

# CROI 2007

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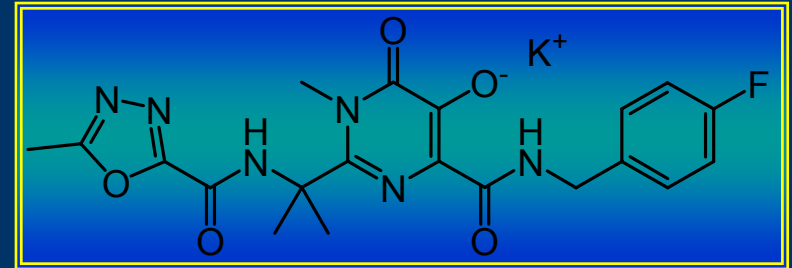
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# Raltegravir:

## A Novel HIV-1 Integrase Inhibitor

- A new mechanism of action
- Potent *in vitro* activity
  - $IC_{95} = 33 \text{ nM} \pm 23 \text{ nM}$  in 50% human serum
  - Active against:
    - multi-drug resistant HIV-1
    - CCR5 and CXCR4 HIV-1
  - HIV resistant to raltegravir remain sensitive to other ARTs
  - Synergistic *in vitro* with all ARTs tested
- Potent activity in combination therapy in Phase II studies
  - in ART-naive patients at Week 24 (Markowitz et al, IAC 2006, Abst THLB0214)
    - 85 – 95% with HIV RNA < 50 copies/mL
  - In patients failing therapy with triple class resistant virus at Week 24 (Grinsztejn et al, ICAAC 2006, Abst H-1670b)
    - 57-67% with HIV RNA < 50 copies/mL



# BENCHMARK-1 and BENCHMARK-2: Phase III Studies of Raltegravir (MK-0518) a Novel HIV-1 Integrase Inhibitor

By the BENCHMARK-1 and BENCHMARK-2 Study  
Teams

- BENCHMARK: *Blocking integrase in treatment  
Experienced patients with a Novel Compound  
against HIV: MeRcK, MK-0518*
- BENCHMARK-1 (Protocol 018)
  - Europe, Asia/Pacific, Peru
- BENCHMARK-2 (Protocol 019)

# BENCHMARK 1 and 2: Trial Design

2 identical ongoing Phase III studies (in different countries)  
Randomized (2:1), double-blind, placebo controlled

**ART-Experienced adult patients**

Documented genotypic/phenotypic resistance to  $\geq 1$  drug in each of 3 classes (NNRTI + NRTI + PI)  
HIV RNA > 1000 copies/mL

**Raltegravir (400 mg BID) + OBT  
(n=462)**

**Placebo + OBT  
(n=237)**

**Primary Endpoints (Week 16):  
HIV RNA and CD4 counts  
Adverse experiences**

Patients virologically failing after  $\geq 16$  weeks could enter open-label RAL arm

# Baseline Patient Characteristics

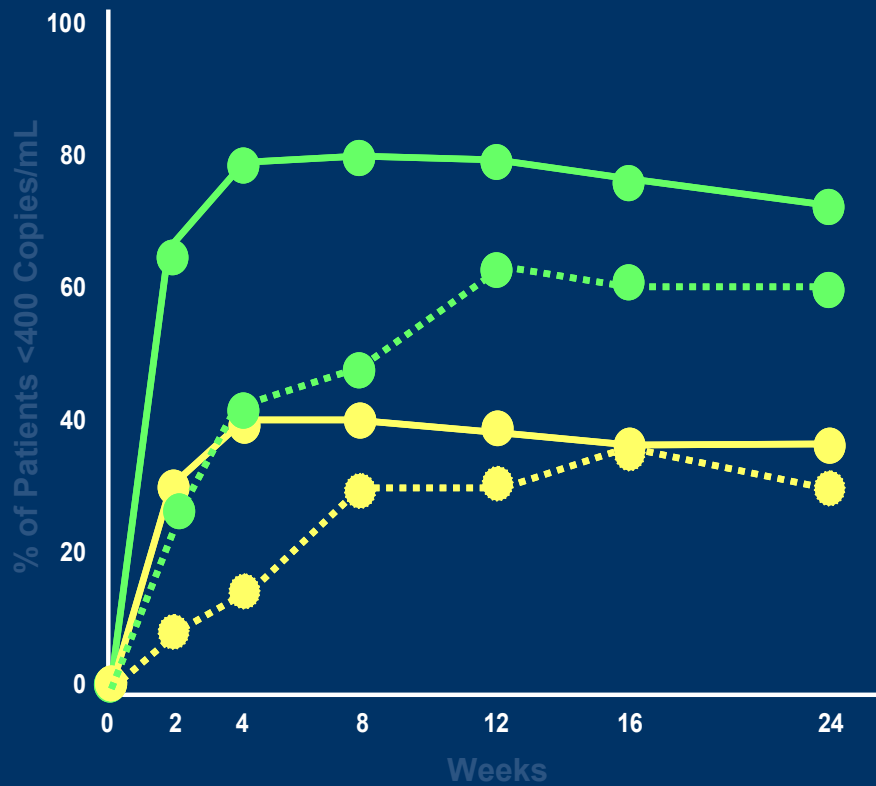
	BENCHMRK-1		BENCHMRK-2	
	RAL (n = 232)	Placebo (n = 118)	RAL (n = 230)	Placebo (n = 119)
Mean Age, yrs (SD)	46 (9)	44 (8)	45 (9)	46 (8)
% Male	84	87	91	90
% Caucasian	75	81	55	65
Mean CD4 Count, cells/mm <sup>3</sup>	156	153	146	163
GM Viral Load, copies/mL (log <sub>10</sub> HIV RNA)	40519 (4.6)	31828 (4.5)	48366 (4.7)	47789 (4.7)
% AIDS	94	90	91	92
Median Yrs of Prior ARTs (median # ART)	11 (12)	10 (12)	10 (12)	10 (12)
% Hep B+/% Hep C+	8/15	4/20	10/3	3/4
% GSS <sup>§</sup> 0/1	30/33	29/41	20/44	26/40
% PSS <sup>§</sup> 0/1	19/29	18/33	10/34	19/27
% new enfuvirtide in OBT	21	20	19	20
% new darunavir in OBT	27	25	45	50

§ GSS/PSS = total ART in OBT to which pt's virus showed geno/phenotypic sensitivity by Phenosense GT assay. Enfuvirtide and darunavir use in naïve patients were each counted as + 1 active agent and added to GSS/PSS

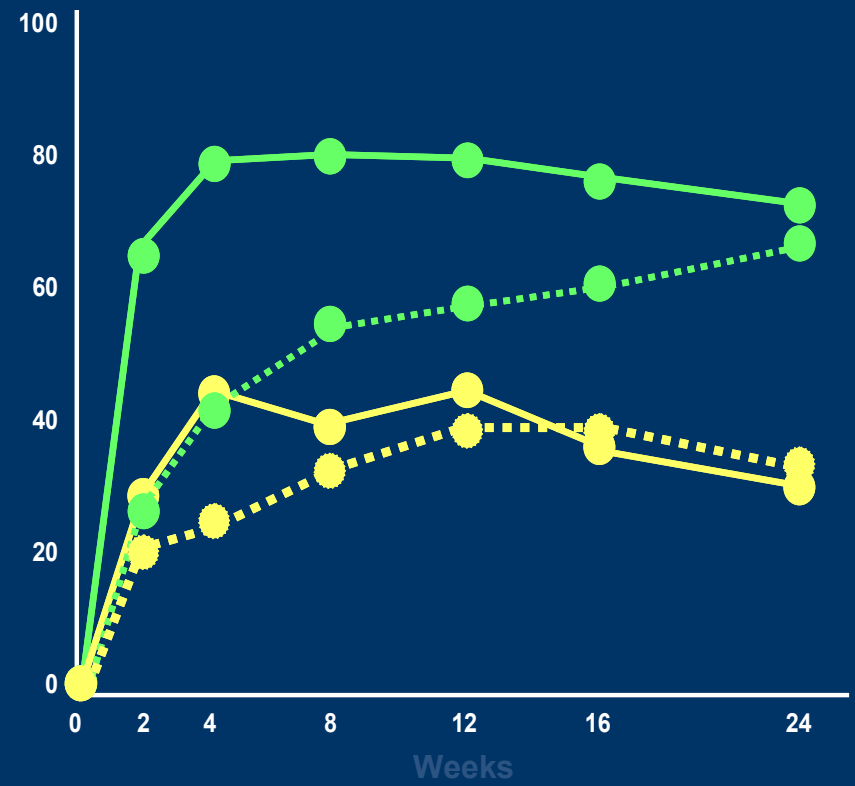
# Percent <400 and <50 Copies/mL (ITT, NC=F)

—●— RAL <400      —●— Placebo <400  
- - -●- - - RAL <50      - - -●- - - Placebo <50

BENCHMRK 1



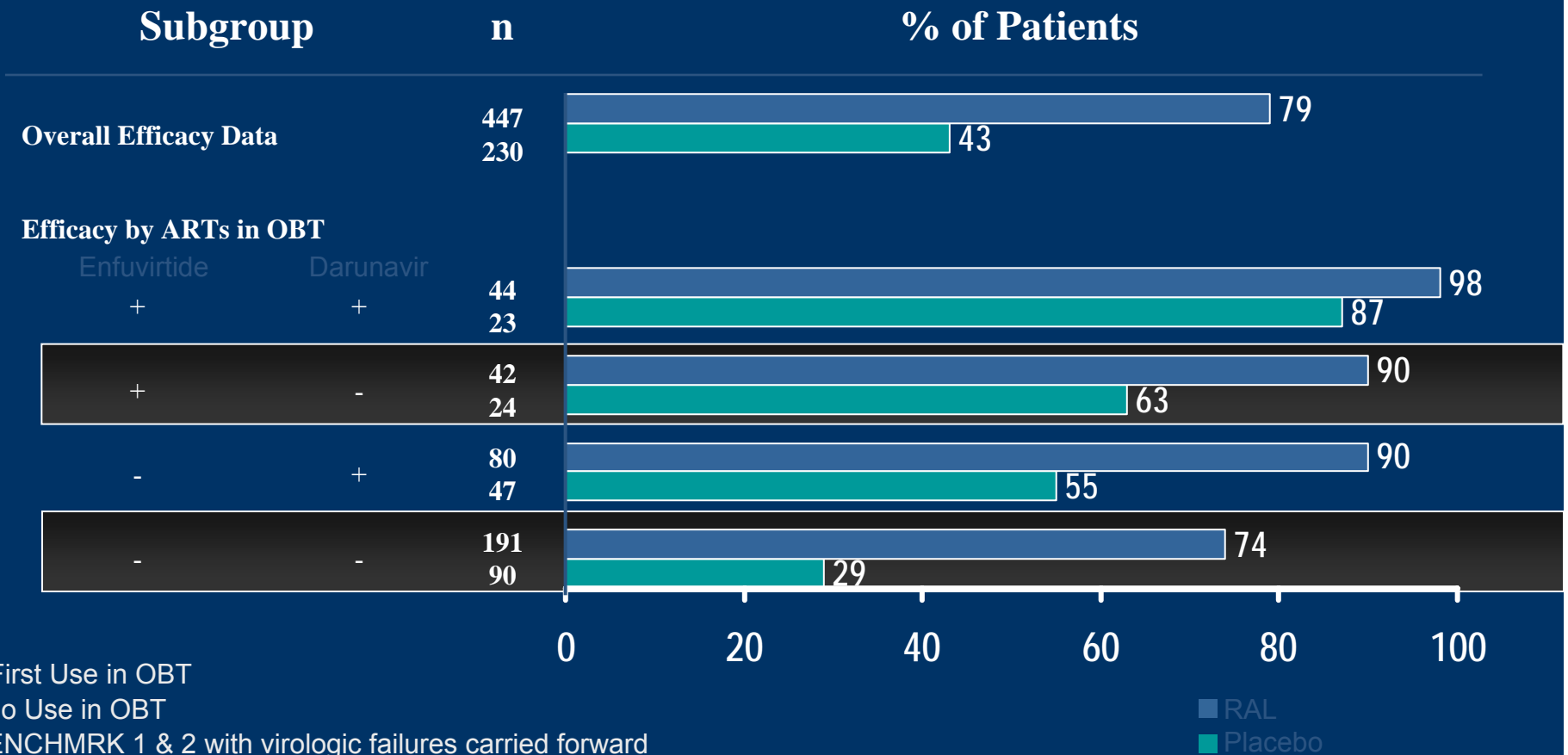
BENCHMRK 2



( $P < 0.001$  at Week 16 for all parameters)

# Combined Efficacy (1)

% Patients with HIV RNA <400 copies/mL at Week 16 by Selected ARTs in OBT\*



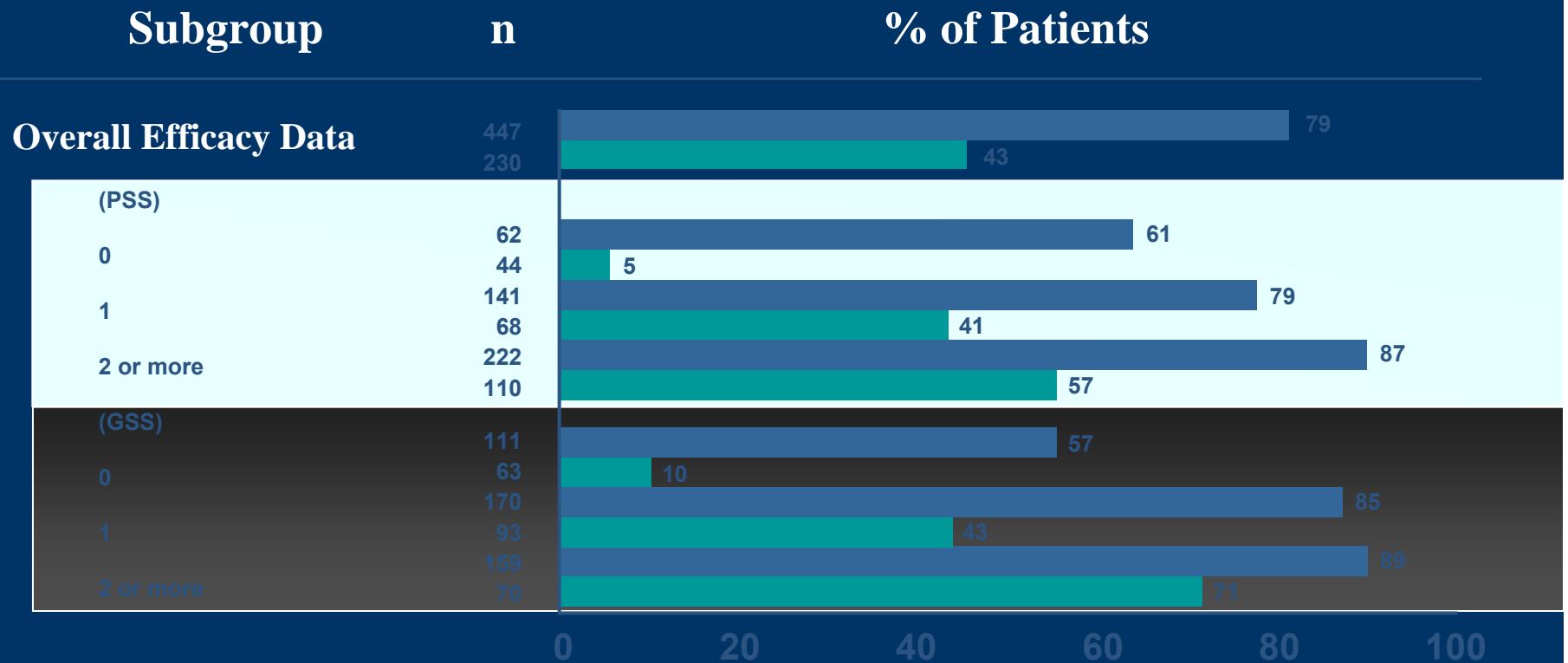
+ : First Use in OBT

- : No Use in OBT

\* BENCHMRK 1 & 2 with virologic failures carried forward

# Combined Efficacy (2)

% Patients with HIV RNA <400 copies/mL at Week 16 by PSS/GSS of OBТ\*



+ : First Use in OBТ

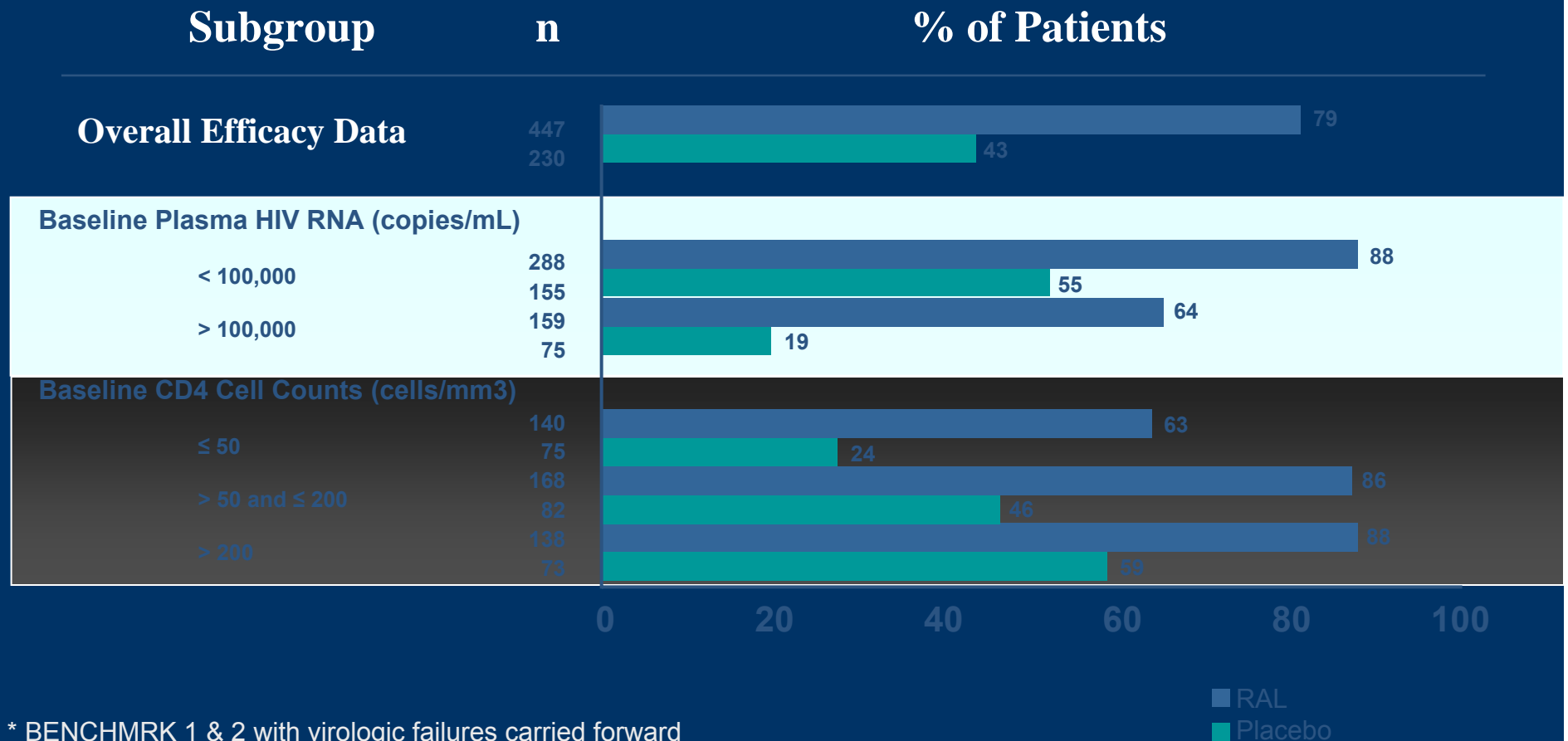
- : No Use in OBТ

\* BENCHMRK 1 & 2 with virologic failures carried forward

■ RAL  
■ Placebo

# Combined Efficacy (3)

% Patients with HIV RNA <400 copies/mL at Week 16 by Baseline HIV RNA and CD4 Cell Count\*



\* BENCHMRK 1 & 2 with virologic failures carried forward

# Clinical Adverse Events (%)

Adverse Experiences	BENCHMRK-1		BENCHMRK-2	
	RAL (n = 232)	Placebo (n = 118)	RAL (n = 230)	Placebo (n = 119)
Mean Exposure (weeks)	26.0	23.0	25.3	22.5
Any AE	81.0	83.1	80.9	86.6
Drug-related* AE	43.5	50.8	53.0	52.1
Serious AE	10.8	13.6	9.6	14.3
Serious drug- related* AE	2.2	0.0	1.3	2.5
Death	1.3	0.8	1.3	0.0
AE leading to discontinuation	1.7	3.4	1.7	0.8

\*Drug-related = any grade; relationship to drug by investigator to RAL/placebo ± OBT or to OBT alone; No significant differences between arms for any AE

# Drug Related Clinical Adverse Events (%) (3% - mild, moderate and severe)

	BENCHMRK-1		BENCHMRK-2	
	RAL (n = 232)	Placebo (n = 118)	RAL (n = 230)	Placebo (n = 119)
Mean Exposure (Wks)	26.0	23.0	25.3	22.5
Abdominal Distension	0.4	3.4	3.9	0.8
Abdominal Pain	1.3	3.4	4.3	0
Diarrhea	6.5	11.0	12.2	9.2
Nausea	3.9	6.8	9.1	8.4
Headache	2.6	6.8	7.8	4.2
Fatigue	1.7	0	4.3	2.5

# Laboratory Abnormalities (%)

( $\geq 1$  % in at least one treatment group)

BENCHMRK-1

BENCHMRK-2

Test	Toxicity Criteria*	RAL (n = 232)	Placebo (n = 118)	RAL (n = 230)	Placebo (n = 119)
ANC	<750 c/uL	2.6	1.7	4.8	5.1
Hgb	<7.5 gm/dL	1.3	0.8	0.4	0
#LDL-C	$\geq 190$ mg/dL	6.0	2.8	1.4	0.9
# Chol	>300 mg/dL	6.5	3.4	2.2	4.2
# TG	>750 mg/dL	5.6	2.5	3.9	7.5
Creatinine	$\geq 1.9$ x ULN	0	0	1.7	2.5
Panc. amylase	$\geq 2.1$ x ULN	3.0	2.5	3.4	2.5
AST	2.6 – 5.0 x ULN (Gr 2)	9.9	2.5	8.3	7.6
	$\geq 5.1$ x ULN	2.2	2.5	2.1	3.3
ALT	2.6 – 5.0 x ULN (Gr 2)	6.9	8.5	6.5	9.2
	$\geq 5.1$ x ULN	5.6	2.5	1.3	1.6

Grade 3 or 4 per DAIDS toxicity criteria for all tests except grade 2-4 for AST and ALT

# Lipids done fasting

# Background on GS-9137

- Dihydroquinoline carboxylic acid strand transfer inhibitor of HIV integrase
- Serum-free  $IC_{50} = 0.2 \text{ nM}$ ;  $EC_{90} = 1.2 \text{ nM}$  in PBMCs
- Active against NRTI-, NNRTI-, and PI-resistant isolates tested
- No dose-limiting chronic animal toxicity
- Generic name is elvitegravir (el-vye-teg'-ra-vir)

# Phase 1 Clinical Data

- Boosted with 100 mg qd ritonavir
  - Half-life of 9-11 hours
  - 20-fold higher systemic exposure
- 6/6 patients treated with GS-9137 50 mg/ ritonavir 100 mg qd for 10 days had  $>1.5$   $\log_{10}$  copies/mL reductions in HIV RNA
- Well-tolerated without discontinuations of study drug

# Phase 2 Study Design

- Randomized, active-control, partially-blinded (dose of GS-9137), dose-finding study
- Initially designed as non-inferiority study of GS-9137 (boosted with 100 mg ritonavir) and boosted PIs in treatment-experienced patients
- Optimized Background Therapy (OBT) consisted of nucleos(t)ide reverse transcriptase inhibitors
  - T-20 use was at investigator's discretion
  - PI use in GS-9137 arms was initially prohibited
- Primary endpoint was time-weighted average change from baseline in HIV RNA through 24 weeks (DAVG<sub>24</sub>)

# Phase 2 Study Schema

278 patients  
HIV RNA  $\geq 1000$  copies/mL  
Any CD4 cell count  
 $\geq 1$  protease resistance mutation

OBT = NRTIs +/- T-20  
NNRTIs not allowed in OBT  
Stratified by T-20 use in OBT

CPI\* (n=63)

GS-9137 20 mg (n=71)

GS-9137 50 mg (n=71)

GS-9137 125 mg (n=73)

\*CPI included 49% darunavir, 27% tipranavir

# Elvitegravir (GS 9137) Study Design

Phase II study

Randomized, partially-blinded (EVG dose)

278 ARV-experienced patients

HIV RNA  $\geq 1000$  copies/mL; Any CD4 cell count;  $\geq 1$  protease resistance mutation

All patients received OBT\*  
Stratified by T-20 use in OBT

CPI\*\*  
(n=63)

EVG (20mg)  
(n=71)

EVG (50mg)  
(n=71)

EVG (125mg)  
(n=73)

Primary endpoint: time-weighted average change from baseline in HIV RNA through 24 weeks (DAVG<sub>24</sub>)

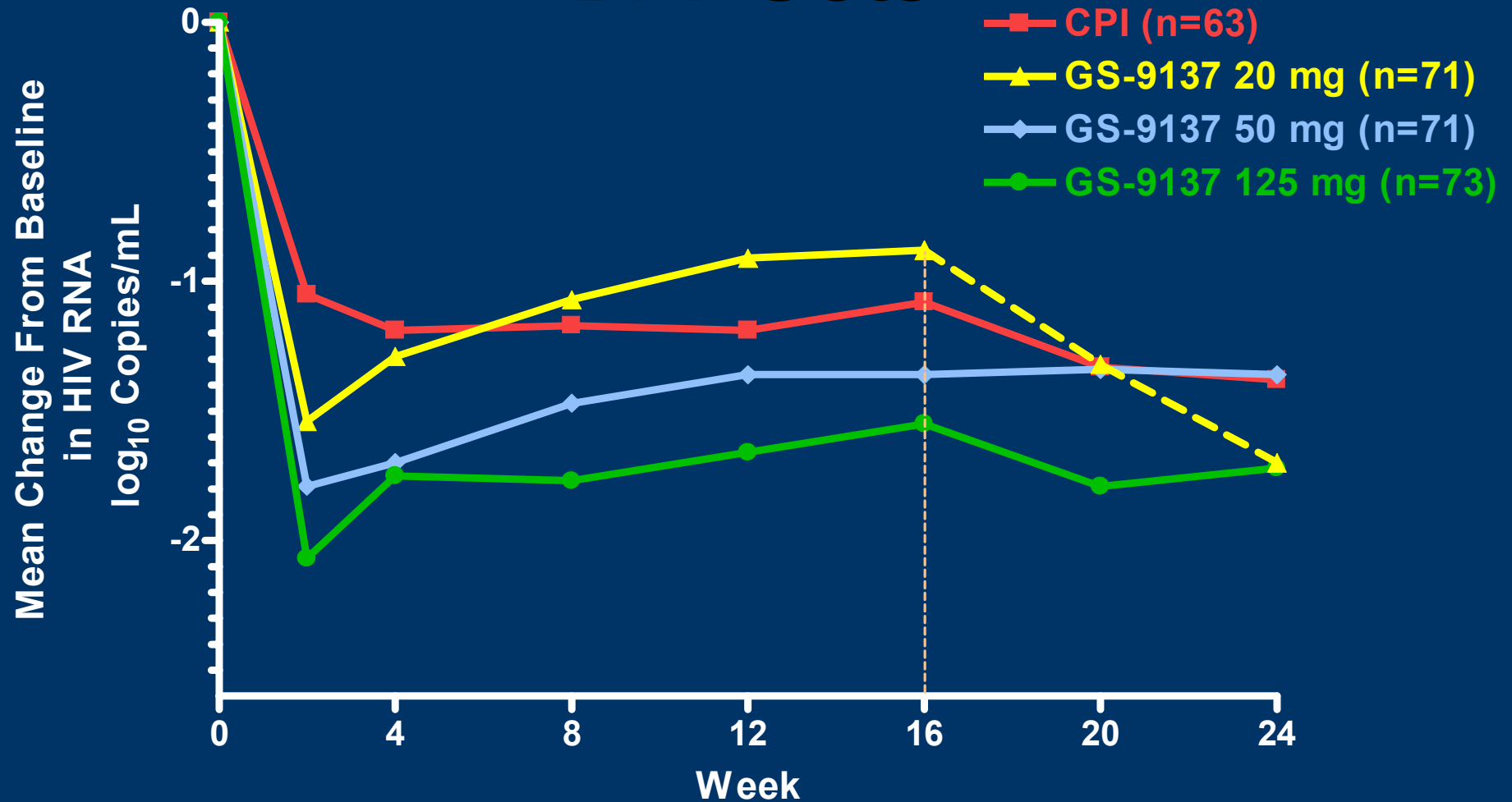
\*OBT = NRTIs +/- T-20; NNRTIs not allowed in OBT; PIs initially barred in EVG arms

\*\*CPI included 49% darunavir, 27% tipranavir

# Week 8 DSMB Recommendations

- Close GS-9137 20 mg arm due to high rate of virologic failure; patients were offered open-label GS-9137 125 mg
- Due to new data indicating lack of drug-drug interactions, permit addition of darunavir or tipranavir to ongoing GS-9137 arms
  - Prior to Week 24, 15% of GS-9137 50 and 125 mg patients added a PI
  - Only 4 patients added a PI before Week 16: used as latest time for comparison of GS-9137 vs. PI

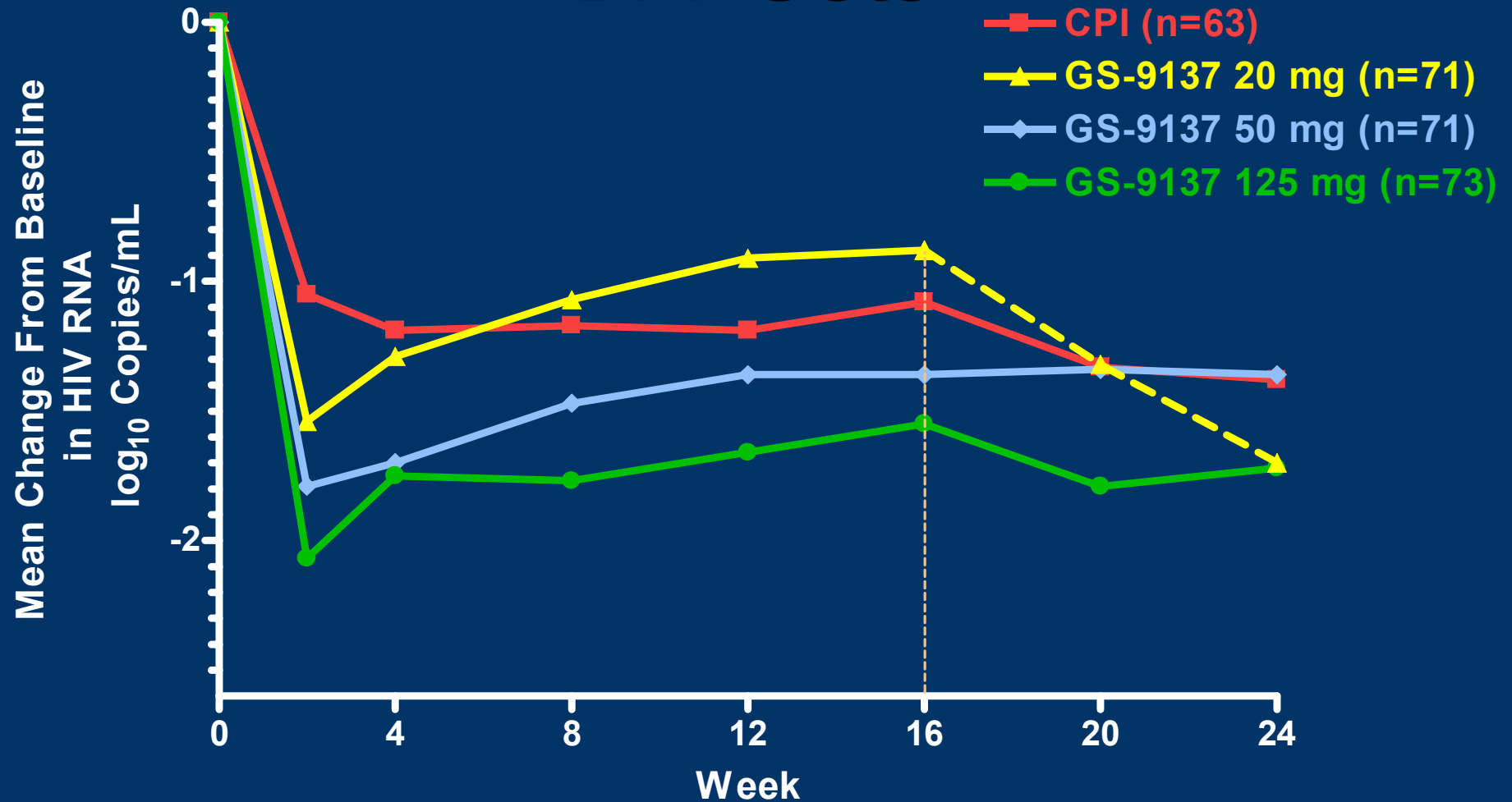
# Change from Baseline in HIV RNA: ITT Sets



37% of CPI patients switched to GS-9137 beginning at Week 16

GS-9137 20 mg patients switched to open-label GS-9137 125 mg beginning at Week 16 (dashed line)

# Change from Baseline in HIV RNA: ITT Sets



37% of CPI patients switched to GS-9137 beginning at Week 16

GS-9137 20 mg patients switched to open-label GS-9137 125 mg beginning at Week 16 (dashed line)

## Study Outcomes

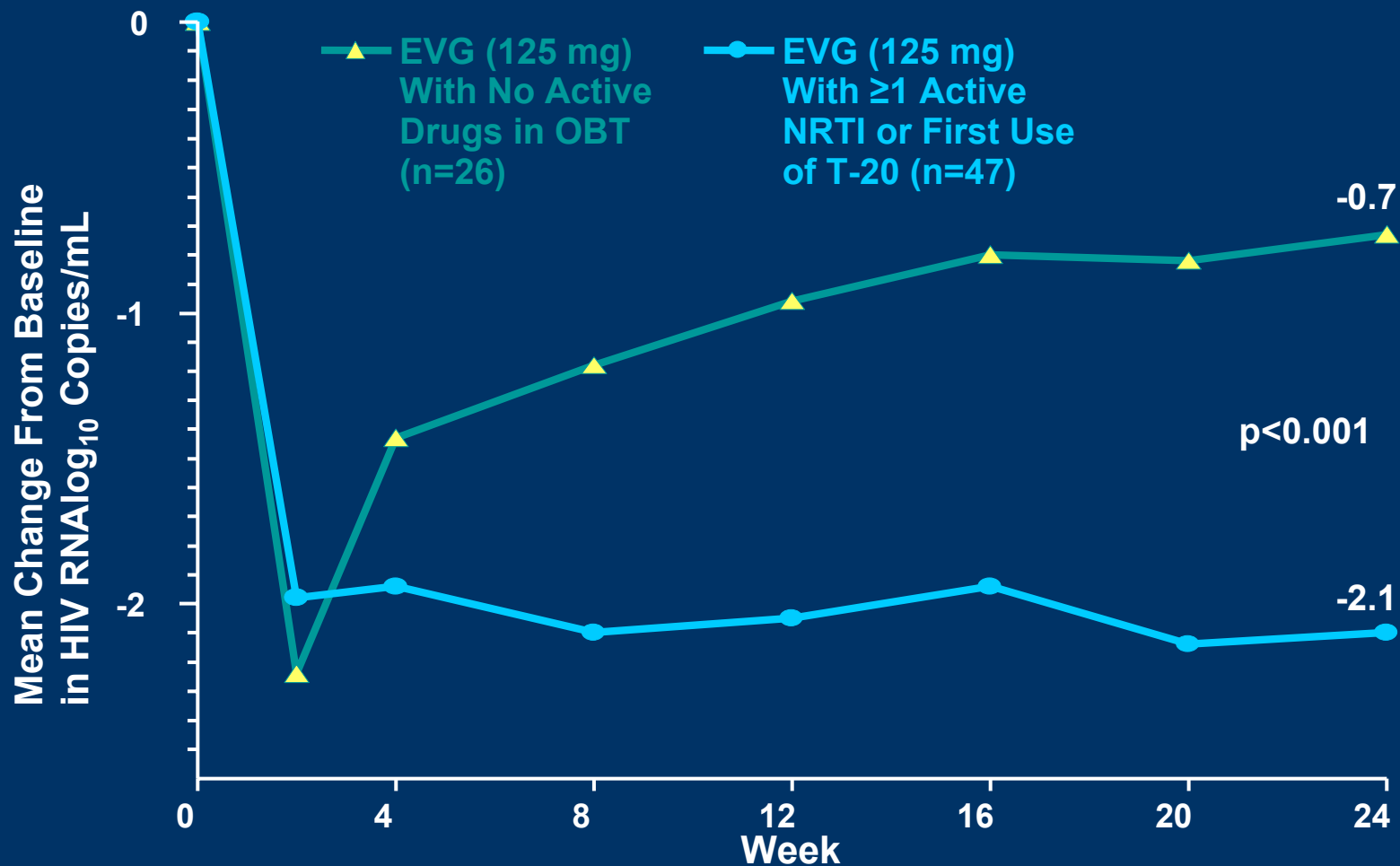
- EVG (20 mg) stopped due to inferior outcomes
- EVG (50 and 125mg) superior to a boosted PI at week 16

ITT	CPI/r	50 mg	125 mg
DAVG <sub>16</sub> mean log drop	-1.2	-1.5 P=0.09	-1.7 P=0.01

- All patients allowed to add a boosted PI as drug-drug interaction data available

**DAVG: Time-weighted average change from baseline in HIV RNA**

## Change in HIV RNA With EVG (125 mg) Influence of Activity of OBT\*



\*Data from EVG (125 mg) patients after addition of a PI were excluded

# Adverse Events and Laboratory Abnormalities

Week 24	CPI N = 63	GS-9137 20 mg N = 71	GS-9137 50 mg N = 71	GS-9137 125 mg N = 73
Adverse events leading to study drug discontinuation	2 (3%)	1 (1%)	2 (3%)	1 (1%)
Grade 3 and 4 adverse events	9 (14%)	13 (18%)	9 (13%)	10 (14%)
Grade 3 and 4 laboratory abnormalities	20 (32%)	21 (30%)	15 (21%)	15 (21%)

# Integrase Resistance Mutations

- Data from Merck Phase III studies<sup>1</sup>:
- Virologic rebound in 16% RAL versus 51% on control arm
- Two pathways to resistance:

**Primary**

**Secondary**

**N155H**

**E92Q, V151I, T97A, G163K, L74M**

**Q148K/R/H** **G140S/A, E138K**

- Eivitegravir resistance mutations *in vitro*<sup>2</sup>
- Two pathways to resistance:

**Primary**

**Secondary**

**T66I**

**F121Y, S153Y, R263K**

**E92Q**

**S147G, H51Y, E157Q**

Concern for cross resistance between these by *in vitro* fold change

1. Cooper D and Steigbigel R, et al. 14th CROI, Los Angeles, CA, February 25-28, 2007. Absts. 100aLB and 105bLB.  
2. Jones G, et al. Ibid. Abst.627.

# Effects of TH9507, a Growth Hormone Releasing Factor (GRF) Analog, on HIV-associated Abdominal Fat Accumulation: A Multi-center, Double-blind Placebo-controlled Trial with 412 Randomized Patients

Julian Falutz<sup>1</sup>, Soraya Allas<sup>2</sup>, Koenraad Blot<sup>2</sup>,  
Donald Kotler<sup>3</sup>, Michael Somero<sup>4</sup>, Daniel Berger<sup>5</sup>,  
Stephen Brown<sup>6</sup>, Gary Richmond<sup>7</sup>,  
Jeffrey Fessel<sup>8</sup>, and Steven Grinspoon<sup>\*9</sup>

Montreal General Hospital, McGill University Health Center<sup>1</sup>~ Theratechnologies, Inc., Montreal, Canada<sup>2</sup>~ St.Lukes Roosevelt Hospital Center, Columbia University College of Physicians and Surgeons<sup>3</sup>~ Palm Springs, CA<sup>4</sup>~ Northstar Health Care, Chicago, IL<sup>5</sup>~ AIDS Research Alliance, West Hollywood, CA<sup>6</sup>~ Fort Lauderdale, FL<sup>7</sup>~ Kaiser Foundation Research Institute, San Francisco, CA<sup>8</sup>~ and MGH and Harvard Medical School<sup>9</sup>

# Metabolic Abnormalities in HIV Patients Receiving HAART

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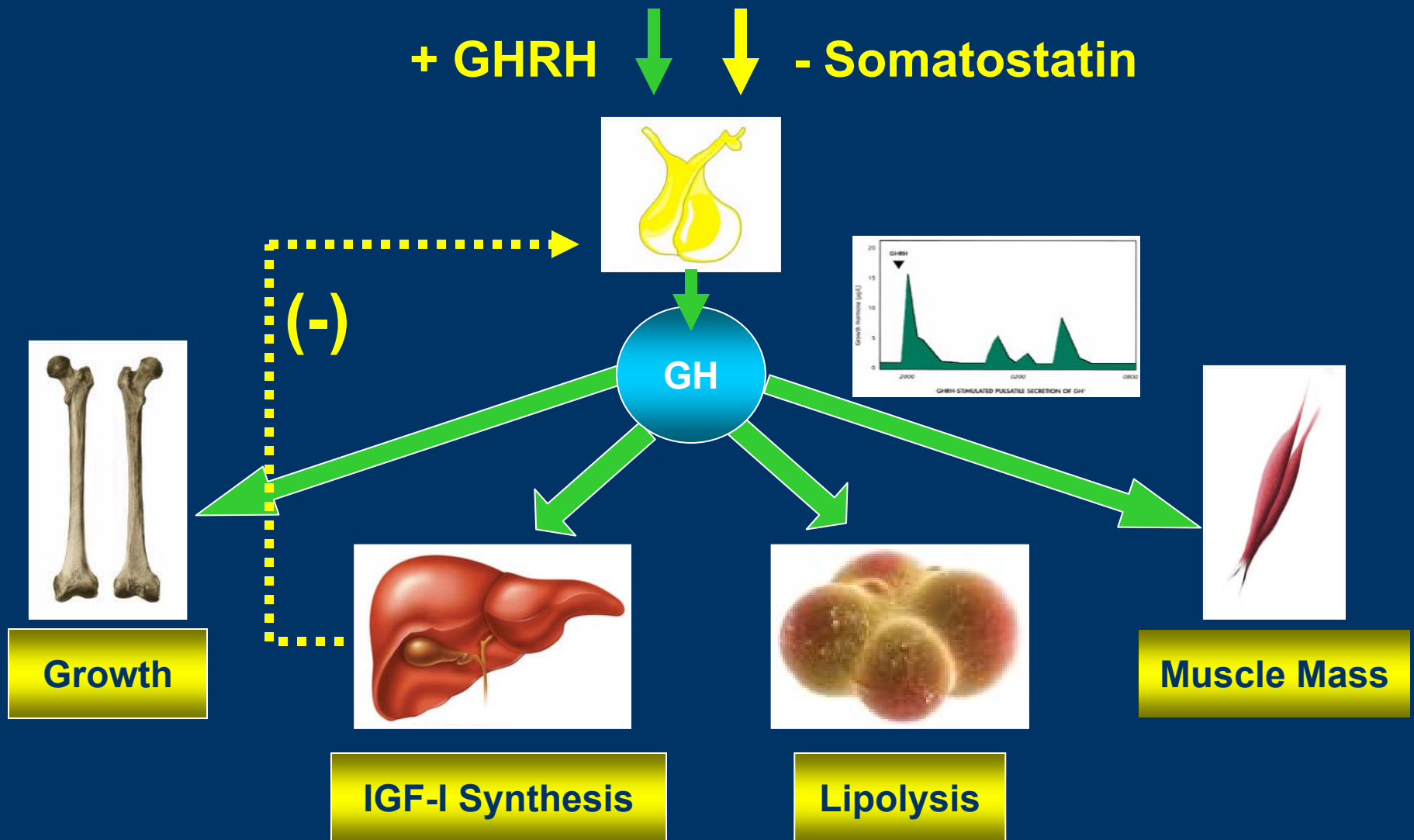
- Characterized in many patients by excess visceral adiposity and increased waist circumference, dyslipidemia, and insulin resistance (Carr and Grinspoon, NEJM 2005)
- GH secretion is reduced among HIV-infected patients with fat redistribution, suggesting the potential utility of a strategy to increase GH secretion and reduce abdominal adiposity in this population (Reitschel JCEM 2001)
- Strategies which reduce abdominal adiposity may improve CVD risk in HIV patients

# Excess Abdominal Adiposity and Related Treatment Strategies

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- Waist circumference and excess abdominal adiposity are independent predictors of CAD in non HIV-infected patients adjusting for other CVD risk factors (Yusuf Lancet 2004)
- GH has been shown to reduce visceral fat among HIV-infected patients but has resulted in supraphysiological levels and significant side effects, including hyperglycemia, at the doses used (Kotler JAIDS 2004)
- In contrast, GHRH analogs increase GH in a physiological manner, and have been shown to safely reduce truncal fat in small, short-term preliminary studies (Falutz AIDS 2005, Koutkia JAMA 2004)

# GH Regulation and Physiology



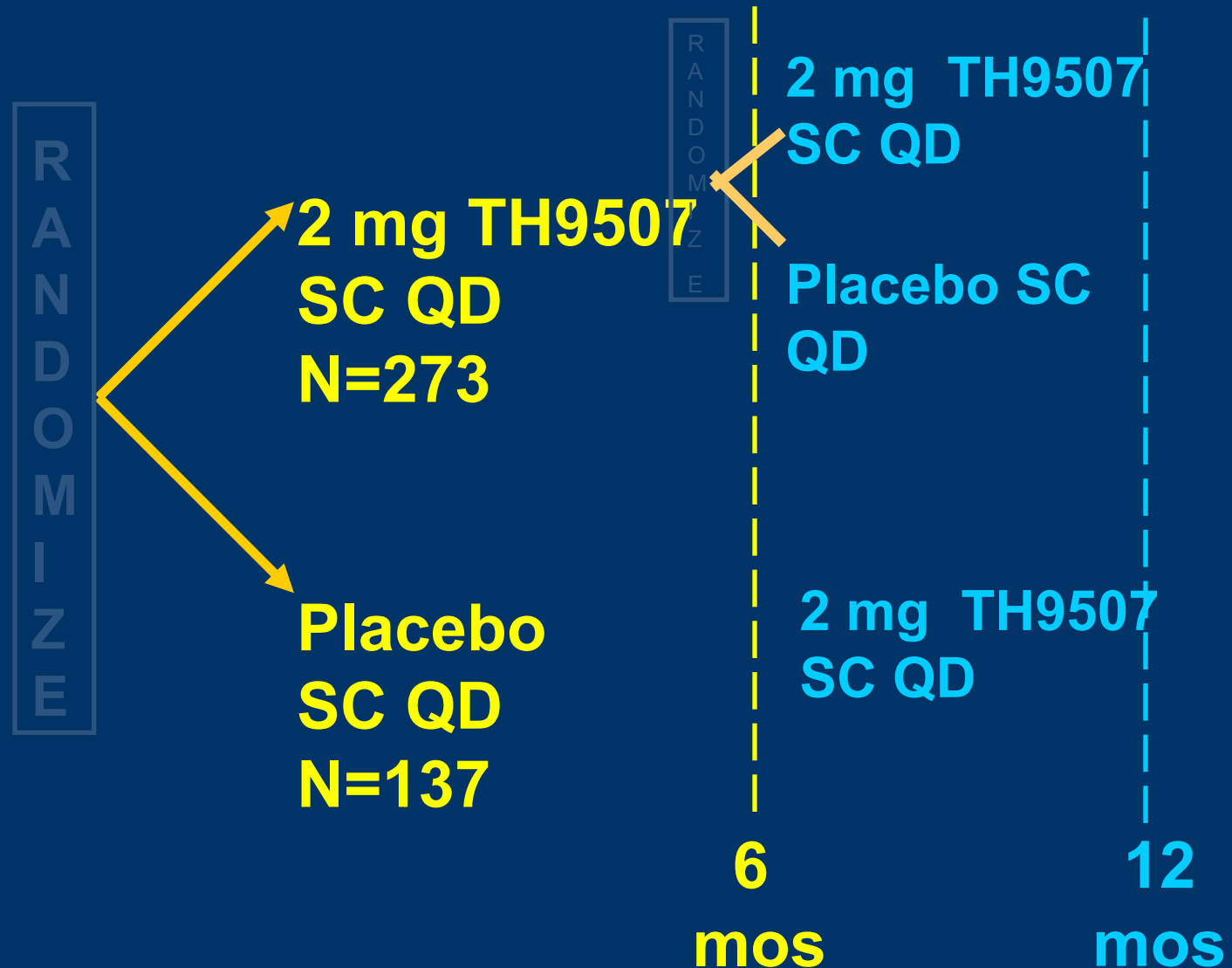
# TH9507, a human GRF Analog

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- Synthetic human 1-44 GRF analog
  - Hydrophobic chain at N-terminus
- Increased in vitro half life as compared to natural hGRF
- Raises GH secretion in a pulsatile manner resulting in increased IGF-I levels generally within the physiological range
- Well tolerated at single doses up to 2 mg/day including with regard to glycemic control in type 2 diabetic patients (Clemmons Endo Soc 2004)

# TH9507 in HIV-Infected Patients with Abdominal Fat Accumulation

(performed at 43 Sites throughout US and Canada)



# Study Endpoints

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## ■ Primary

- % VAT decrease from baseline vs placebo by CT Scan at L4-L5

## ■ Secondary

- Lipids (Triglyceride, total cholesterol/HDL ratio)
- Serum IGF-I levels
- Patient reported outcomes\*
- Safety Parameters (Insulin, glucose and others)

\* Data not yet available

# Data Analysis and Power

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- The study was analyzed by intent to treat analysis and ANCOVA, including baseline as a covariate, with last observation carried forward to determine treatment differences between TH9507 and placebo.
- The study had 90% power to detect an 8% difference in VAT between TH9507 and placebo.

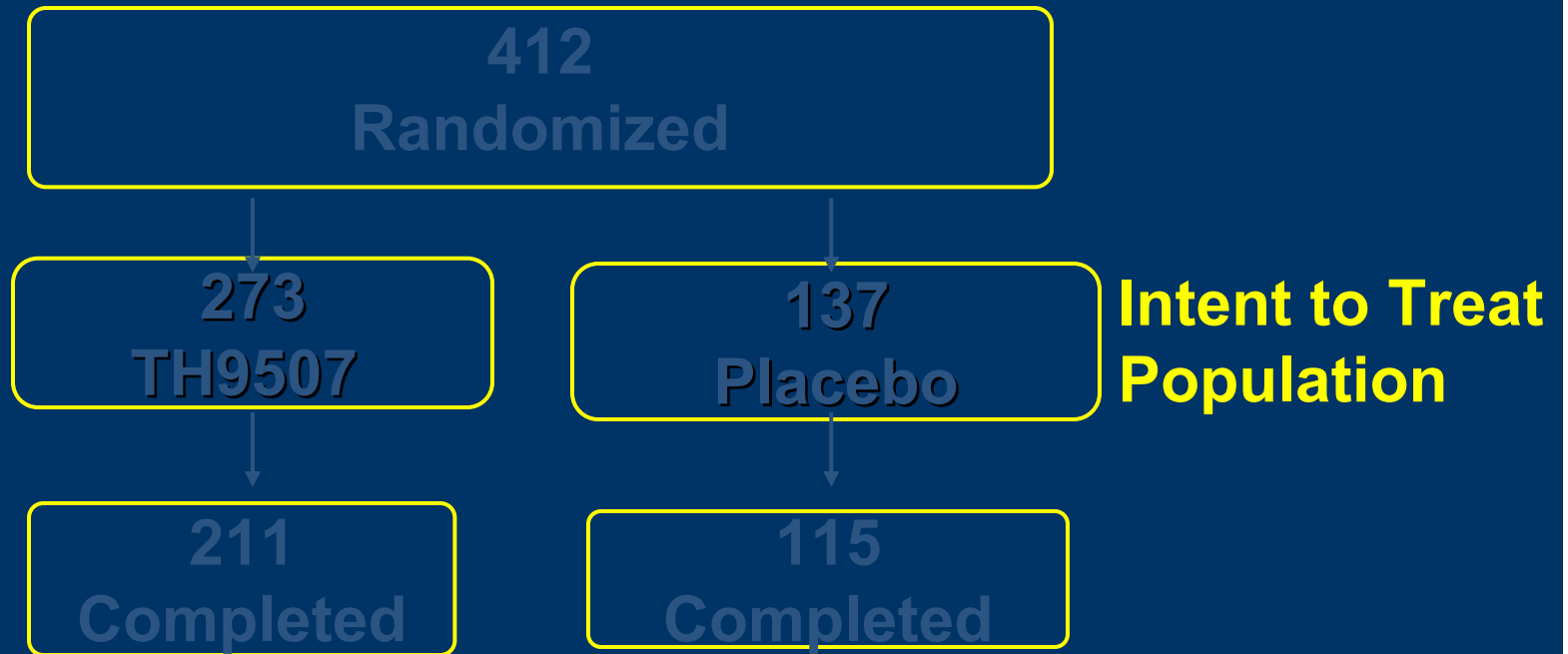
# Eligibility Criteria

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- HIV positive male or female subject
- Stable ART for at least 8 weeks, CD4 > 100 cells/mm<sup>3</sup> and viral load < 10,000 copies
- Abdominal fat accumulation occurring in the context of treatment for HIV infection
  - WC<sub>≥</sub> 95 cm and WHR<sub>≥</sub> 0.94 for males
  - WC<sub>≥</sub> 94 cm and WHR<sub>≥</sub> 0.88 for females
- Fasting glucose ≤ 150 mg/dL
- Stable lipid-lowering agents permitted
- Use of antidiabetic, insulin sensitizing, GH or GH agonists exclusionary

# Patient Disposition

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# Baseline Characteristics

	TH9507 (n=273)	Placebo (n=137)	P-value
Age (y)	47±7	48±7	0.22
Gender (Male/Female)	87/13%	84/16%	0.43
Race (W/AA/H)	77/14/9%	72/16/12%	0.73
BMI (kg/m <sup>2</sup> )	29.2±4.2	29.2±4.2	0.99
Waist Circumference (cm)	104±10	105±9	0.68
Viral Load			
Undetectable	68.4%	70.8%	
50-400	22.4%	20.4%	0.90
>400	9.2%	8.8%	
CD4 (cells/mm <sup>3</sup> )	616±299	585±284	0.31
PI (%)	55.1%	64.2%	0.09
NRTI (%)	97.8%	97.8%	0.99
NNRTI (%)	53.7%	41.6	<b>0.03</b>

# Baseline Characteristics

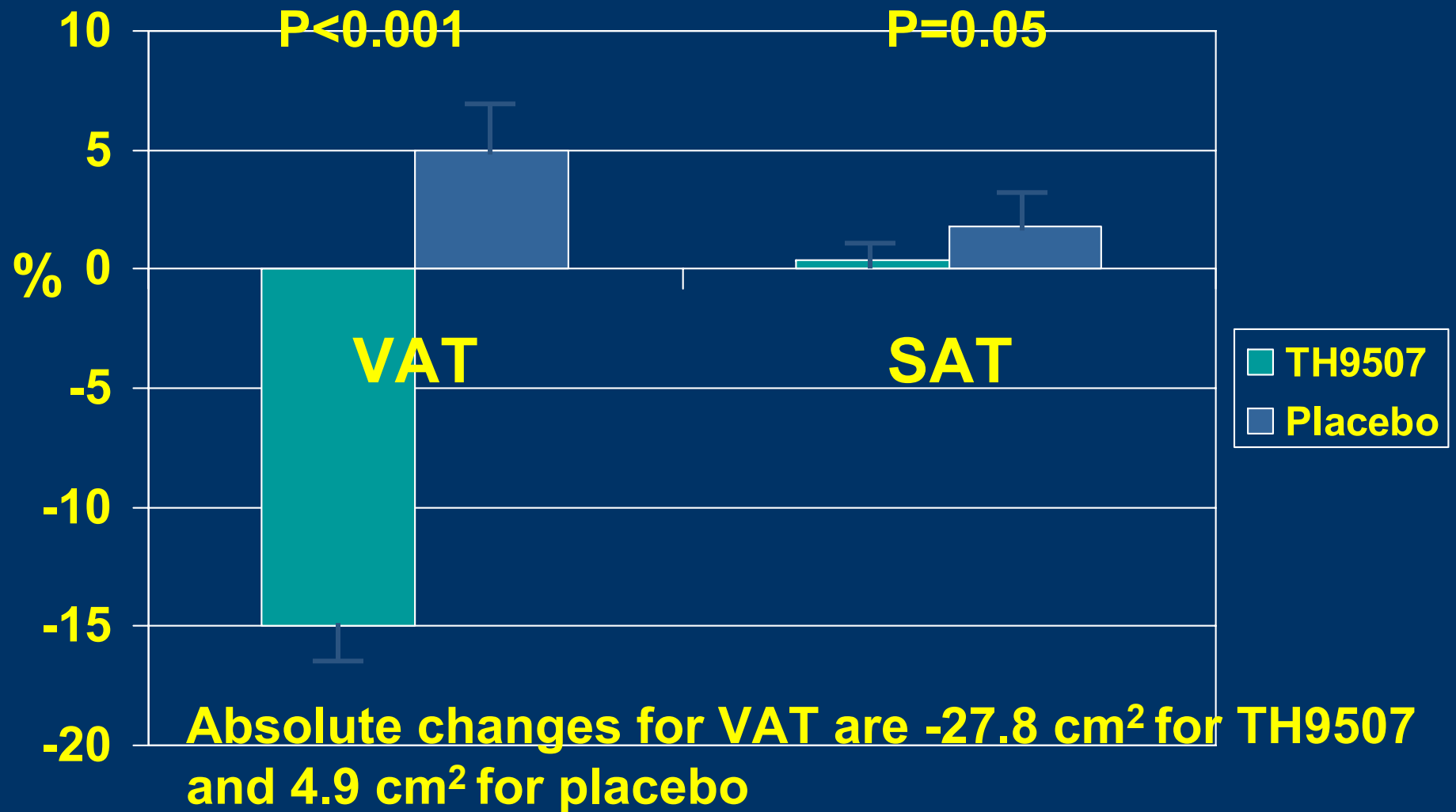
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	TH9507 (n=273)	Placebo (n=137)	P-value
VAT (cm <sup>2</sup> )	178±77	171±77	0.40
SAT (cm <sup>2</sup> )	231±127	239±133	0.56
Trunk Fat (kg)	14.9±5.6	15.3±5.8	0.55
Limb Fat (kg)	7.1±4.3	7.7±4.7	0.23

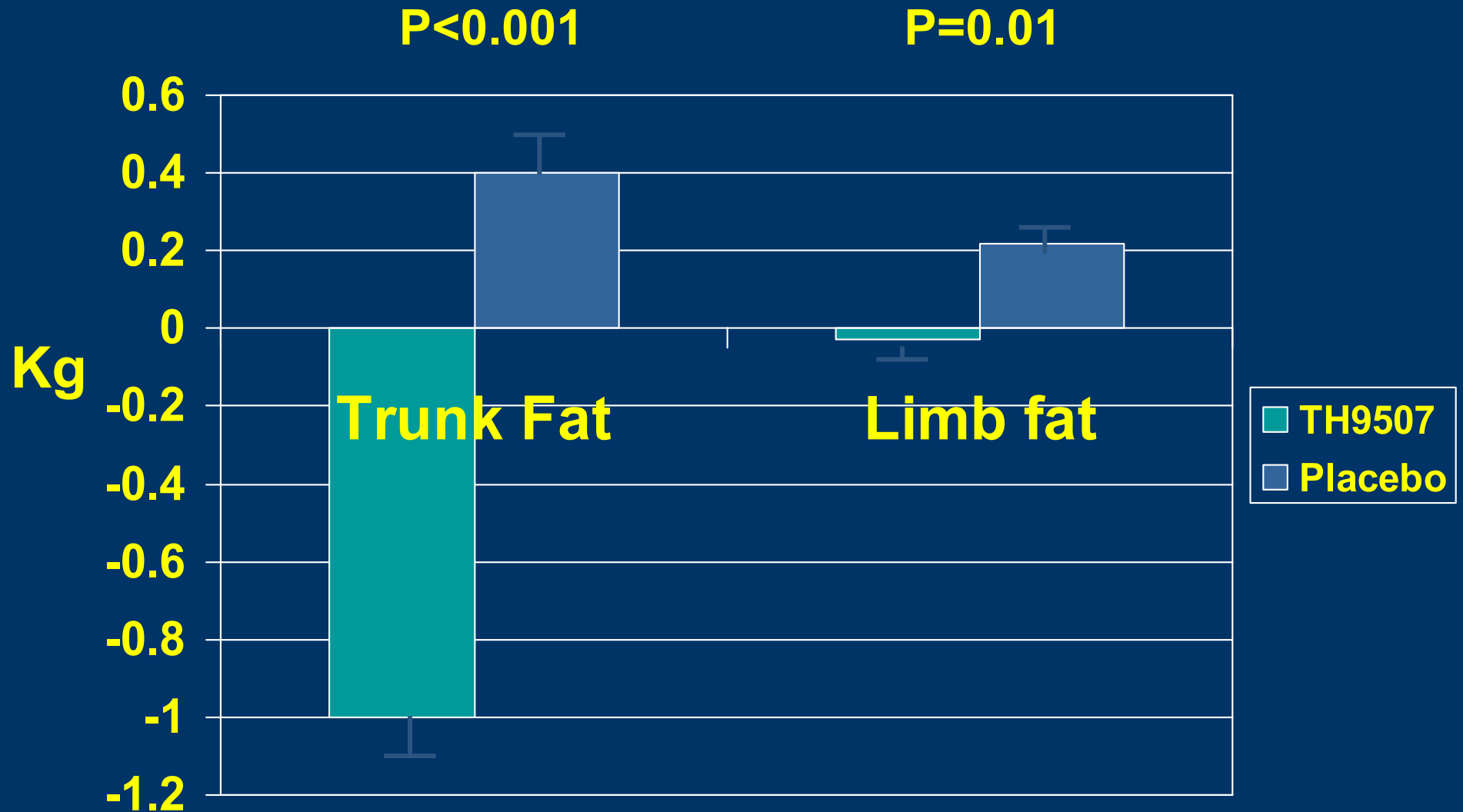
# Baseline Characteristics

	TH9507 (n=273)	Placebo (n=137)	P-value
IGF-I (ng/mL)	161±59	168±75	0.31
Cholesterol (mmol/L)	5.1±1.1	5.0±1.0	0.55
HDL (mmol/L)	1.2±0.4	1.2±0.4	0.43
Triglyceride (mmol/L)	2.9±2.1	2.6±1.6	0.31
Chol:HDL	4.5±1.4	4.3±1.2	0.14
Glucose (Fasting)	5.4±0.7	5.4±0.7	
< 6 mmol	80.8%	81.3%	0.87
6.1-6.9 mmol	16.9%	15.7%	
>6.9 mmol	2.3%	3.0%	

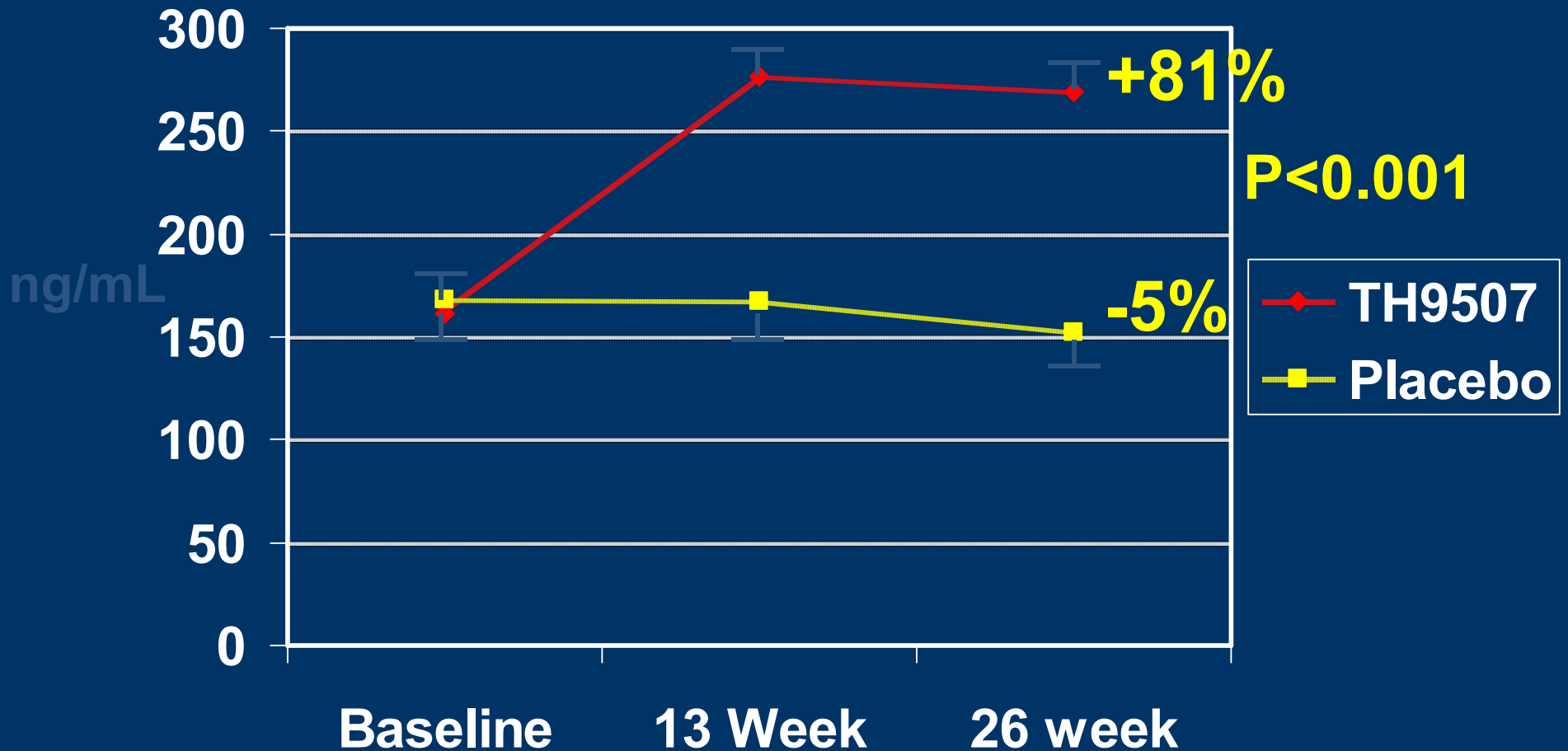
# % Change in VAT and SAT (Mean $\pm$ SEM)



# Change in Trunk and Limb Fat (Mean $\pm$ SEM)



# IGF-I Levels (Mean $\pm$ SEM)



# Change in Metabolic Parameters

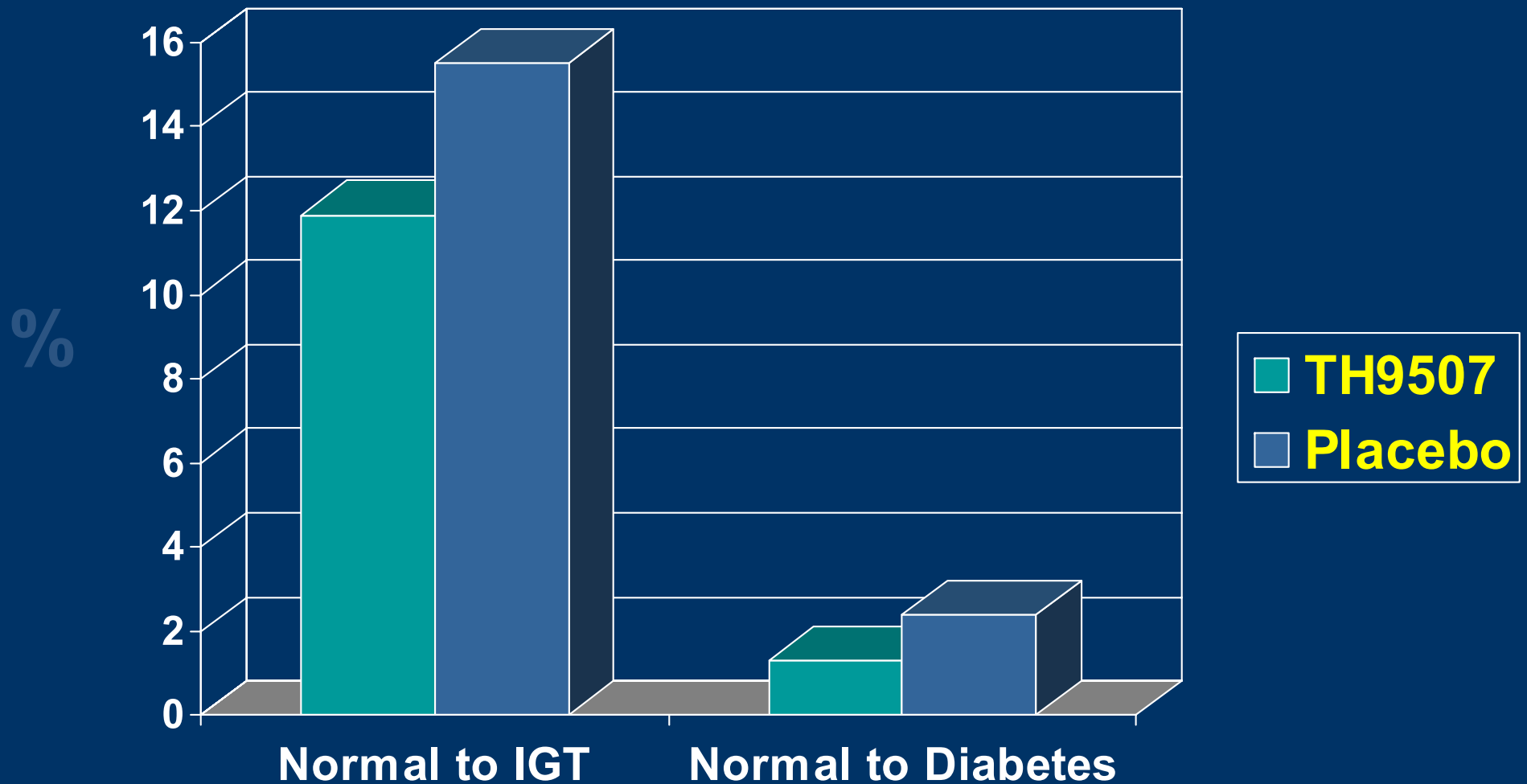
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	TH9507 (n=273)	Placebo (n=137)	P-value
$\Delta$ Glucose (mmol/L)	0.17 $\pm$ 0.75	0.03 $\pm$ .82	0.28
$\Delta$ 2hr Glucose (mmol/L)	0.06 $\pm$ 2.10	0.45 $\pm$ 2.43	0.17
$\Delta$ Insulin (pmol/L)	11.9 $\pm$ 203	17.4 $\pm$ 153	0.93

# Change in Immune Parameters

	TH9507 (n=273)	Placebo (n=137)	P-value
$\Delta$ CD4 (cells/mm <sup>3</sup> )	-2 $\pm$ 160	-0 $\pm$ 171	0.58
Viral Load (Baseline)			
Undetectable	68.4%	70.8%	
50-400	22.4%	20.4%	0.88
>400	9.2%	8.8%	
Viral Load (6 mos)			
Undetectable	66.8%	70.2%	
50-400	23.2%	20.2%	0.80
>400	10.0%	9.6%	

# Impact on Clinical Glucose Parameters (% changing category)



# Treatment-emergent Adverse Events

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Value	TH9507 (n=273)	Placebo (n=137)	P
■ % subjects with any AE	82%	75%	0.12
% with related AE's	53%	34%	<0.001
% discontinuing due to AE	12%	3%	<0.01
% with SAE's	5%	2%	0.29

# Treatment-emergent Adverse Events ( $\geq 5\%$ and $> 10\%$ )

	TH9507	Placebo	
Headache	16.1%	17.5%	P=0.78
Arthralgia	13.2%	10.2%	P=0.43
Injection site bruising	9.2%	9.5%	
Diarrhea	8.1%	9.5%	
Edema peripheral	7.7%	5.1%	
Myalgia	7.7%	2.2%	
Pain in extremity	5.9%	6.6%	
URI	5.5%	6.6%	
Nasopharyngitis	5.9%	5.1%	
Hypoesthesia	5.5%	0%	
Rash	6.2%	0%	
Paresthesia	5.1%	1.5%	

# Hypersensitivity Reactions

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- 6 on TH9507 experienced urticaria and/or rash (2%)
  - Most of them after 4+ months of treatment, often accompanied by flare-ups at previous sites of injection, and moderate eosinophilia
  - One of them had more systemic reactions
    - Sweating, tachycardia, shortness of breath
  - There were no SAEs related to these reactions, subjects were discontinued out of precaution
- These subjects tested + for anti-TH9507 IgG, and the immunology of this reaction is not yet fully characterized:
  - IgG prevalence within the population, Titers, IgE, neutralizing

## Conclusions

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- TH9507 (GHRH1-44 analog) may be useful to preferentially decrease VAT and improve lipid parameters in HIV-infected patients with abdominal fat accumulation, thereby improving cardiovascular risk in this population
- TH9507 appears generally well tolerated and does not significantly effect insulin resistance or glucose levels over 26 weeks, even among HIV patients with IGT or diabetes.

# Efficacy of High-Dose Recombinant Hepatitis B Rechallenge Vaccination

- Poster 883
- 144 HIV+ adults with anti-HBs titer <10 IU/L after 1<sup>st</sup> series
- Revaccination with 20 ug HBVaxPro at 0, 1, 2 months
- Anti-HBs testing at 3 months

# Hepatitis B re-vaccination (2)

- 51% response rate overall
- Univariate analysis of response
  - Female vs male: OR of response 3
  - Age 10 yr increase: OR of response 0.6
  - HIV-RNA load modifier of age
    - Undetectable HIV VL age  $p = .48$
    - Detectable HIV VL age  $p = <.001$

# Long Term Immunogenicity of a Prime-Boost Strategy: ANRS 114

- Poster 866
- 7-valent PCV + 23-valent PPV vs 23-valent PPV
- 96 week follow-up serology
- Proportional Odds ratio of response
  - Prime boost vs PPV            1.56        p 0.087
  - HCV + vs -                        .43        p .063
  - Ever smoker vs non            .45        p .040

# Pneumococcal vaccination (2)

## ANRS 114 Pneumovac Study

	PCV + PPV	PPV
Bact. Pneu. suspect	6	6
Pneumococcal confirmed	0	1
Legionella pneum. Pneu.	2	0
Other cases w/o pathogen	4	5