



Bari 7-10 Novembre

# SOPHY

STANDARD OPERATING PROCEDURES FOR HYPOGONADISM

STANDARD OPERATING PROCEDURES FOR HYPOGONADISM

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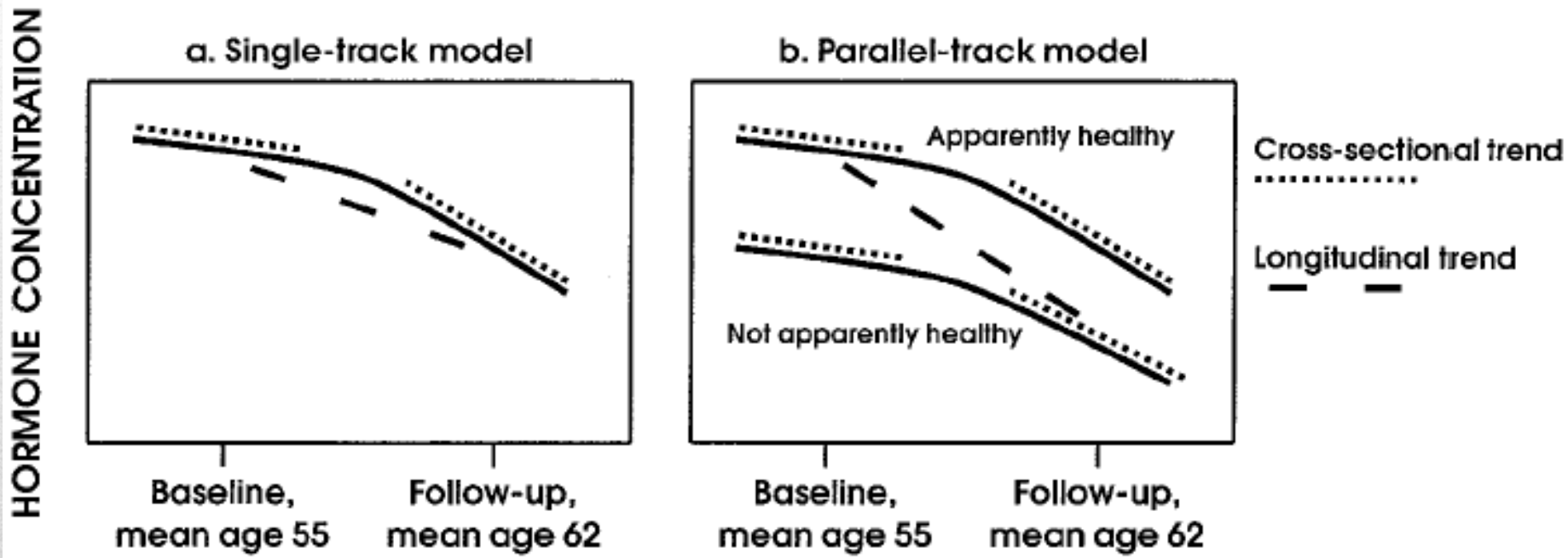
# Key points

- Prevalence of **Testosterone Deficiency (TD)** increases with age in particular in pts with metabolic syndrome (about 50%) and sexual dysfunction
  - Low Testosterone levels are associated with reduced longevity and quality of life:
    - increase of fatal cardiovascular events, obesity, sarcopenia, osteoporosis, depression, reduced sexual drive, erectile dysfunction and other chronic diseases
  - Testosterone treatment in Metabolic Syndrome reduces waist circumference, BMI and insulin resistance
  - Young men with TD should also be treated. In older men benefits and risks of testosterone replacement should be carefully assessed
  - Nevertheless, even though these systemic complications, TD is underestimated and undertreated
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# MMAS (Massachusetts Male Aging Study)



**Testosterone levels = good indicator of healthy**



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## Lethality of major cardiovascular events and testosterone levels

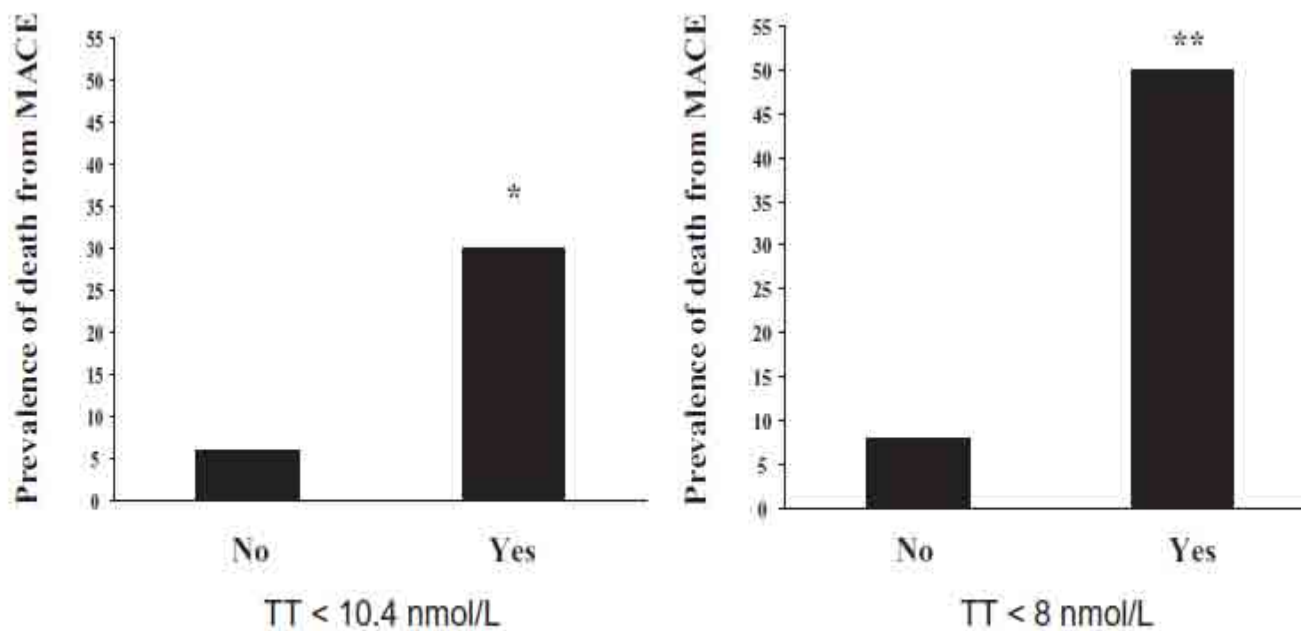


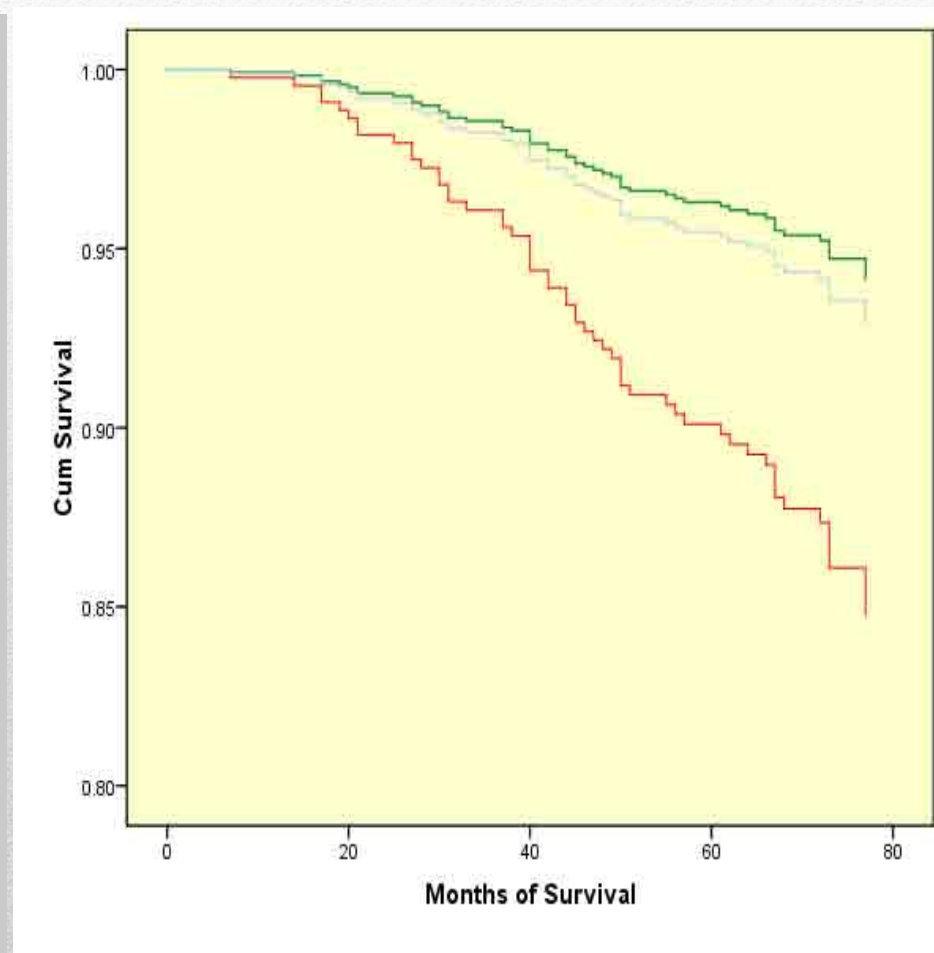
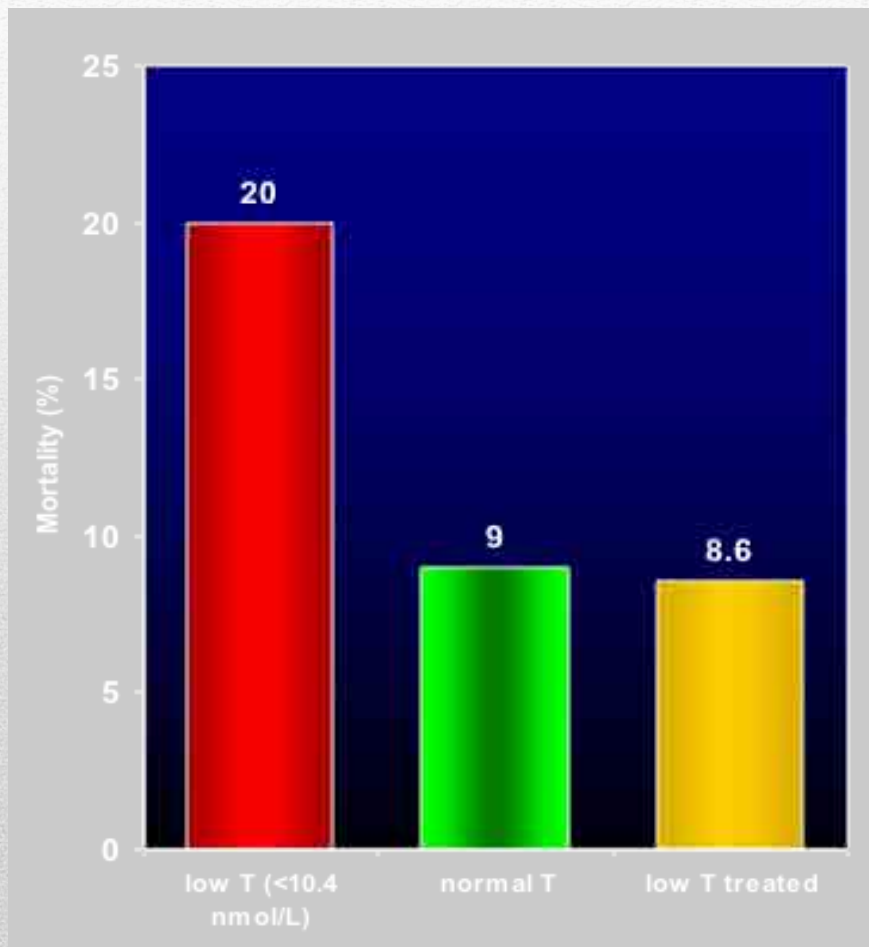
Figure 2 Lethality of major adverse cardiovascular events (MACE) according to hypogonadal status. \* $P < 0.001$ , \*\* $P < 0.0001$ .



# Low testosterone predicts increased mortality and testosterone therapy improves survival in 587 men with type 2 diabetes (mean follow-up: 5.8 years)



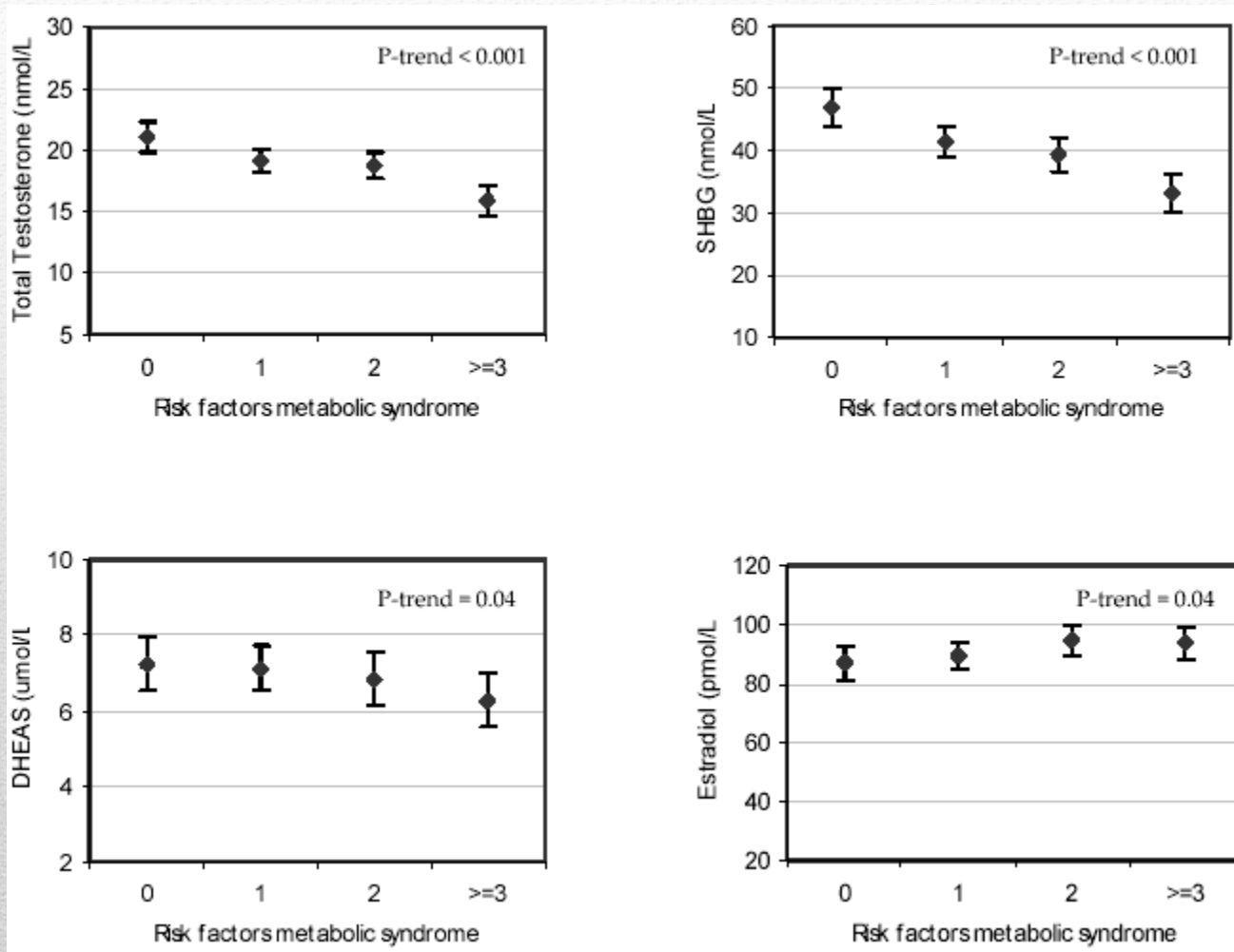
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## Metabolic syndrome and hypogonadism





# The BLAST study



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**A 30-week double blind placebo controlled study of long-acting testosterone undecanoate versus placebo in men with type 2 diabetes**

550 men identified from Diabetes register

488 consented and attended pre-screening visits

211 patients screened (mean age 62)

- 12 screen failures
- 1 AF, 10 raised PSA of which 9 were BPH and 1 new CaP – 1 withdrew consent

199 Randomised

- 97 randomised to TESTOSTERONE UNDECANOATE 1000 mg for 30 weeks
- 102 randomised to matching placebo for 30 weeks

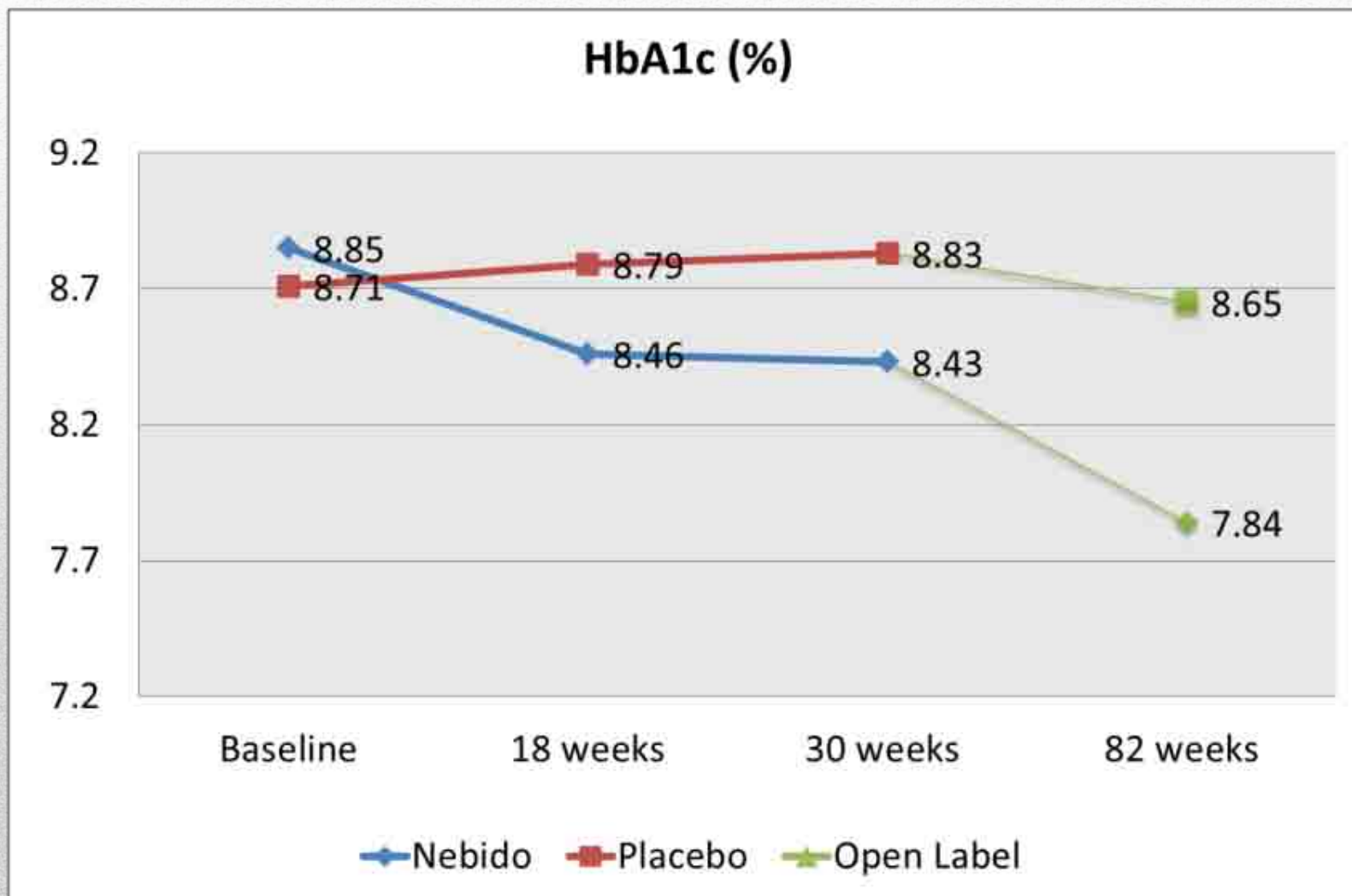
190 Completed

- 4 SAEs – 3 treatment-unrelated deaths and 1 new CaP in PLACEBO arm – 5 withdrawn consent
- 106 entered 52-week open-label extension



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## HbA1c open-label: Poorly controlled patients (N=45)

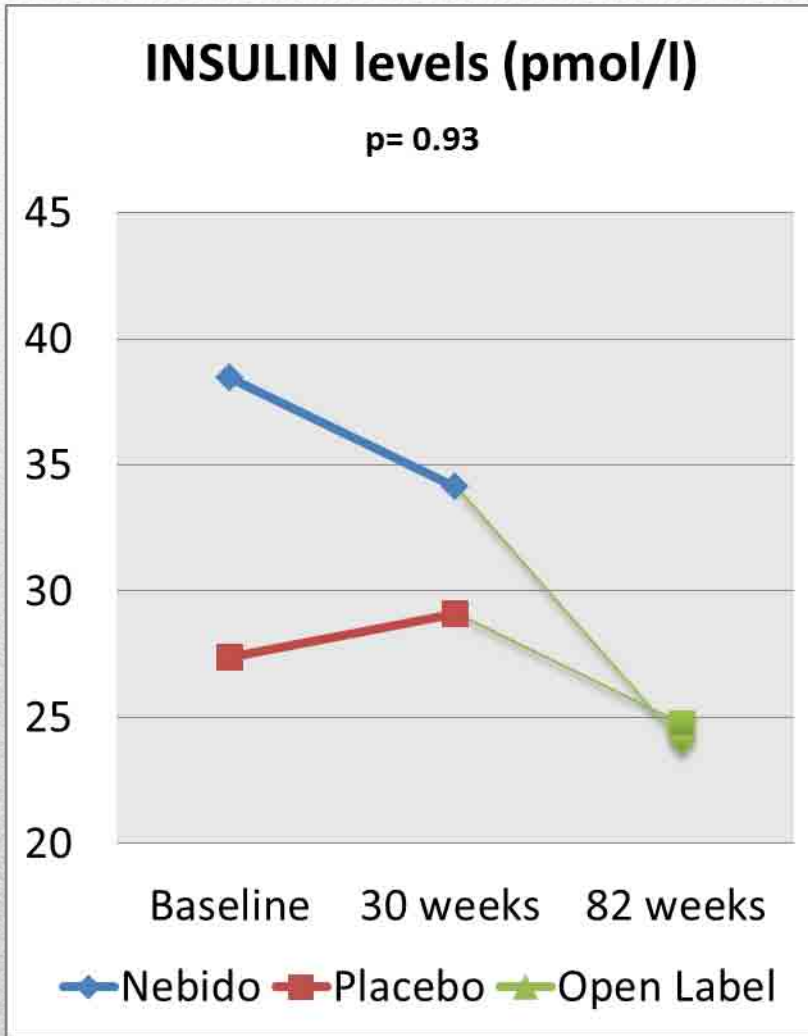
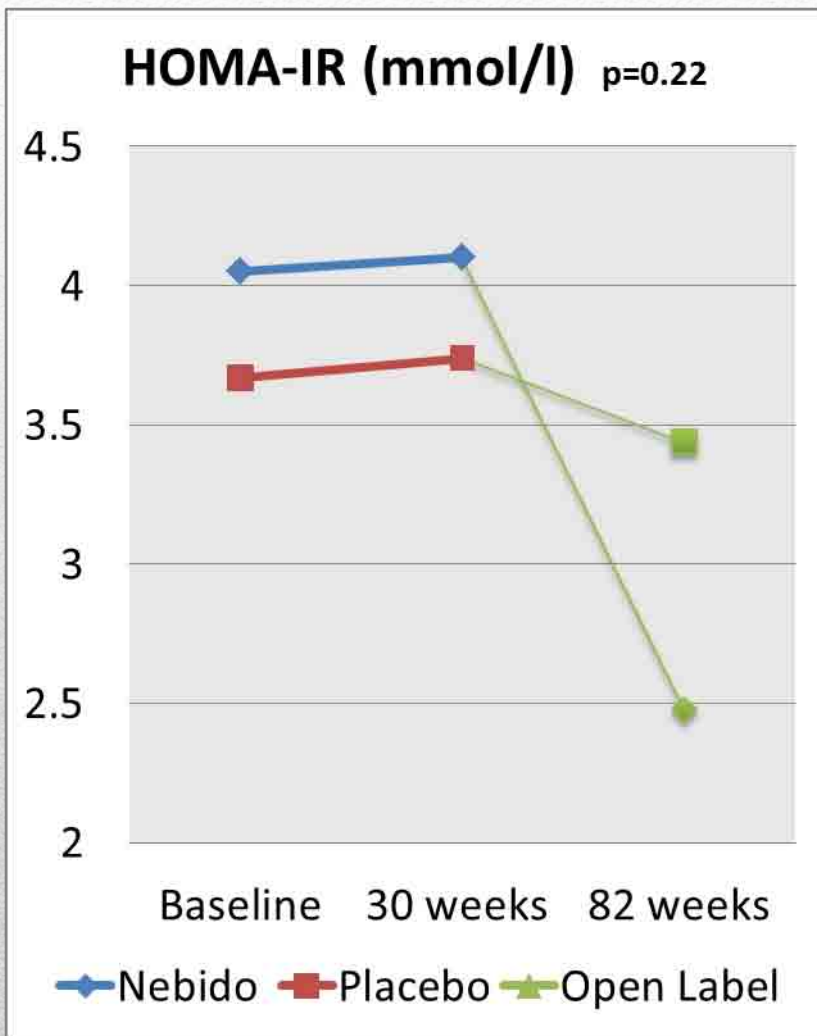






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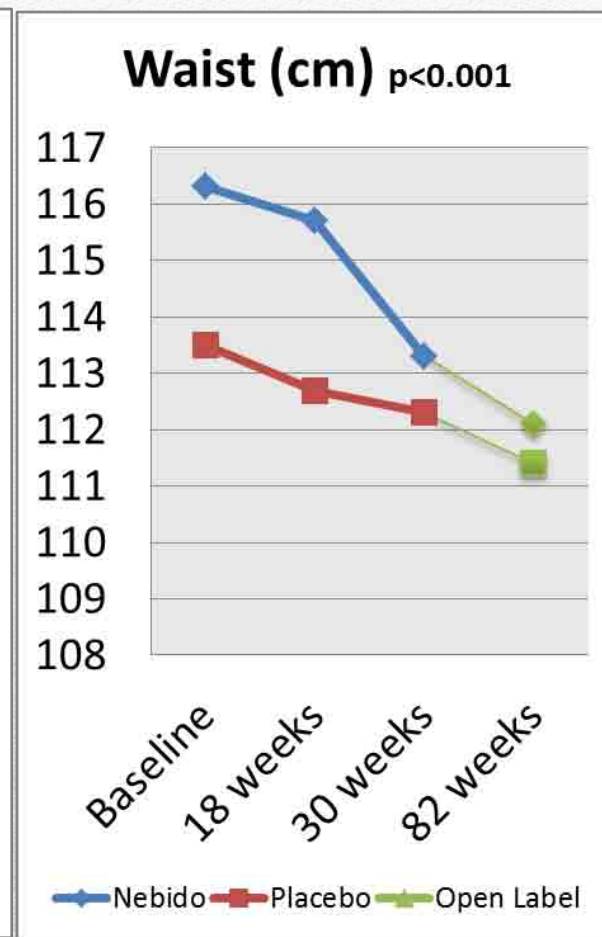
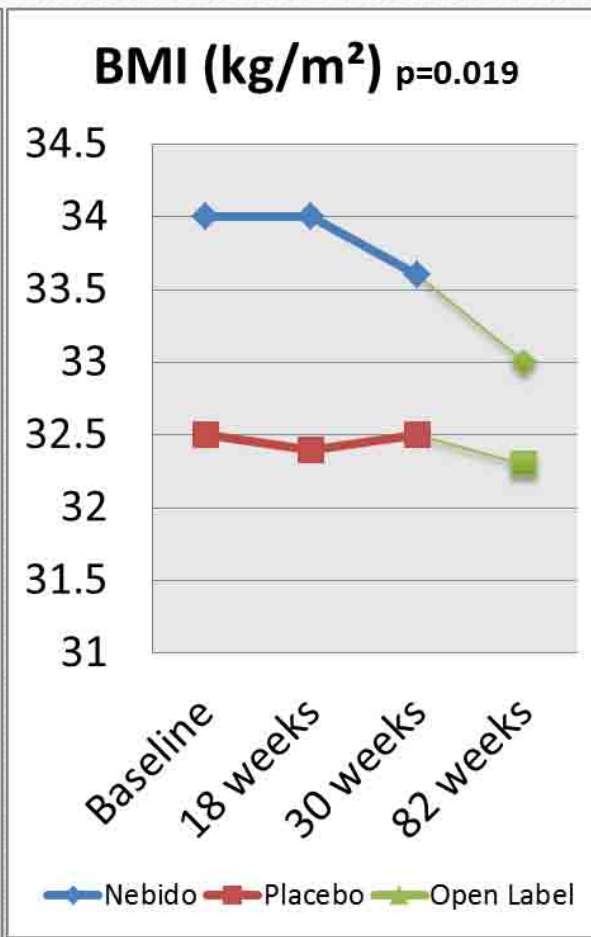
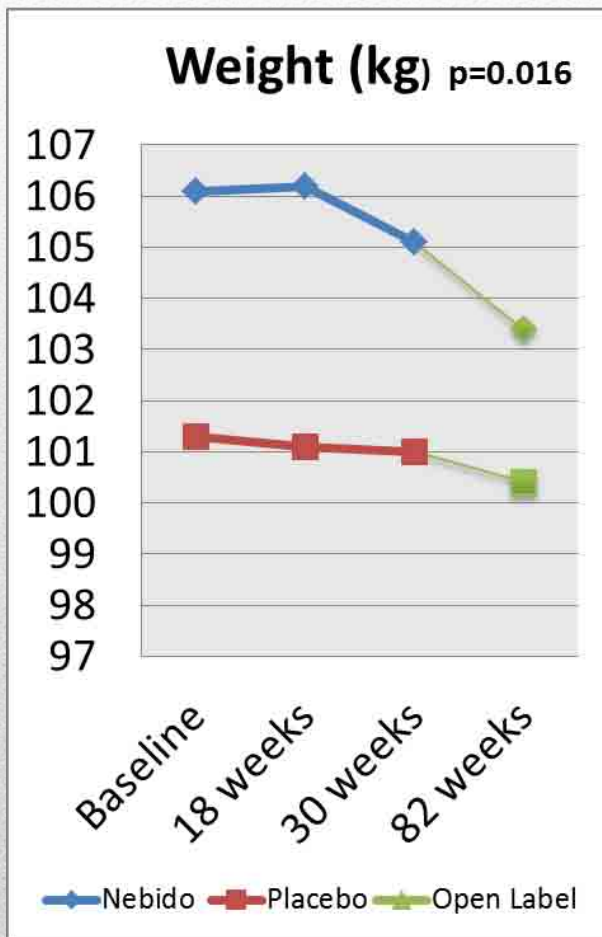
# HOMA-IR and serum INSULIN levels





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# Weight, BMI and waist circumference open-label study (N=106)





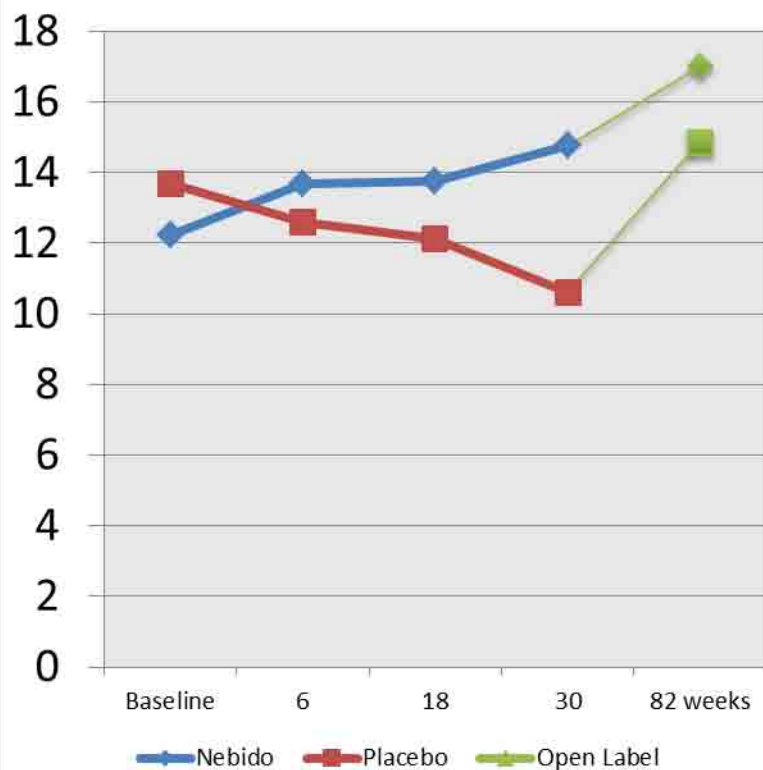
# BLAST open-label – IIEF (N=106)



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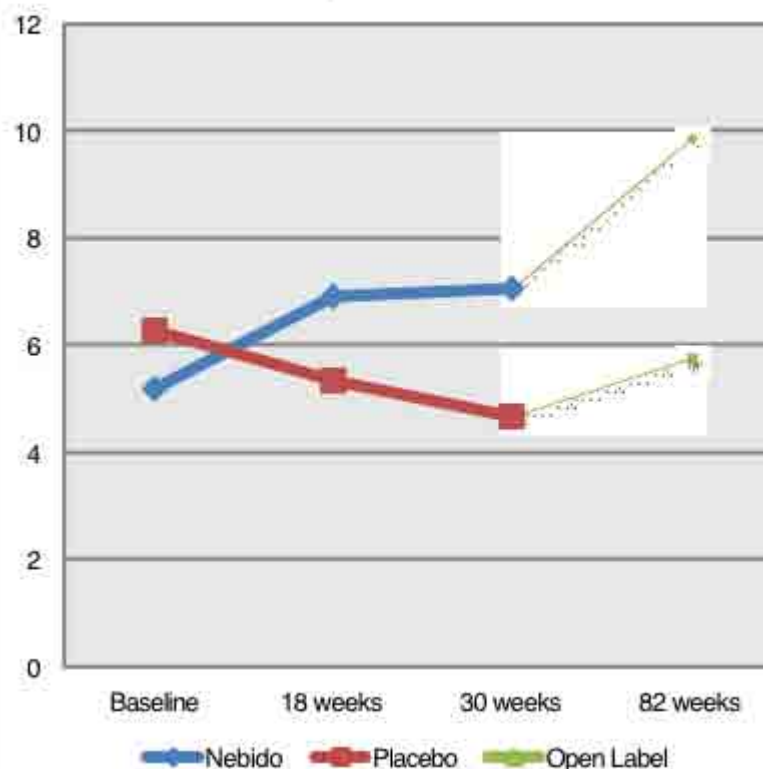
### IIEF: Erectile Function

p=0.003



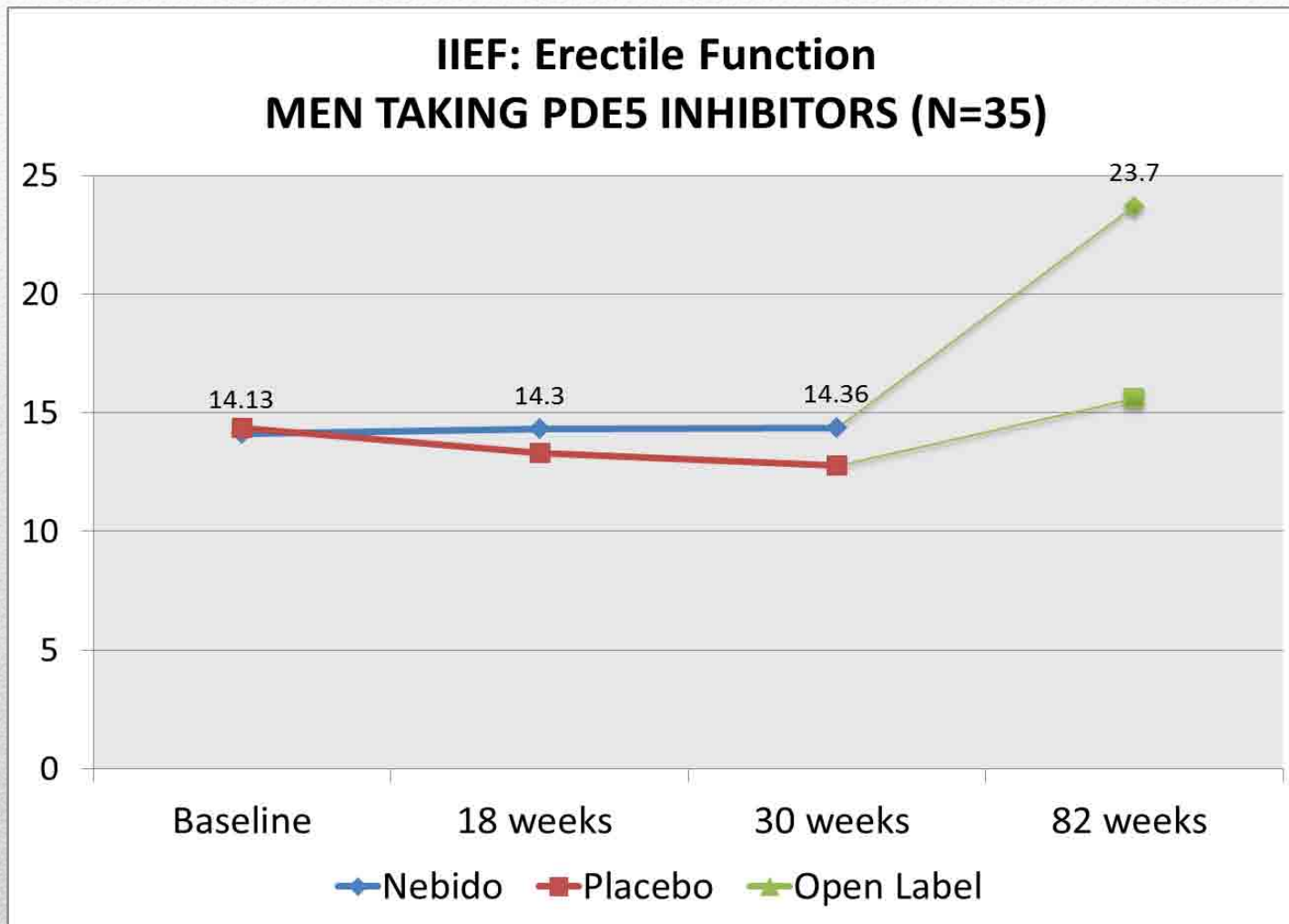
### IIEF: Intercourse Satisfaction

p=0.005



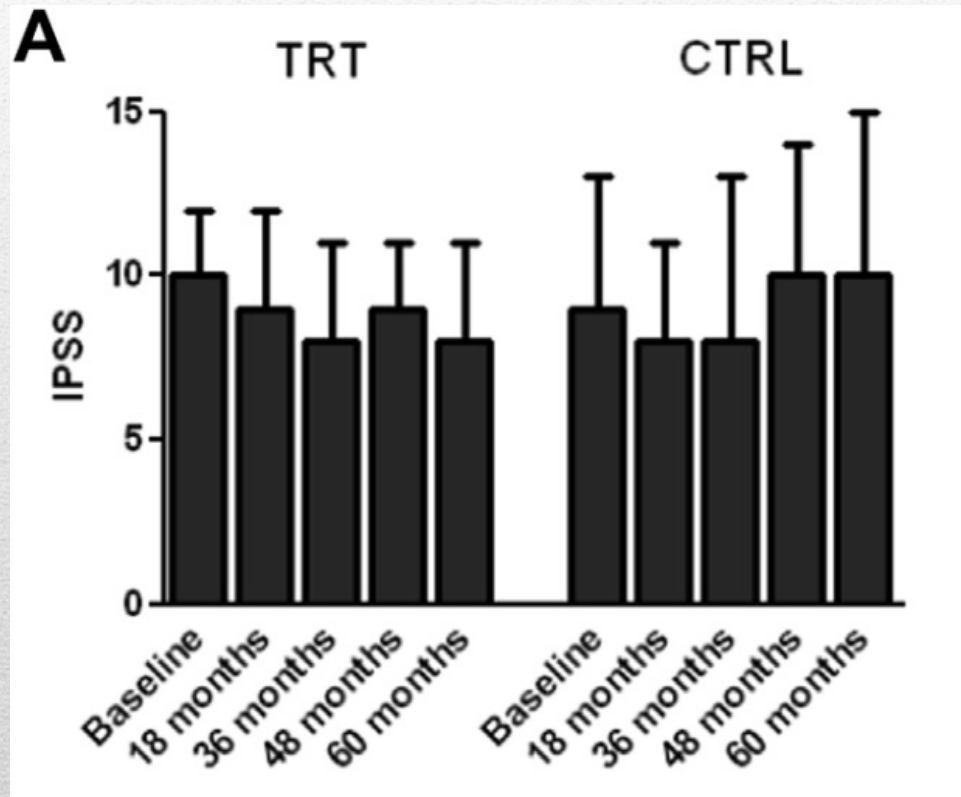


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# Effects of 5-Year Treatment With Testosterone Undecanoate on Lower Urinary Tract Symptoms in Obese Men With Hypogonadism and Metabolic Syndrome

Davide Francomano, Alessandro Iacqua, Roberto Bruzziches, Andrea Lenzi, and Antonio Aversa; Urology, 2013 in press



Variations in total International Prostate Symptom Score (IPSS)



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## Testosterone Therapy in Men With Prostate Cancer: Scientific and Ethical Considerations

Abraham Morgentaler\*,†

*From Men's Health Boston and the Department of Urology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts*

**Conclusions:** Although no controlled studies have been performed to date to document the safety of testosterone therapy in men with prostate cancer, the limited available evidence suggests that such treatment may not pose an undue risk of prostate cancer recurrence or progression.



# IPASS - Nebid



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## IPASS: A Study on the Tolerability and Effectiveness of Injectable Testosterone Undecanoate for the Treatment of Male Hypogonadism in a Worldwide Sample of 1,438 Men

Michael Zitzmann, MD, PhD,\* Andreas Mattern, PhD,<sup>†</sup> Jens Hanisch, PhD,<sup>†</sup> Louis Gooren, MD, PhD,<sup>‡</sup> Hugh Jones, MD, PhD,<sup>§¶</sup> and Mario Maggi, MD, PhD\*\*

J Sex Med. 2013 Feb;10(2):579-88

- N=1438 / 1493 patients included in safety population
  - 1123 patients completed the study and received all 5 injections (78.1% continuation rate)
  - In total, 6333 TU injections were administered
  - Mean observation period: 9.2 ± 3.1 months
-



# IPASS Safety data



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## PSA (ng/mL)

	n	Mean	SD
<b>Baseline</b>	938	1.10	0.94
<b>Visit 2</b>	708	1.20	1.08
<b>Visit 3</b>	676	1.30	1.18
<b>Visit 4</b>	537	1.20	1.03
<b>Visit 5</b>	455	1.10	1.05

## Hematocrit (%)

	n	Mean	SD
<b>Baseline</b>	843	42.8	6.56
<b>Visit 2</b>	725	44.0	5.83
<b>Visit 3</b>	684	44.7	6.05
<b>Visit 4</b>	534	44.7	6.18
<b>Visit 5</b>	474	44.5	6.12

PSA, prostate-specific antigen; SD, standard deviation



# Testosterone Deficiency in Men(TD)/Late Onset Hypogonadism (LOH)

.....nevertheless, even though these systemic complications.....  
TD is underestimated and undertreated!

Why?

- Understimulated: Symptoms and signs of late onset are even milder, unspecified and difficult to recognize
  - Undertreated: fear that testosterone replacement causes
    - prostate cancer or its progression  
(in particular in men without severe TD)
    - Polycythemia
- Long term systemic complications: increment of morbidity and mortality
- Correct diagnosis, clinical assessment and treatment (International Guidelines)



## Standard Operating Procedures for Hypogonadism

- **SIAMS** realised **SOPHY** (simple and updated diagnostic chart for TD) in order to make easier and promote the diagnosis of testicular deficiency, where is frequent but underestimated, as in the practice of diabetologist, internist, cardiologist, endocrinologist, urologist.
- «*EDUCATION*»



Bayer HealthCare



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# Symptoms of adult vs pre-puberal hypogonadism

**Table 2** Symptoms, signs, and conditions indicative of Testosterone Deficiency [3,5,6,13,41].

Most specific signs and symptoms	Less specific signs and symptoms	Most specific conditions
Reduced sexual desire and activity Decreased spontaneous erections Erectile Dysfunction	Decreased energy, motivation, initiative Delayed ejaculation Reduced muscle bulk and strength	Type 2 diabetes mellitus Metabolic syndrome Chronic obstructive lung disease, Obstructive Sleep Apnea Syndrome
Hot flushes, sweats Decreased testicle size Loss of pubic hair, reduced requirement for shaving Increased BMI, visceral obesity	Diminished physical or work performance Mild anemia (normocytic, normochromic) Depressed mood, irritability	End-stage renal disease, hemodialysis Osteoporosis HIV- associated weight loss
Height loss, low trauma fractures, reduced BMD	Poor concentration and memory Sleep disturbances, sleepiness	History of infertility, cryptorchidism, pituitary disease, delayed puberty Treatment with opioids or glucocorticoids

\*Wu FCW, 2010



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## Threshold Levels for the Biochemical Diagnosis of TD

There are no generally accepted lower limits of normal TT (total testosterone).

There is, however, general agreement that:

- **TT > 12 nmol/L (3.5 ng/mL or 350 ng/dL)** does not usually require substitution (EBMI1)
- Based on the data of young hypogonadal men, men with **TT < 8 nmol/L (2.3 ng/mL or 230 ng/dL)** usually benefit from T treatment (EBMI1)
- Between these levels:
  - measuring FT (free testosterone) by equilibrium dialysis or *calculating it from TT and SHBG levels\* may be helpful in case of TT between 8 and 12 nmol/L.*
- A lower limit of **225 pmol/L (65 pg/mL)** is accepted by many (EBMI3)

[\\*www.issam.ch/freetesto.htm](http://www.issam.ch/freetesto.htm).



# SOPHY Project

## Standard Operating Procedures for Hypogonadism



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&



- In the pilot phase of SOPHY:*
- 5 centers, 47 physicians*
- From December 2013 available on SIAMS site



Milano  
Luca Persani

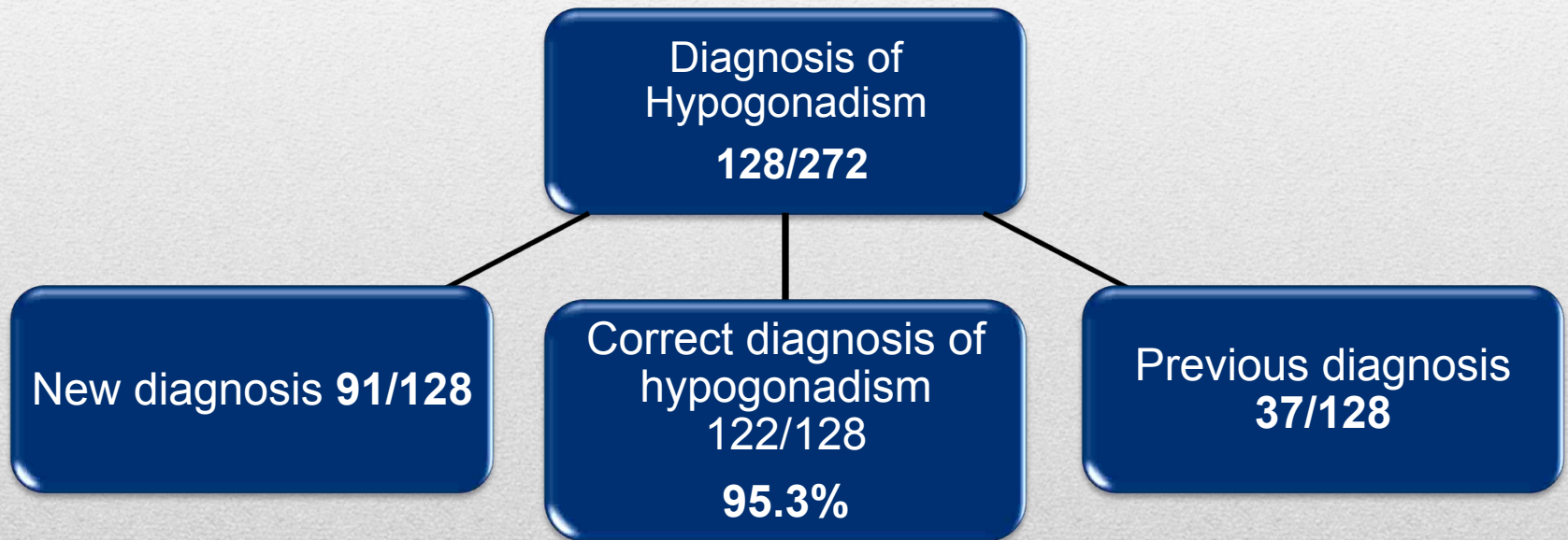
Udine  
Franco Grimaldi



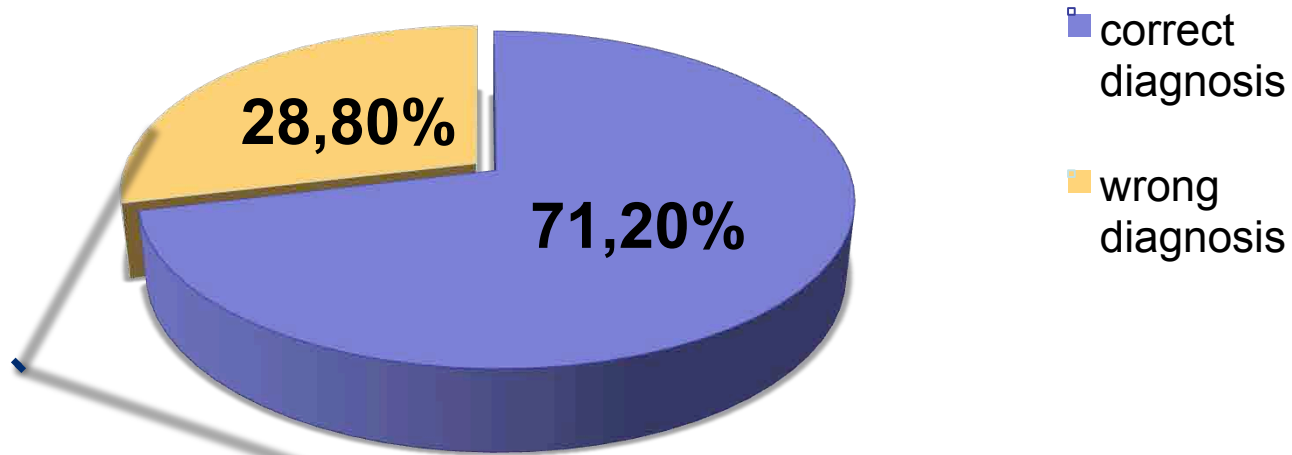
Coordinator: Alessandro Pizzocaro MD

# Analysis of current situation

26 active physicians, 319 filled questionnaires, 272 analyzed



# Exclusion of Hypogonadism



## Causes of error

Total testosterone Borderline (NO SHBG)	32.5%
NO testosterone assay in presence of symptoms	55%
Other	12.2%

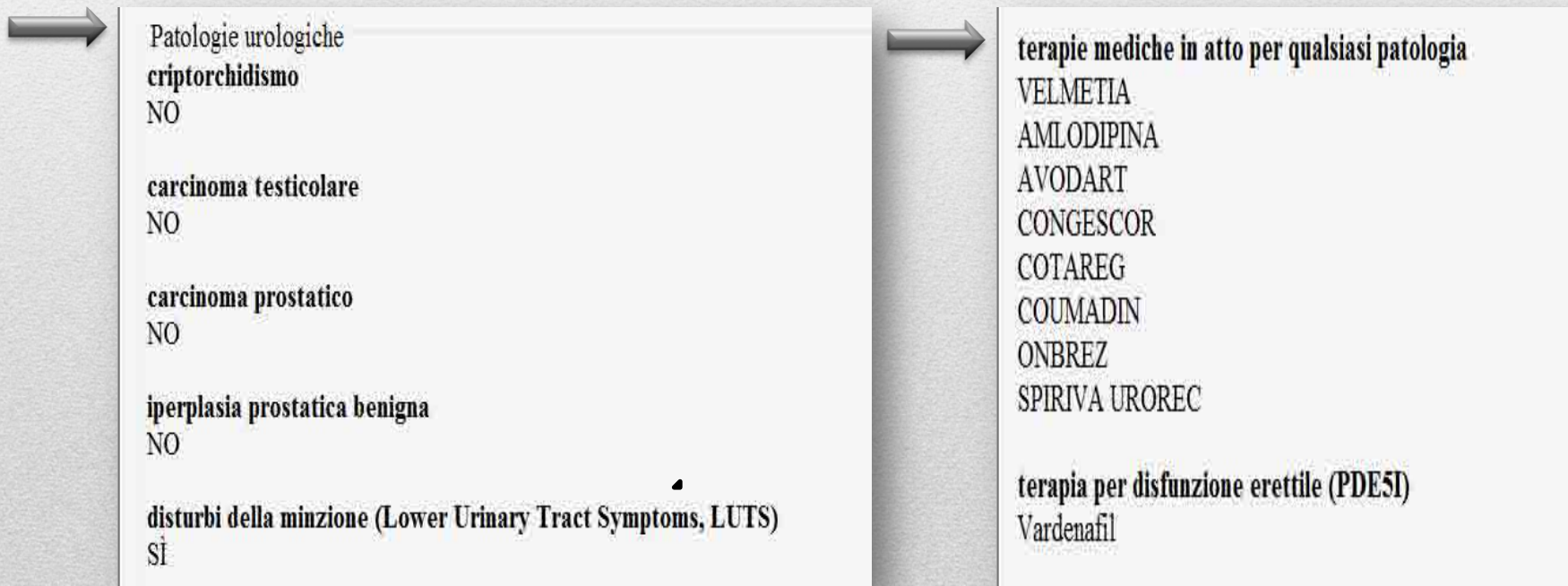


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# Exclusion of Hypogonadism: wrong diagnosis

## Specialist in Diabetology

- Patient: 71years old, married, 2 sons, with hypertension, diabetes, cardiovascular disease, BPH, BPCO







# Hypogonadism Symptoms



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<i>"ha avuto più o meno desiderio di fare l'amore nel corso degli ultimi tre mesi?"</i>	SÌ
<b>desiderio sessuale ipoattivo: specifiche</b> sì, ma meno rispetto a prima	
<i>"le è mai capitato di svegliarsi con un'erezione negli ultimi 3 mesi?"</i>	SÌ
<b>Riduzione del numero delle erezioni notturne e mattutine: specifiche</b> sì, ma meno frequenti di prima	
<b>Disfunzione erettile (nel raggiungimento e/o nel mantenimento dell'erezione negli ultimi 3 mesi)</b>	SÌ
<b>disfunzione erettile dettaglio</b> difetto nel mantenimento	<b>disfunzione erettile mantenimento</b> qualche volta < 25% dei casi
<b>numero dei rapporti sessuali nel periodo (es: 3/mese)</b> 3/MESE	
<i>"ha notato una riduzione (volume) della quantità di sperma (eiaculato) negli ultimi 3 mesi?"</i> Sì, un po' ridotto	
<i>"le capita di venire troppo alla svelta?"</i> Sì	
<b>eiaculazione precoce (EP)</b>  <b>da quanto tempo è presente?</b>	
<i>"ha difficoltà a raggiungere l'orgasmo o di venire troppo tardi o addirittura di non venire?"</i>	NO
<b>ridotta frequenza rasatura della barba</b>	NO
<b>astenia</b>	SÌ
<b>tristezza</b>	NO
<b>ridotta capacità a compiere esercizi fisici intensi</b>	SÌ
<b>ridotta capacità di concentrazione</b>	SÌ



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# Clinical diagnosis and laboratory analysis

**mammelle dettaglio**  
normali

**volume**  
aumentato

**noduli**  
NO

**superficie**  
regolare

**consistenza**  
aumentata

**dolore**  
NO

**testosterone totale** unità di misura  
2.35 NG/ML

**glicemia basale** unità di misura  
110 mg/dl

**insulina basale**

**HbA1c (emoglobina glicosata)** unità di misura  
6.8 %

**colesterolo totale** unità di misura  
235 mg/dl

**HDL** unità di misura  
57 mg/dl

**trigliceridi** unità di misura  
112 mg/dl

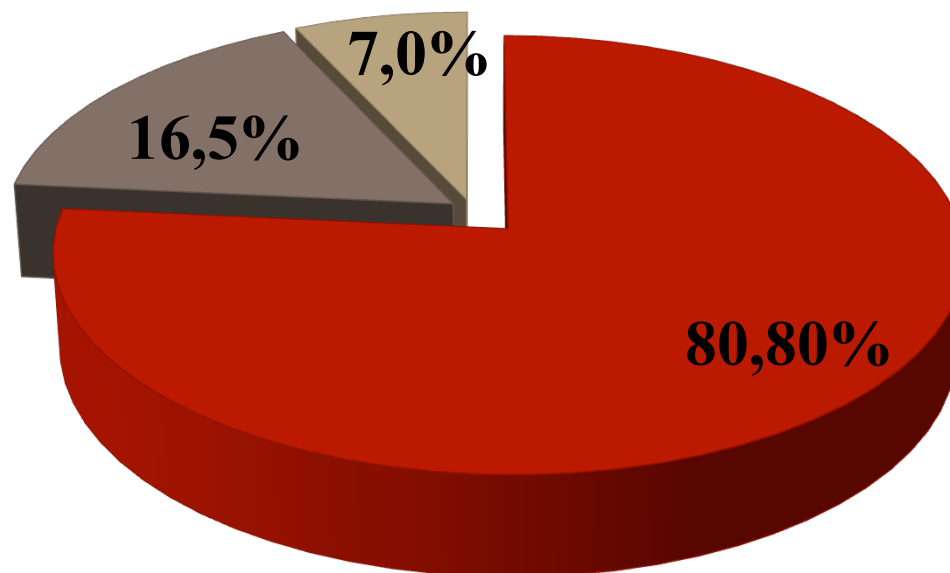
**Nuova diagnosi di ipogonadismo** NO



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# Hypogonadism Treatment Percentage in diagnosed cases

## Hypogonadism Treatment



■ Treated    ■ Not treated    ■ Not treated (other Specialist)

# Hypogonadism Not Treated

## Specialist in Endocrinology

- Patient: 45 years old, married, no sons, familiar with T2 diabetes mellitus and cardiovascular disease; 1 cigar; < 2 drink; no sport

Patologie endocrinologiche

**ipogonadismo (già noto)**

NO

**patologie tiroidee**

SÌ

**patologie tiroidee: quali?**

ipotiroidismo primitivo autoimmune

**patologie surrenaliche**

NO

**patologie ipofisarie**

SÌ

**patologie ipofisarie: quali?**

adenoma non secernente

**osteopenia**

SÌ

**Altro:** Dislipidemia

Terapia: Eutirox mcg/die,  
Omeprazolo mg, Vytorin.

**testosterone totale** unità di misura  
2.72 ng/ml

**ematocrito**  
42.1 %

**PSA totale**  
0.39 ng/ml

**LH**  
1.8 UI/L

**prolattina** unità di misura  
4.5 ng/ml

**FSH**  
2.7 UI/L

**SHBG (sex hormone binding globulin)**

**colesterolo totale** unità di misura  
157 mg/dl

**HDL** unità di misura  
42 mg/dl

**trigliceridi** unità di misura  
79 mg/dl

**peso**  
85 kg

**altezza**  
175 cm

**circoferenza vita**

**span**

**proporzioni eunucoidi**  
NO

**frequenza cardiaca**  
72 bpm

**pressione arteriosa sistolica**  
130 mmHg

**pressione arteriosa diastolica**  
75 mmHg

**pene normale**  
SÌ

Non valutati: didimi e prostata



# Hypogonadism Symptoms



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<i>"ha avuto più o meno desiderio di fare l'amore nel corso degli ultimi tre mesi?"</i>	SI
<b>desiderio sessuale ipoattivo: specifiche</b>	
<i>"le è mai capitato di svegliarsi con un'erezione negli ultimi 3 mesi?"</i>	SI
<b>Riduzione del numero delle erezioni notturne e mattutine: specifiche</b>	
<b>Disfunzione erettile (nel raggiungimento e/o nel mantenimento dell'erezione negli ultimi 3 mesi)</b>	SI
<b>disfunzione erettile dettaglio</b>	<b>disfunzione erettile raggiungimento</b>
<ul style="list-style-type: none"><li>• difetto nel raggiungimento</li><li>• difetto nel mantenimento</li></ul>	<b>disfunzione erettile mantenimento</b>
<b>numero dei rapporti sessuali nel periodo (es: 3/mese)</b>	
<i>"ha notato una riduzione (volume) della quantità di sperma (eiaculato) negli ultimi 3 mesi?"</i>	
SI, molto ridotto	

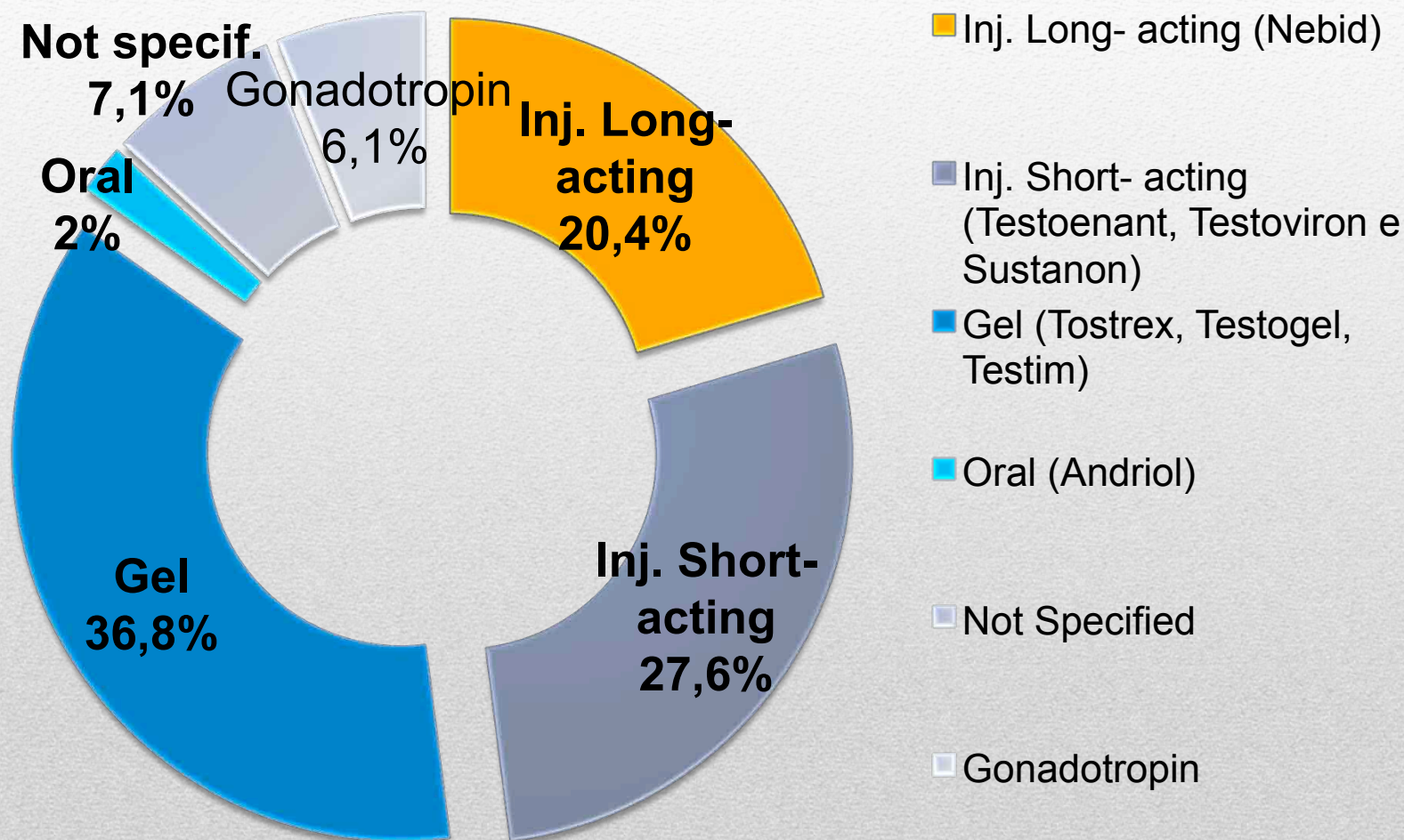
## Diagnosis

<b>Nuova diagnosi di ipogonadismo</b>	SI
<b>Viene instaurata/modificata la terapia?</b>	NO
<b>Il paziente viene inviato a ulteriore specialista?</b>	NO



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# Formulation





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# SOPHY



**Thanks for your  
attention!**

**Alessandro Pizzocaro**

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