HEPAGENE

Discovery, Development and Delivery of Innovative Medicines For Metabolic Liver Diseases

August 2024

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Investment Highlights

- **U.S.-based clinical-stage biotechnology company focused on liver disease and GI indications**
  - **Complementary and proprietary pipeline to deliver next-generation novel therapies for MASH/IBD/PBC/PSC**
    - HPG1860 Phase 2a accomplished FXR agonist with multiple indication expansions in MASH/IBD/PBC/PSC
    - HPG7233 Phase 1 ready THR-β for MASH/hyperlipidemia
  - **Combination approach represented by HPG7233 and HPG1860 is potentially best-in-class for MASH/MASLD**
    - First generation of MASH drugs have limitations with modest efficacy (resmetirom) and safety issues (OCA)
    - Current KOL consensus suggests that combination therapy with complementary mechanisms is needed
  - **Strong potential market demand for MASH treatment projected to reach USD $15B+ in 2030**
  - **Established proprietary GalNAc-siRNA drug delivery platform for precision MASH treatment partnering-ready**
- **Global IP rights, patents granted in major countries out to 2043**

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Pipeline Overview

Asset	Target	Indication	Preclinical	Phase 1	Phase 2	Upcoming Milestones
MASH/Metabolic						
HPG1860	FXR	MASH				Ph 2a Complete
		IBD				Ph 2 IND Q4/24; Ph 2 Readout Q4/25
		PBC/PSC				Potential initiation pending funding
HPG7233	THR-β	MASH Hyperlipidemia				Ph 1 Readout Q2/25
HPG7233+HPG1860 Combo		MASH				Ph 2a Initiation Q2/25; Ph 2a Readout Q1/26
HPG5119	GLP-1R (Oral)	MASH/Obesity				IND Submission Q3/25
Oncology						
HPG3466	IAP	Solid Tumor/HBV				Available for licensing
Proprietary GalNAc Delivery Platform						

Novel siRNA delivery platform established in house to enable precision MASH development or licensing to 3rd parties

Hepagene Owns the Elements for Strong Combination Therapy

Developing combination therapy with two clinical-stage lead assets to improve efficacy and safety over most recently FDA-reviewed/approved modalities

HPG1860 FXR Agonist

- ✓ Significant liver fat content (LFC) reduction and highly differentiated pruritus and LDL-C profile in patients

OCA: Modest efficacy with safety concerns

- **~12.8%** ≥1 stage improvement in fibrosis without worsening of MASH
- Safety concerns: pruritus, liver injury and cardiovascular risk

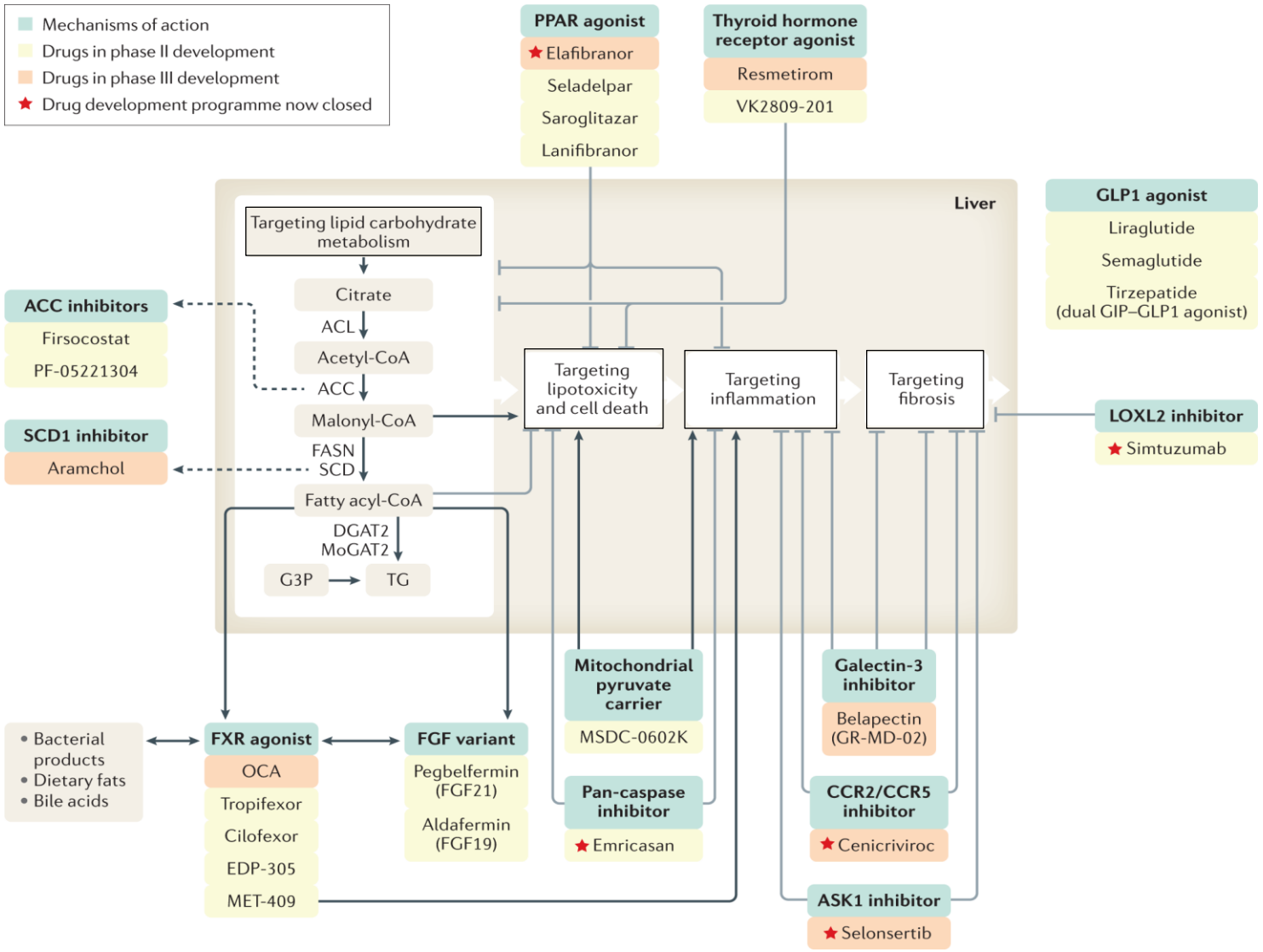
HPG7233 THR-β Agonist

- ✓ Improved potency and liver selectivity based on existing published data

Resmetirom (Madrigal): Modest efficacy with benign safety concerns

- **~12%** ≥1 stage improvement in fibrosis without worsening of MASH
- **~20%** MASH resolution without worsening of fibrosis stage
- Safety concerns: diarrhea (34%) and nausea (22%)

Mechanism of Action of Pharmacologic Treatments for MASH



Nat Rev Gastroenterol Hepatol 18, 373–392 (2021). https://doi.org/10.1038/s41575-020-00408-y

HPG1860: A Potential Best-in-Class FXR Agonist

HPG1860 is a Potential Best-in-Class FXR Agonist

Potency

- EC_{50} at 16nm in cellular assay

Selectivity

- Highly selective against TGR5 & 13 other nuclear receptors

Safety

- Excellent GLP-Tox profiles (13 weeks)
- Low DDI potential
- Differentiated pruritus and LDL-C profile in patients (12 weeks)

ADME

- Favorable PK profiles with liver enrichment
- Simple metabolite profile without active metabolites

Efficacy

- Significant MASH improvement (animal model) and LFC reduction in patients for 12 weeks

CMC

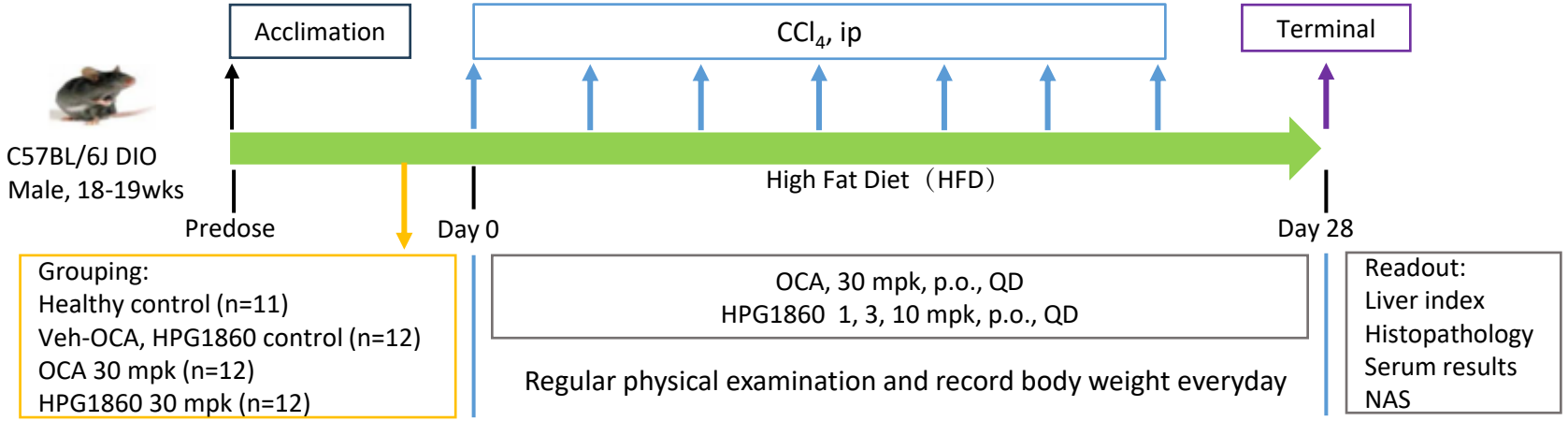
- Efficient and economic CMC process (up to 5kg)
- Stable for DS (48M, RT) and DP (36M, RT)

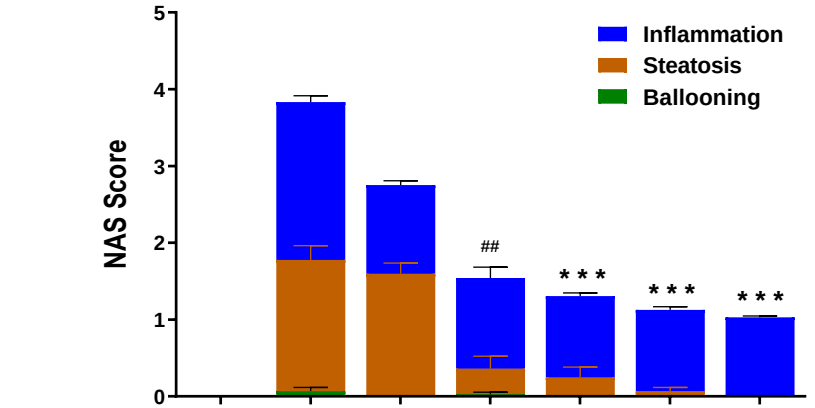
FXR Agonists in Clinical Development: Global Competitor Landscape

Company	Compound	Indication	Status
Novartis	tropifexor	MASH	Phase 2b
Gilead	cilofexor	MASH	Phase 2 Combo
Hepagene	HPG1860	MASH	Phase 2a
ENYO	vonafexor	Alport syndrome and CKD	Phase 2a
Organovo	FXR314	IBD	Phase 2/3
Intercept	obeticholic acid (OCA)	MASH	NDA Rejected

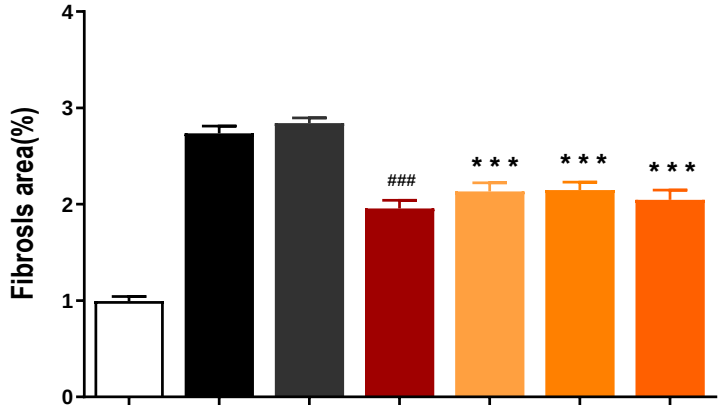
HPG1860: *In Vivo* Efficacy in HFD+CCl_4 MASH Model

HPG1860 improves NAS score and liver fibrosis in HFD+CCl_4 induced MASH mice





HFD+CCl4	-	+	+	+	+	+	+
Vehicle	Veh-1860	Veh-1860	Veh-OCA	-	-	-	-
INT747 (OCA)	-	-	-	30 mpk	-	-	-
HPG1860	-	-	-	-	1 mpk	3 mpk	10 mpk



HFD+CCl4	-	+	+	+	+	+	+
Vehicle	Veh-1860	Veh-1860	Veh-OCA	-	-	-	-
INT747 (OCA)	-	-	-	30 mpk	-	-	-
HPG1860	-	-	-	-	1 mpk	3 mpk	10 mpk

p≤0.01
p≤0.001 vs. MASH control (Veh-OCA)
*** p≤0.001 vs. MASH Control (Veh-1860)

- HPG1860 at 1 mg/kg displays better or equal efficacy than OCA at 30 mg/kg in MASH model

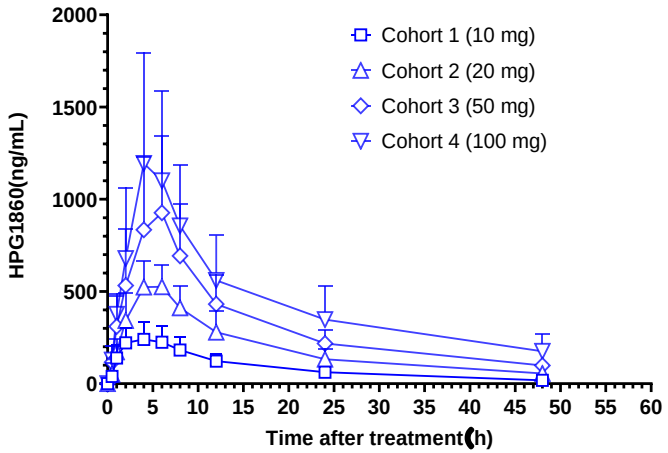
HPG1860 FIH USA Phase 1: Good Safety Profile and Strong Target Engagement

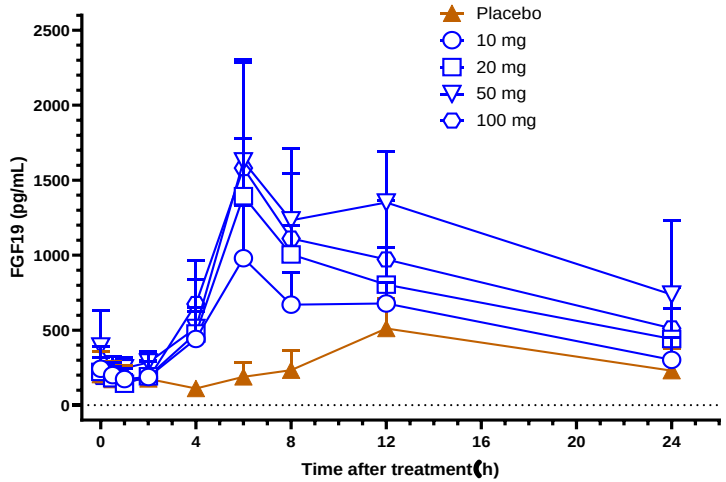
SAD N=32

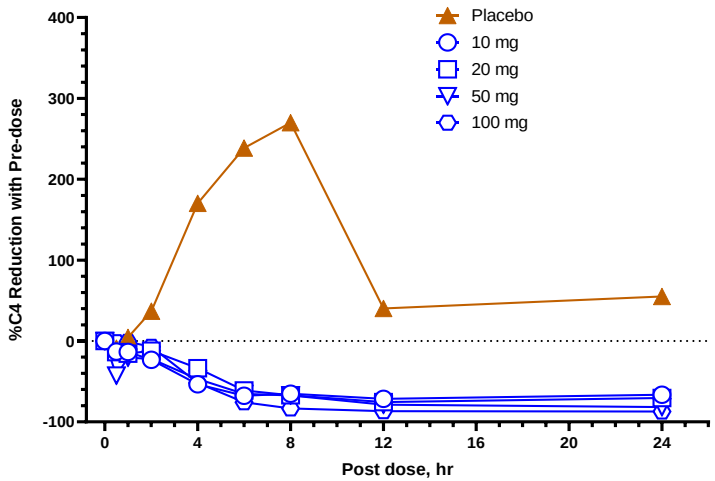
- Cohort 1: 10 mg n=8
- Cohort 2: 20 mg/Food Effect n=8
- Cohort 3: 50 mg n=8
- Cohort 4: 100 mg n=8

MAD N=24

- Cohort 1: 5 mg QD X 14 Day n=8
- Cohort 2: 10 mg QD X 14 Day n=8
- Cohort 3: 20 mg QD X 14 Day n=8





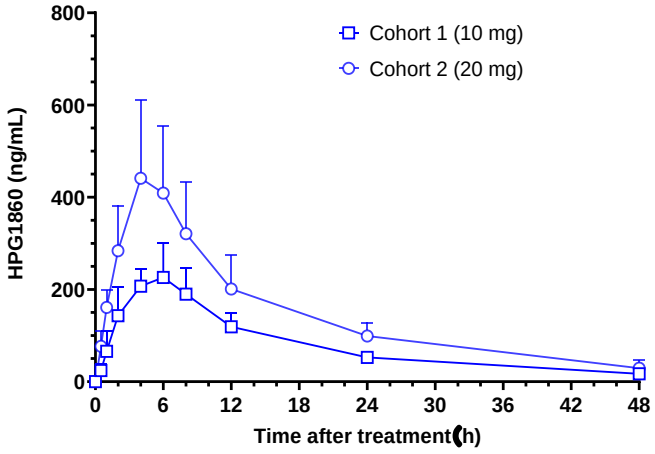


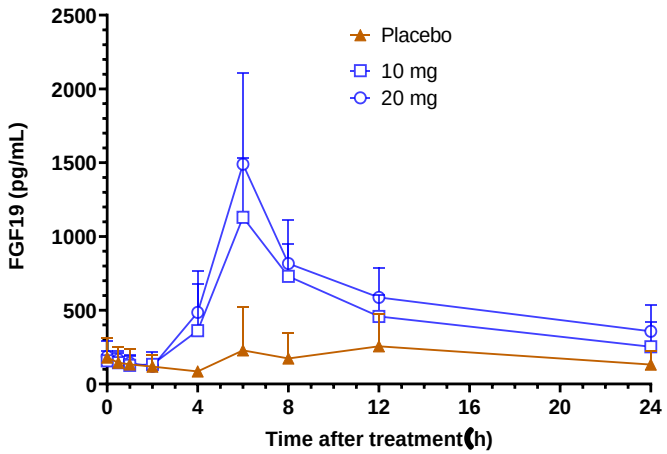
- Clinically meaningful pruritus was only observed at highest MAD dose (20 mg/day) with no significant LDL elevation
- Benign safety profile with no SAE during the Phase 1 trial
- Strong target engagement with sustained C4 reduction and FGF19 activation
- Dose-dependent PK exposure profile suitable for once daily administration

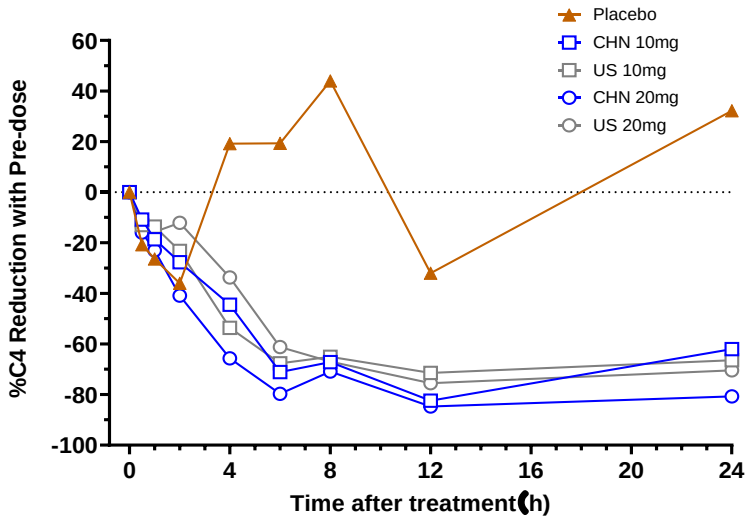
HPG1860 China Phase 1: Consistent with US Phase 1 Observations

SAD N=16
- Cohort 1: 10 mg n=8
- Cohort 2: 20 mg n=8

MAD N=8
- Cohort 1: 5 mg QD X 14 Day



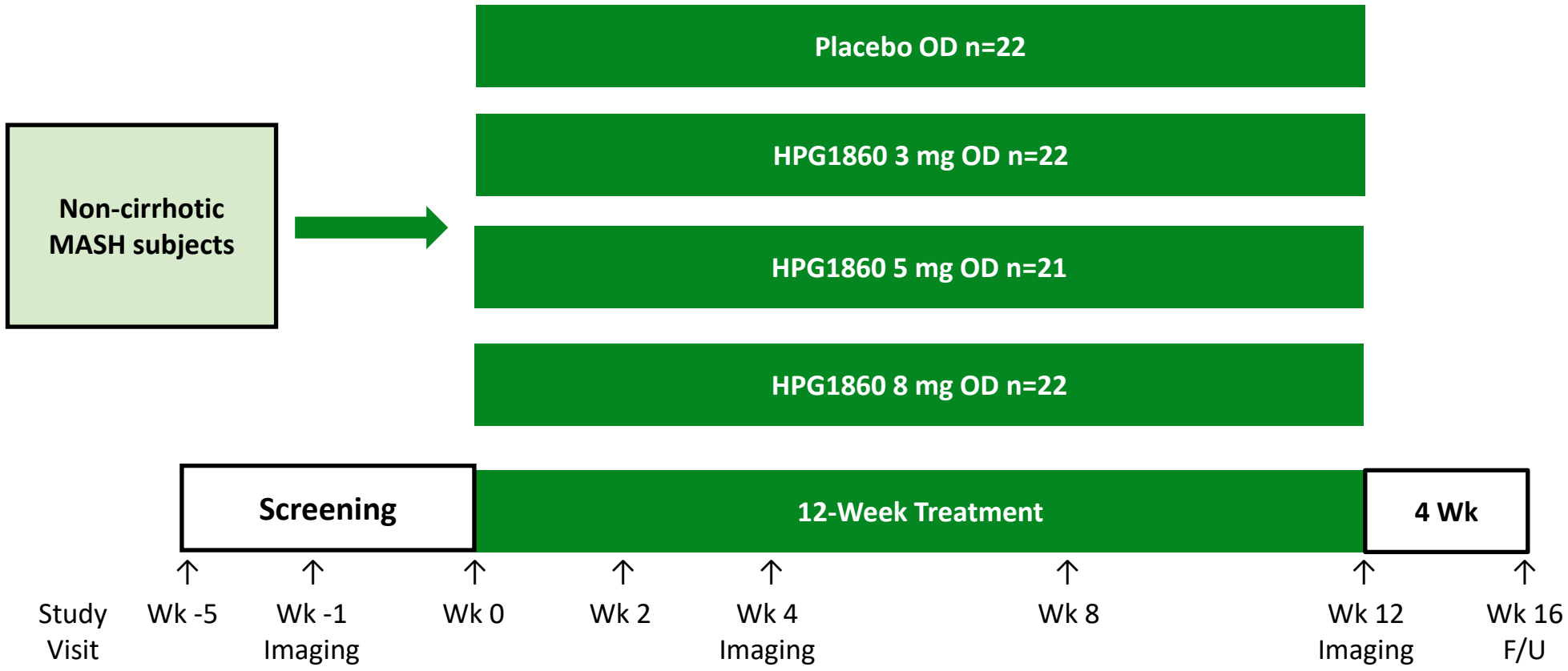




- No pruritus or significant trend of LDL elevation was observed
- No treatment related AE was observed in the study
- Strong target engagement with sustained C4 reduction and FGF19 activation
- Dose-dependent PK exposure profile suitable for once daily administration

Phase 2a RISE Study: Evaluate the Efficacy and Safety in Subjects with MASH

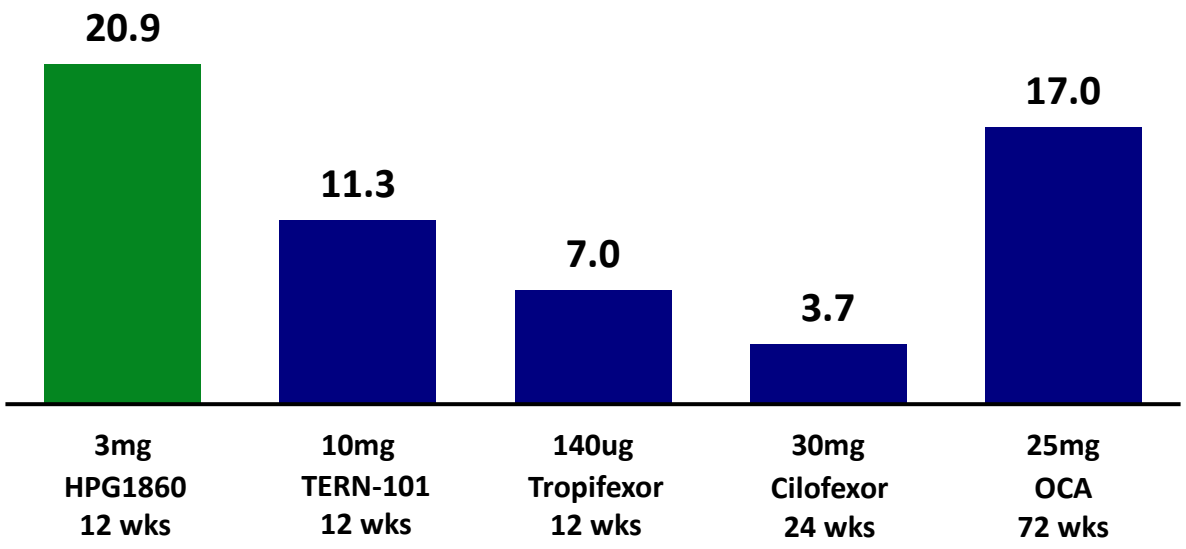
Primary Outcome Measures: Safety and tolerability; MRI-PDFF at Week 12; Enrolled 87 subjects



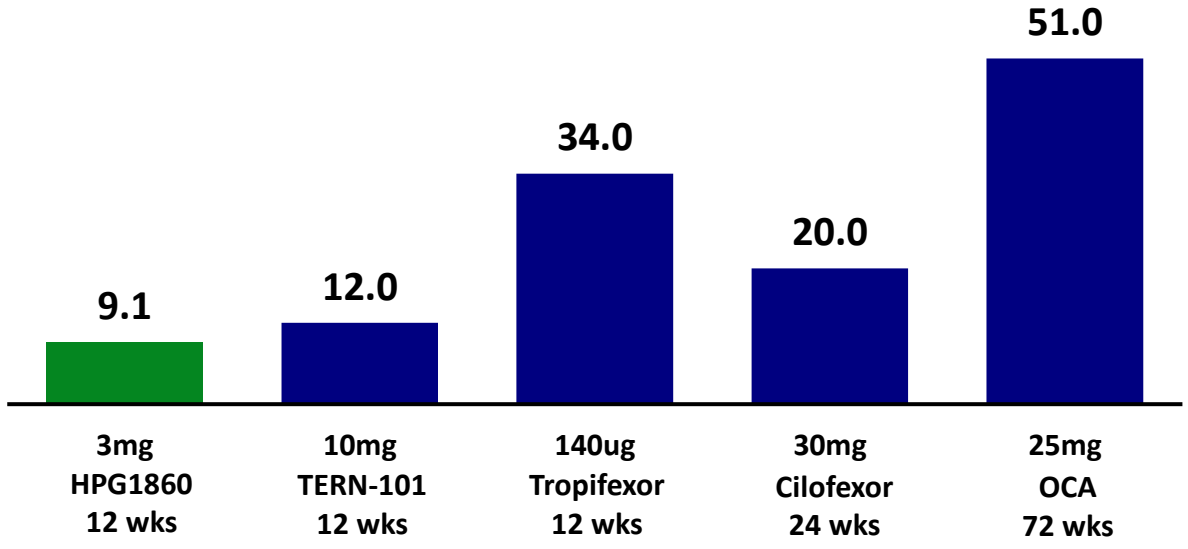
Phase 2a RISE Study: Top-line Safety and Efficacy Data

- Generally well-tolerated and most AEs were mild
- Significantly reduced LFC over 12 weeks in patients with MASH at 3 mg (p=0.004) and 8 mg (p<0.001)
- Demonstrated a highly differentiated pruritus and LDL-C profile, providing favorable risk-benefit potential
- Dose-dependent reduction in ALT in patients with elevated ALT at Week 12

MRI-PDFF Relative LFC Reduction % (Placebo Corrected)



Pruritus % (Absolute)



*All comparative data is relative to previously published studies, not head-to-head
LFC: Liver Fat Content through MRI-PDFF

HPG7233: A Potential Best-in-Class THR-β Agonist, Phase 1 Ready in US

HPG7233 is a Potential Best-in-Class THR-β Agonist

Potency

- More potent resmetirom

ADME

- Superior PK profile with liver enrichment and low extrahepatic distribution

Selectivity

- Selective activation of THR-β over THR-α, better than VK2809

Safety

- Excellent GLP-Tox profiles, no adverse findings related to THR-α isoform

Efficacy

- Significant MASH improvement and lipid-lowering effect in mouse MASH model

CMC

- Efficient and economic CMC process

THR-β Agonists in Clinical Development: Global Competitor Landscape

Company	Compound	Indication	Status
Madrigal	resmetirom	MASH	Approved in US
Viking	VK2809	MASH	Phase 2b
Terns	TERN-501	MASH	Phase 2a
Aligos	ALG 055009	MASH	Phase 2a
Hepagene	HPG7233	MASH	IND Accepted in US

HPG7233: *In Vitro* Advantages

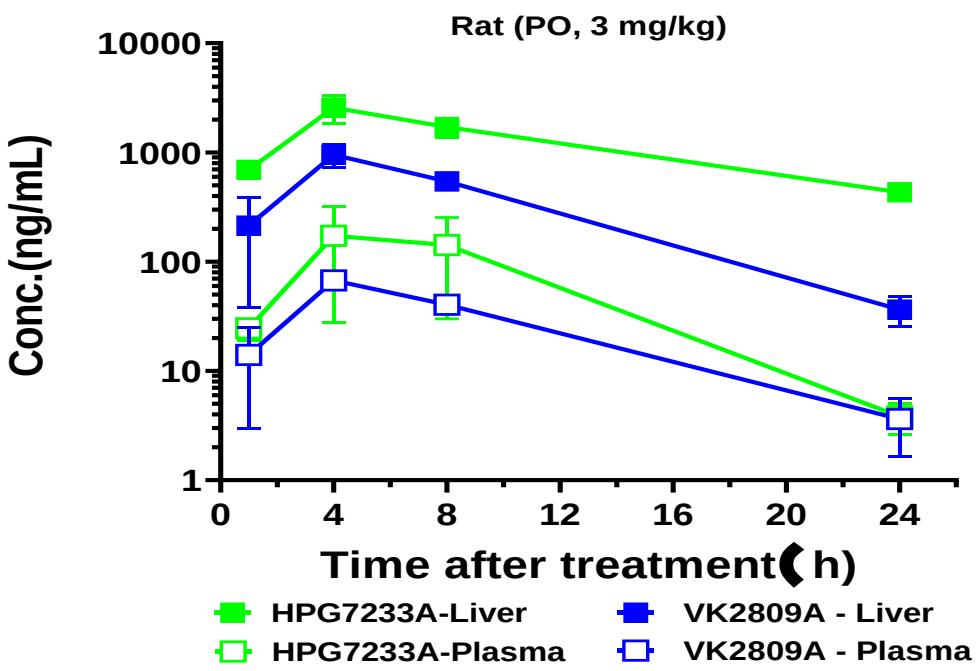
Greater potency and higher selectivity			
Compound	**Binding (EC_{50}, μM)**		**Relative Selectivity (β/α)***
	THRα	**THRβ**	**Fold**
HPG7233A (Active)	**0.041**	**0.012**	**7.0**
VK2809A (Active)	0.051	0.033	2.9
resmetirom	3.74**	0.21**	35**
T3	0.0002	0.0004	1.0

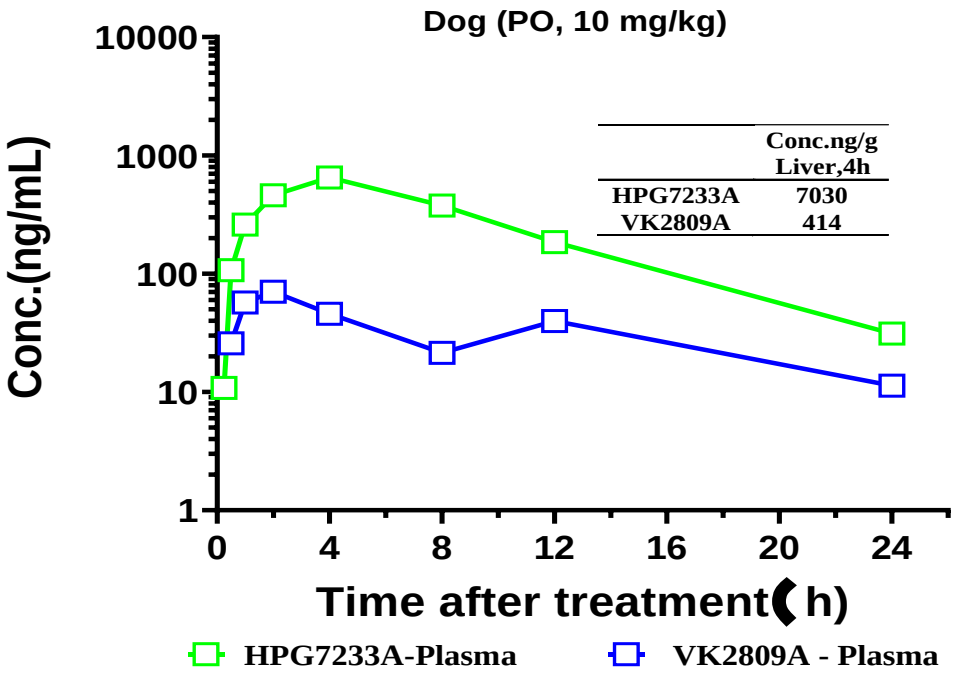
- ~17-fold higher potency over resmetirom with respect to THR-β
- Expect better efficacy and much lower clinical dose than resmetirom
- A higher selectivity by ~2-3-fold and a greater potency with ~2-3-fold of VK2809A

*: Selectivity calculation is based on the ratio of THRα to THRβ potency normalized by T3
**: Public data disclosed by Madrigal

HPG7233: *In Vivo* Advantages

Favorable pharmacokinetic profile

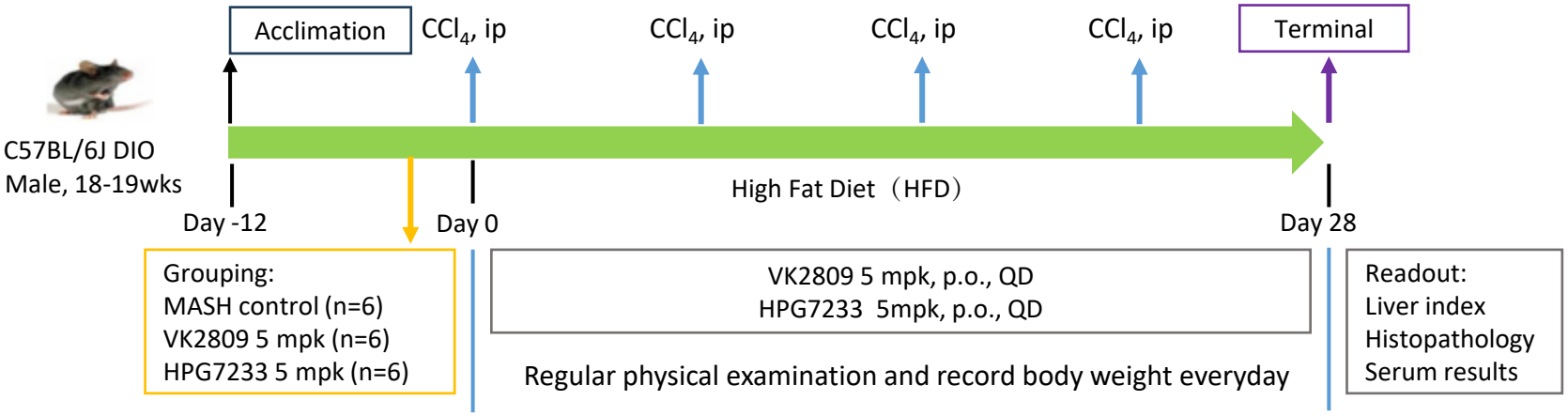


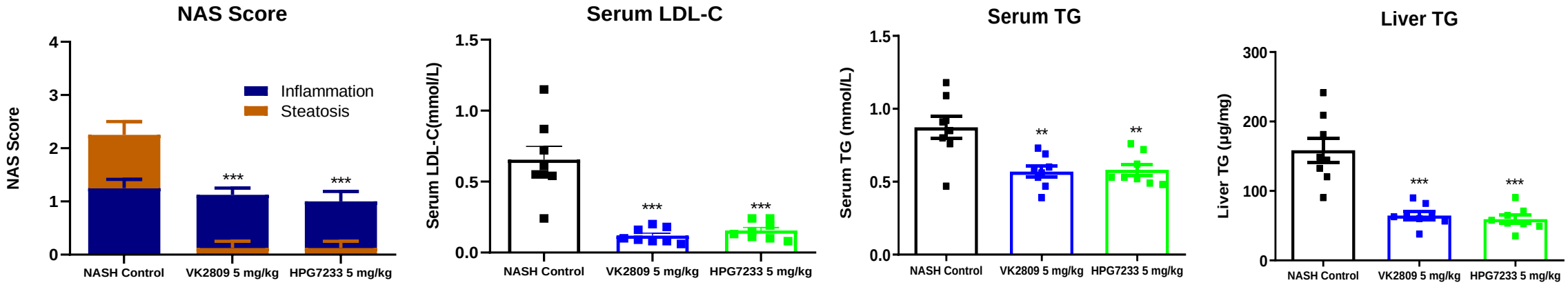


- Mainly distributes to the liver, and little to no penetration into other tissues
- Liver targeting effect of HPG7233 is not via hepatocyte transporter, differentiated from resmetirom, therefore expect lower DDI risk
- A greater liver enrichment with ~2-3-fold of VK2809A

HPG7233: *In Vivo* Efficacy Data in HFD+CCl4 Induced DIO Mouse MASH Model

HPG7233 significantly improves NAS score and decreases serum LDL-C, serum TG and liver TG level

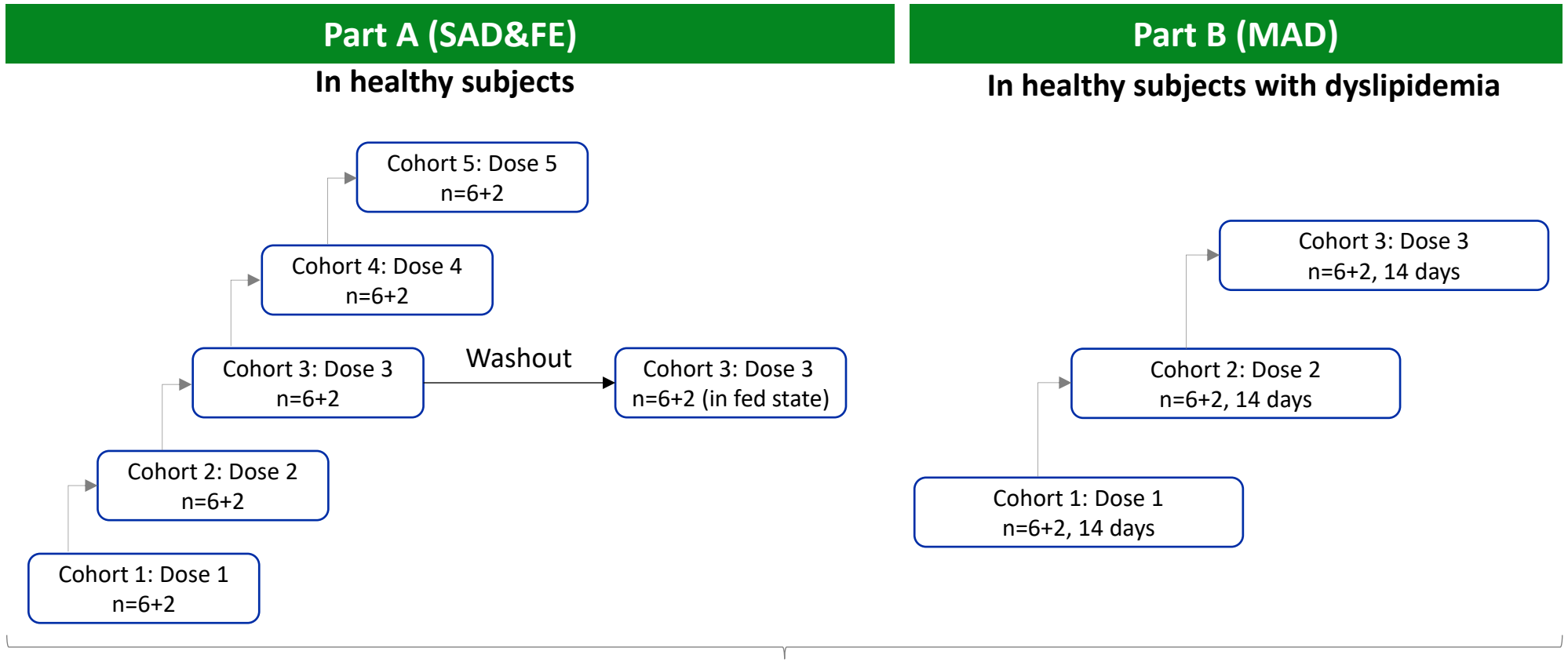




- HPG7233 significantly reduced serum LDL-C, serum and liver TG level
- HPG7233 significantly reduced NAS at 5 mg/kg in mice

** p≤0.01 ***p≤0.001 vs. MASH Control

HPG7233: Phase 1 (SAD & MAD) US



Evaluate safety and tolerability; characterize PK and PD, and food effect on drug exposure

Potential best-in-class THR-β agonist with improved potency and safety profile (GI)

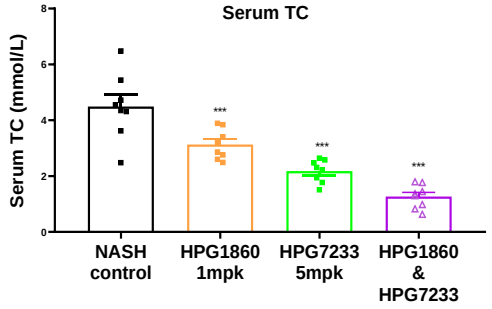
HPG1860 and HPG7233 Patent Status Overview

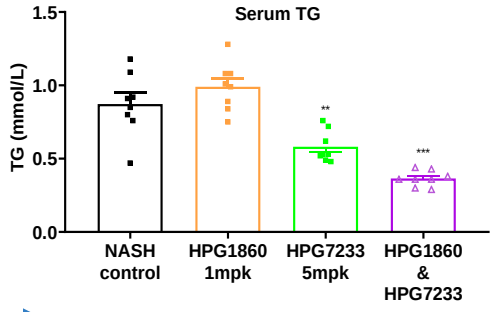
Compound	Status	Expires
FXR HPG1860 (Composition of Matters)	Granted in U.S., EP, Japan, China, South Korea, Australia, HK	2037
FXR HPG1860 (Solid Form)	National Phase Entry	2043
THR Beta HPG7233 (Composition of Matters)	Filed in U.S., granted in UK, China National phase in other countries	2040

Potentially Synergistic Effect of Combo Therapy

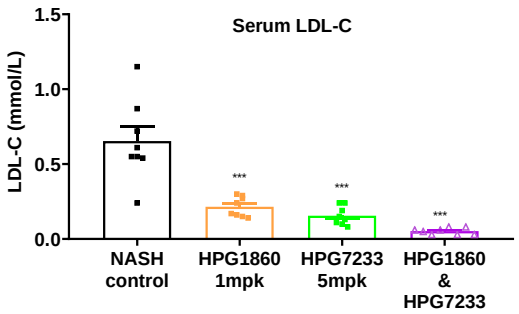
FXR Agonist

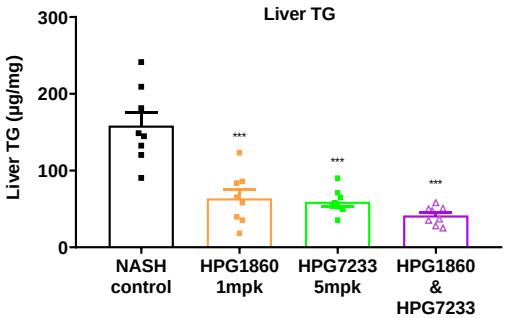
- ✓ Reduce Bile Acid Synthesis
- ✓ Diminish Hepatic Lipogenesis
- ✓ Inhibit Inflammation and Fibrosis





POTENTIAL SYNERGY EFFECT OF COMBO THERAPY



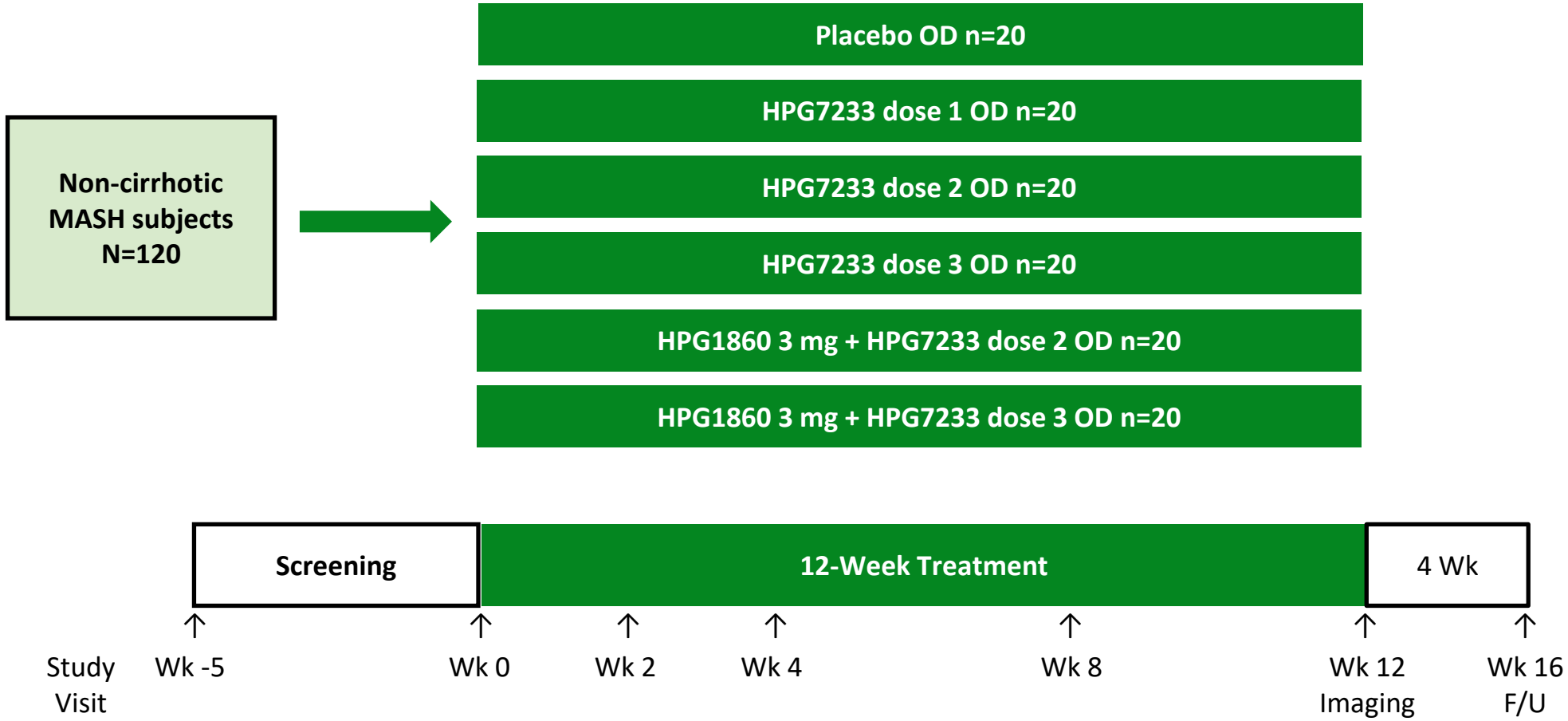


THR-β Agonist

- ✓ Stimulate Mitochondrial Biogenesis
- ✓ Promote Fatty Acid Decomposition
- ✓ Reduce Liver Fat Content and LDL

- Serum TC, TG and LDL-C are more reduced in combo treatment group, with 71.8%, 58.2% and 92.0% reduction, respectively
- Liver TG reduction in combo is better than mono treatment with 73.8% reduction in combo treatment

HPG7233 Accelerated Approach: Phase 2a Combined Mono- and Combo-Study



- Primary Endpoints: Safety, tolerability
- Secondary Endpoints: Primary efficacy (CFB of liver fat content at week 12), plasma biomarkers

Delivery Platform

GalNAc, Novelty and Creativity

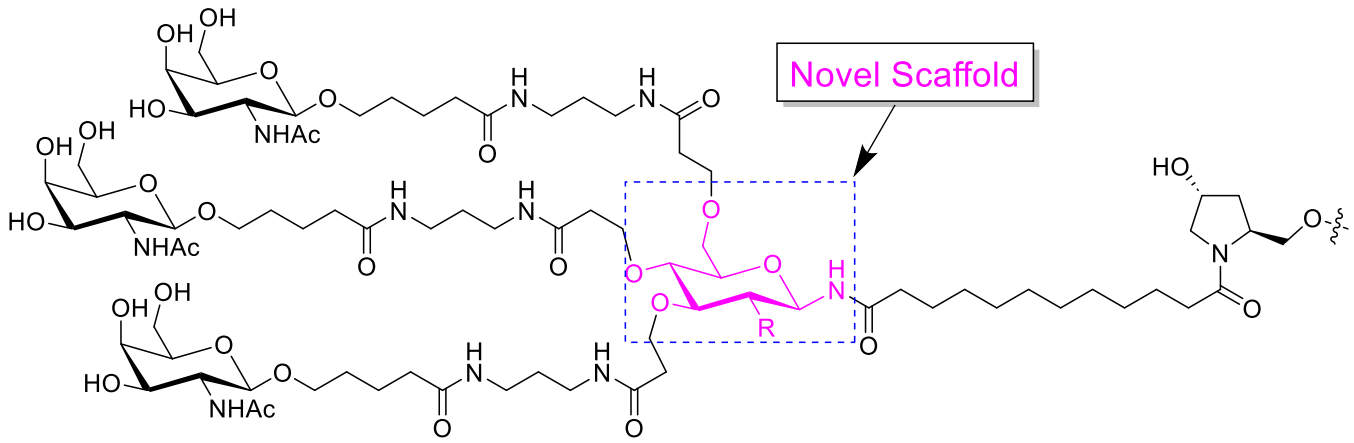
Discovery

GalNAc: Platform Ready for MASH Development and/or Licensing

Design strategy of Hepagene GalNAc platform: Endogenic component as branching group

Platform Features:

- Endogenic components as branching group
- Highly efficient synthesis
- Novelty and creativity (positive FTO report from Foley)
- Global IP rights (WO2023011597A1, National Phase)



Commercial Outlook and Application:

- Developing RNAi drugs for undruggable and existing druggable liver targets
- Licensing IP or usage rights to external partners to accelerate innovation development

Upcoming Catalysts

Event	Program	Timing
Initiation of Phase 1 Trial	HPG7233 for MASH	Q4/2024
IND Phase 2 IBD	HPG1860 FXR for IBD (non-core)	Q4/2024
Phase 1 Data Readout	HPG7233 THR for MASH	Q2/2025
Phase 2a Initiation (Mono & Combo)	HPG7233 THR for MASH	Q2/2025
IND Submission	HPG5119 GLP for MASH	Q3/2025
Phase 2 Data Readout	HPG1860 FXR for IBD (non-core)	Q4/2025
Phase 2a Data Readout	HPG1860/HPG7233 Combo	Q1/2026

Investment Summary

- **U.S.-based clinical-stage biotechnology company focused on liver disease and GI indications**
  - **Complementary and proprietary pipeline to deliver next-generation novel therapies for MASH/IBD/PBC/PSC**
    - HPG1860 Phase 2a accomplished FXR agonist with multiple indication expansions in MASH/IBD/PBC/PSC
    - HPG7233 Phase 1 ready THR-β for MASH/hyperlipidemia
  - **Combination approach represented by HPG7233 and HPG1860 is potentially best-in-class for MASH/MASLD**
    - First generation of MASH drugs have limitations with modest efficacy (resmetirom) and safety issues (OCA)
    - Current KOL consensus suggests that combination therapy with complementary mechanisms is needed
  - **Strong potential market demand for MASH treatment projected to reach USD $15B+ in 2030**
  - **Established proprietary GalNAc-siRNA drug delivery platform for precision MASH treatment partnering-ready**
- **Global IP rights, patents granted in major countries out to 2042**

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THANK YOU