1672.HK

Ascletis Pharma Inc.

A Hong Kong Stock Exchange Listed Biotech

July 2021

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Ascletis Overview

Multi-disease platform of both small molecules and biologics

China & US based biotech with experienced management team and ~ 300 FTEs

Significant partnerships:

Healthy cash reserve: Cash balance of US$416 million as of Dec 31,2020 ; cash runway into 2025

Ascletis Overview

NASH

- Global leading pipeline of 6 assets including 3 fixed-dose combinations
- 2 assets ready for pivotal trials

Oncology

- Unique pipeline of cancer lipid metabolism and oral checkpoint inhibitors

Viral diseases

- 3 marketed HCV/HBV products in China
- Global leading immunotherapy for functional cure of HBV

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Non-alcoholic Steatohepatitis (NASH)

About Gannex

Gannex, a wholly-owned company of Ascletis, is dedicated to the R&D and commercialization of new drugs in the field of NASH. Gannex has three clinical stage drug candidates against three different targets – FASN, THR-β and FXR, and three combination therapies.

NAFLD and NASH Represent a Large and Growing Health Problem

- A large prospective study evaluated the prevalence and severity of NAFLD/NASH in an asymptomatic middle-aged population attending outpatient colonoscopy in the United States.

Middle-aged population (U.S.)

The prevalence of NAFLD is approximately 38%

Significant liver fibrosis 5.9%

Bridging liver fibrosis 1.6%

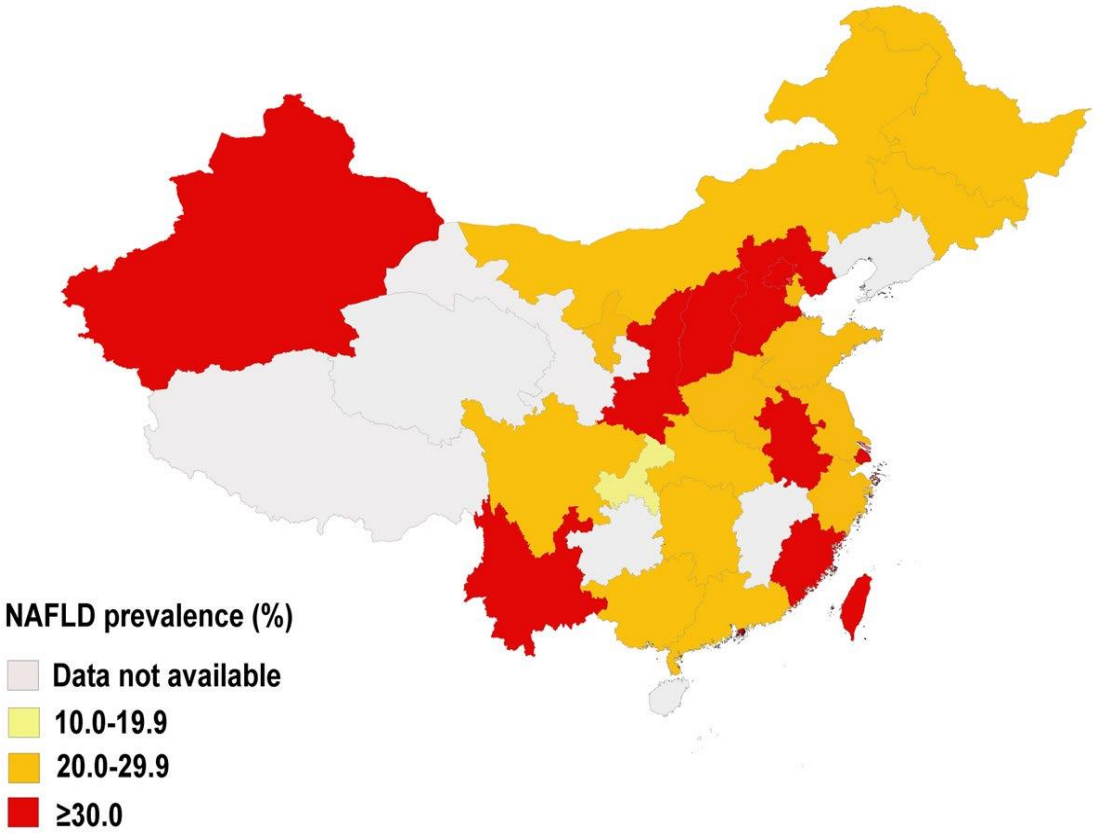
The prevalence of NASH is approximately 14%

Obesity and Diabetes are risk factors for progression to NASH

Harrison S A, Gawrieh S, Roberts K, et al. Prospective evaluation of the prevalence of non-alcoholic fatty liver disease and steatohepatitis in a large middle-aged US cohort [J]. Journal of hepatology 2021, DOI: 10.1016/j.jhep.2021.02.034..

NAFLD and NASH Represent a Large and Growing Health Problem

- A large meta-analysis revealed that the prevalence of NAFLD in China was as high as **29.2%** from various perspectives.



NAFLD prevalence statistics in China

Highest NAFLD prevalence age group

- Age 50~59 (**32.9%**; 95% CI, 30.3-35.5)

Prevalence of NAFLD in people with obesity

- **51.6%**, 5 times higher than non-obese population (10.8%)

The prevalence of NAFLD in China is increasing rapidly

- 2008 ~ 2010 (25.4%) vs. 2015 ~ 2018 (32.3%)
- Twice as high as in Western countries, and already exceeds the average prevalence (29.2% vs. 25.2%)

Zhou F, Zhou J, Wang W, et al. Unexpected Rapid Increase in the Burden of NAFLD in China From 2008 to 2018: A Systematic Review and Meta-Analysis [J]. Hepatology 2019, 70(4): 1119-33. DOI: 10.1002/hep.30702.

NASH Pipeline: Single Agent and Combo Therapies[1]

Target	Drug Candidates	Commercial Rights	Pre-IND	IND	Phase I	Phase IIa	Phase IIb/III
FASN	ASC40	Greater China[2]			*U.S. FDA Fast Track*		
THR-β	ASC41	Global					
FXR	ASC42	Global		*U.S. FDA Fast Track*			
THR-β + FXR	ASC43F One-Pill, Once-a-Day FDC	Global					
FASN + FXR	ASC44F One-Pill, Once-a-Day FDC	Global[2]					
FASN + THR-β	ASC45F One-Pill, Once-a-Day FDC	Global[2]					

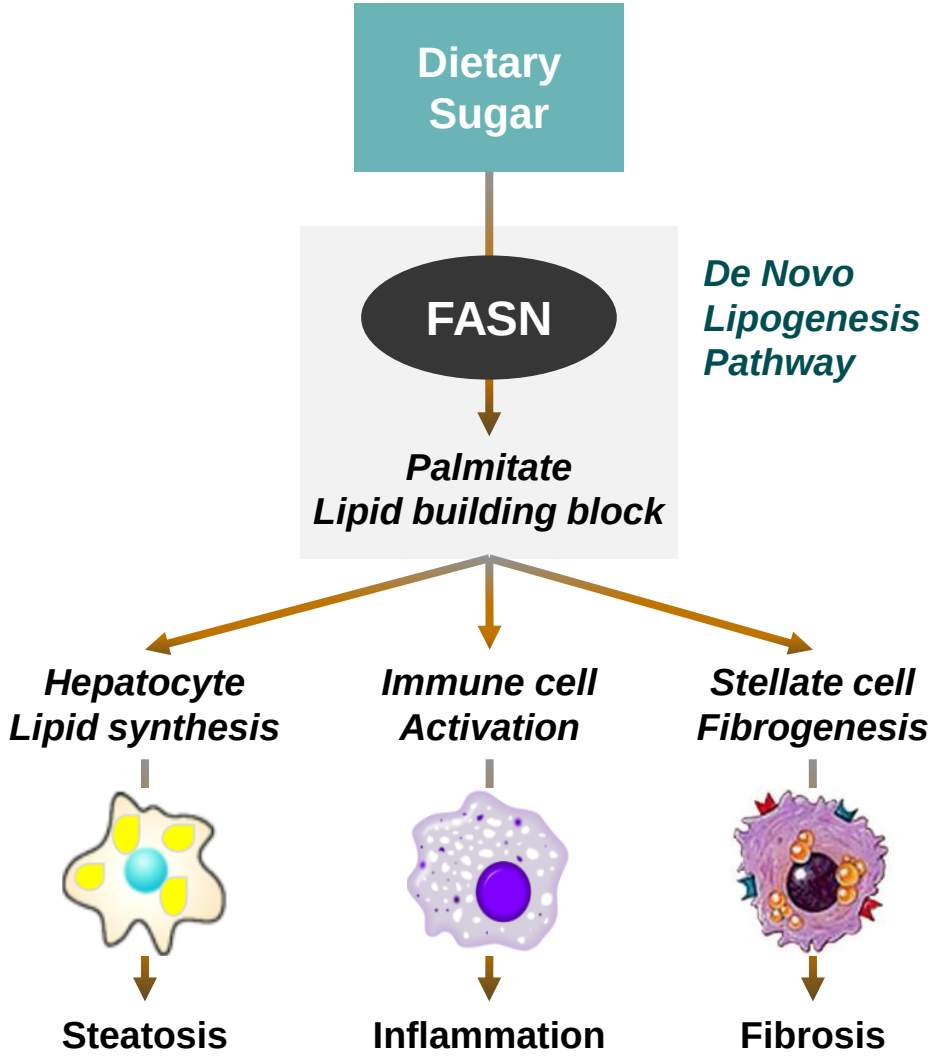
Notes: 1. NASH pipeline is owned by Gannex Pharma Co., Ltd., an independent biotech which is currently wholly-owned by Ascletis Pharma Inc.(1672.HK).
2. ASC40 is licensed from Sagimet Biosciences Inc. ("Sagimet") (previously known as 3-V Biosciences, Inc.) for the exclusive rights in the Greater China.

FASN: Fatty Acid Synthase THR-β: Thyroid Hormone Receptor Beta FXR: Farnesoid X Receptor FDC: Fixed Dose Combination

ASC40: First-in-Class Oral Fatty Acid Synthase (FASN) Inhibitor

FASN is an important rate-limiting step in intrahepatic fatty acid synthesis as well as De novo lipogenesis (DNL)

- Reduces steatosis by blocking DNL
- Reduces inflammation by decreasing cytokine secretion and Th17 differentiation
- Blunts fibrosis by reducing procollagen and profibrotic gene expression



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Phase II U.S. Cohort: ASC40 Clinical Trial Design in NASH Patients

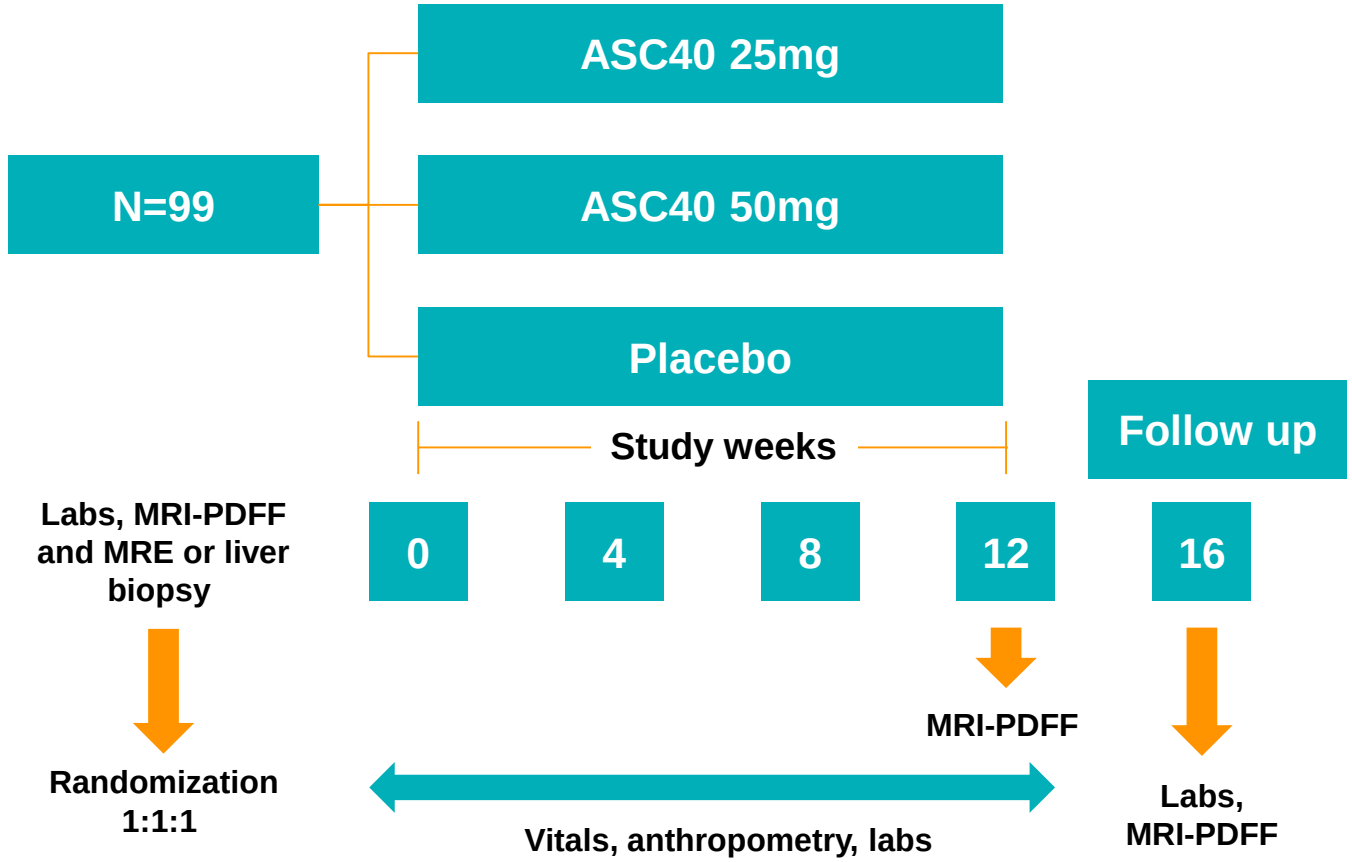
Multicenter, randomized, placebo-controlled trial 1:1:1 25mg:50mg:placebo (N=99)

Criteria

- Inclusion
  - ≥ 8% liver fat
  - MRE ≥ 2.5kPa or recent biopsy
- Exclusion
  - Evidence of cirrhosis
  - Other chronic liver disease

Endpoints

- Primary
  - Liver fat reduction by MRI-PDFF
  - Safety
- Secondary
  - % pts ≥30% reduction of liver fat
  - ALT, AST
  - Biomarkers



Rohit Loomba et al. 2020, Hepatology 72;103. EASL 2020 Oral Presentation

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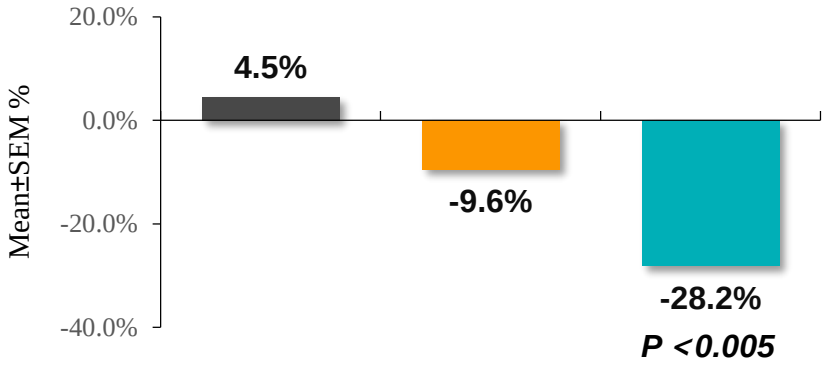
Phase II U.S. Cohort: ASC40 Significantly Reduces Liver Fat Content

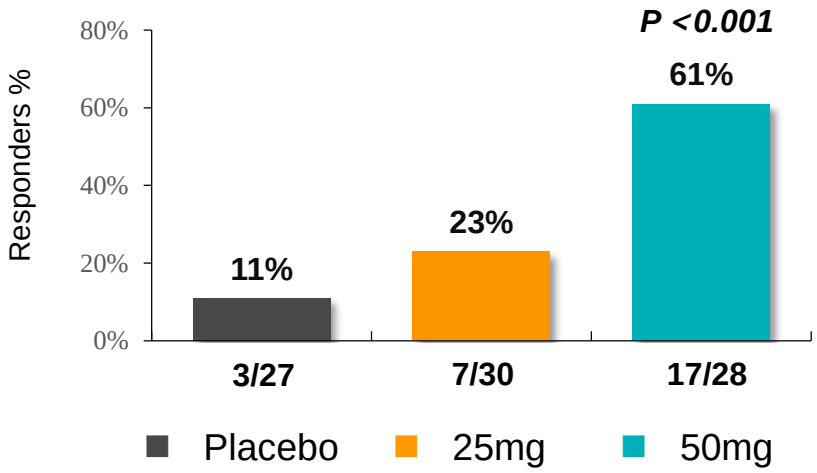
Mean relative liver fat reduction

MRI-PDFF at week 12

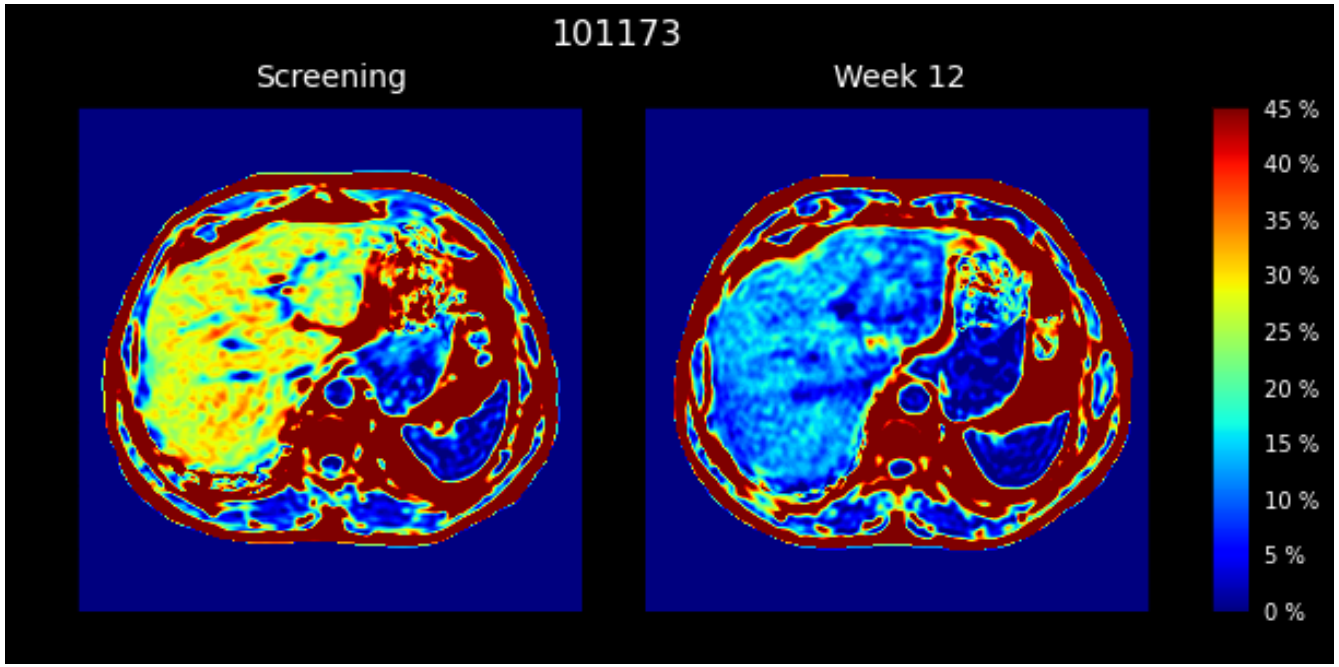


Responder frequency

Patients with ≥30% relative reduction



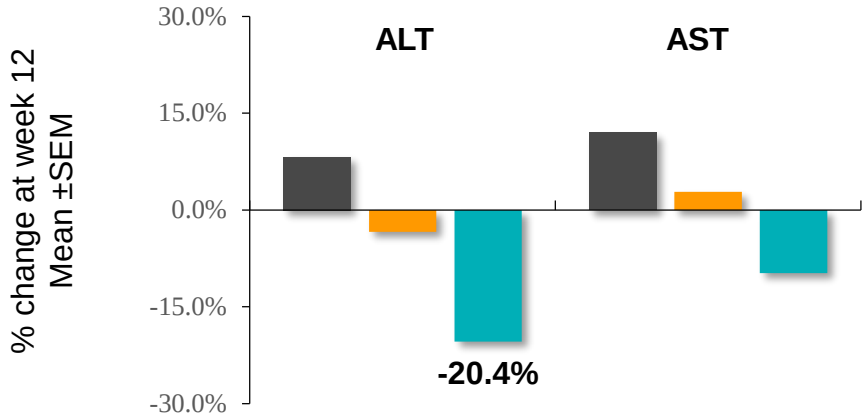
Significant reduction in liver fat content over 12 weeks of treatment



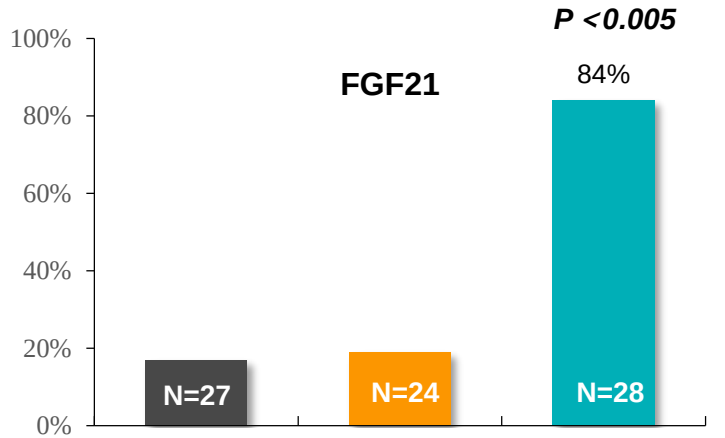
MRI-PDFF responders were defined as those with ≥ 30% MRI-PDFF decline relative to baseline

Phase II U.S. Cohort: ASC40 Significantly Improves NASH-related Metrics

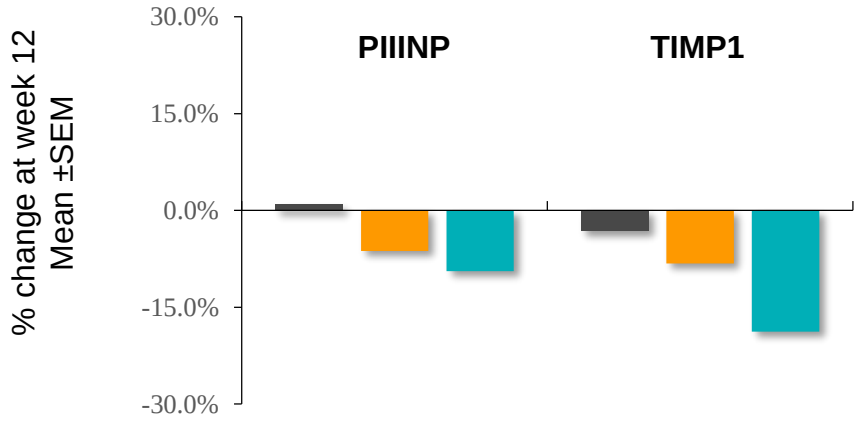
Dose-dependent response in reducing ALT/AST



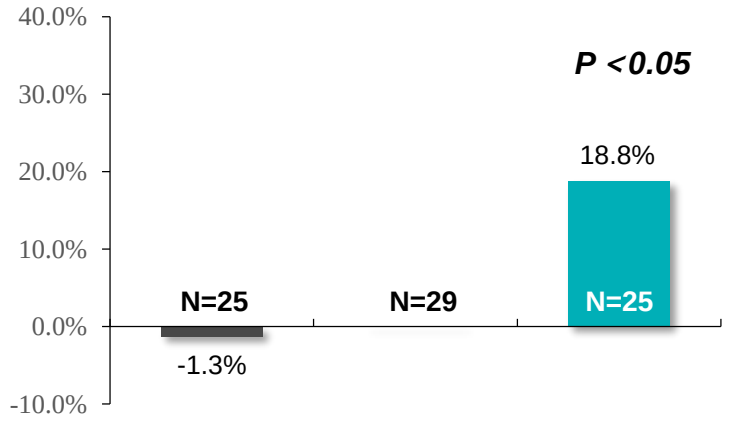
Improves markers of hepatic insulin sensitivity



Decreases fibrosis markers



Adiponectin



Placebo 25mg 50mg

Rohit Loomba et al. 2020, Gastroenterology & Hepatology 72;103 AASLD 2020 Oral Presentation

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Phase II ASC40 Compares Favorably With Other Phase II/III NASH Drugs

Drug Candidate	Company	Target	Dose	Weeks	≥ 30% liver fat reduction responder rate, %		Placebo adjusted ≥ 30% liver fat reduction responder rate, %	Safety
					Drug	Placebo		
ASC40[1]	Gannex /Sagimet	FASN	50 mg	12	60.7	11.1	49.6	minimal side effects
Firsocostat[2]	Gilead	ACC	20mg	12	47.8	15.4	32.4	TG ↑
Tropiflexor[3]	Novartis	FXR	200μg	12	64	20	44	LDL-C ↑, pruritus
Resmetirom[4]	Madrigal	THR-β	80mg	36	74.4	29.4	45	diarrhea, nausea

Non-head to head research

1、Rohit Loomba et al. 2020,Hepatology 72;103.EASL 2020 Oral Presentation
2、Eric J Lawitz et al. Clin Gastroenterol Hepatol. 2018 Dec;16(12):1983-1991
3、 Marcos Pedrosa et al. Contemp Clin Trials. 2020 Jan;88:105889.
4、Stephen A Harrison et al. Lancet. 2019 Nov 30;394(10213):2012-2024

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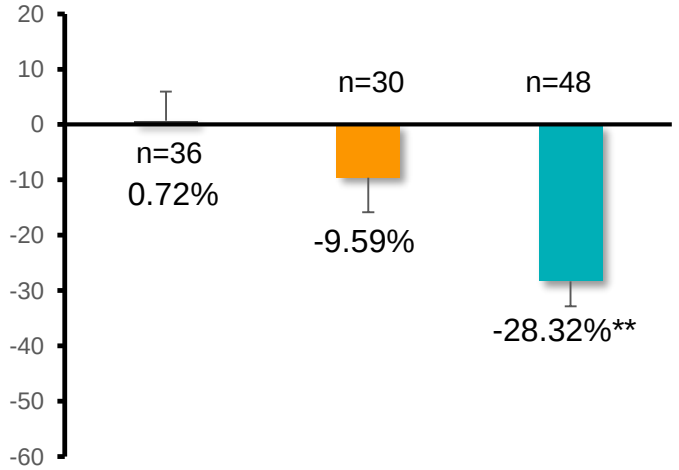
Phase II China Cohort: ASC40 Clinical Trial in NASH Patients

Phase II, multicenter, randomized, placebo-controlled trial 2:1 50mg:placebo (N=30)

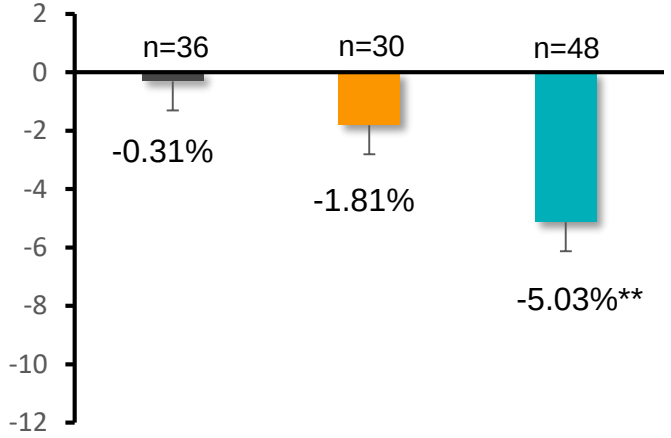
- ASC40 meaningfully reduced liver fat, the primary efficacy endpoint of this trial, with a 50% responder rate (patients achieving ≥30% reduction)
- ASC40 showed a statistically significant decrease in ALT by 29.8% (*P*=0.0499) (mean decrease of 33 U/L at week 12)
  - Indicates reduction of liver inflammation
- In 63% of patients on ASC40, ALT decreased by17 U/L or greater, which has been shown to correlate with liver biopsy response in NASH patients
- ASC40 was well tolerated with no serious adverse events. All treatment emergent adverse events were grade 1 or 2 and there were no statistically significant changes in serum triglycerides
- Data from the China cohort are consistent with those of the U.S. cohort, previously reported at the AASLD Liver Meeting in November 2020
- Based on the positive Phase II data, doses for the Phase IIb/III NASH trial in China have been selected

Phase II Combined U.S. & China Cohorts: ASC40 Reduces Liver Fat

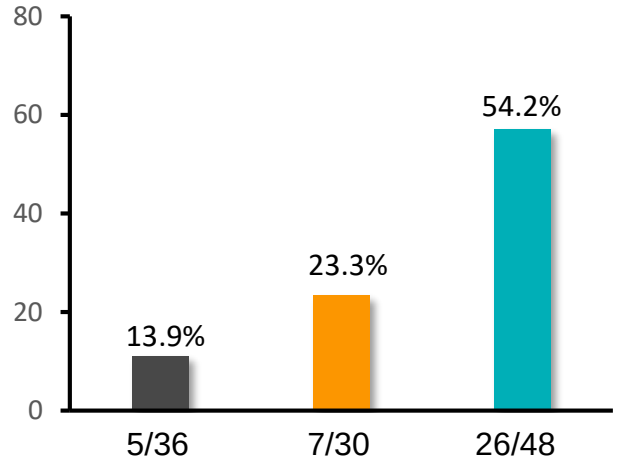
Mean relative liver fat reduction
MRI-PDFF at week 12



Mean absolute liver fat reduction
MRI-PDFF at week 12



Responder frequency
Patienct with ≥30% relative reduction



Placebo **25mg** **50mg**

p<0.05,p<0.01 Mean ± SEM LSM difference versus placebo for liver fat.Common risk difference for responder frequence*

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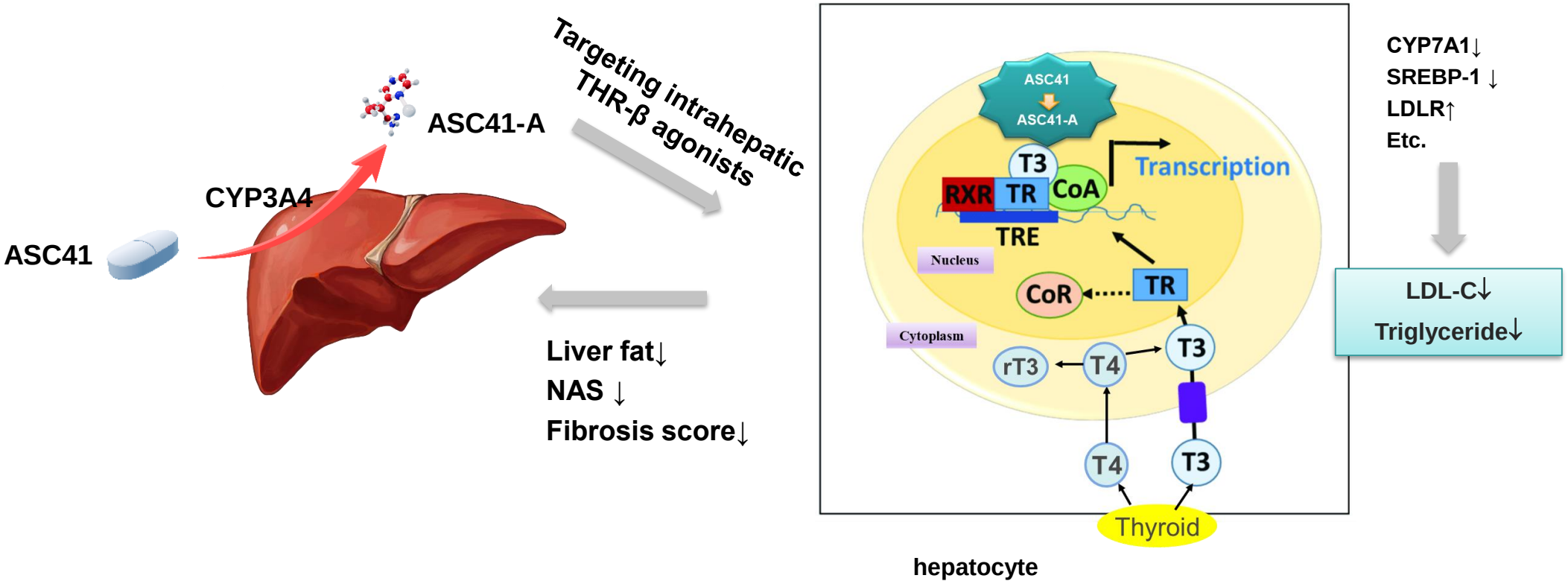
ASC41: A Liver Targeting Thyroid Hormone Receptor Beta (THR-β) Agonist

- ASC41 is a liver targeted small molecule which is converted to its active metabolite ASC41-A - a potent and selective THR-β agonist



Gannex data

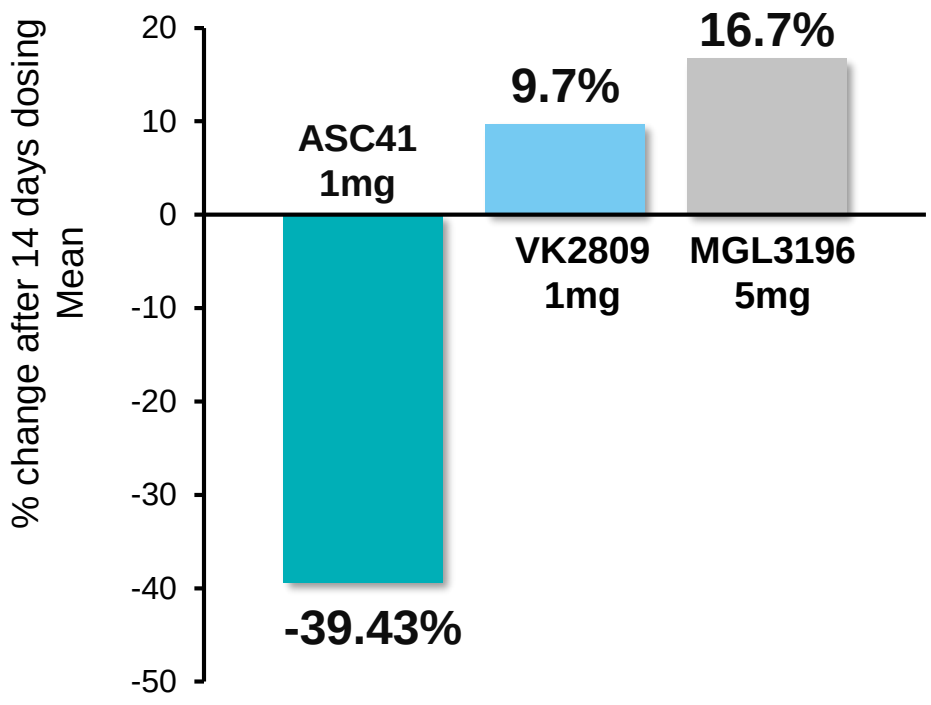
ASC41: Currently a Third-in-class THR-β Agonist in USA
First-in-class in China

- In two NASH animal models, at 1/10th dose of MGL-3196, ASC41 demonstrated the same improvement in liver steatosis, inflammation and fibrosis.
- Commercially ready oral tablet formulation developed with in-house proprietary technology
- 2 Phase Ⅰ studies completed
  - Single doses (1, 2, 5, 10, 20 mg) and 14 day multiple doses (1, 2, 5 mg) in 65 subjects with elevated LDL-C > 110 mg/dL
  - Food effect in 12 healthy subjects
- U.S. IND approved Feb 2021
- 1 Phase Ⅰb study completed
  - 28 day, 10 mg in 20 overweight and obese subjects with elevated LDL-C > 110 mg/dL
- Based on above studies, doses have been selected for Phase II trials in patients with NASH

THR-β Differentiations: Gannex vs Viking and Madrigal

	Gannex ASC41[1]	Viking VK2809[2]	Madrigal MGL3196[3]
Oral formulation	Tablet, room temp storage, commercially ready	Capsule, refrigerated	Tablet, room temp storage, commercially ready
Dosing frequency	Once a day	Once every two days	Once a day
Human dose needed for > 30% TG reduction	1 mg	2.5 mg	50 mg

Placebo adjusted triglyceride reduction from baseline after 14 day dosing



1.Gannex data 2.EASL2020 Abstract No. AS073.
3.Stephen A Harrison et al. Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. www.thelancet.com Published online November 11, 2019 https://doi.org/10.1016/S0140-6736(19)32517-6

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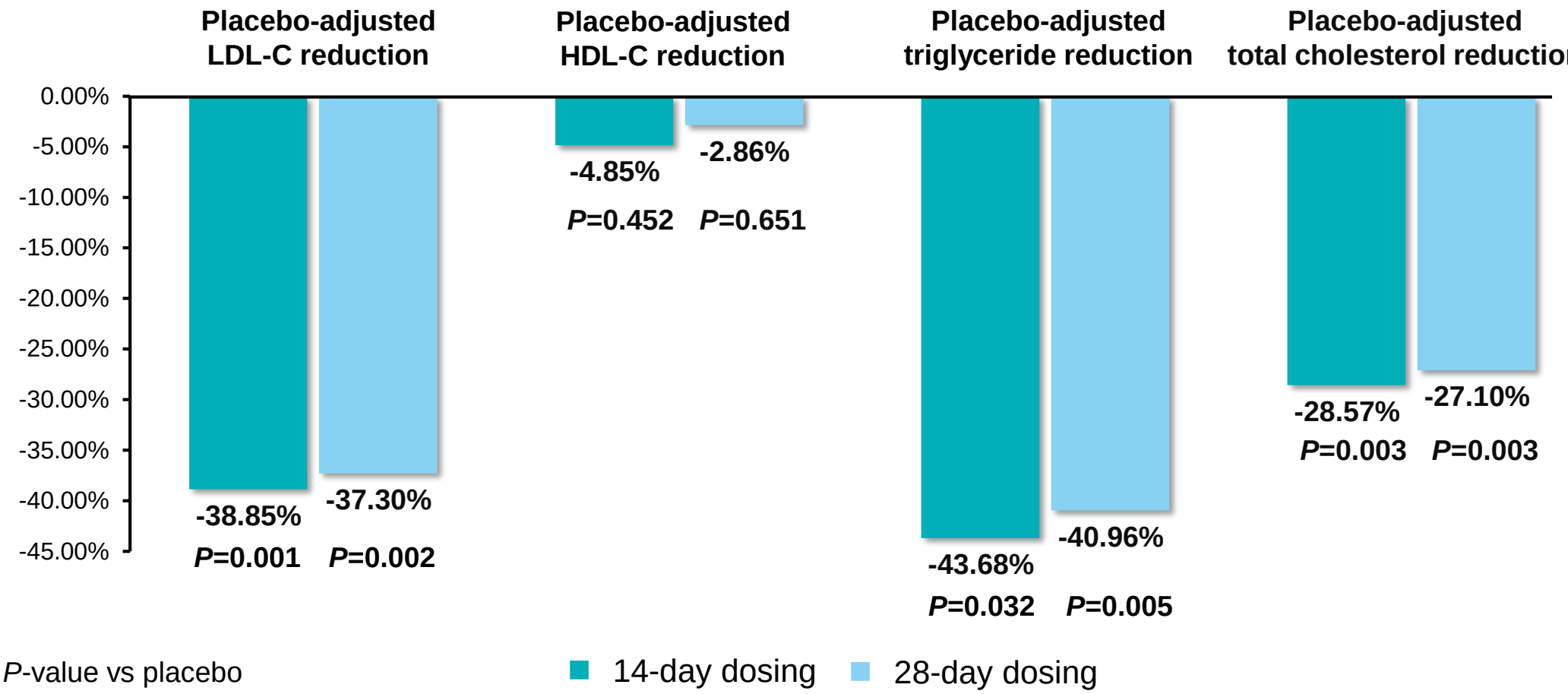
Positive Clinical Results in Overweight and Obese Subjects

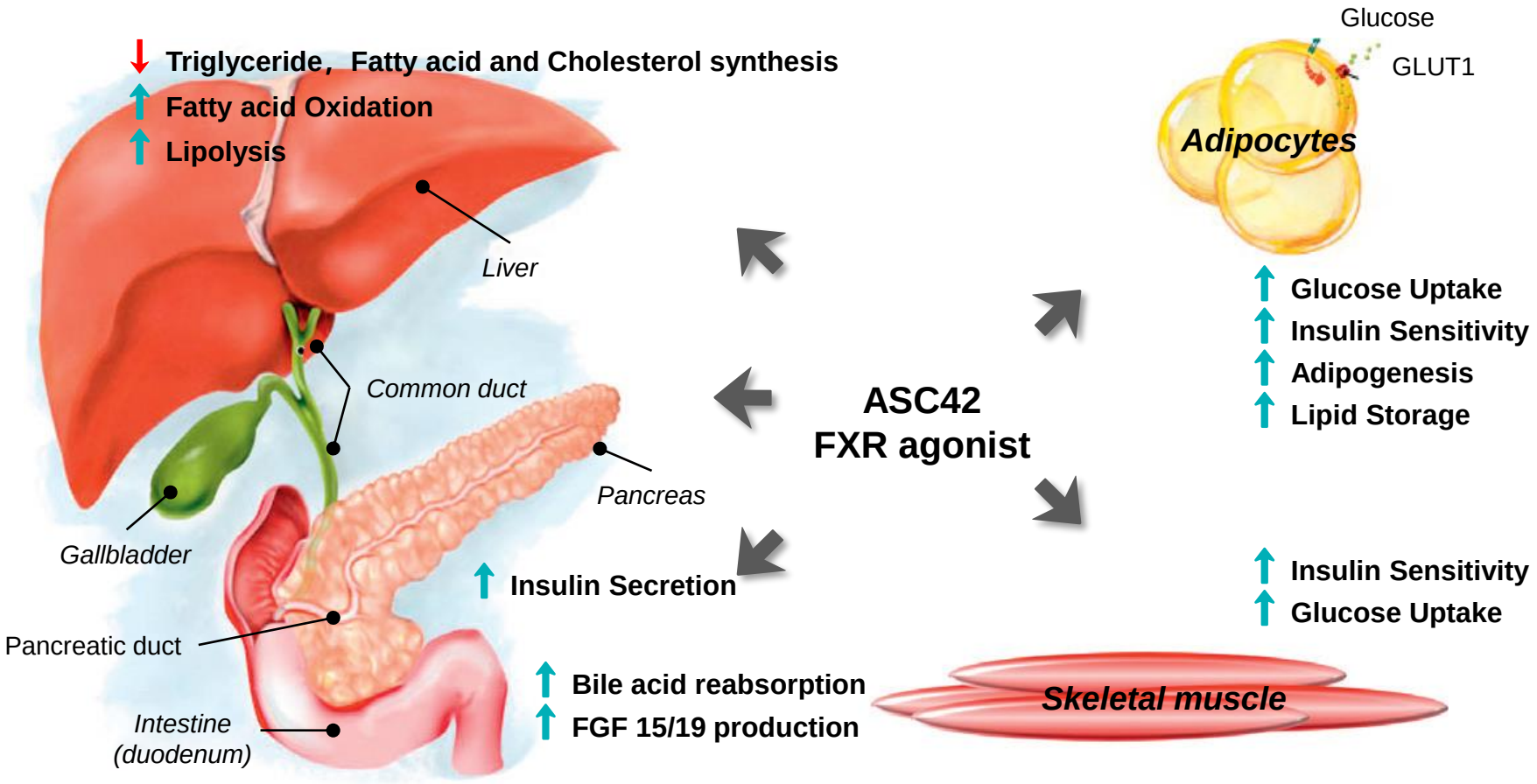
Placebo-adjusted relative change (mean) from baseline after 14 or 28 days of once daily oral dosing of 10 mg ASC41 tablets in overweight and obese subjects



P-value vs placebo

Gannex data

ASC42: A Farnesoid X Receptor (FXR) Agonist



- Increased insulin sensitivity of adipocytes and skeletal muscle cells increases glucose uptake in peripheral tissues and increases energy consumption
- Reduced the synthesis of triglycerides, fatty acids and cholesterol in the liver, promoted liver fat decomposition and fatty acid oxidation

Luciano Adorini et al. Farnesoid X receptor targeting to treat nonalcoholic steatohepatitis. Drug Discovery Today Volume 17, Numbers 17/18 September 2012

ASC42: A Novel Non-steroidal, Selective, Potent FXR Agonist

- Potentially best-in-class, no pruritus at human therapeutic doses
- U.S. FDA IND approval in Oct 2020
- U.S. FDA Fast Track Designation in Dec 2020
- U.S. Phase Ⅰ trials completed
  - Single ascending doses and multiple ascending doses
  - Food effect
- Oral tablet formulation developed with in-house proprietary technology and stable at room temperature

ASC42: Topline Results of the U.S. Phase I Trial

- No pruritus observed during 14-day treatment of the once-daily human therapeutic dose of 15 mg.
- FXR target engagement biomarker FGF19 increased 1632% on Day 14 of treatment with 15 mg, once-daily
- FXR target engagement biomarker C4 decreased 93% on Day 14 of treatment with 15 mg, once-daily
- Mean LDL-C values remained within the normal range during 14-day, once daily treatment with 15 mg
- There were no treatment-emergent ALT and AST elevations during 14-day, once daily treatment with 15 mg
- Doses selected for Phase II trial in patients with NASH, which will be initiated by the end of 2021

Combo Therapies: Synergies among ASC40, ASC41 and ASC42

Treatment Goals	Monotherapy			Combo therapy One-Pill, Once-a-Day		
	ASC40 FASN	ASC41 THR-β	ASC42 FXR	ASC43F THR-β + FXR	ASC44F FASN + FXR	ASC45F FASN + THR-β
Liver fat reduction	★★★	★★★	★★	★★★	★★★	★★★
Anti-inflammation	★★	★★	★★	★★	★★	★★
Anti-fibrosis	★★	★★	★★★	★★★	★★★	★★
Lowering LDL-C and TG		★★★		★★★		★★★

Cancer Lipid Metabolism

Cancer Molecular Therapies

Category	Mechanism	Examples of Approved drugs
Signal Transduction	Angiogenesis and proliferation inhibitor	Bevacizumab, Imatinib, Erlotinib, Sorafenib, Ibrutinib, Tofacitinib, Palbociclib
Immunotherapy	Checkpoint inhibitor	Keytruda®, Opdivo®, Tecentriq®, Bavencio®, Imfinz®
Metabolism	Control aberrant energy and substance needs, inhibit toxic metabolites	Ivosidenib, Enasidenib

Cancer Metabolism: Long History, Recent Breakthrough

Warburg Effect (~1921)
Increased glucose uptake and fermentation of glucose to lactate even in the presence of completely functioning mitochondria

Enasidenib Approved for AML (2017)

FDA approves first-in-class cancer metabolism drug

The FDA approved Agios' and Celgene's enasidenib for acute myeloid leukaemia (AML), validating metabolism-modulating drugs as a means of killing cancer cells.

Enasidenib (formerly AG-221) is a first-in-class inhibitor of mutated isocitrate dehydrogenase 2 (IDH2). The IDH enzymes normally metabolize isocitrate into α-ketoglutarate. When they are mutated in cancers, they also convert α-ketoglutarate into 2-hydroxyglutarate, an oncometabolite that causes cell differentiation defects by impairing histone demethylation.

In clinical trials of enasidenib, 23% of treated patients had complete responses or complete responses with partial haematologic recovery lasting a median of 8.2 months. The most common side effects were nausea, vomiting, diarrhoea, elevated bilirubin and decreased appetite. The agency approved the drug with a black box warning noting the risk of differentiation syndrome, a potentially fatal complication that is associated with certain forms of AML.

Nature Reviews Drug Discovery, **2017**,*16*, 593

RESEARCH 10.1126/science.aaw5473

REVIEW Science 2020

CANCER

Metabolic reprogramming and cancer progression

BJC 2020 British Journal of Cancer www.nature.com/bjc

EDITORIAL
Cancer Metabolism

Development of cancer metabolism as a therapeutic target: new pathways, patient studies, stratification and combination therapy

Cancer metabolism has undergone a resurgence in the last decade, 70 years after Warburg described aerobic glycolysis as a feature of cancer cells. A wide range of techniques have elucidated the complexity and heterogeneity in preclinical models and clinical studies. What emerges are the large differences between tissues, tumour types and intratumour heterogeneity. However, synergies with inhibition of metabolic pathways have been found for many drugs and therapeutic approaches, and a critical role of window studies and translational trial design is key to success.

British Journal of Cancer (2020) 122:1–3; https://doi.org/10.1038/s41416-019-0666-4

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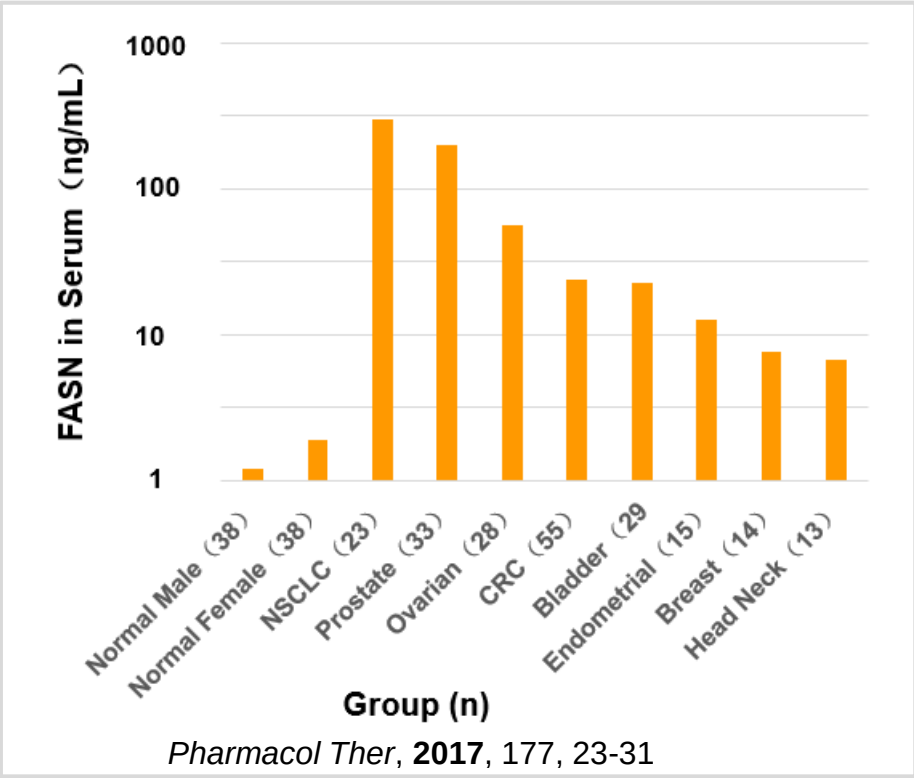
Cancer Metabolism: Approved Drugs and Clinical Stage Candidates

Drug	Target	Indication	Development phase and Company
Ivosidenib (AG-120)	**Mutant IDH1** TCA cycle metabolism	AML with IDH1 Mutation	Approved Agios Pharmaceuticals/Celgene
Enasidenib (AG-221)	**Mutant IDH2** TCA cycle metabolism	AML with IDH2 Mutation	Approved Agios Pharmaceuticals/Celgene
Vorasidenib (AG-881)	**Mutant IDH1/2** TCA cycle metabolism	Low grade glioma	Phase III Agios Pharmaceuticals
Devimistat (CPI-613)	**Pyruvate dehydrogenase/α-ketoglutarate dehydrogenase** TCA cycle metabolism	Lymphoma, Leukemia, Pancreatic cancer	Phase II / Pivotal Rafael Pharmaceuticals
INCB001158	**Arginase inhibitor** Maintains arginine levels	Relapsed or Refractory multiple myeloma	Phase II Incyte Corporation
AZD3965	**Monocarboxylate transporter 1** Lactate metabolism	Advanced cancer	Phase I Cancer Research UK
TVB-2640 (ASC40)	**Fatty acid synthase** Lipid metabolism	GBM, Breast cancer and other solid tumors	Phase II Ascletis (Greater China)/Sagimet Biosciences (outside Greater China)

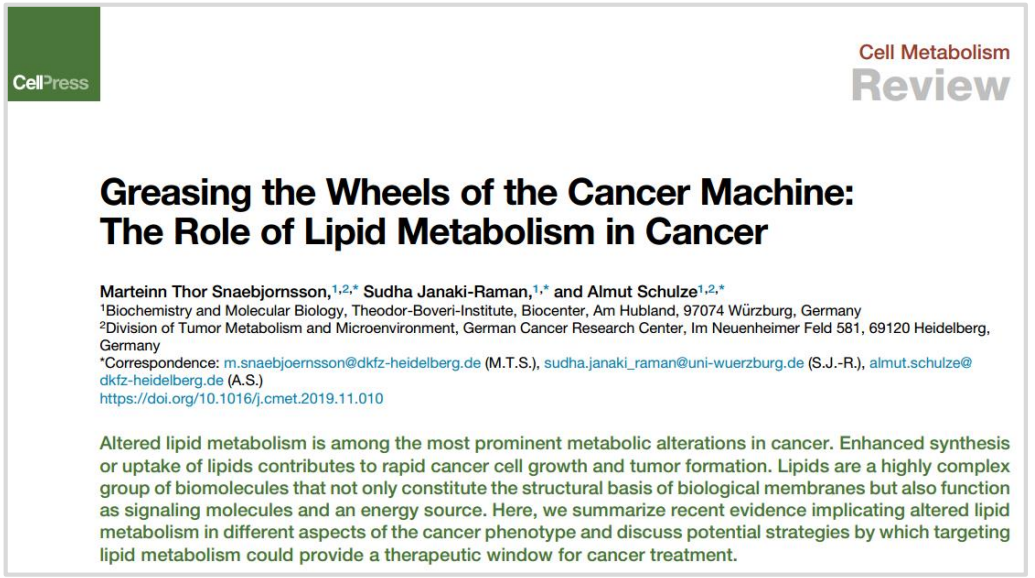
Fatty Acid Synthase, A Promising Cancer Drug Target

Fatty Acid Synthase (FASN):

- Synthesis palmitic acid from acetyl-CoA and malonyl-CoA
- Discovered as Oncogenic Antigen 519 (OA-519) in 1990's
- Over expressed in many cancer, prognosis marker



Pharmacol Ther, **2017**, 177, 23-31


CellPress

Cell Metabolism
Review

Greasing the Wheels of the Cancer Machine: The Role of Lipid Metabolism in Cancer

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https://doi.org/10.1016/j.cmet.2019.11.010

Altered lipid metabolism is among the most prominent metabolic alterations in cancer. Enhanced synthesis or uptake of lipids contributes to rapid cancer cell growth and tumor formation. Lipids are a highly complex group of biomolecules that not only constitute the structural basis of biological membranes but also function as signaling molecules and an energy source. Here, we summarize recent evidence implicating altered lipid metabolism in different aspects of the cancer phenotype and discuss potential strategies by which targeting lipid metabolism could provide a therapeutic window for cancer treatment.


FULL PAPER

BJC

British Journal of Cancer (2018) 118, 43–51 | doi: 10.1038/bjc.2017.374

Keywords: acetyl-CoA carboxylase; cancer; metabolism; membrane characteristics; metastasis; soraphen A; proliferation; tumour growth

Targeting *de novo* lipogenesis as a novel approach in anti-cancer therapy

Katharina Stoiber[1,2], Olga Nagło[1], Carla Pernpeintner[2,3], Siwei Zhang[1], Andreas Koeberle[4], Melanie Ulrich[1], Oliver Werz[4], Rolf Müller[5], Stefan Zahler[1], Theobald Lohmüller[2,3], Jochen Feldmann[2,3] and Simone Braig[*,1]

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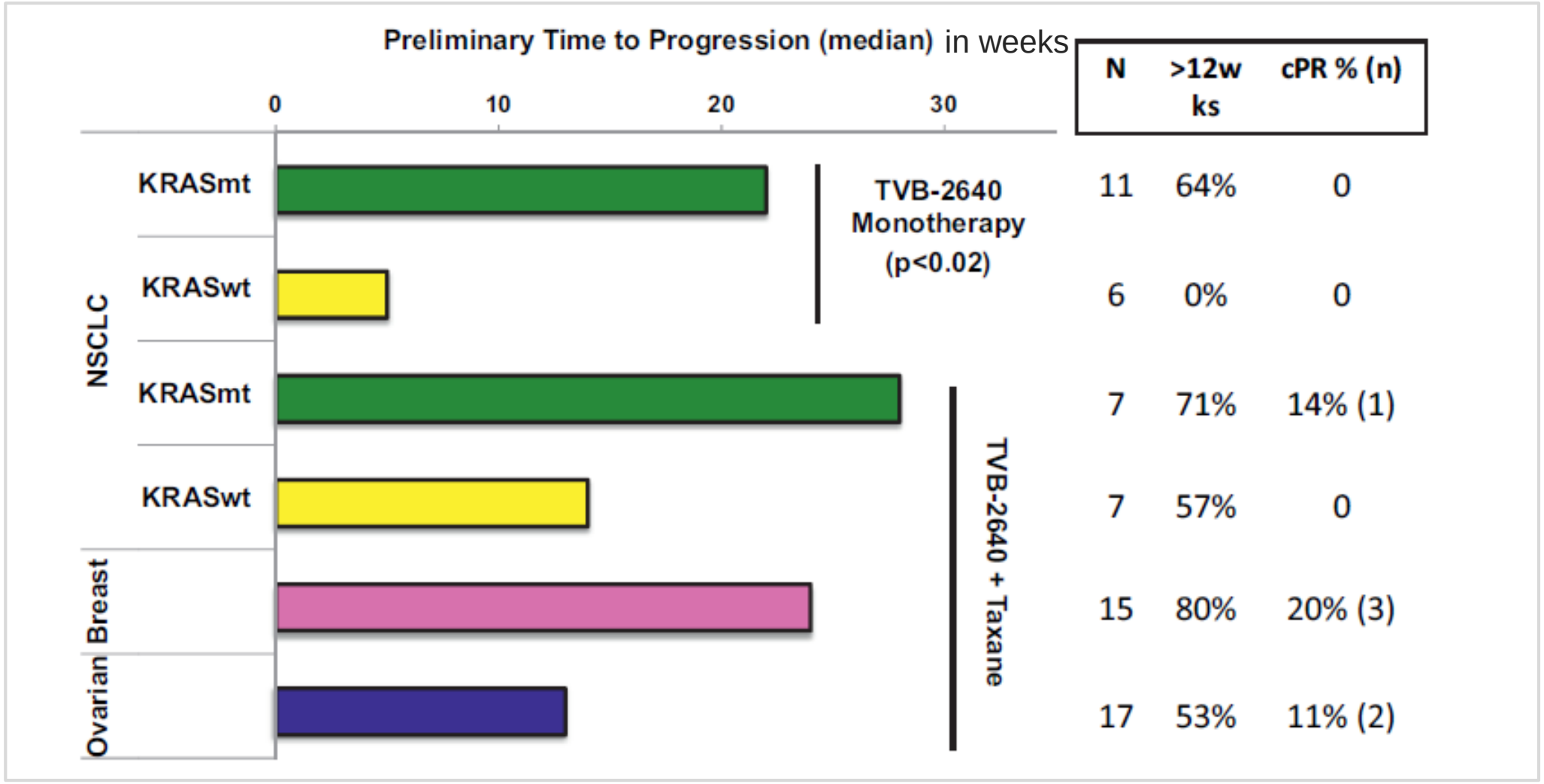
Cancer Lipid Metabolism: Recent Breakthrough of FASN Inhibitors

- Investigator sponsored Phase II trial of TVB-2640 with Bevacizumab in Patients with First Relapse of High-Grade Astrocytoma (recurrent glioblastoma)
  - 25 patients enrolled
  - All patients received ASC40 (TVB-2640) (100mg/m^2 PO QD) plus bevacizumab (10mg/kg IV D1,15) until treatment-related toxicity or progressive disease
- The overall response rate (ORR) for ASC40 (TVB-2640) plus bevacizumab of 65%
  - Complete response (CR) of 20%
  - Partial response (PR) of 45%
- Progression-free survival at six months (PFS6) for ASC40 (TVB-2640) plus bevacizumab was 47%
  - Representing a statistically significant improvement in PFS6 over historical bevacizumab monotherapy (BELOB 16%, *P*=0.01)
- ASC40 (TVB-2640) in combination with bevacizumab was safe and well tolerated in such patient population
- Presented at European Society for Medical Oncology 2020

Median Time to Progression among TVB-2640 Monotherapy and Combination Therapy Patients with KRAS^{MUT} versus KRAS^{WT} Non-small Cell Lung, Breast, and Ovarian Cancer



G. Falchook et al. / EClinicalMedicine 34 (2021) 100797

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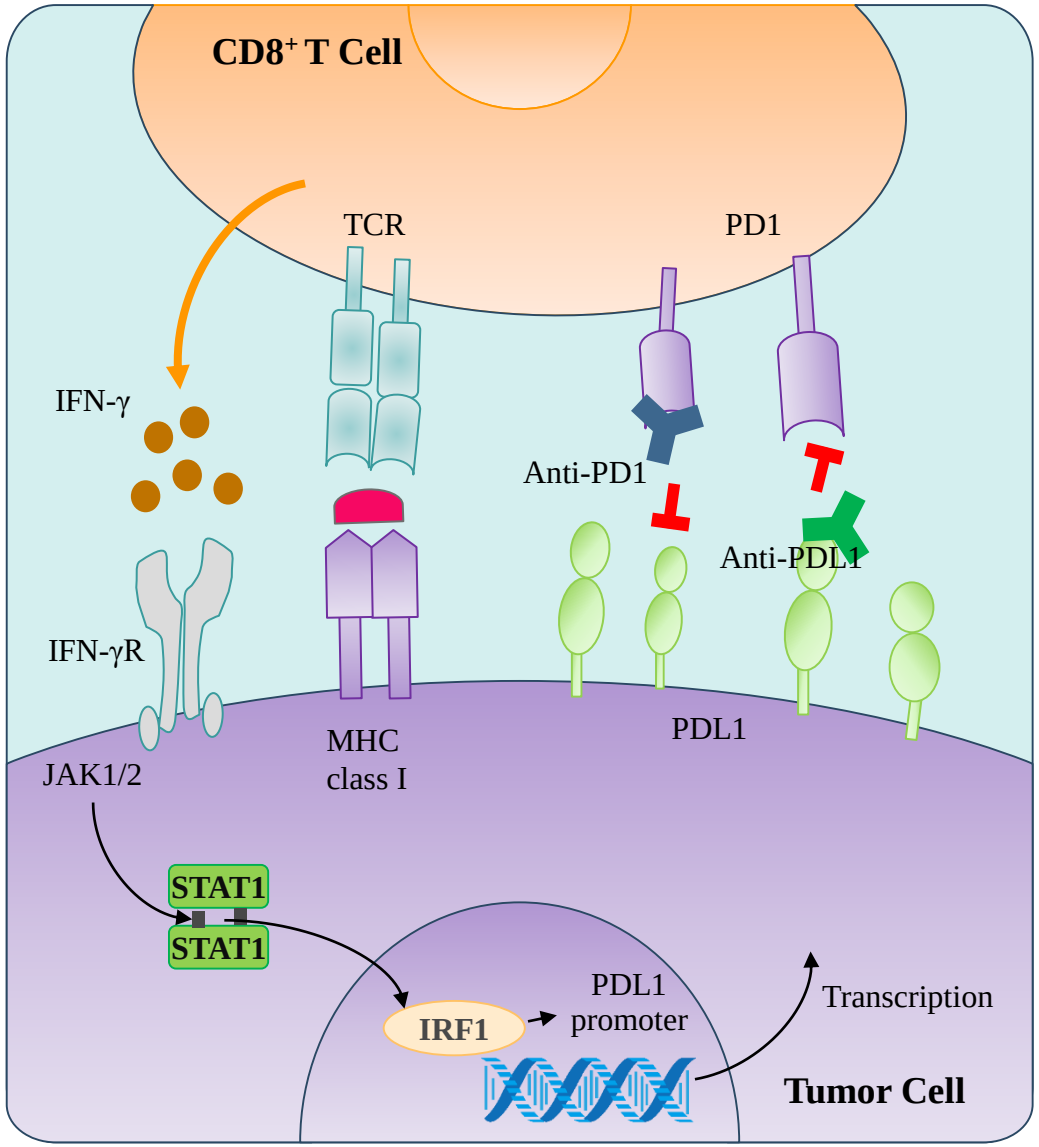
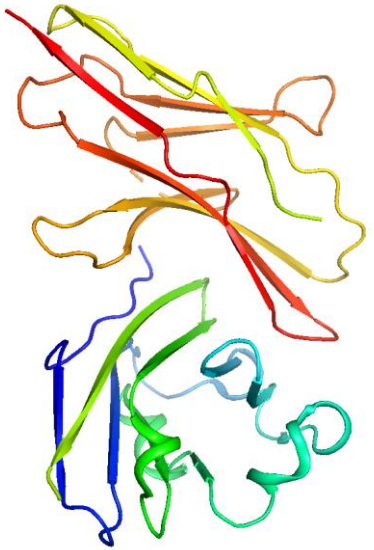
Oral Checkpoint Inhibitors

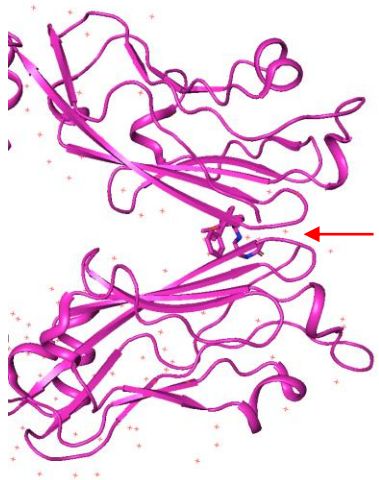
Immunotherapies: Great Success for mAb, It is Time for Oral Drugs

- BMS is the first company working on oral PD-L1 inhibitors
  - Filed patents for oral PD-L1 small molecule inhibitors in 2013
  - BMS stopped working PD-L1 inhibitors later due to drugability issues etc
- Gilead is one of leaders in oral PD-L1 inhibitors
  - A few years ago, Gilead announced its oral PD-L1 inhibitors for HBV
  - At JP Morgan virtual conference in 2021, Gilead announced its oral PD-L1 inhibitor GS-4224 was in Phase I for NSCLC
- Incyte is another leader in oral PD-L1 inhibitors
  - At SITC 2020, Incyte announced its oral PD-L1 inhibitor INCB86550 was in Phase I for solid tumors

PD-L1 Small Molecule Inhibitors: Challenges and Opportunities







- Antibodies block PD-1/PD-L1 interface
- Traditional small molecules not good at inhibiting protein-protein interaction

- PD-L1 small molecule inhibitors induce PD-L1 dimerization and internalization, preventing PD-1/PD-L1 interaction

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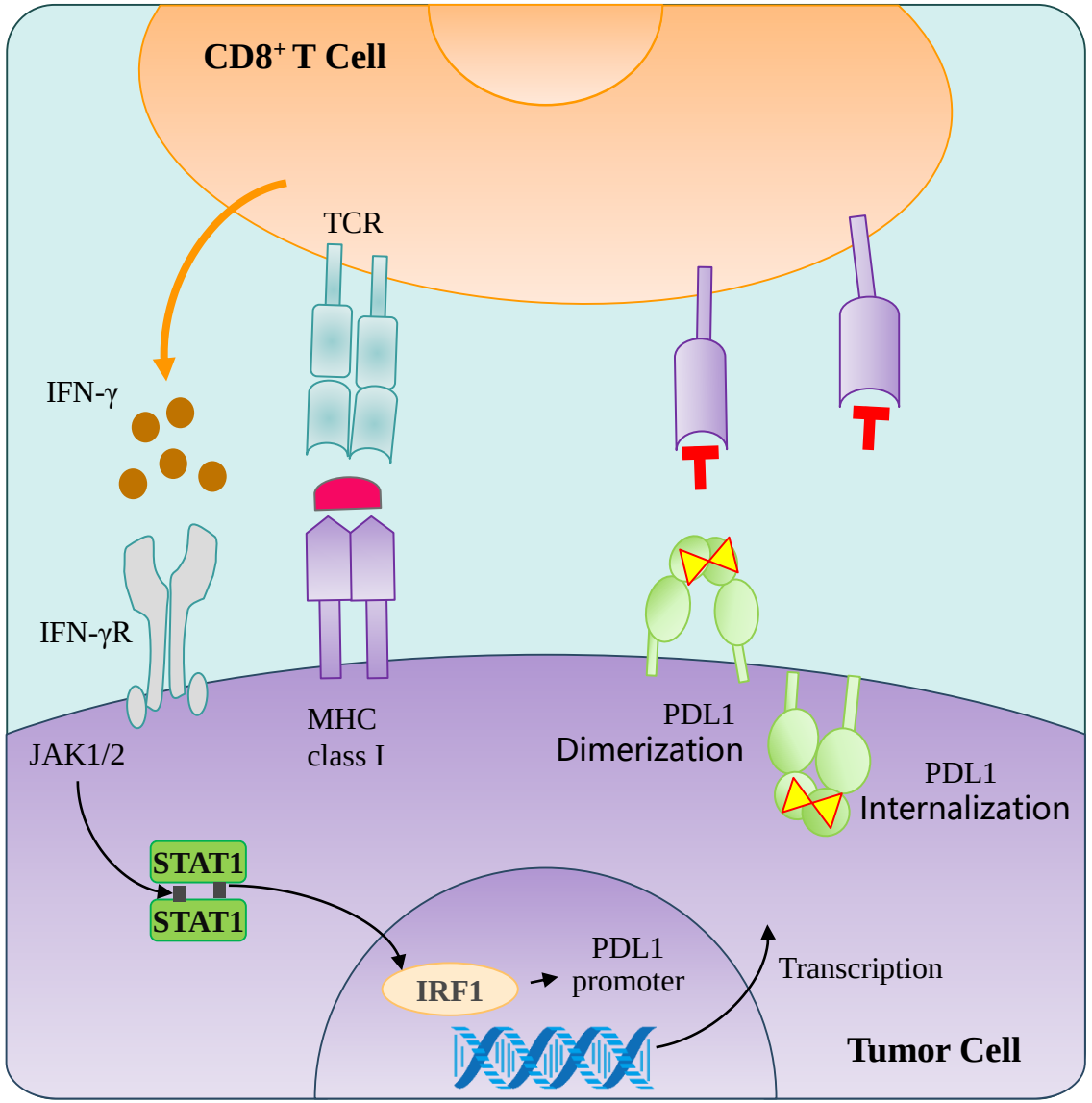
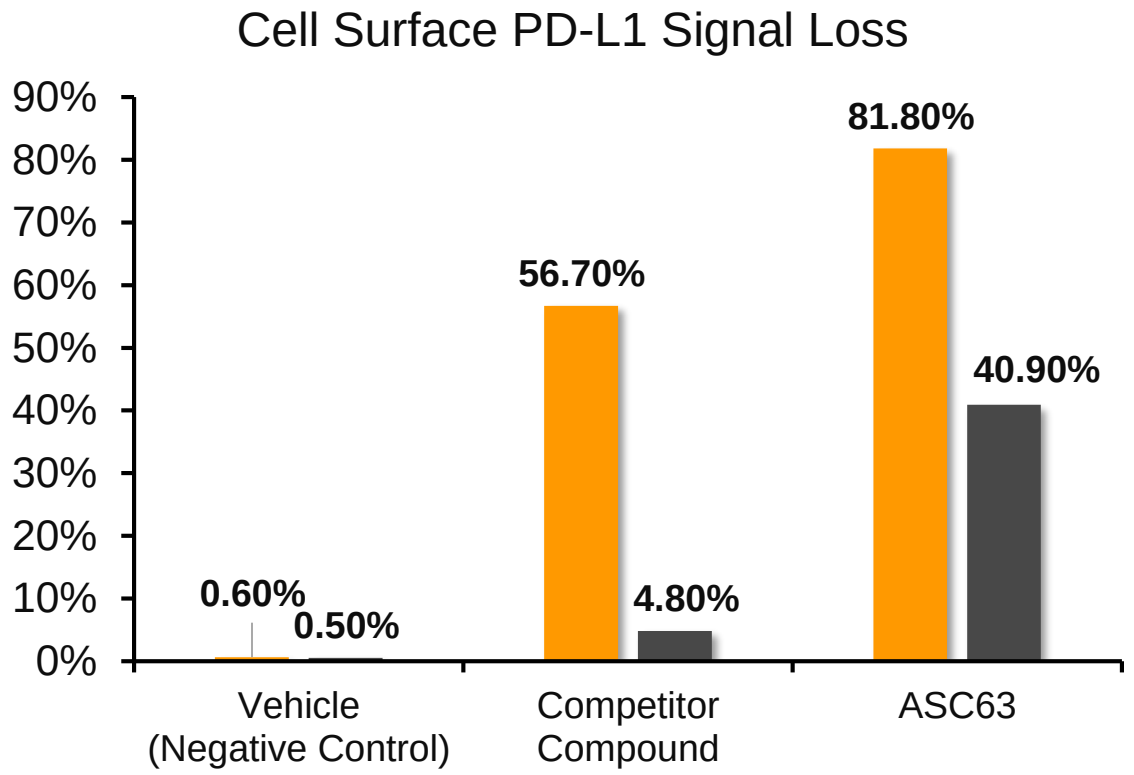
ASC63: Induce PD-L1 Dimerization and Sustained Internalization





Ascletis' ASC63

- Potently induce PD-L1 dimerization and internalization (orange)
- Induce long-lasting PD-L1 signal loss from cell surface (after compound removed from medium for 16 hours, still resulted in 40% PD-L1 signal loss) (black)

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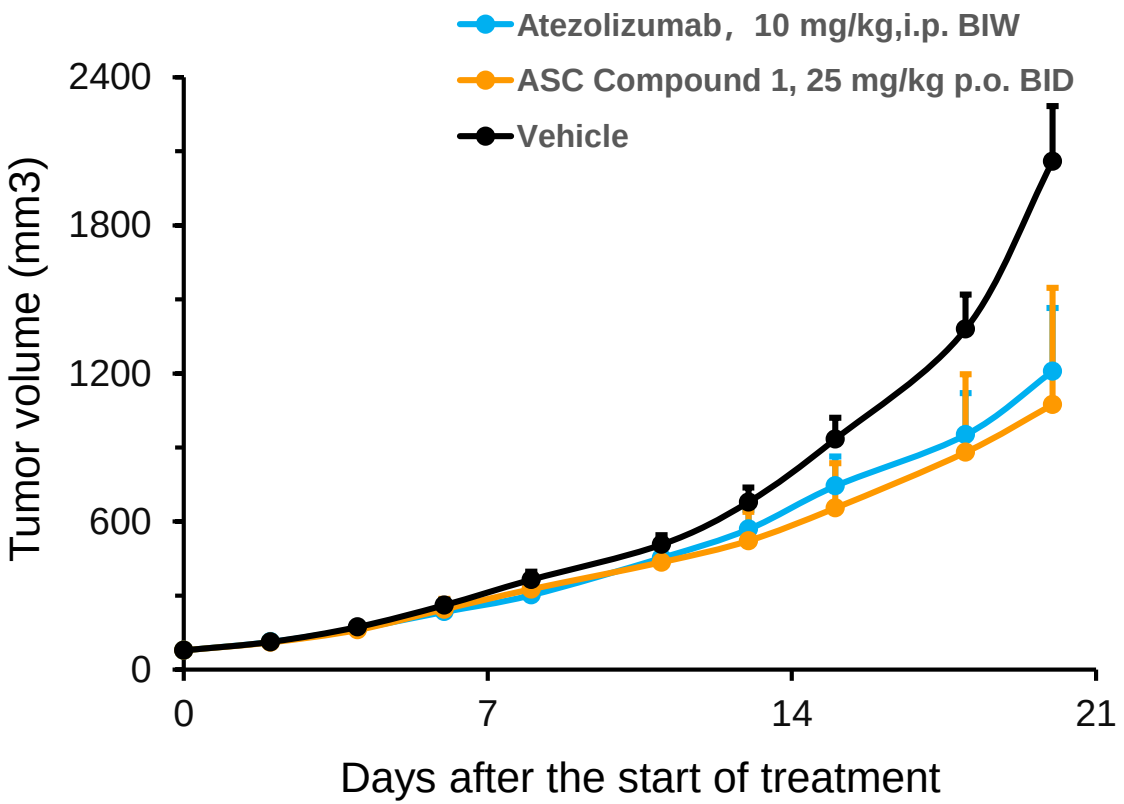
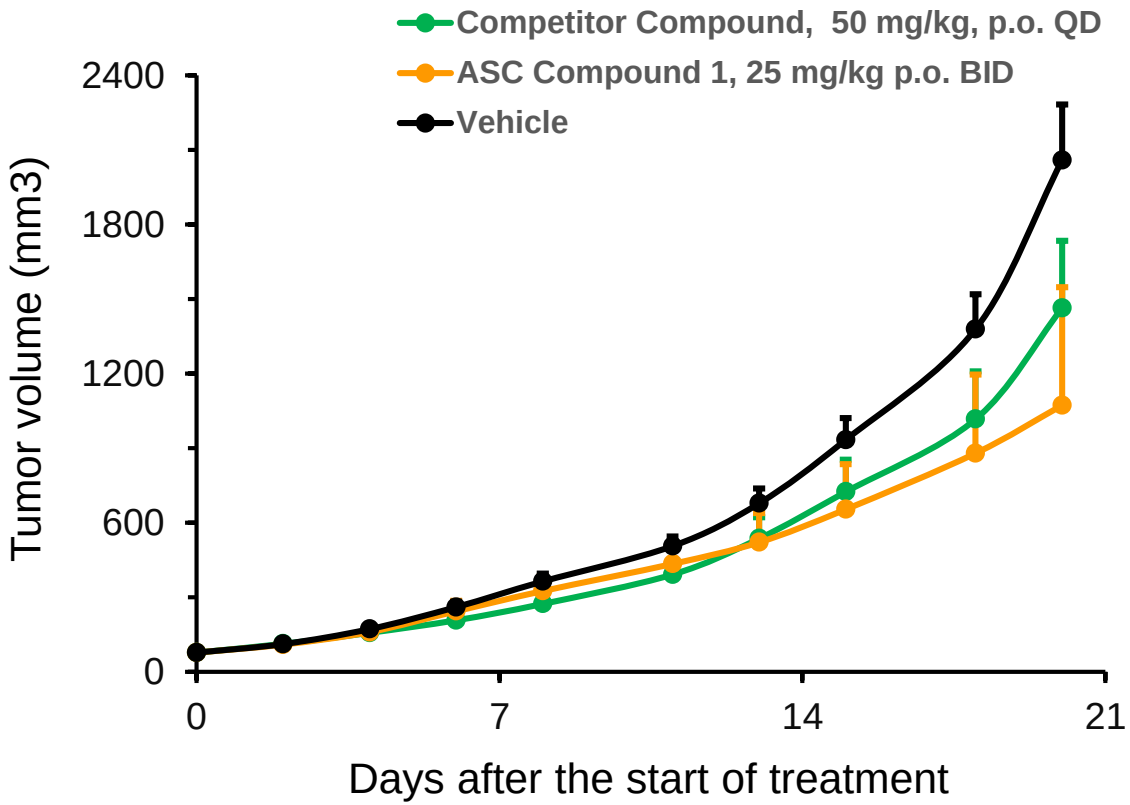
Ascletis' Oral PD-L1 Inhibitor: Anti-Tumor Activity in Syngeneic Mouse Model





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Cancer Lipid Metabolism and Oral Checkpoint Inhibitors

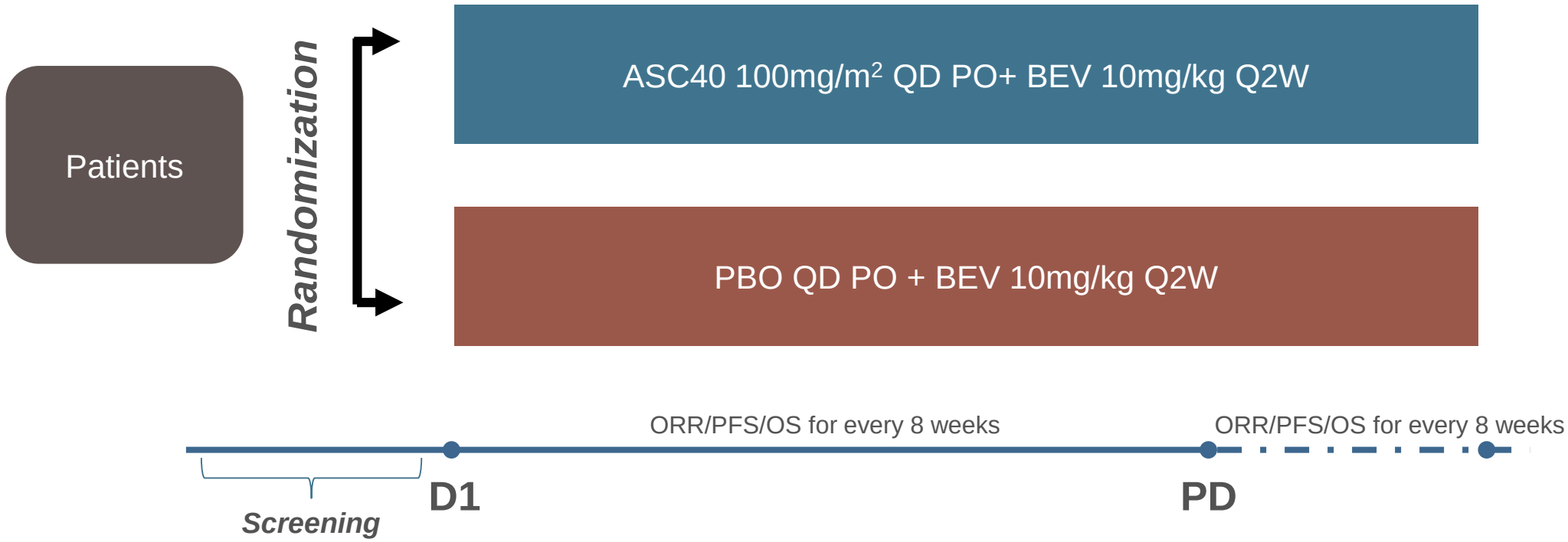
Target	Drug Candidates	Indication	Commercial Rights	Pre-IND	IND	Phase I	POC	Pivotal
FASN+VEGF	ASC40 (Oral) +Bevacizumab	Glioblastoma	Greater China[1]			*IST Phase II Completed*		
FASN	ASC40 (Oral)	Multiple Solid Tumors	Greater China[1]					
FASN	ASC60 (Oral)	Multiple Solid Tumors	Greater China[1]					
PD-L1	ASC61 (Oral small molecule)	Multiple Tumors	Global					
PD-L1	ASC63 (Oral small molecule)	Multiple Tumors	Global					

Notes: 1. ASC40 and ASC60 are licensed from Sagimet for the exclusive rights in the Greater China.

FASN: Fatty Acid Synthase VEGF: Vascular Endothelial Growth Factor PD-L1: Programmed Cell Death-Ligand 1

Recurrent Glioblastoma

- A Pivotal Randomized, Double Blind, Placebo Controlled Trial of ASC40 in Combination with Bevacizumab to treat Chinese Patients with Recurrent Glioblastoma



PD: Progression disease

Viral Diseases

Marketed Products in China

GANOVO®
(Danoprevir)
Indication: HCV

ASCLEVIR®
(Ravidasvir)
Indication: HCV

聚乙二醇干扰素α-2a(40KD)注射液
派罗欣
PEGASYS®
peginterferon alfa 2a (40KD)

Pegasys®
(Peginterferon alfa-2a)
Indication: HBV

Notes: 1. Pegasys® is licensed from Shanghai Roche Pharmaceuticals Ltd. for the exclusive rights in the Mainland China.
2. GANOVO® is licensed from Roche (F. Hoffmann-La Roche AG) for the exclusive rights in the Greater China.
3. ASCLEVIR® is licensed from Presidio Pharmaceuticals, Inc. for the exclusive rights in the Greater China.

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Viral Diseases

HBV functional cure

Target	Durg Candidates	Commercial Rights	Pre-IND	IND	Phase I	Phase IIa	Phase IIb/III
PD-L1	ASC22	Greater China[1]					
FXR	ASC42	Global					
Undisclosed	Candidate identified	Global					

HCV cure

Target	Durg Candidates	Commercial Rights	Pre-IND	IND	Phase I	Phase IIa	Phase IIb/III
Dual Targeted FDC	ASC18	Greater China					

HIV immune restoration / functional cure

Target	Durg Candidates	Commercial Rights	Pre-IND	IND	Phase I	Phase IIa	Phase IIb/III
Protease	ASC09F (ASC09 / Ritonavir FDC)	Mainland China and Macau[2]					
PD-L1	ASC22	Greater China[1]					

Notes: 1. ASC22 is licensed from Suzhou Alphamab Co.,Ltd. (“Alphamab”) for the exclusive rights in the Greater China. 2. ASC09 is licensed from Janssen R&D Ireland for the exclusive rights in Mainland China and Macau. 3. The tablet formulation of Ritonavir that the Group develops has completed bioequivalence (BE) studies of the tablets on healthy volunteers. ANDA of Ritonavir was accepted by NMPA on August 22, 2019.

FASN: Fatty Acid Synthase VEGF: Vascular Endothelial Growth Factor PD-L1: Programmed Cell Death-Ligand 1 FDC: Fixed Dose Combination

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HBV Functional Cure

HBV: Partial Cure vs Functional cure

Measure	Partial Cure	Functional cure
Serum HBV DNA	Negative	Negative
Serum HBsAg	Positive	Negative

Therapeutic approaches leading functional cure

Immune therapies

Direct antivirals

Combination of direct antivirals and immune therapies

most promising

Ascletis: Building HBV Franchise Leading to Functional Cure

- Cornerstones: Marketed Pegasys® and subcutaneously injected PD-L1 antibody - ASC22
- Pegasys® in combination with in-house developed drug candidates against novel targets such as FXR
- PD-L1 antibody ASC22 in combination with in-house developed drug candidates against novel targets such as FXR
- Pegasys® or PD-L1 antibody ASC22 - Partner with drug candidates of industrial leaders
  - siRNA
  - Core Inhibitors
  - HBV Entrylinhibitors
  - Therapeutic Vaccine

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MOA of PD-L1 Antibody Against Chronic Hepatitis B

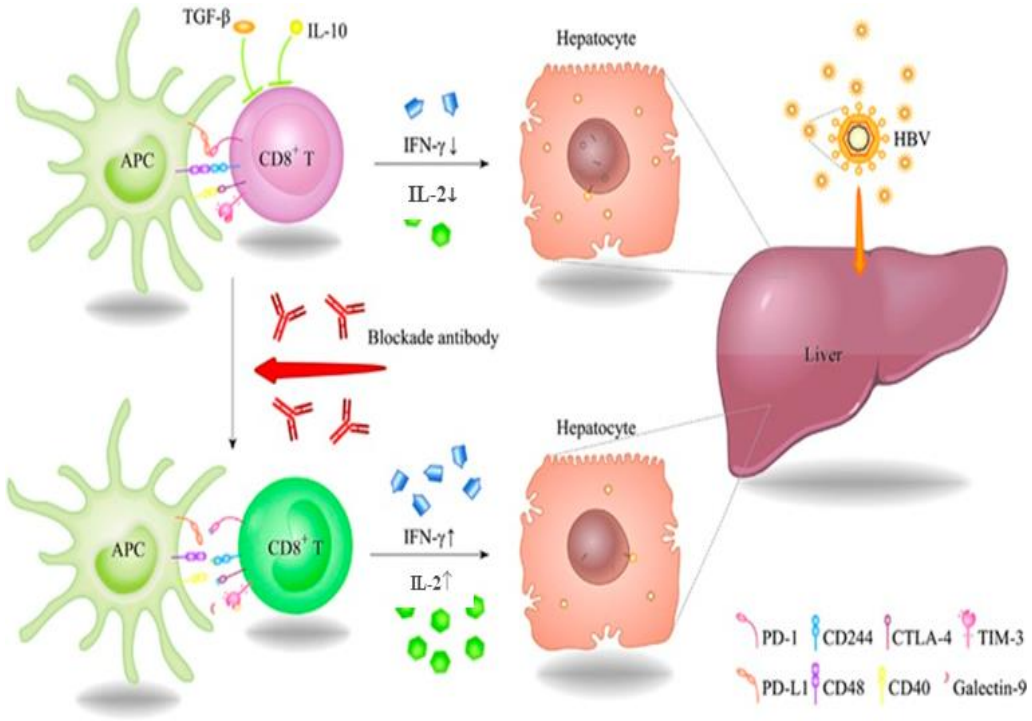
- ASC22 (KN035) can block the PD-1/PD-L1 pathway to restore T Cell immune function and eliminate HBV.

PD-1/PD-L1 interaction leads to T cell exhaustion

—— Persistent HBV infection

Blockade of PD-1/PD-L1 pathway restores T cell function

—— Elimination of HBV



1. Peng G, et al. PD-1 upregulation is associated with HBV-specific T cell dysfunction in chronic hepatitis B patients. Mol Immunol. 2008;45(4):963-70.
2. B Ye, et al. T-cell exhaustion in chronic hepatitis B infection: current knowledge and clinical significance. Cell Death Dis. 2015 Mar 19;6:e1694.

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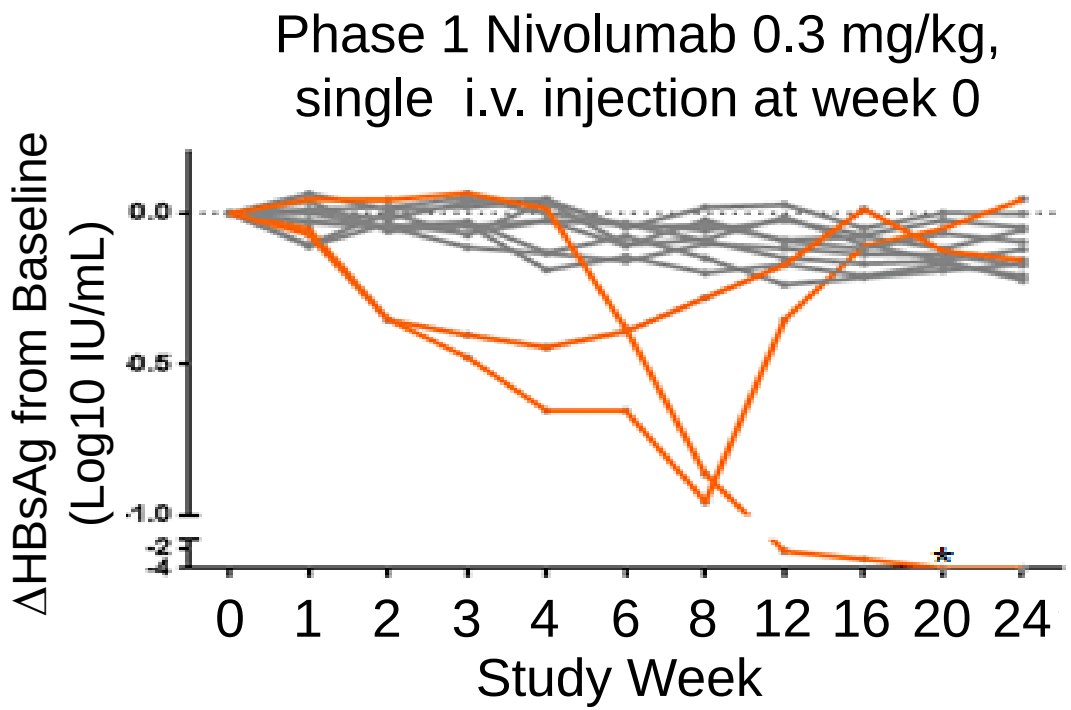
PD-1/PD-L1 Antibodies in Clinical Trials for HBV Functional Cure

- Ascletis
  - PD-L1 antibody (ASC22 (Envafolimab)), subcutaneous injection
  - Phase IIa single dose escalation (0.3, 1.0 and 2.5 mg/kg) completed
  - Phase IIb multiple doses (1.0 and 2.5 mg/kg, Q2W for 24 weeks) ongoing
- Gilead
  - PD-1 antibody Opdivo (Nivolumab), i.v. injection in combination with TLR8+siRNA+TAF, Phase II to start
- Vaccitech
  - PD-1 antibody Opdivo (Nivolumab), i.v. injection in combination with therapeutic vaccine(s)
- Henlix
  - PD-1 antibody (HLX10), i.v. injection
  - Phase II ongoing, up to 3 doses of HLX10 at 1 mg/kg, Q4W

HBV Functional Cure: PD-1 Antibody - Opdivo (Nivolumab)

Nivolumab: Monoclonal antibody against PD-1 Approved for solid organ tumors and lymphomas



- 1/10 patient Achieved HBsAg loss at week 16 and maintained negative during follow-up
- 1/10 patient experienced 1 log HBsAg decline at week 8 but rebounded afterwards
- 1/10 patient had moderate HBsAg decline

Human Proof of Concept study demonstrated HBsAg loss and its sustainability by single i.v. injection of PD-1 antibody.

Gane, EASL 2017

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Cure for HBV: First-in-class Subcutaneously Injected PD-L1 Ab

ASC22 (Envafolimab) is a single domain PD-L1 antibody. As an immunotherapy, ASC22 has a potential to lead to a significant breakthrough towards a functional cure for chronic Hepatitis B.

Global First-in-class

Blockade of PD-1/PD-L1 pathway to restore specific T-cell function

Immunotherapy for HBV

Only subcutaneously administered PD-1/PD-L1 antibody with a biologic license application (BLA) submitted for oncology indication

Demonstrated good safety profile

- Phase IIa data showed ASC22 is safe and well tolerated in chronic hepatitis B (CHB) patients and Phase IIb clinical trial has been initiated
- In addition to CHB patients, 1000+ cancer patients exposed in multiple clinical trials in US, China and Japan, Including two pivotal trials in China

Differentiated Profile

- Subcutaneous route of administration
- Good stability at room temperature

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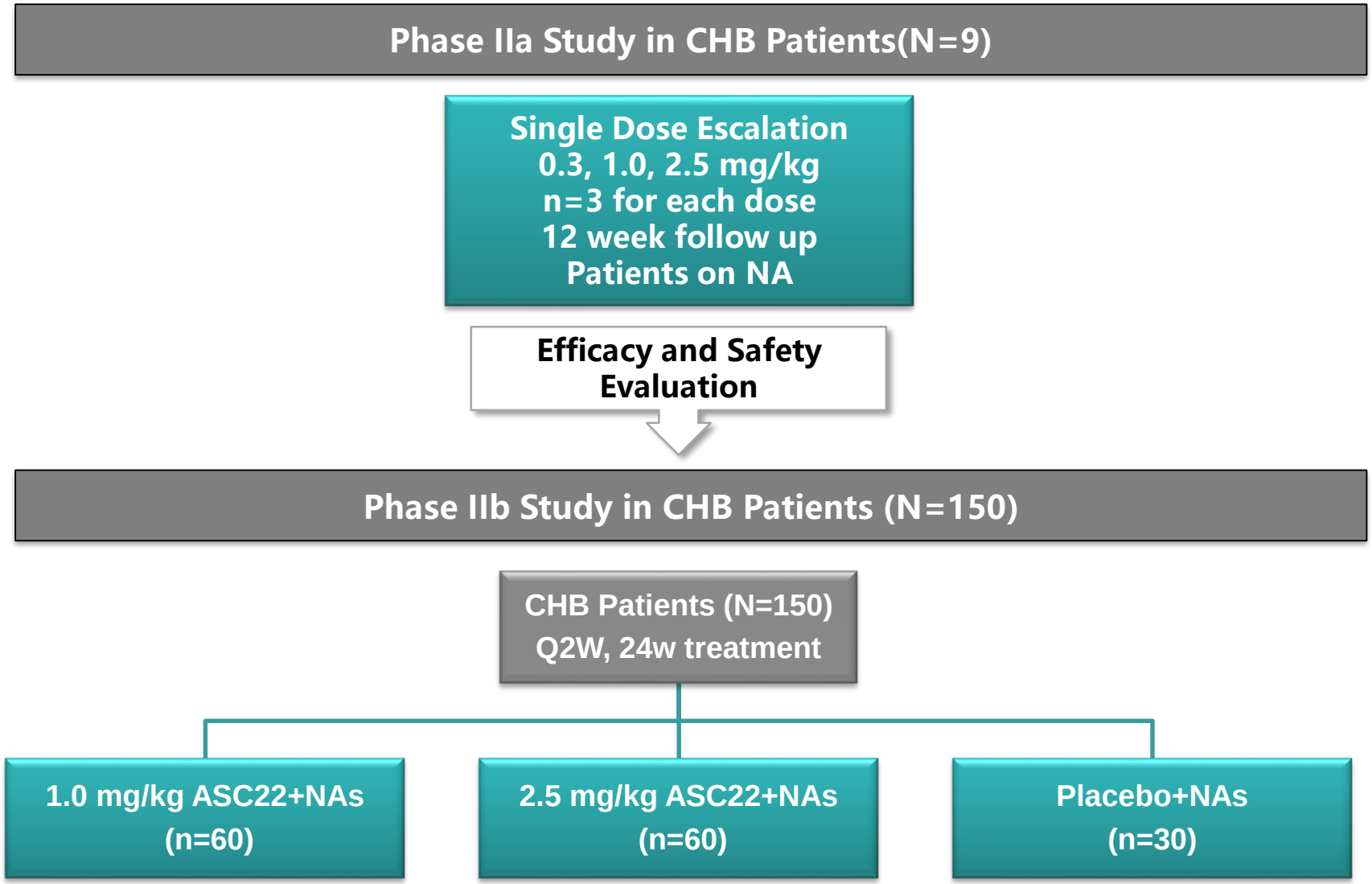
HBV Functional Cure: s.c. PD-L1 Ab ASC22 vs i.v. PD-L1 Abs

Company	Roche	MSD	AstraZeneca	Ascletis
Product	Atezolizumab	Avelumab	Durvalumab	ASC22（Envafolimab）
Target	PD-L1	PD-L1	PD-L1	PD-L1
Dose	1200 mg/3 weeks	800mg/2 weeks	10mg/kg/2 weeks	1-2.5mg/kg/2 week
Administration	I.V	I.V	I.V	S.C
Indication	Late stage or metastasized Urothelial Carcinoma; Unresectable late stage NSCLC	Adult or Adolescent metastasized Merkel Cell Carcinoma； Late stage or metastasized Urothelial Carcinoma	Late stage or metastasized Urothelial Carcinoma; Unresectable late stage NSCLC	Hepatitis B

1. ASC22 (Envafolimab) has lower dose, with advantage in administration route and storage condition.
2. ASC22 (Envafolimab) is the first PD-1/PD-L1 antibody with subcutaneous injection entering into late phase clinical trial.
3. Phase IIa data showed ASC22 (Envafolimab) is safe and well tolerated in chronic hepatitis B (CHB) patients and Phase IIb clinical trial has been initiated.
4. ASC22 (Envafolimab) has been investigated in several studies conducted in China, USA, and Japan involving greater than 1000 subjects in oncology with proven safety.

ASC22 Phase IIa/IIb Chronic Hepatitis B Study Design for Functional Cure



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Positive Efiicacy Data from ASC22 Phase IIa Single Dose Study

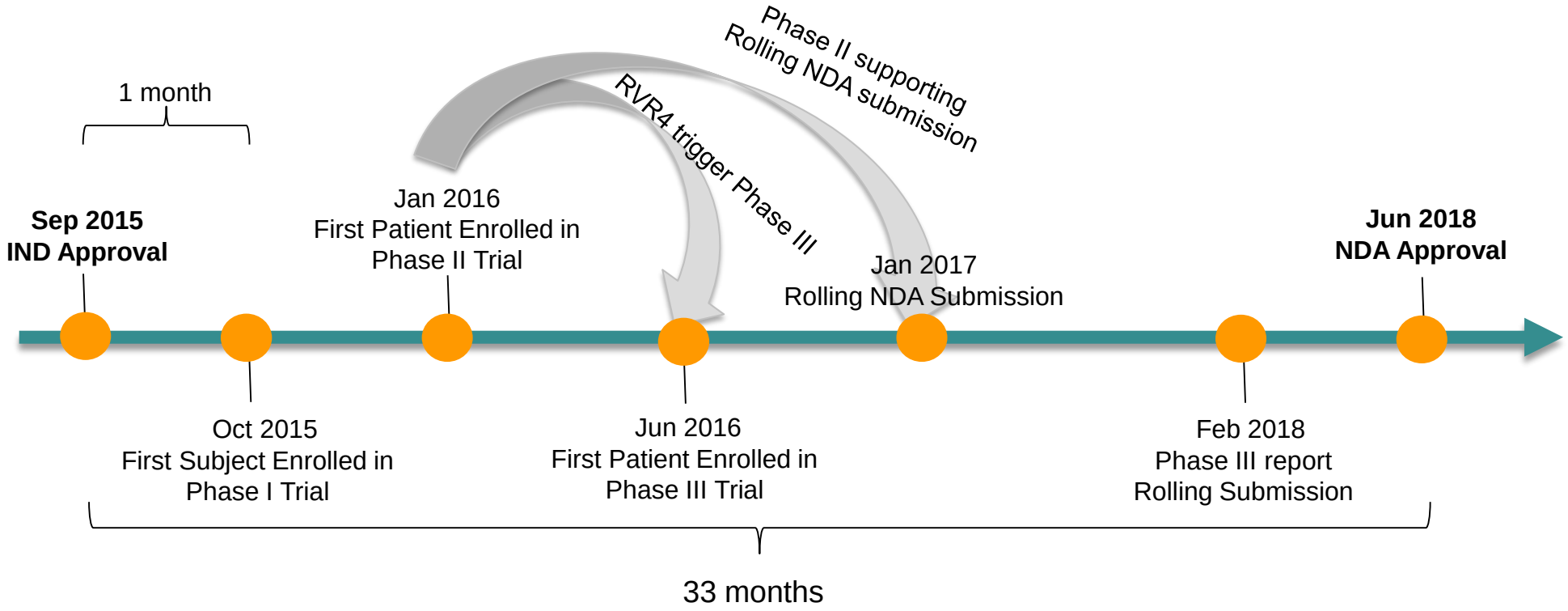
- Trend of dose dependent HBsAg reduction after single dose administration of 0.3, 1.0 or 2.5 mg/kg ASC22 (Envafolimab).
- 8/9 patients treated with ASC22 (Envafolimab) exhibited some decline in HBsAg at the end of 12-week follow-up.
- Among 3 patients receiving 2.5 mg/kg dose, 1 patient achieved a maximum HBsAg reduction of 1.2 log10 IU/mL during the 12-week follow-up.

Good Safety Data from ASC22 Phase IIa Single Dose Study

- ASC22 (Envafolimab) is safe and well tolerated at all three dose levels with only grade 1 adverse effects.
- There were no grade 2 or above adverse effects observed during 12-week follow-up.
- There were no SAE and no discontinuations.
- Single dose administrations up to 2.5 mg/kg ASC22(Envafolimab) did not affect alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels (all below upper limit of norm) during 12-week follow-up.

R&D Execution Excellence
GMP Manufacturing Capacity
Commercialization Capability

R&D Efficiency : GANOVO® from IND to NDA Approval: 33 months



Company (Target)	IND Approval	NDA Approval	IND approval to NDA approval (months)
Ascletis (HCV NS3/4A)	Sept 2015	June 2018	33
BMS (HCV NS3/4A and 5A)	June 2013	June 2017	48

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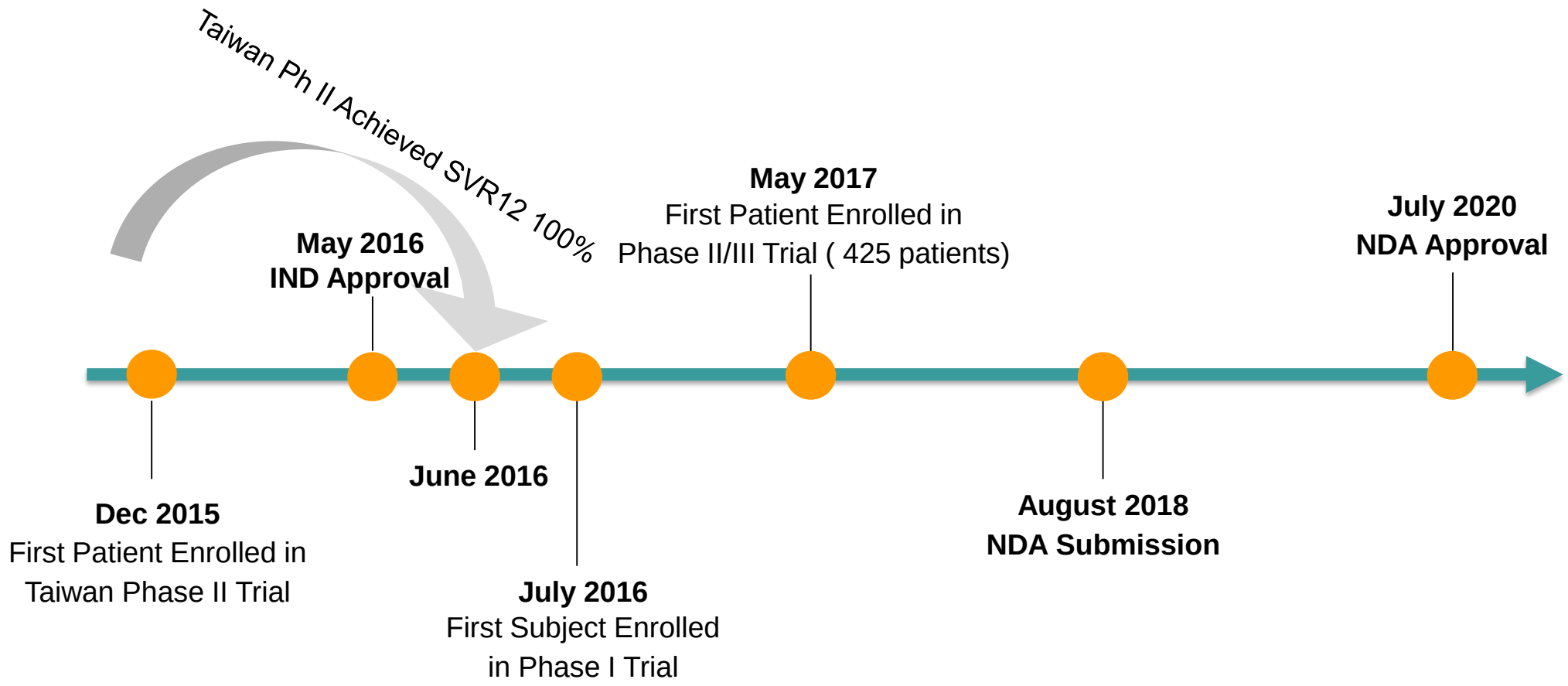
R&D Efficiency: ASCLEVIR® from IND to NDA Approval: 50 months



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GMP Manufacturing Facilities

中华人民共和国

药品GMP证书

CERTIFICATE OF GOOD MANUFACTURING PRACTICES FOR PHARMACEUTICAL PRODUCTS
PEOPLE'S REPUBLIC OF CHINA

证书编号：ZJ20180068
Certificate No.

企业名称：歌礼药业（浙江）有限公司
Manufacturer: Ascletis Pharmaceuticals Co., Ltd.

地　址：绍兴滨海新城沥海镇云海路1号
Address: No.1, Yunhai Road, Lihai District, Binhai New Town, Shaoxing City

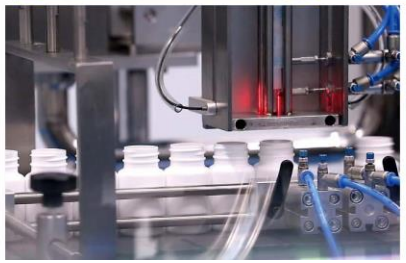
认证范围：片剂
Scope of Inspection: Tablets

经审查，符合中华人民共和国《药品生产质量管理规范》要求。
特发此证。
This is to certify that the above-mentioned manufacturer complies with the requirements of Chinese Good Manufacturing Practices for Pharmaceutical Products.

有效期至 2023 年 06 月 13 日
This certificate remains valid until 06/13/2023

发证机关：
Issued By
Date for Issuing 06/14/2018 2018 年 06 月 14 日

国家食品药品监督管理总局制
CHINA FOOD AND DRUG ADMINISTRATION



GMP Certified	Quality Assurance	International Standards	Supply ensured
▪ Quality-by-design approach implemented ▪ Complied with cGMP	▪ State-of-art equipment with cutting-edge technology capabilities	▪ Experienced manufacturing employees from MNCs	▪ Production capacity of 130 million tablets

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Experienced and Extensive Sales Network

Experienced Team

Roche · Bristol-Myers Squibb · GILEAD · gsk GlaxoSmithKline · NOVARTIS · MERCK

√ **5** major units including medical affairs, sales, marketing strategy, market access, and channel / distribution

√ Directors and above management have 10+ years experience of HCV and HBV at the above representative companies

Network Coverage

- **~1,000** Hospitals located in regions where hepatitis B&C is most prevalent in China
- **~5,400** specialists and key opinion leaders covered in the hepatitis field
- **22** distribution agreements with major distributors, enabling nationwide coverage and timely delivery of products.

Strategy

- Branding Activities and Market Research
- Patients Research and Analysis
- HCV/HBV Awareness Raising

GANOVO®

19 Days

2018

NDA Approved	GMP Certified	Inaugural Sales
June 8	**June 14**	**June 27**

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Global Business Development Strategy

Global Partnerships

Roche

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

PRESIDIO

康宁杰瑞 ALPHAMAB

SAGIMET BIOSCIENCES

Galmed Pharmaceuticals

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Global BD Strategy

2 License-Out

3 License-In

1 Co-Development

4 Strategic Investment

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Co-Development: Areas of Interest

HBV

- ASC22 (subcu PD-L1antibody) + siRNA
- ASC22 + Capsid inhibitor
- ASC22 + Entry inhibitor

NASH

GLP-1/GLP-1R

- ASC42 (FXR) + subcu weekly GLP-1 / GLP-1R
- ASC40(FASN) + subcu weekly GLP-1 / GLP-1R

SGLT

- ASC42 (FXR) + oral QD SGLT drug
- ASC41 (THR-β) + oral QD SGLT drug

Oncology

- GBM: ASC40 (lipid metabolism drug)+bevatzamab
- mBC: ASC40 + other drug
- KRAS mutation: ASC40 + other drug

License-Out: Areas of Interest

NASH

- ASC41 (THR-β)
- ASC42 (FXR)

HBV

Oncololgy

License-In: Areas of Interest

HBV

Oncololgy

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