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### Aligos Development Portfolio Multiple Milestones/Data Readouts Anticipated in 2023

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All timelines are approximate and subject to change based on enrollment and operational considerations. Presentations at conferences are subject to abstract approvals.

AASLD = American Association for the Study of Liver Diseases; APASL = Asian Pacific Association for the Study of the Liver; CAM-E = capsid assembly modulator (empty); CHB = chronic hepatitis B; Covid-19 = coronavirus disease of 2019 (SARS-CoV-2); CTA = clinical trial application; EASL = European Association for the Study of the Liver; GLP = good laboratory practice; HV = healthy volunteers; MAD = multiple ascending doses; MOA = mechanism of action; NASH = nonalcoholic steatohepatitis; PK = Pharmacokinetics; SAD = single ascending doses; siRNA = small interfering ribonucleic acid (RNAi); THR-β = thyroid hormone receptor beta. 2



## NASH

ALG-055009, small molecule THR-β agonist



### **ALG-055009** More Potent and Selective In Vitro than MGL-3196 and VK-2809

### Relative THR- $\alpha$ and THR- $\beta$ Activity in Cell-Based Assays

	EC <sub>50</sub> α (nM)	EC <sub>50</sub> β (nM)	Relative THR- $\beta$ Selectivity ( $\alpha/\beta$ )
Т3	14.2	11.6	1.2
MGL-3196	5927	2366	2.5
VK-2809 parent	366	269	1.4
ALG-055009	191	50	3.8

In vitro, ALG-055009 is 5-47x more potent compared to resmetirom (MGL-3196) and 2-3x more selective for THR-β than VK-2809\*

High  $\beta$  selectivity and potency may improve risk-benefit profile



### ALG-055009 Best In Class Potential vs. 1<sup>st</sup> Generation THR-β Agonists

Parameter		VK-2809	Resmetirom	ALG-055009
	28 day mouse DIO TC, LDL lowering	28%	28%	Up to 44%
Efficacy	Percent of patients with ≥30% change from baseline in MRI-PDFF (Ph2)	76%-100%	60%	High Expected
	BCRP, OATP substrate	?	Yes	No (NTCP)
	AUC/Cmax interindividual variability	Limited	High	Low
	PK linearity	Yes	No	Yes
Safety	β Selectivity (α/β)*	1.4	2.5	3.8
	Potential cardiosafety (i.e., $\alpha$ ) liability	Yes	Νο	No
	Reactive metabolites in vitro* (GSH adduct) / Risk for DILI	Yes	No	Νο
	Possible Prodrug liability	Yes**	Νο	No
DDI	CYP inhibition >50% @10 μM*	>60% for 5 isozymes >90% for 2C9 & 2C19 CYP3A4-dependent activation	91% for 2C8	Νο

#### Potential for enhanced efficacy/PK vs. resmetirom and enhanced efficacy/safety vs. VK-2809

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Abbreviations: AUC = area under the curve, BRCP = breast cancer resistance protein, Cmax = maximum concentration, CYP = cytochrome P450, DILI = drug induced liver injury, DIO = diet induced obesity; GSH = glutathione, LDL = low density lipoprotein, MRI-PDFF = magnetic resonance imaging – proton density fat fraction; OATP = organic anion transporting polypeptide, TC = total cholesterol, \* ALG-055009 clinical data from Charfi et al., EASL 2022. Competitor data derived from in-house studies.

\*\*Same pro-drug as Pradefovir (pro-drugged adefovir). Pradefovir, but not adefovir, found carcinogenic in mice and rats (http://media.corporate-ir.net/media\_files/IROL/89/89839/PipelineAug07.pdf).

### Study ALG-055009-301 Single Ascending Dose (SAD) PK, Safety Data

- Oral doses evaluated: 0.1, 0.3, 0.9, 2.6, 4.0 mg
- PK
  - Dose proportional, with low variability
  - $t_{1/2} = 20-24$  hours (supports once daily (QD) dosing)
- Safety: well tolerated
  - No serious adverse events (SAEs), premature discontinuations, Grade ≥3 treatment emergent adverse events (TEAEs), or clinical hyper/hypothyroidism



Single (≤ 4 mg) ALG-055009 doses well tolerated with favorable PK properties



# SAD Biomarker Data

- Expected dose related thyromimetic effects observed
  - Increases in Sex Hormone Binding Globulin (SHBG; target engagement)
  - Decreases in lipids
    - > Triglycerides (TG), LDL, Apolipoprotein-B (Apo-B)
  - Decreases in thyroid hormones
    - > Thyrotropin (TSH), T3, T4

Expected thyromimetic effects observed, including evidence of anti-lipid activity



### Study ALG-055009-301 Multiple Ascending Dose (MAD) PK, Safety Data

- Oral doses evaluated: 0.3, 0.5, 0.6, and 1.0 mg QD x 14 days
- PK: favorable profile (dose-proportional, low variability (≤27%), 2x accumulation)
- Safety: well tolerated, no clinical evidence of hypo or hyperthyroidism
  - No SAEs, discontinuations
  - All TEAEs Grade ≤2
  - No concerning labs, ECGs, vital signs, physical examinations



#### Multiple doses (≤1 mg) well tolerated with favorable PK



### Study ALG-055009-301 MAD Biomarkers – SHBG



Dose proportional increases in SHBG



### Study ALG-055009-301 MAD Biomarkers - Lipids



Dose responsive reductions in LDL cholesterol Similar pattern observed for Apo-B, Triglycerides



### Study ALG-055009-301 MAD Biomarkers – Thyroid Hormones



Dose responsive reduction in free T4 Up to ~20% declines (while remaining in normal range) for doses ≤0.6 mg Greater declines for 1 mg dose Similar pattern observed for other thyroid hormones



# Summary of Phase 1 Data

- PK demonstrates a favorable profile that is differentiated vs. resmetirom
- Safety well tolerated without clinical safety signals
- PD generally dose proportional
  - Increases in SHBG
  - Decreases in thyroid hormones
  - Decreases in LDL, triglycerides, Apo-B

Anti-lipid effects for 0.5-1 mg ALG-055009 similar to resmetirom ALG-055009 doses in the 0.3 to <1 mg range well suited for advancement into Phase 2



### ALG-055009 Favorably Differentiated from Resmetirom

- More uniform exposure may lead to more consistent efficacy and safety across patient populations
- Low risk of drug-drug interactions in a NASH population which often requires polypharmacy
  - ALG-055009 shows no inhibition of any cytochrome P450 or transporters at clinically relevant exposures
- Greater potency leads to similar anti-lipid activity at >80-fold lower doses



### ALG-055009 Next Steps

Complete Last Cohort of Phase 1 (Relative Bioavailability/Food Effect Study)



13 Week GLP Toxicology Studies

Phase 2 Drug Supply



On track to complete Phase 2 enabling activities and file Phase 2 CTA in Q4 2023





## Coronavirus

• ALG-097558 (CoV Protease Inhibitor)



### ALG-097558 Aligos' Potent COVID-19 Protease Inhibitor

- Despite the availability of prophylactic vaccines, a need for therapeutics still exists
  - New variants are continuously emerging
  - Large segments of global population lack access to, or are opposed to, vaccination
  - Especially needed to prevent hospitalization in high-risk groups where standard of care is contraindicated
- Current therapeutics lack sufficient efficacy (molnupiravir, Merck), require ritonavir boosting (nirmatrelvir, Pfizer) or are delivered parenterally (remdesivir, Gilead; mAbs)
- In collaboration with KU Leuven/Rega Institute/CD3, we have identified ALG-097558
  - 7-27 times more potent than nirmatrelvir in both biochemical and cell-based assays
  - Can be dosed orally without the need for ritonavir
  - Broadly active against a diverse range of coronaviruses with a high barrier to resistance
  - Can be combined to prevent emergence of resistance and provide broader strain coverage

ALG-097558 is a potent pan-coronavirus protease inhibitor that does not require ritonavir boosting



### ALG-097558 Superior Biochemical Potency Against SARS-CoV-2

SARS-CoV-2 3CLpro	IC <sub>50</sub> (nM)¹	Hillslope	K <sub>i</sub> (nM)
PF-07321332	2.92	0.91	2.03
PBI-0451	3.6	1.74	3.4
S-217622	4.0	1.31	2.6
ALG-097558	0.26	1.99 <sup>2</sup>	0.074

ALG-097558 K<sub>i</sub> is 27-46 fold more potent vs. competitors in the 3CLpro biochemical assay



### ALG-097558 Superior Cell-Based Potency Against SARS-CoV-2 and Variants

	Virus	Variant/Cell line	EC <sub>50</sub> (μΜ)			
			Pardes PBI-0451	Shionogi S-217622	Pfizer PF-07321332	Aligos ALG-097558
Beta –	SARS-CoV-2	<b>03021/2020</b> Vero E6+CP	n.d.	n.d.	0.116	0.010
		B.1.1.7 (alpha) A549-ACE2-TMPRSS2	0.038	0.023	0.099	0.012
		B.1.617.2 (delta) A549-ACE2-TMPRSS2	0.126	0.141	0.217	0.013
		B.1.1.529 (omicron) VeroE6-GFP+CP	0.136	0.095	0.059	0.008
	SARS-CoV-1	Vero-E6+CP	0.323	0.154	0.173	0.022
Alpha –	OC43 (β-hCoV)	HeLa EC <sub>50</sub>	0.168	n.d.	0.047	0.009
	229E (α-hCoV)	Huh-7 EC <sub>50</sub>	0.281	6.30	0.476	0.017

ALG-097558 demonstrates pan-coronavirus antiviral activity ALG-097558 is more active than PF-07321332, PBI-0451 and S-217622 across all CoV's tested At least 7-fold more active than competitors against SARS-CoV-2 Omicron variant



### ALG-097558 Oral Therapeutic Treatment in the SARS-CoV-2 Hamster Model



Significant reduction in infectious virus titers after therapeutic treatment with ALG-097558 Use of ritonavir is only needed in the hamster model



5 Hamsters / group, intranasal infection, B.1.617.2 (1 x 10<sup>4</sup> TCID<sub>50</sub>). Treatment started before or after infection as indicated, administered by oral gavage BID over 3-days. RTV administered 1 h before the ALG cpd, RTV and ALG-097558 formulated as a solution in 43% Ethanol + 27% PG in water. Sacrifice and assessment of infectious virus in lung at day 4. 19

### ALG-097558 SARS-CoV-2 3CLpro L50F E166A L167F Mutant

 ALG-097558 has the least loss of activity against a triple mutant conferring resistance to other SARS-CoV-2 PIs

	Biochemical	VeroE6+CP	
Compound Name	L50F/E166A/L167F (fold change versus WT)	L50F/E166A/L167F EC <sub>50</sub> [µM] (fold change)	
PF-07321332 (Pfizer)	66 (n=6)	3.5-3.7 (38-fold)	
PBI-0451 (Pardes)	>65 (n=2)	7.6-8.4 (25-fold)	
S-217622 (Shionogi)	>67 (n=2)	15-16 (59-fold)	
ALG-097558 (Aligos)	3 (n=3)	0.11-0.14 (9-fold)	

Potential for ALG-097558 to retain significant potency against resistant mutants



### ALG-097558 Coronavirus Protease Inhibitor Drug Candidate

- Potent pan-coronavirus protease inhibitor drug candidate
  - Additional candidates from the series advancing as backup compounds
- Superior preclinical profile versus PF-07321332 (Pfizer)
  - 7-27 fold more potent in biochemical and cell-based assays vs. SARS-CoV-2
    - > 7-fold more potent vs. the omicron variant (cell-based assay)
  - Greater cellular potency across other coronavirus strains
  - Retains activity against resistant variants
  - Excellent efficacy in the SARS-CoV-2 hamster model
- Potential for more convenient, less complex treatment regimen
  - PK profile in preclinical species predicts a projected human efficacious dose of 350-600 mg BID without ritonavir
- Timelines: Phase 1 enabling activities ongoing, HV dosing starts H1 2023

ALG-097558 is a ritonavir-free, highly differentiated, pan-coronavirus protease inhibitor





## **Chronic Hepatitis B**



### Therapeutic Approaches to CHB Functional Cure

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# **Inhibiting Viral Replication**

• ALG-000184 (CAM-E)



### ALG-000184 Phase 1 Study in CHB Subjects

#### Multiple Doses in Currently Not Treated/Treatment Naïve CHB Subjects HBV DNA > 2000 IU/mL, HBeAg- or HBeAg+ Up to 6 cohorts (n=10 per Cohort, n=8 ALG-000184, n=2 Placebo) 28 daily oral doses Endpoints: PK, safety, antiviral activity (e.g., DNA, RNA)



Parts 1-2 (complete): SAD/MAD in HV – good safety, PK Part 3: ALG-000184 mono-rx for 28 days in HBeAg- (100, 50, 10 mg) or HBeAg+ (100, 300, 10 mg) – good safety, PK



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### ALG-000184-201 Part 3 Cohorts 1-5 Antiviral Activity – HBV DNA and HBV RNA

#### Mean (SEM) Serum HBV DNA and HBV RNA Levels Change from Baseline Through the End of Study



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\*\*Roche Cobas® assay. The HBV RNA Investigational assay is not approved in any market (LLÒQ =10 copies/mL). Yuen et al., Poster #SAT-145 EASL 2022; Hou et al., Poster #1329, AASLD 2022.

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### ALG-000184 Antiviral Activity vs. Competitor CAM-Es (HBeAg Negative)

	Current Status	Dose	HBV DNA		
Drug Name			Mean Decline from BL to EOT (Log <sub>10</sub> IU/mL)	% < LLOQ at Day 28	
ALG-000184	Phase 1	10 mg	3.7	100	
EDP-514 <sup>5,**</sup>	Phase 1b	200 mg	2.9	N/A	
		800 mg	3.4	N/A	
Vebicorvir <sup>1,2</sup>	Discontinued	300 mg	2.5	25	
JNJ-6379 <sup>3,4,*</sup>	Discontinued	250 mg	2.7	56	
AB-836 <sup>6</sup>	Discontinued	100 mg	3.1	N/A	

#### 10 mg ALG-000184 has more potent antiviral activity than competitor CAM-Es dosed at 100-800 mg

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### ALG-000184 HBsAg Reductions Observed in 28-Day Monotherapy



28-day monotherapy at 100 and 300 mg PO QD results in 0.2-0.8 log<sub>10</sub> IU/mL HBsAg decline in 5 subjects Best in class activity – no other CAM-E has reported same extent of HBsAg reductions in 28 days Longer duration cohorts (<u>+</u> entecavir) are currently being enrolled/dosed in Part 4



### ALG-000184-201 Part 4 Study Design – up to 48 Weeks of Dosing







### ALG-000184-201 (Part 4) ALG-000184 + ETV Lowers DNA/RNA More Than ETV Alone



Reduction at Week 10	Placebo + ETV, N=3	ALG-000184 100 mg + ETV, N=7	ALG-000184 300 mg + ETV, N=6
HBV DNA, mean (SEM) log <sub>10</sub> lU/mL	-3.7 (0.43)	-4.9 (0.28)	-5.2 (0.3)
HBV RNA, mean (SEM) log <sub>10</sub> copies/mL	0.08 (0.05)	-2.7 (0.21)	-3.3 (0.29)

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### ALG-000184-201 (Part 4) 300 mg ALG-000184 + ETV Lowers HBsAg Over Time



Clear downward trend over 10 weeks for HBsAg among majority of 300 mg ALG-000184 treated subjects



### ALG-000184-201 Ongoing Phase 1b Cohorts

- Enrollment/dosing in multiple longer duration (≤48 weeks) cohorts is ongoing
- Cohorts designed to address several key questions, including
  - Impact of treatment with/without entecavir
  - Antiviral activity in different patient populations (high/normal baseline ALT, HBeAg positive or negative)
- Available cohort data to be presented at APASL, EASL, and AASLD in 2023

Longer dosing duration (≤48 weeks) cohorts currently being enrolled and dosed Data will be presented at scientific conferences throughout 2023





# Lowering S-Antigen Burden

• ALG-125755 (siRNA)



### **Short Interfering Nucleic Acid ALG-125755** Discovery and Advancement of a Differentiated siRNA

- siRNAs have demonstrated clinical validation in CHB infected patients
- We have designed our siRNA sequences using our proprietary technology and liver targeting conjugation to maximize in vitro and in vivo potency
  - Proprietary patterns discovered to increase potency and stability/duration of action
  - Exclusive license to GalNAc technology applicable for liver targeting across oligo modalities
- Our siRNA approach may have safety, stability and potency advantages vs. competitor siRNAs

Aligos oligonucleotide know-how and proprietary technologies have resulted in a differentiated siRNA



### ALG-125755 Repeat Dosing in the AAV-HBV Mouse Model vs. VIR-2218

#### **VIR-2218\***

ALG-125755



ALG-125755 demonstrates a more sustained reduction in HBsAg vs. competitor siRNAs

![](_page_35_Picture_5.jpeg)

![](_page_36_Figure_1.jpeg)

SAD in HV: Part 1 Cohorts 1-4 (20 mg, 60 mg, 100 mg and 200 mg) completed dosing SAD in CHB: Part 2 Cohort 1 enrollment completed (50 mg)

![](_page_36_Picture_3.jpeg)

### **Clinical Experience with siRNAs** HBsAg Reduction After 28 Days in CHB Patients

![](_page_37_Figure_1.jpeg)

Consistent reductions of ~0.5 log<sub>10</sub> IU/mL noted for competitor siRNAs 28 days after a single dose

![](_page_37_Picture_3.jpeg)

![](_page_38_Picture_0.jpeg)

# Boosting the Immune Response

• Liver Targeted Oral PD-L1 Inhibitor (Small Molecule)

![](_page_38_Picture_3.jpeg)

- Exhaustion of HBV specific T-cells contributes to the persistence of CHB
- Proof of concept in CHB with anti-PD1 antibodies has been established
  Multiple clinical studies have demonstrated HBsAg reductions in CHB infected patients
- Aligos has discovered several potent series of small molecule PD-L1 inhibitors
  - Potential for oral delivery and targeting to the liver
    - Liver targeting may avoid the safety liabilities seen with parenterally delivered anti-PD1 antibodies while improving efficacy
- Lead compound is a novel liver-targeted small molecule PD-L1 inhibitor
  - Biochemical and cell-based potency established
  - Activation of HBV specific T-cells demonstrated with similar potency as durvalumab
  - Liver targeting achieved with lead compound

### Aligos CHB Portfolio Consists of the Key Pillars Which are Likely Necessary for Enhanced Functional Cure Rates

![](_page_40_Figure_1.jpeg)

![](_page_40_Picture_2.jpeg)

# Aligos Therapeutics is Advancing Multiple Drug Candidates in the Clinic

- NASH
  - THR-β agonist (ALG-055009) more uniform exposure may lead to more consistent efficacy and safety across patient populations
  - Merck collaborations are progressing
- Coronavirus Protease Inhibitor (ALG-097558)
  - On track to complete FIH enabling nonclinical studies and dose in Phase 1 in H1 2023
- CHB 3 MOAs which, when combined, may increase functional cure rates
  - CAM-E (ALG-000184) best in class HBsAg, DNA, RNA data. Ph1b (≤48 weeks) ongoing
  - siRNA (ALG-125755) is differentiated in AAV-HBV, dosing in CHB ongoing
  - PD-L1 liver-targeted, small molecule advancing towards candidate selection
- As of September 30, 2022; cash balance was \$142.3M\*; fully diluted common shares: 52,897,859

![](_page_41_Picture_11.jpeg)

# ALIGOS THERAPEUTICS