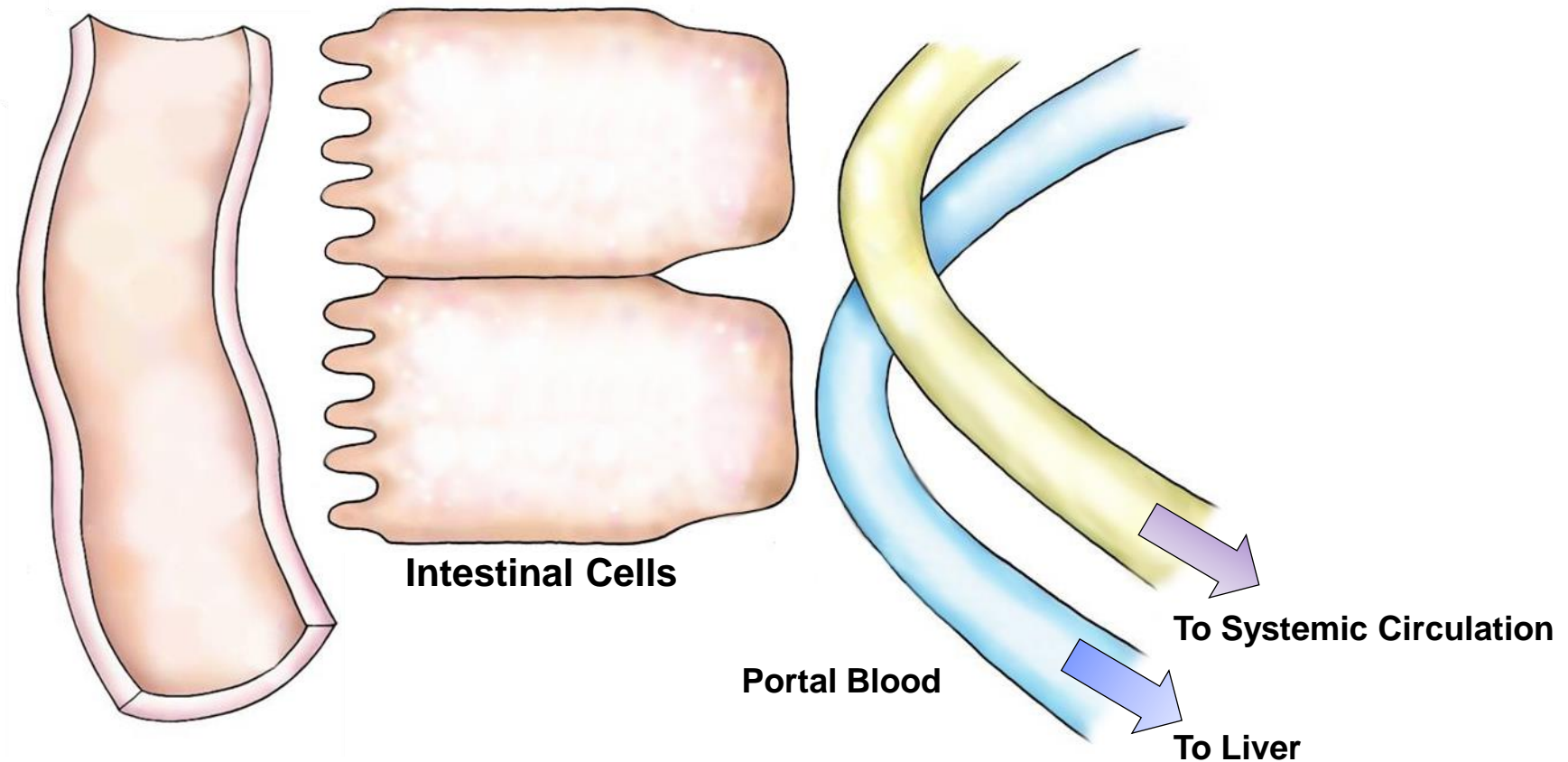
- **Replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone:**
 - ▶ Primary hypogonadism (congenital or acquired): testicular failure due to conditions such as cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals
 - ▶ Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation

JATENZO's Active Ingredient is Testosterone Undecanoate (TU) – a Testosterone Prodrug

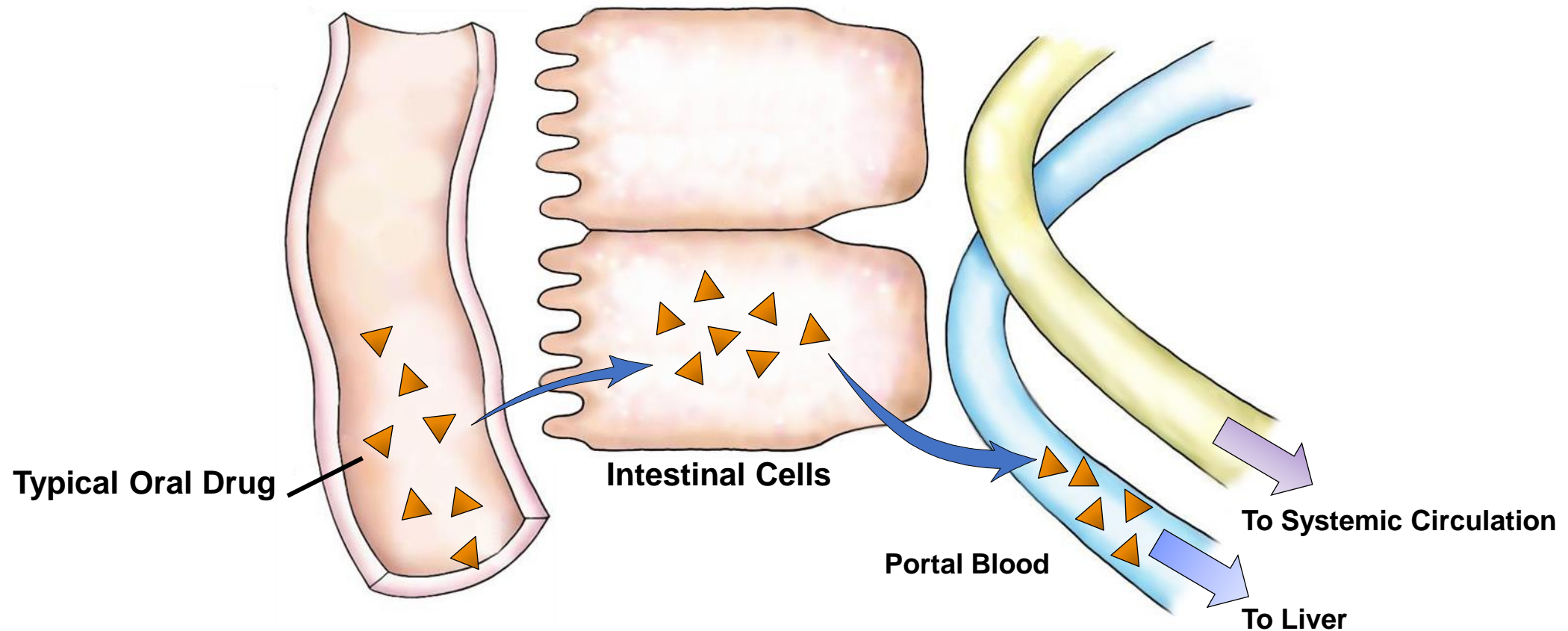


- **Fatty acid esters of T have been used safely for decades**
 - ▶ T prodrug in all injectable TRTs (e.g., T-enanthate, T-cypionate, T-undecanoate)
- **Oral TU widely available outside the U.S. in different, lower strength formulation than JATENZO**
- **Unlike alkylated T derivatives (e.g., methyl-T), TU is not hepatotoxic**

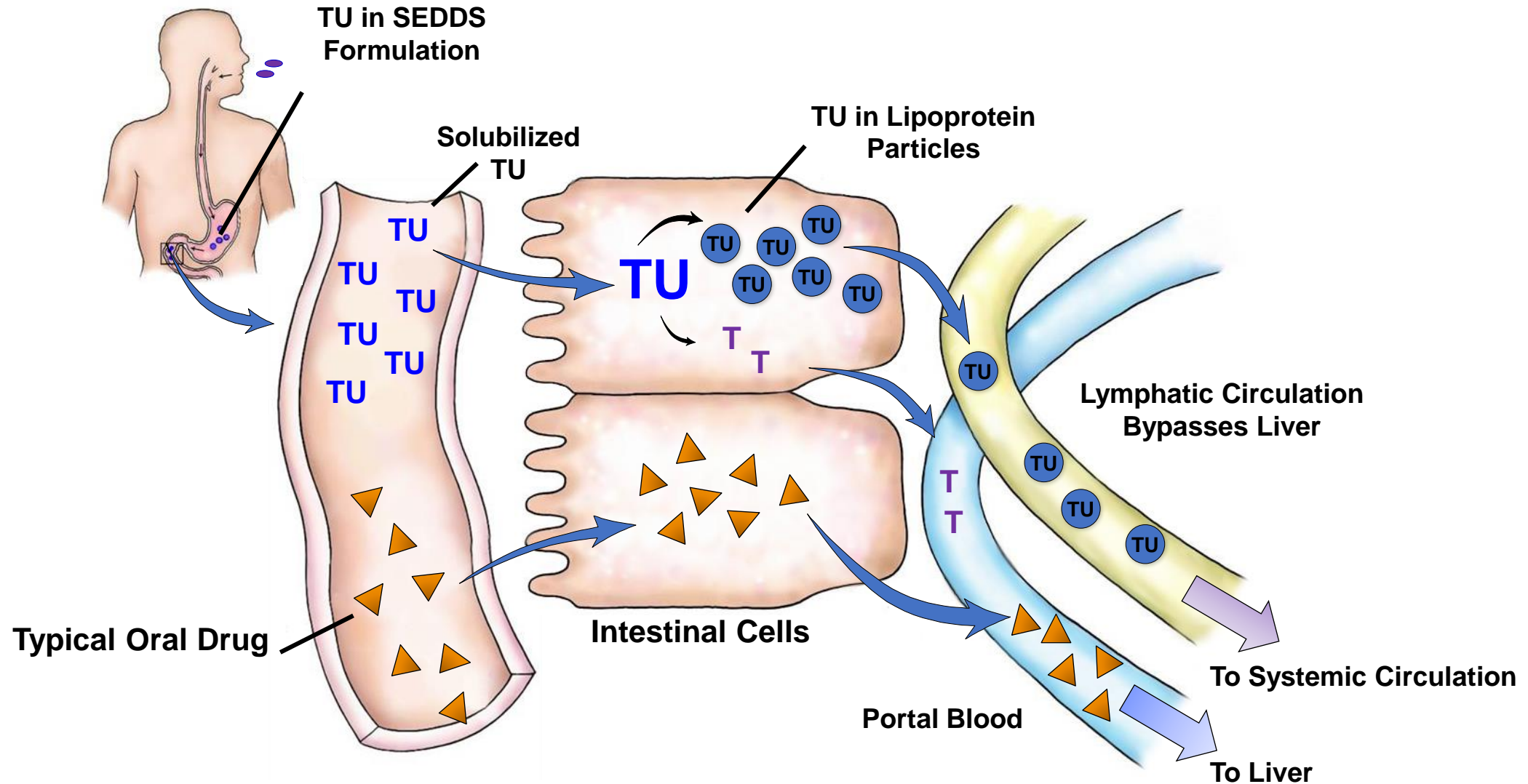
JATENZO: Testosterone Undecanoate (TU) Absorbed via Intestinal Lymphatic Pathway



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Importance of Blood Collection Method in Study 15012

- **Non-specific esterases in blood can catalyze conversion of TU to T after blood is collected**

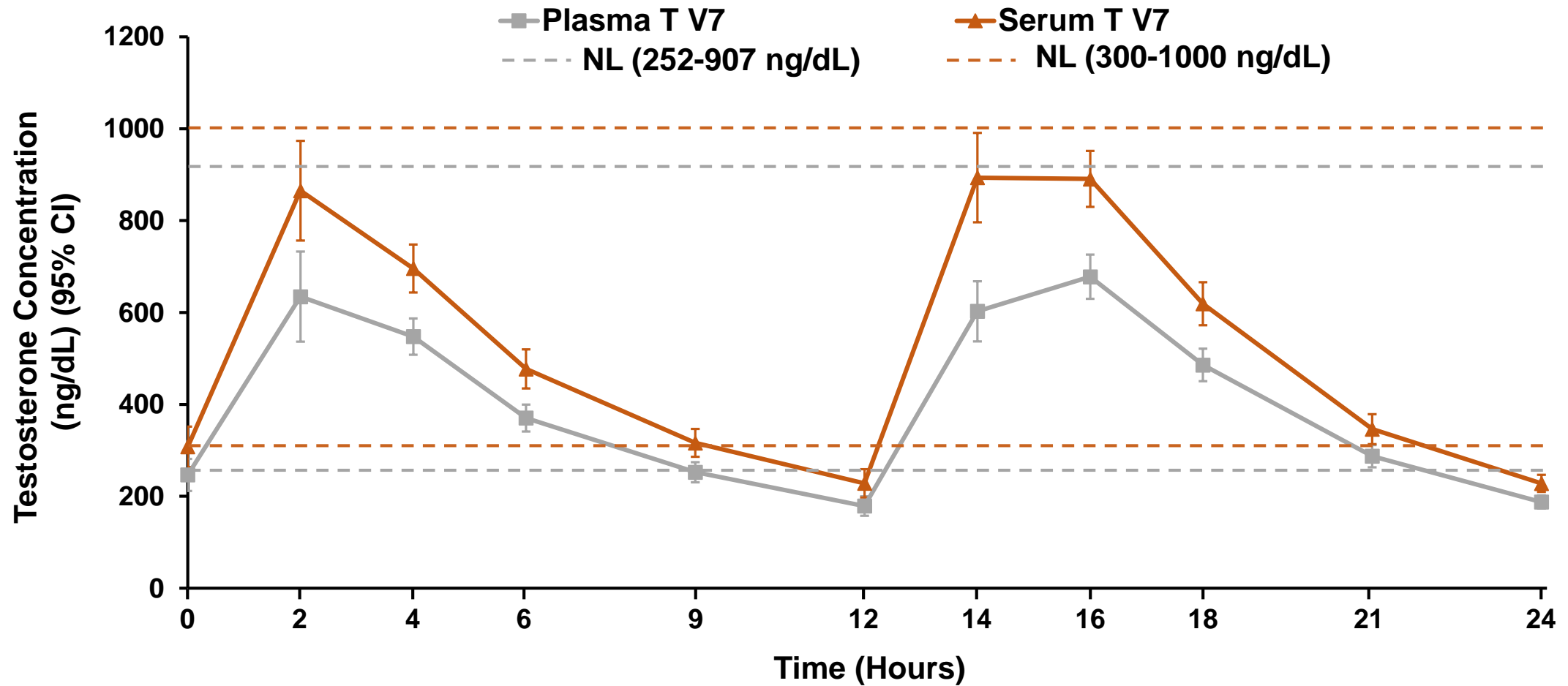
Importance of Blood Collection Method in Study 15012

- **Non-specific esterases in blood can catalyze conversion of TU to T after blood is collected**
- **Blood collection method critical in PK efficacy trials of oral TU to prevent post-collection conversion to avoid over-estimation of T**
 - ▶ Accurate and consistent measurement of T necessary for dose-titration decisions and efficacy measures (C_{avg} and C_{max})

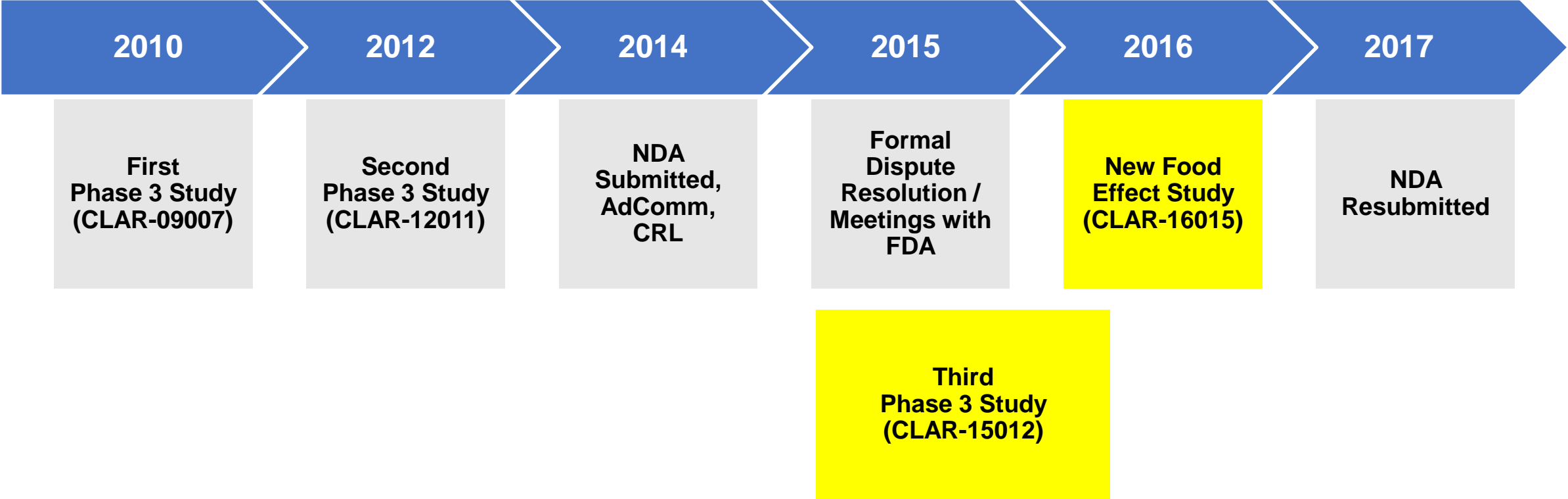
Importance of Blood Collection Method in Study 15012

- **Non-specific esterases in blood can catalyze conversion of TU to T after blood is collected**
- **Blood collection method critical in PK efficacy trials of oral TU to prevent post-collection conversion to avoid over-estimation of T**
 - ▶ Accurate and consistent measurement of T necessary for dose-titration decisions and efficacy measures (C_{avg} and C_{max})
- **Collection of blood in the presence of esterase inhibitor (e.g., NaF) solves efficacy evaluation problem but necessitated use of**
 - ▶ NaF-EDTA vs. plain (red-top) tubes
 - ▶ Eugonadal T range established when blood collected in NaF-EDTA tube for efficacy analysis

Study 15012: Visit 7 Plasma and Serum T Concentrations



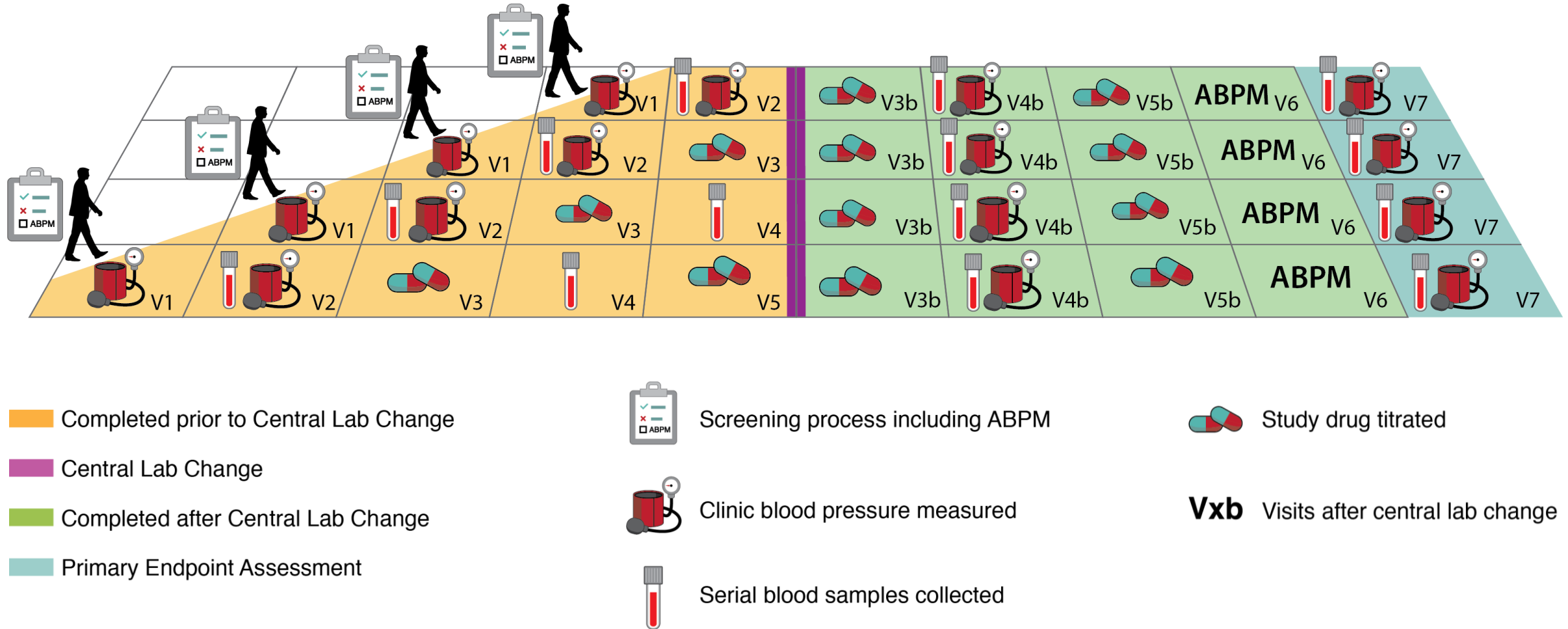
JATENZO Development Milestones



Key Lessons Learned From New Studies to Support Re-submission of NDA

- **Proper blood collection critical to prevent conversion of TU to T**
- **Improved dose-titration algorithm employed in new Phase 3 study (15012) yield substantially better efficacy**
 - ▶ Lower starting dose with minimum need for down-titration
 - ▶ Revised titration boundaries
- **Meal fat content results in clinically insignificant effects on T bioavailability**
- **JATENZO has no clinically significant effect on adrenal function**
- **JATENZO associated with 3-5 mmHg mean increase in systolic blood pressure**

Study 15012: Central Lab Change Did Not Impact Study Integrity or Outcome



Major Themes for Today's Presentation

- **JATENZO effectively restores circulating T levels**
 - ▶ Refined dose-titration algorithm that achieved FDA efficacy target
 - ▶ Titration algorithm allows HCPs to tailor dose to individual patient needs and guides discontinuation decisions
- **General safety profile similar to approved TRTs with some exceptions**
 - ▶ BP elevations may occur thus BP should be monitored and changes managed accordingly
 - ▶ JATENZO lowered HDL nominally more than topical TRTs but may not affect overall HDL functionality
- **Confirmation that meal fat content results in small, clinically insignificant effect on T response after JATENZO**

Presentation Agenda

Medical Landscape	John K. Amory, MD, MPH, MS Professor of Medicine, University of Washington School of Medicine, Seattle, WA
Efficacy	Ronald S. Swerdloff, MD Distinguished Professor of Medicine, David Geffen School of Medicine at UCLA and Chief, Division of Endocrinology, Harbor-UCLA Medical Center, Torrance, CA
Assessment of General Safety	Theodore Danoff, MD, PhD Chief Medical Officer, Clarus Therapeutics
Cardiovascular Safety Assessment	William B. White, M.D. Professor of Medicine and Chief, Hypertension and Clinical Pharmacology Division, University of Connecticut Health, Farmington, CT
Safety Conclusions and Risk Mitigation	Theodore Danoff, MD, PhD Chief Medical Officer, Clarus Therapeutics
Clinical Practice Perspective	Jed Kaminetsky, MD Clinical Assistant Professor, Department of Urology, NYU Langone Health, Medical Director, Manhattan Medical Research, New York, NY
Closing Comments	Robert Dudley, PhD, DABT President & CEO, Clarus Therapeutics, Inc.

Medical Landscape

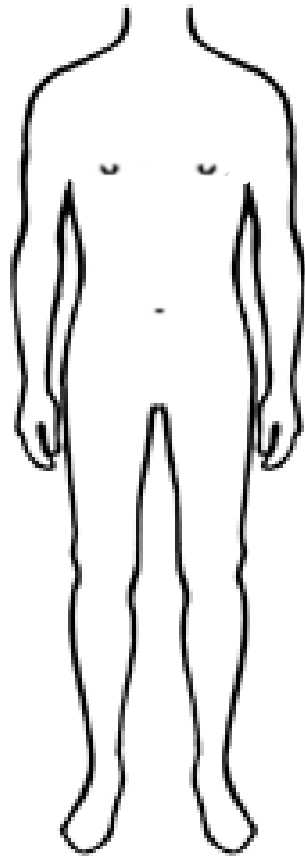
John K. Amory, MD, MPH, MSc

Professor of Medicine

University of Washington School of Medicine

Seattle, WA

Hypogonadism: Broad Spectrum of Clinical Manifestations



Eugonadal Male

Brain and Sexuality

↓ Libido
↓ Secondary Sex Characteristics

Muscle

↓ Strength and Volume

Fat

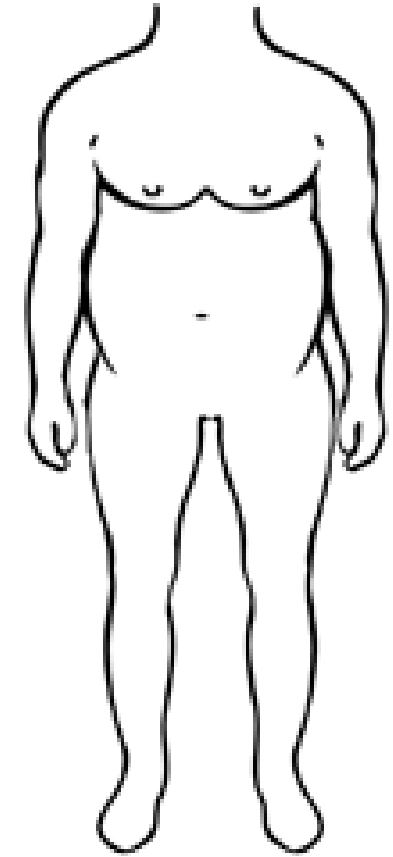
↑ Adiposity / Obesity

Bone

↓ Bone Mineral Density

Blood

↓ Erythropoiesis



Hypogonadal Male

Example of Clinical Manifestations in Identical Twins



Newnham, et al., *N Engl J Med* 2008.

Diagnosis of Male Hypogonadism

- **Low morning testosterone concentrations on two separate days**
 - ▶ Total serum T <300 ng/dL (lower end of eugonadal range)
- **Signs consistent with hypogonadism**
 - ▶ Decreased bone density
 - ▶ Anemia
 - ▶ Reduced muscle mass and strength
- **Symptoms consistent with hypogonadism**
 - ▶ Reduced libido
 - ▶ Diminished sexual function
 - ▶ Hot flushes/sweats
 - ▶ Decreased energy/motivation/initiative

Positions on Testosterone Replacement Therapy (TRT)

Professional Society

Position on TRT

American Urological Association

- Appropriate treatment for patients with clinically significant hypogonadism
- Testosterone therapy in the absence of hypogonadism is inappropriate
- Treatment requires follow-up and medical monitoring

Endocrine Society

- Demonstrable low T and associated symptoms induce and maintain secondary sex characteristics and to improve their sexual function, sense of well-being, muscle mass and strength, and bone mineral density
- Aim is to achieve T testosterone concentrations during treatment in the mid-normal range
- Men receiving testosterone therapy should be monitored

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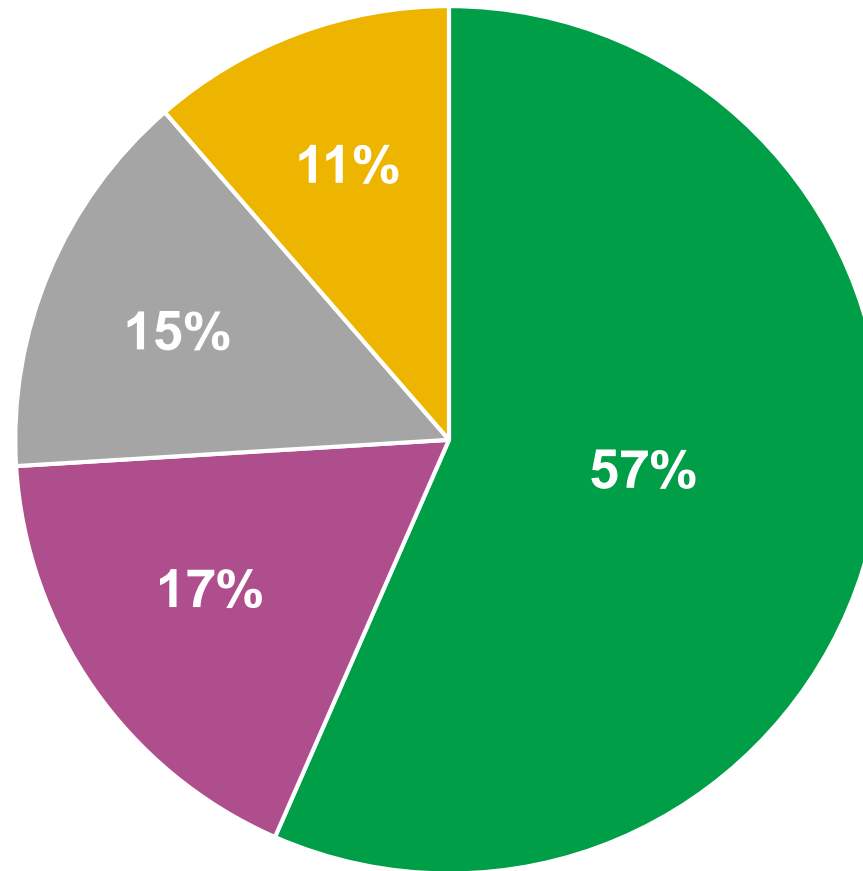
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- Men receiving testosterone therapy should be monitored

Prescribers of Testosterone

■ PC/IM ■ Urology ■ Endocrinology ■ Other

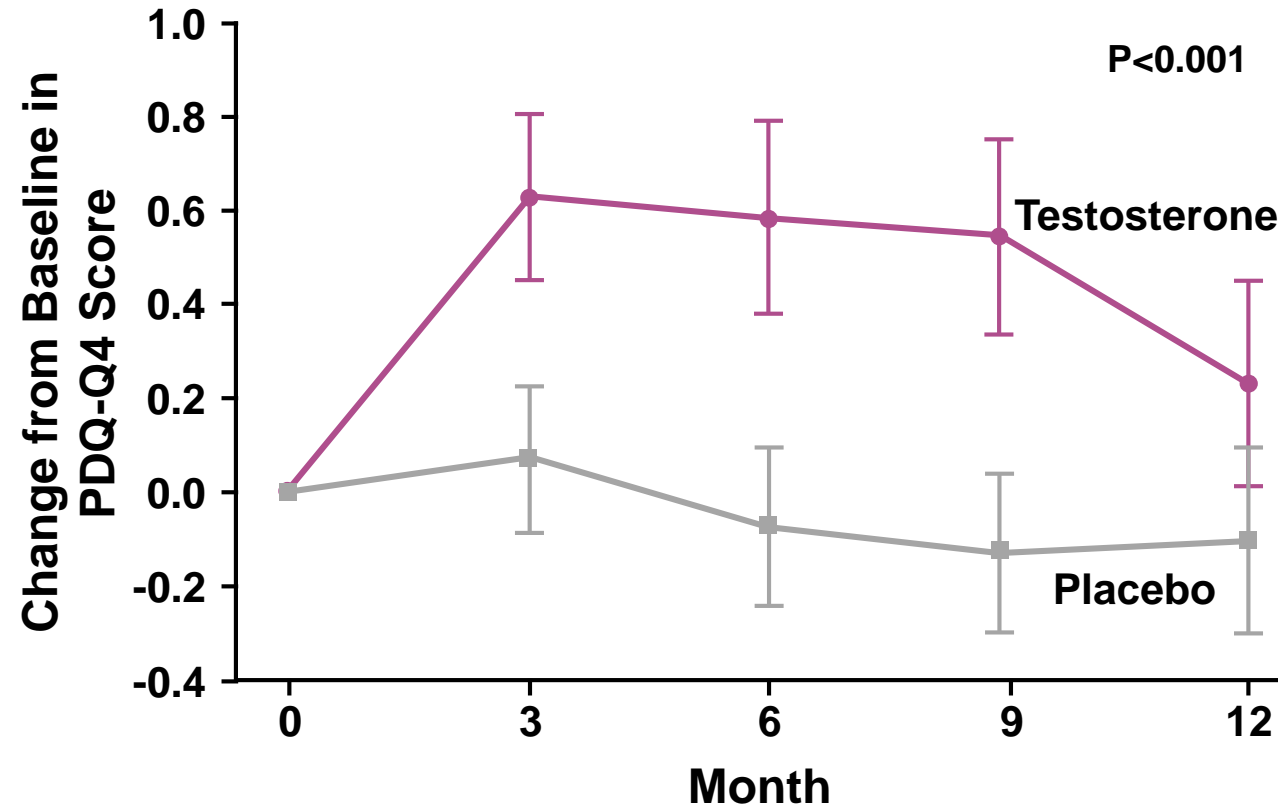


Source: IMS NPA data November 2017

Benefits of TRT

- **↑ Libido and sexual function**
- **↑ Bone mineral density**
- **↑ Muscle mass and strength**
- **↓ Central obesity**
- **↓ Anemia**

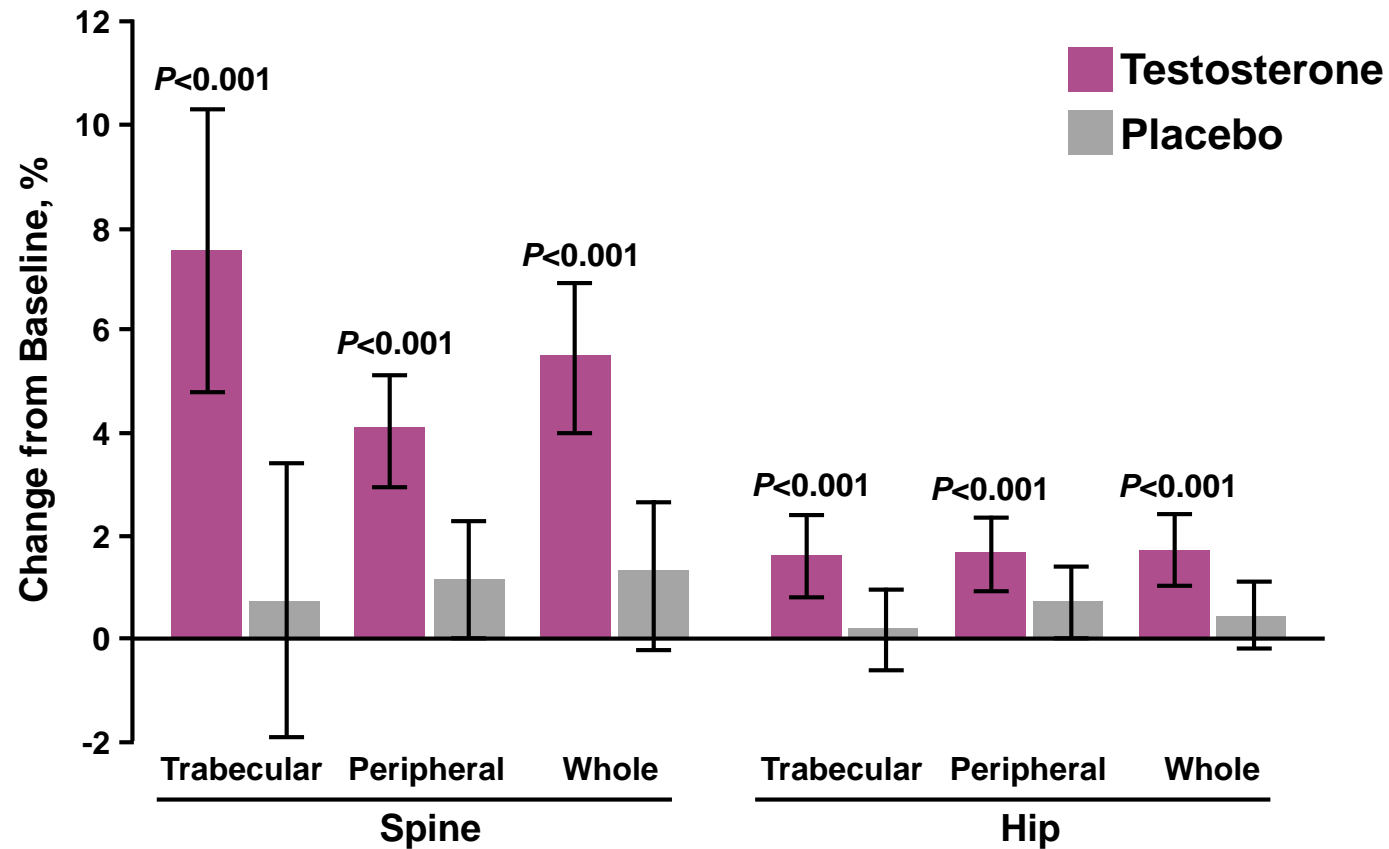
T Trial: Testosterone Treatment Improves Sexual Function in Older Men



No. at Risk					
Testosterone	230	205	208	205	193
Placebo	229	198	189	190	193

T Trial: Testosterone Improves Bone Density in Older Men

Effects of Testosterone or Placebo Treatment for 12 Months on Volumetric Bone Mineral Density and Estimated Bone Strength of Trabecular, Peripheral and Whole Bone of the Spine and Hip as Assessed by Quantitative Computed Tomography



T Trial: Adverse Events During First Year (Treatment Period)

Event	Placebo N=394	Testosterone N=394
	<i>No. of Participants</i>	
Prostate-related event		
Increase in PSA level by ≥ 1.0 ng/ml	8	23
Prostate cancer	0	1
Urinary Symptoms (IPSS >19)	26	27
Hemoglobin ≥ 17.5 g/dl	0	7
Cardiovascular event		
Myocardial infarction (definite or probable)	1	2
Stroke (definite or probable)	5	5
Death from cardiovascular causes	1	0
Myocardial infarction, stroke, or death from cardiovascular causes	7	7
Serious adverse events		
Death	7	3
Hospitalizations	78	68
Other	6	7

Snyder et al. *New Engl J Med* 2016.

Currently Approved TRT Products

Route of Administration	Selected Examples	Product-specific Limitations
Commonly Prescribed		
Transdermal gels and solutions	AndroGel AndroGel 1.62 Axiron	Transference Application site reactions
Transdermal patch	Androderm	Reaction to patch
IM injections	T Enanthate T Cypionate Aveed (TU)	Injection site pain Anaphylaxis Acute injection reactions (POME)
Uncommonly Prescribed		
Oral	Methyltestosterone	Liver toxicity
Buccal	Striant	Falls off application site
Intranasal	Natesto	TID; messy
Implantable pellets	Testopel	Surgical procedure; extrusion

Labeled Class Effects of TRT

- **Increased PSA**
- **Increased hematocrit**
- **Lipid changes**
- **VTE/PE**
- **Azoospermia**
- **Edema**

Standard Monitoring During TRT

- **Determine if symptoms improve**
- **Regularly check testosterone concentrations for improvement and need for dose adjustment**
- **Regularly monitor for potential cardiovascular effects, including changes in blood pressure (One month after initiation or dose titration)**
- **PSA and rectal examination every 6 to 12 months**
- **Hematocrit/hemoglobin at 6 months and then yearly**

Summarizing the Medical Landscape of TRT

- **Appropriate for men with demonstrably low T and symptoms of hypogonadism**
- **Side effects well known and consistent across current product options**
- **Generally safe and well-tolerated when used and monitored appropriately**
- **Current standard options limited by routes of administration**
- **Needs acceptable oral option**

Efficacy

Ronald S. Swerdloff, MD

*Distinguished Professor of Medicine
David Geffen School of Medicine at UCLA*

*Chief, Division of Endocrinology
Harbor-UCLA Medical Center*

Study 15012: Four Main Goals for Evaluating Efficacy

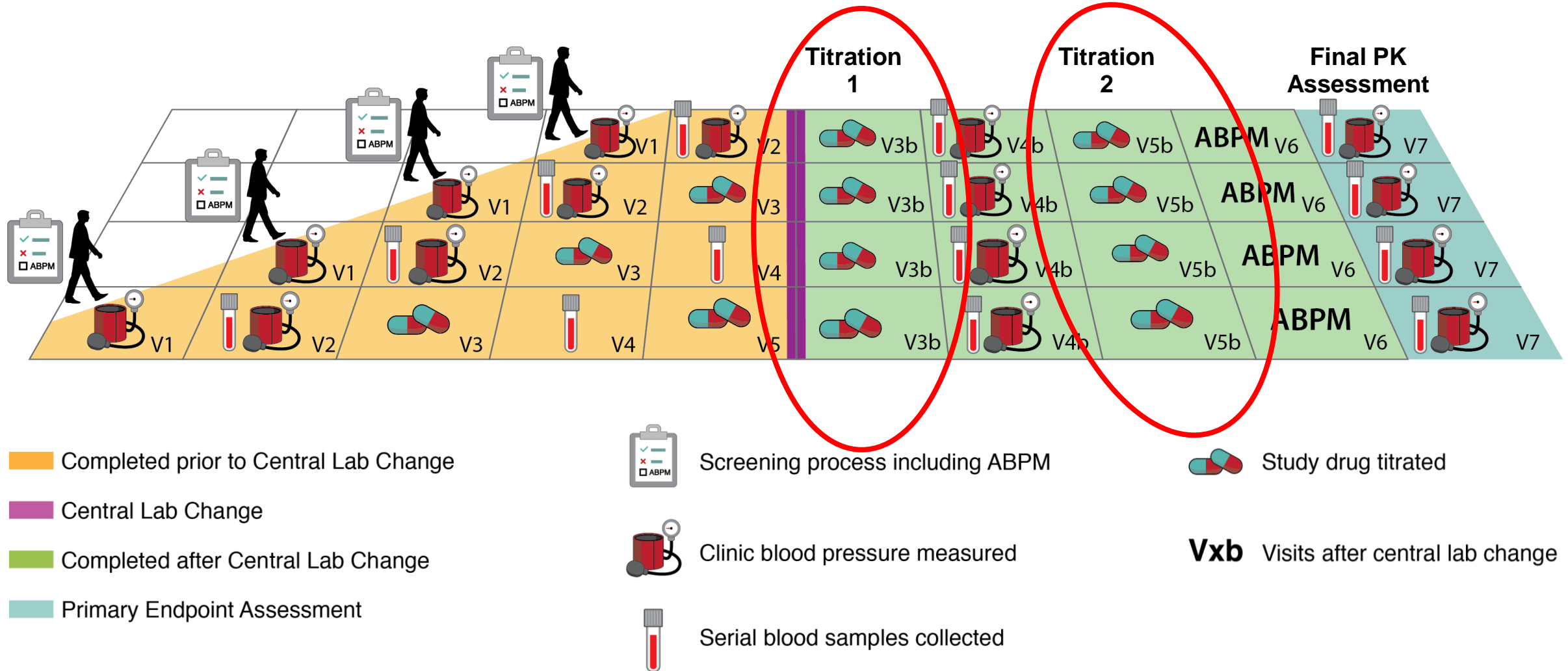
Clarus designed 15012 trial to accomplish four main goals identified by FDA and previous advisory committee:

1. Test a titration scheme refined from those in earlier studies
2. Study a starting dose lower than in previous studies, reducing the risk of treating patients with unnecessarily high starting doses
3. Ensure that participants followed their usual diets on PK sampling days
4. Enhance patient retention

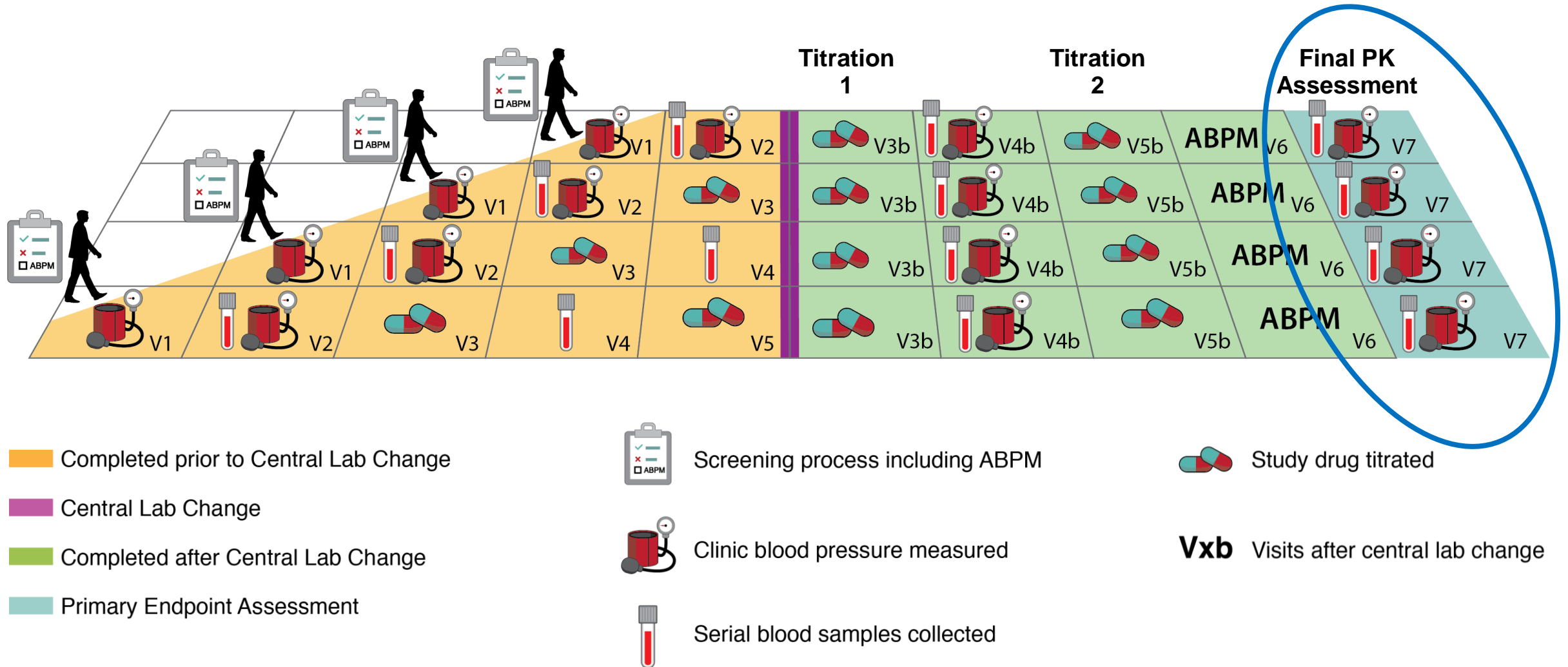
Study 15012: Primary Efficacy Study

- **Randomized (3:1), 2-arm, open label study of JATENZO and Axiron**
- **JATENZO: N=166, Axiron: N=55**
- **Hypogonadal men ($T < 300$ ng/dL on 2 occasions with symptoms)**
- **92% completed the study**

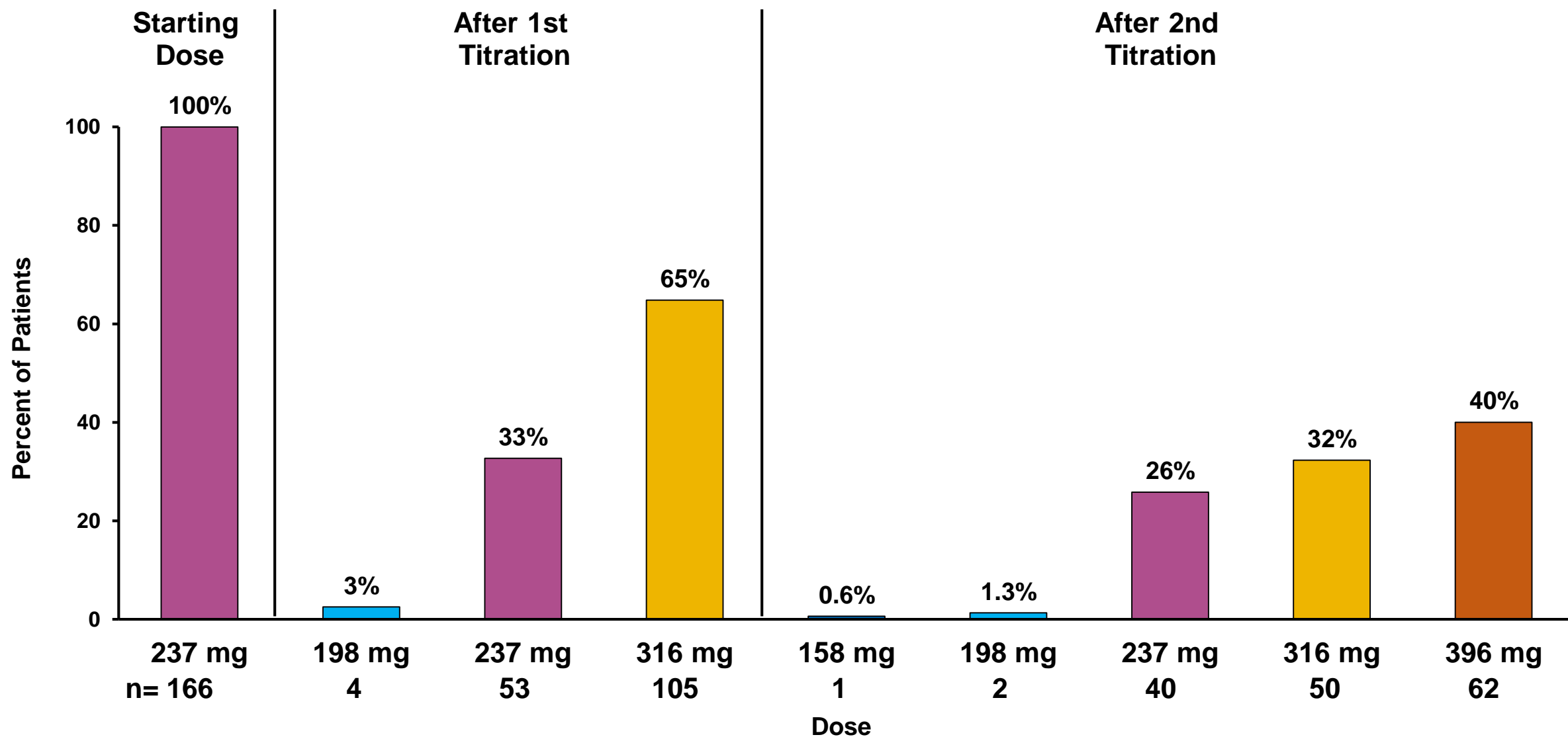
Study 15012: Study Design



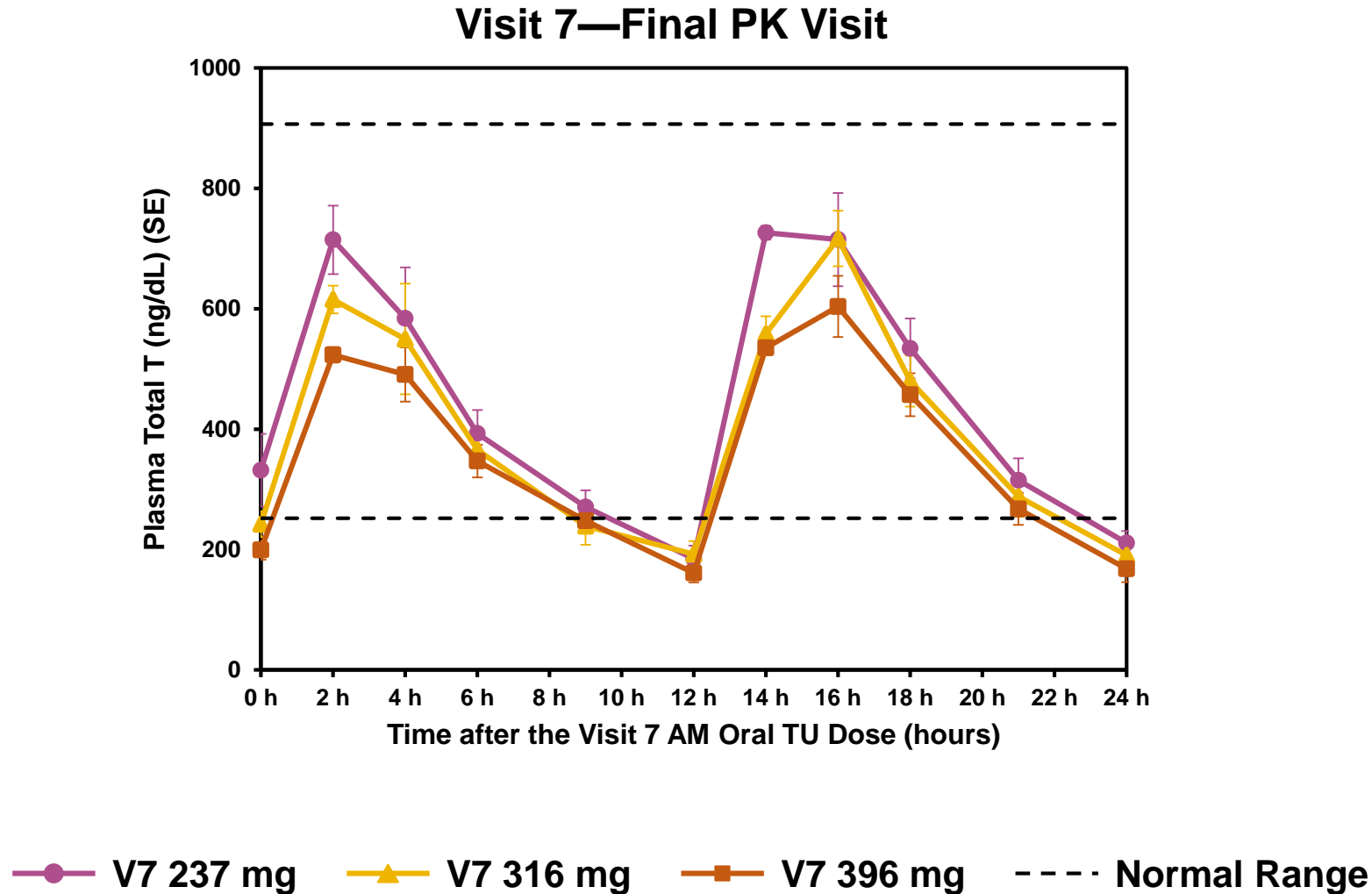
Study 15012: Study Design



Study 15012: JATENZO Dose Changes With Titration



Study 15012: Titration Algorithm Achieves Desired Efficacy by Visit 7



FDA Efficacy Target Endpoints for Circulating T

	Percent of Phase 3 Patients Required to Satisfy FDA Targets	Testosterone PK Endpoints
Primary	≥75%	Average T levels in reference range ¹
Efficacy C _{avg}	≥65%	Lower bound of 95% CI

1. Eugonadal range (252-907 ng/dL) for normal men when blood collected in NaF-EDTA tubes to prevent post-collection conversion of TU to T.

Study 15012: Primary Efficacy – Achieved FDA Target

	FDA Target	JATENZO N=166	Axiron N=55
TC _{avg}	≥75%	87.3%	87.3%
95% CI lower bound	≥65%	81.3%	75.5%

Modified Intention-To-Treat population with Last Observation Carried Forward for subjects with missing data due to non-study-related causes.

FDA Efficacy Target Endpoints for Circulating T

	Percent of Phase 3 Patients Required to Satisfy FDA Targets	Testosterone PK Endpoints
Primary Efficacy C_{avg}	$\geq 75\%$	Average T levels in reference range ¹
	$\geq 65\%$	Lower bound of 95% CI
Secondary Efficacy C_{max}	$\geq 85\%$	Peak circulating T <1,500 ng/dL
	$\leq 5\%$	Peak circulating T 1,800-2,500 ng/dL
	0 ²	Peak circulating T >2,500 ng/dL

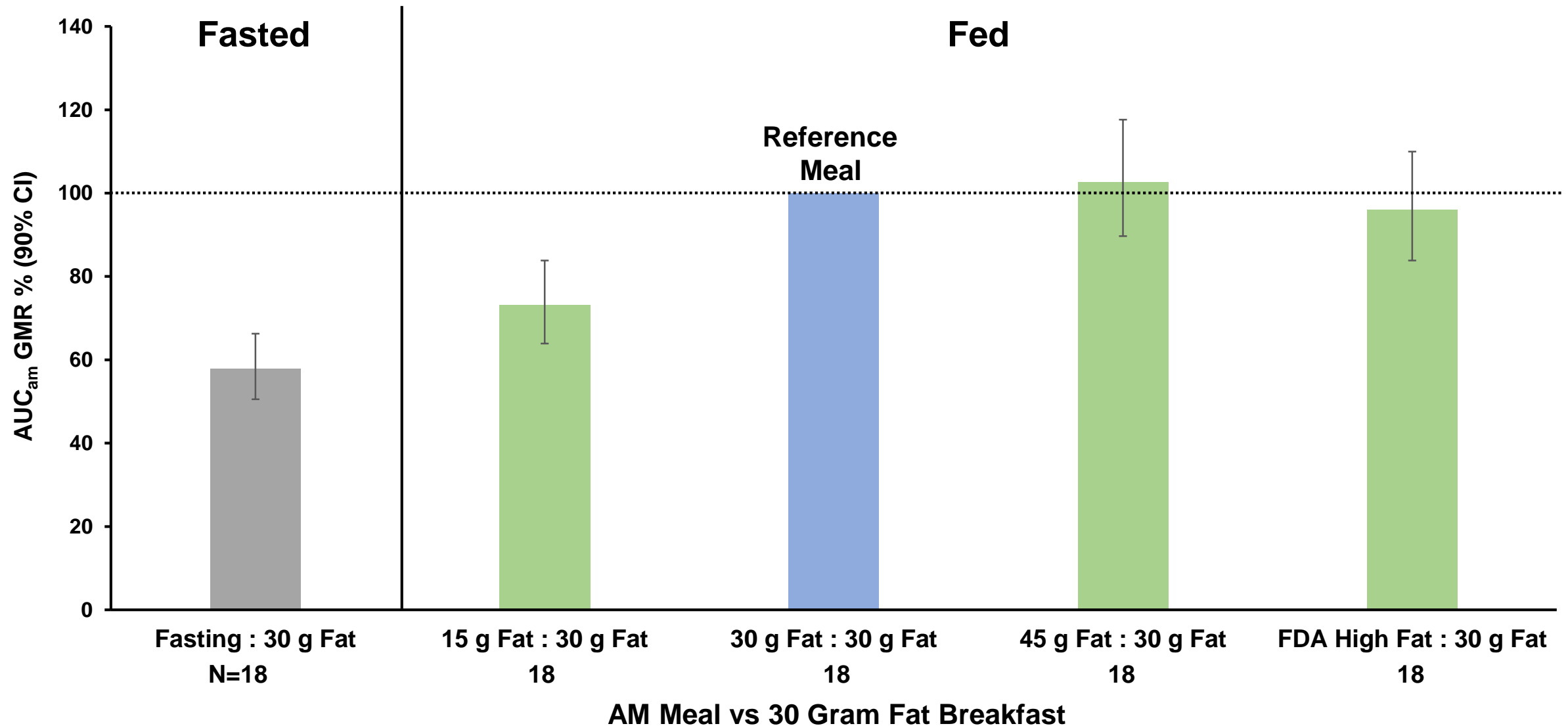
1. Eugonadal range (252-907 ng/dL) for normal men when blood collected in NaF-EDTA tubes to prevent post-collection conversion of TU to T.
2. Both AndroGel 1.62% and Axiron were approved with patients with c_{max} values greater than 2500.

Study 15012: C_{max} Targets at Visit 7 (Final PK Visit) - Achieved 2 of 3 Targets

C _{max} Category	FDA Target	JATENZO N=151	Axiron N=48
≤1500 ng/dL	≥85%	90.7%	97.9%
1800 – 2500 ng/dL	≤5%	2.0%	2.1%
≥2500 ng/dL	0	2.0% (N=3*)	0

* Possible sample contamination.

Study 16015: Effect of Dietary Fat on Testosterone Exposure (Crossover Design)



JATENZO Efficacy Overview

- **Clarus designed Study 15012 to provide**
 - Lower starting dose
 - Real world diet for patients
 - Improved dose-titration algorithm
- **Efficacy results**
 - 87.3% of patients attained eugonadal T range
 - Two out of three C_{\max} targets achieved
- **Food effect study demonstrated that a meal with greater than 30g fat content did not increase testosterone levels above reference meal**

Assessment of General Safety

Theodore Danoff, MD, PhD

*Chief Medical Officer
Clarus Therapeutics*

Phase 3 Studies: Exposure

	Study 09007		Study 12011	Study 15012	
	JATENZO N=161	AndroGel 1% N=160	JATENZO N=144	JATENZO N=166	Axiron N=55
Total duration of exposure to study drug (days)					
Mean (SD)	321.7 (99.5)	333.6 (86.3)	104.8 (25.3)	139.4 (24.8)	133.8 (33.7)
Median	364	365	113	141	141
Minimum, Maximum	4, 409	3, 394	4,126	41, 211	18, 184

Phase 3 Studies: Demographics for Safety Pool

Characteristic	Study 09007		Study 12011	Study 15012	
	JATENZO N=161	AndroGel 1% N=160	JATENZO N=144	JATENZO N=166	Axiron N=56
Age (years)					
Mean	55.0	54.7	54.8	51.6	53.4
Range	20-75	24-74	27-75	24-65	31-65
Race, %					
Asian	0	3.1	9.0	1.8	3.6
Black or African American	11.2	14.4	10.4	17.5	19.6
White	87.6	80.0	79.2	80.1	75.0
Ethnicity, %					
Hispanic or Latino	9.9	11.3	13.2	15.1	26.8
Body Mass Index, kg/m²					
Mean	30.0	29.9	29.9	31.8	30.9
Range	17-39	20-37	19-38	17-38	21-38
Baseline clinical characteristics, %					
Pre-diabetic	38.5	35.0	31.3	36.1	33.9
Diabetes mellitus	19.3	20.0	17.4	24.1	26.8
Hypertensive	41.0	47.5	45.1	52.4	46.4

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Range	20-75	24-74	27-75	24-65	31-65
Race, %					
Asian	0	3.1	9.0	1.8	3.6
Black or African American	11.2	14.4	10.4	17.5	19.6
White	87.6	80.0	79.2	80.1	75.0
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Study 15012: Overview of Treatment Emergent Adverse Events (TEAEs)

	JATENZO N=166 %	Axiron N=55 %
Subjects with any Event		
Any TEAE ¹	47	36
Any serious TEAE ¹	1.2 (n=2)	0
Any TEAE leading to discontinuation	1.8 (n=3)	1.8 (n=1)
Any TEAE leading to death	0	0

1.TEAEs are those events which occurred only after the patient received drug.

Study 15012: Treatment Emergent Adverse Events (1 of 2)

System Organ Class Preferred Term, %	JATENZO N=166	Axiron N=55
Subjects with any TEAE	47.0	36.4
Gastrointestinal Disorders	12.0	0
Diarrhea	1.2	0
Nausea	2.4	0
Eructation	1.2	0
Dyspepsia	1.8	0
Infections and Infestations	9.6	9.1
Upper respiratory tract infection	3.6	0
Injury, Poisoning and Procedural Complications	3.6	7.3
Overdose	0.6	3.6
Skin and Subcutaneous Tissue Disorders	3.0	10.9
Rash	1.2	3.6
Acne	0.6	0

TEAEs are those events which occurred only after the patient received drug. Adverse events were considered treatment-related if the relationship to study drug was deemed related by, probably related, or possibly related. By investigator. Events with missing relationship were imputed as related to study drug and included in the summary.

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Rash	1.2	3.6
Acne	0.6	0

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Study 15012: Treatment Emergent Adverse Events (2 of 2)

System Organ Class Preferred Term, %	JATENZO N=166	Axiron N=55
Subjects with any TEAE	47.0	36.4
Investigations	13.9	3.6
Hematocrit increased	4.8	0
High-density lipoprotein decreased	3.0	0
Prostatic-specific antigen increased	1.2	0
Nervous System Disorders	7.2	7.3
Headache	4.8	1.8
Dizziness	0.6	1.8
Musculoskeletal and Connective Tissue Disorders	6.0	5.5
Vascular Disorders	3.6	0
Hypertension	3.0	0
General Disorders and Administration Site Conditions	3.0	7.3
Edema peripheral	1.8	1.8

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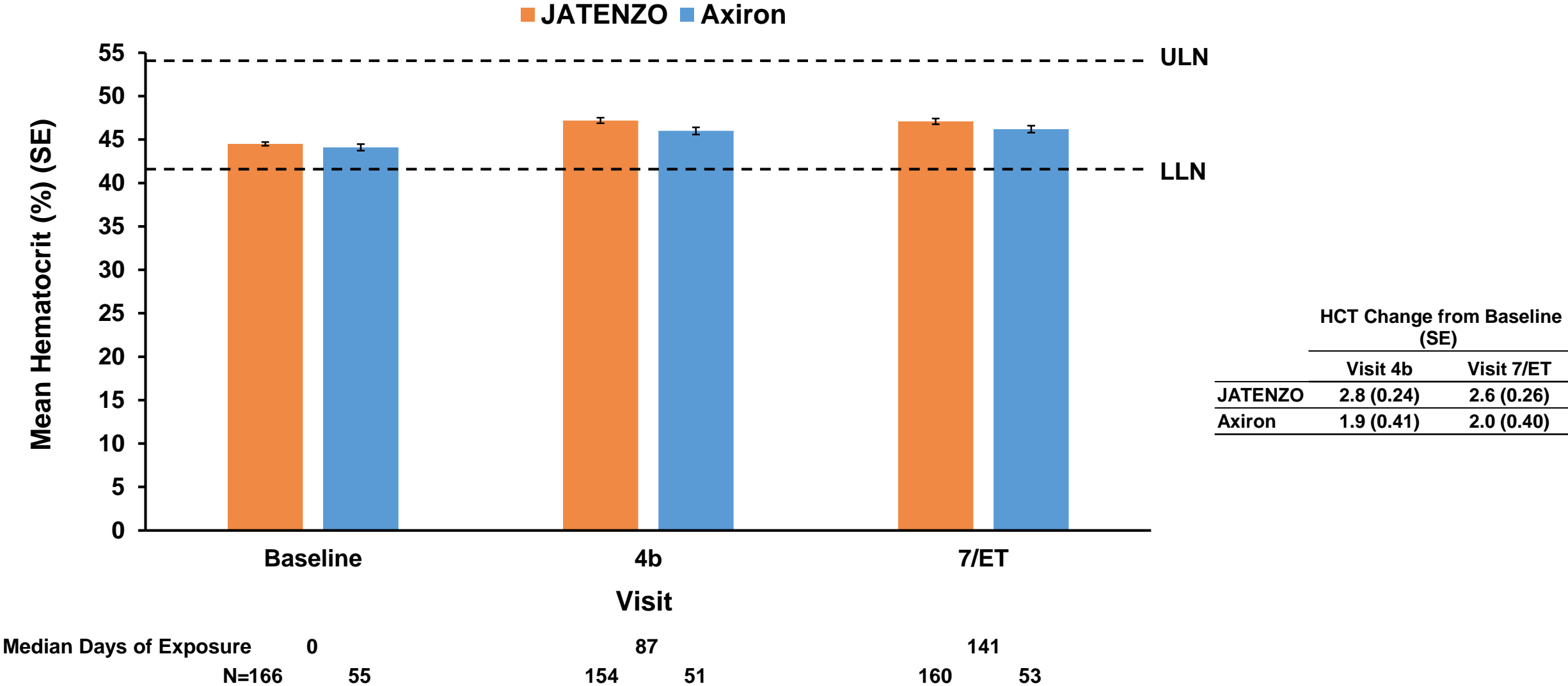
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Phase 3 Studies: Overview of Treatment Emergent Adverse Events

	JATENZO N=471 %	Transdermal T N=215 %
Subjects With Any Event		
Any TEAE	54.8	56.3
Any serious TEAE	3.2	2.8
Any TEAE leading to discontinuation	3.0	3.3
Any TEAE leading to death	0	0

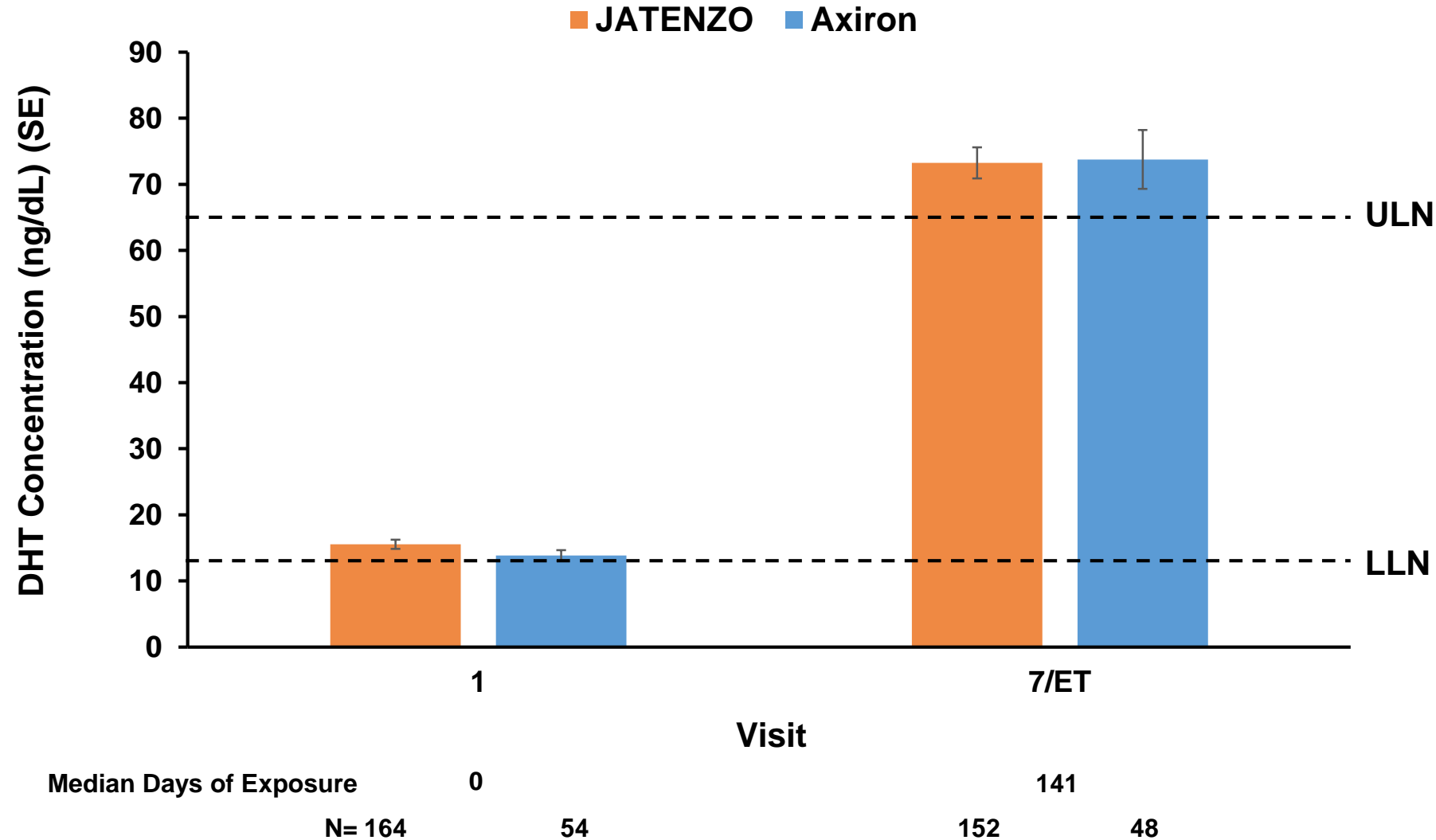
Study 15012: HCT Concentrations Increase With Testosterone Replacement



Study 15012: Patients With HCT >54%

- **8 subjects on JATENZO had a HCT greater than 54% at any time in the study**
- **No clinical events associated with these increases**
- **No patient had to discontinue treatment due to elevated HCT**

Study 15012: DHT Concentrations Increase With Testosterone Replacement



Study 15012: DHT Excursions Above Upper Limit of Normal (ULN) at Visit 7

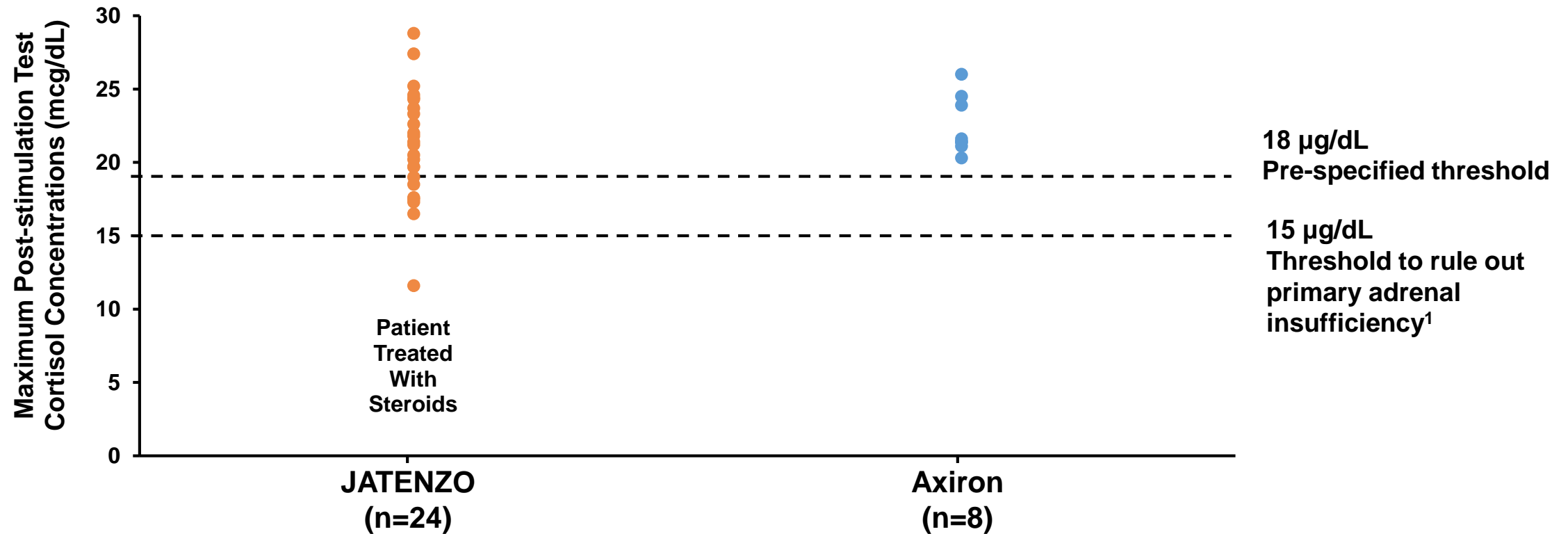
ULN Criterion	Concentration	DHT C _{avg24}		DHT C _{max24}	
		JATENZO N=152 n (%)	Axiron N=48 n (%)	JATENZO N=152 n (%)	Axiron N=48 n (%)
>ULN	>65 ng/dL	84 (55.3)	25 (52.1)	134 (88.2)	38 (79.2)
>2xULN	>130 ng/dL	8 (5.3)	3 (6.3)	52 (34.2)	8 (16.7)
>3xULN	>195 ng/dL	1 (0.7)	0	10 (6.6)	2 (4.2)
>5xULN	>325 ng/dL	0	0	0	0

Study 15012: DHT Excursions Above Upper Limit of Normal (ULN) at Visit 7

ULN Criterion	Concentration	DHT C _{avg24}		DHT C _{max24}	
		JATENZO N=152 n (%)	Axiron N=48 n (%)	JATENZO N=152 n (%)	Axiron N=48 n (%)
>ULN	>65 ng/dL	84 (55.3)	25 (52.1)	134 (88.2)	38 (79.2)
>2xULN	>130 ng/dL	8 (5.3)	3 (6.3)	52 (34.2)	8 (16.7)
>3xULN	>195 ng/dL	1 (0.7)	0	10 (6.6)	2 (4.2)
>5xULN	>325 ng/dL	0	0	0	0

Study 15012: Cosyntropin-stimulated Cortisol Levels Unaffected by Treatment

Cosyntropin Stimulation Testing (250 µg IV) Done in Subset of Subjects at Visit 8



1. Dorin et al, Diagnosis of Adrenal Insufficiency, *Annals of Internal Medicine*, 2003.

Summary of General Safety

- **Adverse event profile similar to transdermal T formulations except for GI events: mild, tolerable, and probably related to oral route**
- **Data suggest that changes, although small, in hematocrit should be monitored similar to other TRTs**
- **No evidence of clinically significant adrenal function suppression**

Cardiovascular Safety Assessment

William B. White, M.D.

*Professor of Medicine and Division Chief, Hypertension and Clinical Pharmacology,
Calhoun Cardiology Center*

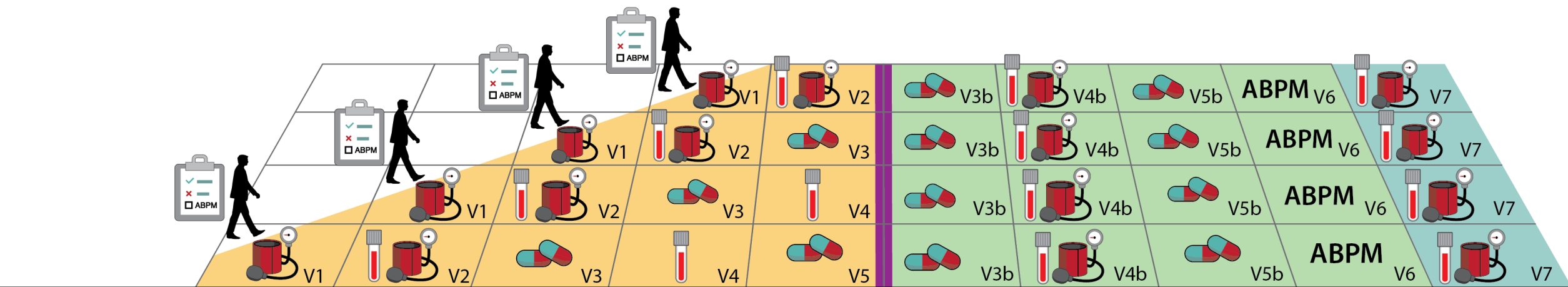
University of Connecticut School of Medicine, Farmington

Past President, American Society of Hypertension (2012-2014)

Blood Pressure Assessment

- **Blood pressure assessments in first two Phase 3 studies (CLAR-09007 and CLAR-12011) showed small increases from baseline on JATENZO**
- **To better evaluate BP changes on JATENZO, with FDA input, integrated BP assessments incorporated into 15012 protocol**
 - ▶ Clinic BP assessed at key time points to define magnitude and time course of changes in study
 - ▶ Ambulatory BP (ABPM) used to define relation of BP to dosing twice daily (Q12 hours)

Study 15012: Study Design



Median Days of Exposure	22		74	87	108	139	141
JATENZO N=	166	166	163	161	159	155	155
Axiron N=	55	55	52	51	50	50	49

- Completed prior to Central Lab Change
- Central Lab Change
- Completed after Central Lab Change
- Primary Endpoint Assessment



Screening process including ABPM



Clinic blood pressure measured



Serial blood samples collected



Study drug titrated

Vxb

Visits after central lab change

Study 15012: Clinic Blood Pressure Assessment

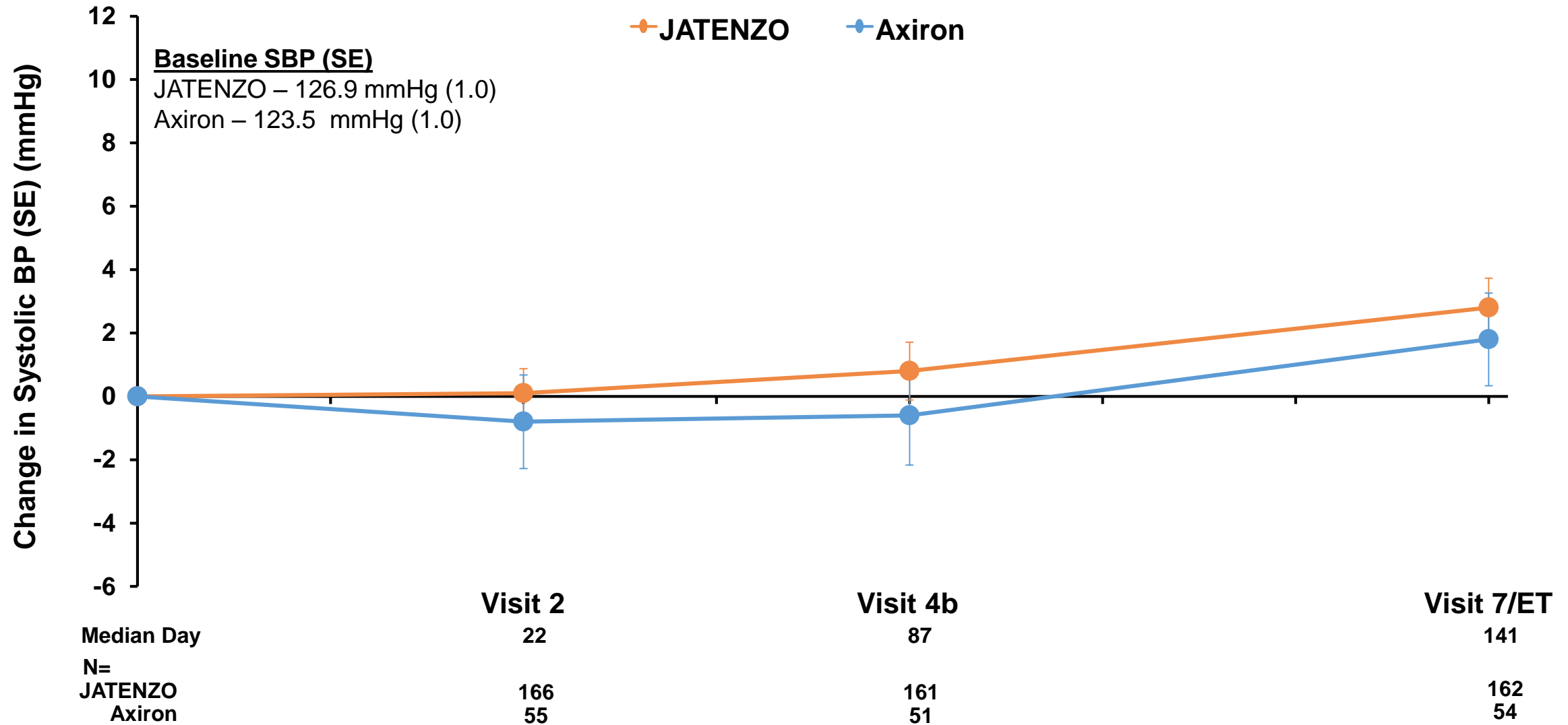
- **Clinician measurements standardized according to AHA guidelines:**
 - ▶ Blood pressures measured in the seated position, with back supported, feet on the floor, arm supported at heart level, and after at least ≥ 5 minutes of rest
 - ▶ Blood pressures measured in triplicate at 1-2 minute intervals using a digital oscillometric device in the non-dominant arm with attention to proper cuff size
 - ▶ Clinic triplicate BPs were averaged

Study 15012: Clinic SBP (mmHg) at Baseline and Change From Baseline to Last Post-baseline Value

	Last Post-Baseline Value			
	JATENZO N=166		Axiron N=55	
	Baseline	Change from Baseline	Baseline	Change from Baseline
Mean (SD)	127 (11.5)	2.98	124 (13.2)	0.30
95% CI	--	1.28, 4.68	--	-2.66, 3.26
LS Mean difference between treatment groups (95% CI) ¹	2.68 (- 0.75, 6.10)			

1. Analysis of covariance with treatment group as a factor and baseline value as the covariate.

Study 15012: Change From Baseline in Clinic Systolic BP by Visit (All Treated Patients)

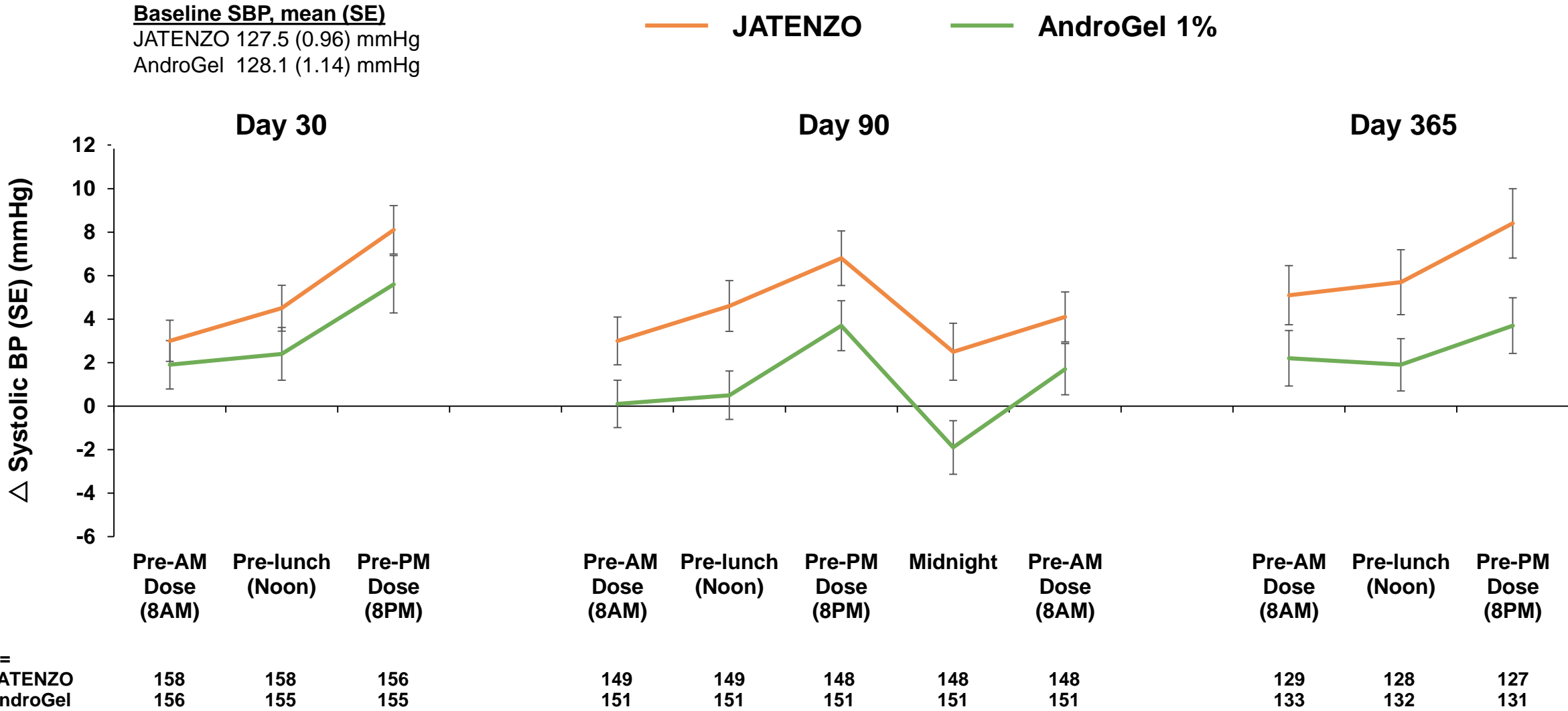


Study 09007: Changes from Baseline in Mean Systolic Blood Pressure Stable Over Time

Baseline SBP, mean (SE)

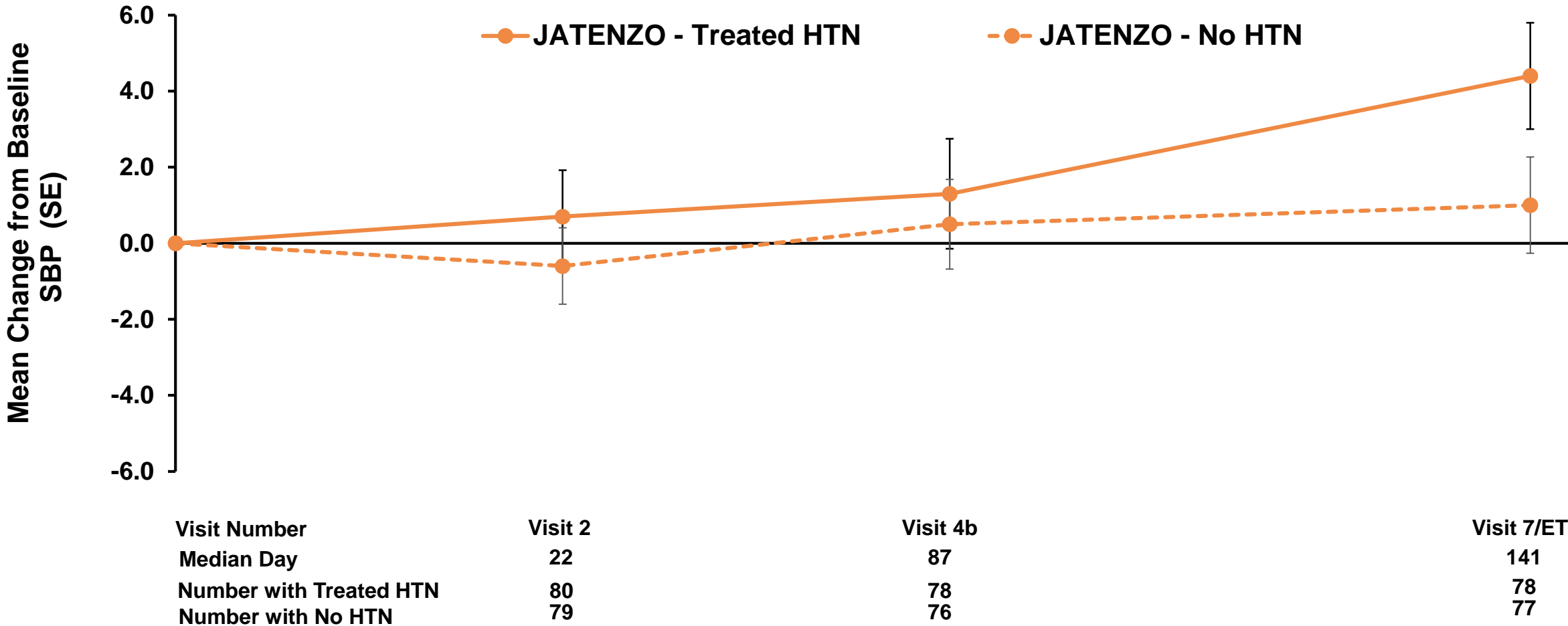
JATENZO 127.5 (0.96) mmHg

AndroGel 128.1 (1.14) mmHg



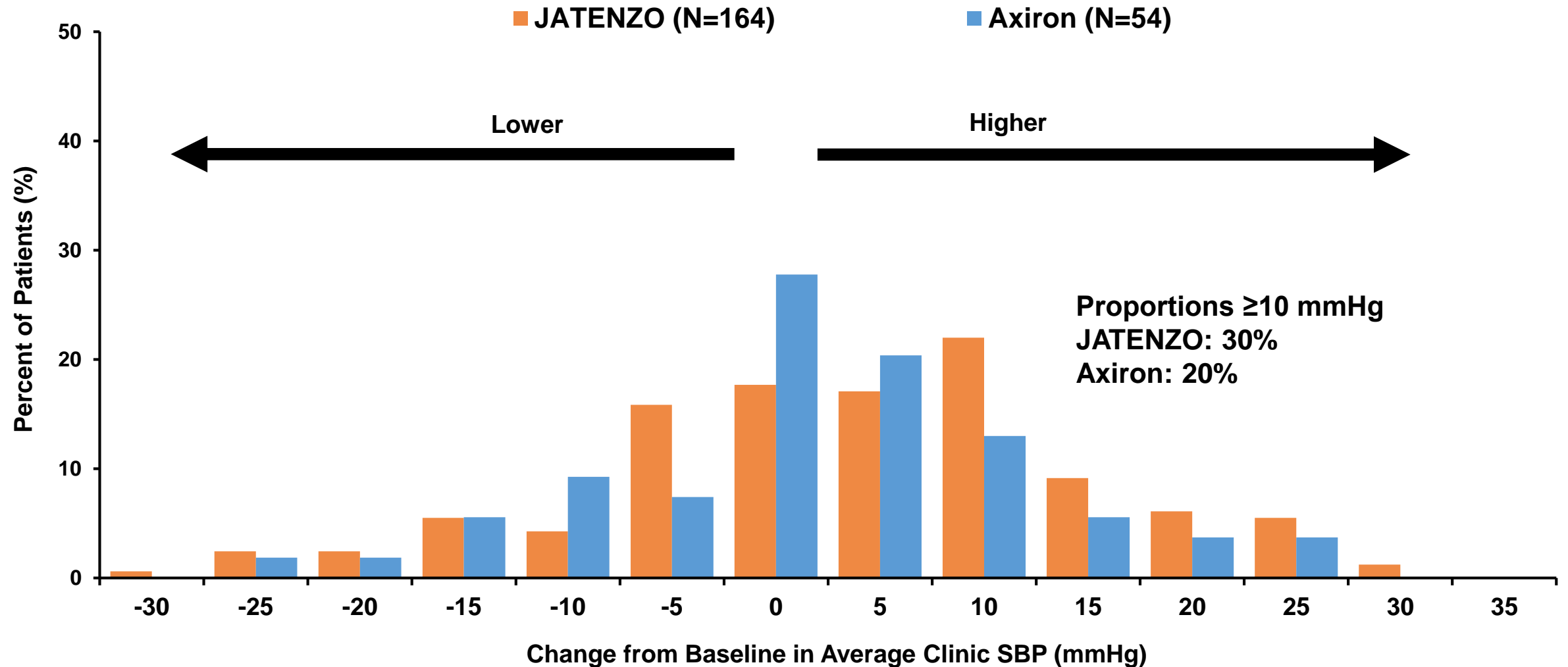
Times are approximate

Study 15012: Increase in Clinic Systolic BP With JATENZO Greater in Patients With Hypertension



Derived from the Safety population

Study 15012: Distribution of Changes in Clinic Systolic BP From Baseline to Visit 7/ET



Study 15012: Patients With ≥ 10 and ≥ 20 mmHg Increases in Clinic Systolic BP with Resultant Values at Final Visit

	JATENZO N=162 n (%)	Axiron N=54 n (%)
Δ SBP ≥ 10 mmHg		
And SBP ≥ 140	25 (15.4)	5 (9.3)
And SBP ≥ 150	10 (6.2)	3 (5.6)
And SBP ≥ 160	3 (1.8)	0
Not Meeting Above Criteria	137 (84.6)	49 (90.7)
Δ SBP ≥ 20 mmHg		
And SBP ≥ 140	9 (5.6)	3 (5.6)
And SBP ≥ 150	4 (2.5)	2 (3.7)
And SBP ≥ 160	1 (0.6)	0
Not Meeting Above Criteria	153 (94.4)	51 (94.4)

Study 15012: Shifts in 2017 ACC/AHA Classification by Clinic BP From Baseline to Final Post-Baseline Visit

Treatment Group	Baseline Classification*	Post-baseline Classification			
		Normal	Elevated	Stage 1 HTN	Stage 2 HTN
JATENZO N=162	Normal (22%)	12%	5%	4%	1%
	Elevated (13%)	3%	3%	4%	3%
	Stage 1 HTN (51%)	5%	6%	21%	19%
	Stage 2 HTN (14%)	1%	4%	5%	4%
Axiron N=54	Normal (41%)	19%	9%	11%	2%
	Elevated (13%)	2%	4%	6%	2%
	Stage 1 HTN (37%)	6%	4%	17%	11%
	Stage 2 HTN (9%)	2%	2%	0%	6%

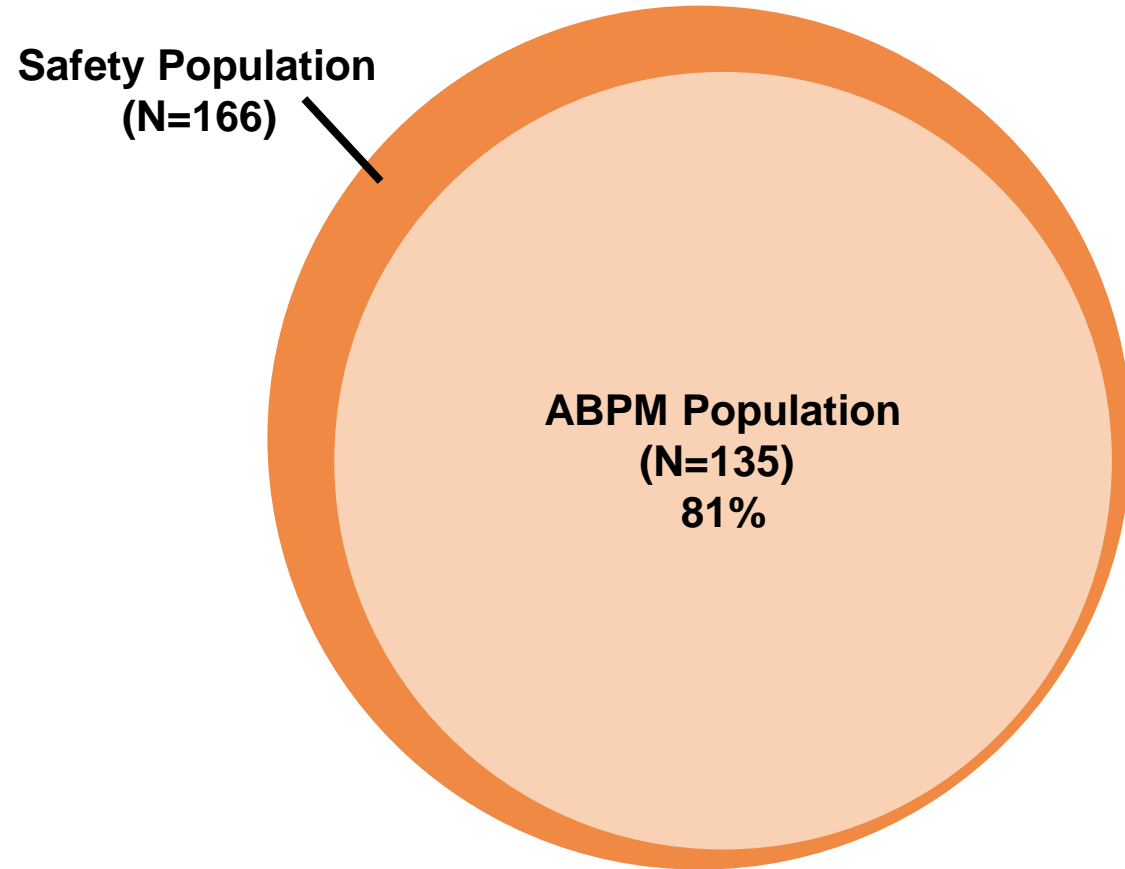
- **Comparable percentage of patients in each treatment group shifted upwards into Stage 1 (130-139/80-89 mmHg) or Stage 2 (\geq 140/90 mmHg) hypertension categories:**

JATENZO: 31%
Axiron: 32%

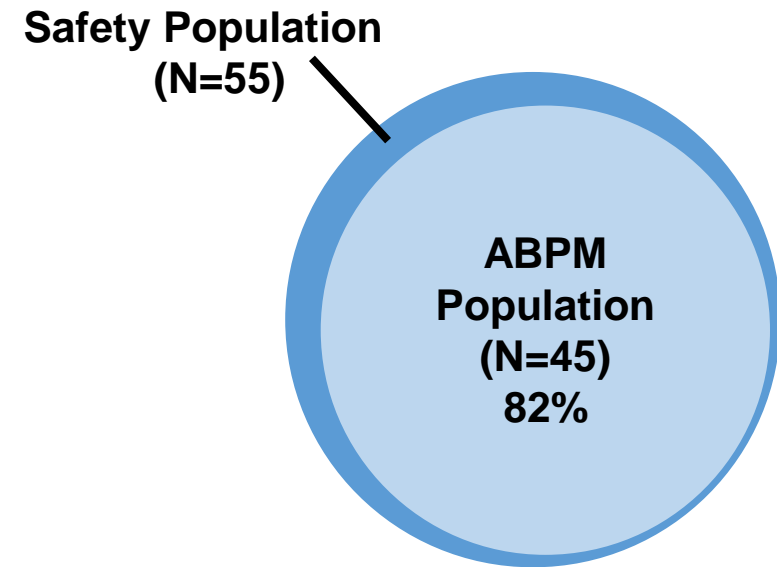
* 4 JATENZO subjects and 1 Axiron subject did not have follow up values and are not included.

Study 15012: Safety and ABPM Populations

JATENZO



Axiron



Safety Population: All patients who received at least one dose of study drug.

Clinic BP measured at Visit 1 (Baseline), Visit 2, Visit 4b, and Visit 7.

ABPM Population: All patients who have interpretable ABPM readings at both Screening and Visit 6.

Study 15012: Ambulatory BP Methodology

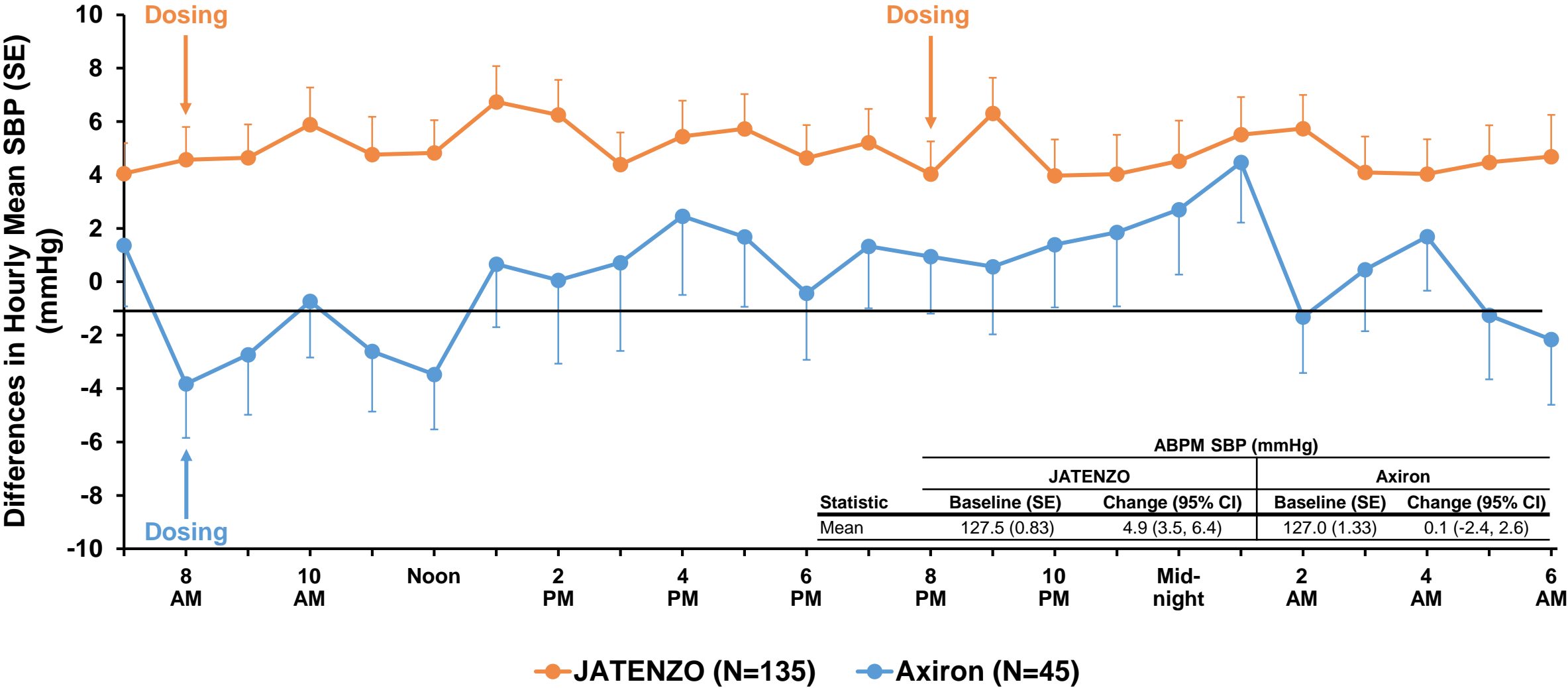
- **Ambulatory BP evaluated at baseline and Visit 6 (median day 136) using the Spacelabs 90207 recorder at 30 minute intervals for 24 hour period**
- **Quality control criteria: At least 23 hours of recording time; >2 hours of missing data with <80% device accepted values was not acceptable**
- **Analyses of ambulatory BP included 24 hour mean, daytime, nighttime, and hourly mean changes from baseline**

Study 15012: 24-hour ABPM SBP (mmHg) at Baseline and Change From Baseline to Visit 6

	Visit 6 (Median Day 136)			
	JATENZO N=135		Axiron N=45	
	Baseline	Change from Baseline	Baseline	Change from Baseline
Mean (SD)	127.5 (9.7)	4.9	127.0 (13.2)	0.1
95% CI	--	3.5, 6.4	--	-2.4, 2.6
LS Mean difference between treatment groups (95% CI) ¹	4.8 (1.9, 7.8)			

¹ Analysis of covariance with treatment group as a factor and baseline value as the covariate

Study 15012: Hourly Changes From Baseline in 24-hour Systolic BP (ABPM)



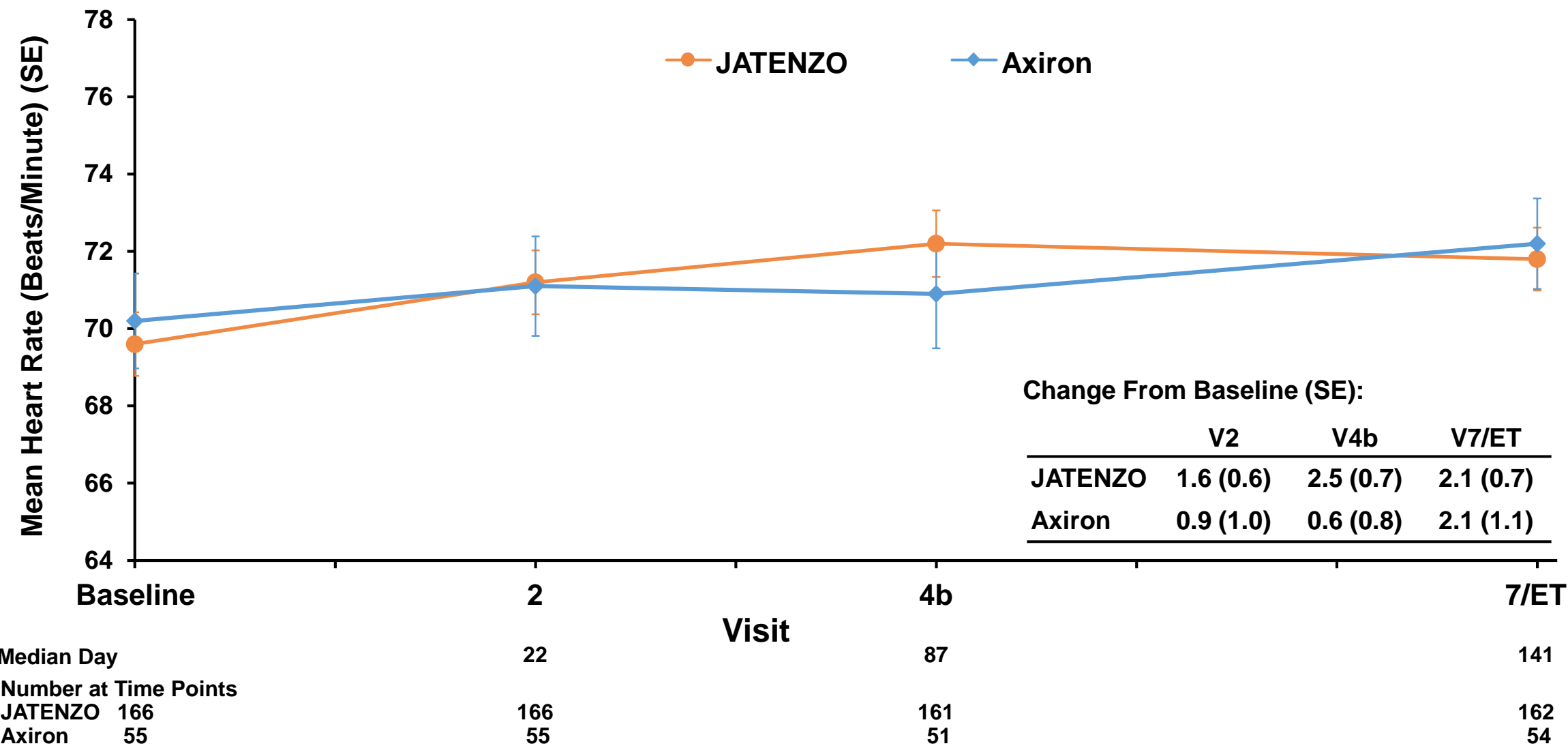
Study 15012: Mechanistic Assessments for JATENZO

SBP Elevations Did Not Identify Explanatory Factor

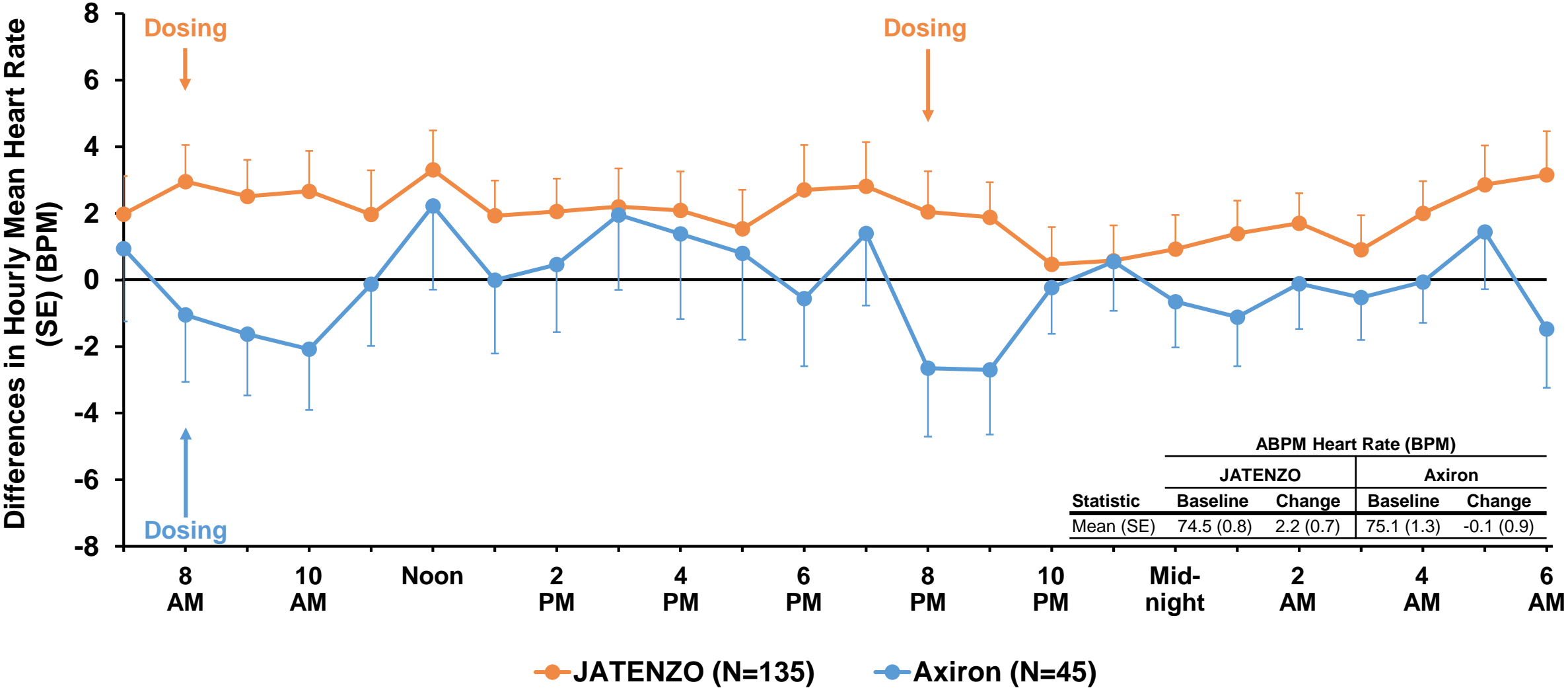
Potential Explanatory Factor	Clinic (V7-V1) R-squared	24-hour ABPM (V6-Screen) R-squared
Δ Hematocrit	0.008	0.013
Final Hematocrit	0.010	0.001
Δ Serum Potassium	0.004	0.017
Final Serum Potassium	0.001	0.000
Δ Heart Rate, clinic	0.004	NA
Final Heart Rate, clinic	0.001	NA
Δ Heart Rate, 24-hour ABPM	NA	0.055
Final Heart Rate, 24-hour ABPM	NA	0.012
Final Testosterone C _{avg}	0.008	0.025
Final Testosterone C _{max}	0.008	0.015

NA = Not Applicable

Study 15012: Clinic Heart Rates



Study 15012: Hourly Changes From Baseline in Heart Rate (From ABPM)



Blood Pressure and Heart Rate Summary

- **At baseline, patients randomized to JATENZO had higher clinic SBPs and greater number had medical history of hypertension**
- **Changes in clinic BP greater in treated hypertensives**
- **Outlier proportions of clinical relevance similar for JATENZO and Axiron**
 - ▶ No patient developed severe hypertension or required urgent management
- **Evaluation for mechanism failed to find scientific rationale for BP changes**
- **Heart rate changes (1-2 bpm) on JATENZO not clinically significant¹**

1. Hansen TW, Thijs L, Boggia J et al. Hypertension 2008; 52: 229-235.

Assessment of Lipids

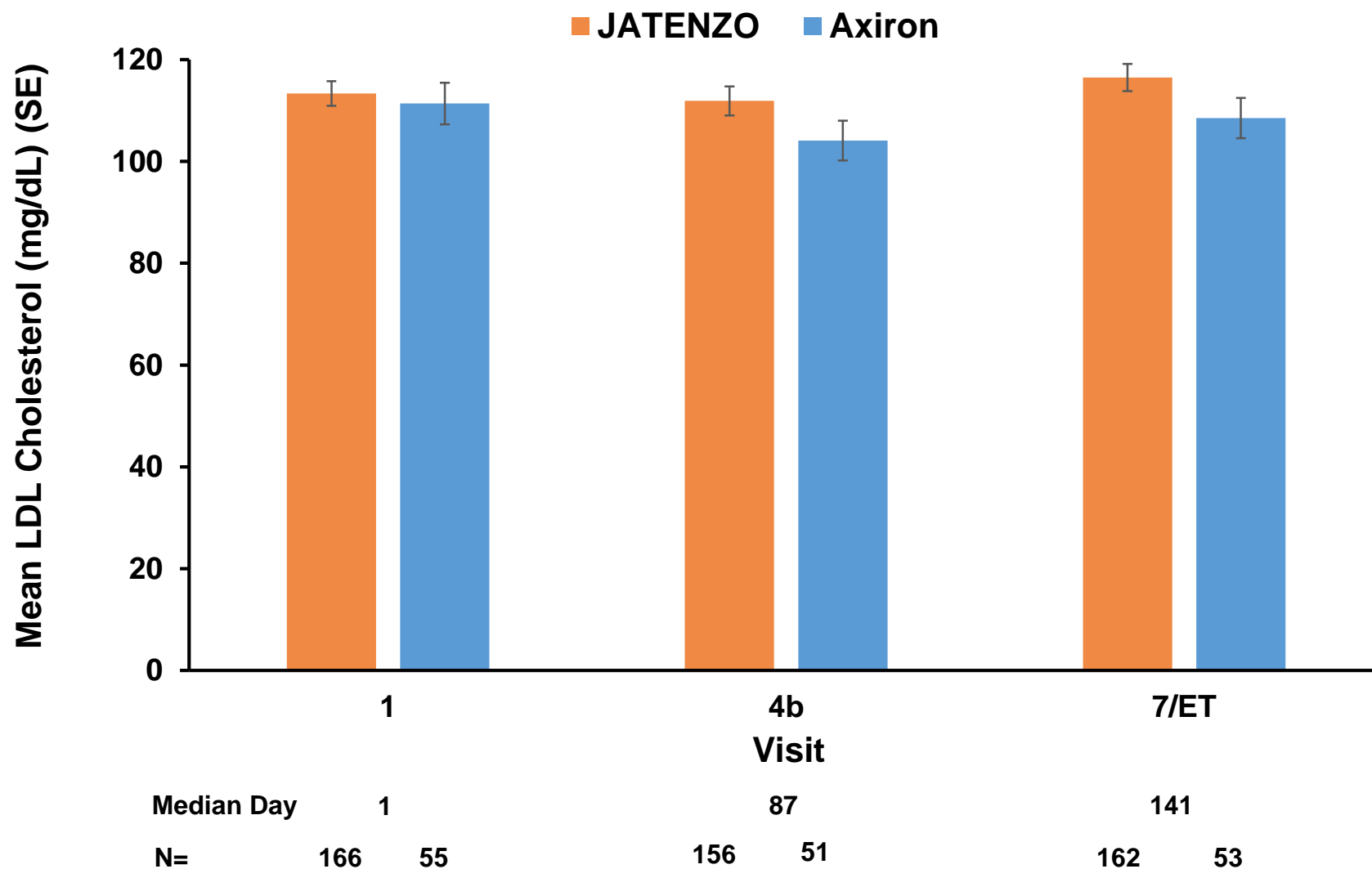
- **Study 15012**

- ▶ Fasting lipid profiles were obtained at baseline, Visit 4b (Median Day 87) and Visit 7 (Median Day 141)

- **Study 09007**

- ▶ Fasting lipid profiles were obtained at baseline, Day 30, Day 90 and Day 365

Study 15012: Mean LDL Cholesterol



Mean Change from Baseline (SE):

Visit 4b:

JATENZO: -1.20 mg/dL (1.92)

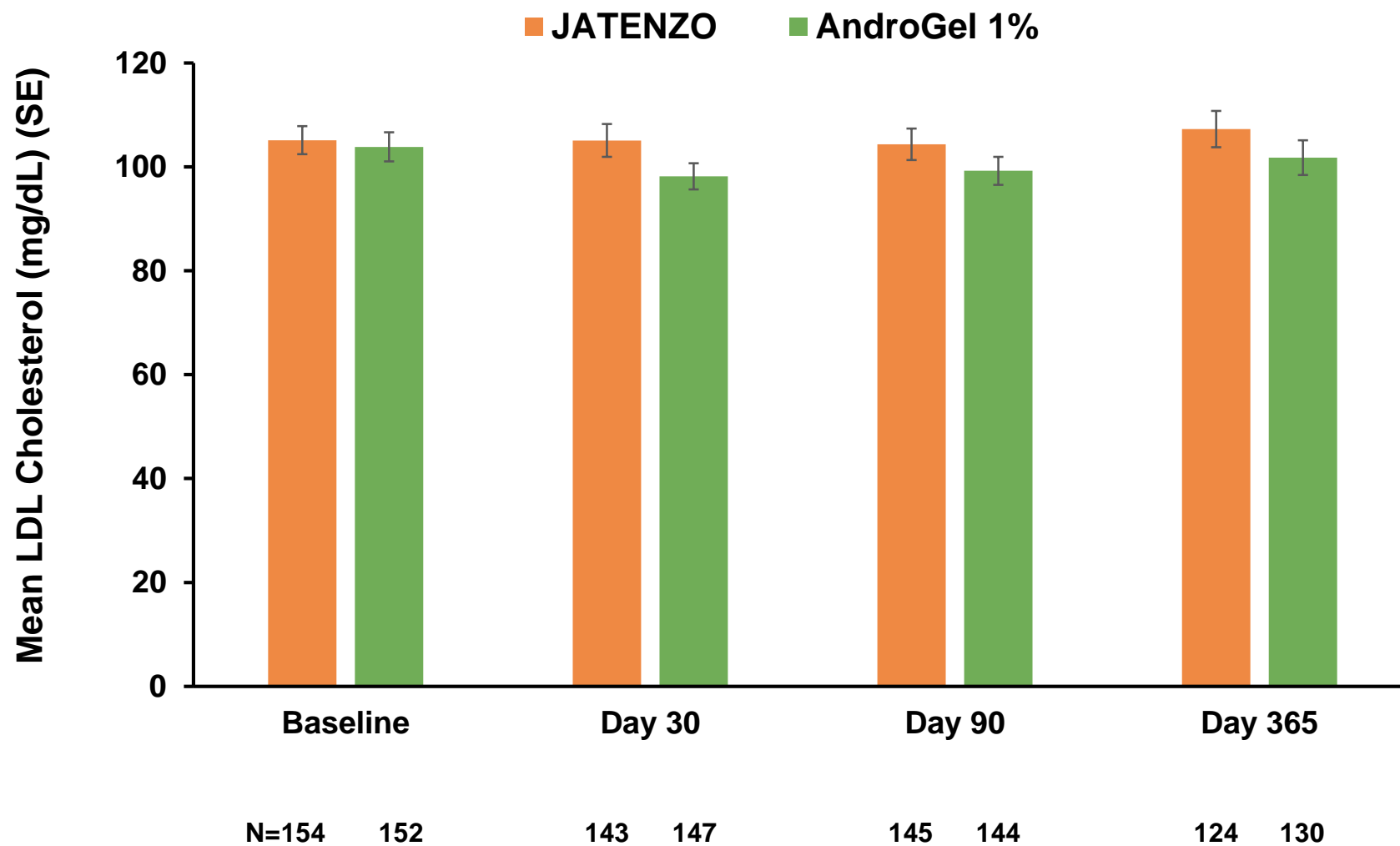
Axiron: -8.65 mg/dL (2.63)

Visit 7:

JATENZO: 3.51 mg/dL (2.00)

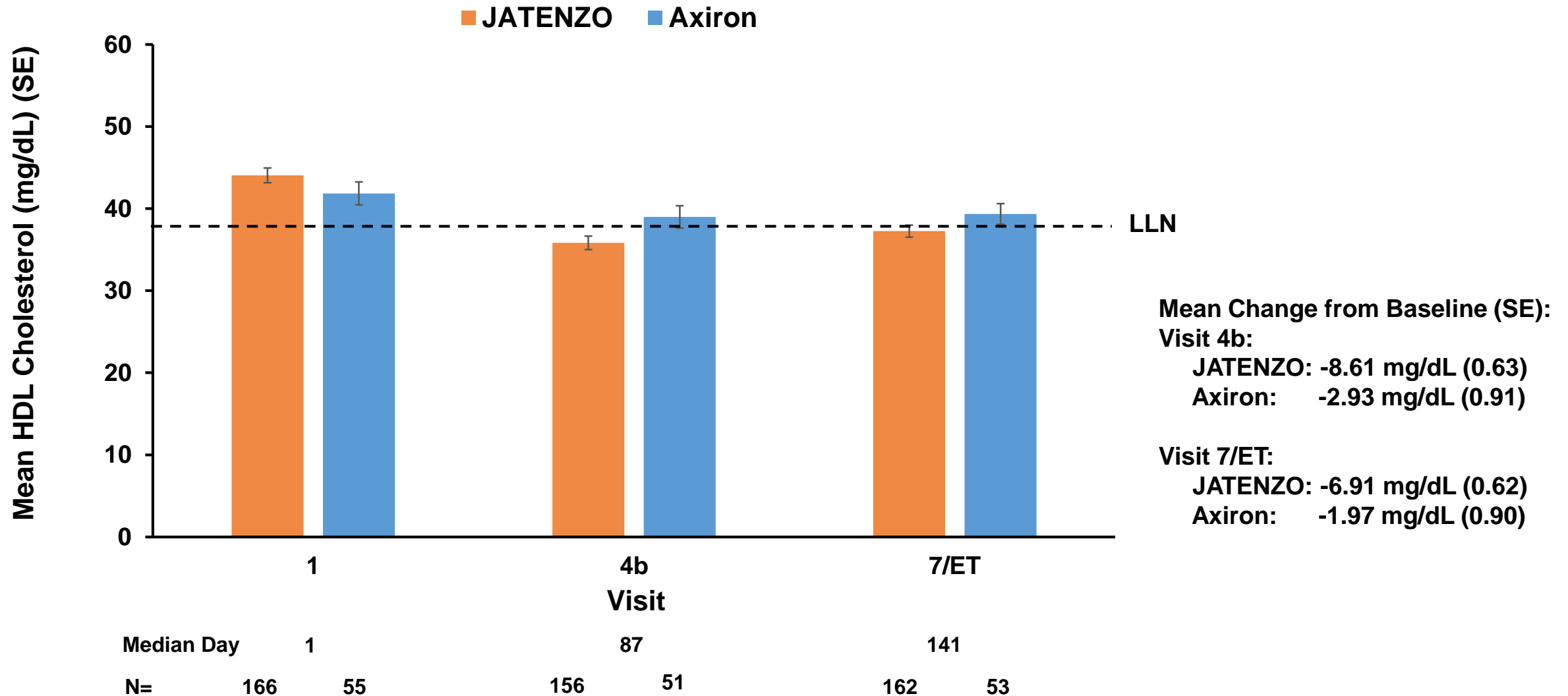
Axiron: -4.02 mg/dL (2.46)

Study 09007: Mean LDL Cholesterol

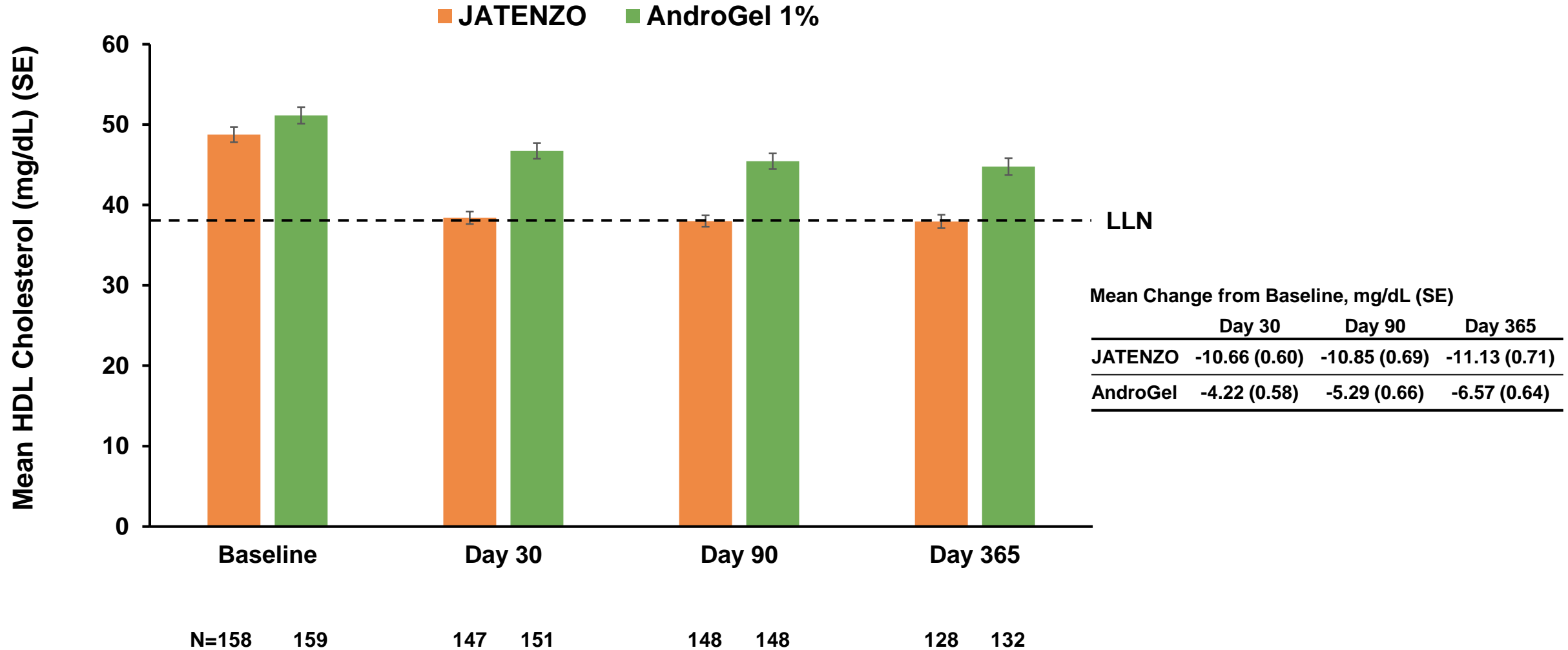


Mean Change from Baseline, mg/dL (SE)			
	Day 30	Day 90	Day 365
JATENZO	0.48 (2.07)	-1.39 (2.30)	-0.48 (2.37)
AndroGel	-5.94 (1.73)	-4.04 (1.88)	0.36 (2.14)

Study 15012: Mean HDL Cholesterol



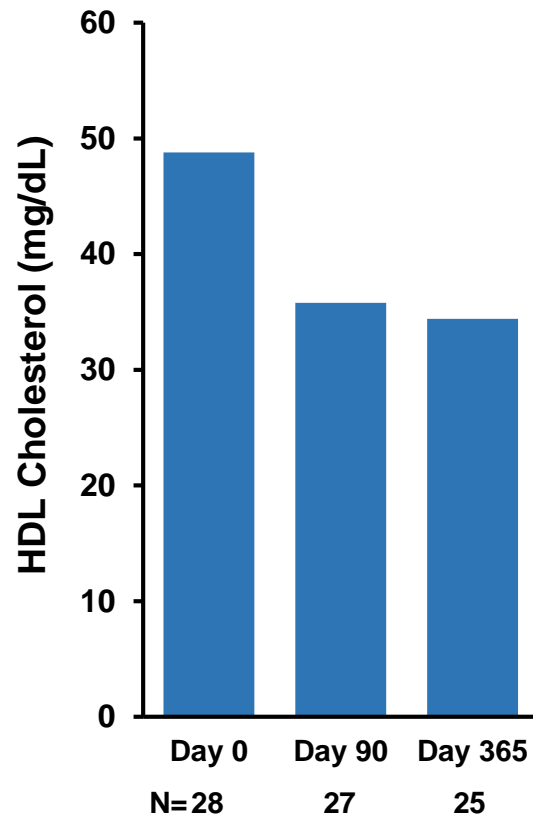
Study 09007: Mean HDL Cholesterol



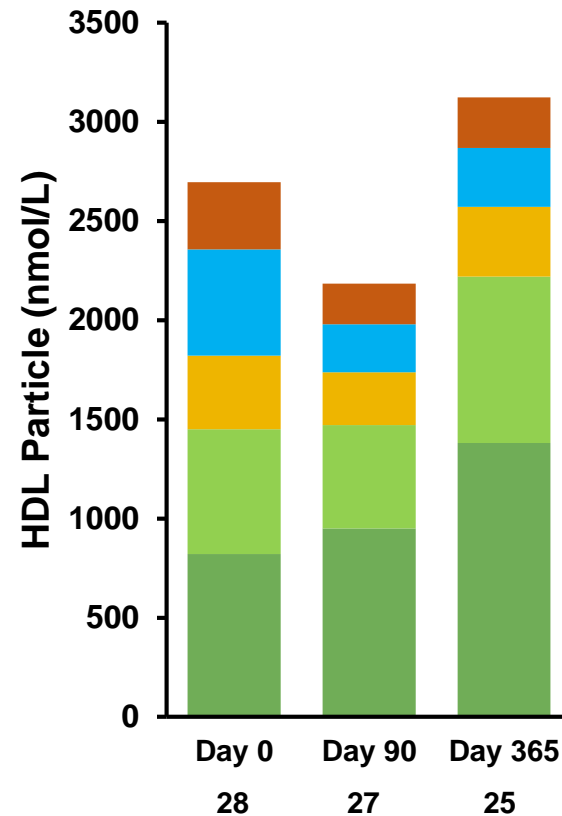
Study 09007 (CV Substudy): Reduction in HDL Cholesterol Not Reflected in HDL Particle Concentration

JATENZO

HDL Cholesterol

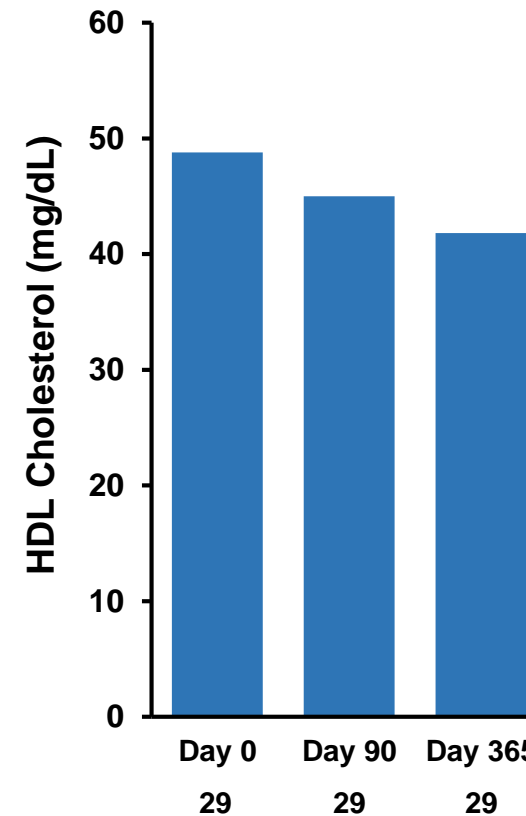


HDL Particle Concentrations¹

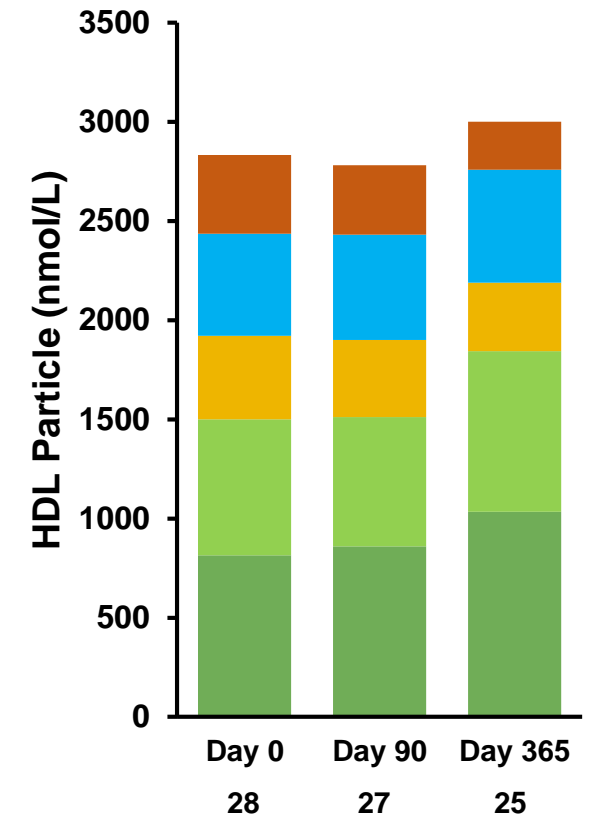


AndroGel 1%

HDL Cholesterol



HDL Particle Concentrations¹



Very Small (HDL3c) Small (HDL3b) Medium (HDL3a) Large (HDL2a) Very Large (HDL2b)

¹ Assayed by Ion Mobility Analysis per Caulfield, Krauss, et al. *Clinical Chemistry* 2008; 54: 1307-16.

Major Adverse CV Events in All Phase 3 Studies¹

	JATENZO N=471 n (%)	Transdermal T* N=215 n (%)
Patients	5 (1.1)	2 (0.9)
Events		
Non-fatal myocardial infarction	2 (0.4)¹	0
Coronary revascularization	2 (0.4)	1 (0.5)
Non-fatal stroke	2 (0.4)	1 (0.5)
Death	0	0

* Either Axiron or AndroGel 1%

¹ One Study 15012 patient with a history of multiple coronary events had a small, nonfatal MI that occurred after his final safety visit, when he was off therapy for ≈2 week. Since this event occurred when the patient was outside of the study window, it is not part of the safety database.

Cardiovascular Safety Summary

- **Moderate increases in systolic BP on JATENZO**
- **Small heart rate increases observed but not of clinical relevance**
- **Changes in hematocrit observed, testosterone class effect**
- **Changes in lipoproteins observed**
 - ▶ LDL changes small and inconsistent between studies
 - ▶ HDL particles involved in cholesterol efflux preserved despite HDL cholesterol decrease.
- **Cardiovascular events were infrequent and balanced – no causal relationship evident**

Management of JATENZO-associated CV Effects

- **Blood pressure values are assessable by all healthcare providers**
- **Clinic measurements can detect clinically important BP increases; changes in SBP with ambulatory monitoring were comparable to clinic**
- **Blood pressure increases can be managed**
 - ▶ Initiate or up-titrate antihypertensive therapy or
 - ▶ If clinically indicated, discontinue JATENZO
- **Increases in hematocrit, a known effect of testosterone replacement therapy, can be monitored and managed accordingly**
- **Monitoring of lipids indicated**
 - ▶ Manage LDL as typical in clinical practice
 - ▶ HDL changes need to be viewed in light of evolving understanding of HDL particle data

Safety Conclusions and Risk Mitigation

Theodore Danoff, MD, PhD

Chief Medical Officer, Clarus Therapeutics

General and CV Safety Conclusions

JATENZO's safety profile generally similar to other TRTs

- **Minor GI symptoms**
- **Decreases in HDLc not reflected by parallel decrease in HDL particles**
- **Increases in HCT are a class effect**
 - ▶ All TRT labels direct prescribers to monitor and manage HCT
 - ▶ Increases >54%: overall incidence with JATENZO was low (~5%), often transient, easily detectable, and treatable
- **SBP elevations measurable, monitorable, and manageable**
 - ▶ Increases not unique to JATENZO

Blood Pressure Risk Mitigation

Blood pressure should be routinely monitored and managed

- **Important for safe use of JATENZO as well as other TRT products**
- **History of hypertension suggests increased magnitude of BP elevations**
 - ▶ Hypertensives (already monitored and treated) need more careful monitoring
- **Check BP at 1, 3, and 6 months after starting JATENZO and as indicated**
- **After starting JATENZO, if BP elevated (per guidelines)**
 - ▶ Decide whether benefit of JATENZO warrants continuation
 - ▶ Manage BP according to guidelines and patient/HCP decision
 - ▶ If BP management difficult, consider alternative TRT or no TRT

Blood Pressure Risk Mitigation

Clarus will disseminate this information via

- **Medication guide distributed to patient with every prescription**
- **Medication guide available on web site**
- **Dear HCP letter to relevant groups (e.g., AUA and Endocrine Society members, high TRT prescribers)**
- **HCP education at regional/national meetings**
- **MSLs and specifically-trained sales reps**

Proposed Post-marketing Commitments

- 1. Enhanced pharmacovigilance**
- 2. Observational cohort study for MACE events**
- 3. Study to evaluate impact of JATENZO on pituitary-adrenal axis regulation of cortisol production**
- 4. Drug utilization study**

PM 1. Enhanced Pharmacovigilance

- **Enhanced data capture when adverse drug reactions (ADRs) related to MACE or abnormal adrenal function reported**
 - ▶ Develop data-capture forms to prompt reporter to give details including
 - Details of event
 - Comorbid conditions
 - Relevant laboratory values
 - Concomitant medications
 - JATENZO history including dose titration details
- **Follow up with the ADR reporter to obtain complete information**
- **Information will help in evaluation of causality**
 - ▶ Could trigger additional observational research

PM 2. Observational Cohort Study for MACE Events

Complements ongoing FDA-mandated TRT CV consortium trial

- **Objectives:** Assess rate of MACE among JATENZO-treated patients compared to those receiving alternate TRTs (such as topicals), adjusting for potential confounding
- **Source:** Electronic healthcare database(s)
- **Study Type:** Observational cohort
 - ▶ Consistent with studies requested by FDA to assess CV risk (e.g., mirabegron/Myrbetriq)¹
- **Duration:** Function of JATENZO uptake to generate adequate number of users
- **Study size:** TBD

1. Marguilis et al. *Eur J Clin Pharmacol*. 2017 Nov 13.

PM 3. Impact of JATENZO on Cortisol Production

Addresses recommendation by FDA endocrinology reviewer

- **Design:** Randomized open-label, 6 month ACTH-stimulation study of hypogonadal men treated with JATENZO or Axiron (randomized 1:1)
- **Objectives:**
 - Primary: Proportion of patients with a peak cortisol level ≥ 18 mcg/dL post-ACTH stimulation at 6 months
 - Secondary: Peak cortisol levels post-stimulation at 6 months
- **Endpoints:**
 - Cortisol and ACTH levels (pre-, 30, and 60 minute post-stimulation) at baseline and 6 months
 - Other – Total and free testosterone levels, CBG levels, free cortisol
- **Testing:** Cosyntropin stimulation (250 mcg IV) with time standardized at 8AM
- **Number of patients:** TBD (based on discussion with FDA and results from Study 15012)

PM 4. Drug Utilization Study

Addresses age and demographic distribution of patients prescribed JATENZO, and how it compares to other TRTs

- **Objective:** Proportion of JATENZO and other TRT prescriptions for patients 0-39 years, 40-64 years, 65-74 years, and >75 years
- **Source:** Drug-utilization databases
- **Study Type:** Observational
- **Impact of Study:**
 - ▶ Evaluate whether the prescribing landscape for TRTs, as reflected in age and other demographics of patients, has changed with the addition of JATENZO
 - If evidence of greater prescribing to certain subgroups (e.g., elderly), then increase HCP education regarding appropriate use of TRTs

Clinical Practice Perspective

Jed Kaminetsky, MD

*Clinical Assistant Professor of Urology, NYU School of Medicine
Medical Director, Manhattan Medical Research*

Testosterone Deficiency: Who to Treat

- **Signs and/or symptoms of hypogonadism**
- **Serum testosterone below the normal range (<300 ng/dL) on two sequential AM measurements**
- **History: no contraindications**
 - ▶ Severe untreated lower urinary tract symptoms
 - ▶ Presence or suspicion of prostate or breast cancer
 - ▶ Erythrocytosis
 - ▶ Untreated severe sleep apnea
 - ▶ Active cardiovascular disease
- **Physical exam including blood pressure**

Currently Approved TRT Products

Route of Administration	Selected Examples	Product-specific Limitations
Commonly Prescribed		
Transdermal gels and solutions	AndroGel AndroGel 1.62 Axiron	Transference Application site reactions
Transdermal patch	Androderm	Skin reaction to patch
IM injections	T Enanthate T Cypionate Aveed (TU)	Injection site pain Anaphylaxis Acute injection reactions (POME)
Uncommonly Prescribed		
Oral	Methyltestosterone	Liver toxicity
Buccal	Striant	Falls off application site
Intranasal	Natesto	TID; messy
Implantable pellets	Testopel	Surgical procedure; Extrusion

Monitoring Patients on T Replacement: One Month Follow Up

- **Symptoms**
- **T levels**
- **Titration**
- **Side effects**
- **Blood pressure**

Monitoring and Managing Blood Pressure Risk at One Month Follow Up

- **If blood pressure clinically significantly elevated, bring back for repeat blood pressure**
- **If elevated blood pressure confirmed**
 - ▶ Manage blood pressure and continue JATENZO, or
 - ▶ Stop JATENZO and start other TRT, or
 - ▶ Discontinue TRT

Monitoring and Managing JATENZO: Three and Six Month Follow Up

- **Symptoms**
- **Side effects**
- **T levels and dose adjustment if necessary**
- **Blood pressure**
 - If blood pressure clinically significantly elevated
 - Manage blood pressure and continue JATENZO, or
 - Stop JATENZO and start other TRT, or
 - Discontinue TRT
- **CBC**
 - If HCT elevated, confirm and manage
- **Lipids**
- **PSA**

Monitoring and Managing JATENZO: Three and Six Month Follow Up

- **Symptoms**
- **Side effects**
- **T levels and dose adjustment if necessary**
- **Blood pressure**
 - If blood pressure clinically significantly elevated
 - Manage blood pressure and continue JATENZO, or
 - Stop JATENZO and start other TRT, or
 - Discontinue TRT
- **CBC**
 - If HCT elevated, confirm and manage
- **Lipids**
- **PSA**



Potential Limitations of JATENZO and Their Management

Limitations

- **Class effects**
 - ▶ Increased hematocrit
 - ▶ Lipids
 - ▶ Increased PSA
- **GI adverse effects**
- **Not appropriate for patients with abnormal GI anatomy or function**
- **Meal time BID dosing**
- **Elevated BP**

Management

- **Patient selection**
- **Routine TRT monitoring**
- **Patient education**
- **Alternative therapy**
- **Lifestyle modification**
- **Blood pressure**
 - ▶ Monitoring
 - ▶ Managing

JATENZO's Potential Benefits

- **Easy to take oral treatment**
- **Start low approach to dosing**
- **Ability to customize dose**
- **Effective at bringing patients into eugonadal range**
- **Offers benefits associated with TRTs**
- **Avoids the risks of other delivery methods**
- **Should improve adherence necessary for chronic therapy**

JATENZO Risk/Benefit Conclusion

- **Provides the same benefits as other TRTs**
- **Acceptable general safety relative to TRT class**
- **Limitations associated with JATENZO easily monitored and managed**
- **Identifiable criteria for patients for whom JATENZO should not be prescribed**
- **Without limitations and inconvenience of other commonly prescribed TRTs**

Closing Comments

Robert Dudley, PhD, DABT

*Pharmacologist/Toxicologist and President & CEO
Clarus Therapeutics*

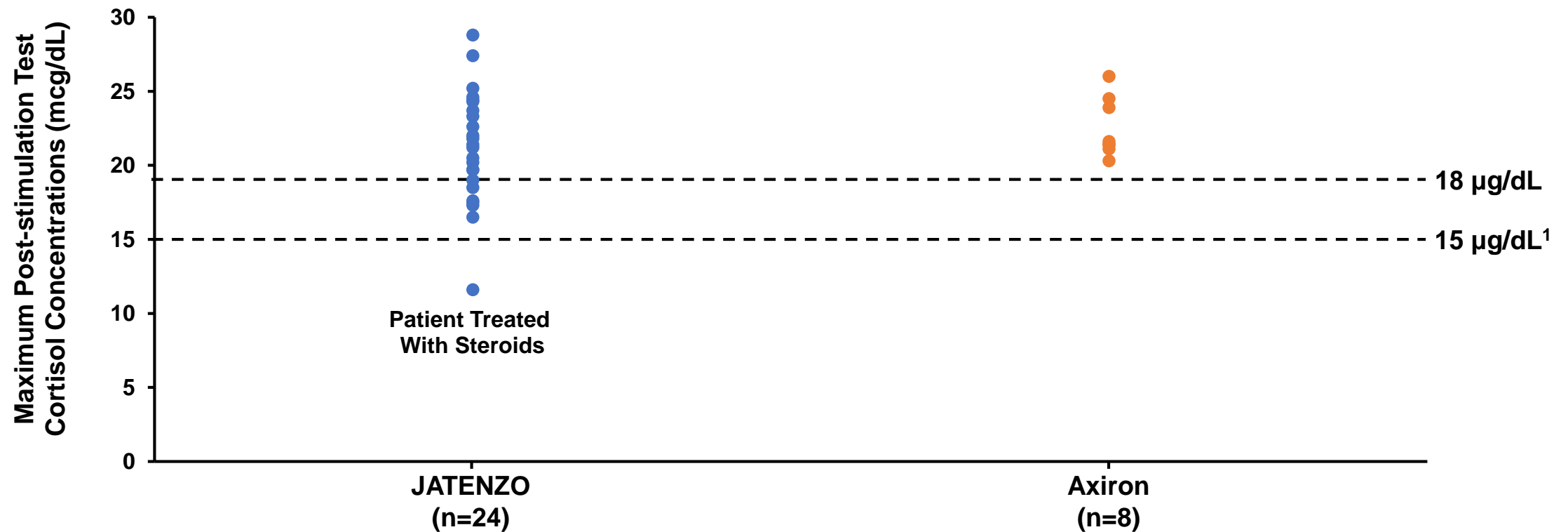
Additional Responders

Marc Gittelman, MD, FACS	UroMedix and South Florida Medical Research, Aventura, FL
James Dalton, PhD	Professor and Dean University of Michigan School of Pharmacy
Jim Longstreth, PhD	Pharmacokinetics Consultant
Nastya Kassir, PharmD, PhD, FCP	Director Certara Strategic Consulting (Pharmacokinetics Modeling and Simulation)
James H. Nichols, PhD, DABCC, FACB	Professor of Pathology, Microbiology and Immunology Vanderbilt University School of Medicine
Stephanie Page, MD, PhD	Robert B. McMillen Professor in Lipid Research Professor, Department of Medicine, Section Head Division of Metabolism, Endocrinology and Nutrition Harbor View Medical Center University of Washington
Sylvain Lachance, PhD	Associate Director Bioanalysis, Early Phase Syneos Health
Janet Wittes, PhD	President Statistics Collaborative, Inc.

Backup Slides Shown

Study 15012: Cosyntropin-Stimulated Cortisol Levels Unaffected by Treatment

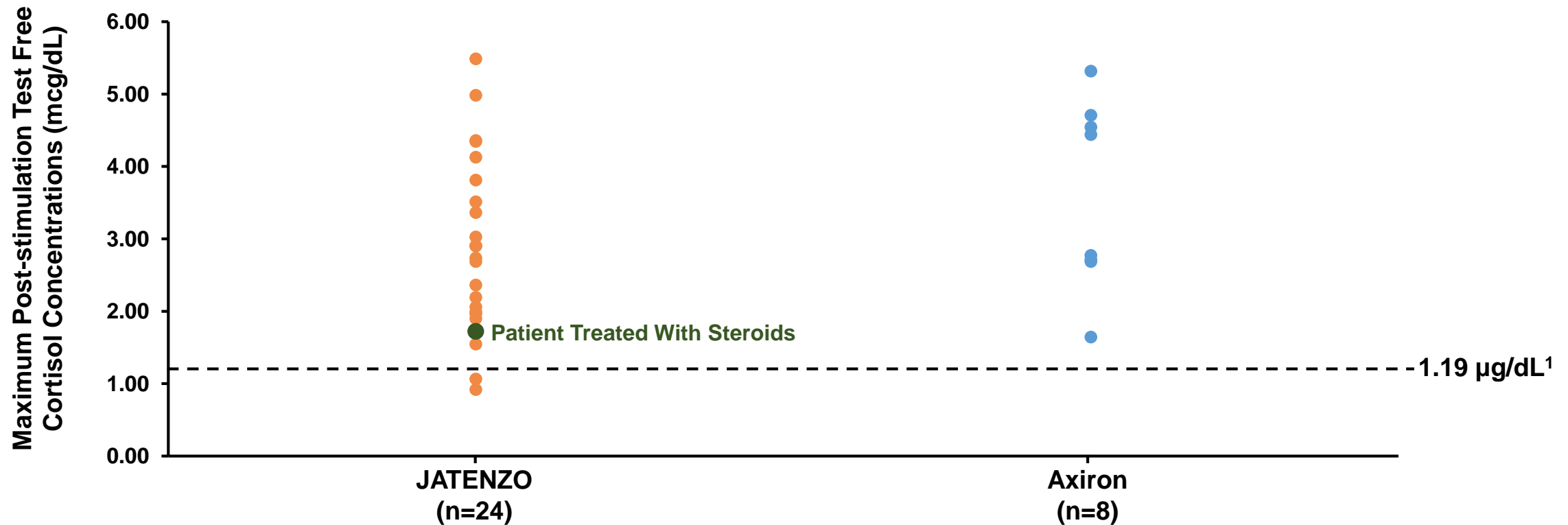
Cosyntropin stimulation testing (250 µg IV) done in subset of subjects at Visit 8



1. Dorin et al, Diagnosis of Adrenal Insufficiency, *Annals of Internal Medicine*, 2003.

Study 15012: Cosyntropin-Stimulated Calculated Free Cortisol Levels Unaffected by Treatment

Cosyntropin stimulation testing (250 µg IV) done in subset of subjects at Visit 8



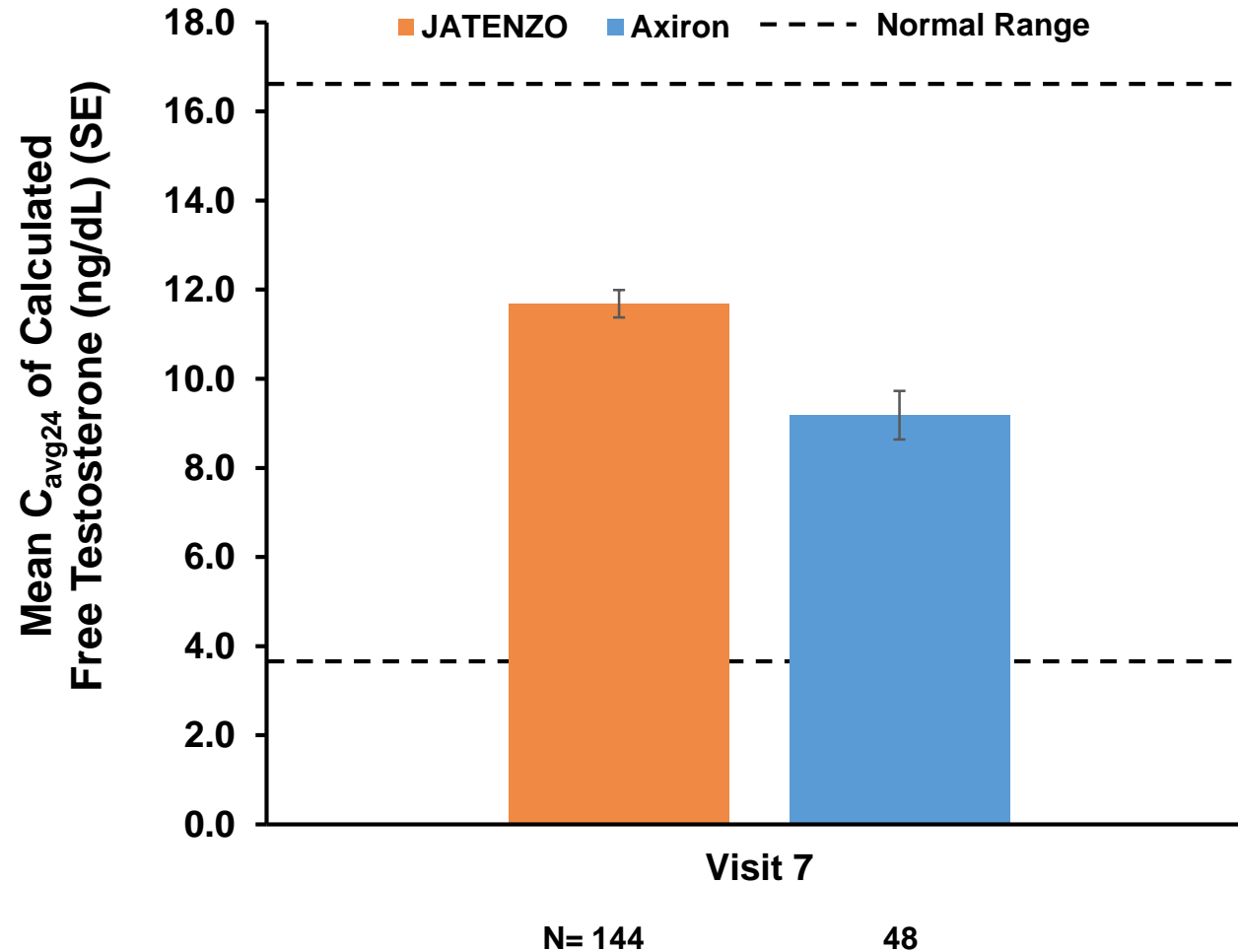
¹ Bancos I et al, Performance of free versus total cortisol following Cosyntropin stimulation testing in an outpatient setting. *Endocr Pract* 2015;21:1353-1363.

Three Phase 3 Studies: Key Dose-Titration Parameters

	Phase 3 Study		
	Study 09007	Study 12011	Study 15012
Starting JATENZO	316 mg BID ^a	316 mg BID ^a	237 mg BID
Available JATENZO	158, 237, 316, 396, and 474 mg	158, 237, 316, 396, and 474 mg	158, 198, 237, 316, and 396 mg
Testosterone Measure Used for Dose-Titration Decisions	C ₄₋₆ (sample drawn 4 to 6 hours postdose)	C ₃₋₅ (sample drawn 3 to 5 hours postdose)	24-hour C _{avg} (samples drawn during 24-hour period postdose)
Matrix Used for Monitoring Testosterone Concentration	Serum from Plain blood collection tube	Serum from Plain blood collection tube	Plasma from NaF-EDTA blood collection tube
Titration Boundaries	250 to 1100 ng/dL	250 to 700 ng/dL	350 to 800 ng/dL

Abbreviations: C_{avg} = average serum concentration; EDTA = ethylenediaminetetraacetic acid; NaF = sodium fluoride
^a In the original submission, the dose of JATENZO was described in testosterone equivalents, where 158 mg JATENZO is the molar equivalent of 100 mg testosterone.

Study 15012: Calculated Free-T Levels



Study 15012: Maximal Cortisol Concentration (µg/dL) Following Cosyntropin Stimulation at Visit 1 and Visit 8 by Treatment Group

	JATENZO N=23		Axiron N=8		p-value	
Maximal Cortisol Concentration (µg/dL)	Visit 1/Day 1 (Baseline)	Visit 8	Visit 1/Day 1 (Baseline)	Visit 8	Visit 1	Visit 8
Preinjection						
Mean (SD)	9.14 (3.304)	10.11 (3.676)	7.39 (3.631)	10.85 (4.441)		
Median	9.80	9.30	6.95	9.55		
Min, max	1.5, 15.4	3.1, 17.5	2.1, 13.5	6.5, 18.2		
Max concentration						
Mean (SD)	23.30 (2.688)	21.62 (3.271)	25.20 (5.495)	23.50 (3.095)	0.2064	0.1661
Median	24.00	21.40	22.70	22.65		
Min, Max	18.9, 29.0	16.5, 28.8	20.6, 35.4	20.3, 29.4		
Change from preinjection						
Mean (SD)	14.17 (3.747)	11.50 (3.633)	17.81 (5.136)	12.65 (3.700)	0.1056	0.1916
Median	14.00	11.30	16.85	13.60		
Min, Max	5.1, 20.2	3.7, 18.6	13.1, 29.0	7.8, 16.9		
Within treatment p-value	<0.0001	<0.0001	<0.0001	<0.0001		
Difference in Maximum Concentration Postinjection (Visit 8 - Visit 1)					0.5255	
Mean (SD)	-1.69 (3.456)		-1.70 (3.411)			
Median	-1.50		-1.10			
Min, max	-7.5, 7.7		-6.0, 3.9			
Within treatment p-value	0.0287		0.2015			
Difference in Change from Preinjection (Visit 8 - Visit 1)					0.9914	
Mean (SD)	-2.66 (4.384)		-5.16 (4.509)			
Median	-2.60		-4.90			
Min, max	-13.2, 4.5		-12.2, 0.9			
Within treatment p-value	0.0081		0.0143			

Cosyntropin stimulation test sub-study population excluding patient 102-023.

Study 15012: Clinic and 24 Hour ABPM SBP (mmHg) in Same Individuals

JATENZO

Safety Population
(N=166)

ABPM Population (N=135)

	Clinic SBP Mean (SE)	ABPM SBP Mean (SE)
BL	127 (0.91)	128 (0.84)
CFB	3.4 (0.98)	4.9 (0.75)

Axiron

Safety Population
(N=55)

ABPM Population (N=45)

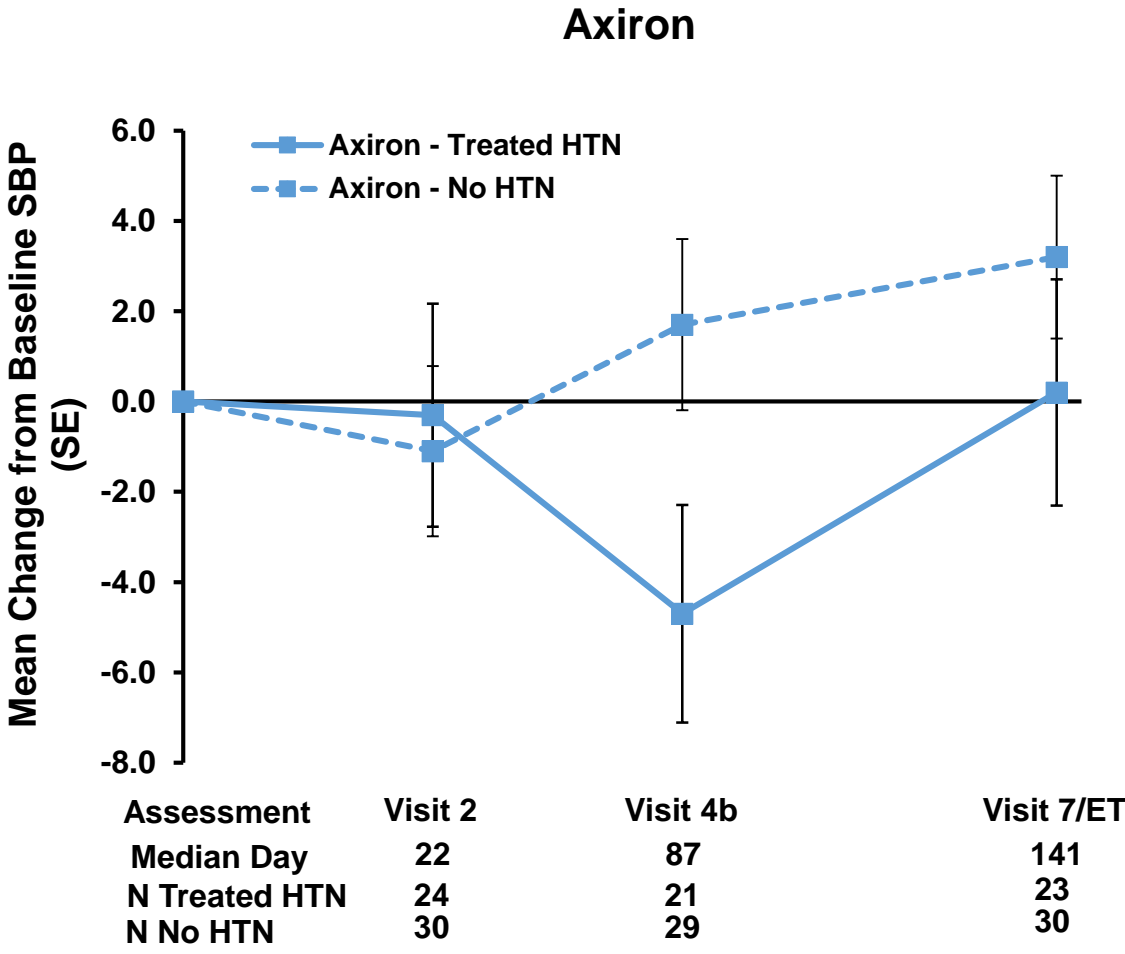
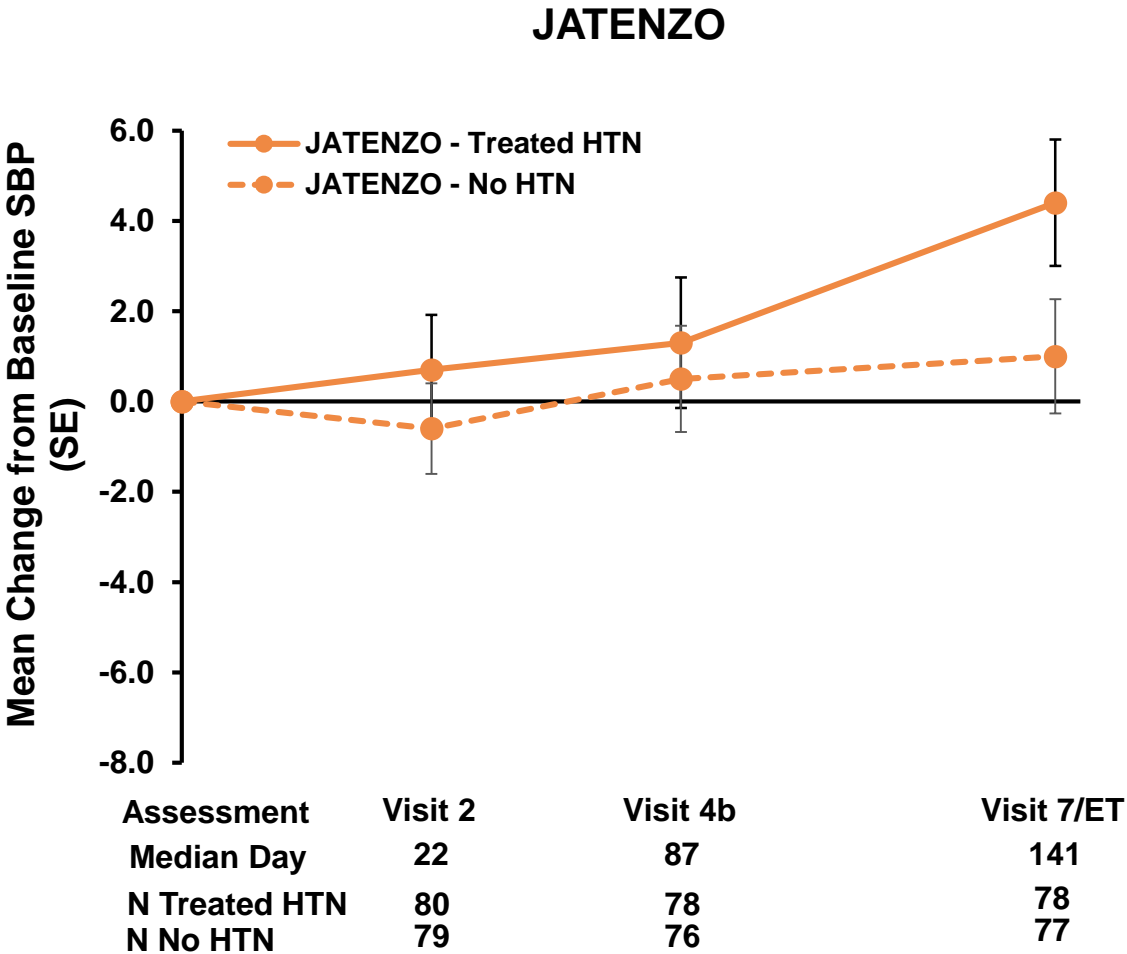
	Clinic SBP Mean (SE)	ABPM SBP Mean (SE)
BL	124 (1.94)	127 (1.97)
CFB	2.0 (1.51)	0.18 (1.40)

Safety Population: All patients who received at least one dose of study drug. Clinic BP measured at Visit 1 (Baseline), Visit 2, Visit 4b, and Visit 7.

ABPM Population: All patients who have interpretable ABPM readings at both Screening and Visit 6.

BL=baseline; CFB=change from baseline

Study 15012: Change From Baseline in Clinic SBP by Treatment and Hypertension History



Relative AR Binding Efficacy of TU and DHTU at High Concentrations Observed in Hypogonadal Men (Study 09007) is <1%

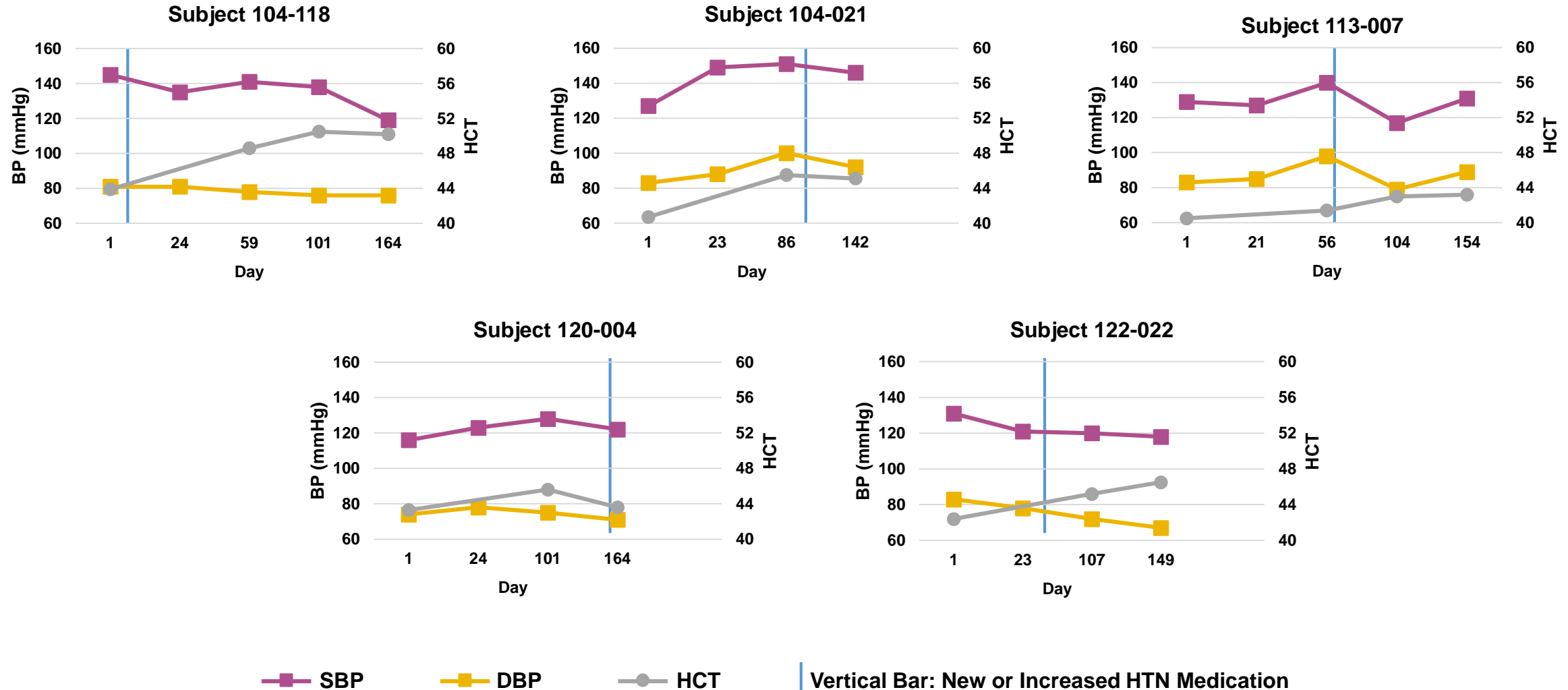
	10µM Screen (% Inhibition)	AR Binding (Ki, nM)	Relative Potency	Relative AR Binding Efficacy	
				Molar AUC* Relative Potency (% of Total)	Molar C _{max} * Relative Potency (% of Total)
T	101%	1.12	1	522.8 (55.7%)	58.1 (63.7%)
DHT	-	0.28*	4	412.4 (43.9%)	31.6 (35.2%)
TU	76%	1200	0.00093	2.1 (0.2%)	0.7 (0.8%)
DHTU	29%	-	<0.00093	1.4 (0.15%)	0.3 (0.3%)

*Miller, DD, et al (2013). “Chapter 40: Men’s Health” in *Foye’s Principles of Medicinal Chemistry*, 7th Edition, Lemke, TL et al (editors). Lippincott Williams & Wilkins, Baltimore.

Study 15012: Subjects Who Received New or Changed Anti-hypertensives

- **12 JATENZO subjects received a new or changed dose of antihypertensive medication**
 - ▶ Prior history of hypertension on treatment – 8 patients
 - ▶ Prior history of hypertension not treated – 2 patients
 - ▶ No history of hypertension reported – 2 patients
- **Response to added/increased medication**
 - ▶ Reduced BP – 5 patients
 - ▶ No change in BP – 3 patients
 - ▶ Increased BP – 2
 - ▶ Unevaluable – 2 (medication stated at end of study)

Study 15012: JATENZO Subjects Treated for Increased Blood Pressure – BP Decreased (N=5)



Why Did Clarus Switch From Plain to NaF-EDTA Collection Tubes for Study 15012?

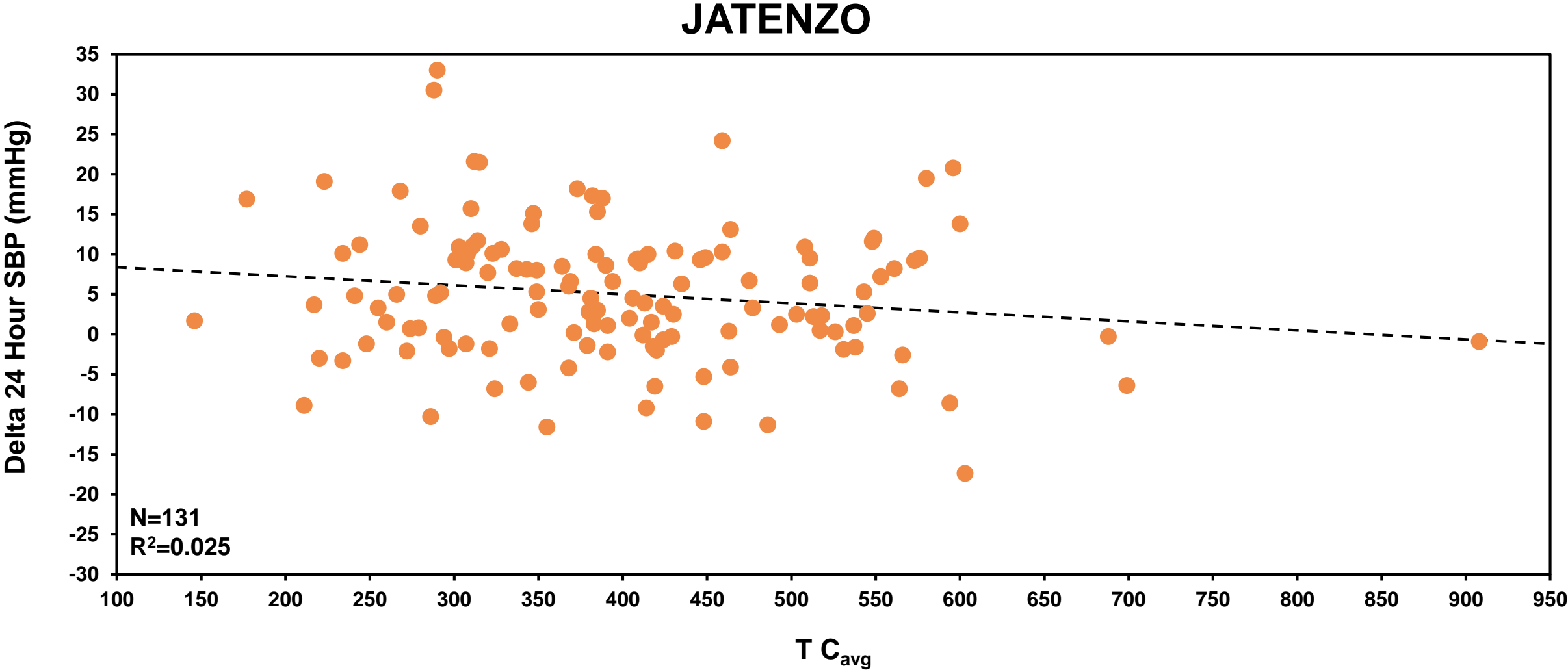
- **Studies conducted to evaluate esterase-mediated conversion of T-esters in blood** *[Wang et al (2008) Steroids 73: 1345-1352]*
 - T-enanthate (TE) and T-undecanoate (TU) added to whole blood with and without NaF
 - Excess conversion of TE → T observed but blocked by NaF
 - No conversion of TU → T
- **Flaw identified by Lachance et al** *[(2015) Future Sci OA 1(4), FSO55]*
 - TU is completely soluble in 5% ethanol + 95% phosphate buffer
 - BUT when solubilized TU added to whole blood per Wang et al study, TU precipitates and cannot be acted upon by non-specific esterases
- **Clarus confirmed the data of Lachance et al and used NaF-EDTA tubes for CLAR-15012** *[Submitted for publication]*

Lachance et al: Conversion of TU into T at Different TU Concentrations and Incubation Times

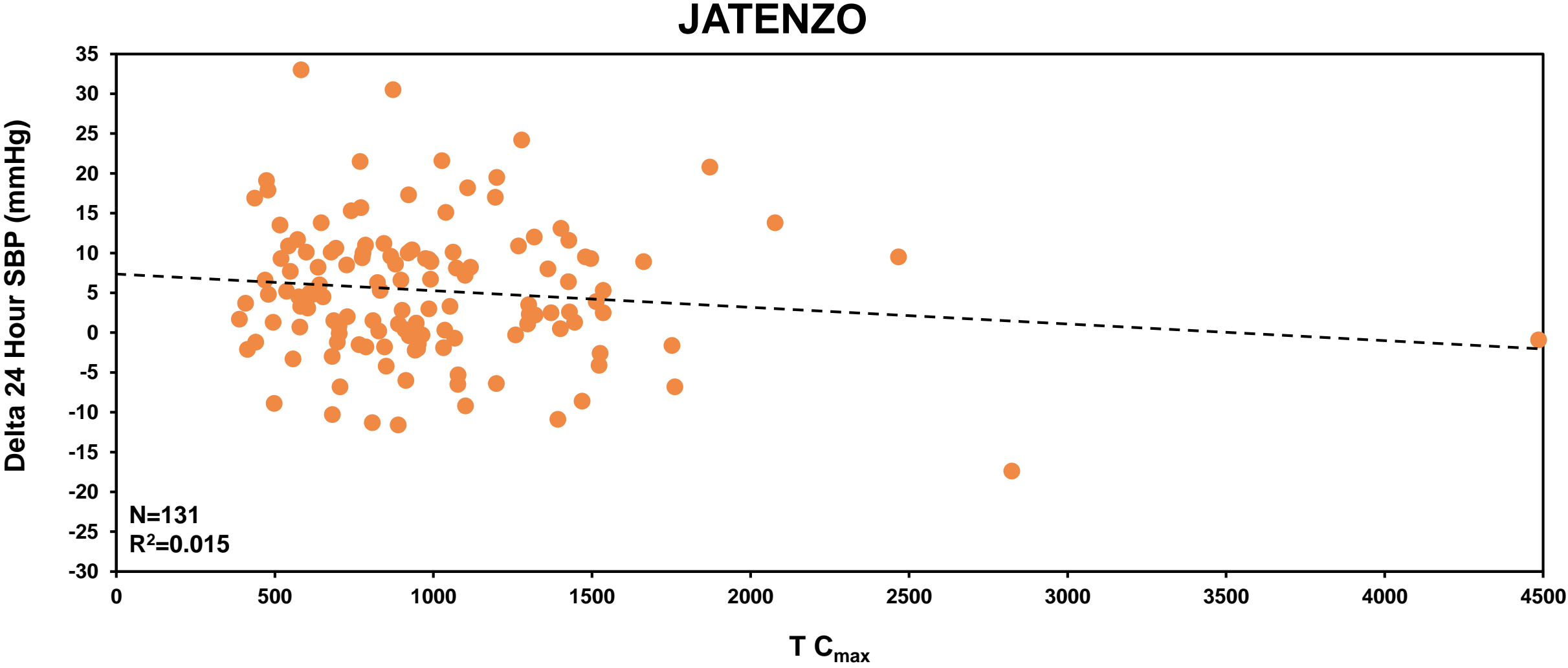
TU Concentration Fortified (ng/dL)	Duration of Incubation (min)	Concentration Testosterone Measured (ng/dL)	% Difference vs TU=0	% Difference 30 vs 60 min
0	0	23.75	-	-
1500	30	36.76	54.8	24.6
	60	45.80	92.9	
10,000	30	152.66	542.8	65.8
	60	253.18	966.0	
30,000	30	306.02	1188.5	73.9
	60	532.19	2140.8	
70,000	30	732.49	2984.2	72.4
	60	1262.81	5217.1	

Lachance, Dhingra, Bernstein *et al.*
Future Sci.OA, (2015)
TU=testosterone undecanoate; T=testosterone

Study 15012: Relationship of 24 Hour SBP (Change from Baseline) to T C_{avg} at Visit 7/ET



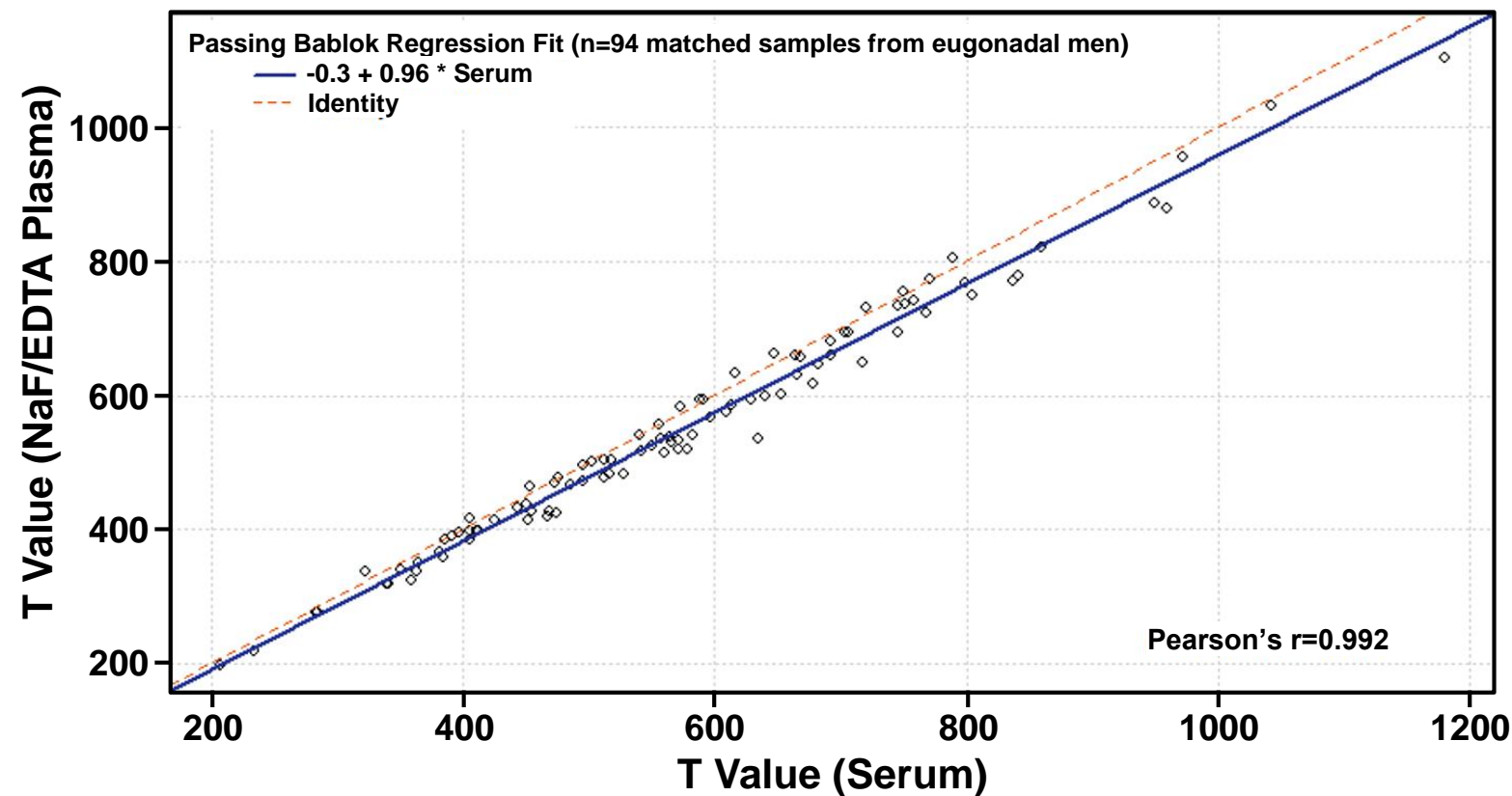
Study 15012: Relationship of 24 Hour SBP (Change from Baseline) to T C_{max} at Visit 7/ET



Use of NaF-EDTA Collection Tubes in Real-World Clinical Practice

- **Potential post-collection conversion of TU → T is an issue for any oral TU product**
 - Collection of blood into Na-EDTA tube inhibits conversion to yield most accurate T value
- **NaF-EDTA tubes commercially available on large scale**
- **Clarus actively working with major commercial clinical laboratories to validate NaF-EDTA matrix for T assay as well as manufacturers of platform immunoassays**
 - LC/MS-MS: LabCorp; Quest Diagnostics
 - Immunoassay platforms: Roche Diagnostics; Abbott; Siemens; Beckman-Coulter, Ortho
- **Preliminary data indicates little appreciable difference in T values from 'normal' matrix (e.g., serum) v. NaF-EDTA plasma**
 - NaF does not interfere with assay
- **Use of standard collection tube may overestimate T by about 15% but in most cases, this will not result in incorrect dose adjustment for patients prescribed JATENZO**
 - Bias toward under dosing and lower risk of high T levels

Study 16014: Passing Bablok Regression Fit of T Values for NaF-EDTA Plasma v. Serum [Roche Cobas *Electrochemiluminescence Immunoassay*]



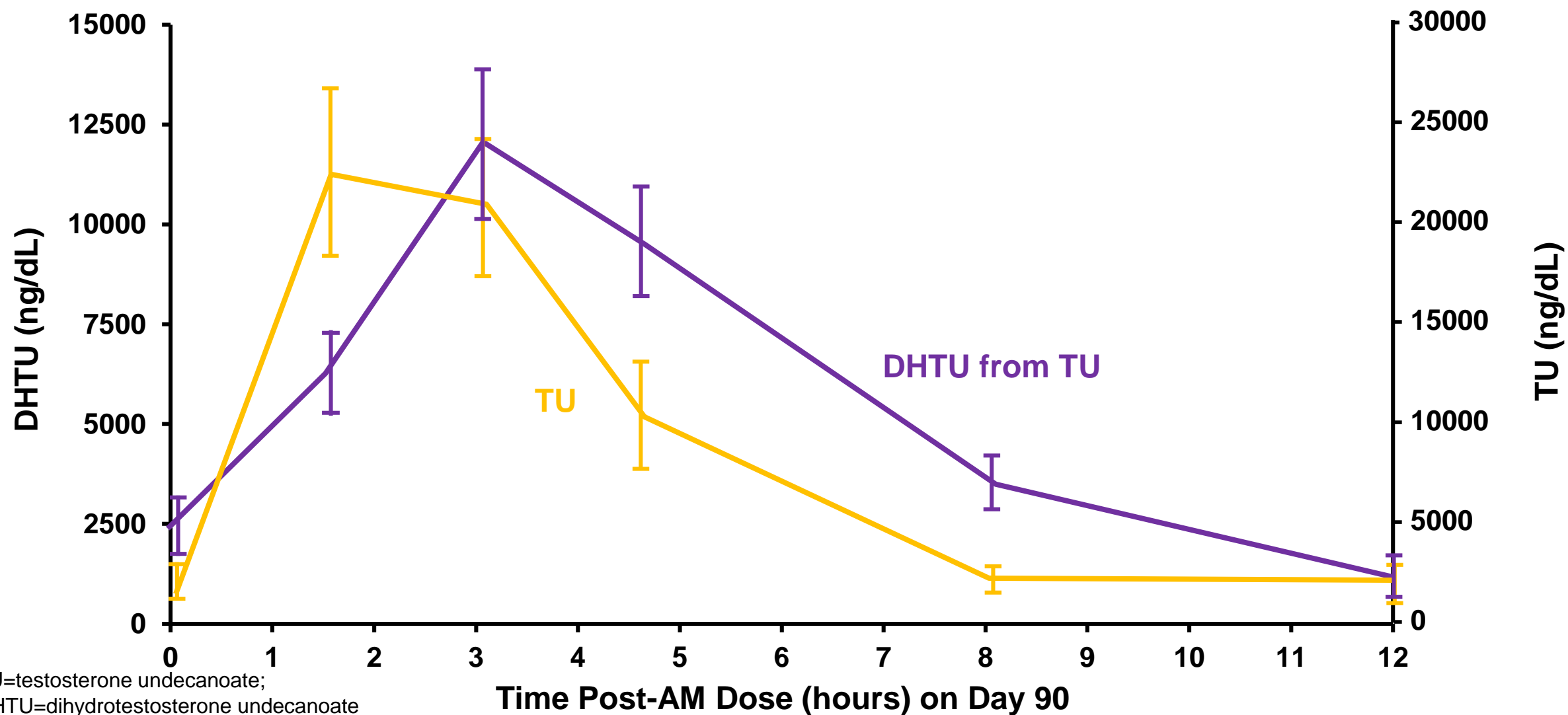
	R Estimate (95% CI)	Medcalc Estimate (95% CI)
Intercept	-0.30 (-14.1, 14.9)	-0.30 (-14.1, 14.9)
Slope	0.96 (0.93, 0.99)	0.96 (0.93, 0.99)
Pearson's r	0.992	0.991

Abbott Testosterone Immunoassay Accommodates NaF-EDTA Plasma Matrix

- **Assay: Abbott Architect i2000 analyzer with 2nd Gen Testosterone II Reagents**
- **Samples: 3 Male Volunteers had blood drawn into Li-heparin tube (standard tube for assay) and NaF-EDTA tube**

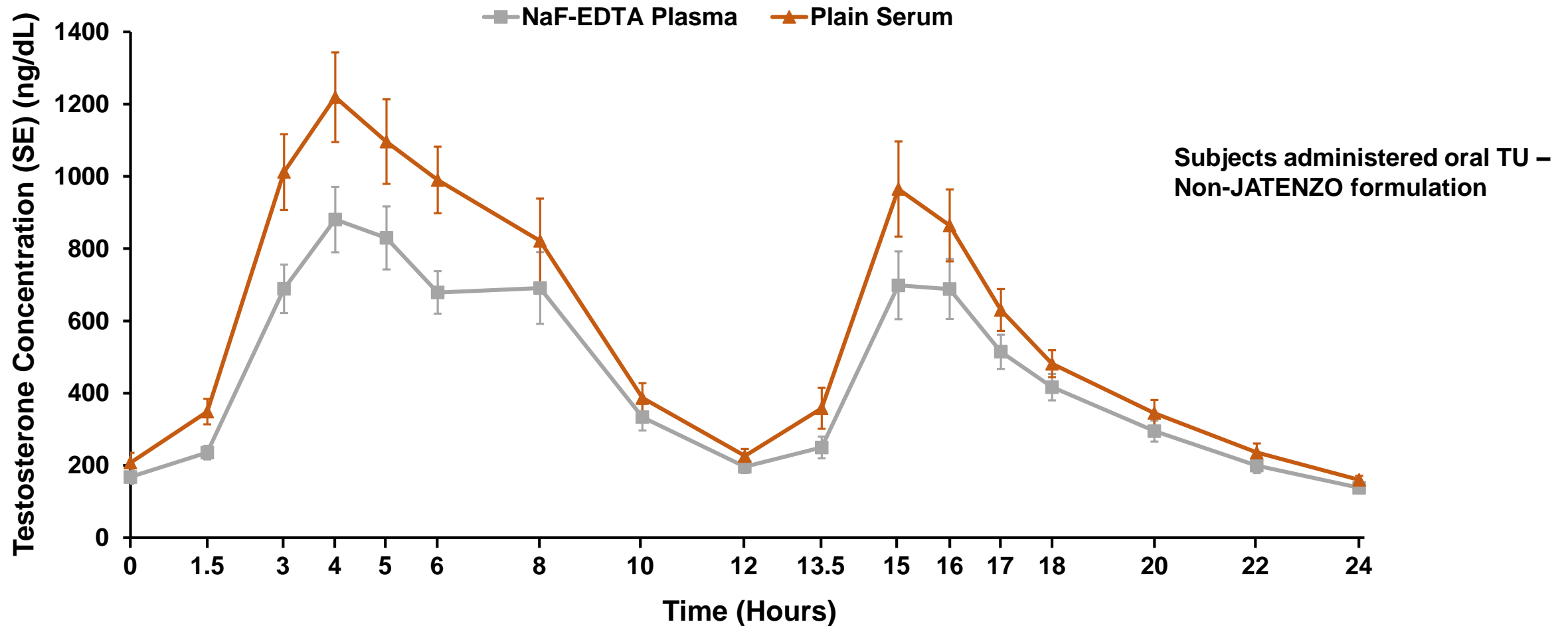
Volunteer	Standard (Li-Heparin) (ng/dL)	NaF-EDTA (ng/dL)	% Difference
1	240.60	225.33	-6.4%
2	471.12	487.93	+3.6%
3	229.03	256.83	+12.1%

Study 09007: Serum TU and DHTU on Day 90 (N=26)



TU=testosterone undecanoate;
DHTU=dihydrotestosterone undecanoate
Mean \pm SE

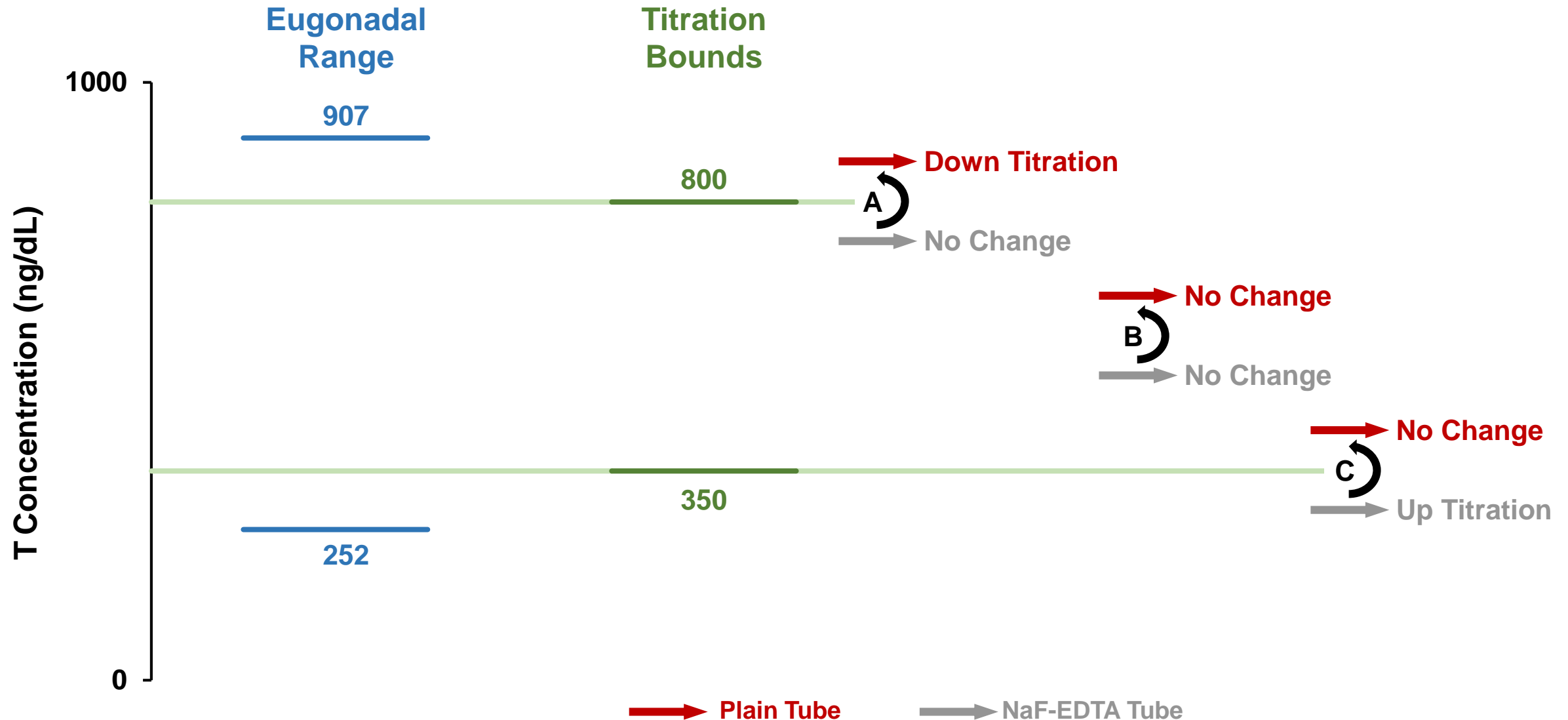
Lachance, et al: T Concentrations in NaF-EDTA Containing Tubes and Plain (Red Top) Tubes



Lachance, et al. *Future Sci.* OA. 2015

Plasma from blood collected in NaF-EDTA containing tubes. Serum from blood collected in plain red top tubes.

Potential Impact of Collecting Status Sample in Plain (Red-Top) Tube Rather than NaF-EDTA Tube



Significantly Lower Stimulated Cortisol on Testosterone

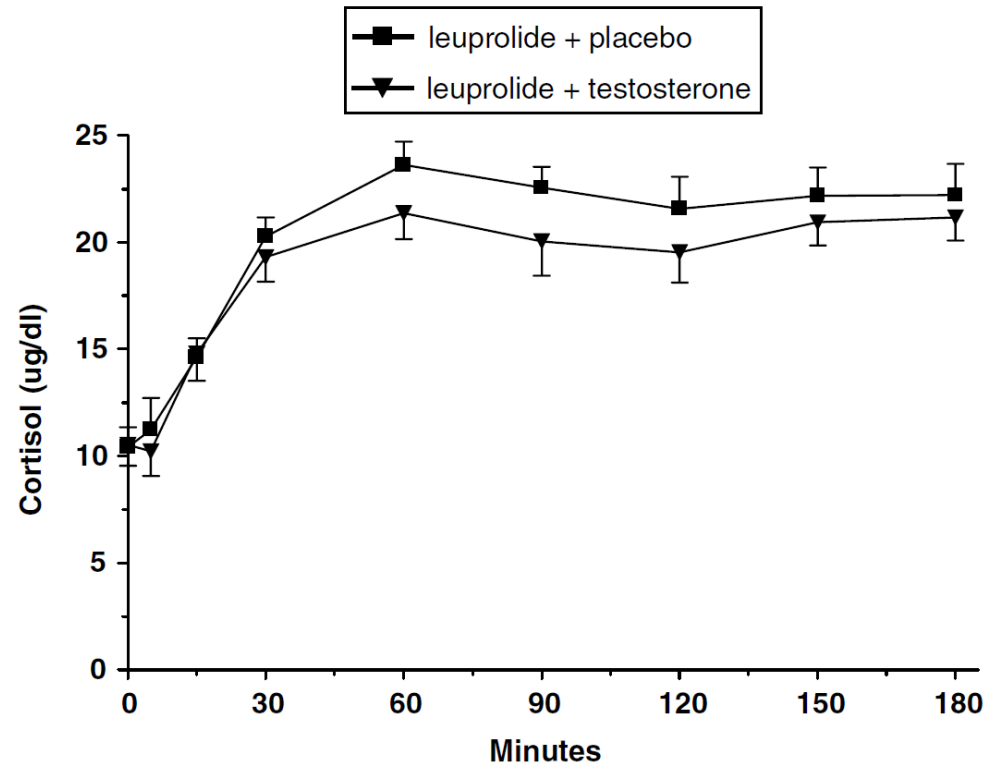


Figure 1 CRH-stimulated cortisol and ACTH levels (mean \pm SE) during hypogonadal (leuprolide plus placebo) and testosterone replaced (leuprolide plus testosterone) conditions in men. Significantly lower stimulated cortisol levels ($p < 0.05$) and significantly higher stimulated ACTH levels ($p < 0.05$) are seen during testosterone administration.