Session 3: Clinical Pharmacology
Approaches to Support Dose Finding for Clinical Trials for NASH and Cholestatic Liver Diseases

1:15 pm – 2:40 pm
Clinical Pharmacology Considerations in Dose Selection for NASH and Cholestatic Liver Diseases

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Office of Clinical Pharmacology (OCP)
Office of Translational Sciences / CDER / FDA

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Disclaimer

• This presentation reflects the views of the presenter and does not necessarily reflect the official policies or guidance of the FDA.

• Throughout the talk, representative examples of commercial products will be used to illustrate a narrative point or analysis. No commercial endorsement is either implied or intended.
Outline

• Current trends in drug development and challenges in dose selection for NASH and cholestatic liver diseases
• Clinical pharmacology considerations in dose selection
  – Early phase proof-of-concept (POC) trials
  – Late phase 2 dose finding and phase 3 trials
• Case studies
• Summary
Potential Therapeutic Targets for NASH

Steatosis

Chronic Inflammation (NASH)

Fibrosis

Cirrhosis

**Metabolic target:**
- PPAR agonist*
- FXR agonist*
- GLP-1R agonist
- SCD inhibitor*
- ASBT inhibitor
- FGF19; FGF-21
- GHRH
- ACC inhibitor
- THRβ agonist*
- Sulfated oxysterol
- ASO
- HMG-CoA reductase inhibitor

**Anti-inflammatory/oxidative stress/apoptosis:**
- Antioxidant
- PDE inhibitor
- CCR2/CCR5 antagonist*
- Caspase inhibitors
- ASK1 inhibitor*
- IKKe/TBK1 inhibitor
- VAP-1 inhibitor

**Anti-fibrotic:**
- LOXL2 antibody
- Galectin-3 inhibitor

**Others:**
- Bile acid sequestrant
- Lipase inhibitor
- Bovine colostrum
- Antibiotic
- Gut microbiome modulator

**Combination therapy**

*Ongoing/recently completed phase 3 trials with NASH (ClinicalTrials.gov)
Challenges in Dose Selection with NASH and other Cholestatic Liver Diseases

- Currently only histology endpoints are accepted to reasonably likely predict clinical outcomes for NASH
- Lack of noninvasive surrogate biomarkers for assessing efficacy/disease progression in NASH
- Uncertainty of relationship between biomarkers and surrogate endpoints
- Limited information for liver exposure
  - Dose/exposure-response for liver efficacy and safety: challenges in liver biopsy sampling to confirm liver exposure
General Considerations in Dose Selection for NASH Development Program

• Early phase 2a proof-of-concept (POC) trial
  – Utilizing PK and biomarker response from HVs or other patient populations
  – Primary endpoints: noninvasive disease-specific biomarkers, liver injury, imaging, liver stiffness assessment, or hepatic fat content are acceptable as POC study endpoints

• Late phase 2b trial
  – A dose finding study with multiple dose levels selected based on PK and biomarker response from early phase 2a
  – Primary endpoints: histology endpoints (same as in phase 3)
  – Biomarkers: supporting evidence for efficacy and safety
Dose Selection for Phase 2a Proof-of-Concept Trial Based on PK and Biomarkers

• PK characterization:
  – Generally conducted in healthy subjects in phase 1 studies
  – Prior PK/PD information in other populations (if applicable)

• Biomarkers related to mechanism of action:
  – Lipid metabolism modulation, glycemic control
  – Anti-inflammatory, oxidative stress, apoptosis
  – Fibrosis assessment

• Explore dose-response and exposure-response relationships
Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment

Guidance for Indu

Sponsors should consider the following during early phase 2 trials for drug development for treatment of noncirrhotic NASH with liver fibrosis:

- FDA recognizes that, for sponsors, POC trials are desirable before embarking on extensive clinical development programs. Sponsors should provide adequate rationale and justification for the design of POC trials, including enrollment criteria, duration of the trials, and the choice of endpoints. Sponsors can seek proof of concept in respect to improvement on markers of steatohepatitis, fibrosis, or both.

- Noninvasive, disease-specific biomarkers: standard measures of liver injury (aspartate aminotransferase (AST) and alanine aminotransferase (ALT)); and imaging modalities that assess liver stiffness or hepatic fat content are acceptable as POC study endpoints as long as the sponsor can scientifically justify them.

- In these early trials, baseline histologic documentation of NASH may not always be needed, depending on the endpoints to be assessed. Sponsors can enroll patients based on either a known histological diagnosis of NASH or a combination of biochemical criteria
Exploratory Biomarkers in NASH

**Metabolic:**
- Lipid profile
- Glycemic (HbA1c, insulin, HOMA-IR), C4, FGF-19

**Inflammatory/oxidative stress:**
- hs-CRP, IL-1β, IL-6, IL-8, TNF-α, MCP-1, fibrinogen

**Liver biochemistry and function:**
- ALT, AST, GGT, ALP, total and direct bilirubin, albumin, INR, and platelets

**Fibrotic:**
- Cytokeratin-18 (CK-18), enhanced liver fibrosis (ELF), fibrosis-4 (FIB-4), TIMP1, Pro-C3, AST/ALT, AST:platelet ratio index

**Imaging:**
- MRI-PDFF, Fibroscan, Magnetic resonance elastography (MRE)

Case Example 1: Dose Selection for Initial Phase 2 POC Trial Based on Biomarkers Related to MOA

- MGL-3196 (thyroid hormone receptor-β agonist)
  - Phase 1 data from subjects with mildly elevated LDL cholesterol (>110 mg/dL)
  - 5, 20, 50, 80, 100, or 200 mg QD for 14 days

References:
Case Example 2: Dose Selection for Phase 2b Trial Based on Data from POC Study

- Aramchol (stearoyl-CoA desaturase-1 inhibitor)
- Phase 2a in NASH: 100 mg, 300 mg, or placebo QD for 12 weeks (n=20/group).
  - Primary: liver fat content by magnetic resonance spectroscopy (MRS)
  - Secondary: liver enzymes, endothelial dysfunction, insulin resistance, SCD1 activity and cholesterol synthesis and lipid levels

https://clinicaltrials.gov/ct2/show/NCT01094158?term=NCT01094158&draw=2&rank=1
https://clinicaltrials.gov/ct2/show/NCT02279524?term=NCT02279524&draw=2&rank=1
Considerations for Late Phase 2/Phase 3 Dose Selection for NASH

• Generally phase 2 dose-ranging study is recommended to support future phase 3 program dose selection
• Evidence of efficacy based on histological endpoints (reasonably likely to predict clinical benefit for accelerated approval)
• Duration: at least 12–18 months
• Explore exposure-response relationships for efficacy/safety
  – Diagnostic biomarkers that may provide evidence of disease progression/disease severity
  – Prognostic biomarkers that may predict liver-related complications
### Examples of Late Phase 2 and Phase 3 Dosages for NASH

<table>
<thead>
<tr>
<th>Drug</th>
<th>MOA</th>
<th>Phase 2 Dosage</th>
<th>Phase 3 Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Elafibranor</strong></td>
<td>PPARα,δ agonist</td>
<td>80 and 120 mg QD for 52 weeks</td>
<td>120 mg QD for 72 weeks</td>
</tr>
<tr>
<td><strong>Obeticholic acid</strong></td>
<td>FXR agonist</td>
<td>10, 20, and 40 mg QD; 25 mg QD for 72 weeks</td>
<td>10 and 25 mg QD for 18 months</td>
</tr>
<tr>
<td><strong>Aramchol</strong></td>
<td>Stearoyl-CoA desaturase-1 (SCD1) inhibitor</td>
<td>100 and 300 mg QD for 3 months; 400 and 600 mg QD for 52 weeks</td>
<td>300 mg BID for 52 weeks</td>
</tr>
<tr>
<td><strong>MGL-3196</strong></td>
<td>Thyroid hormone receptor agonist</td>
<td>80 mg (dose adjust +/-20 mg at W4) QD for 36 weeks</td>
<td>80 and 100 mg QD for 52 weeks</td>
</tr>
<tr>
<td><strong>Selonsertib</strong></td>
<td>Apoptosis signal-regulating kinase 1 (ASK1) inhibitor</td>
<td>6 and 18 mg for 24 weeks</td>
<td>6 and 18 mg for 48 weeks</td>
</tr>
<tr>
<td><strong>Cenicriviroc</strong></td>
<td>C-C chemokine receptor (CCR)2/5 Inhibitor</td>
<td>150 mg QD for 12 months</td>
<td>150 mg QD for 12 months</td>
</tr>
</tbody>
</table>

Summary

• Lack of validated noninvasive surrogate biomarker(s) that is predictive of clinical benefits for NASH

• Early phase proof-of-concept trial:
  – PK and biomarker information to guide starting dose selection

• Late phase 2 dose finding/phase 3:
  – Efficacy: histology endpoints, biomarkers
  – Safety: liver safety biomarkers, hepatic impairment study

• Dose-response and exposure-response relationship analyses
Acknowledgement

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FDA Workshop Planning Committee

OCP/DIIP leadership
• Dr. Chandra Sahajwalla
Biomarkers for Drug Development for NASH and Cholestatic Liver Diseases

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Disclaimer

- The views and opinions expressed here are my own and do not represent official guidance from the FDA
- I have no financial conflicts
A Biomarker is:

• A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions

• Molecular, histologic, radiographic, or physiologic characteristics are types of biomarkers. A biomarker is not an assessment of how an individual feels, functions, or survives
BEST: BIOMARKERS, ENDPOINTS, AND OTHER TOOLS RESOURCE

- A glossary of terminology and uses of biomarkers and endpoints in basic biomedical research, medical product development, and clinical care
- Created by the NIH-FDA Biomarker Working Group
Biomarker Categories: BEST Definitions

- **Susceptibility/Risk**: Indicates potential for developing disease or medical condition in an individual who does not currently have clinically apparent disease or the medical condition.

- **Diagnostic**: Detects or confirms the presence of a disease or condition of interest or to identify individuals with a subset of the disease.

- **Monitoring**: Assesses status, through serial measurement, of a disease or medical condition including degree or extent of disease.

- **Prognostic**: Identifies likelihood of a clinical event, disease recurrence or progression, in patients who have the disease or medical condition of interest in the absence of a therapeutic intervention.

- **Predictive**: Identifies patients who are more likely to experience a favorable or unfavorable effect from a specific treatment.

- **Pharmacodynamic/Response**: Indicates that a biological response has occurred in a patient who has received a therapeutic intervention. May become clinical trial endpoints and for a very small subset, surrogate endpoints.

- **Safety**: Indicates the likelihood, presence, or extent of toxicity to a therapeutic intervention when measured before or after that intervention.
Key Regulatory Considerations for Biomarker Use

- Although a biomarker may be used by clinical or basic science research communities, regulatory acceptance focuses on a drug development context that is supported by data. Considerations include:

  - Clinically valid biomarker
  
  - Reproducibility of data (e.g., high rate of discordant conclusions for biomarkers in the published literature)
  
  - Adequacy of the analytic device/assay to assess biomarker accurately and reliably
  
  - Feasibility of the biomarker measurement
Regular Approval Pathway

- Also known as traditional or full approval

- Evidentiary framework requires substantial evidence of effectiveness through adequate and well-controlled investigations (typically 2 or more trials)

- Efficacy endpoints are direct measurements of how a patient feels, functions or survives or validated surrogates:
  - Examples include overall survival (mortality), patient-reported outcomes (PROs – valid symptom measurements) or disease-free survival (morbidity).

- Noninferiority trial designs acceptable when appropriate
Accelerated Approval Pathway

• Ensures that therapies for serious conditions are approved and available to patients as soon as it can be concluded that the therapies’ benefits justify their risks

  Section 506(c) of the FD&C Act, as amended by section 901 of FDASIA

  • Subpart H - drugs (21 CFR 314)

  • Subpart E – biologics (21 CFR 601)

• Evidentiary framework similarly requires substantial evidence of efficacy through adequate and well-controlled investigations (typically 2 or more trials)

• May be granted based on surrogate endpoints that are “reasonably likely to predict clinical benefit”

• Requires confirmatory post-marketing trial(s) to verify the findings using clinical benefit endpoints
  – Should generally be underway at the time of accelerated approval
Surrogate Endpoint

• “A Correlate does not a Surrogate Make”

• Criteria for Surrogate Endpoints
  ▪ Measurable/Interpretable
  ▪ Sensitive
  ▪ On the Pathway to a Clinically Meaningful Endpoint

Fleming and deMets, 1996
Why is histology accepted as a surrogate endpoint?

- Histopathology maybe a surrogate that is reasonably likely to predict clinical benefit
  - Fibrosis stage, but no other histologic feature of steatohepatitis, has been associated independently with increased mortality, transplantation, and liver-related events
  - Currently, there are no data to support that a one stage reduction in fibrosis is clinically meaningful – this is a theoretical assumption

The limitations of Surrogate Endpoints

Surrogate on **causal pathway** modulated by drug

Surrogate **not on causal pathway** by which drug leads to benefit, or **multiple pathways of leading to clinical outcome**, BM *may or may not* reflect key pathways

Drug may induce **adverse effects on desired clinical outcome** through a pathway *not reflected* by BM, or may lead to other toxicities = BM does not reflect benefit (or risk)
The Gamut of NASH Biomarkers

https://www.nature.com/articles/s41575-018-0014-9
Biomarkers for Non-cirrhotic NASH Drug Development

• Early Phase trials:
  ▪ Based on MOA, ALT/AST (but are not predictive of histological changes);
  ▪ Imaging BM- elastography, MRI-PDFF, MRS, MRE etc.
• Phase 2b trials:
  ▪ Improvement in NAS as assessed by histology (acceptable)
• Phase 3 trials:
  ▪ Improvement of fibrosis by ≥1 stage with no worsening of NASH* OR
  ▪ Resolution of NASH with no worsening of fibrosis
• Phase 4 trials:
  ▪ Progression to cirrhosis on histopathology
  ▪ Hepatic decompensation events
  ▪ ↑ MELD from ≤12 to > 15
  ▪ Transplant
  ▪ All-cause mortality
Limited Biomarkers for Detecting Drug-induced liver-injury (DILI)

• **New molecular entities** (NMEs) pose the risk of unknown off-target effects

• Assessment of DILI can be challenging **even in** patients with normal liver **undergoing** treatment of chronic diseases (e.g., malignancy, neurodegenerative diseases, anti-infectives, etc.) with NMEs

• In subjects with pre-existing liver disease, assessment of DILI is **extremely** challenging
Limited Biomarkers for Detecting Drug-induced liver-injury (DILI) (cont’d)

• Persistent Knowledge Gaps
  ▪ Differentiating liver adaptation from liver injury in early stages of drug development
  ▪ Limited biomarkers available to assess DILI (liver biochemistries, liver biopsy)
  ▪ Lack of concordance between biochemical biomarkers and presence of liver injury
  ▪ Timely recognition of cholestatic type DILI
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  Courtesy of: Stephanie O. Omokaro
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- DGIEP
Approaches to Dose Selection for NASH: An Industry Perspective

Art Bergman, PhD
Clinical Pharmacology
Early Clinical Development
Pfizer, Inc.

FDA Public Workshop: Clinical Pharmacology in Drug Development for Liver Diseases

December 9, 2019
Typical Dose Selection Considerations for Early Clinical Development

**Phase of Development**
- Preclinical
- Phase 1
- Phase 2a
- Phase 2b/3

**Data Collected**
- Toxicology
  - Animal PK/PD Data
  - In vitro Data
- Ascending Dose Study(s)
  - PK / Safety / Tolerability
  - Target Engagement Assessment
- “Patient” Studies
  - PK / Safety / Tolerability
  - Proof of Concept/Pharmacology
- Target patient population(s)
  - PK / Safety / Tolerability
  - Registration Endpoints

**Dose Selection**
- Translational Modeling / Extrapolation of Preclinical Data
- Exposure / Dose Response (Biomarkers/ Safety)
- Exposure / Dose Response (Efficacy / Safety)
Acetyl-CoA Carboxylase Inhibitor (ACCi): Potential Target for Treatment of NASH

Liver-targeted ACC Inhibitor (PF-05221304)

hACC1 = 7.5 nM
hACC2 = 8.2 nM

Ross et al, AASLD-2019 (08-12Nov2019)

Previous Clinical Evidence that ACC inhibition results in decreases in liver fat and increases in serum TG

Key clinical question for phase 1: Can we attain sufficient target engagement without elevating serum TG?

At near-maximal DNL inhibition, previous study showed decreased liver fat and increased serum TG.
Inhibition of DNL by 70% Expected to normalize DNL in patients with NAFLD (targeted therapeutic effect)

Multiple Ascending Dose (MAD) Study (C1171001, Part 2) to Assess Safety, Tolerability, PK and PD (target engagement) in Healthy Participants

- Randomized, dose-escalating 7-cohort design (with 8 subjects receiving PF-05221304 and 2 subjects receiving placebo in each cohort) where with the exception of Day 14, PF-05221304 was given with a standard meal.

- On Day 14 and a corresponding baseline day (Day -6), subjects received oral fructose doses every 0.5 hours for 9.5 hours. Hepatic de novo lipogenesis (DNL) was assessed by evaluating the incorporation of deuterated water (administered prior to oral fructose loading) into triglyceride palmitate.
The targeted 70% DNL inhibition was attained at doses that did not increase serum triglycerides in healthy participants.

However, a steep sigmoidal dose-response was observed, with higher doses resulting in 40-50% increase in serum triglycerides.

A similar dose response was observed with postprandial triglycerides (data not shown).
Systemic Exposure of ACC Inhibitors has Potential to Alter Platelet Count

Previous development program with systemically distributed ACCi (PF-05175157):
- Decrease in platelet count within the normal range was observed.
- Program terminated.

Preclinical experiments showed that ACC is necessary for platelet maturation.
- Ex vivo platelet maturation studies
- Monkey studies

An ACCi clinical candidate that is asymmetrically distributed to the liver (PF-05221304) via OATP liver uptake is being investigated clinically.
Assessing Therapeutic Index Between DNL Inhibition and Platelets

- Reductions of platelets within the normal range were observed at higher doses tested.
- However, reductions in platelets were minimal for doses that inhibited DNL >~80%
- A semi-mechanistic model informed by clinical and preclinical data was used to extrapolate expected effect on platelets over course of planned Phase 2 study.

Modeling of Key Endpoints in Phase 1 to Support Phase 2a Dose Selection

- Average DNL inhibition over the dosing interval was projected based on population PK and exposure-response analysis of fructose-stimulated DNL inhibition.

- Fasting TG projected via dose (total daily dose)-response analysis.

- % change in platelets was projected based on semi-mechanistic model.

- Purple lines represent QD doses selected for the 16-week phase 2 study.

- Assumes similar response in patient population as healthy subjects – tested in Phase 2.

Kelly et al, AASLD-2019 (08-12Nov2019)
Design of Phase 2a Study (C1171002)

ALT, alanine aminotransferase; BMI, body mass index; MRI-PDFF, magnetic resonance imaging – proton density fat fraction; NASH, non-alcoholic steatohepatitis; NAFLD, non-alcoholic fatty liver disease; PBO, placebo; T2DM, type 2 diabetes mellitus; ULN, upper limit of normal; wks, weeks

1st tier stratification

NAFLD

• ≥2 of 5 features of metabolic syndrome plus
• ALT ≤ ULN and ≤1.25x ULN and
• Liver stiffness on FibroScan® <7.0 kPa

Non-T2DM

(1st tier) NASH

• Biopsy-proven NASH in ≤24-months OR
• ≥2 of 5 features of metabolic syndrome plus
• ALT > ULN and ≤5x ULN and
• Liver stiffness on FibroScan® ≥7.0 kPa

1st tier stratification

2nd tier stratification

Non-T2DM

T2DM

T2DM

Adult patients with NAFLD defined as liver fat of ≥8% and BMI ≥25 kg/m² (Western sites) or 22.5 kg/m² (Asian sites)

Amin et al, AASLD-2019 (08-12Nov2019)

ALT, alanine aminotransferase; BMI, body mass index; MRI-PDFF, magnetic resonance imaging – proton density fat fraction; NASH, non-alcoholic steatohepatitis; NAFLD, non-alcoholic fatty liver disease; PBO, placebo; T2DM, type 2 diabetes mellitus; ULN, upper limit of normal; wks, weeks
Results: Percentage change in liver fat (via MRI-PDFF)

Entire population

- Reduction in percentage liver fat (MRI-PDFF) starting at Week 4 and continuing to Week 16 with separation from placebo at top three doses

- Proportion of patients who achieve relative reductions ≥30% at Week 16:
  - Placebo, 6%
  - PF’1304 2 mg QD, 22%
  - PF’1304 10 mg QD, 74%
  - PF’1304 25 mg QD, 87%
  - PF’1304 50 mg QD, 90%

CI, confidence interval; LS, least-squares; MRI-PDFF, magnetic resonance imaging – proton density fat fraction; QD, once daily
Changes in liver function tests over time (presumed) NASH stratum

Amin et al, AASLD-2019 (08-12Nov2019)

Alk phos, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; GGT, gamma-glutamyl transferase; FU, follow-up; LS, least-squares; NASH, non-alcoholic steatohepatitis
Changes in fasting lipid panel over time

Entire population

Amin et al, AASLD-2019 (08-12Nov2019)
Conclusions: 16-week ACCi Study

• PF’1304 reduces liver fat in adults with NAFLD
  – Significant reductions ≥30% relative to placebo at doses ≥10 mg QD

• Clear dose-responsive reduction in non-specific marker of overall liver function, ALT, with PF’1304 in adults with (presumed) NASH

• PF’1304 was generally well tolerated in adults with NAFLD
  – However, TG ↑ with PF’1304 doses 25 and 50 mg QD are undesirable because of their potential implications for long-term cardiometabolic health
    – Especially with accompanying effect on other lipid parameters – ↓ in direct LDL-C, HDL-C, Apo A1 with ↑ Apo B, C3, and E, and no change in total cholesterol

• Encouraging results for some biomarkers including AST, CK18-M30 and -M65, suggest potential for improvement in biopsy endpoints with longer treatment
FDA Guidance: Codevelopment of Two or More New Investigational Drugs in Combination

Guidance for Industry

Codevelopment of Two or More New Investigational Drugs for Use in Combination

“Codevelopment should ordinarily be reserved for situations that meet all of the following criteria:

• The combination is intended to treat a serious disease or condition.
• There is a strong biological rationale for use of the combination
• A full nonclinical characterization or a short-term clinical study on an established biomarker, suggests that the combination may provide a significant therapeutic advance over available therapy and is superior to the individual agents. A nonclinical model should demonstrate that the combination has substantial activity and provides greater activity, a more durable response, or a better toxicity profile than the individual agents.
• There is a compelling reason why the new investigational drugs cannot be developed independently”
Preclinical data suggest that co-administration of ACCi/DGAT2i may provide greater efficacy than either agent administered alone and fully mitigates elevation of circulating TG levels observed with ACCi alone.

- A clinical DDI study was conducted between the 2 agents showing no clinically meaningful PK interaction.

- A randomized, double blind, placebo controlled, Ph2a factorial study (NCT03776175) evaluating co-administration of ACCi:DGAT2i vs monotherapy and placebo on liver fat content in patients with NAFLD is presently underway.

Ross et al, AASLD-2019 (08-12Nov2019)
Challenges for Dose Selection of Combination Dose Ranging Studies

• Dose-Response of each agent may be different in the setting of coadministration of the other agent.

• Therefore, an “optimal” design may be a full factorial design.
  • Assuming 3 dose levels for each agent and the need to study each individual agent alone ➔ 16 arms!!
  • Feasibility of such studies quickly becomes problematic.

• How can we leverage clinical pharmacology to streamline clinical development for combination drug development in NASH?
  • Develop combination PK/PD models that would alleviate the need for a full factorial design.
  • Work quantitatively linking biomarker response to biopsy registration endpoints is critical.
  • Mechanistic Quantitative systems pharmacology (QSP) modeling.
Quantitative Systems Pharmacology (QSP) in Evaluating Dose Selection for Combinations

- Vehicle to integrate all relevant preclinical and clinical data in a single mechanistic model.

- Quantitatively evaluate suitability of potential combinations before initiating clinical program.

- Use limited clinical data to determine optimal combination doses that should be assessed in clinical studies.

- Evaluate the relationship of modulating metabolic processes on clinical endpoints.

Rieger et al. ACoP, October 2018
Summary

• Standard clinical pharmacology methods can be used for dose selection in early clinical development
  • Exposure / response for target engagement markers
  • Exposure / response for other markers of interest

• With metabolic diseases such as NASH, population matters when assessing metabolic parameters
  • Response may be different between healthy participants, NAFLD patients and NASH patients

• No clear way to predict registration endpoint dose-response based on Phase 2a biomarker response – need for additional research

• Combination therapy may be a promising way to treat NASH with fibrosis
  • Dose selection and clinical development plan may be challenging – potential role of PK/PD and QSP modeling to streamline combination development
Session 3: Panel Discussion

Clinical Pharmacology Approaches to Support Dose Finding for Clinical Trials for NASH and Cholestatic Liver Diseases
Population: Patients at high risk of NASH

Randomize Additional Patients

N=XX Dose 3
N=XX Dose 2
N=XX Dose 1
Placebo = XX

Utility function: overall analysis

Interim Analysis at Weeks 12 or 16 or 24
Safety stop criteria
Efficacy criteria based on non-invasive biomarkers
Adaptations

Weeks 48 or 52 or 72
Biopsy driven endpoints
Safety/ Efficacy

AD provides an opportunity for prospectively planning potential modifications of one or more aspects of an ongoing study:
- Adding or dropping treatment arms
- Re-estimating sample size
- Changes in the allocated proportion of subjects in one or more arms

**Potential Advantages**

- Enrol patients with biopsy confirmed NASH earlier in development
- Evaluation of data from different stages for a combined analysis
- Utility function may increase optimal dose finding
- Same subjects can move from one study phase to another, reducing the need to find additional subjects

**Potential Limitations**

- Longer set up time
- Higher initial cost
- Operational complexity
- Need to control stat & operational bias
Adaptive Trial Design in NASH Cirrhosis with Clinical Signs of Portal Hypertension

Population:
- Patients with NASH cirrhosis
- CTP A only
- No varices
- Clinical signs of portal hypertension
  - Thrombocytopenia
  - Spleen size ≥ 15 mm
  - Evidence of collaterals by imaging

Interim Analysis at Months 12 or 18 m
- Incidence of varices
- Safety stop criteria
- Adaptations (randomization rate, patient population)

Accelerated approval
- Incidence of varices
- Progression to large varices or red wales
- Liver outcomes

Utility function?
Session 3: Panel Discussion

Clinical Pharmacology Approaches to Support Dose Finding for Clinical Trials for NASH and Cholestatic Liver Diseases
Session 3: Clinical Pharmacology Approaches to Support Dose Finding for Clinical Trials for NASH and Cholestatic Liver Diseases

9 Dec 2019 Silver Spring Meeting
Duke-Margolis Center for Health Policy and the U.S. Food & Drug Administration
Dose-related Sustained Reduction in Liver Fat on MRI-PDFF

Exposure and Biomarker of Liver Concentration Correlate with MRI-PDFF Response (≥30% hepatic fat reduction)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Placebo, n (%)</th>
<th>n</th>
<th>Resmetirom, n (%)</th>
<th>Odds ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 36 ≥30% fat reduction</td>
<td>34</td>
<td>10 (29.4%)</td>
<td>74</td>
<td>50 (67.6%)</td>
<td>4.9 (2.0–11.9)</td>
<td>0.0006</td>
</tr>
<tr>
<td>High exposure group</td>
<td>43</td>
<td></td>
<td>43</td>
<td>32 (74.4%)</td>
<td>6.9 (2.5–19.3)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Low exposure group</td>
<td>31</td>
<td></td>
<td>31</td>
<td>18 (58.1%)</td>
<td>3.1 (1.1–8.9)</td>
<td>0.032</td>
</tr>
<tr>
<td>High SHBG group</td>
<td>44</td>
<td></td>
<td>44</td>
<td>34 (77.3%)</td>
<td>8.3 (2.9–23.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Low SHBG group</td>
<td>30</td>
<td></td>
<td>30</td>
<td>16 (53.3%)</td>
<td>2.5 (0.9–7.2)</td>
<td>0.084</td>
</tr>
<tr>
<td>F2–F3</td>
<td>18</td>
<td>4 (22.2%)</td>
<td>31</td>
<td>21 (67.7%)</td>
<td>7.3 (1.9–28.6)</td>
<td>0.0040</td>
</tr>
</tbody>
</table>

## Exposure, Biomarker of Liver Concentration and MRI-PDFF Response Correlate with Improved NASH

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Placebo</th>
<th>n</th>
<th>Resmetirom</th>
<th>Least squares mean difference (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver biopsy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in NAS, mean (SE)</td>
<td>34</td>
<td>-1.0 (0.21)</td>
<td>73</td>
<td>-1.4 (0.14)</td>
<td>-0.4 (-0.9 to -0.1)</td>
<td>0.082</td>
</tr>
<tr>
<td>High exposure group</td>
<td>..</td>
<td>..</td>
<td>43</td>
<td>-1.6 (0.18)</td>
<td>-0.6 (-1.2 to -0.1)</td>
<td>0.029</td>
</tr>
<tr>
<td>Low exposure group</td>
<td>..</td>
<td>..</td>
<td>30</td>
<td>-1.2 (0.22)</td>
<td>-0.2 (-0.8 to 0.4)</td>
<td>0.51</td>
</tr>
<tr>
<td>High SHBG group</td>
<td>..</td>
<td>..</td>
<td>44</td>
<td>-1.7 (0.18)</td>
<td>-0.7 (-1.2 to -0.1)</td>
<td>0.016</td>
</tr>
<tr>
<td>Low SHBG group</td>
<td>..</td>
<td>..</td>
<td>29</td>
<td>-1.1 (0.22)</td>
<td>-0.1 (-0.7 to 0.5)</td>
<td>0.77</td>
</tr>
<tr>
<td>MRI-PDFF responder</td>
<td>..</td>
<td>..</td>
<td>46</td>
<td>-1.9 (0.16)</td>
<td>-0.9 (-1.4 to 0.4)</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

*Source: Harrison et al, Lancet 394, 2012-2024, 2019*
PDFF at the time of the initial treatment with resmetirom was considered the baseline value.

The primary efficacy population (n=23) included former placebo patients and resmetirom treated patients who had a dose increase during the extension study, all on at least 80 mg.

All patients had at least 20% fat reduction; 88% had ≥30% fat reduction; 100% on the 100 mg dose had ≥30% fat reduction.

A lower response >20% and <30% fat reduction was observed in 2 patients with >10% weight gain during the study.
Liver enzymes

Decrease in liver enzymes over time, coincident with increase in sex hormone binding globulin (SHBG) which reflects hepatic level of resmetirom.

Liver enzymes (Ext week 36)

<table>
<thead>
<tr>
<th></th>
<th>ALT</th>
<th>GGT</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 80 mg</td>
<td>-23</td>
<td>-22</td>
</tr>
<tr>
<td>All 100 mg</td>
<td>-24</td>
<td>-24</td>
</tr>
<tr>
<td>n=29 p=0.0001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>n=21 p&lt;0.0001</td>
<td>p=0.01</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>n=7 p&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALT/AST/GGT (n=31)

SHBG (n=31)

Change from BL (IU/L)
Session 3: Panel Discussion

Clinical Pharmacology Approaches to Support Dose Finding for Clinical Trials for NASH and Cholestatic Liver Diseases
Session 4: Clinical Trial Design and Endpoint Selection—Clinical Pharmacology Approaches to Optimizing the Safety and Efficacy of Therapies for NASH and Cholestatic Liver Diseases

2:40 pm – 3:55 pm
Elafibranor

From Bench to Bedside

Duke-Margolls/FDA
Leveraging Clinical Pharmacology to Optimize Drug Development for Nonalcoholic Steatohepatitis (NASH) and Cholestatic Liver Diseases
Silver Spring, MD

Carol Addy, M.D. MMSc
December 9, 2019
PPARs have key homeostatic actions in NASH

*Elafibranor – Dual Agonist of PPAR α/δ*
Challenges in Development of Novel Therapeutics for NASH

Selection of Preclinical Models

- Limited preclinical models > 10 years ago
- No “ideal” model
- Consistency in efficacy data across 4 models tested
  - Mouse model of NASH - high fat diet (HFD)-fed foz/foz mouse
  - Mouse NAFLD model - C57BI/6J or diabetic db/db mice by 4 to 7 weeks of methionine- and choline-deficient (MCD) diet
  - Rat model of carbon tetrachloride (CCL4)-induced hepatic fibrosis
  - Rat model of fibrosing NASH - Wistar rats fed with a choline-deficient and L-amino acid-defined (CDAA) diet supplemented with 1% cholesterol
Elafibranor and histologic changes in the foz/foz model

**NASH Induction**

- **CTRL**
- **12w**

**Intervention**

- No Tt
- ELA

**NAFLD activity score**

**Steatosis**

**Ballooning**

**Inflammation**

**Graphs**

- Number of cases
  - 0
  - 1
  - 2
Elafibranor and fibrosis changes in the foz/foz model

**NASH Induction**

CTRL

12w

**Intervention**

No Tt

ELA

**CPA (%)**

<table>
<thead>
<tr>
<th>CTRL</th>
<th>12w</th>
<th>No Tt</th>
<th>ELA</th>
</tr>
</thead>
<tbody>
<tr>
<td>% stained area</td>
<td>*</td>
<td>**</td>
<td>***</td>
</tr>
</tbody>
</table>

**TIMP1 mRNA**

<table>
<thead>
<tr>
<th>CTRL</th>
<th>12w</th>
<th>No Tt</th>
<th>ELA</th>
</tr>
</thead>
<tbody>
<tr>
<td>fold induction</td>
<td>***</td>
<td>*</td>
<td>***</td>
</tr>
</tbody>
</table>
Elafibranor and glycemic control in the foz/foz model

NASH Induction  Intervention

Blood glucose

Blood Insulin
Elafibranor and changes in atherosclerotic lesions and plasma lipid profile in hApoE2KI mice

Atherosclerotic lesions area

Triglycerides

Cholesterol

No Tt

ELA

CTR

ELA 10 mg/kg

ELA 30 mg/kg

No Tt

ELA

CTR

ELA 10 mg/kg

ELA 30 mg/kg
Elafibranor Phase 2A Studies

- Male and post-menopausal women with atherogenic dyslipidemia and abdominal obesity (80 mg x 28d)
- Impaired fasting glucose +/- abdominal obesity (80 mg x 35d)
- Type 2 diabetes (80 mg x 12w)

Significant improvement observed:
- **Plasma lipids** (decreased TG, LDL-C and pro-atherogenic lipoproteins; increased HDL-C and anti-atherogenic lipoproteins)
- **Inflammatory markers** (decreased haptoglobin, fibrinogen, hsCRP)
- **Liver chemistries** (decreased GGT, ALP, ALT)
Elafibranor: Hepatic and Peripheral Insulin Sensitivity

*GFT505-2106 Phase IIa: patients with HOMA>3.0; 2month-treatment, GFT505 (80mg/day) vs. placebo in cross-over design*
Elafibranor Phase 2b
Liver-Specific Histologic Endpoints

"NASH Resolution Without Worsening of Fibrosis"

ITT and all other analyses

<table>
<thead>
<tr>
<th>Population</th>
<th>120mg</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All / ITT</td>
<td>19% (n=89)</td>
<td>12% (n=92)</td>
<td>0.045</td>
</tr>
<tr>
<td>NAS≥4</td>
<td>19% (n=75)</td>
<td>9% (n=75)</td>
<td>0.013</td>
</tr>
<tr>
<td>NAS≥4 w/ fibrosis</td>
<td>20% (n=71)</td>
<td>11% (n=66)</td>
<td>0.009</td>
</tr>
<tr>
<td>NAS≥4 3 arms</td>
<td>26%</td>
<td>5%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Based on the objective and approved definition of "NASH resolution" defined by regulators as Ballooning = 0 & Inflammation = 0 (or 1)


Centers with randomization in all arms, to take into account the well known heterogeneity in the standard of care of NASH patients in different centers (n=120)
Elafibranor Phase 2b Results:
Change in Ballooning and Inflammation Correlates with Change in Fibrosis

Reducing Ballooning & Inflammation correlates with Fibrosis improvement
Worsening Ballooning & Inflammation correlates with Fibrosis worsening

Change in Activity Index (Ballooning + Inflammation = NASH disease activity)

Mean Change in Fibrosis Score

\[ \text{Balloonings} \]
Elafibranor Phase 2b Results: Cardiometabolic Risk Factors

Phase 2b results showed association of elafibranor with improved cardiometabolic profile in patients with NASH.

Elafibranor 120mg (n=78) vs Placebo (n=77) on Lipid Markers

Elafibranor 120mg (n=35) vs Placebo (n=28) on Glucose Homeostasis and Insulin Sensitivity in Patients with NASH and Type 2 Diabetes

Significant decrease in HbA1c vs placebo

** : p<0.01
*** : p<0.001

# : p<0.05
## : p<0.01
Elafibranor Phase 3
RESOLVE-IT

ACCELERATED MARKET AUTHORIZATION
- SUBPART H (FDA)
- CONDITIONAL APPROVAL (EMA)

FIRST TREATMENT PERIOD 18 MONTHS

Placebo
Elafibranor 120mg
2:1

TRIAL INITIATION Q1 2016

Study population: patients at risk of progression to clinical events
- NASH with a NAS ≥4
- Fibrosis stage F2 and F3
- (F1 + cardiometabolic risk)

End of enrollment first ~1000 patients for Subpart H: April 2018

DSMB 18-month ✓
DSMB 24-month ✓
DSMB 30-month ✓
DSMB 36-month ✓

72-WEEK INTERIM ANALYSIS

Histological primary endpoint
NASH RESOLUTION WITHOUT WORSENING OF FIBROSIS
- Ballooning = 0
- Inflammation = 0 (or 1)
- Without worsening fibrosis (1 stage)

Histological key secondary endpoint
improvement of histological fibrosis (potential additional labeling claim)

Read-out ~1000 patients: ~Q1 2020

EXTENSION PERIOD

Placebo
Elafibranor 120mg
2:1

Prevention of NASH associated clinical events, including cirrhosis and all cause mortality

Read-out ~2000 patients: based on occurrence of a pre-defined number of events

END OF STUDY

DSMB 18-month ✓
DSMB 24-month ✓
DSMB 30-month ✓
DSMB 36-month ✓

~ 1000 patients

~ 2000 patients
THANK YOU
Optimizing safety and efficacy of FXR agonists in NASH and PBC

Michael Badman
Duke FDA meeting, Silver Spring, MD
December 9th 2019
FXR: attractive target for liver disease

- Abundant expression in liver and gut
- FXR agonism has pleiotropic effects important in the post-prandial state
- Addresses many modes of NASH and cholestatic pathophysiology
- FGF19 is a biomarker of FXR activity and is also a metabolic regulator
- NASH and PBC indications have biomarkers linked to efficacy
**Tropifexor: a non-bile acid FXR agonist**

- Tropifexor is the most potent FXR agonist in the clinic
- Non-bile acid structure includes unique bicyclic nortropine-substituted benzothiazole carboxylic acid

![Model of LJN452 docked into FXR ligand binding domain](image)

Tully et al 2017
In cell-based assays, tropifexor has an EC$_{50}$ of 0.3 nM

>30,000 fold selectivity over other nuclear receptors

In vivo tropifexor potently and transiently induced FXR target genes

FGF15 assay allowed modeling of PK-PD in preclinical species

Wistar Han rats gavaged for 14 days; FGF15 levels measured 1h or 7h after final dose of tropifexor. Mean ± SEM; n = 3/group.

Tully et al 2017
Efficacy in rodent cholestatic model

- Tropifexor demonstrates efficacy in alpha-naphthylisothiocyanate model

Reduction in circulating markers of liver damage

Improvement in fibrosis by tropifexor (Picro sirius red staining)
PK modeling informed FIH dose

- Rat and mouse: low clearance, moderate T$_{1/2}$, and low oral bioavailability
- Dog: low clearance, moderate T$_{1/2}$, and low oral bioavailability
- Mechanistically based PK modeling performed with GastroPlus®
- Predicted human PK: low dose
  - 40 to 130 μg tropifexor daily

<table>
<thead>
<tr>
<th>Efficacy model</th>
<th>Efficacious AUC$_{0-24}$ (0-24h.)</th>
<th>Tropifexor Predicted Human PK</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANIT</td>
<td>5.8 h*Nm</td>
<td>0.5 to 1.7 ml/min/kg, 17, 40 to 130 μg/day</td>
</tr>
</tbody>
</table>

PK modeling based on efficacy in rat alpha-naphthylisothiocyanate cholestasis model at 0.01 mg/kg/day

Tully et al 2017
FIH optimized for target populations

- Safety, tolerability, PK, and PD of tropifexor in healthy subjects
  - Single ascending doses 10 µg - 3 mg of tropifexor (SAD)
  - Tropifexor in a pilot food effect sub-study
  - Multiple ascending doses 10 µg - 100 µg of tropifexor (MAD)
  - Cohort of volunteers with Class II obesity

- 95 subjects received at least 1 dose of tropifexor or matched placebo

- 4 SAE (1 related to 100µg tropifexor)
  - ALT >5xULN (1 similar AE 1 >3xULN)

CLJN452X2201 Study Design

Badman et al 2016
**Tropifexor displayed predictable PK**

- $T_{\text{max}}$ 4 hours (range: 3-8 hours); $T_{1/2}$ 13.5-22 hours
- Approximately dose-proportional exposure from doses 10 µg - 3 mg
- Exposure of tropifexor was increased by ~60% with a high fat meal

![Plasma concentration tropifexor in single dose study](image1.png)

- Plasma concentration tropifexor in single dose study

![Plasma concentration tropifexor during multiple dose study](image2.png)

- Plasma concentration tropifexor during multiple dose study

Badman et al 2016
Multiple dose PK

- Steady-state achieved by Day 4
- Similar time to $t_{\text{max}}$ at Day 1 and Day 14
- Accumulation ratio less than 2 ($R_{\text{acc}} = 1.2-1.9$)

Badman et al 2016
FGF19: marker of target engagement

- Dose dependent increases in FGF19 observed from 10 µg - 1 mg tropifexor
- Informed initial tropifexor doses in PBC (30 µg) & NASH (10 - 90 µg) patients
- ADME and hepatic impairment study run concurrent with Ph 2

Badman et al 2016
ADME study at multiple of clinical dose

- A single dose of 1 mg \([14C]\)tropifexor administered to 4 male HVs
- Samples were collected at specified intervals for up to 312 hr post-dose
  - Blood
  - Plasma
  - Excreta
- Tropifexor was well absorbed average minimum absorption \(~68\%\)
- Study drug was safe and well tolerated by all four subjects.

- Radioactivity from \([14C]\)tropifexor excreted via fecal and urinary route

A single dose of 1 mg \([14C]\)tropifexor administered to 4 male HVs. Mean (SD) cumulative excretion of tropifexor-related radioactivity in excreta of healthy male subjects (N=4).

Wang-Lakshman et al 2019
Tropifexor is main plasma component

- Unchanged tropifexor in the plasma comprised ~92% of total radioactivity

Mean plasma tropifexor and total radioactivity concentration-time profiles in healthy male subjects (N=4)

Representative metabolite profiles of tropifexor in pooled human plasma

Wang-Lakshman et al 2019
Hepatic impairment study

- An open-label, single-dose, parallel group study in 6 to 8 each of:
  - Mild [Child-Pugh A]
  - Moderate [Child-Pugh B]
  - Severe [Child-Pugh C]
  - Matched HVs
- Single dose of 200 µg (fasting)
- Severe patients dosed after half of mild / moderate subjects completed
- Tropifexor was well tolerated
CLJN452X2201: Study design for Part1

Dose escalating design – 4 weeks of 30, 60 or 90 µg tropifexor

Part 1 Cohorts ~15 PBC patients on UDCA with ALP ≥1.67×ULN or total bilirubin>ULN

- **Cohort 1**
  - Screening
  - Tropifexor 30 µg qd or Placebo (2:1)
  - Follow Up
  - Day 1, Day 28, Day 56, Day 84

- **Cohort 2**
  - Screening
  - Tropifexor 60 µg qd or Placebo (2:1)
  - Follow Up
  - Day 1, Day 28, Day 56, Day 84

- **Cohort 3**
  - Screening
  - Tropifexor 90 µg qd or Placebo (2:1)
  - Follow Up
  - Day 1, Day 28, Day 56, Day 84

Follow-up meetings and interim analysis

NCT02516605

IA of Cohorts 1-3 (manuscript in preparation for complete study)

Schramm et al 2018 EASL Paris
Dose-dependent decrease in GGT

Schramm et al. 2018 EASL Paris

*P < 0.05 vs placebo
Decreases in ALP during treatment

Schramm et al 2018 EASL Paris
Dose dependent decrease in ALT

- Tropifexor 30 µg qd
- Tropifexor 60 µg qd
- Tropifexor 90 µg qd
- Placebo qd

% mean change from baseline (Day 1)

*P < 0.05 vs placebo

Schramm et al 2018 EASL Paris
## Acceptable safety and tolerability at 30-90 µg

<table>
<thead>
<tr>
<th></th>
<th>Tropifexor 30 µg qd N = 11</th>
<th>Tropifexor 60 µg qd N = 9</th>
<th>Tropifexor 90 µg qd N = 12</th>
<th>Placebo qd N = 17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with at least one AE</td>
<td>9 (81.8)</td>
<td>8 (88.9)</td>
<td>11 (91.7)</td>
<td>14 (82.4)</td>
</tr>
<tr>
<td>AE with frequency ≥4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (9.1)</td>
<td>1 (11.1)</td>
<td>2 (16.7)</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>2 (16.7)</td>
<td>3 (17.6)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>1 (9.1)</td>
<td>0 (0.0)</td>
<td>1 (8.3)</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Viral upper respiratory tract infection</td>
<td>2 (18.2)</td>
<td>0 (0.0)</td>
<td>1 (8.3)</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td><strong>Pruritus (any type)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>2 (18.2)</td>
<td>2 (22.2)</td>
<td>3 (25.0)</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1 (9.1)</td>
<td>4 (44.4)</td>
<td>3 (25.0)</td>
<td>4 (23.5)</td>
</tr>
</tbody>
</table>

- No discontinuations due to itch; no incidence of severe itch in cohort 1-3
- No drug related AEs related to elevation in liver transaminases ALT and AST in cohort 1-3

Schramm et al 2018 EASL Paris
Transient changes in cholesterol

*P < 0.05 vs placebo

Schramm et al 2018 EASL Paris

268 Duke / FDA Meeting 9th Dec 2019
Study design: FLIGHT-FXR Part C

Phase 2 randomized, double blind, placebo-controlled, 3-part, adaptive-design study

- In Parts A and B, 198 patients with phenotypic or biopsy proven NASH were randomized to 12 weeks placebo, or tropifexor at doses up to 90 μg daily
Rapid and sustained reduction in ALT

Data are presented as LS mean change (SE) with 2-sided $P$ values by repeated measures ANCOVA
ALT, alanine aminotransferase; ANCOVA, analysis of covariance; LS, least square; SE, standard error

Sanyal et al 2019 AASLD Boston
Significant decrease in GGT

Data are presented as LS mean change (SE) with 2-sided P values by repeated measures ANCOVA
ALT, alanine aminotransferase; ANCOVA, analysis of covariance; LS, least square; SE, standard error

*S<0.001 versus placebo

Sanyal et al 2019 AASLD Boston

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Reduction in hepatic fat at week 12

Significant decrease in hepatic fat fraction with highest tropifexor dose

Reduction in HFF

Proportion of patients with ≥30% reduction in HFF

Data are presented as LS mean change (SE) with 2-sided P values by repeated measures ANCOVA.

ALT, alanine aminotransferase; ANCOVA, analysis of covariance; LS, least square; SE, standard error; TXR, tropifexor; W, week.

Sanyal et al 2019 AASLD Boston

Duke / FDA Meeting 9th Dec 2019

272 Duke / FDA Meeting 9th Dec 2019
## Safety and tolerability up to week 12

### More dose reduction / discontinuation in tropifexor 200 µg group

<table>
<thead>
<tr>
<th>Incidence, n (%)</th>
<th>Placebo (N = 51)</th>
<th>Tropifexor 140 µg (N = 50)</th>
<th>Tropifexor 200 µg (N = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects with at least one AE</td>
<td>36 (71)</td>
<td>44 (88)</td>
<td>44 (86)</td>
</tr>
<tr>
<td>Number of subjects with at least one SAE</td>
<td>1 (2)</td>
<td>0</td>
<td>1 (2)</td>
</tr>
<tr>
<td>AEs leading to dose reduction/discontinuation</td>
<td>2 (4)</td>
<td>3 (6)</td>
<td>14 (27)</td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

### Most frequent AEs

<table>
<thead>
<tr>
<th>AE</th>
<th>Placebo (N = 51)</th>
<th>Tropifexor 140 µg (N = 50)</th>
<th>Tropifexor 200 µg (N = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>6 (12)</td>
<td>17 (34)</td>
<td>20 (39)</td>
</tr>
<tr>
<td>Pruritus generalized</td>
<td>0</td>
<td>5 (10)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (4)</td>
<td>6 (12)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>4 (8)</td>
<td>5 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (8)</td>
<td>4 (8)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1 (2)</td>
<td>3 (6)</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>
Changes in lipid profile up to week 12

Decrease of HDL-C and increase of LDL-C with tropifexor

**LDL-cholesterol**

**HDL-cholesterol**

- Placebo
- Tropifexor 140 μg
- Tropifexor 200 μg

Sanyal et al 2019 AASLD Boston
No evidence of tropifexor induced liver injury in NASH patients

Sanyal et al 2019 AASLD Boston
Conclusions

- Use of mechanistically based PK modeling benefited early clinical development
- Biomarker modeling from tropifexor FIH gave confidence of likely efficacy
- Timing of ADME and hepatic impairment studies will provide data prior to EoP2
- Tropifexor shows dose dependent biomarker efficacy in PBC and NASH
- At higher doses, the FXR-class effects on itch and cholesterol become evident
- No evidence of tropifexor mediated liver damage in treated NASH patients
Quantitative tools to inform clinical trial design
Who: The Critical Path Institute

- Form pre-competitive, area-specific consortia with participants from industry, academia, advocacy groups, and regulators to address unmet medical needs

  - Regulatory qualification of preclinical and clinical biomarkers for use in safety, efficacy, and trial enrichment
  - Development and qualification of clinical outcome assessment tools
  - Development of quantitative modeling and simulation tools
  - Regulatory acceptance of nonclinical tools for medical product development
  - Impact on regulatory science
  - Forming and managing large international consortia
  - Data acquisition, management, curation, and integration
  - Clinical data standards development support
Challenges to clinical trial design in NASH

Disease progression Models
- Disease diagnosis/staging, patient identification/selection
- Identification and validation of less invasive biomarkers
- Identification and validation of less invasive biomarkers

PBPK models
- Dose finding and dose optimization for patients with varying degrees of liver diseases.
- Dose finding and dose optimization for patients with varying degrees of liver diseases.
Using PBPK modeling to inform drug development in NASH

**Need**
- In NASH/NAFLD functional mass of liver is reduced → reduced metabolism of the drug
- Translational models of NASH are not reliable
- Hard to predict liver concentration of the drug just based on systemic concentration

**Difficulty in predicting efficacious human dose**

Use PBPK models

**Advantages**
- PBPK models are flexible
  - Enzyme levels could be changed
  - Altered physiology of liver could be incorporated
- PBPK models can be modified to include patient characteristics → Personalized medicine
- Virtual population could be generated to understand population PK

**Drug specific parameters**

**Pathophysiological parameters (NASH)**
PBPK models: Incorporating liver pathophysiology

Reduction in CYP3A4 activity in NASH

Simcyp PBPK implementation: changing CYP levels

Altered physiology in liver cirrhosis

MATLAB implementation: changing liver physiology

125 mg oral

10 mg IV

Healthy Cirrhosis

Jamwal et al Mol. Pharmacetics 2018, 15, 2621−2632

PBPK models: generation of population PK

Kraus et al, npj Syst Biol Appl 2017

 Implemented in PK SIM, MOBI, and MATLAB
In summary:

• PBPK models are becoming more popular
  - Increased number of regulatory submissions

Certain challenges remain:

• Not entirely ‘physiological’,
  - parameter estimates are based on empirical relationships.
• Most PBPK software are proprietary
  - harder to explore under the hood.
  - Reduced flexibility.
• Independent implementation is difficult
  - requires extensive validation/verification.
What are disease progression models?

Disease progression models could be used for:
- Stratification
  - Age/demographics/gender etc
- Population selection
  - Which stage of the disease?
- Coming up with the enrichment criteria
- Can be combined with dropout models and drug effect models to generate a clinical trial simulator.
Previous learnings: disease progression models as foundation of clinical trial simulators

**Need**
- Neurodegenerative diseases like Parkinson’s Disease (PD) and Alzheimer’s Disease (AD) have seen many failed clinical trials for variety of reasons
- Can clinical trial design be optimized?

**Action**
- Integrated data from several clinical trials to develop clinical trial simulators (CTS)

**Outcome**
- Mild to moderate AD clinical trial simulator: used by sponsors to optimize registration trials
- Early motor Parkinson’s Disease identification uses a DAT imaging biomarker to stratify population
- Predementia model (incorporates left hippocampal volume) - received letter of support from the EMA
How the tool was developed?

\[ \mu_{TMS,ij}(t_{ij}) = (f_{b1}(X) + a_{b1} + a_{b1ij}) + (f_{r}(X) + a_{r} + a_{r,ij})t_{ij} + \varepsilon_{TMS,ij} \]

\[ P(Y_{TFC,ij} = k) = P(\tau_{k-1} < Y^* < \tau_k|X) \]

\[ Y^* = X\beta + Za + \epsilon \]

\[ Y_{TFC} = \begin{cases} 6, & Y^* \leq \tau_1 \\ 7, & \tau_1 < Y^* \leq \tau_2 \\ \vdots \\ 12, & \tau_7 < Y^* \leq \tau_8 \\ 13, & \tau_8 \leq Y^* \end{cases} \]
Example of a CTS and its features

Graphical and tabular output of results, including power estimates and confidence interval of power

Selection of patient population characteristics (demographics, biomarker values, etc.)

Selection of trial design characteristics (parallel design, delayed start, duration, etc.)

Adjustment of simulation parameters (number of trial simulations, desired power, etc.)

Graphical and tabular output of results, including power estimates and confidence interval of power
What would we need to make a CTS for NASH?

Longitudinal observational & clinical trial data
What would we need to make a CTS for NASH?

DCA: Data Contribution agreements are legal agreements
- Allow data sharing
- Companies/Sponsors are in full control of how their data will be accessed
In summary:

Clinical trial simulators/Disease progression models:
- Can optimize clinical trial design
- Clinically relevant biomarkers can enter the model either as covariates or endpoints (if linked to a clinically relevant outcome measure)

Extensive ‘patient level’ data is required:
- Formal pre-competitive collaboration has shown to facilitate data sharing
  - Data contribution agreements gives full control to contributors on the access of their data

Questions for NASH/NAFLD drug development
- Is there industry support for precompetitive engagement?
- What are the existing datasets that could support quantitative solutions for NASH drug development
Conclusion

• Different tools for different contexts
  - PBPK models could help with dose determination
  - CTS tools could help with optimizing clinical trial design

• Data sharing could help development of tools to address clinical design question

• Promote open science
  - Easier/faster to develop tools
Session 4: Panel Discussion

Clinical Trial Design and Endpoint Selection—Clinical Pharmacology Approaches to Optimizing the Safety and Efficacy of Therapies for NASH and Cholestatic Liver Diseases
Timing and Design of Hepatic Impairment Study for Drug Development for NASH

Dilara Jappar, Ph.D.
Gastroenterology and Hepatology Products Team
Division of Inflammation and Immune Pharmacology
Office of Clinical Pharmacology
Disclaimer

The views and opinions expressed here are my own and do not represent official guidance from the FDA
General Timing of Clinical Trials

Phase 1
- SAD, MAD

Phase 2
- POC
- Dose Finding

Phase 3
- Safety & Efficacy
- NDA Submission

- ADME
- DDI
- Food Effect

- Hepatic Impairment
- Renal Impairment
- TQT
Recommended Timing of Clinical Trials in NASH Drug Development

Phase 1
SAD, MAD

Phase 2
POC
Dose Finding

Phase 3
Safety & Efficacy

NDA Submission

• ADME
• Hepatic Impairment
• Renal Impairment
• DDI
• Food

TQT

Patients with liver diseases:
• can have concurrent HI and RI
• often have comorbidities that require medications
Design of Hepatic Impairment Study

• Population:
  – Etiology of Cirrhosis: mostly alcoholic, viral hepatitis
  • PK change due to cholestatic cirrhosis may be underestimated in cirrhosis due to other etiologies

• Dose: Single vs. Multiple
  – A multiple-dose is desirable when the drug or an active metabolite have nonlinear or time-dependent PK
QSP/QST Modeling Support for NASH Drug Development

December 9, 2019

Scott Q. Siler, Chief Scientific Officer
DILIsym Services Division, Simulations Plus

*DILIsym®, NAFLDsym®, MITOsym®, ADMET Predictor®, GastroPlus® and SimPops® are registered trademarks, and SimCohorts™, IPFsym™, and RENAsym™ are trademarks, of DILIsym Services Inc. and/or SLP for computer modeling software and for consulting services.
Quantitative Systems Pharmacology (QSP) Supports Clinical Development by Emphasizing Mechanistic Understanding of Pathophysiology and Treatment

- The complex, interconnected pathophysiology of many diseases poses challenges to developing effective treatments
- QSP models, such as NAFLDsym, help enhance the understanding of the disease pathophysiology and its treatment
  - Reduce knowledge gaps
  - Ability to predict response to combination treatments
- QSP models provide the ability to predict responses to treatments while accounting for inter-patient variability as well as mechanistic feedback loops
- QSP models can provide ability to predict disease progression
- QSP model validation adhering to similar framework as PBPK modeling (Kuemmel 2019)

There is an expectation that the use of QSP will reduce the cost of R&D and the risks associated with uncertainties and gaps in our knowledge while bringing new therapies to patients.
Mathematical Models Mechanistically Represent Disease Pathophysiology

Pathophysiology can be mathematically described to varying degrees of complexity

Mechanistic PK-PD

QSP

Complexity of pathophysiology invokes development of QSP model of NAFLD/NASH

Mager and Jusko 2008

Rieger and Musante 2016
QSP/QST Models Predict Efficacy via the Intersection Between Pathophysiology Mechanisms, Compound Exposure, and PD

Mechanistic representation of underlying biochemistry describing pathophysiology is foundation of QSP/QST models

Predicted compound concentrations at site of target often require PBPK models

PD effects and interactions with underlying biochemistry unique for most compounds; QSP model needs to be flexible to provide ability to represent these effects
Pathophysiologic Variability Represented in NAFLD/NASH SimPops

- SimPops are population samples with variability across key areas of NAFLD/NASH pathophysiology
- Multiple parameters are varied to produce diverse possible simulated patients
- Simulated patients are compared with a multitude of clinical data to validate pathophysiology
- Response data (e.g., dietary intervention) have been used to validate the SimPops

Clinical Data and Simulation Results

Variables Used to Construct SimPops

- Body weight
- Adipose FA release
- De novo lipogenesis
- RNS-ROS clearance
- Mitochondria function
- VLDL-TG secretion rates
- Plasma glucose
- Hepatic glucose uptake
- Plasma TG clearance
- Apoptotic sensitivity to RNS-ROS
- Necrotic sensitivity to ATP reductions
- Hepatocyte regeneration
- Extracellular vesicle release
- Inflammatory mediator production
- Stellate cell activation
- Collagen synthesis and degradation

NASH SimPops Includes Progression of Disease due to Weight Gain

- Change in body weight has been reported to influence NASH disease progression (Wong 2010)
  - NASH patients studied longitudinally, including liver biopsies and histology
  - Based on histologic scoring
  - Patients with increased NAS had increased BMI
  - 3 year time interval between biopsies

- Simulated weight gain over 20 years in SimCohorts recapitulated NASH disease progression (Akpinar Singh 2019)
  - 20-30% increase in body weight via increased food intake (McTigue 2002)
  - Increase in food intake and weight gain elicit increases in steatosis
  - Increased NAS score over time due to lipotoxicity and increased hepatocellular apoptosis and hepatic inflammation
  - Release of pro-fibrotic mediators also drives increased fibrosis

- Enables prediction of disease status over time
  - Prediction of treatment vs. placebo in phase III clinical trials

Table 4  Factors associated with increased non-alcoholic fatty liver disease (NAFLD) activity score from baseline to month 26

<table>
<thead>
<tr>
<th>Factors</th>
<th>Increased NAFLD activity score</th>
<th>Static or decreased NAFLD activity score</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>26</td>
<td>26</td>
<td>0.66</td>
</tr>
<tr>
<td>Age (years)</td>
<td>45±9</td>
<td>44±9</td>
<td>0.86</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>16 (62)</td>
<td>18 (69)</td>
<td>0.58</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>15 (69)</td>
<td>11 (42)</td>
<td>0.27</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>12 (46)</td>
<td>14 (54)</td>
<td>0.50</td>
</tr>
<tr>
<td>Metabolic syndrome, n (%)</td>
<td>18 (66)</td>
<td>17 (66)</td>
<td>0.77</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.4±4.1</td>
<td>27.4±4.3</td>
<td>0.99</td>
</tr>
<tr>
<td>Change in body mass index (kg/m²)</td>
<td>0.6±1.6</td>
<td>-0.8±1.7</td>
<td>0.003</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>92.9±11.1</td>
<td>92.5±6.7</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Wong 2010

Akpinar Singh 2019
The complex, interconnected pathophysiology of many diseases poses challenges to developing effective treatments.

QSP models, such as NAFLDsym, help enhance the understanding of the disease pathophysiology and its treatment:
- Reduce knowledge gaps
- Ability to predict response to combination treatments

QSP models provide the ability to predict responses to treatments while accounting for inter-patient variability as well as mechanistic feedback loops.

QSP models can provide ability to predict disease progression.

QSP model validation adhering to similar framework as PBPK modeling (Kuemmel 2019).
DILIsym Software Overview

- **Multiple species:** human, rat, mouse, and dog
  - Population variability
- **The three primary acinar zones of liver represented**
- **Essential cellular processes** represented to multiple scales in interacting sub-models
- **Over 70 detailed representations of optimization or validation compounds with 80% success**
- **Single and combination drug therapies**
DILIsym Services, Inc.

“Our vision is safer, effective, more affordable medicines for patients through modeling and simulation.”

- DILIsym Services, Inc. offers comprehensive program services:
  - DILIsym software licensing, training, development (DILI-sim Initiative)
  - NAFLDsym software licensing, training, development
  - DILIsym and NAFLDsym simulation consulting projects
  - Consulting and data interpretation; *in vitro* assay experimental design and management
  - RENAsym, RADAym, and IPFsym software in development
Where are you in the research process?

Save resources and get to market faster with our solutions.
Session 5: Synthesis Discussion and Next Steps

4:10 pm – 4:50 pm