#709

VISCERAL FAT REDUCTION WITH TESAMORELIN ASSOCIATED WITH METABOLIC SYNDROME REVERSAL

R. BEDIMO[1], T. GONZALO[2], C.S. McGARY[2], T.A. McLAUGHLIN[2]

[1]University of Texas Southwestern, Dallas, Texas, USA, [2]Medical Affairs Theratechnologies Inc, Montréal, Canada

Background

- Metabolic Syndrome (MetS), with central adiposity as a major component, is associated with increased risk of cardiovascular disease, stroke, and type 2 diabetes in people with HIV (PWHIV)[1,2].
- Increasing incidence of MetS and diabetes is a major concern in PWHIV[3]
- Tesamorelin, a growth hormone releasing hormone analogue, has previously been shown to reduce visceral adipose tissue (VAT) by over 15% in 26 weeks in PWHIV with lipohypertrophy[4].
- Due to the association between excess visceral abdominal fat (EVAF) and MetS, we investigated whether treatment with tesamorelin was associated with changes in MetS classification.

Is treatment with tesamorelin in PWHIV associated with changes in Metabolic Syndrome?

Methods

STUDY DESIGN

Baseline → **Week 26**

816 PWHIV randomized → 2:1 randomization → Tesamorelin (n=543) / Placebo (n=263)

Key inclusion criteria

- Males WC>95cm; WHR>0.94
- Females WC>94cm; WHR>0.88

WC: Waist circumference; WHR: Waist to Hip Ratio

Key exclusion criteria

- Fasting glucose > 150mg/dl (8.33 mmol/L)
- Fasting triglycerides > 0.99 g/dl (11.3 mmol/L)
- T1DM or T2DM on medication
- Untreated Hypertension (> 140 mmHg and diastolic pressure > 90 mmHg)

- Data from two Phase III trials of tesamorelin among PWHIV with excess VAT was leveraged, where participants were randomized to tesamorelin (2mg) vs placebo daily for 26 weeks[4-6] .
- A post-hoc analysis of 400 participants receiving tesamorelin per-protocol classified participants as responders or non-responders
- A total of 263 PWHIV were defined as VAT responders using the *a priori* definition of >8% reduction in VAT at 26 weeks
- Participants were longitudinally classified for MetS using the 5 components defined by the 2005 NCEP guidelines and 2006 IDF guidelines for US clinics

Metabolic Syndrome Classification NCEP/IDF

Risk Factor	NCEP (any three features)	IDF (Large waist plus two other features)
Large waist circumference		
Men	≥102 cm (40in)	≥102 cm (40in)*
Women	≥88 cm (35in)	≥88 cm (35in)*
High triglyceride level	≥150 mg/dL (1.7 mmol)	≥150 mg/dL (1.7 mmol)
Reduced HDL cholesterol		
Men	<40 mg/dL (1.03 mmol)	<40 mg/dL (1.03 mmol)
Women	<50 mg/dL (1.29 mmol)	<50 mg/dL (1.29 mmol)
Increased blood pressure	≥130/ ≥85 mmHg	≥130/ ≥85 mmHg
Elevated fasting plasma glucose	≥110 mg/dL (6.1 mmol/L)	≥ 100 mg/dL (5.6 mmol/L)

NCEP: National Cholesterol Education Program; IDF: International Diabetes Federation; *IDF guidelines recommend ATP III WC for US clinics

Results

Prevalence of Metabolic Syndrome decreased in tesamorelin-treated responder patients after 26 weeks of treatment vs non-responders

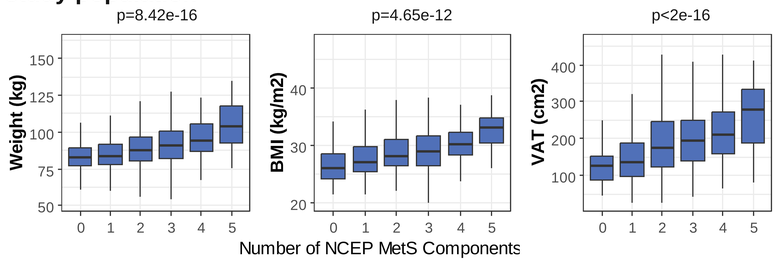
Table 1: Prevalence of MetS and baseline characteristics in full study population

- **NCEP: 36.2% of study participants had MetS at baseline**
- **IDF: 29.2% of study participants with MetS at baseline**

	No MetS (n=510)	MetS			
		NCEP (n=296)	p-val*	IDF (n=238)	p-val*
Age (years)	47.61 (7.53)	47.6 (7.35)	0.98	47.4 (7.4)	0.699
Sex – Male†	438 (85.9)	247 (83.4)	0.39	189 (79.4)	**0.03**
Race†			0.052		0.165
White	376 (73.7)	237 (80.1)		187 (78.6)	
Black or African American	79 (15.5)	26 (8.8)		25 (10.6)	
Hispanic	41 (8.0)	28 (9.5)		23 (9.7)	
Asian	4 (0.8)	1 (0.3)		0 (0.0)	
Other	10 (2.0)	4 (1.4)		3 (1.3)	
Weight (kg)	86.5 (12.1)	93.7 (16.1)	**<0.001**	96.2 (16.3)	**<0.001**
BMI mean (kg/m²)	28.4 (3.9)	30.12 (4.5)	**<0.001**	31.0 (4.36)	**<0.001**
BMI Category†			**<0.001**		**<0.001**
Normal	91 (17.8)	32 (10.8)		11 (4.6)	
Overweight	282 (55.3)	121 (40.9)		88 (37.0)	
Obese	137 (26.9)	143 (48.3)		139 (58.4)	
CD4 Count (cells/mm³) ‡	575.7 (268.9)	640 (319.8)	**0.002**	639.3 (300.4)	**0.003**
HIV Viral Load (copies/mL)†			**0.049**		0.071
<50	375 (74.4)	232 (78.9)		188 (79.0)	
50-400	94 (18.7)	36 (12.2)		29 (12.2)	
>400	35 (6.9)	26 (8.8)		21 (8.8)	
HIV Duration (years)‡	13.7 (5.4)	13.7 (5.5)	0.98	13.5 (5.46)	0.65
ART Duration (years)‡	4.5 (3.1)	4.4 (2.9)	0.79	4.46 (2.9)	0.98

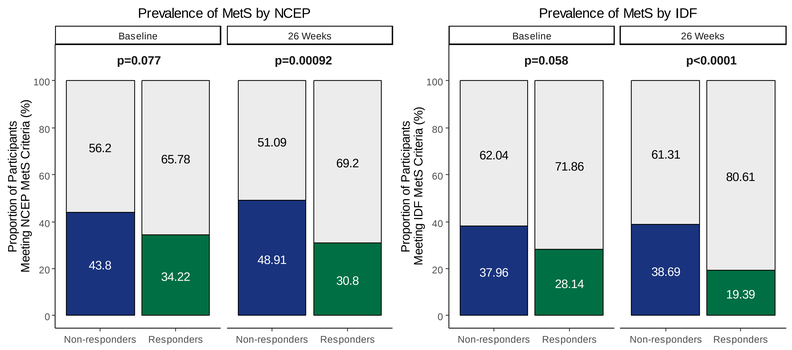
*: Unadjusted comparison to No MetS group; †: values reported as n (%); ‡: values reported as Mean (SD)

Figure 1: Body Composition is related to NCEP MetS severity in full study population



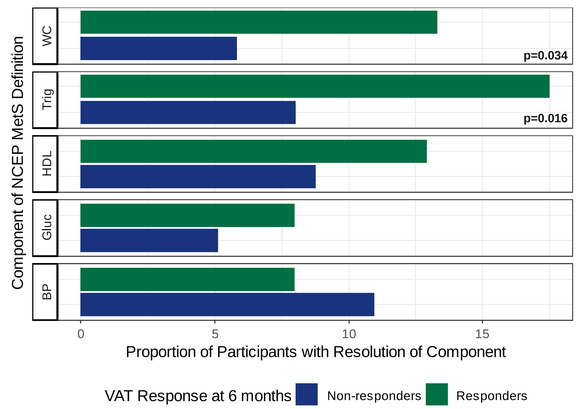
Participants were evaluated for each of 5 components of MetS using the NCEP thresholds at baseline. For each participant, the number of criteria that were met were totaled. Box and whiskers represent the median and IQR for each of three body composition metrics for participants with each number of MetS components. One-way ANOVA was performed to evaluate differences in weight, BMI and VAT across MetS scale.

Figure 2: Prevalence of MetS is lower in responders compared to non-responders after 26 weeks of tesamorelin treatment



Participants were evaluated for MetS by NCEP and IDF criteria at baseline and 26 weeks. The prevalence of MetS amongst responders and non-responders was evaluated using chi-square tests at each time point. Unadjusted p-values are reported. *Not Shown: The prevalence of MetS defined by IDF criteria was significantly lower at week 26 compared to baseline amongst responders (p=0.024) but non-responders (p=1).*

Figure 3: Responders more likely than non-reponders to resolve MetS components at 26 weeks of tesamorelin treatment



Participants were evaluated for each of 5 components of MetS using the NCEP thresholds at baseline and 26 weeks. For each component, the percent of participants who met the MetS criteria at baseline and went on to normalize by 26 weeks is reported. Differences between responders and non responders were evaluated using chi-square tests comparing resolution to no resolution at 26 weeks. Unadjusted p-values are reported.

Conclusions

- VAT reduction with tesamorelin is associated with a reversal of MetS classification among PWHIV.
- This is consistent with previous data indicating that visceral fat reduction is associated with improvements in metabolic profiles of PWHIV, supporting the use of tesamorelin in PWHIV with central adiposity to improve metabolic profiles.

Author Contact: **Roger.Bedimo@va.gov**

[1]Vecchi et al, Curr Pharm Des, 2014; [2]Grinspoon et al. JClinEndocrin 2007; [3]Jerico et al. Diabetes 2005 [4]Falutz et al. AIDS 2008; [5]Falutz et al. JAcquirImmuneDeficSyndr. 2010; [6]Falutz et al. JClinEndocrinolMetab. 2010