LIPOCINE®

ENHANCING HEALTH

Enabling oral drug delivery to improve patient compliance

# Corporate Presentation

January 2019

# Forward-Looking Statements

This presentation contains forward-looking statements about Lipocine Inc. (the "Company"). These forward-looking statements are made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These forward-looking statements relate to the Company's product candidates, the expected timing of the FDA review process related to our resubmitted NDA for TLANDO™, clinical and regulatory processes and objectives, potential benefits of the Company's product candidates, intellectual property and related matters, all of which involve known and unknown risks and uncertainties. Actual results may differ materially from the forward-looking statements discussed in this presentation.

Accordingly, the Company cautions investors not to place undue reliance on the forward-looking statements contained in, or made in connection with, this presentation. Several factors may affect the initiation and completion of clinical trials, the potential advantages of the Company's product candidates and the Company's capital needs. Among other things, the projected commencement and completion of the Company's clinical trials may be affected by difficulties or delays. We may encounter delays or other issues in the FDA approval process, including that the FDA may determine there are deficiencies in our resubmitted NDA. We are also subject to risks related to the possibility of an advisory committee meeting related to TLANDO™. In addition, the Company's results may be affected by its ability to manage its financial resources, difficulties or delays in developing manufacturing processes for its product candidates, preclinical and toxicology testing and regulatory developments. Delays in clinical programs, whether caused by competitive developments, adverse events, patient enrollment rates, regulatory issues or other factors, could adversely affect the Company's financial position and prospects. Prior clinical trial program designs and results are not necessarily predictive of future clinical trial designs or results. If the Company's product candidates do not meet safety or efficacy endpoints in clinical evaluations, they will not receive regulatory approval and the Company will not be able to market them. The Company may not be able to enter into any strategic partnership agreements. The Company's commercial success depends on its ability to manufacture, market and sell products without infringing the proprietary rights of third parties. Operating expense and cash flow projections involve a high degree of uncertainty, including variances in future spending rates due to changes in corporate priorities, the timing and outcomes of clinical trials, competitive developments and the impact on expenditures and available capital from licensing and strategic collaboration opportunities. If the Company is unable to raise additional capital when required or on acceptable terms, it may have to significantly delay, scale back or discontinue one or more of its drug development or discovery research programs. The Company is at an early stage of development and may not ever have any products that generate significant revenue. The forward-looking statements contained in this presentation are further qualified by the detailed discussion of risks and uncertainties set forth in the Company's annual report on Form 10-K and other periodic reports filed by the Company with the Securities and Exchange Commission, all of which can be obtained on the Company's website at www.lipocine.com or on the SEC website at www.sec.gov. The forward-looking statements contained in this document represent the Company's estimates and assumptions only as of the date of this presentation and the Company undertakes no duty or obligation to update or revise publicly any forward-looking statements contained in this presentation as a result of new information, future events or changes in the Company's expectations.



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# Unique Specialty Pharmaceutical Company

## Advanced Pipeline

### Men's Health

***Oral Testosterone Replacement Therapy ("TRT")***

***Oral Androgen Therapy for Fatty Liver Disease ("NAFLD"/ "NASH")***

### Women's Health

***Oral Therapy for Prevention of Preterm Birth ("PTB")***

**Proprietary Drug Delivery Platform**

**Significant Unmet Need In Both Therapeutic Areas**



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# Late-Stage Pipeline

## Oral Product Candidates Targeting Significant Opportunities

| | PRODUCT *(Indication)* | PRECLINICAL | PHASE 1 | PHASE 2 | PHASE 3 | NDA |
|---|---|---|---|---|---|---|
| MEN'S HEALTH | **TLANDO™** *(Oral Testosterone Replacement Therapy, TRT)* | → | → | → | → | ABPM Study Ongoing |
| MEN'S HEALTH | **LPCN 1111** *(Next Gen. Oral TRT)* | → | → | → | Phase 2 Completed | |
| MEN'S HEALTH | **LPCN 1144** *(Oral Treatment for NASH)* | → | Liver Fat Imaging POC Study Ongoing | | | |
| WOMEN'S HEALTH | **LPCN 1107** *(Prevention of Preterm Birth, PTB)* | → | → | → | EOP2 Completed | |



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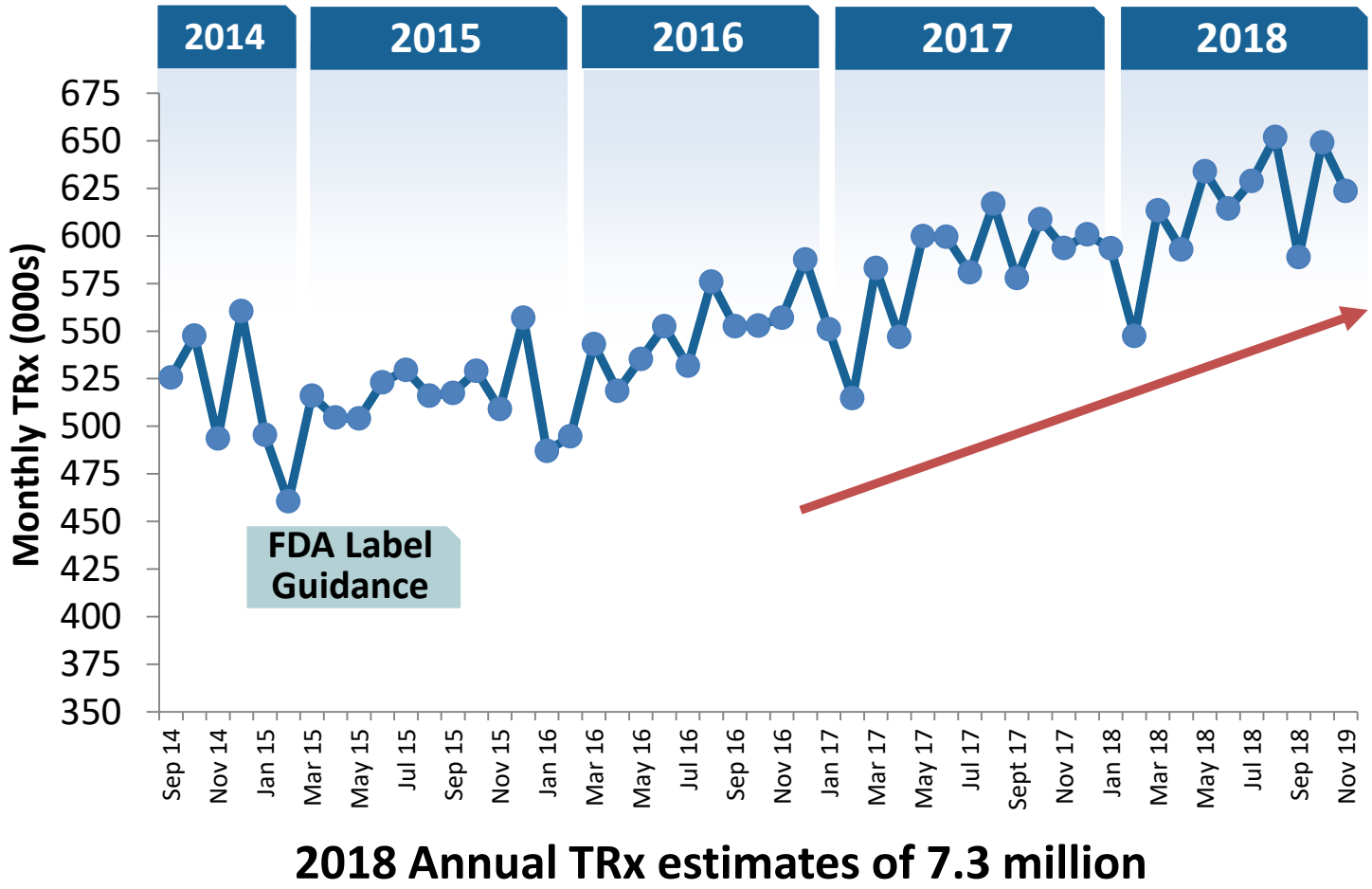
# TLANDO™

Targeted for Testosterone Replacement Therapy

# Monthly TRT TRx Trend

## TRT Market is Growing




**2018 Annual TRx estimates of 7.3 million**

Source: IMS database
TRx = Total prescriptions



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# Issues with Current Non-oral TRT Options

## Potential Barrier To Newly Diagnosed and Existing Patients

- **Black Box Warning**
  - Secondary exposure to testosterone
  - Pulmonary oil micro embolism (POME) and anaphylaxis shock
- **Inconvenient application or painful injection**
- **Poor persistence reflects need for oral**
  - Average days on therapy is 100 days
- **More than 50% of patients need dosage adjustment**
  - Burdensome for patients due to multiple doctor visits



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# TLANDO™: Path Forward for Resubmission Confirmed

## Next Steps in Bring TLANDO to Patients

**Deficiencies and Plan for Resolution**

**Determine extent, if any, of ex vivo conversion of TU to T**

- Top-line results suggest no statistically significant *ex vivo* conversion when sample collection and processing is consistent with manufacturer's recommended conditions and with Phase 3 instructions

**Obtain definitive evidence pre-approval via ambulatory blood pressure monitoring study to exclude whether TLANDO causes clinically meaningful increase in blood pressure**

- ABPM study enrollment complete; results expected 1Q 2019

**Provide justification for non-applicability of Cmax based secondary endpoints**

- Additional analyses of existing data for resubmission

**Determine the appropriate stopping criteria that can be reproducibly and accurately identify patients who should discontinue use of TLANDO**

- Additional analyses of existing data for resubmission



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# TLANDO™: Definitive Phlebotomy Study

## *Ex Vivo* Conversion Assessment

- Study objective:
  - To evaluate the extent, if any, of clinically meaningful *ex vivo* conversion of TU to T in serum blood collection tubes to confirm the reliability of TLANDO data results
- Study design:
  - Open-label, single dose study (N=12)
  - Blood sampling post 225 mg TU dose: at 3 hr. and 5 hr. post dosing (N=24)
    - Control : Time zero (immediately processed) plasma tubes with EDTA (“PT”)
    - Test : Serum separation tubes (“SST”) per manufacturer’s recommendation-30 min.)
- Top-line results:
  - Mean percentage difference and the associated percentage standard deviation post dose of T concentrations measured between SST samples and PT samples are -1.0% and 9.2%, respectively
  - The difference was not statistically significant (p = 0.91)

# TLANDO™: Potential First Oral Option

## Profile Demonstrated Clinically with Target Label Regimen

### Efficacy

- Met primary endpoint
  - 80% response rate in "worst-case analysis" vs. FDA requirement of 75%
- Met key secondary endpoint
  - No eligible subjects with T levels >2500 ng/dL
- Other secondary endpoints generally consistent with approved products

### Safety

- 591 subject exposure
- Well tolerated in 52 week exposure
  - AE profile comparable to active control, including GI
  - No cardiac, hepatic or drug related SAEs
  - No increase in mean BP with cuff measurements
- No apparent correlation of the observed Cmax excursions
  - ADRs, AEs, Meaningful changes in critical lab parameters

### Clear Benefits

- Preferred oral option
  - No risk of accidental T transference
  - Non-invasive
  - Less cumbersome
  - Less burdensome
  - Simpler to prescribe
  - Fewer doctor visits
  - Easier for patients to properly use



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# LPCN 1144

Targeted for Non Alcoholic Steatohepatitis (NASH)

A silent killer that affects 30 million Americans[1]

Global market estimated to be ~$35 billion[1]

1. CNBC; published December 30, 2018

# LPCN 1144: Well Positioned for Success

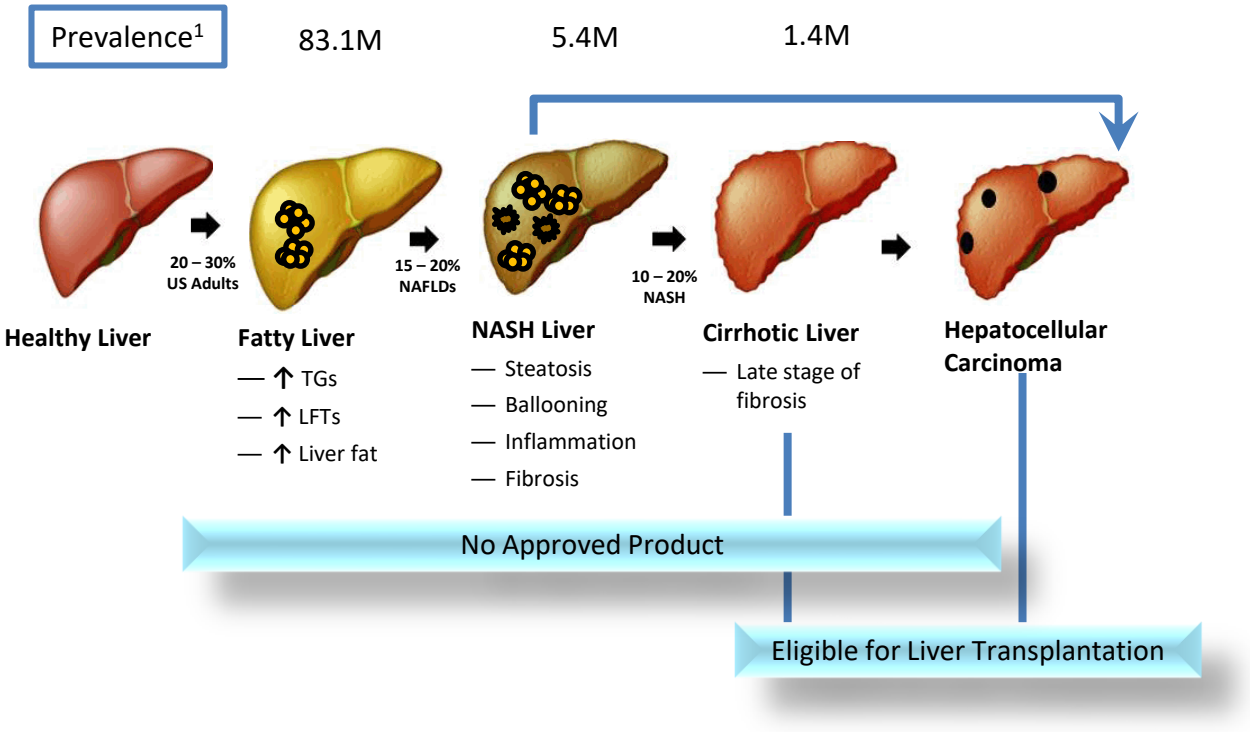
## Unique Mechanism of Action and Well Tolerated Safety Profile

- Unique Mechanism Targeting Full Spectrum of NASH Pathogenesis + Collateral Health Benefits
  - Testosterone deficiency in men is prevalent across the full spectrum of NAFLD
  - LPCN 1144 results suggest therapy has potential for collateral health benefits
- Well Tolerated Safety Profile
  - Prodrug of a bio-identical hormone
  - Demonstrated with 591 subjects in 12 studies with up to 52 week exposure
- Compelling Clinical Biomarker Data
  - Significant reductions in both the key ALT and TG serum NASH biomarkers
  - Good potential of histological improvement in NASH and fibrosis

# Non-Alcoholic Fatty Liver Disease (NAFLD)

## Clinical Progression

**Fatty liver is a reversible condition wherein large vacuoles of triglyceride (TG) fat accumulate in liver cells via the process of steatosis**




1 . Estes et.al. Hepatology, 2018:

LFTs: Liver function test, especially Alaninine amino transferase (ALT) and Aspartame amino transferase (AST)
NASH: Non-alcoholic Steatohepatitis, TG: Triglyceride



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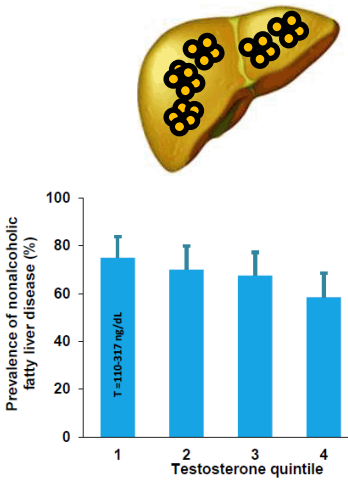
# Clinical Relationship Between Testosterone and NAFLD

## Across the Full Histological Spectrum

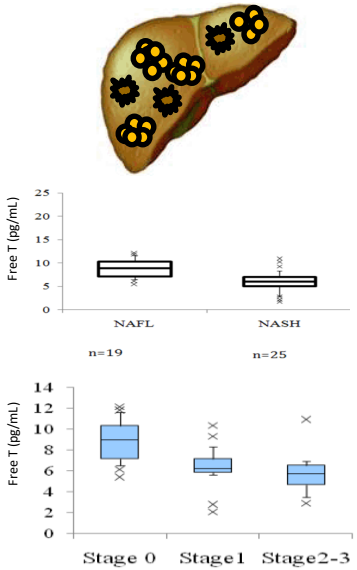
### Hepatic Steatosis

"Men with low testosterone are at high risk for NAFLD." [1]



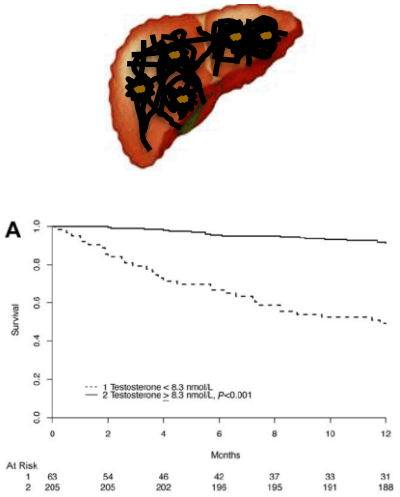

### NASH

"Levels of free T decreased significantly with the increased incidence of lobular inflammation, hepatocyte ballooning, NAFLD activity score, and fibrosis." [2]




### Cirrhosis

"Low T levels in cirrhotic men are associated with the combined outcome of death or transplantation." [3]




1 Kim et al, Gastroenterol 2012; 2 Sumida et al, Gastroenterol Hepatol 2015; 3 Sinclair et al, Liver Trans 2016



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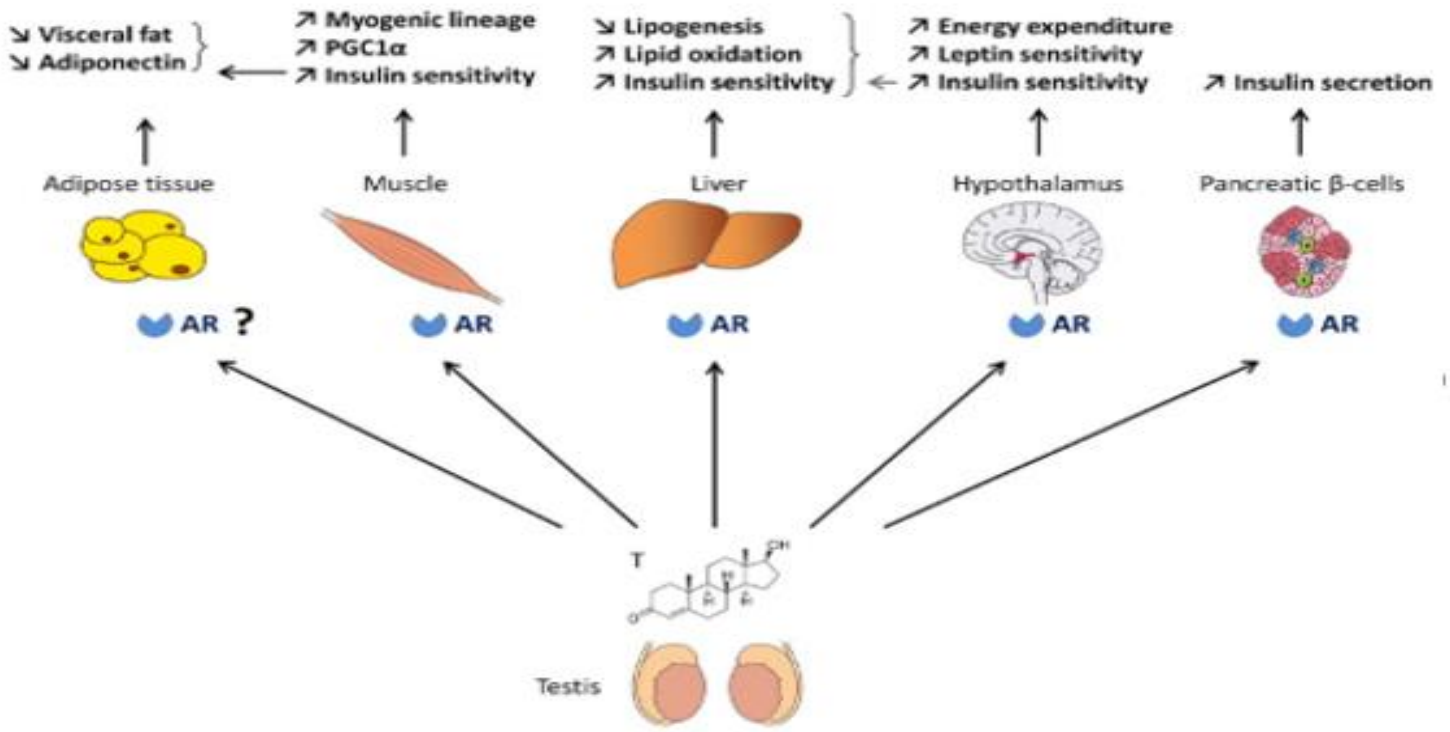
# Proposed Mechanism of Action

## Androgen Action via Androgen Receptor ("AR") in Males*




Normal level and signaling of androgens prevent hepatic fat accumulation in males**



* Navarro et al, Obesity 2015

** Shen and Shi, Int J Endocrinol 2015

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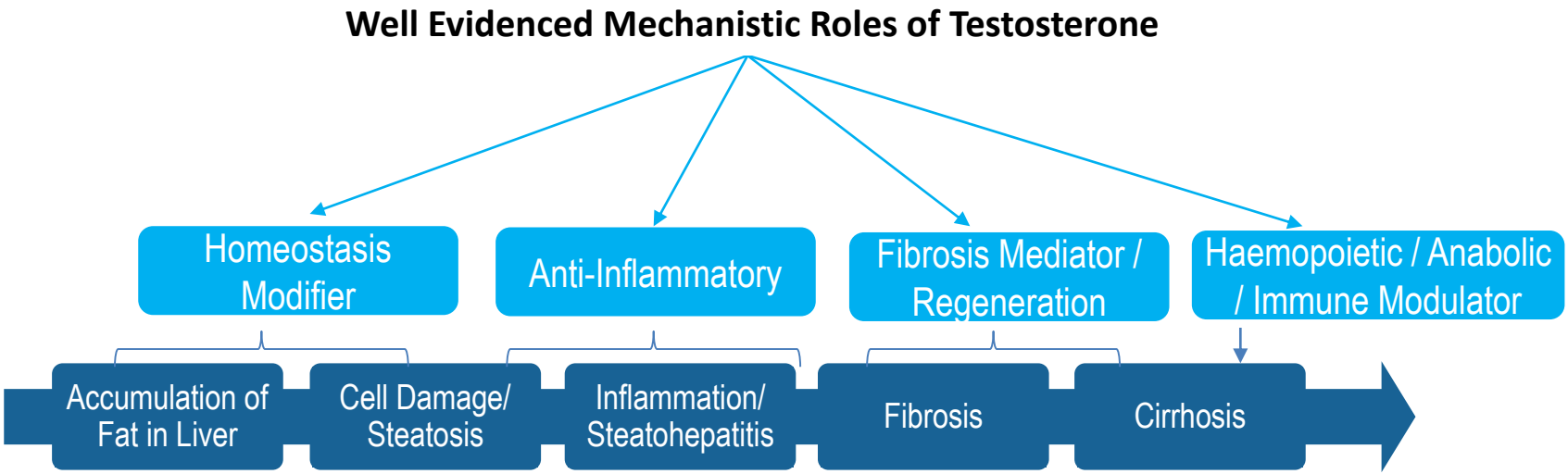
# LPCN 1144: Targeting Full Spectrum Of NASH Pathogenesis

## Plus Collateral Health Benefits




NASH Pathogenesis

- Reduction of elevated ALT levels generally predicts liver histological improvement in NASH[1]
- A 29% reduction in liver fat as measured by MRI-PDFF was associated with a histologic response in non-alcoholic steatohepatitis, Histologic responders had a statistically significant reduction in MRI-PDFF of −4.1% ± 4.9[2]

1 Hoffnagle et al., APT 2013, 2 Patel et al., Therap Adv Gastroenterol. 2016 Sep; 9(5): 692–701..



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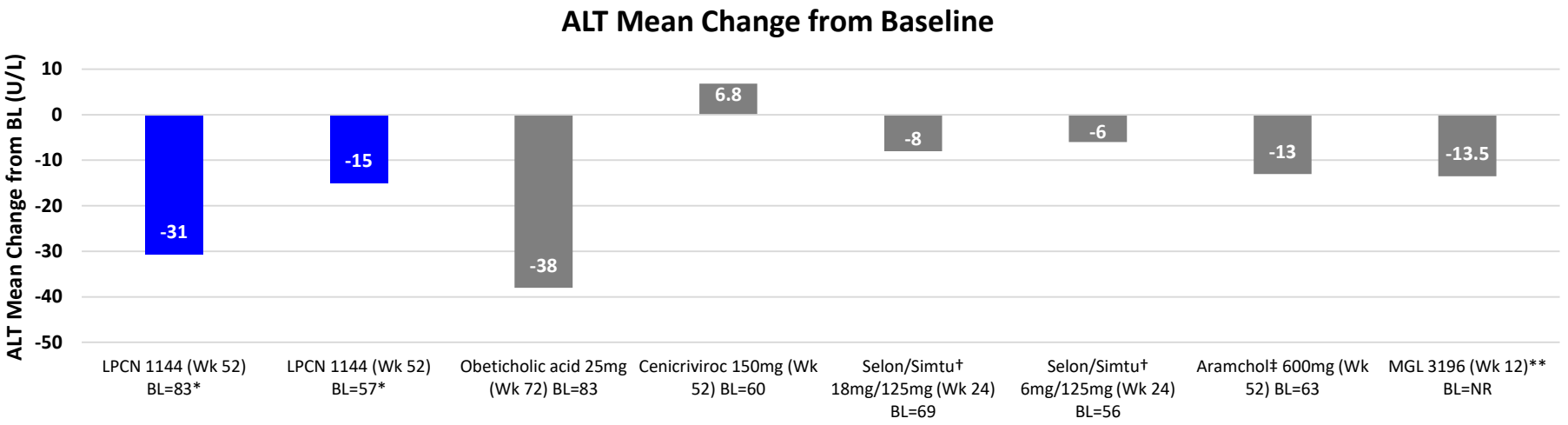
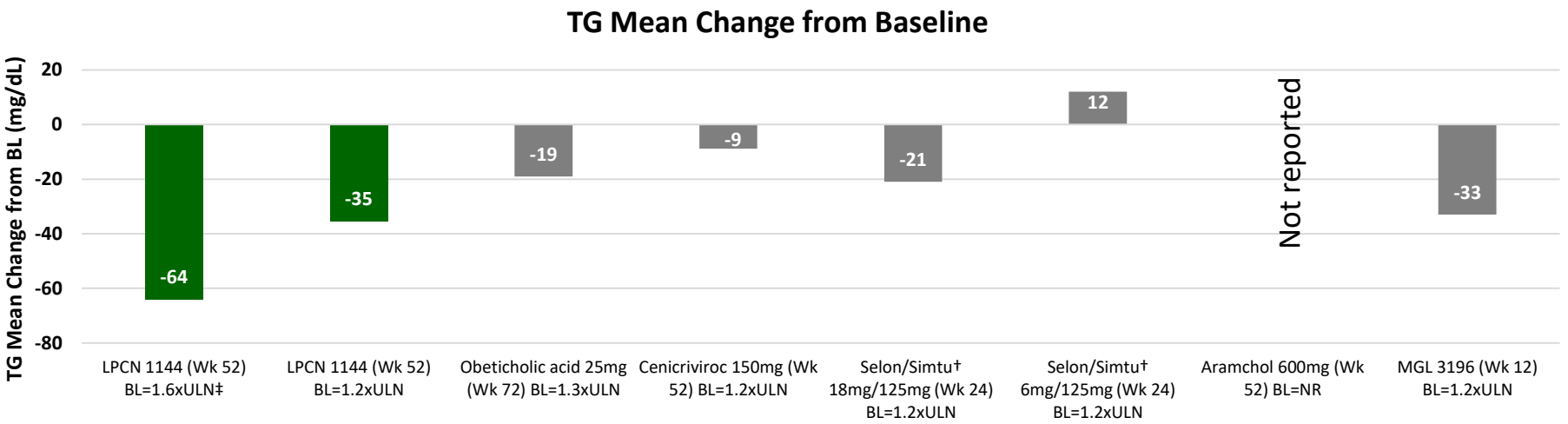
# LPCN 1144: Compelling Clinical Biomarker Data

## Comparison to Product Candidates in Advanced Development




* LPCN 1144 SOAR Trial Patients for mean BL=83 and 57 U/L are with ALT ≥ 75 and 45 U/L, respectively, at baseline; ** MGL 3196 patients are males with ALT > 45 U/L and females > 30 U/L at baseline.
‡ TG ULN for LPCN 1144 SOAR Trial is 200 mg/dL while typical TG ULN is 150 mg/dL.; Mean BL=1.6xULN for LPCN 1144 is with TG > 200mg/dL.



Obeticholic acid: Neuschwander-Tetri et al, Lancet 2015; Cenicriviroc: Friedman et al, Hepatology 2018, Suppl. Table 5 ; Elafibranor: Ratziu et al, Gastroenterol 2016 ; Selon/Simtu: Loomba et al, Hepatology 2018 ; MGL 3196: EASL Apr 2018; Aramchol: Galmed Corp PPT, Jun 2017

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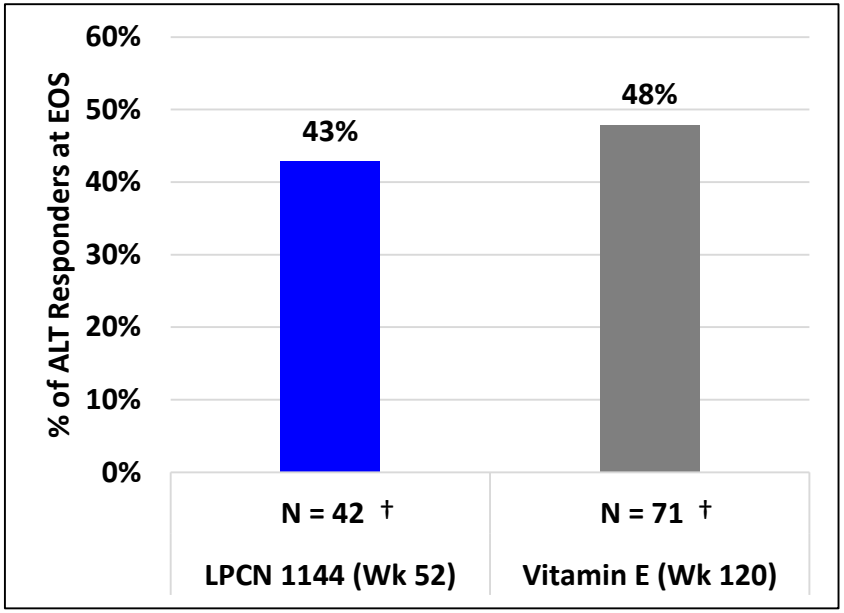
# LPCN 1144: Robust ALT Response

## Good Potential for Histological Improvement in NASH and Fibrosis[1]

- Comparable LPCN1144 ALT response to Vitamin E in PIVENS Trial[2]

| | Vitamin E | | |
|---|---|---|---|
| **Histological feature** | **ALT R* (*n* = 34)** | **ALT NR* (*n* = 37)** | ***P* value** |
| Mean change in steatosis score | −1.1 | −0.4 | <0.001 |
| Mean change in inflammation score | −1.1 | −0.3 | <0.001 |
| Mean change in Ballooning score | −0.8 | −0.2 | 0.01 |
| Mean change in NAS† score | −3.0 | −0.8 | <0.001 |
| Mean change in Fibrosis score | −0.5 | −0.2 | 0.34 |
| Decrease in NAS by ≥2 points | 82% | 32% | <0.001 |
| Resolution of NASH‡ | 44% | 22% | 0.07 |
| Mean change in Weight (kg) | −0.9 | 1.8 | 0.03 |

* ALT Responders: Patients with ALT > 40 U/L at baseline, ending with ≤ 40 U/L and more than 30% reduction at end of study post therapy
† Total non-alcoholic fatty liver activity score (NAS), comprising the sum of scores for steatosis, inflammation, and ballooning cell injury
‡ Resolution of histological features that fulfil the criteria for diagnosis of NASH




† Total N is for patients with ALT > 40 U/L at baseline (ALT normal range is ≤ 40 U/L)

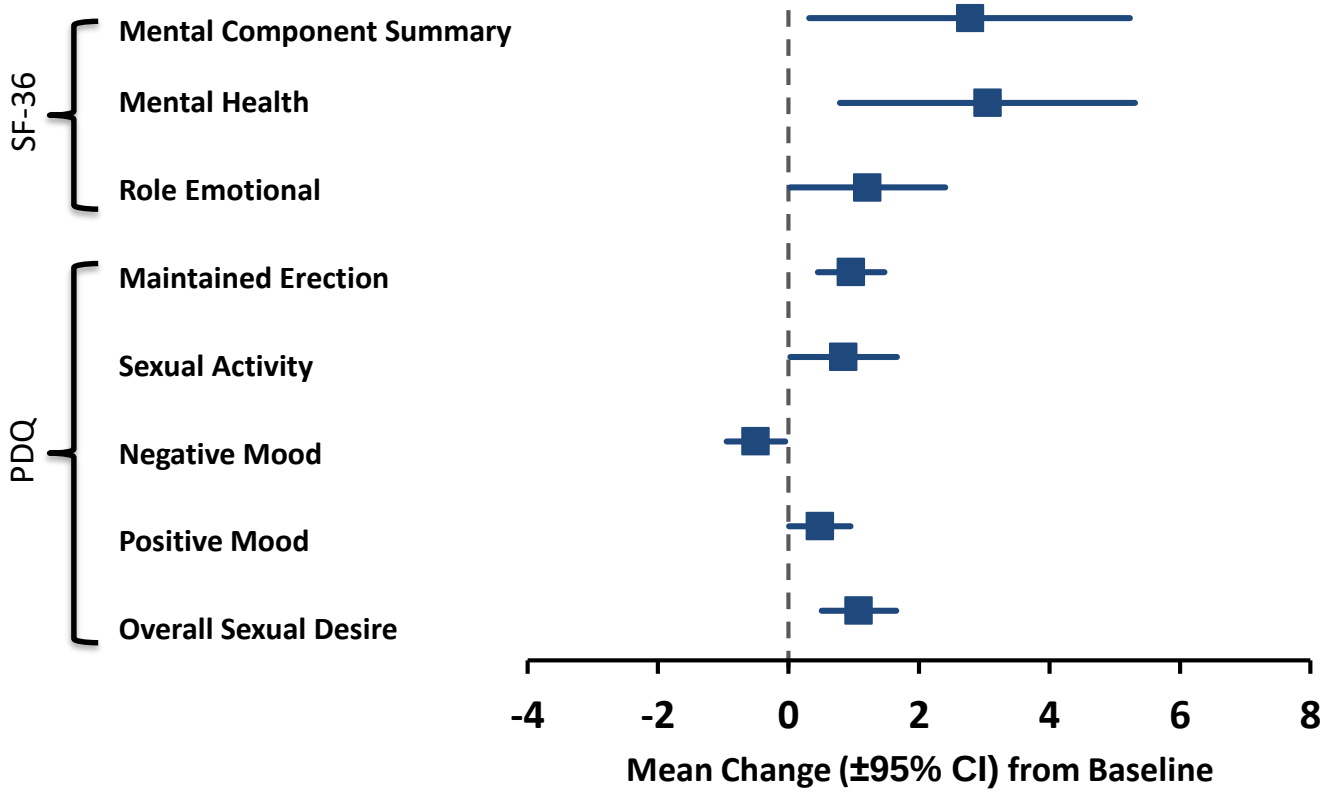


1 Hoffnagle et al. APT 2013

2 Sanyal et al, New Eng J Med, 2010

# LPCN 1144: Collateral Health Benefits

## Observed in Hypogonadal Subjects with Elevated ALT*




SF-36, Short Form-36 (0-100); PDQ, Psychosexual Daily Questionnaire (0-7); * ALT > 40 U/L at Baseline in 52 week SOAR Trial (N=33)



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# LPCN 1144: Ongoing T Therapy Liver Fat Imaging Study

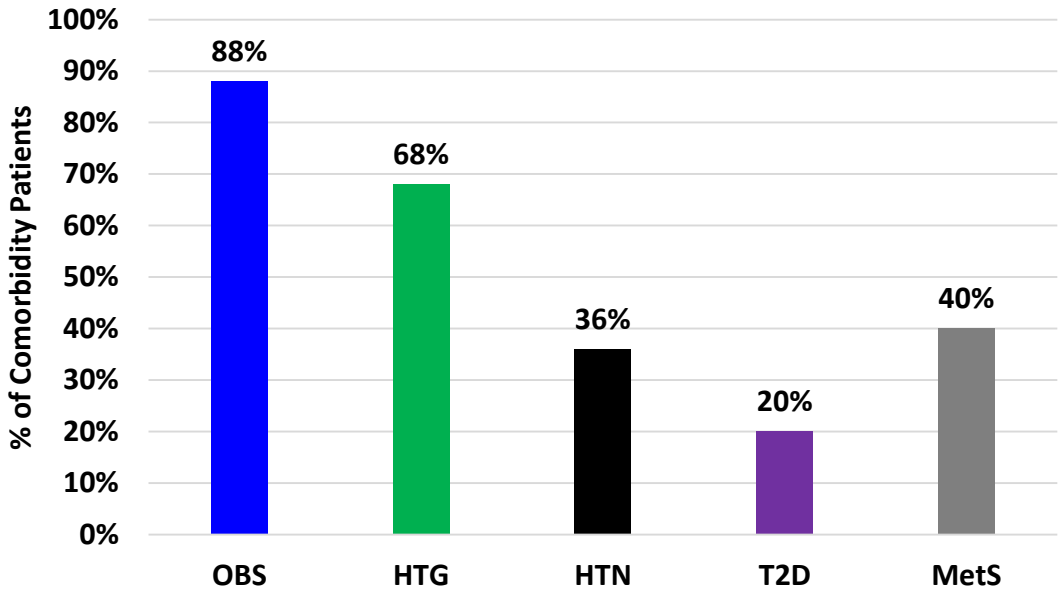
## Assesses Change from Baseline via MRI-PDFF

- Study design
  - Open-label, multi-center, single arm “Liver Fat Study”
  - Treatment: LPCN 1144 225mg BID
  - Study duration: 16 weeks with interim analysis
  - Population: hypogonadal males (N=36)
- Baseline Demographics
  - Mean T level: 199±61 ng/dL
  - Mean BMI: 34±6 $Kg/m^2$
- The prevalence of features of the metabolic syndrome in hypogonadal patients (N=36)
  - 81% obese, 58% hypertriglyceridemia, 28% hypertensive, and 17% type 2 diabetes

# LPCN 1144: Ongoing T Therapy Liver Fat Imaging Study

## Prevalence of Morbidity in NAFLD* Confirmed Subjects

- Obesity and hypertriglyceridemia are most prevalent in NAFLD confirmed hypogonadal patients




OBS: Obesity, HTG: Hypertriglyceridemia, HTN: Hypertension, T2D: Type2 Diabetes, MetS: Metabolic Syndrome (OBS+HTN+T2D)

* NAFLD Confirmed by MRI-PDFF based liver fat ≥ 5%



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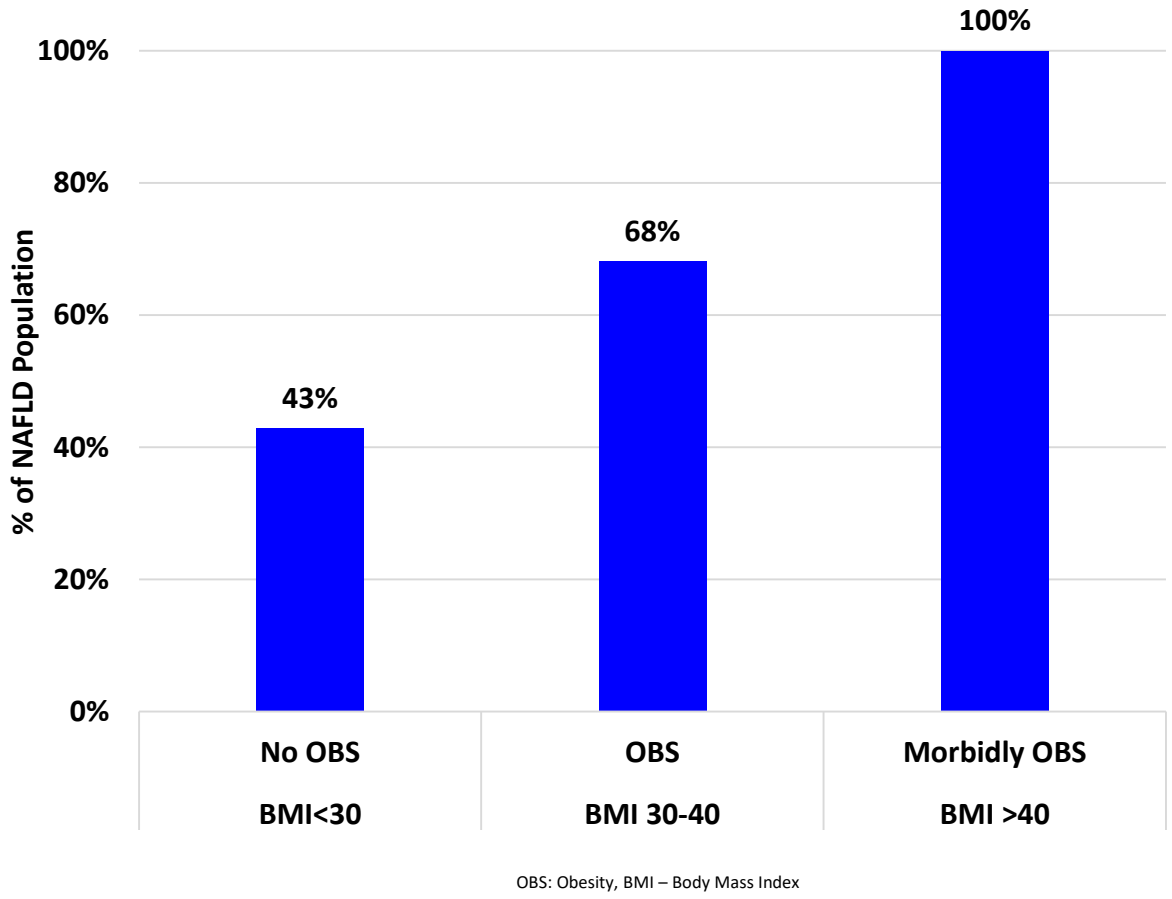
# LPCN 1144: Ongoing T Therapy Liver Fat Imaging Study

## Increased Prevalence of NAFLD* with Increasing BMI




OBS: Obesity, BMI – Body Mass Index

* NAFLD Confirmed by MRI-PDFF based liver fat ≥ 5%



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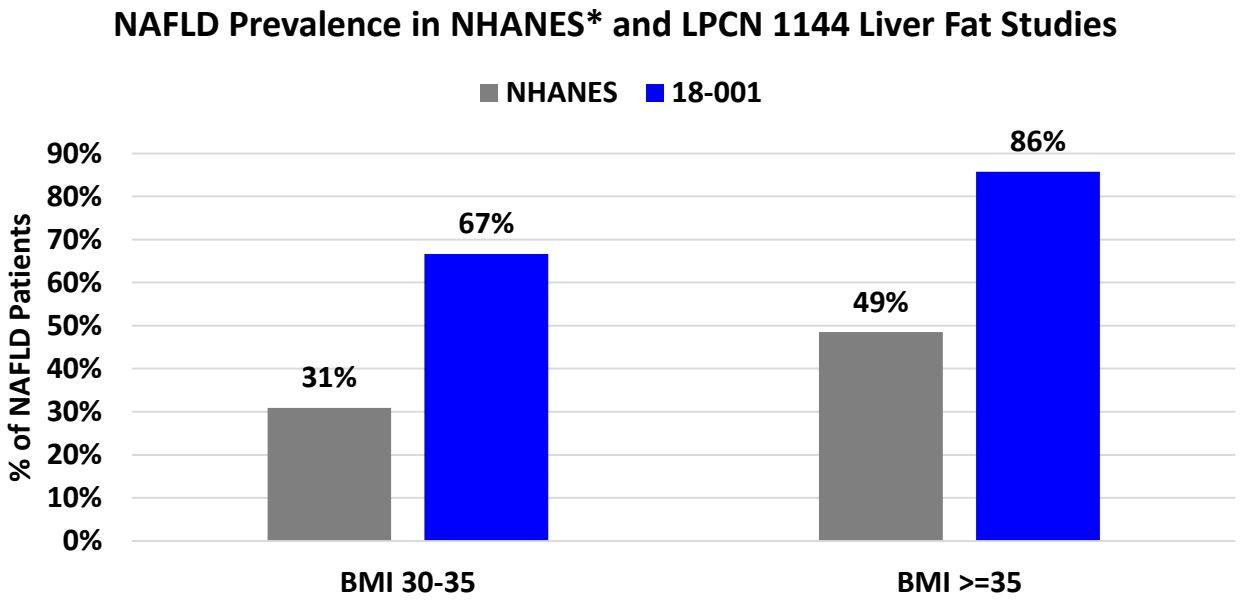
# LPCN 1144: Ongoing T Therapy Liver Fat Imaging Study

## Substantially Increased NAFLD† in Hypogonadal Obese Patients

- NAFLD in hypogonadal patients are over presented with obesity




† NAFLD: Identified by Ultrasonography in US population (NHANES) and confirmed by MRI-PDFF based liver fat ≥ 5% (LPCN 1144 Liver Fat Study)
* Lazo et al., AJE 2013



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# LPCN 1144: Oral Testosterone for Treatment of NASH

## Summary and Next Steps

- Unique Mechanism Targeting Full Spectrum of NASH Pathogenesis + Collateral Health Benefits
  - Testosterone deficiency in men is prevalent across the full spectrum of NAFLD
  - LPCN 1144 results suggest therapy has potential for collateral health benefits
- Well Tolerated Safety Profile
  - Prodrug of a bio-identical hormone
  - Demonstrated with 591 subjects in 12 studies with up to 52 week exposure
- Compelling Clinical Biomarker Data
  - Significant reductions in both the key ALT and TG serum NASH biomarkers
  - Good potential of histological improvement in NASH and fibrosis
- Next Steps
  - POC clinical study to assess liver fat changes via MRI-PDFF imaging in NAFLD/NASH patients – Interim and top-line results in 1Q 2019
  - In-vivo model Proof-Of-Concept (POC) study in biopsy-confirmed NASH – Study to be complete in 1Q 2019

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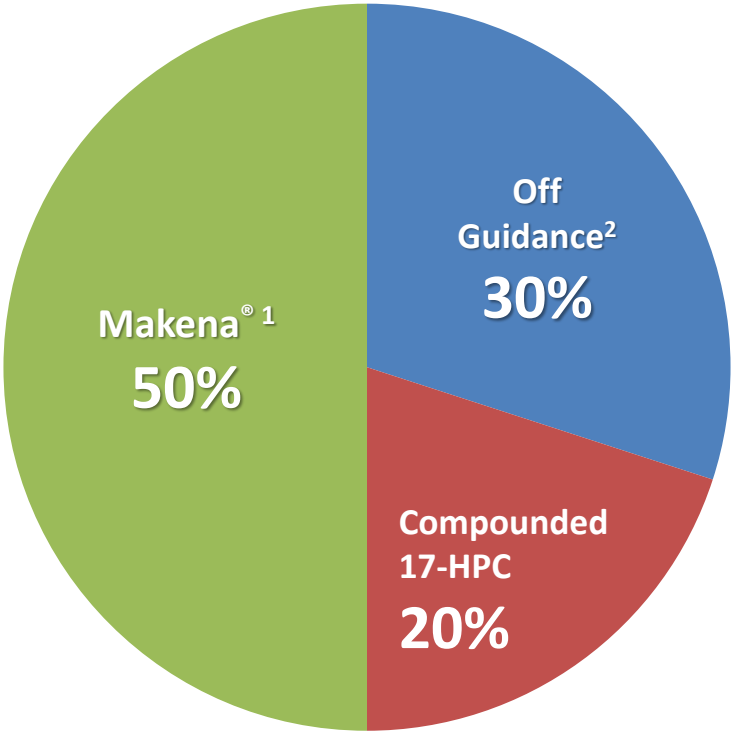
# LPCN 1107

# LPCN 1107: Prevention of Preterm Birth (PTB)

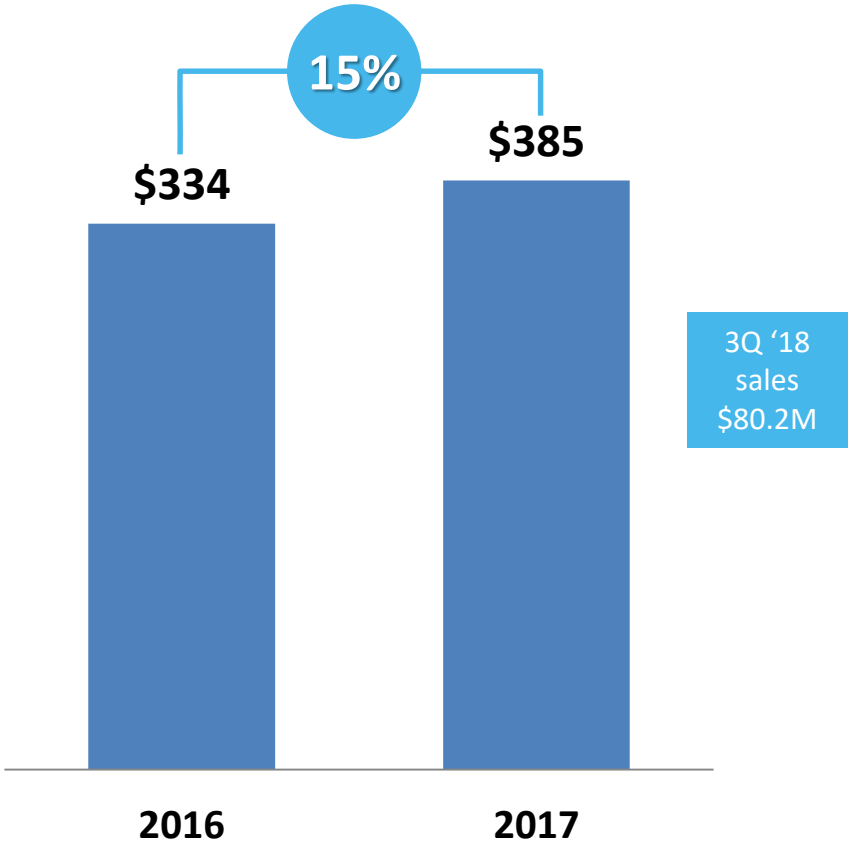
## United States Market Landscape

**December 31, 2017**




**$1B Market Opportunity[3]**

**Makena Net Revenue ($M)[4]**




1. Amag estimates Makena market share based on distributor dispensing data and all other market share based on physician market research data conducted by AMAG.
2. Off guidance represents patients treated outside of guidance of Society for Maternal Fetal Medicine, including patients treated with unapproved therapies and untreated patients.
3. Based on 140,000 patients, >16 injections/patient and net revenue of ~$425-$450/injection.
4. AMAG SEC filings



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# LPCN 1107: First Oral PTB Candidate

## Addresses Unmet Need

**LPCN 1107- Oral HPC**

- Potential for superior efficacy with Phase 3 target dose
- No patient discomfort upon administration
- Steady state achieved in 7 days
- Orphan drug designation
  - Major contribution to patient care
- Next steps:
  - Explore partnering opportunities



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# Upcoming Milestones

## Near Term Value Drivers

| | Event | Expected Timing |
|---|---|---|
| **TLANDO™** | ABPM study results | **1Q 2019** |
| **LPCN 1144** | Interim and Top-line POC clinical study results assessing liver fat changes via MRI-PDFF imaging in NAFLD/NASH patients | **1Q 2019** |
| | Complete In-vivo model Proof-Of-Concept study in biopsy-confirmed NASH | **1Q 2019** |

# Key Financial Metrics

## Stock Price, Market Cap, Cash Balance

| | |
|---|---|
| Ticker Symbol | **LPCN (Nasdaq Capital Market)** |
| Closing Stock Price (1/3/19) | **$1.56/share** |
| Market Capitalization (1/3/19) | **$33.9 million** |
| Fully Diluted Shares Outstanding (9/30/18) | **25.3 million** |
| Cash Balance (9/30/18) | **$21.9 million*** |
| Bank Debt (9/30/18) | **$10.0 million** |

* $5 M restricted

# Lipocine Investment Highlights

## Innovative Technology with Advanced Products

### Proven Proprietary Technology Platform

MEN'S HEALTH

- **TLANDO™**: Potential first oral TRT option
  - Differentiated product targeting ~$2.0 billion established US TRT market
- **LPCN 1144**: Oral prodrug of bio-identical testosterone for NASH
  - Compelling clinical biomarker data in patients with typical comorbidities of NASH
- **LPCN 1111**: Next generation potential once-daily oral TRT option
  - Positive top-line Phase 2b study results

WOMEN'S HEALTH

**LPCN 1107:**
**Orphan designated oral alternative for the prevention of preterm birth**

- EOP2 meeting completed
- Phase 3 protocol submitted to FDA via Special Protocol Assessment



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# Appendix

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# TLANDO™

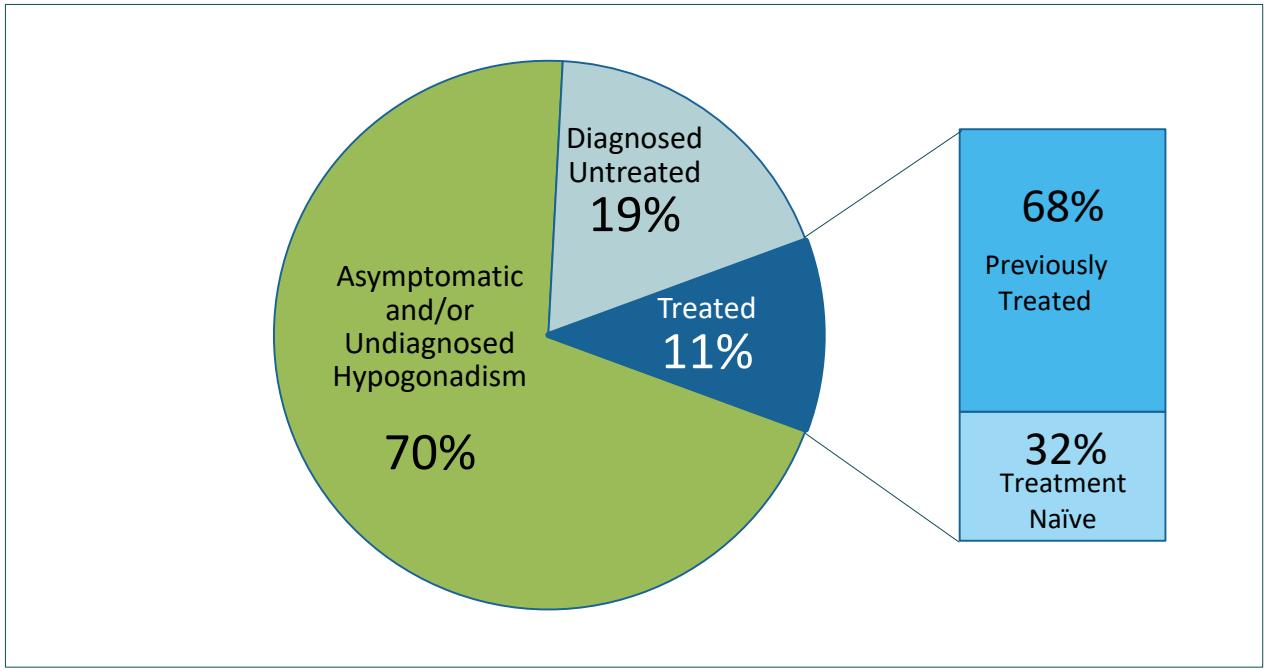
# Hypogonadism Affects Up to 20 M American Men[1,2]

## Significant Number of Untreated Hypogonadal Males

**~6M**
Men with diagnosed hypogonadism[3]

**2.2M**
Men currently being treated[4]

**700,000**
New naïve patients each year[5]




1. US Census data. http://www.infoplease.com/us/census/data/demographic.html. 2. Mulligan T, et al. *Int J Clin Pract.* 2006 Jul;60(7):762-9. 3. Araujo, et al. *J Clin Endo* Metabol 2007. 92(11):4241-7. 4. Symphony Healthcare 2014 for FDA Advisory Meeting. 5. IMS Health Sept 2015.



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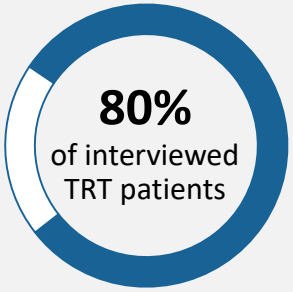
# TLANDO™: Patient Market Research

## Patient Enthusiasm Evident About Oral TRT

**Likely or Highly Likely to Ask Physician to Prescribe TLANDO**




**What Most Like About TLANDO?**

**30%**
**"Oral Form"**

**30%**
**"It's not Gel",**
**" Not Injection"**
**" Ease of Use"**

**40%**
**Other**

- TLANDO generates strong patient enthusiasm among current and prior TRT users
  - Oral administration and lack of transference viewed as key benefits
- For transdermal users, most common concern is transference risk
  - ***"Always worry with the kids.";*** **"Right now we have to plan sex."**
  - Gels and roll-on are messy to apply and often cause skin irritation
- Injectable users complain about swings in testosterone levels resulting in "crash" before next dose
  - ***"I keep crashing two weeks after the injection"***
  - Needle phobia/needle fatigue are common
- Both transdermal and injection users also want better symptomatic efficacy



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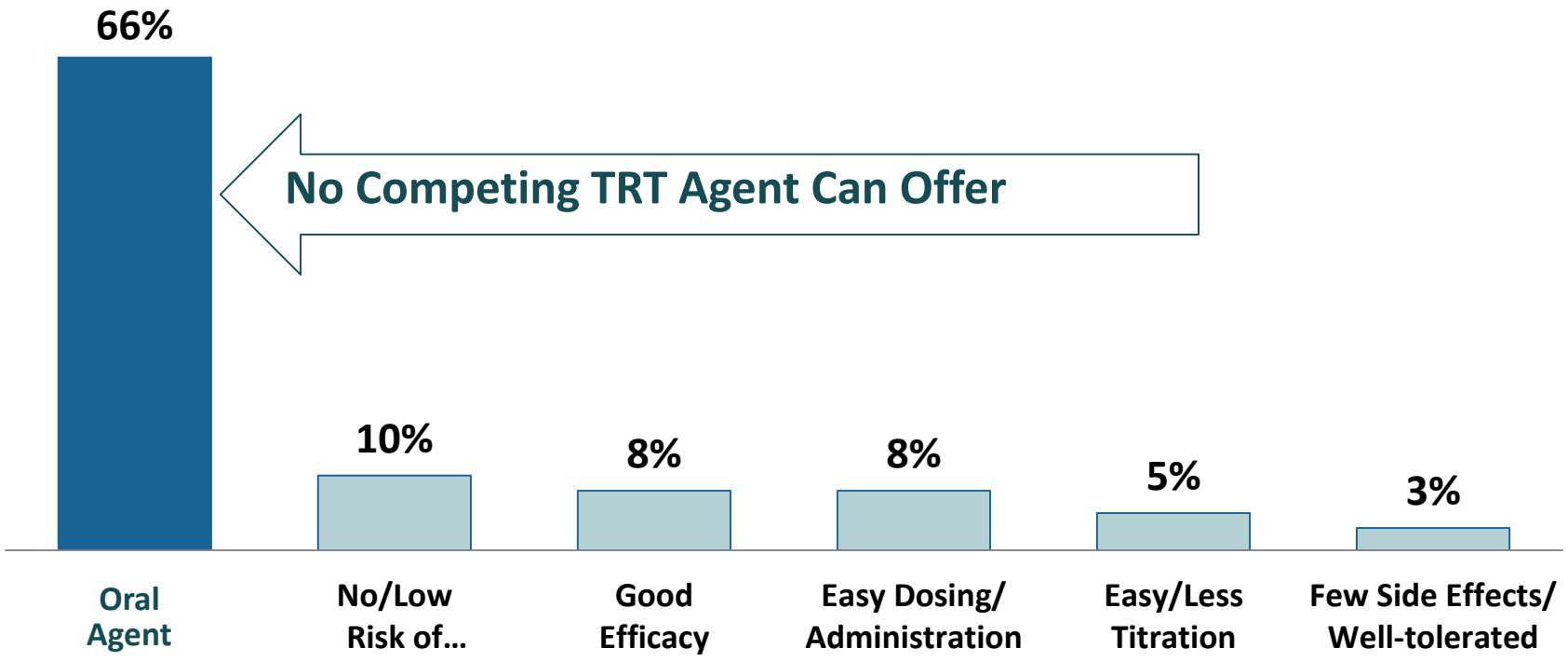
# TLANDO™: Physician Market Research

## Oral Agent is Most Important Attribute for Prescribers

**QUESTION:**
**What is the most important advantage of TLANDO?**




N=212 (All Respondents; URO=54, ENDO=53, PCP=105), TVG conducted market research.
Q35a. In your opinion, what is the most important advantage of TLANDO?



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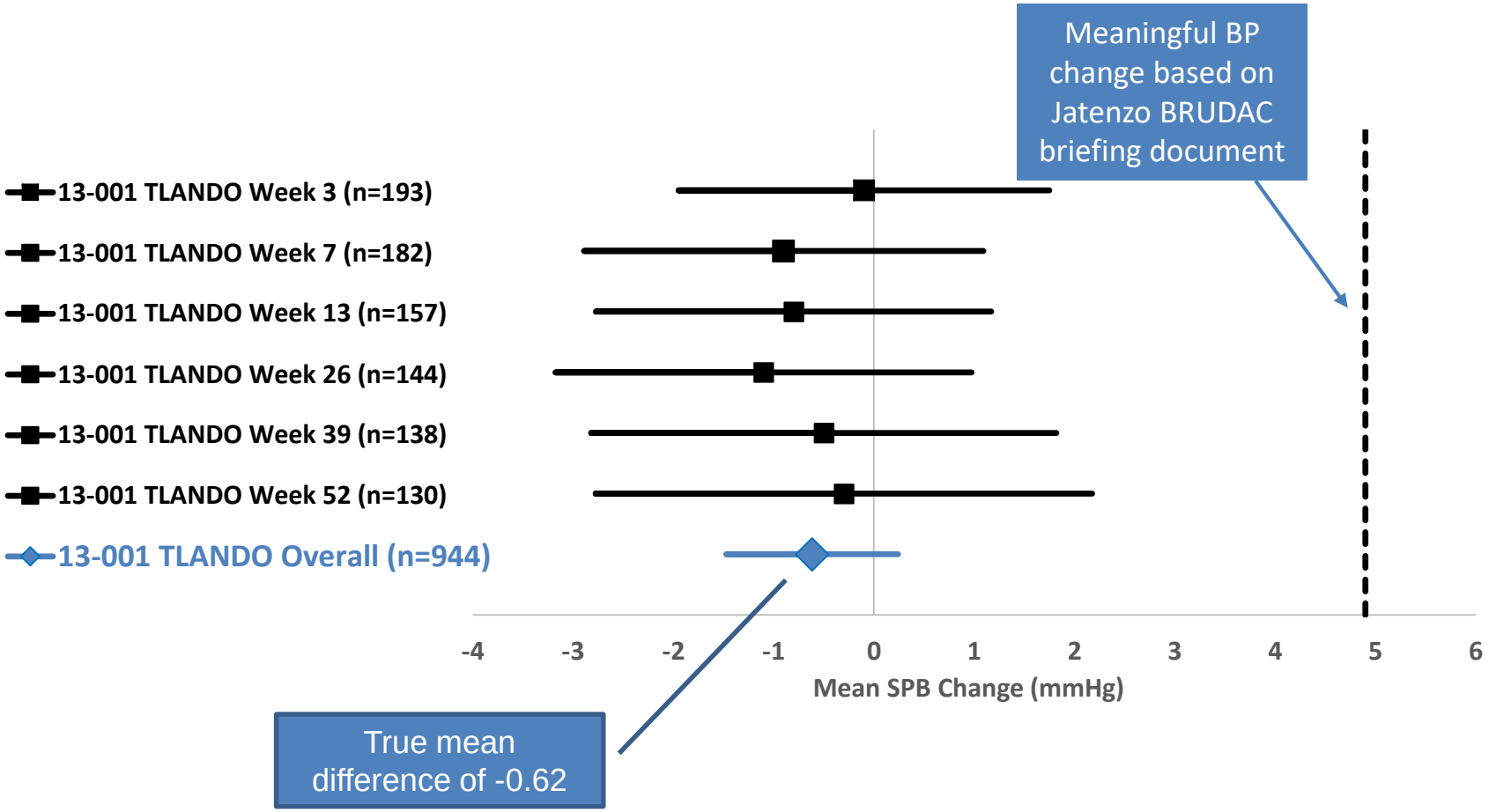
# TLANDO™ SOAR Study Blood Pressure Data

## Systolic Clinic BP Measurement - Change from Baseline




**Minimal change in BP from baseline at each visit throughout the SOAR study**



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# Oral TU: Dose - Systolic BP Relationship

## Differences Between Single/Triplicate/ABPM Measurements

| Brand | Mean Single SBP | | Mean Triplicate SBP | | Mean ABPM Daytime SBP | |
|---|---|---|---|---|---|---|
| | Study / Dose | ΔSBP from baseline | Study / Dose | ΔSBP from baseline | Study / Dose | ΔSBP from baseline |
| **JATENZO (High Dose)** | CLAR 09007 Day30 / Pre-titration **316mg BID** | **3.0** | CLAR 15012 Day102 / mean **325mg BID** | **3.4** | CLAR 15012 Day102 / mean **325mg BID** | **5.05** |
| | CLAR 09007 Day90 / mean **292mg BID** | **3.0** | | | | |
| **JATENZO (Low Dose)** | CLAR 12011 Day114 /post titration mean **241mg BID** | **0.1** | CLAR 15012 Visit2 / pre-titration **237mg BID** | **0.2** | | |
| **TLANDO** | LPCN 13-001 Wk3 / pre-titration **225mg BID** | **-0.1** | | | | |
| **TLANDO** | LPCN 16-002 Day24 / Fixed **225mg BID** | **-0.5** | | | | |
| | LPCN 16-002 Day25 / Fixed **225mg BID** | **0.2** | | | | |



37

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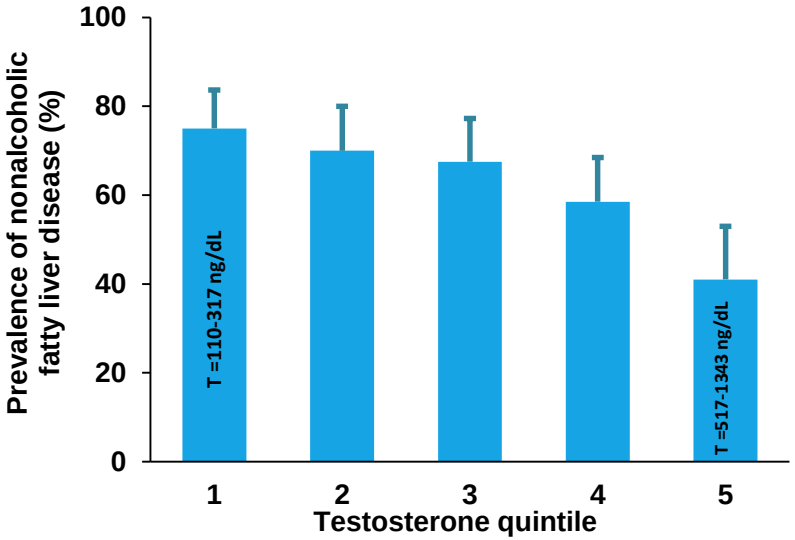
# LPCN 1144

# Low T Association with NAFLD and Cirrhosis

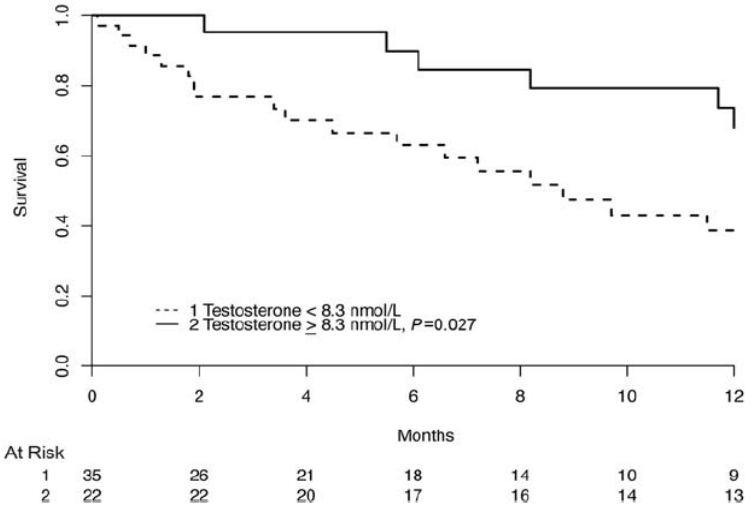
**Increased prevalence of hepatic steatosis is associated with low serum testosterone in men***

**NAFLD and Low T[1]**




✓ After adjusting for age, smoking, diabetes, exercise, BMI, TG and HDL, the lowest T quintile (110 – 317 ng/dL) have OR† of 5.12 (2.43 – 10.77) for NAFLD

**Cirrhosis survival and Low T[2]**




✓ Low T (<8.3 nmol/L; 239 ng/dL) remained a significant predictor of reduced survival in cirrhotic patients



1. Kim et al, Gastroenterol 2012
2. Sinclair et al, Liver Trans 2016

* Volzke et al, Int J Androl 2010

† OR: Odds Ratio

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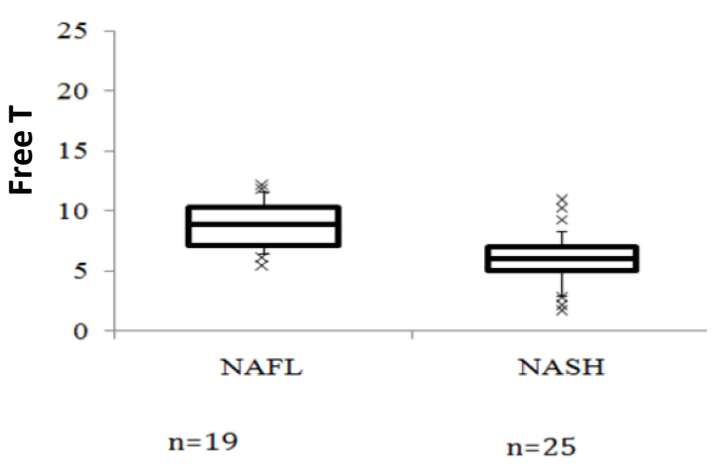
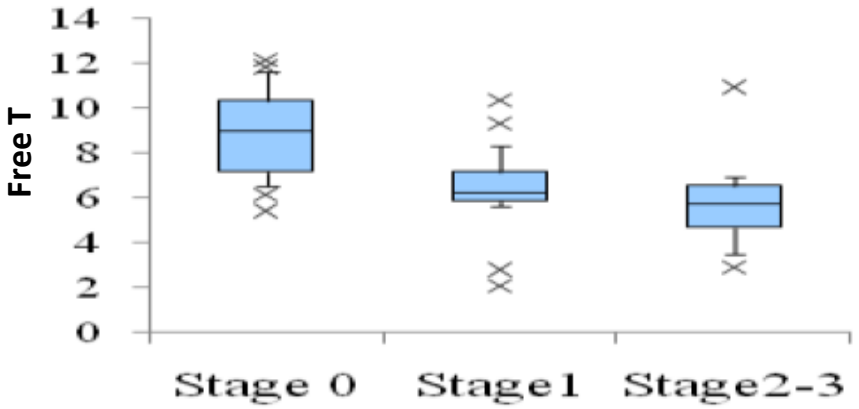
# Free T Association with NASH Progression

**Patients with NASH show significantly lower free T than those with non-alcoholic fatty liver (NAFLD)***

**Free T and NAFL/NASH**




**Free T and Stages of NASH Fibrosis**






* Sumida et al, Gastroenterol Hepatol 2015

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# LPCN 1144: Oral T

## Proposed Multidimensional Mechanism of Actions

- **Homeostasis Modifier[1, 2]**
  - Alter lipid, cholesterol, and glucose metabolism
  - Reduce visceral abdominal fat
  - Modify activity of hepatic lipase, and skeletal muscle/ adipose lipoprotein lipase
- **Anti-inflammatory[2]/ Immuno-modulator[3]**
  - Low T results in compromised immune system
  - Inflammatory Cytokines, IL-6, TNF-α and IL-1β, inhibit testosterone secretion by their influence on the central (hypothalamic-pituitary) and peripheral (testicular) components of the gonadal axis.
- **Regenerative**
  - Stimulate satellite cells and myocyte precursor resulting in cell differentiation and myocyte proliferation
  - Clinical data demonstrate that adult males who undergo a 40–60% partial hepatectomy experience T levels decline similar to those observed in male rats following a 70% hepatectomy.[4,5]
- **Anabolic effects on muscle, bone and hematopoiesis**
  - Low T is a predictor of mortality in men with advanced liver disease[6]



1. Shen and Shi, Int J Endocrinol 2015
2. Kelly and Jones, J Endocrinol 2013
3. Sinclair et al., J Gastroenterol Hepatol 2015
4. A. Francavilla et al., Digest Dis Sci, 1989
5. Vic et al., Hepatol 1982
6. Sinclair et al., J Gastroenterol Hepatol 2016

# T Therapy Demonstrated Histological Improvement

## Multiple Biopsy Confirmed High Fat/Cholesterol Diet Induced Animal Models

| Testicular Feminized Mouse [1] | Castrated NAFLD Rat [2] | Non-Genomic, Metabolic Syndrome NASH Rabbit [3] | Castrated Pig [4] |
|---|---|---|---|
| | | | |
| ▪ Hepatic lipid deposition ↓<br>▪ Lipogenesis ↓ | ▪ Hepatic steatosis ↓<br>▪ Hepatic apoptosis ↓<br>▪ Vesicular inflammation ↓ | ▪ Hepatic lipid accumulation ↓<br>▪ Hepatic inflammation ↓<br>▪ Hepatic fibrosis ↓ | ▪ Hepatic lipids ↓<br>▪ Liver injury ↓<br>▪ Hepatocellular steatosis ↓ |



1 Kelly et al., Lif Sci 2014; 2 Nikolaenko et al., BMC Endocrinol 2014; 3 Vignozzi et al., Mol Cell Endocrinol 2014; 4 Cai et al., BMC Genomics 2015

# T Therapy Effects in Liver Regeneration

## Hepatectomized Rat Model*

- 90% Hepatectomized rat groups

**Group 1 (n=50)**
**90% Hepatectomized + No treatment**

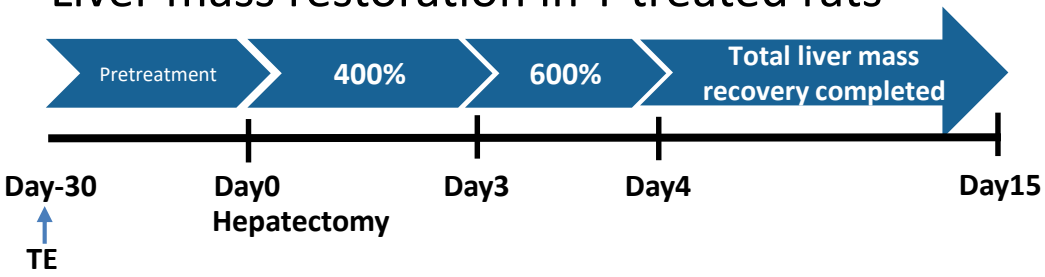
**Group 2 (n=50)**
**90% Hepatectomized + T treatment**

- Results

**Group1**
- Steatosis occurs with cell damage
- 100% died within 40 hrs.

**Group2**
- Cell activity
- 80% survived beyond 40 hrs. (50% had a normal life span)

- Liver mass restoration in T treated rats



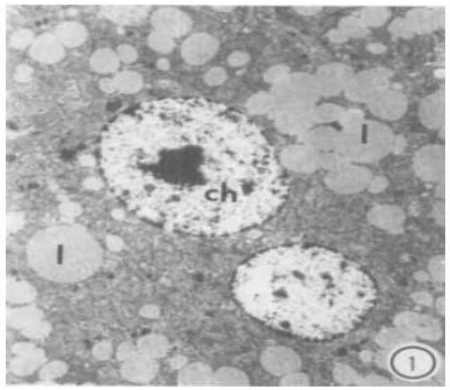




Fig 1. Group 1: 24 hr post hepatectomy. (I) massive steatosis, (ch) rare chromatin, **organelle depletion = cell damage**

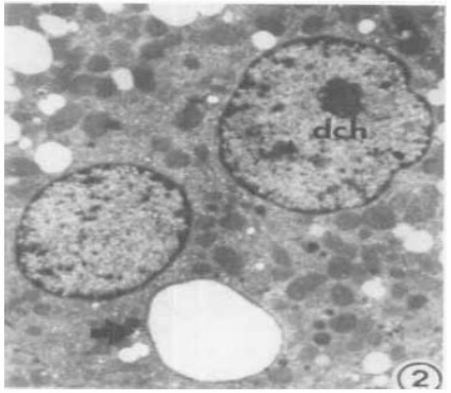



Fig 2. Group 2: 24 hr post hepatectomy. (dch) dispersed rare chromatin, **numerous cytoplasmic organelles = cell activity**



* Vic et al., Hepatol 1982

TE: Testosterone Enanthate

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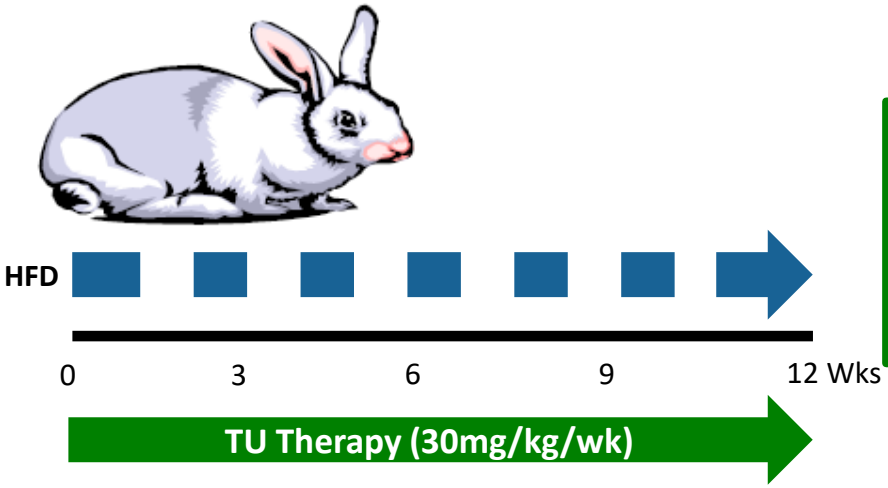
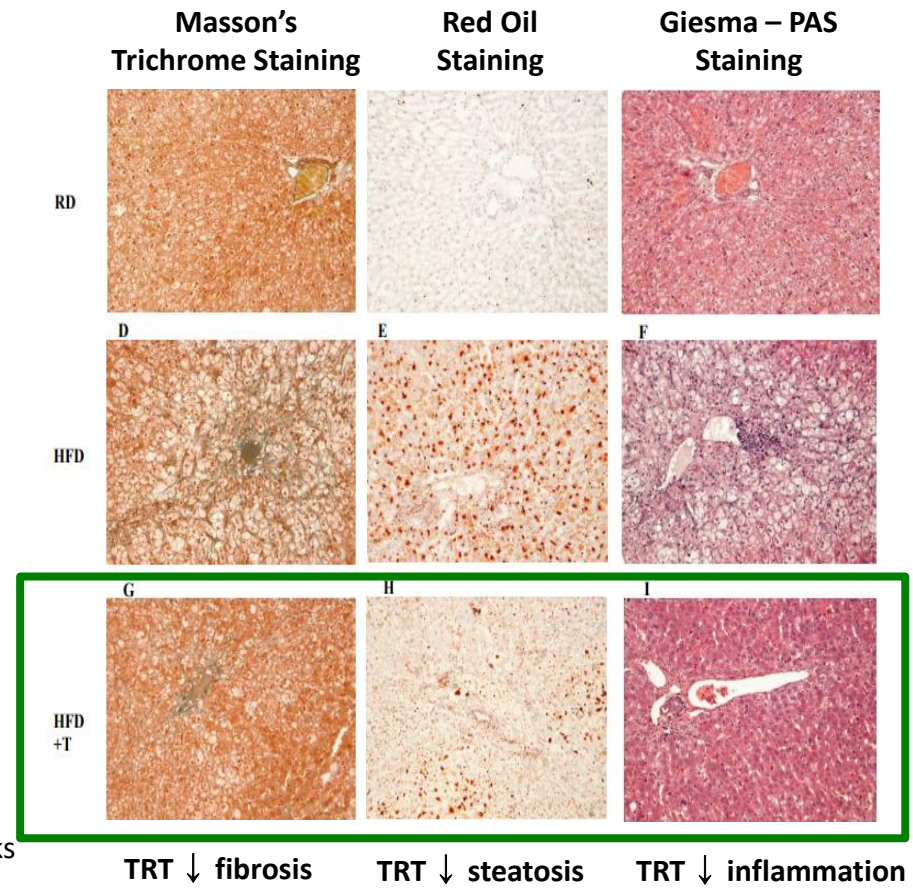
# LPCN 1144: T Therapy Effects on Components of NASH Pathogenesis

## Liver Histological Improvement

- Metabolic syndrome-induced NASH rabbit model*
  - Non-genomic
  - High fat diet (HFD) induced
  - Elevated glycemia, BP, TG, cholesterol, and visceral fat
  - Hypogonadotropic hypogonadism






* Vignozzi et al., Mol Cell Endocrinol 2014

RD: Regular Diet, HFD: High Fat Diet, T: Testosterone, TU: Testosterone Undecanoate

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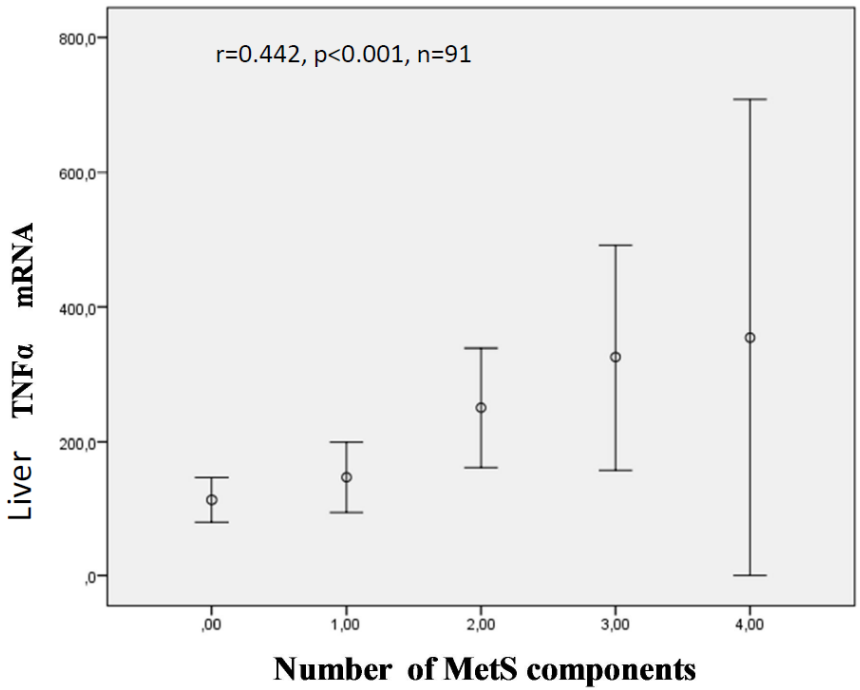
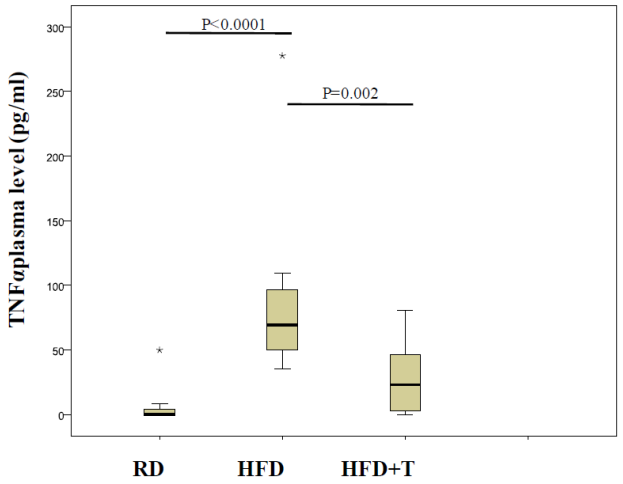
# Anti-inflammatory Effects of T Therapy

## Metabolic Syndrome-induced NASH Rabbit Model*

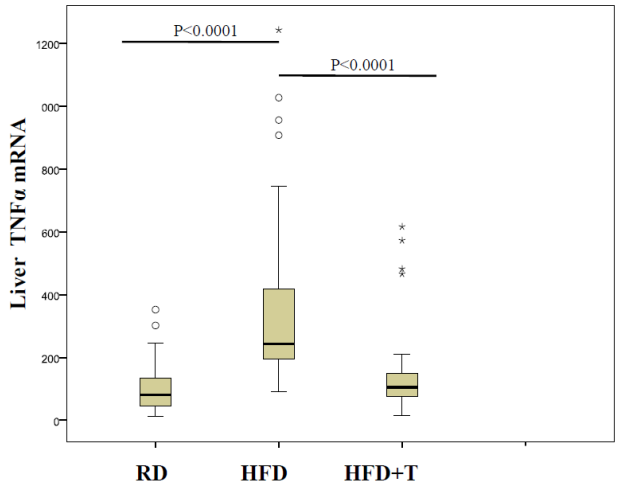
- Liver TNF-α increases as a function of MetS components*




<TNF-α in Plasma>




<TNF-α Genes in Liver Tissue>






* Vignozzi et al., Mol Cell Endocrinol 2014

# LPCN 1144: Post-hoc Analysis Methods

- Analyses of LPCN 1144 therapy results were performed with multiple clinical studies involving hypogonadal male cohorts with baseline liver enzymes* and lipids**
  - Placebo-controlled, randomized, double blind study (**M12-778**) with four week treatment
    - ✓ Analysis of 225mg BID, 300mg BID and Placebo (N=24)
  - Active-controlled, randomized, open label study (**SOAR**, N=210) with 52 week treatment - 225mg ± 75mg BID
  - Single-arm open label study (**16-002**, N=95) with three week treatment – 225mg BID

* ALT, AST, ALP, GGT; Persistent elevated ALT is a biomarker often used in clinical diagnosis of NAFLD/NASH
** Triglyceride is strongly associated with non-alcoholic fatty liver disease

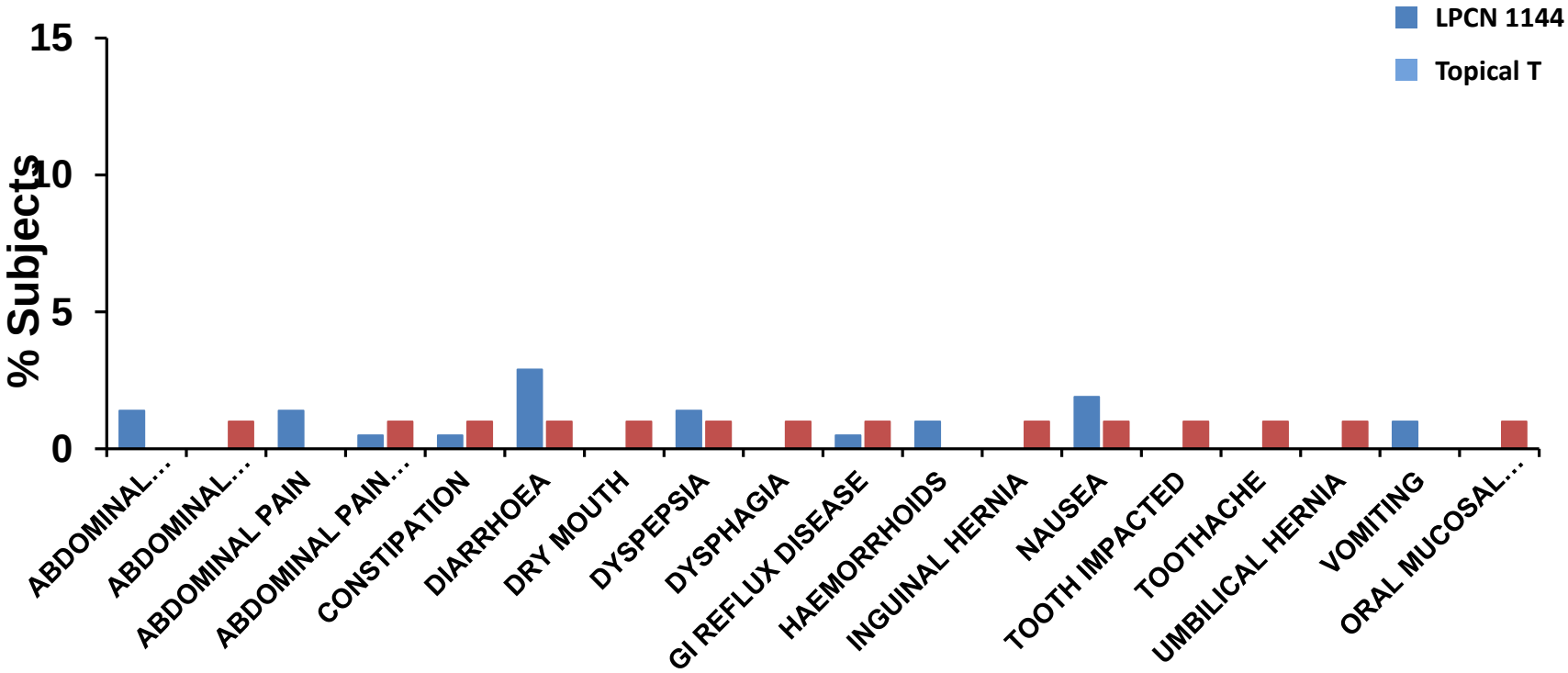
# LPCN 1144: General Safety

- **LPCN 1144 is a prodrug of bioidentical sex hormone**

- **Extensive clinical safety database with LPCN 1144**
  - 591 subjects in 12 studies with up to 52 week exposure
  - Well tolerated with no deaths or MACE events; no drug related SAEs
  - No drug related SAEs
  - Adequate gastrointestinal tolerability
  - No signs of skeletal fragility or nephrotoxicity

# LPCN 1144: Gastrointestinal Safety

## Gastrointestinal Disorders ≥ 1% in SOAR Trial

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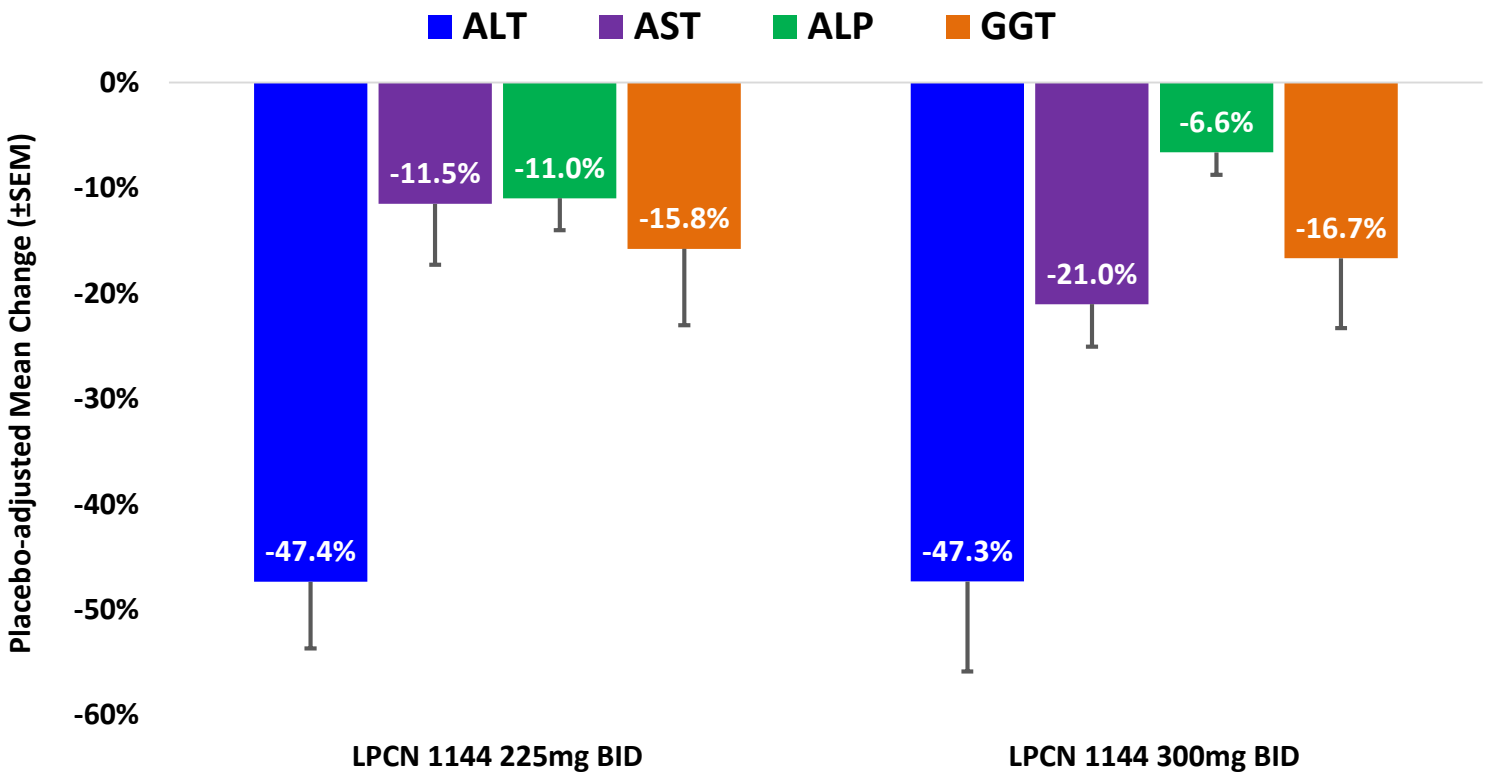
# Significant Reduction in Liver Enzyme Levels

- **Placebo Controlled 4 Week Study (M12-778)**



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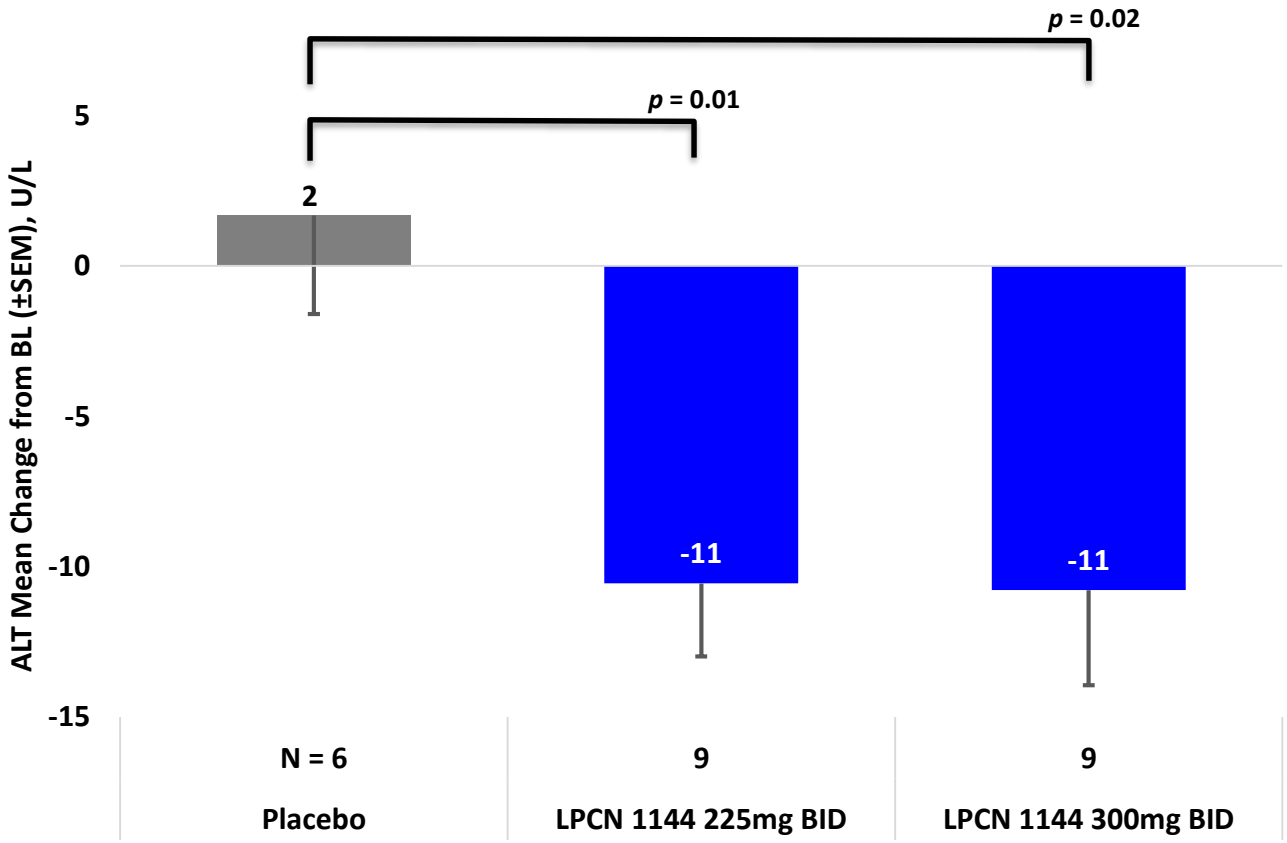
# Significant Reduction in ALT Levels

- **Placebo Controlled 4 Week Study (M12-778)**



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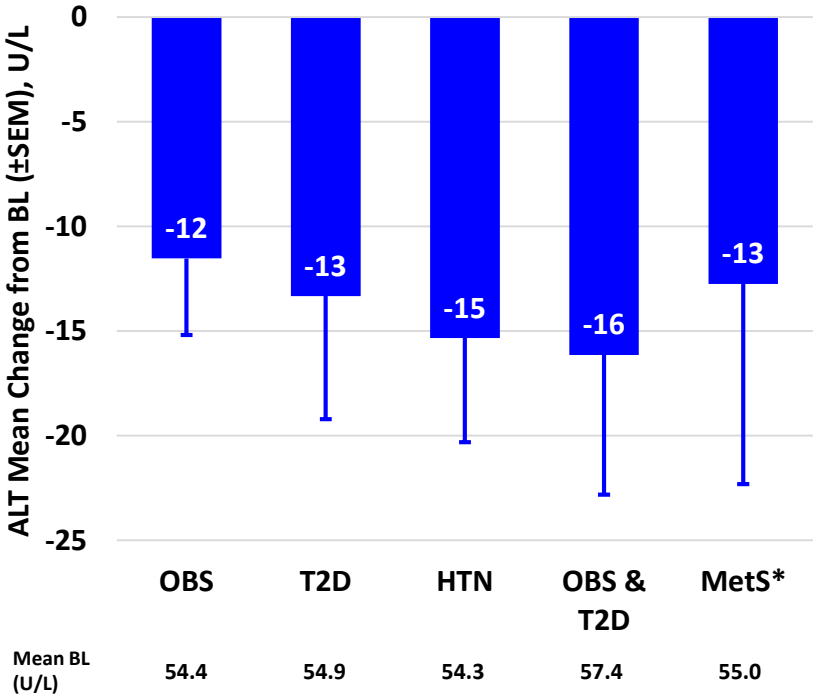
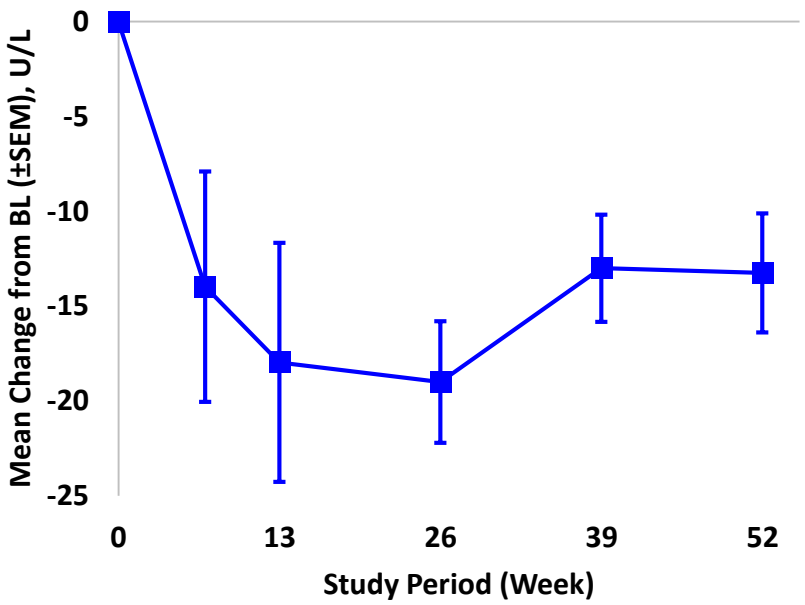
# Reductions of ALT in Patients at Risk of NAFLD

- **52 Week SOAR Trial**

**In Patients† with NAFLD Comorbidity**




**Sustained Reduction of Elevated ALT****




** Patients† with ALT > 40 U/L at BL (N=42); ALT mean BL = 53.6 U/L

† Patients with ALT > 40 U/L at BL in SOAR Trial

* Metabolic syndrome: obesity + diabetes + hypertension

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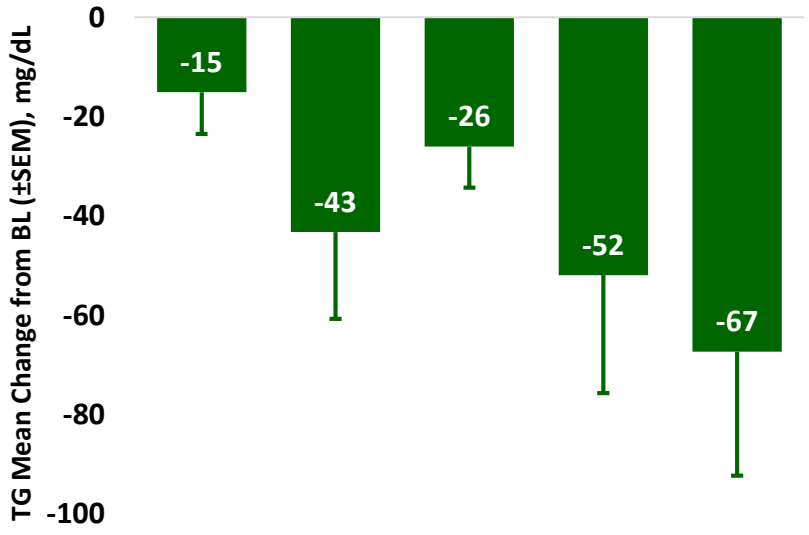
# Reductions of TG in Patients at Risk of NAFLD

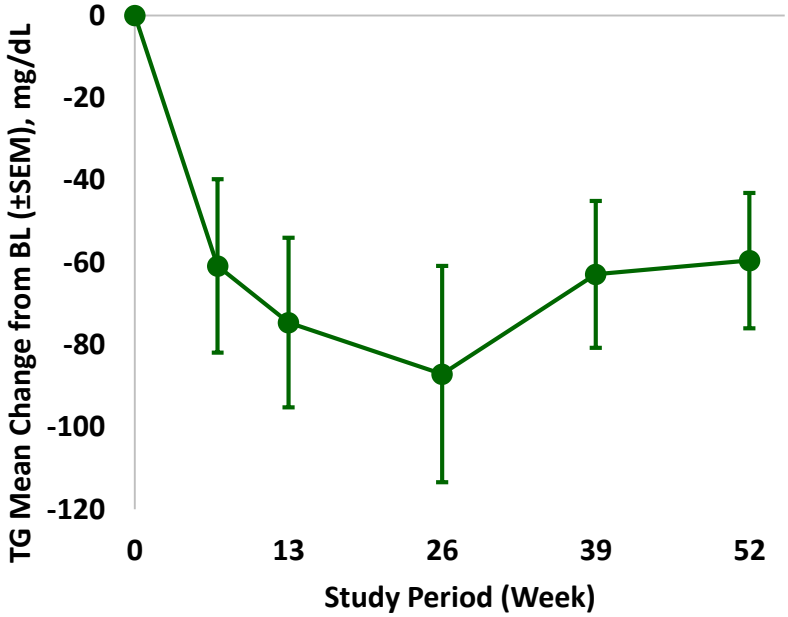
- **52 Week SOAR Trial**

**In Patients† with NAFLD Comorbidity**




| | OBS | T2D | HTN | OBS & T2D | MetS* |
|---|---|---|---|---|---|
| Mean BL (mg/dL) | 205 | 209 | 187 | 237 | 253 |
| N | 118 | 46 | 100 | 25 | 19 |

**Sustained Reduction of Elevated TG***




* Patients+ for TG > 200 mg/dL at BL (N=73); TG mean BL = 320 mg/dL

† SOAR Trial;
* Metabolic syndrome: obesity + diabetes + hypertension



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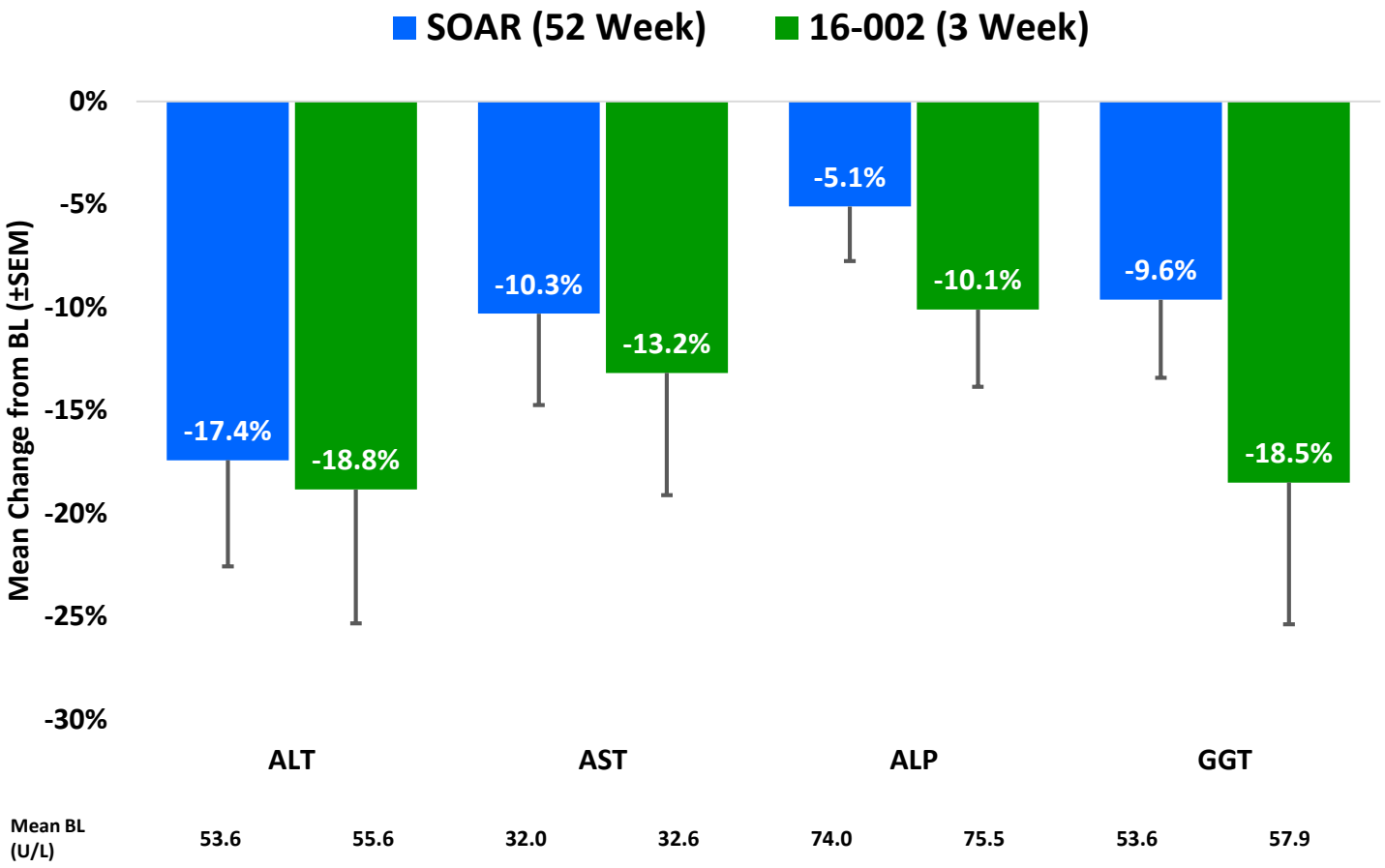
# Consistent Liver Function Improvement Across Studies* - Effect Observed as Early as Week 3




* LPCN 1144 Patients for ALT > 40 U/L at BL; SOAR (N=42), 16-002 (N=13)



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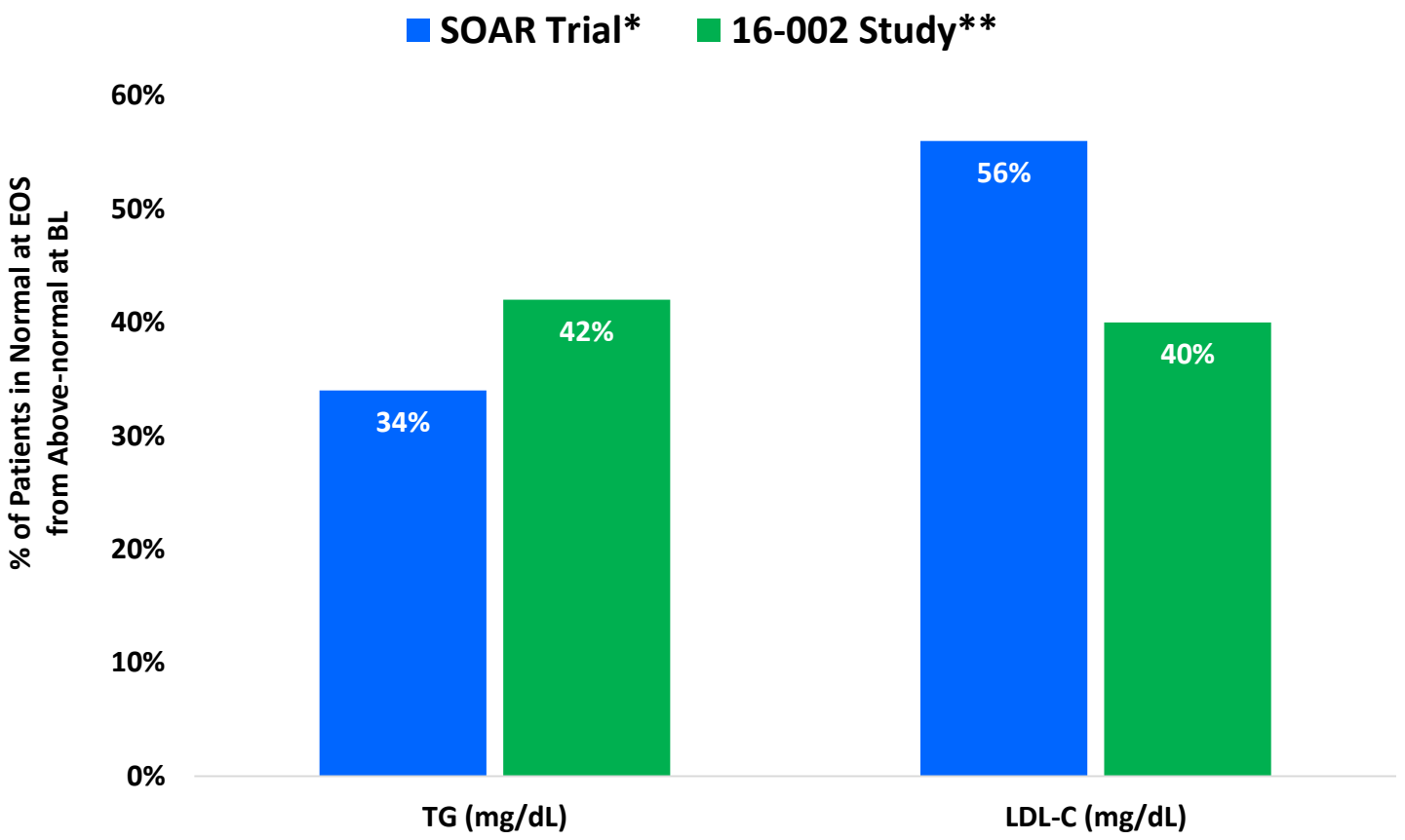
# Significant % of Patients Experienced Normalization of TG and LDL-C




TG and LDL-C normal range upper limit is 200 and 160 mg/dL, respectively; * N=73 (TG) and 26 (LDL-C) for SOAR Trial; ** N=16 (TG) and 10 (LDL-C) in 16-002 Study



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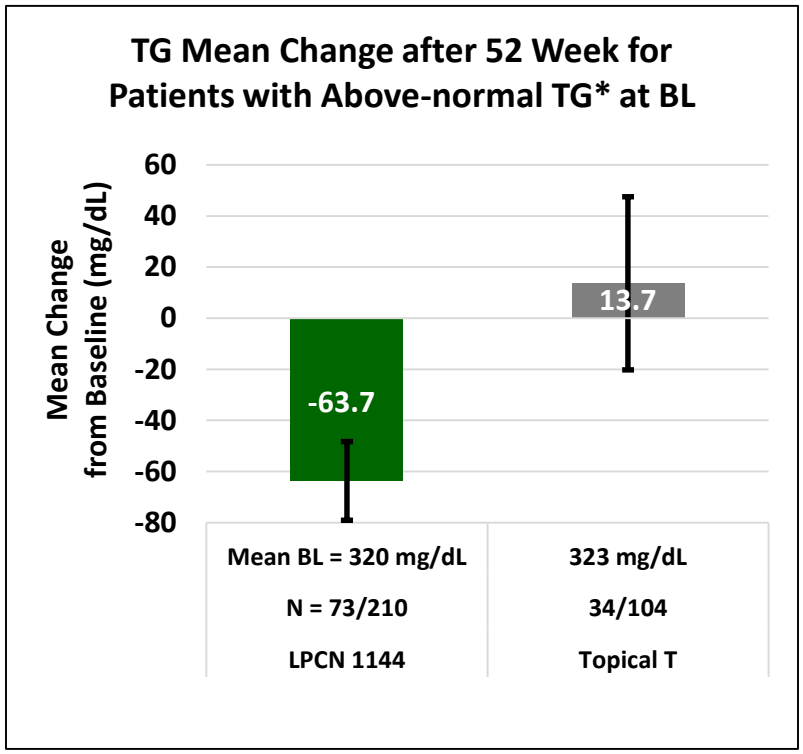
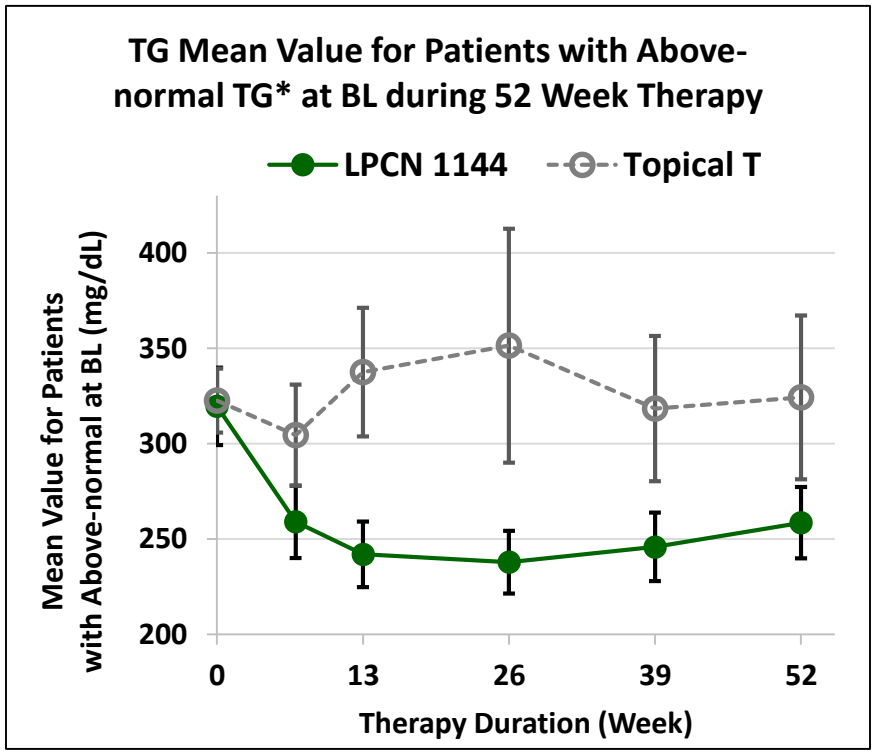
# LPCN 1144: Unique TG Reduction

- **52 Week SOAR Trial**

  TG mean change post therapy in patients on oral T vs non-oral T therapy






* TG normal range in SOAR Trial: 45 – 200 mg/dL

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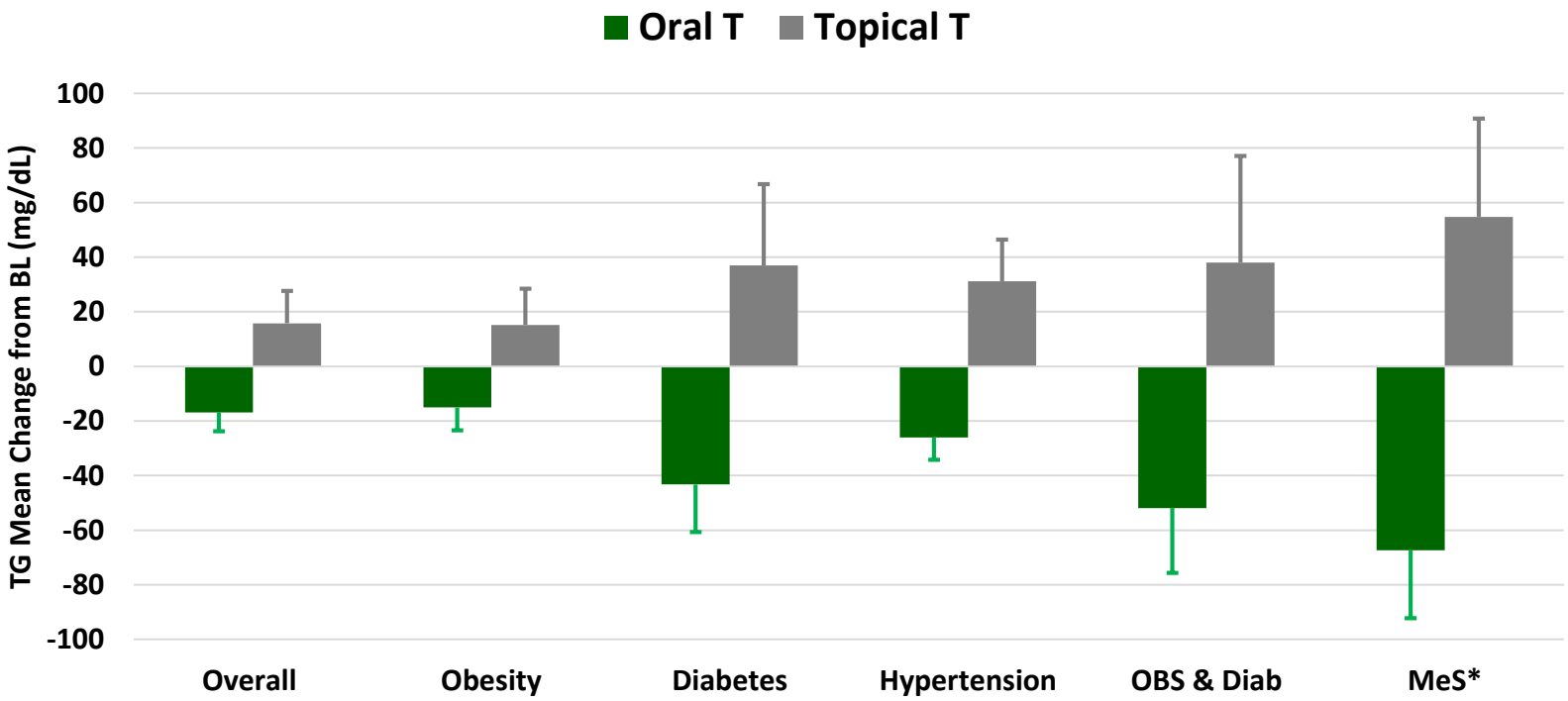
# LPCN 1144: Oral T

## TG Reduction Comparison with Topical T Across Various Comorbidities

- **52 Week SOAR Trial**

  Unique Oral T Therapy in TG Reduction Post 52 Week Therapy in Patients with Comorbidities




| N | Overall | Obesity | Diabetes | Hypertension | OBS & Diab | MeS |
|---|---|---|---|---|---|---|
| Oral T | 210 | 118 | 46 | 100 | 25 | 19 |
| Topical T | 104 | 65 | 36 | 49 | 21 | 15 |

* MeS: Metabolic syndrome (Obesity + Diabetes + Hypertension)



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LPCN 1111 QD

TLANDO

# LPCN 1111

# LPCN 1111: Next-Generation Oral TRT

## Potential Once-Daily Dosing

- Novel prodrug of testosterone for oral delivery
- Once-daily potential expected to sustain and improve market share of oral T franchise
- Once-daily feasibility established in Phase 2a and 2b clinical trials
  - Single-daily oral dose provides T levels in eugonadal range
- Development status
  - Phase 2 study completed
  - FDA Guidance meeting for Phase 3 study design completed

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# LPCN 1107

# High PTB Medical Costs

## ≥ $26 Billion Economic Impact[3]

- 12% of all US pregnancies[1] (475 -500K) result in PTB (< 37 weeks)-a leading cause of neonatal mortality and morbidity
- First year medical costs for PTB infants are ~ 10x higher than for full term infants[2]
- 28% of preterm births are to women with histories of early delivery


1. CDC (2010)
2. J. Maternal-Fetal and Neonatal Medicine, Dec. 2006, 19(12), 773–782
3 . Institute of Medicine of the National Academies. Jul.200




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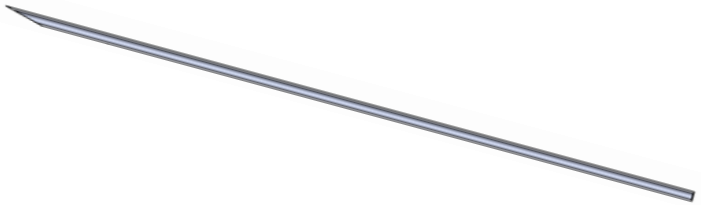
# LPCN 1107: First Oral PTB Candidate

## Characteristics of the Only Approved Product Options for PTB

**Makena 21 gauge needle**



### IM HPC, Makena®:

- 20-25% patients below reported better efficacy HPC level threshold
- Total of 18-22 injections
  - Injection location: Upper-outer quadrant of the gluteus maximus
  - Weekly visit to/by health care provider
  - ~35% of patients experienced injection site pain during clinical trial
  - ~17% of patients reported site swelling-much greater than placebo during clinical trial

### SubQ HPC, Makena®:

- 20-25% patients below reported better efficacy HPC level threshold
- Total of 18-22 injections
  - Approved February 14, 2018
  - Auto injector-ready to use device
  - Injection location:  Upper back of the arm
  - Weekly visit to/by health care provider
  - 37.3% of subjects identified injection site pain as a treatment emergent adverse event compared to only 8.2% of subjects in the IM arm



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# LPCN 1107: Economic Impact

## Potential Lower PTB Rate – US and Resulting Savings

Assuming 4.3% lower PTB rate relative to Makena®

**~6000 fewer annual PTBs‡**

**Estimated annual cost saving in ~$310M‡‡**

‡: Assuming 100% of 140,000 eligible US population treated

‡‡: Assuming ~$51,600 medical costs/PTB



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# LPCN 1107: First Oral PTB Candidate

## Commercial Outlook/Drivers

### First Oral HPC for Prevention of Recurrent PTB

- Preferred route-of-administration is oral

### Strong Exclusivity Position

- Orphan Drug Designation
- Technology/IP protection

### Potential for Superior Efficacy

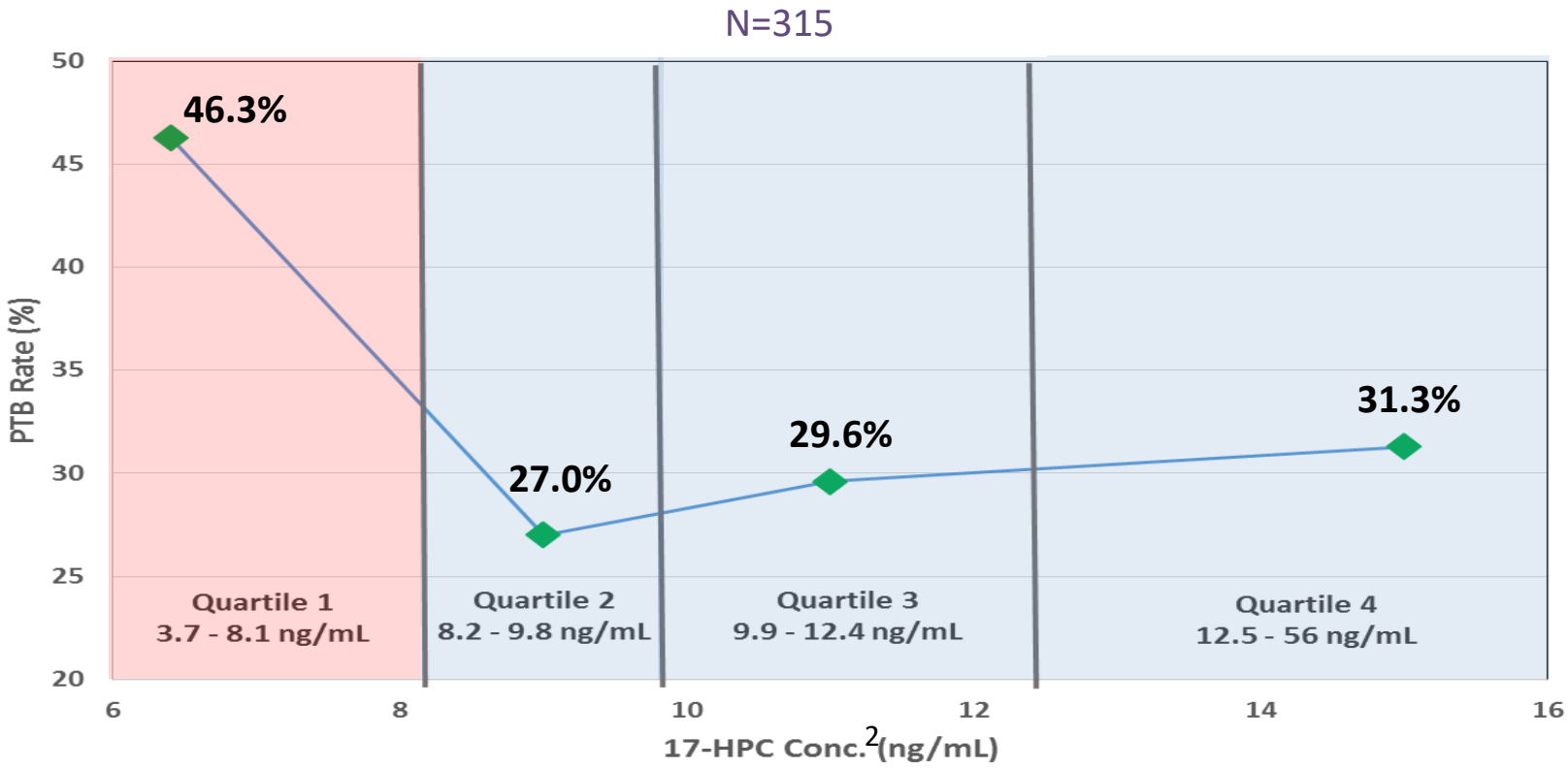
- Fewer PTB babies with significant healthcare cost savings

### Strong Pharmaco-Economic Justification

- Minimize travel related cost/time and healthcare provider cost/time
- Premium pricing potential to generic IM injections

# LPCN 1107: HPC PK-PD Correlation

## HPC Concentration and PTB Rate with IM HPC, Makena[1]




- Lower % PTB rate can be expected with daily $C_{avg}$[2] HPC levels ≥ 8.2 ng/mL

1. Caritis et al., Am J Obstet Gynecol. 2014 (N=315 subjects)
2. $C_{trough} \cong C_{avg}$ for IM Makena®



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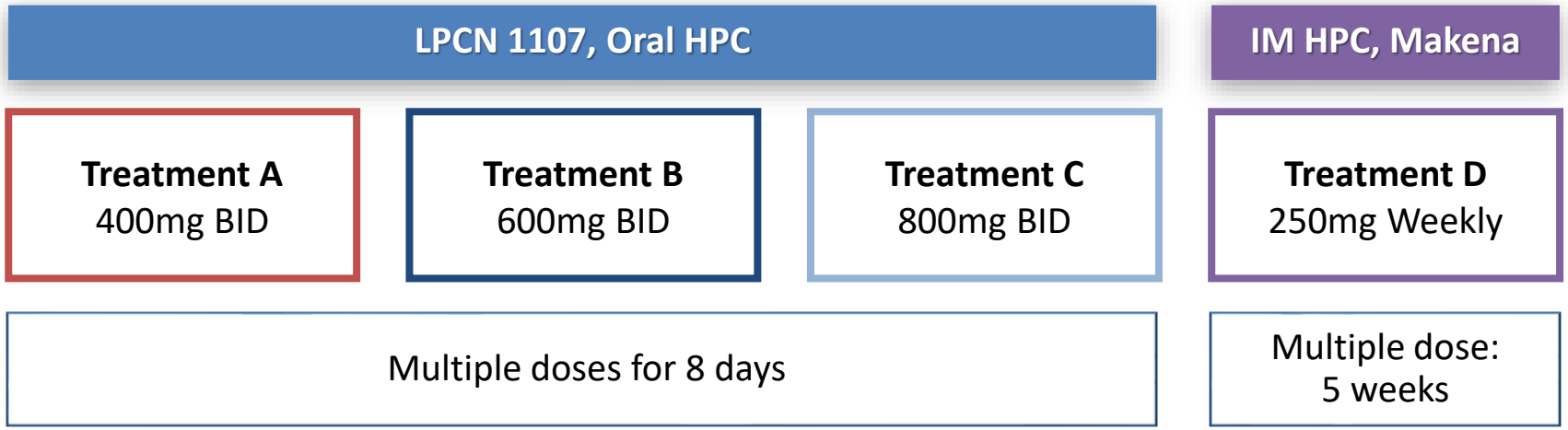
# LPCN 1107: Dose Finding Study Design

## PK Study: Oral LPCN 1107 vs IM HPC, Makena

- Open-label, four-period, four-treatment study
- 12 healthy pregnant women- Ages 18-35 years; 16-18 weeks gestation
- All subjects received all four treatments



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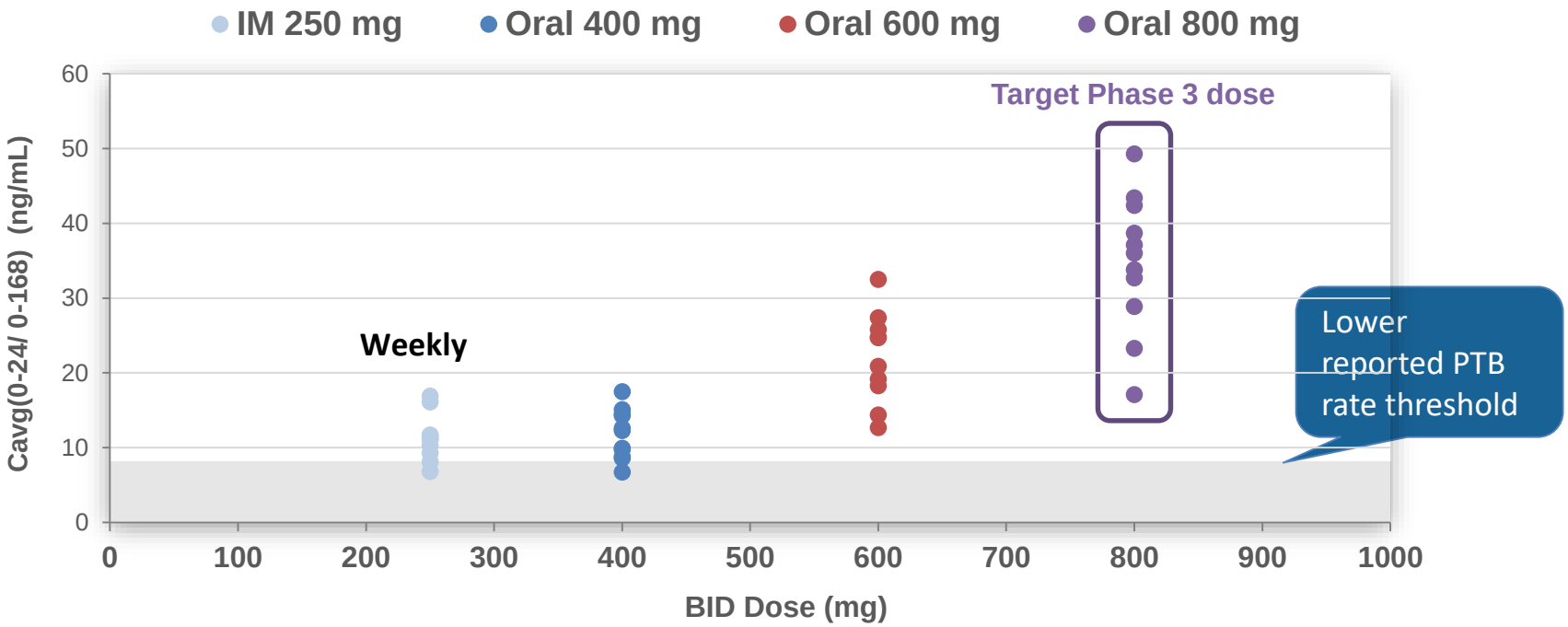
# LPCN 1107: Dose-Finding PK Study Results[1]

## Oral LPCN 1107 vs IM HPC, Makena




- HPC levels below 8.2 ng/mL:
  - Target LPCN 1107 Phase 3 dose was 0% vs 20% subjects using IM HPC Makena per label
- Average HPC levels at target LPCN 1107 Phase 3 dose
  - ~ 3x greater than the comparator, IM HPC, Makena



1. PK results obtained post 8 days of BID dosing for LPCN 1107 and post 5 weeks for weekly IM HPC, Makena

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# LPCN 1107: Advancing to Phase 3 Readiness

## Phase 3 Special Protocol Assessment – Progress

- **Concurrence with FDA to date:**
  - **Study Design Elements**
    - Single Phase 3 study
    - Open label, active comparator, two parallel arms (1:1 randomization)
    - General inclusion and exclusion criteria and treatment duration
    - LPCN 1107 dose of 800 mg BID
  - **Endpoints and Analysis**
    - Primary endpoint of proportion of PTB < 37 weeks
    - Non-inferiority margin of 7%
    - Secondary endpoint: Neonatal mortality and morbidity composite index
    - Interim analysis with ability to resize the study
      - Study size: 500 to 1000 subjects per arm
- **Open Items**
  - Data from food effect study to inform dosing instructions
  - Align on approach to fulfill infant follow up data requirement
- **Next Steps**
  - Continue interactions with FDA on Phase 3 protocol via Special Protocol Assessment
  - Conduct Food/Fat Effect Study in preparation of Phase 3 study