Combination Therapy of Seladelpar and Liraglutide Attenuates Obesity, Hepatic Steatosis and Fibrosis in a Diet-induced and Biopsy-confirmed Mouse Model of NASH

Yun-Jung Choi, Jiangao Song, Jeff D. Johnson, Charles McWherter

NASH-TAG Conference
Park City, Utah
January 4, 2019
Seladelpar
Uniquely able to harness PPARδ mechanisms

- Oral, once-daily PPARδ agonist
- Potent - EC$_{50}$ = 2 nM
- Selective
  - 630-Fold Selective Over PPARα
  - Inactive Against PPARγ
- Clinical experience with exposures over a year
- Clinical activity in PBC at 5 and 10 mg

Currently Enrolling ENHANCE (Global Phase 3) Study in PBC
Seladelpar for NASH
Potential role for PPARδ agonism in the treatment of NASH

Metabolic Stress
Cell Injury
Inflammation
Fibrosis

Selected Examples of Seladelpar (PPARδ) NASH Pharmacology

Reduced liver fat:

Eliminated ballooning:

Decreased macrophages:

Reduced collagen:

Phase 2b NASH POC with MRI-PDFF (12-Week) & Biopsy (52-Week) Underway

Haczeyni et al., Hepatology Communications (2017); Choi et al., AASLD Liver Meeting #1311 (2018)
Liraglutide for NASH
Potential role for GLP-1 analog in the treatment of NASH

LEAN: A Phase 2 Study of Liraglutide in NASH Patients (N=52, 48 weeks)

- **Metabolic Load**: Improvement in NASH & components:
  - Lira v PBO Responders
    - 39 vs 9% resolution
    - 61 vs 32% ballooning
    - 83 vs 45% steatosis
  - NASH response was greater in weight loss responders

- **Cell Stress & Injury**: Improvement in Inflammation: None

- **Inflammation**: Change in fibrosis
  - (Kleiner):
    - Lira v PBO Responders
      - 26 vs 14% improved
      - 9 vs 36% worsened

Armstrong et al., *The Lancet* (2016)

* Treatment differences had p-values < 0.05 using methodology described by Armstrong et al.
Diet-Induced Biopsy-Confirmed NASH in Obese Mice

Study Design

Induce NASH  Liver Biopsy  Randomization  Liver Histology & Biochemistry
Week -43  Week -3  Week -1  Day 1  Week 12

Steatosis (H&E) ≥ 2
Fibrosis (PSR) ≥ 1

Treatment Groups, male C57BL/6J mice†
1. NASH Vehicle
2. Liraglutide - 0.2 mg/kg, SC, BID
3. Seladelpar - 10 mg/kg, PO, QD
4. Liraglutide + Seladelpar – same as mono

† n = 11 to 12/group

Seladelpar and Liraglutide Reduce Body Weight

Additive effect on body weight with seladelpar and liraglutide combination

Body Weight

Body Weight Change at 12 Weeks

- NASH Vehicle
- Liraglutide
- Seladelpar
- Liraglutide + Seladelpar

p < 0.003 between all treatment pairs except liraglutide vs. seladelpar (p > 0.05)
Seladelpar and Liraglutide Decrease Plasma Triglycerides and Cholesterol

Combination led to additional decreases in triglycerides

**Plasma Triglycerides (TG)**

**Plasma Total Cholesterol (TC)**

**** p < 0.0001, *** p < 0.001, ** p < 0.01 vs. NASH Vehicle; # p < 0.05, ## p < 0.01, ### p < 0.001
Seladelpar and Liraglutide Decrease ALT and AST

**Additional decrease in transaminases with seladelpar and liraglutide combination**

![Graph showing the decrease in ALT and AST levels with different treatments.]

Plasma ALT and Plasma AST comparisons:

- **NASH Vehicle**
- **Liraglutide**
- **Seladelpar**
- **Liraglutide + Seladelpar**

**Statistical significance:**

- **** p < 0.0001 vs. NASH Vehicle
- ## p < 0.01 Combination vs. Seladelpar
Seladelpar and Liraglutide Improve Liver Histology

Treatment results in significant areas of improved architecture

NASH Vehicle  Liraglutide

Seladelpar  Liraglutide + Seladelpar

H & E Stain
Seladelpar and Liraglutide Improve NAFLD Activity Score

Magnitude of effect: Ballooning ~ Steatosis > Inflammation
Seladelpar and Liraglutide Reduce Hepatic Steatosis

Seladelpar and liraglutide combination result in significant decreases in hepatic fat

**Absolute Hepatic Fat**

- NASH Vehicle
- Liraglutide
- Seladelpar
- Liraglutide + Seladelpar

**Relative Change in Hepatic Fat**

- NASH Vehicle
- Liraglutide
- Seladelpar
- Liraglutide + Seladelpar

-43% ****
-56% ****
-76% ****

*p < 0.0001 vs. NASH Vehicle, # p < 0.05; ### p < 0.001

† Image analysis of H&E stained slides (Visiomorph, Denmark)
Seladelpar and Liraglutide Reduce Hepatic Triglycerides and Cholesterol

Seladelpar and liraglutide combination result in significant decreases in hepatic triglycerides and cholesterol

Hepatic Triglycerides (TG)

Hepatic Total Cholesterol (TC)

NASH Vehicle  Liraglutide  Seladelpar  Liraglutide + Seladelpar

**** p < 0.0001, *** p < 0.001, * p < 0.05 vs. NASH Vehicle; # p < 0.05,
Seladelpar reduces liver hydroxyproline
Liraglutide has minimal effect

Seladelpar effect is maintained with liraglutide co-treatment

![Graph showing hydroxyproline (mg/g liver) for different treatments: NASH Vehicle, Liraglutide, Seladelpar, and Liraglutide + Seladelpar. The graph indicates that Seladelpar and Liraglutide + Seladelpar reduce hydroxyproline significantly compared to NASH Vehicle.]

*** p < 0.0001 vs. NASH Vehicle
Seladelpar and Liraglutide Reduced Fibrosis-Associated Staining

**Sirius Red**
- NASH Vehicle
- Liraglutide
- Seladelpar
- Liraglutide + Seladelpar

**α-SMA**
- NASH Vehicle
- Liraglutide
- Seladelpar
- Liraglutide + Seladelpar

**Galectin-3**
- NASH Vehicle
- Liraglutide
- Seladelpar
- Liraglutide + Seladelpar

**Col1a1**
- NASH Vehicle
- Liraglutide
- Seladelpar
- Liraglutide + Seladelpar

**Laminin**
- NASH Vehicle
- Liraglutide
- Seladelpar
- Liraglutide + Seladelpar

*** p < 0.001, ** p < 0.01, * p < 0.05 vs. NASH Vehicle; # p < 0.05
Seladelpar and Liraglutide Decreased Fibrosis Marker Transcripts Using RNAseq Analysis

Seladelpar effect is maintained with liraglutide co-treatment

**COL1A1**

**COL3A1**

**TIMP1**

**MMP2**

Expression level (RPKM)

- NASH Vehicle
- Liraglutide
- Seladelpar
- Liraglutide + Seladelpar

**** p < 0.001, *** p < 0.001, * p < 0.05 vs. NASH Vehicle; # p < 0.05
Seladelpar and Liraglutide Decreased Liver Inflammation Transcripts Using RNAseq Analysis

**CD68**

- NASH Vehicle
- Liraglutide
- Seladelpar
- Liraglutide + Seladelpar

**TGFB1**

- NASH Vehicle
- Liraglutide
- Seladelpar
- Liraglutide + Seladelpar

**CCR2**

- NASH Vehicle
- Liraglutide
- Seladelpar
- Liraglutide + Seladelpar

**MCP-1**

- NASH Vehicle
- Liraglutide
- Seladelpar
- Liraglutide + Seladelpar

**F4/80 (EMR1)**

- NASH Vehicle
- Liraglutide
- Seladelpar
- Liraglutide + Seladelpar

**Galectin-3**

- NASH Vehicle
- Liraglutide
- Seladelpar
- Liraglutide + Seladelpar

**** p < 0.001, *** p < 0.001, ** p < 0.01, * p < 0.05 vs. NASH Vehicle; # p < 0.05
Seladelpar Increases Fatty Acid Oxidation Transcripts

Consistent with the PPARδ mechanism
Effect is maintained with liraglutide co-treatment

RNAseq analysis

![Graph showing expression levels of LCAD, IDH1, CPT2, and ACOX1 in NASH Vehicle, Liraglutide, Seladelpar, and Liraglutide + Seladelpar conditions.]

- **LCAD**
- **IDH1**
- **CPT2**
- **ACOX1**

**Expression level (RPKM)**

- NASH Vehicle
- Liraglutide
- Seladelpar
- Liraglutide + Seladelpar

**Statistical significance:**

- **** p < 0.001, ** p < 0.01, * p < 0.05 vs. NASH Vehicle;
- ###### p < 0.0001, ## p < 0.01
Summary of Seladelpar and Liraglutide Combo
*Attenuated obesity, hepatic steatosis and fibrosis*

**Seladelpar**
- Reduced weight, improved lipids, inflammatory markers, liver fat, NASH pathology and fibrosis

**Liraglutide**
- Similar pharmacology except without the effects on fatty acid oxidation and fibrosis

**Seladelpar + Liraglutide**
- Enhanced benefits: Body weight, plasma TG, ALT/AST, NAS, liver fat/TGs
- Seladelpar effects retained on fatty acid oxidation, inflammation, and fibrosis with co-treatment

**Conclusion**
- Seladelpar offers broad pharmacology which is enhanced with a long-acting GLP-1 analog
- Metabolic, inflammation and fibrosis benefits of combination support their clinical evaluation
Disclosures and Acknowledgements

The authors are compensated employees of CymaBay Therapeutics, Inc.

We gratefully acknowledge our CymaBay colleagues for critical discussions.

We gratefully acknowledge the contribution of the Gubra Study Team in Hørsholm, Denmark. They conducted the in-life study and assessments presented here as part of a larger blinded study.