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Corporate Presentation

Ascletis Pharma Inc.

January 2022

Ascletis Overview

China & US based **Global Platform Biotech**, covering the entire value chain from discovery and development to manufacturing and commercialization

Focus on **Viral Diseases, NASH** and **Oncology** where there are significantly unmet medical needs

Potential **First-in-class/Best-in-class** innovative pipelines, global development with high efficiency

Significant partnerships: Roche, Janssen, Pharmaceutical Companies of Johnson & Johnson, SAGIMET BIOSCIENCES, 康宁杰瑞 ALPHAMAB

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Marketed Products

Marketed Regimen for HCV

(Danoprevir； Ritonavir)
GANOVO®

(Ravidasvir)
ASCLEVIR®

Marketed Product for HBV

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

(Peginterferon alfa-2a)
Pegasys®

Included in the NRDL

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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Pipeline Overview

Disease Areas	Target	Candidate	Commercial rights	Pre-IND	IND	Phase I	Phase IIa	Phase IIb	Phase III / Pivotal
Viral Diseases	PD-L1	ASC22 (S.C mAb)	Global	HBV functional cure					
	FXR	ASC42 (Oral small molecule)	Global	HBV functional cure					
	PD-L1	ASC22 (S.C mAb)	Global	HIV functional cure					
	RdRp	ASC10 (Oral small molecule)	Global	COVID 19					
	3CLpro	ASC11 (Oral small molecule)	Global	COVID 19					
Non-alcoholic Steatohepatitis/Primary biliary cholangitis	FASN	ASC40 (Oral small molecule)	Greater China	NASH					
	FXR	ASC42 (Oral small molecule)	Global	PBC					
	THRβ	ASC41 (Oral small molecule)	Global	NASH					
	FXR	ASC42 (Oral small molecule)	Global	NASH					
	THRβ + FXR	ASC43F (Oral FDC)	Global	NASH					
	FASN + FXR	ASC44F (Oral FDC)	Global	NASH					
	FASN+THRβ	ASC45F (Oral FDC)	Global	NASH					
Oncology	FASN	ASC40 (Oral small molecule)	Greater China	rGBM					
	FASN	ASC40 (Oral small molecule)	Greater China	Drug resistant Breast Cancer					
	FASN	ASC40 (Oral small molecule)	Greater China	KRAS mutant NSCLC					
	PD-L1	ASC61 (Oral small molecule)	Global	Solid Tumor					
	FASN	ASC60 (Oral small molecule)	Greater China	Solid Tumor 1					
	FASN	ASC60 (Oral small molecule)	Greater China	Solid Tumor 2					
	PD-L1	ASC63 (Oral small molecule)	Global	Solid Tumor					
Exploratory Indications	FASN	ASC40 (Oral small molecule)	Greater China	ACNE					

NASH/PBC
Viral Diseases
Oncology
Exploratory Indications

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Viral Diseases

HBV (Functional Cure)

Target	Candidate	Commercial rights	Pre-IND	IND	Phase I	Phase IIa	Phase IIb	Phase III	Competitiveness
PD-L1	ASC22	Global[1]							• First-in-class candidate for HBV functional cure through blocking PD-1/PD-L1 pathway • 19% of patients with baseline HBsAg ≤500 IU/mL obtained HBsAg loss and no rebound after the last dosing of ASC22 • Improved compliance with subcutaneous injection
FXR	ASC42	Global							• First-in-class MOA • Inhibit transcription from DNA to RNA • Reduce stability of HBV cccDNA

HIV Immune Restoration/Functional Cure

Target	Candidate	Commercial rights	Pre-IND	IND	Phase I	Phase IIa	Phase IIb	Phase III	Competitiveness
PD-L1	ASC22	Global[1]							• Subcutaneous injection, easier administration

1. ASC22 is licensed from Suzhou Alphamab Co.,Ltd. (“Alphamab”) for the worldwide exclusive rights.

Viral Diseases — Oral Direct-Acting Antivirals Against SARS-CoV-2

Marketed Product

R&D Pipeline

ASC10

oral direct-acting antiviral drug candidate targeting RdRp

In vitro data showed significant activity against SARS-CoV-2. ASC10 is an in-house discovered drug candidate with the global intellectual property and commercial rights. Compared to RdRp-targeted Molnupiravir which was approved by US Food and Drug Administration (FDA), ASC10 has a new and differentiated chemical structure. Ascletis has filed patent applications for multiple compound and use. Animal studies demonstrated that ASC10 has higher bioavailability when compared to Molnupiravir. Ascletis plans to submit investigational drug applications (INDs) for clinical trials in China, USA etc. in the first half of 2022.

ASC11

oral direct-acting antiviral drug candidate targeting 3CLpro

In combination with the authorized ritonavir oral tablets manufactured by Ascletis, to treat SARS-CoV-2 infection. ASC11 is an in-house discovered drug candidate with the global intellectual property and commercial rights. Compared to 3CLpro-targeted Nirmatrelvir which was approved by US FDA, ASC11 has a new and differentiated chemical structure. Ascletis has filed patent application for the compound and use. Ascletis plans to submit INDs for clinical trials in China, USA etc. in the second half of 2022.

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NASH/PBC Pipeline

Target	Candidate	Commercial rights	Pre-IND	IND	Phase I	Phase IIa	Phase IIb	Phase III	Competitiveness
FASN	ASC40 (NASH)	Greater China[1]	***U.S. FDA Fast Track***						• First-in-class, inhibit de novo lipogenesis • US/CN phase II showed significant reduction of liver fat content, and minimal side effects compared to other NASH drug candidates
FXR	ASC42 (PBC)	Global							• No pruritus • CDE approval for Phase II/III clinical trials
THRβ	ASC41 (NASH)	Global							• Third-in-class globally, First-in-class in China • Triglyceride reduction >30% with 1mg per day dosing • No DDI with drugs commonly used by NASH patients
FXR	ASC42 (NASH)	Global	***U.S. FDA Fast Track***						• Potential Best-in-class, no pruritus or LDC-c elevation • Higher elevation of FGF-19, an FXR target engagement biomarker
THRβ + FXR	ASC43F FDC (NASH)	Global							• First-in-class, dual targets to THRβ and FXR
FASN + FXR	ASC44F FDC (NASH)	Global							• First-in-class, dual targets to FASN and FXR
FASN + THRβ	ASC45F FDC (NASH)	Global							• First-in-class, dual targets to THRβ and FASN

1. ASC40 is licensed from Sagimet Biosciences Inc. for the exclusive rights in the Greater China.

Oral Cancer Metabolic Checkpoint and Immune Checkpoint Inhibitors

Target	Candidate	Indication	Commercial rights	Pre-IND	IND	Phase I	POC	Pivotal trial	Competitiveness
FASN + VEGF	ASC40 (Oral) +Bevacizumab	Recurrent glioblastoma	Greater China[1]	***Phase III in China approved***					• FIC, inhibit energy supply and disturb membrane phospholipid composition of tumor cells by blocking de novo lipogenesis • Significantly improved PFS in Phase II study
FASN	ASC40 (Oral)	Drug resistant Breast Cancer	Greater China[1]						• FIC MOA • Preliminary efficacy in phase I study
FASN	ASC40 (Oral)	KRAS mutant NSCLC	Greater China[1]						• FIC MOA • Preliminary efficacy in phase I study
PD-L1	ASC61 (Oral small molecule)	Multiple tumors	Global						• Oral small molecule, easier administration • Comparable efficacy as FDA-approved PD-L1 antibody drugs in animal models
FASN	ASC60 (Oral)	Solid tumor 1	Greater China[1]						• FIC • Better *in vitro* activities compared to ASC40
FASN	ASC60 (Oral)	Solid tumor 2	Greater China[1]						• FIC • Better *in vitro* activities compared to ASC40
PD-L1	ASC63 (Oral small molecule)	Multiple tumors	Global						• Oral small molecule, easier administration • Stronger effects on PD-L1 dimerization and internalization compared to competitor PD-L1 small molecule inhibitor

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

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Exploratory Indications

Acne

Target	Candidate	Commercial rights	Pre-IND	IND	Phase I	Phase II	Phase III	Competitiveness
FASN	ASC40	Greater China[1]						• FIC • Reduced sebum production in a dose-dependent manner in phase I study

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Anticipated Key Milestone(s) in next 12 months*

Viral Diseases

- ASC22/HBV—Progress on **communication with Regulatory Authority** for the **pivotal Phase III trial**
- ASC42/HBV--**Top-line results** from **China phase II** study
- ASC22/HIV—**Initiation** of **China phase II** study

NASH/PBC

- ASC40/NASH--**Interim results** from 52w biopsy **US phase IIb** study
- ASC41/NASH--**First patient dosed** in 52w biopsy adaptive **US phase IIa/IIb** study
- ASC42/NASH--**Submission** for approval of 52w biopsy adaptive **US phase IIa/IIb** study
- ASC43F/NASH--**Top-line results** from **US human PK** study
- ASC42/PBC--**Top-line results** from **China phase II** study

Oncology

- ASC40/rGBM—Completion of **80% patient enrollment** of **Phase III** trial
- ASC40/Solid tumors—**Initiation of phase II** in a solid tumor
- ASC60/Solid tumors--**Initiation of Phase I** in solid tumors
- ASC61/multiple tumors—US and CN **IND approvals** for solid tumors

Exploratory Indications

- ASC40/Acne--**Top-line results** from **China phase II** study

Disclaimer: The above milestones are only expectations and Ascletis makes no guarantees for the achievement of the milestones.

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Significant Market Potential

HBV

HBV (functional cure)

- 86 million hepatitis B virus carriers in China, and 1 million new cases reported every year； 1.59 million of people infected with HBV in the US.
- No functional cure could be achieved with current standard therapy (NAs).

NASH

NASH

- US: 80 million NAFLD, 18.6 million NASH patients；
- CN: 193 million NAFLD with NASH accounting for 20%-25% of NAFLD, which are 38-48 million NASH patients；
- Global: No approved drugs by FDA for NASH.

PBC

Primary biliary cholangitis

- Epidemiology study 2010: the prevalence of PBC in China was 49.2/100,000 persons and as high as 155.8/100,000 in women older than 40 years old, indicating a total of 656,000 PBC patients in China including 440,000 in females over age 40；
- UDCA is the only drug been approved in China with the effect of delaying disease progression; approximately 40% PBC patients have an inadequate response to UDCA or are unable to tolerate UDCA. *Ocaliva* has been approved in the US for patients who had an inadequate response or are unable to tolerate UDCA. However, *Ocaliva had significant side effects such as pruritus (63%) and fatigue (22%)*

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Significant Market Potential

rGBM

Recurrent Glioblastoma

- CN: gliomas has an incidence of 5-8/100,000 population per year, and GBM represents around 57% of gliomas thus has incidence rates of 2.85-4.56 per 100,000 population per year, suggesting approximately 40,000 to 64,000 new cases per yea;
- US: GBM represents 56.6% of gliomas and has an incidence rate of approximately 3.21 per 100,000 population;
- More than 90% glioblastoma patients will relapse after surgery, radiation and chemotherapies;
- Bevacizumab is the only drug approved for rGBM in China (PFS at 6 month is 16%, still need to be improved).

ACNE

Acne

- Eighth most prevalent disease in the world and affects more than 640 million people globally;
- The onset of acne often coincides with pubertal hormonal changes, and affects approximately 85% of adolescents and young adults aged 12 to 25 years. However, acne can also persist into or develop during adulthood;
- The global acne medication market size was US$11.86 billion in 2019, and is projected to reach US$13.35 billion by 2027.

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Viral Diseases

HBV Functional cure

HBV functional cure

6 months after treatment:

- **Normal liver function**
- **Negative serum HBV DNA (<20 IU/ml)**
- **Negative serum HBsAg (<0.05 IU/ml)**

86 million

hepatitis B virus carriers in China

1 million

new cases reported every year in China

1.59 million

Persons infected with HBV

No functional cure could be achieved with current standard therapy (NAs).

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HBV: Partial Cure vs Functional cure

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

Therapeutic approaches leading to functional cure

Immune therapies

Direct antivirals

Combination of direct antivirals and immune therapies

most promising

HBV (Functional Cure)

Target	Candidate	Commercial rights	Pre-IND	IND	Phase I	Phase IIa	Phase IIb	Phase III	Competitiveness
PD-L1	ASC22	Global[1]							• First-in-class candidate for HBV functional cure through blocking PD-1/PD-L1 pathway • 19% of patients with baseline HBsAg ≤500 IU/mL obtained HBsAg loss and no rebound after the last dosing of ASC22 • Improved compliance with subcutaneous injection
FXR	ASC42	Global							• First-in-class MOA • Inhibit transcription from DNA to RNA • Reduce stability of HBV cccDNA

1. ASC22 is licensed from Suzhou Alphamab Co.,Ltd. (“Alphamab”) for the worldwide exclusive rights .

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 Entry Inhibitors
  - Therapeutic Vaccine

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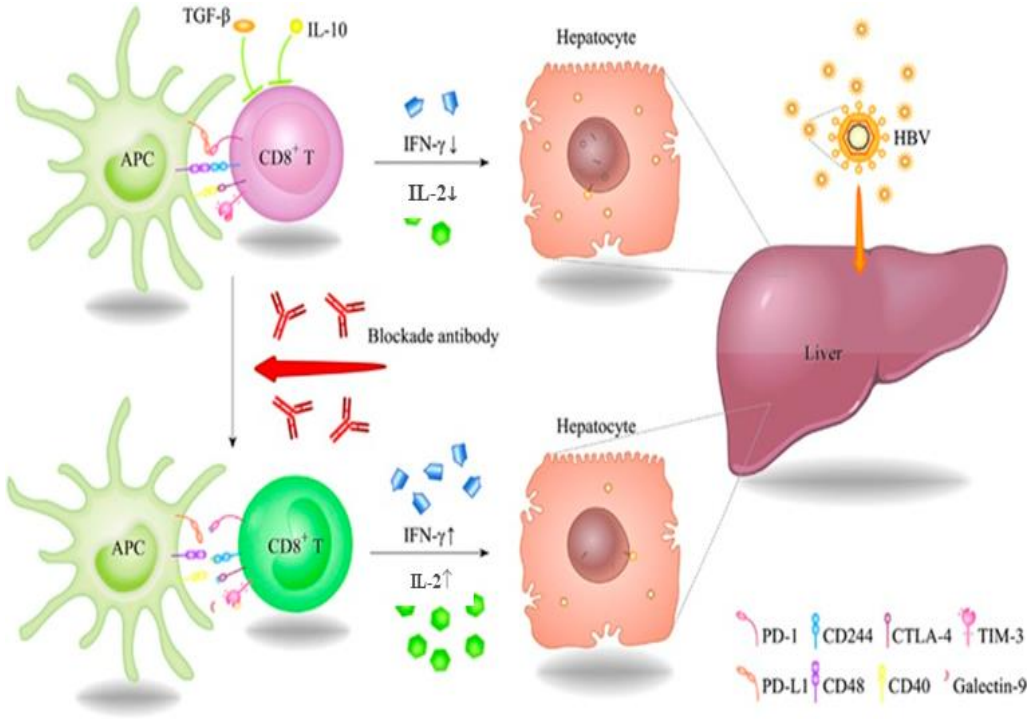
MOA of PD-L1 Antibody Against Chronic Hepatitis B

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



- ASC22 (KN035) can block the PD-1/PD-L1 pathway to restore T cell immune function and eliminate 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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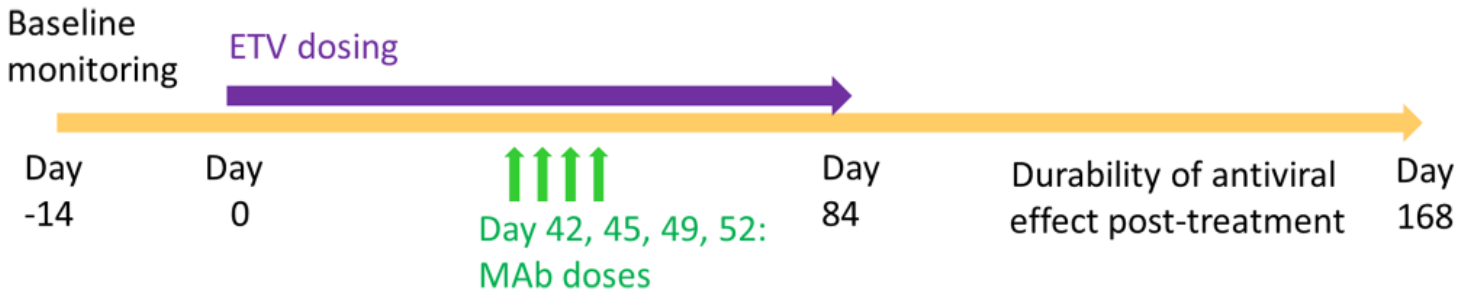
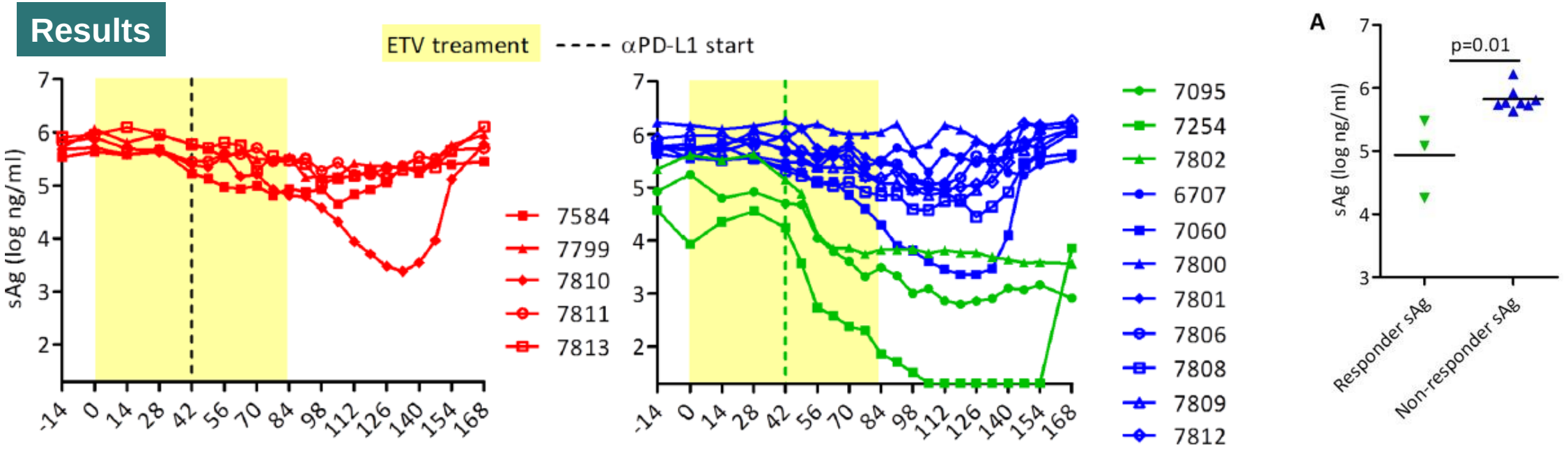
PD-L1 Antibody Study in Woodchuck HBV Model

Design



Results



- **Combination of αPD-L1 Ab with ETV led to the reduction of WHV sAg, especially in animals with a lower pre-treatment sAg level.**

Balsitis, S., et al., PLoS One, 2018, 13(2): e0190058.

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

- Ascletis
  - **ASC22 (Envafolimab)**, a **subcutaneously injected PD-L1 antibody**
  - Single dose escalation (0.3, 1.0 and 2.5 mg/kg) Phase IIa study is completed
  - Multiple doses (1.0 and 2.5 mg/kg, Q2W for 24 weeks) Phase IIb study is ongoing. Interim report showed that 19% (3/16) of patients with baseline HBsAg ≤ 500 IU/mL obtained HBsAg loss and still no rebound occurred up to now after the last dosing of ASC22, indicating a potential HBV functional cure
- Gilead
  - Ongoing Phase II study (PD-1 antibody Opdivo i.v. injection in combination with TLR8+siRNA+TAF)
- Vaccitech
  - Ongoing Phase I/II study (PD-1 antibody Opdivo i.v. injection in combination with therapeutic vaccine)
- Henlix
  - Ongoing Phase II study of PD-1 antibody (HLX10) i.v. injection at 1 mg/kg, Q4W, up to 3 doses

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

- ASC22 (Envafolimab) is a protein fusion of a humanized single-domain PD-L1 antibody and human IgG1 Fc. ASC22 has potential to cure chronic Hepatitis B patients in combination with other therapies.

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) approval for oncology indications

Demonstrated good safety profile

- Phase IIa study showed ASC22 is safe and well tolerated in chronic hepatitis B patients
- 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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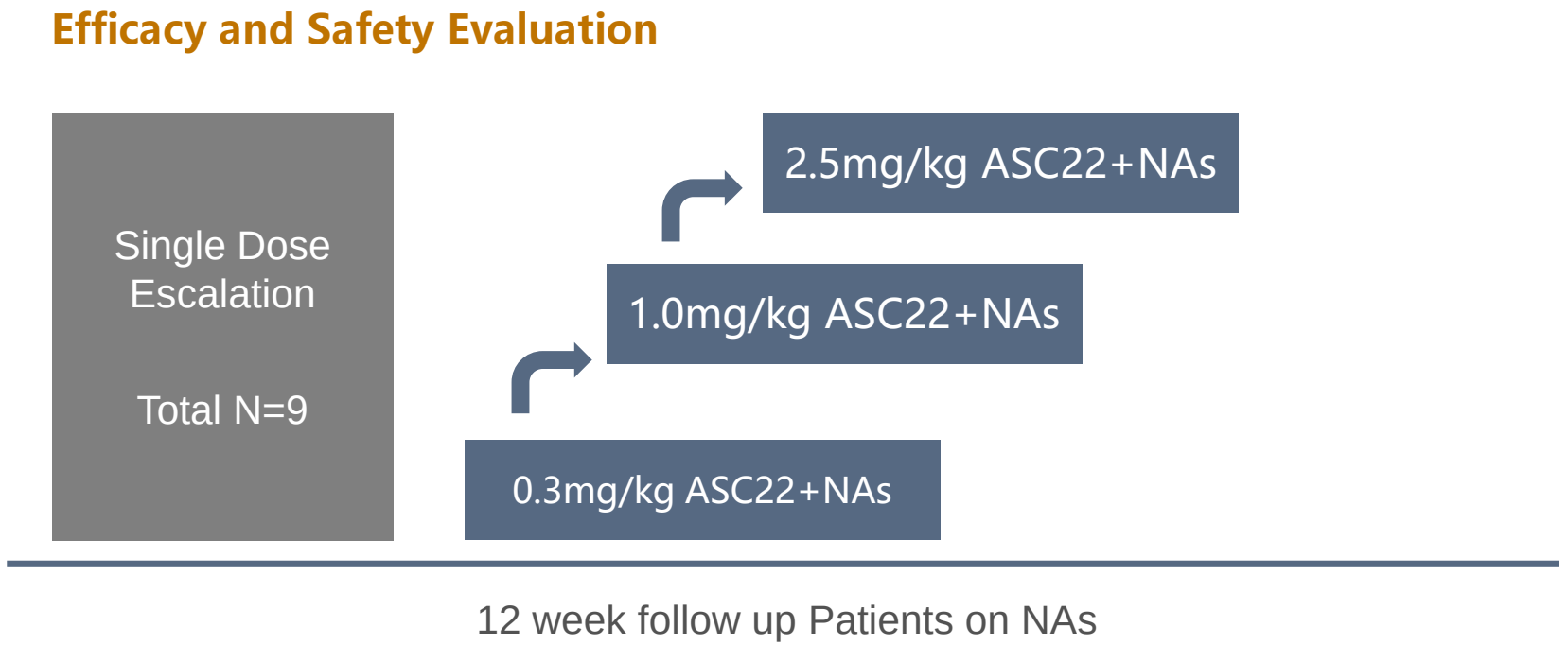
HBV Functional Cure: s.c. PD-L1 Ab ASC22 vs i.v. PD-L1 Abs

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) uses a 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 geneally safe and well tolerated in chronic hepatitis B (CHB) patients.
4. ASC22 (Envafolimab) has been investigated in several oncology studies conducted in China, USA, and Japan involving more than 1000 subjects with proven safety.

ASC22 Phase IIa Chronic Hepatitis B Study Design



Major inclusion criteria:
HBsAg < 10,000 IU/mL, HBV DNA < 20 IU/mL and negative HBeAg

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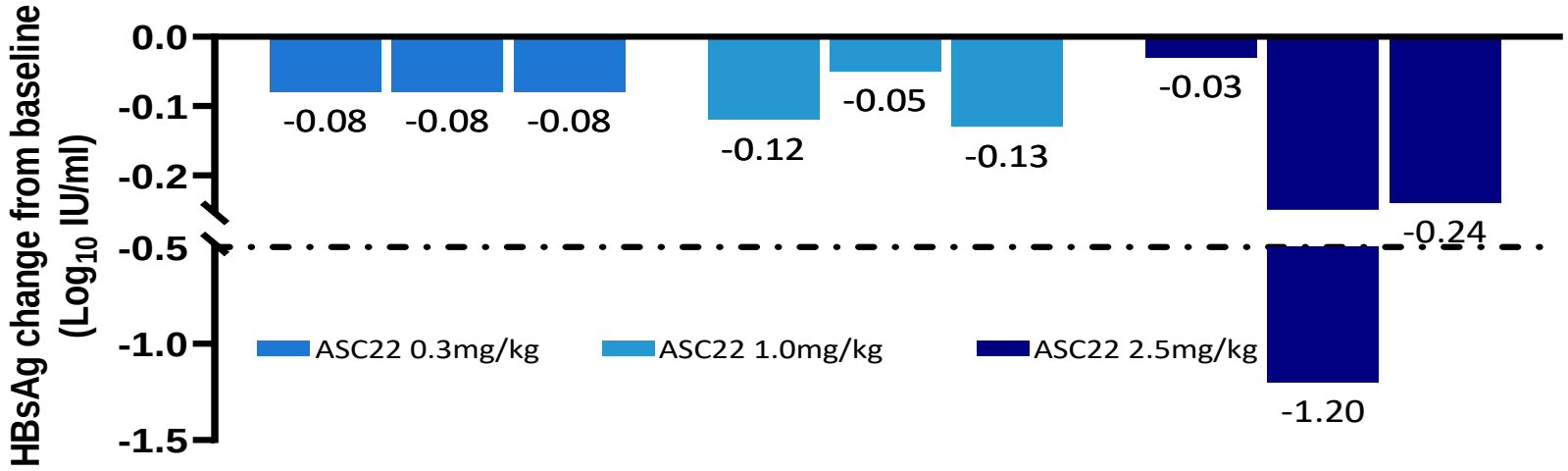
Positive Efficacy Data from ASC22 Phase IIa Single Dose Study

- Trend of dose dependent HBsAg reduction after a single dose administration of 0.3, 1.0 or 2.5 mg/kg ASC22 (Envafolimab).
- Among 3 patients receiving 2.5 mg/kg dose, 1 patient achieved a maximum HBsAg reduction of 1.2 log_{10} IU/mL during the 12-week follow-up.



A Phase IIa trial of Subcutaneously Administered PD-L1 Antibody ASC22 (Envafolimab) in Patients with Chronic Hepatitis B. *72th American Association for the Study of Liver Diseases (AASLD)& The Liver Meeting ®*, November 12-15, 2021. Virtual Conference.

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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 events (AEs) .
- There were no Grade 2 or above AEs observed during 12-week follow-up.
- There were no serious AE and no AE led to discontinuation.
- Single dose administrations of ASC22(Envafolimab) up to 2.5 mg/kg would not affect alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels (all below upper limit of normal) during 12-week follow-up.

A Phase IIa trial of Subcutaneously Administered PD-L1 Antibody ASC22 (Envafolimab) in Patients with Chronic Hepatitis B. *72th American Association for the Study of Liver Diseases (AASLD)& The Liver Meeting* ®, November 12-15, 2021. Virtual Conference.

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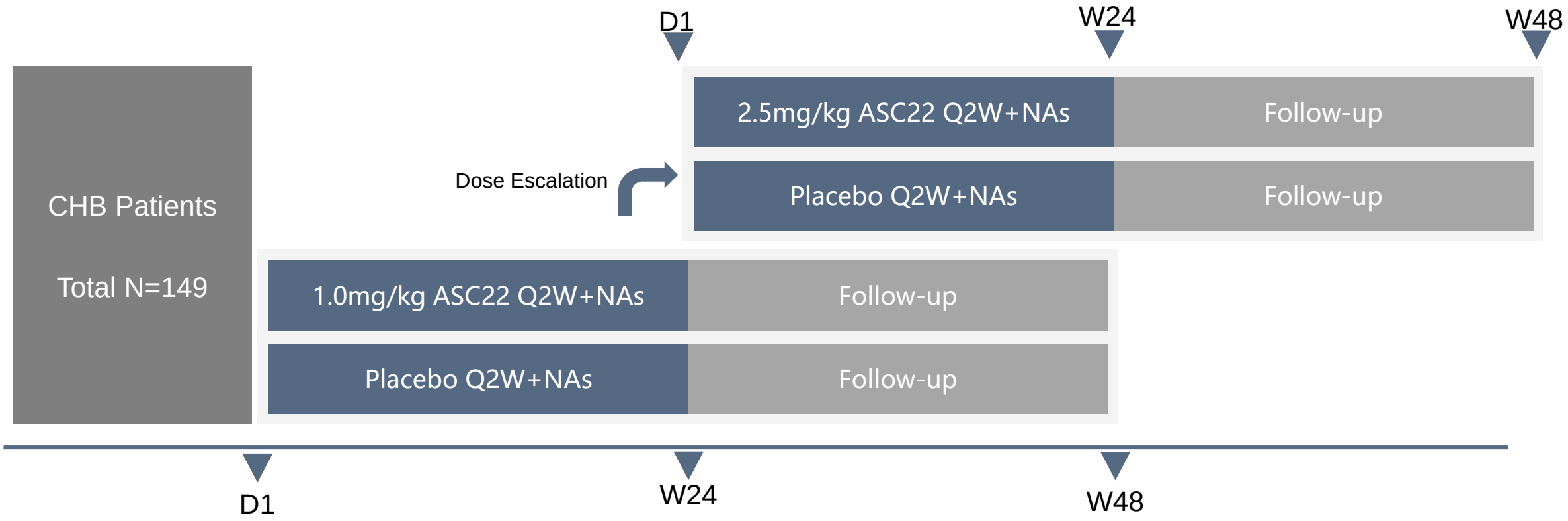
ASC22 Phase IIb Chronic Hepatitis B Study Design



Major inclusion criteria:
HBsAg < 10,000 IU/mL, HBV DNA < 20 IU/mL and negative HBeAg

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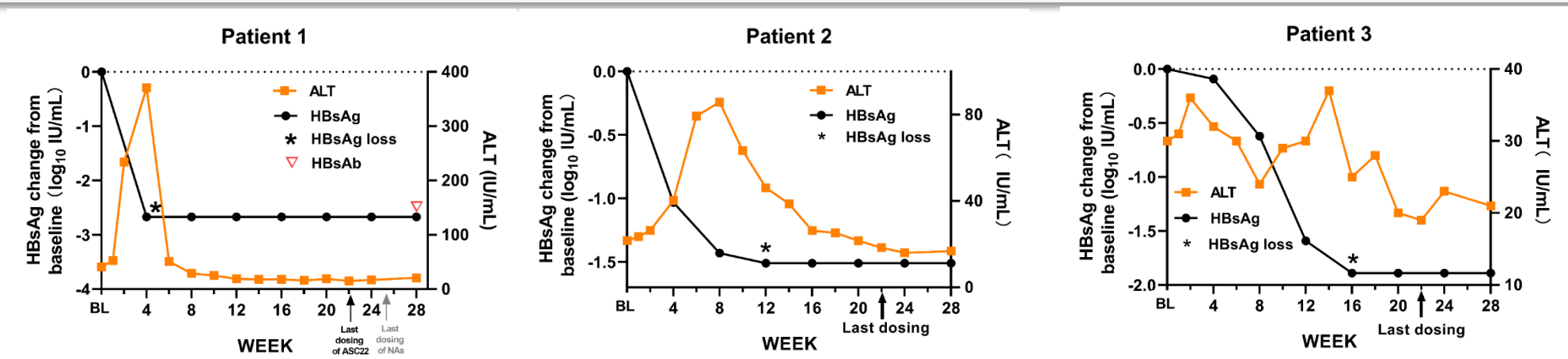
Positive Interim Results of PD-L1 Antibody ASC22 Phase IIb Study in Chronic Hepatitis B (149 Patients)

- HBsAg reduction was observed in the 1 mg/kg ASC22 once every two weeks plus nucleos(t)ide analogs group
  - Greater HBsAg reduction observed in patients with baseline HBsAg ≤ 500 IU/mL
  - **19% (3/16) of patients with baseline HBsAg ≤ 500 IU/mL obtained HBsAg loss and no rebound occurred up to now after the last dosing of ASC22, indicating a potential HBV functional cure**
  - No HBsAg reduction was observed in patients receiving placebo plus nucleos(t)ide analogs
- Receptor occupancy one month after 1 or 2.5 mg/kg dosing are both predicted to be > 90%, suggesting ASC22 has the potential to be given once monthly
- Patients treated with 1 mg/kg ASC22 plus nucleos(t)ide analogs had comparable AE profiles as those treated with placebo plus nucleos(t)ide analogs



Source: HBsAg Loss in Chronic Hepatitis B Patients with Subcutaneous PD-L1 Antibody ASC22 (Envafolimab) plus Nucleos(t)ide Analogs Treatment: Interim Results from a Phase IIb Clinical Trial. *72th American Association for the Study of Liver Diseases (AASLD)& The Liver Meeting* ®, November 12-15, 2021. Virtual Conference.

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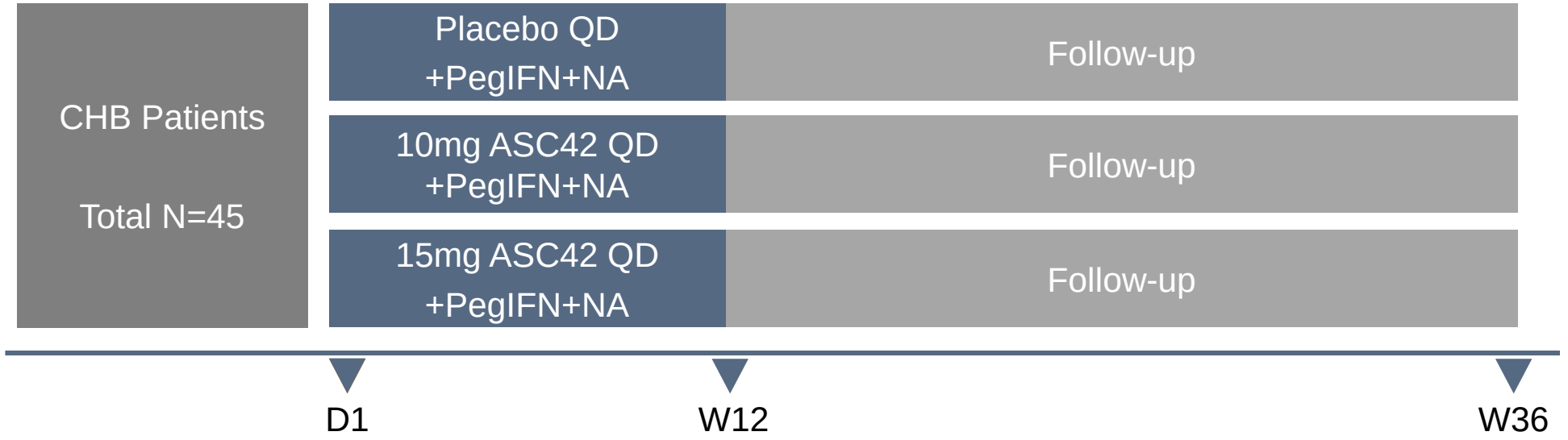
FXR agonist ASC42 has a unique mechanism of action against HBV

- ASC42 inhibits the transcription of HBV cccDNA into HBV RNA, which in turn inhibits the translation of HBV RNA into HBsAg
- ASC42 may also reduce HBV cccDNA stability.
- Both in vitro primary human hepatocyte (PHH) cells and in vivo AAV/HBV mouse studies demonstrated ASC42 significantly inhibited HBsAg and HBV pregenomic RNA (pgRNA)

ASC42: China Phase II Study Design



Non-alcoholic Steatohepatitis (NASH)/ Primary Biliary Cholangitis (PBC)

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, THRβ and FXR, and three fixed-dose combinations.

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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%

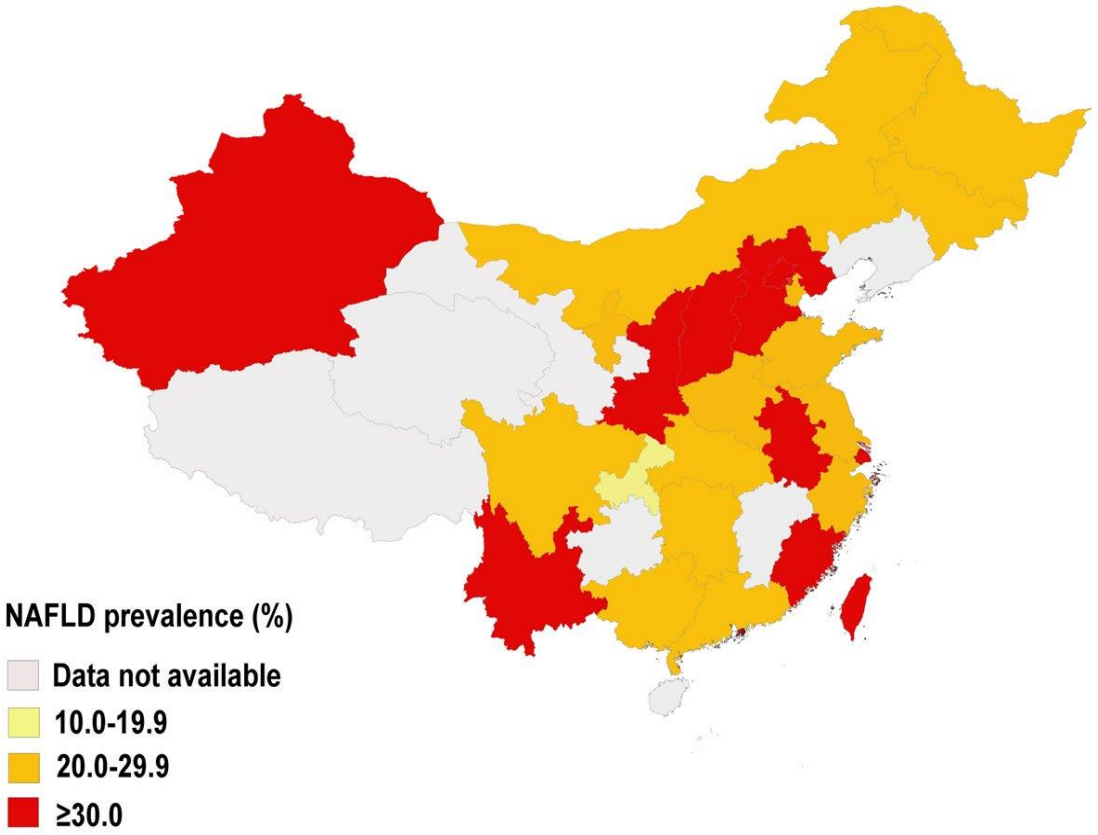
Obesity and Diabetes

are risk factors for progression to NASH

Source: 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%)

Source: 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.

Significant Unmet Medical Needs for the Treatment of PBC

China

- The prevalence of PBC in China was 49.2 cases per 100,000 persons and as high as 155.8 cases per 100,000 in women older than 40 years old, indicating a total of 656,000 PBC patients in China, including 440,000 females over age 40.
- Ursodeoxycholic acid (UDCA) is the only drug approved in China for PBC to delay disease progression. However, approximately 40% PBC patients have inadequate responses to UDCA or have drug intolerance.

US/EU

- 120,000 PBC patients in the US in 2014.
- Obeticholic acid (Ocaliva) has been approved by US FDA for treatment of PBC in combination with UDCA in patients with inadequate responses to UDCA, or as monotherapy in patients with drug intolerance to UDCA.
- Ocaliva has significant side effects, including pruritus (63%) and fatigue (22%).

NASH/PBC Pipeline

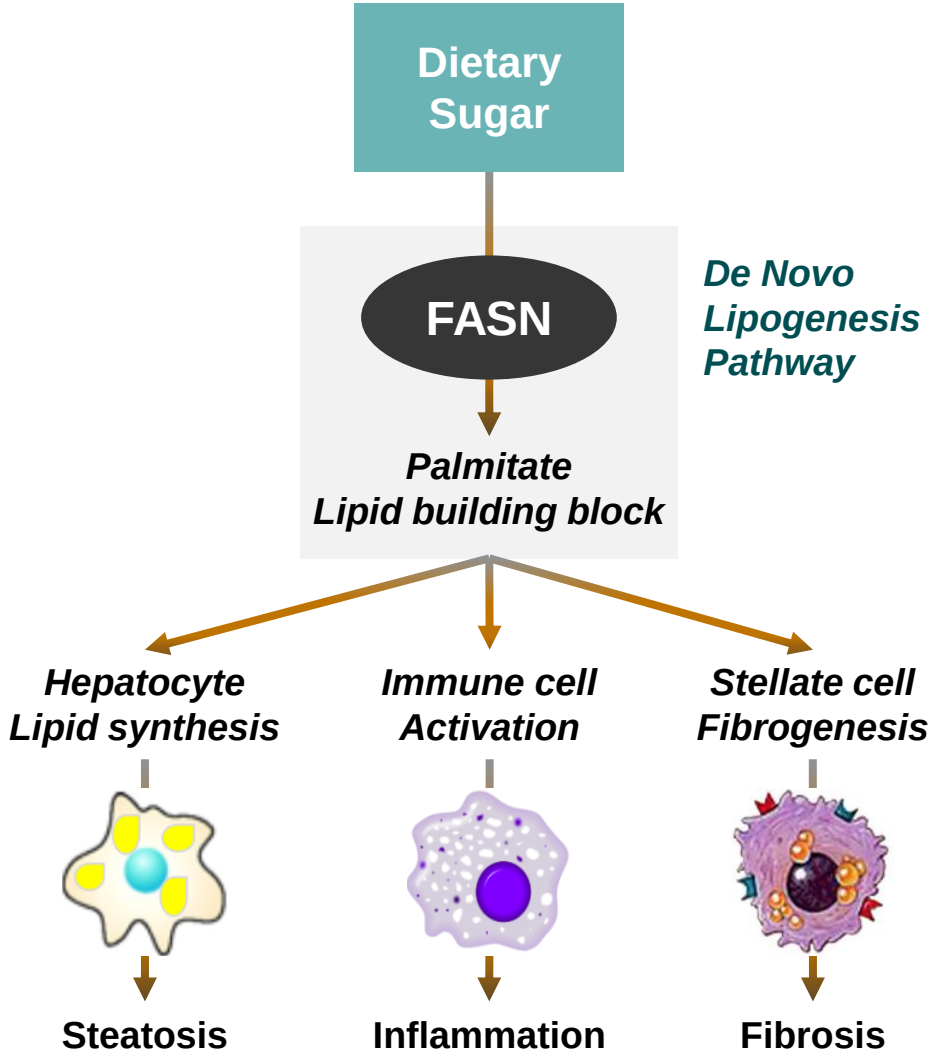
Target	Candidate	Commercial rights	Pre-IND	IND	Phase I	Phase IIa	Phase IIb	Phase III	Competitiveness
FASN	ASC40 (NASH)	Greater China[1]	***U.S. FDA Fast Track***						• First-in-class, inhibit de novo lipogenesis • US/CN phase II showed significant reduction of liver fat content, and minimal side effects compared to other NASH candidates
FXR	ASC42 (PBC)	Global							• No pruritus • CDE approval for Phase II/III clinical trials
THRβ	ASC41 (NASH)	Global							• Third-in-class globally, First-in-class in China • Triglyceride reduction >30% with 1mg per day dosing • No DDI with drugs commonly used by NASH patients
FXR	ASC42 (NASH)	Global	***U.S. FDA Fast Track***						• Potential Best-in-class, no pruritus or LDC-c elevation • Higher elevation of FGF-19, an FXR target engagement biomarker
THRβ + FXR	ASC43F FDC (NASH)	Global							• First-in-class, dual targets to THRβ and FXR
FASN + FXR	ASC44F FDC (NASH)	Global							• First-in-class, dual targets to FASN and FXR
FASN + THRβ	ASC45F FDC (NASH)	Global							• First-in-class, dual targets to THRβ and FASN

1. ASC40 is licensed from Sagimet Biosciences Inc. for the exclusive rights in the Greater China.

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



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

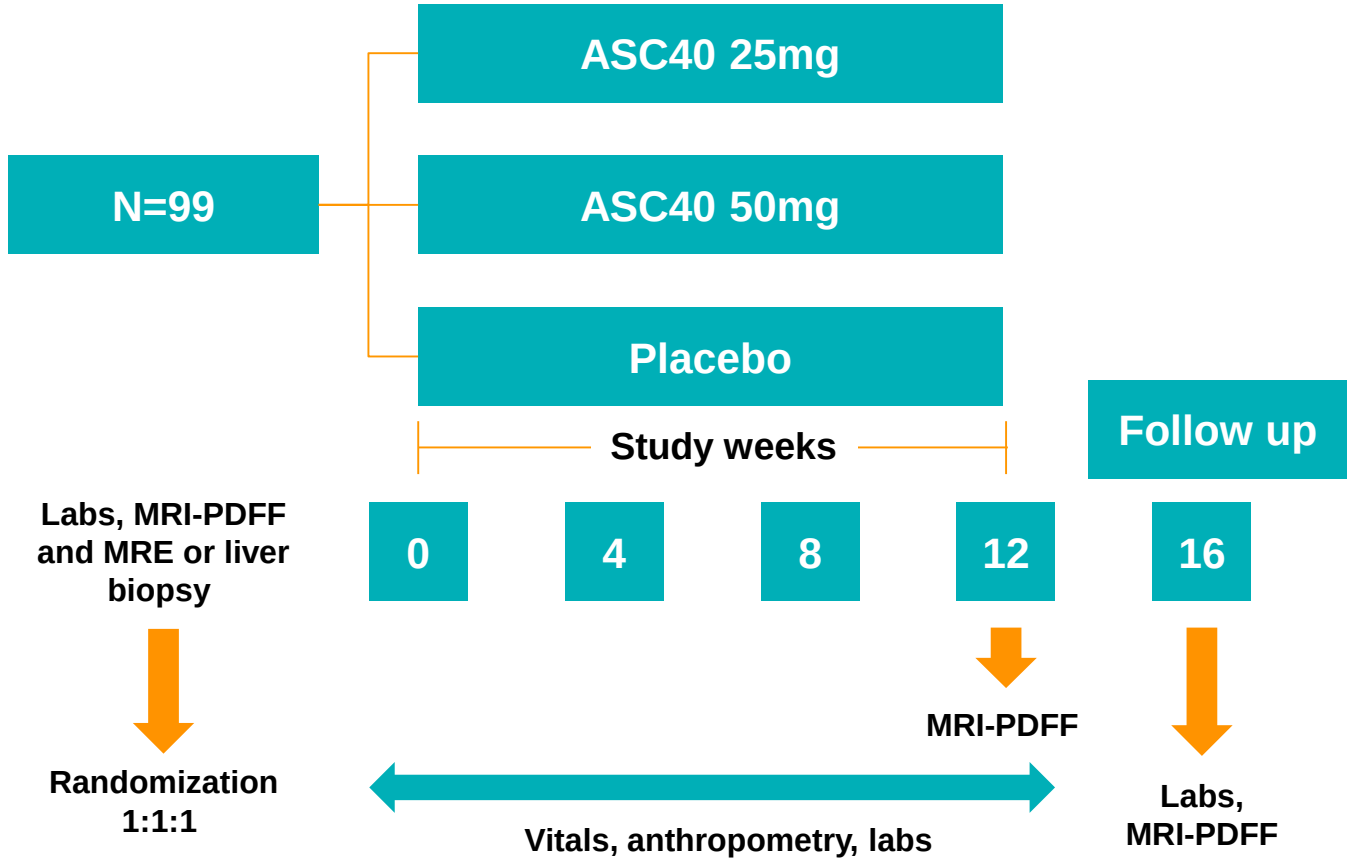
- Multicenter, randomized, placebo-controlled trial 1:1:1 25mg:50mg:placebo (N=99)

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

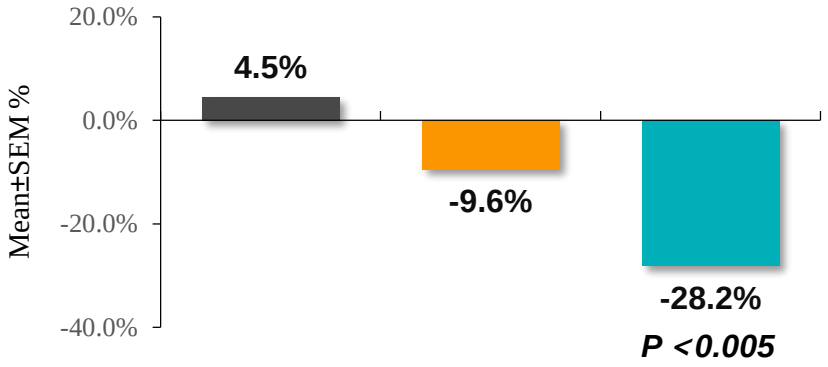


Source: Rohit Loomba et al. 2020,Hepatology 72;103.EASL 2020 Oral Presentation

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

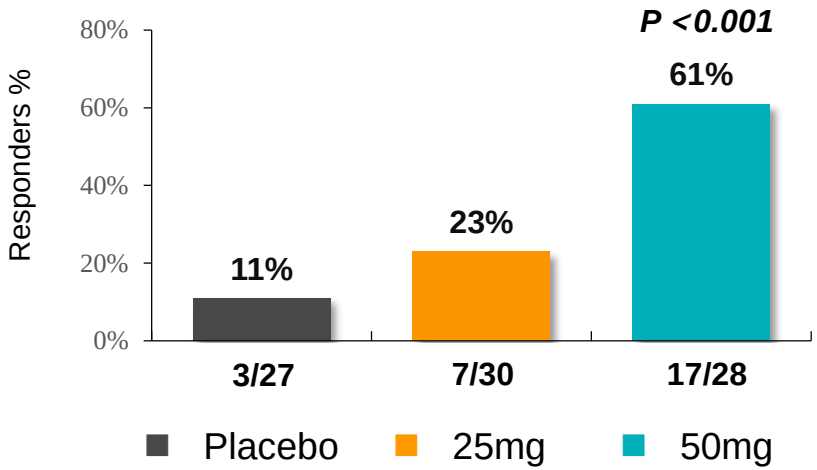
Mean relative liver fat reduction

MRI-PDFF at week 12

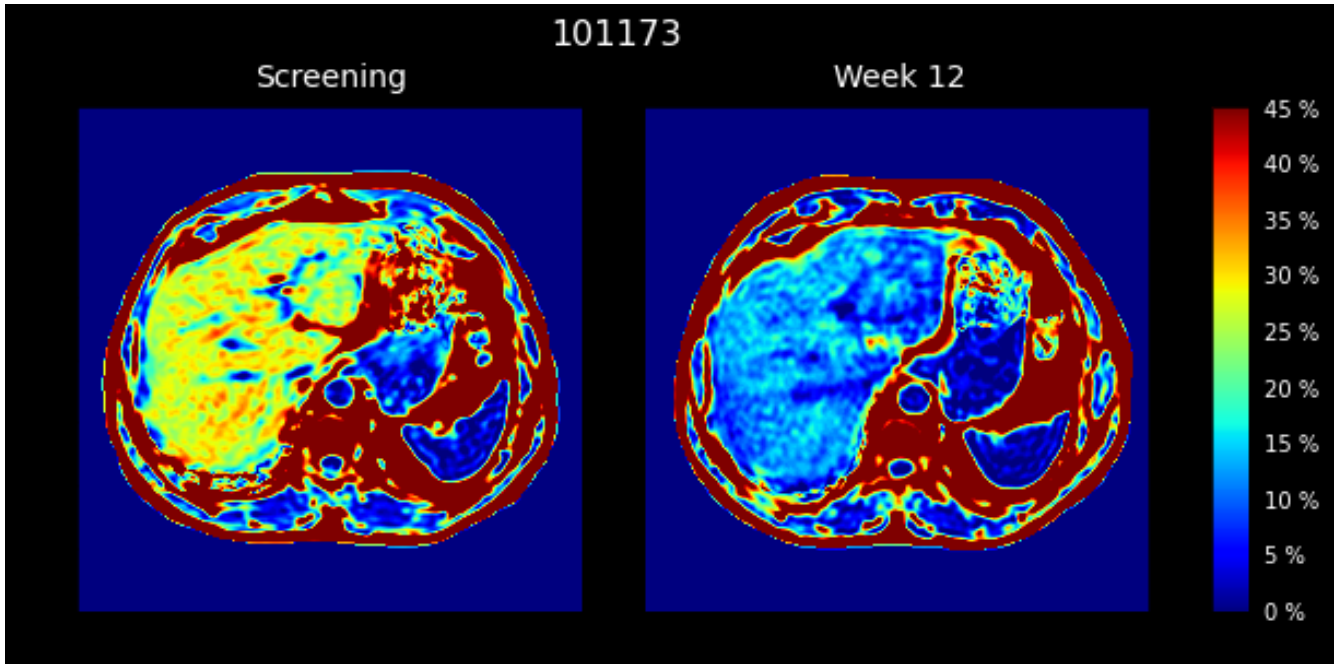


Responder frequency

Patients with ≥30% relative reduction



Significant reduction in liver fat content over 12 weeks of treatment

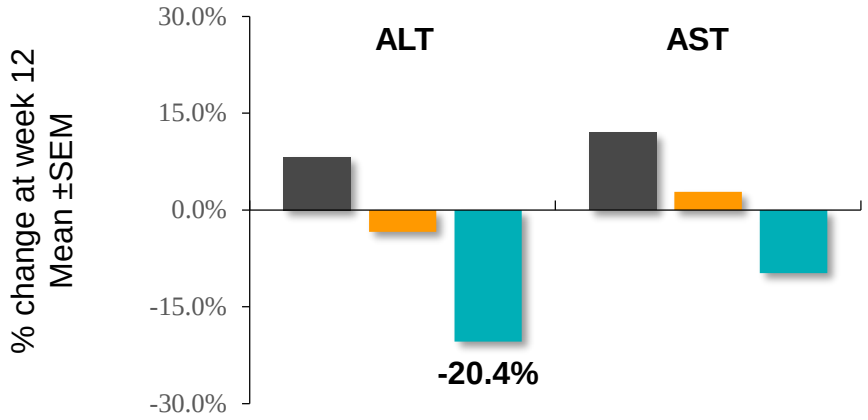


MRI-PDFF responders were defined as those with ≥ 30% MRI-PDFF decline relative to baseline

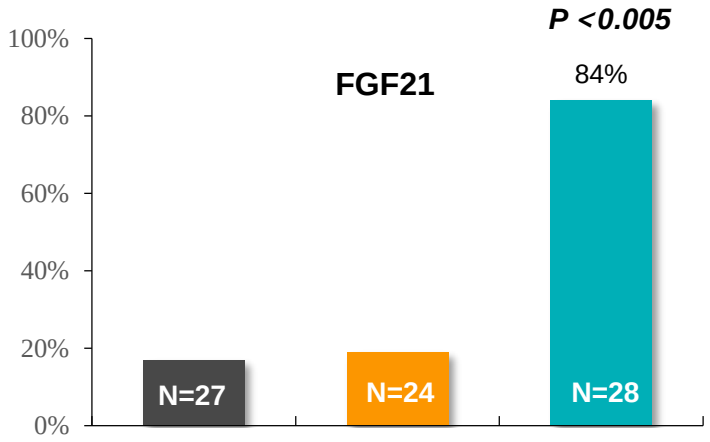
Source: Rohit Loomba et al. 2020, Gastroenterology & Hepatology 72;103AASLD 2020 Oral Presentation

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

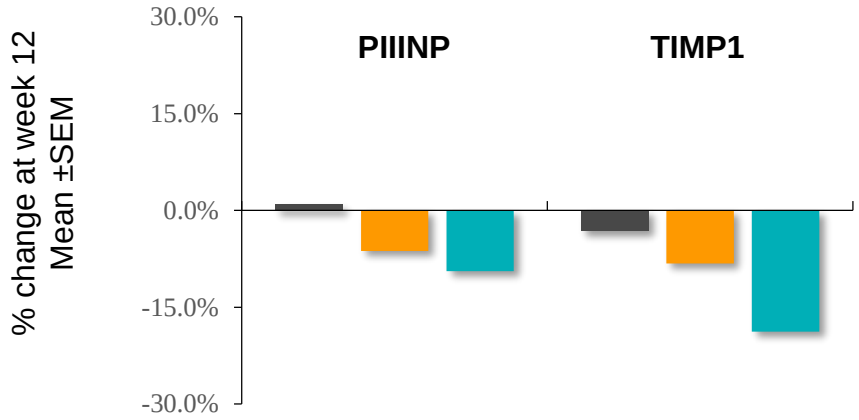
Dose-dependent response in reducing ALT/AST



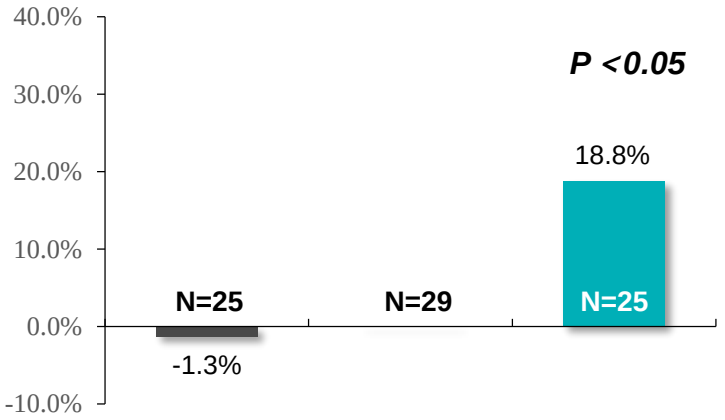
Improves markers of hepatic insunlin sensitivity



Decreases fibrosis markers



Adiponectin



Placebo 25mg 50mg

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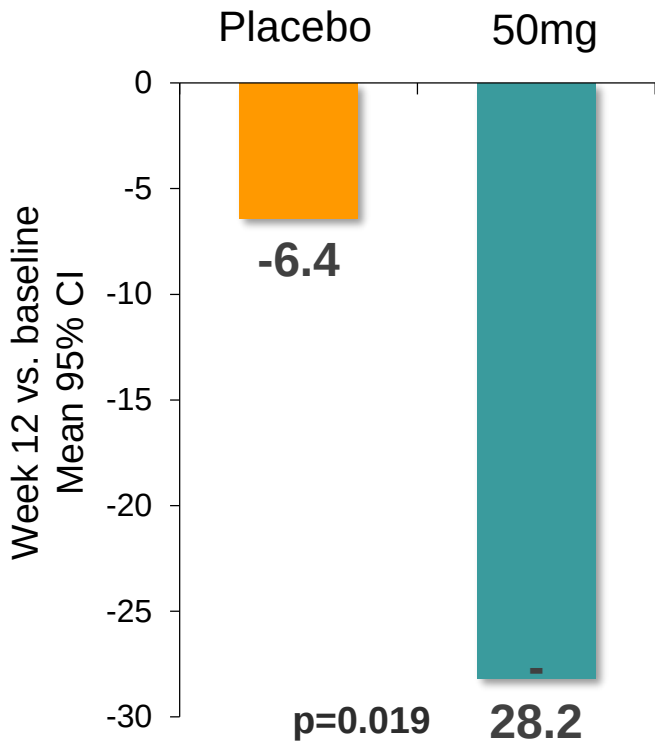
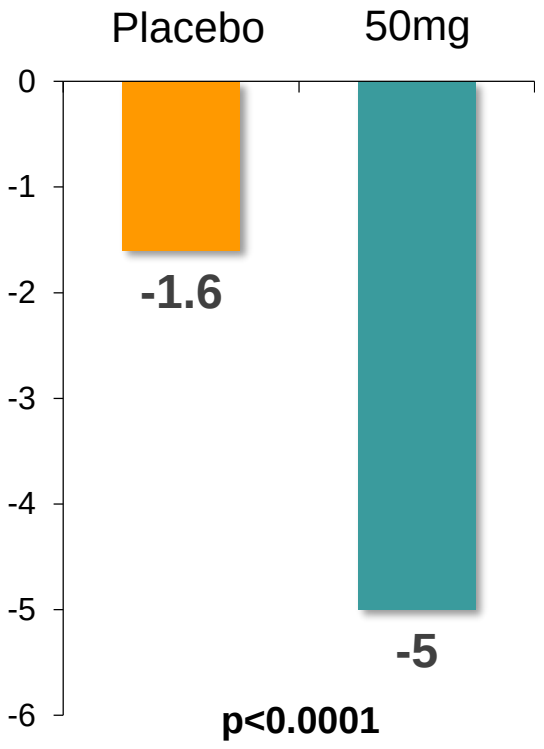
Phase II Combined U.S. & China Cohorts: ASC40 Reduces Liver Fat

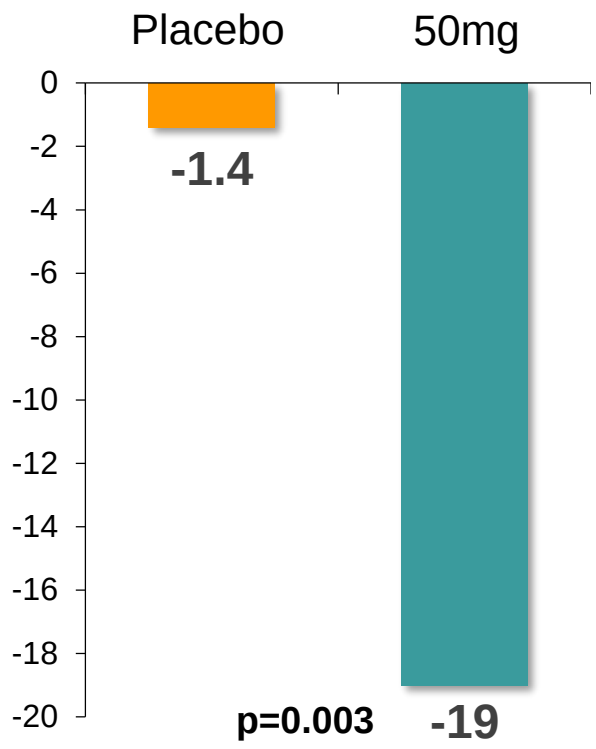
Mean relative liver fat reduction
MRI-PDFF at week 12



Mean absolute liver fat reduction
MRI-PDFF at week 12

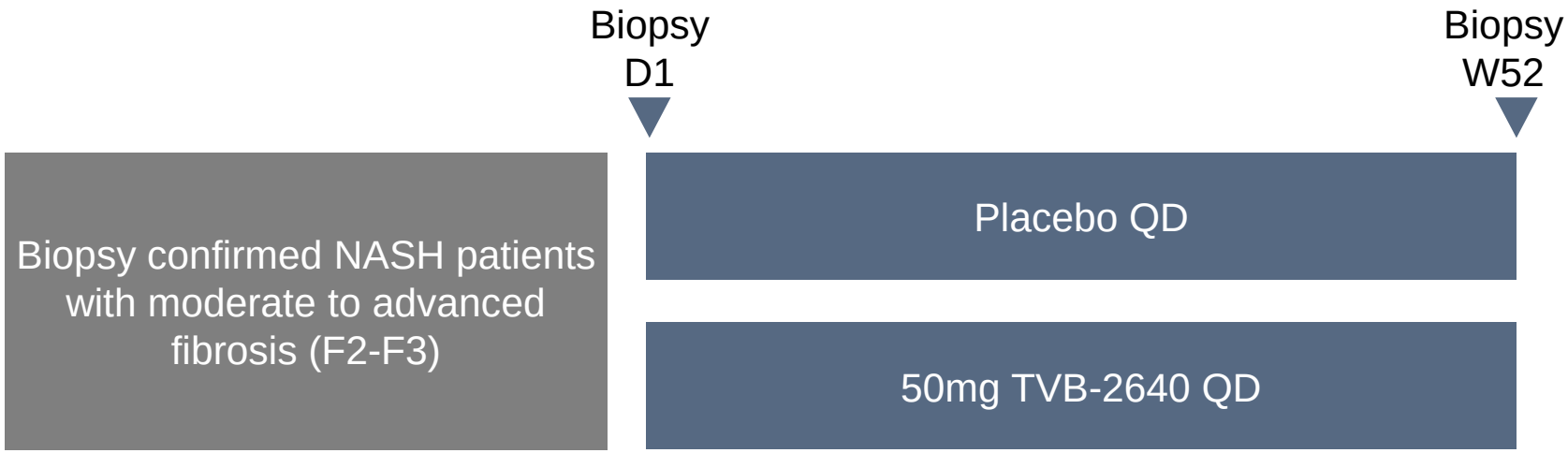


Responder frequency
Patienct with ≥30% relative reduction



Source: *NOVEL, FIRST-IN-CLASS, FATTY ACID SYNTHASE (FASN) INHIBITOR TVB-2640 DEMONSTRATES ROBUST CLINICAL EFFICACY AND SAFETY IN A GLOBAL PHASE 2 RANDOMIZED PLACEBO-CONTROLLED NASH TRIAL (FASCINATE-1) CONDUCTED IN THE US AND CHINA 72th American Association for the Study of Liver Diseases (AASLD)& The Liver Meeting ®*, November 12-15, 2021. Virtual Conference.

ASC40 (TVB2640): US Phase IIb Study Design in NASH

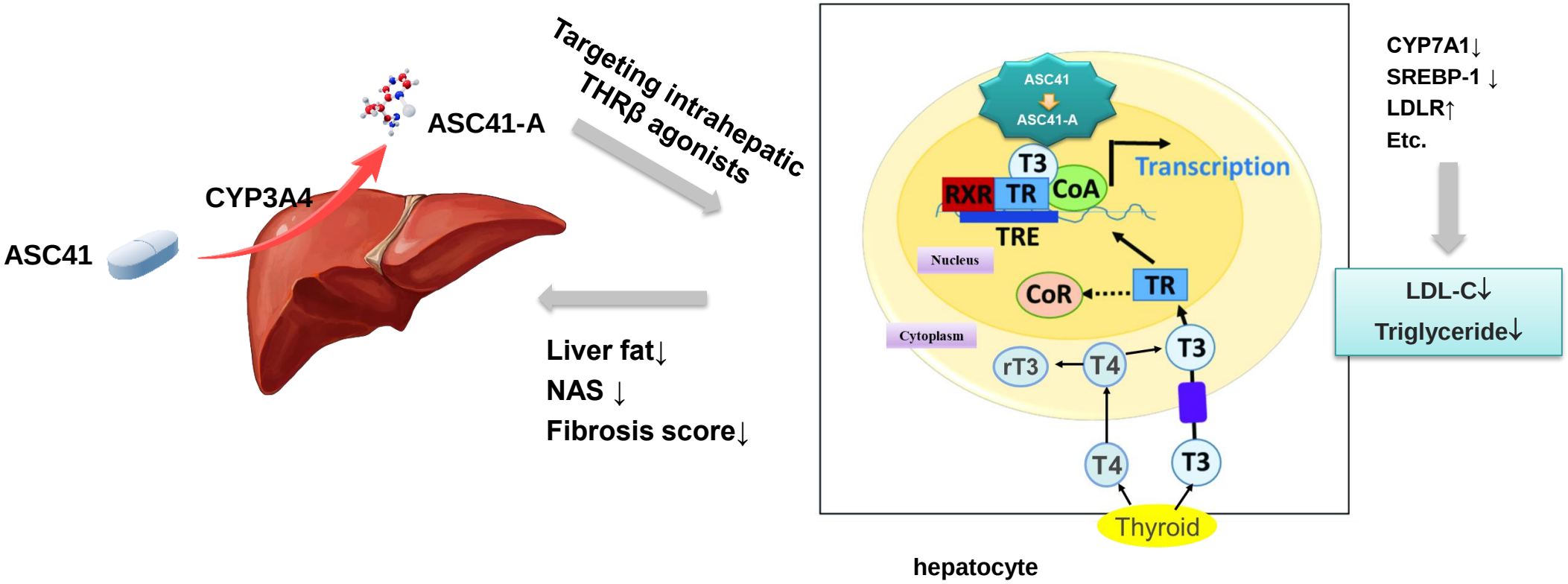


Primary efficacy endpoints:

1. *≥ 2-point improvement in NAS (Nonalcoholic fatty liver disease (NAFLD) Activity Score) that results from reduction of necro-inflammation (inflammation or ballooning), or*
2. *improvement in fibrosis.*

ASC41: A Liver Targeting Thyroid Hormone Receptor Beta (THRβ) Agonist

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



Source: Gannex data

ASC41: Third-in-class THRβ Agonist in USA
First-in-class THRβ Agonist in China

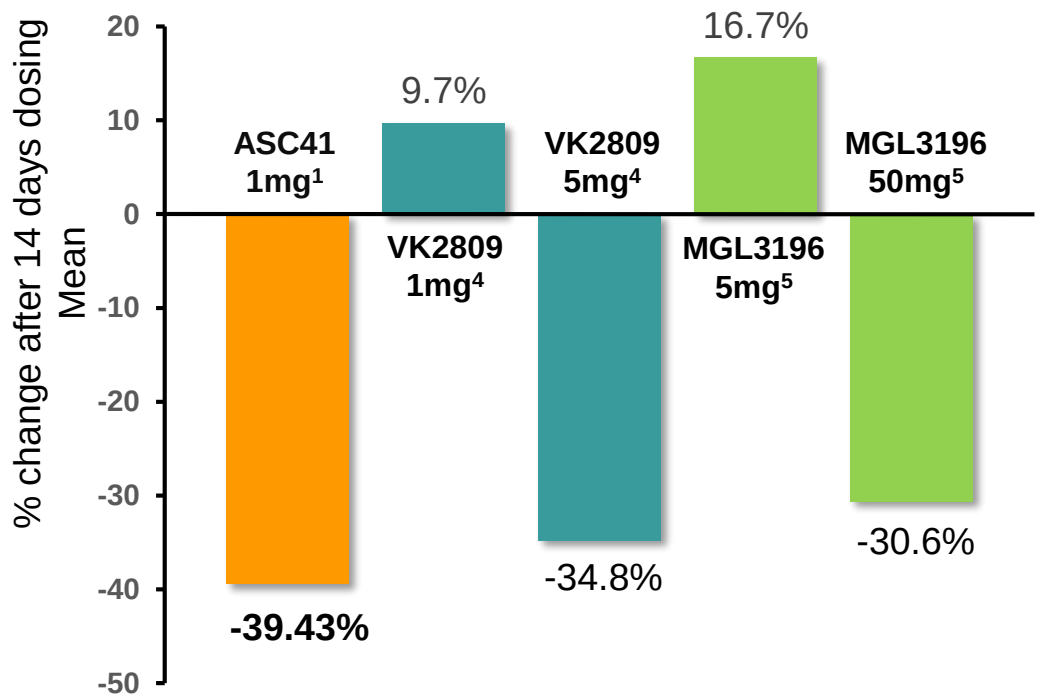
- In two NASH animal models, at 1/10 dose of MGL-3196, ASC41 demonstrated the same improvement of liver steatosis, inflammation and fibrosis.
- Commercially ready oral tablet formulation developed with in-house proprietary technology
- 2 Phase I studies completed
  - Single doses (1, 2, 5, 10, 20 mg) 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
- 1 Phase Ib study completed
  - 28 day, 10 mg in 20 overweight and obese subjects with elevated LDL-C > 110 mg/dL
- US Phase I study showed no significant drug-drug interactions between ASC41/ASC41-A and common used drugs in NASH patients such as antidepressants and statins
- Based on above studies, doses have been selected for Phase II trials in patients with NASH

Source: 1. PO1908. Significant Improvement of NAFLD Activity Scores and Liver Fibrosis by ASC41, a Selective THRβ Agonist, in HIgh Fat Diet Induced NASH SD Rats. Journal of Hepatology 2021 vol. 75(2) | S294–S803
2. PO1851. Significant lipid lowering by ASC41oral tablet, a liver targeted THRβ agonist, in a phase I randomized, double-blind, placebo controlled single- and multiple-ascending dose study. Journal of Hepatology 2021 vol. 75(2) | S294–S803

THRβ 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
DDI	-	+	-
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.EASL 2021 Abstract No. PO-1851 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 4 VK2809 data presented at the 2016 Meeting of the American College of Cardiology 5 Taub et al. Lipid lowering in healthy volunteers treated with multiple doses of MGL-3196, a liver-targeted thyroid hormone receptor-b agonist. Atherosclerosis 230 (2013) 373e380

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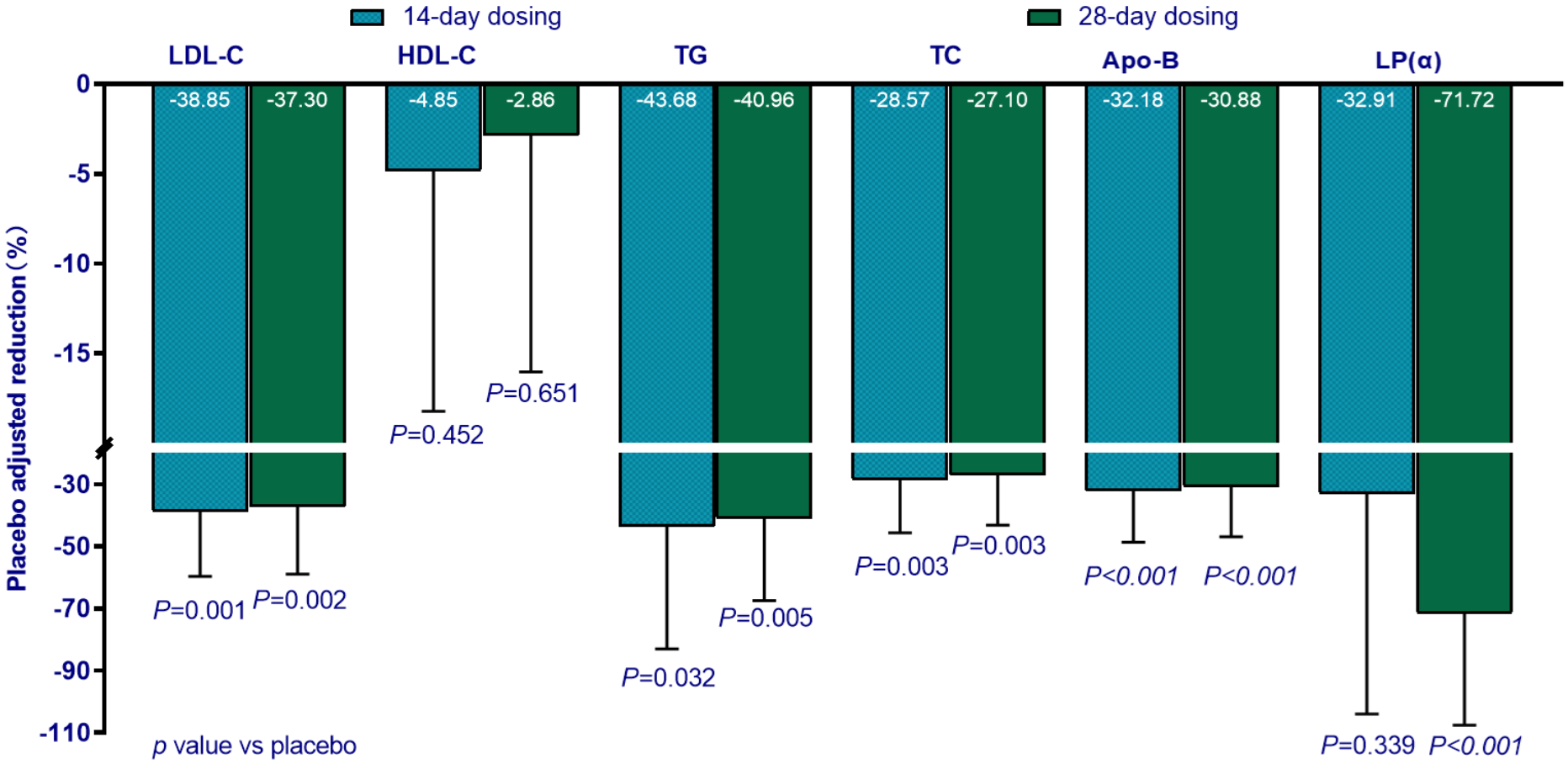
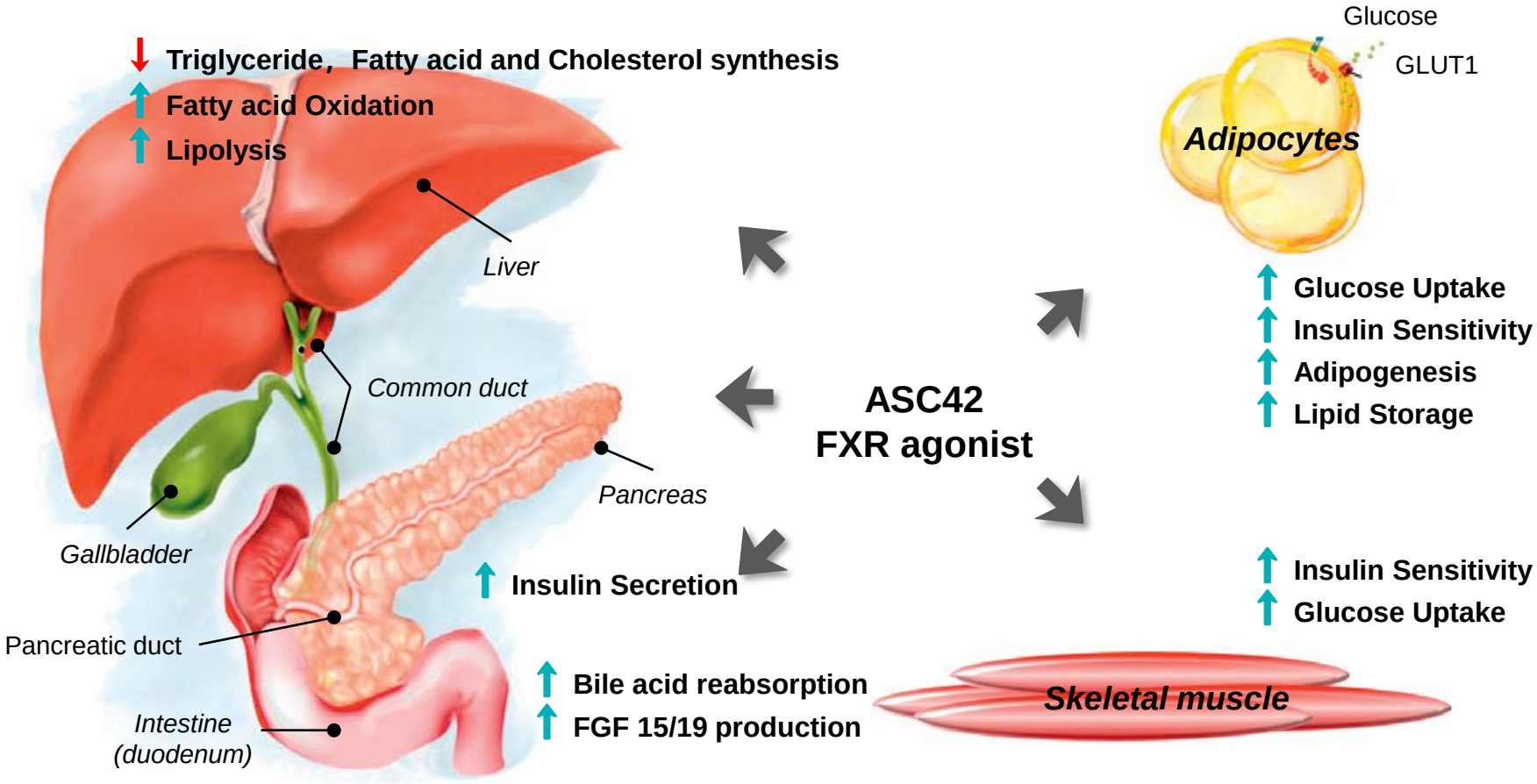
Positive Clinical Results in Overweight and Obese Subjects

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



Source: A Phase Ib Study to Evaluate the Safety, Tolerability and Pharmacokinetics of ASC41, a THR-β Agonist, for 28-days in Overweight and Obese Subjects with Elevated LDL-C, a Population with Characteristics Of NAFLD. 72th American Association for the Study of Liver Diseases (AASLD)& The Liver Meeting®, November 12-15, 2021. Virtual Conference.

ASC42: A Farnesoid X Receptor (FXR) Agonist



- ASC42 increases insulin sensitivity of adipocytes and skeletal muscle cells, increases glucose uptake in peripheral tissues and increases energy consumption.
- ASC42 reduces the synthesis of triglycerides, fatty acids and cholesterol in the liver, and promotes liver fat decomposition and fatty acid oxidation.

Source: 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
- Phase II/III clinical trials for PBC approved in Nov 2021 by China NMPA
- Oral tablet formulation developed with in-house proprietary technology and stable at room temperature

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

Dose（QD）	5mg	15mg
Incidence rate of pruritus during 14 days treatment (%)	0	0
LDL-C change from baseline on Day 14（%, Median）	-6.6	2.43
FGF19 on Day 14 versus baseline（%）	471	1780
C4 reduction on Day 14（%）	53	91
ALT change from baseline on Day 14（U/L, Median）	-1.0	-2.5

Source: ASC42, a Novel Non-steroidal FXR Agonist, Demonstrates a Normal Cholesterol Profile and Lack of Pruritus at Therapeutic Doses in a 14-day Phase I Randomized, Double-blind, Placebo Controlled Study in Healthy Volunteers. 72th American Association for the Study of Liver Diseases (AASLD)& The Liver Meeting ®, November 12-15, 2021. Virtual Conference.

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FDC: Complementary among ASC40, ASC41 and ASC42

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

ASC43F- First-in-Class Dual Targeting (THRβ +FXR) Fixed-dose Combination

- An in-house developed, first-in-class dual targeting fixed-dose combination (FDC) of 5mg ASC41 (a THRβ agonist) and 15mg ASC42 (an FXR agonist)
- THRβ agonists have shown primarily anti-metabolic effects, while FXR agonists have shown primarily anti-fibrotic, as well as anti-inflammatory effects. The combination of ASC41 and ASC42 may complement the advantages of these two agents
- U.S. FDA IND approval in November 2021
- U.S. Phase I trial completed in January 2022
  - ASC43F was safe and well tolerated in healthy volunteers
  - PK parameters of ASC41 and ASC42 from ASC43F are similar to those of ASC41 and ASC42 monotherapy

Oncology

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

Oral Cancer Metabolic Checkpoint and Immune Checkpoint Inhibitors

Target	Candidate	Indication	Commercial rights	Pre-IND	IND	Phase I	POC	Pivotal trial	Competitiveness
FASN + VEGF	ASC40 (Oral) +Bevacizumab	Recurrent glioblastoma	Greater China[1]	***Phase III in China approved***					• FIC, inhibit energy supply and disturb membrane phospholipid composition of tumor cells by blocking de novo lipogenesis • Significantly improve PFS in Phase II study
FASN	ASC40 (Oral)	Drug resistant Breast Cancer	Greater China[1]						• FIC MOA • Preliminary efficacy in phase I study
FASN	ASC40 (Oral)	KRAS mutant NSCLC	Greater China[1]						• FIC MOA • Preliminary efficacy in phase I study
PD-L1	ASC61 (Oral small molecule)	Multiple tumors	Global						• Oral small molecule, easier administration • Comparable efficacy as FDA approved PD-1/PD-L1 antibody drug in animal models
FASN	ASC60 (Oral)	Solid tumor 1	Greater China[1]						• FIC • Better *in vitro* activities compared to ASC40
FASN	ASC60 (Oral)	Solid tumor 2	Greater China[1]						• FIC • Better *in vitro* activities compared to ASC40
PD-L1	ASC63 (Oral small molecule)	Multiple tumors	Global						• Oral small molecule, easier administration • Stronger effects on PD-L1 dimerization and internalization compared to competitor compound

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

Cancer Lipid Metabolism

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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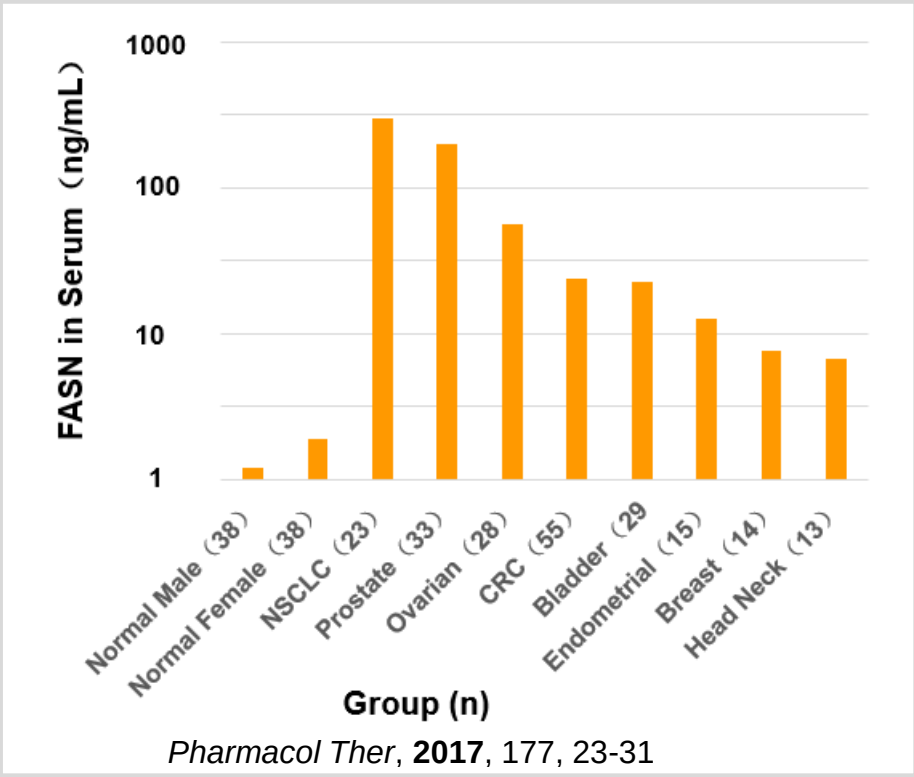
Cancer Metabolism: Approved Drugs and Clinical Stage Candidates

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
ASC40(TVB-2640)	**Fatty acid synthase** Lipid metabolism	GBM, Breast cancer and other solid tumors	Phase III Ascletis (Greater China)/Sagimet Biosciences (outside Greater China)

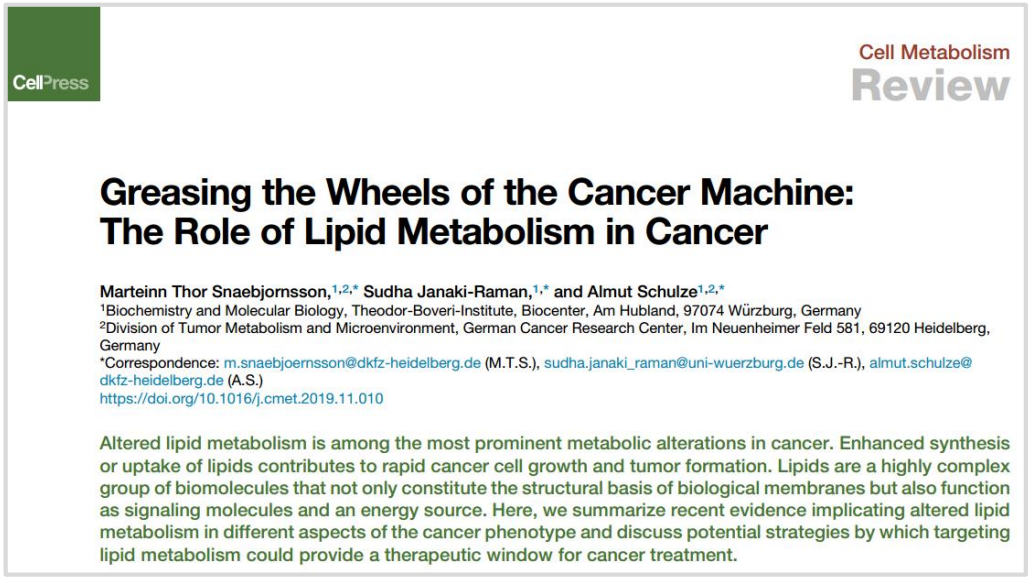
Fatty Acid Synthase, A Promising Cancer Drug Target

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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Glioblastoma

- In China, gliomas has incidence rates of 5-8 per100,000 population per year, and GBM represents around 57% of gliomas thus has incidences of 2.85-4.56 per 100,000 population per year, suggesting approximately 40,000 to 64,000 new cases of GBM per year.
- In the United States, GBM represents 56.6% of gliomas and has an incidence rate of approximately 3.21 per 100,000 population per year.
- More than 90% glioblastoma patients will relapse after surgery, radiation and chemotherapies.

Source: 1. 赫捷, 等. 2017 中国肿瘤登记年报. 人民卫生出版社. 2017
2. Ostrom QT, Gittleman H, Truitt G, Boscia A, Kruchko C, BarnholtzSloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2011-2015. Neuro Oncol. 2018;20(suppl 4):iv1-iv86.
3. 《复发性/进展性胶质母细胞瘤的治疗指南》

Cancer Lipid Metabolism: Recent Breakthrough of FASN Inhibitors in rGBM

- 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 objective 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 for ASC40 (TVB-2640) plus Bevacizumab was 47%
  - Representing a statistically significant improvement in PFS over the historical Bevacizumab monotherapy PFS of 16% (BELOB Trial) (*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

Source: Press Pelease on May 25, 2021

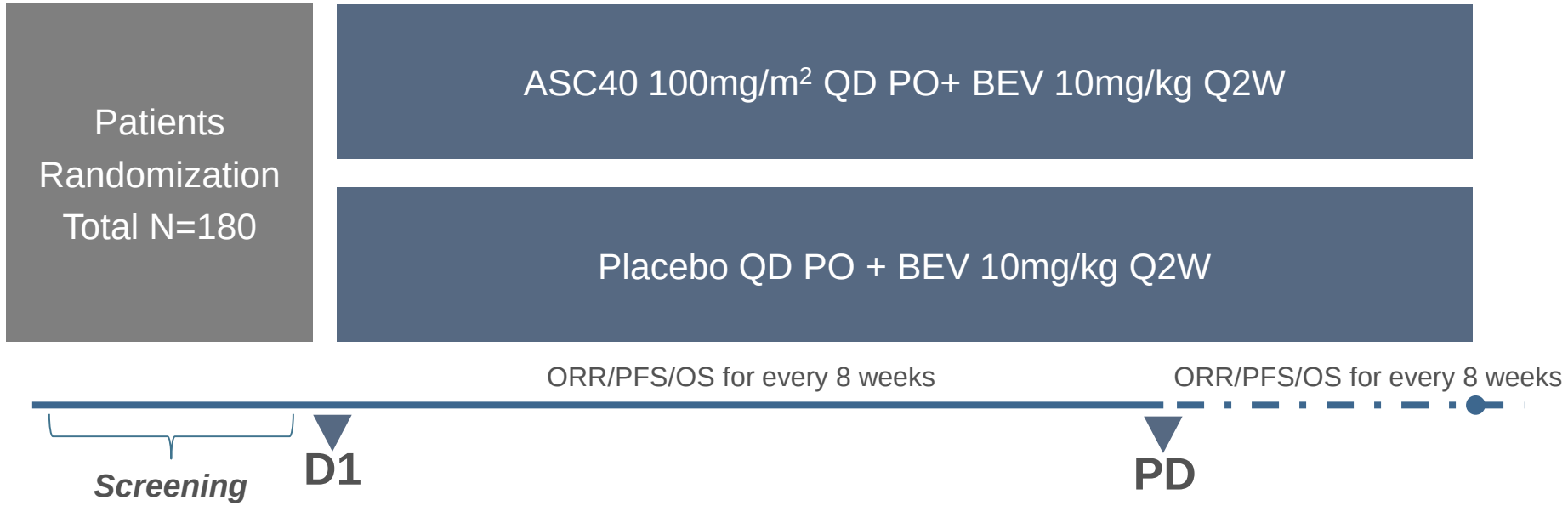
China NMPA Approved Phase III Clinical Trial of ASC40 in Combination with Bevacizumab for Treatment of Patients with Recurrent Glioblastoma

- First Phase III trial of ASC40, a first-in-class drug candidate targeting tumor lipid metabolism
- Bevacizumab is the only drug which has been approved for rGMB indication in China as of September, 2020.
- The data of BELOB Trial indicated that median PFS was three months for patients with rGBM after Bevacizumab treatment.

Source: Press Pelease on July 22, 2021

ASC40: China Phase III Study Design in Recurrent Glioblastoma

- A Randomized, Double Blind, Placebo Controlled, Multi-center Phase III Trial of ASC40 in Combination with Bevacizumab for treatment of Patients with Recurrent Glioblastoma

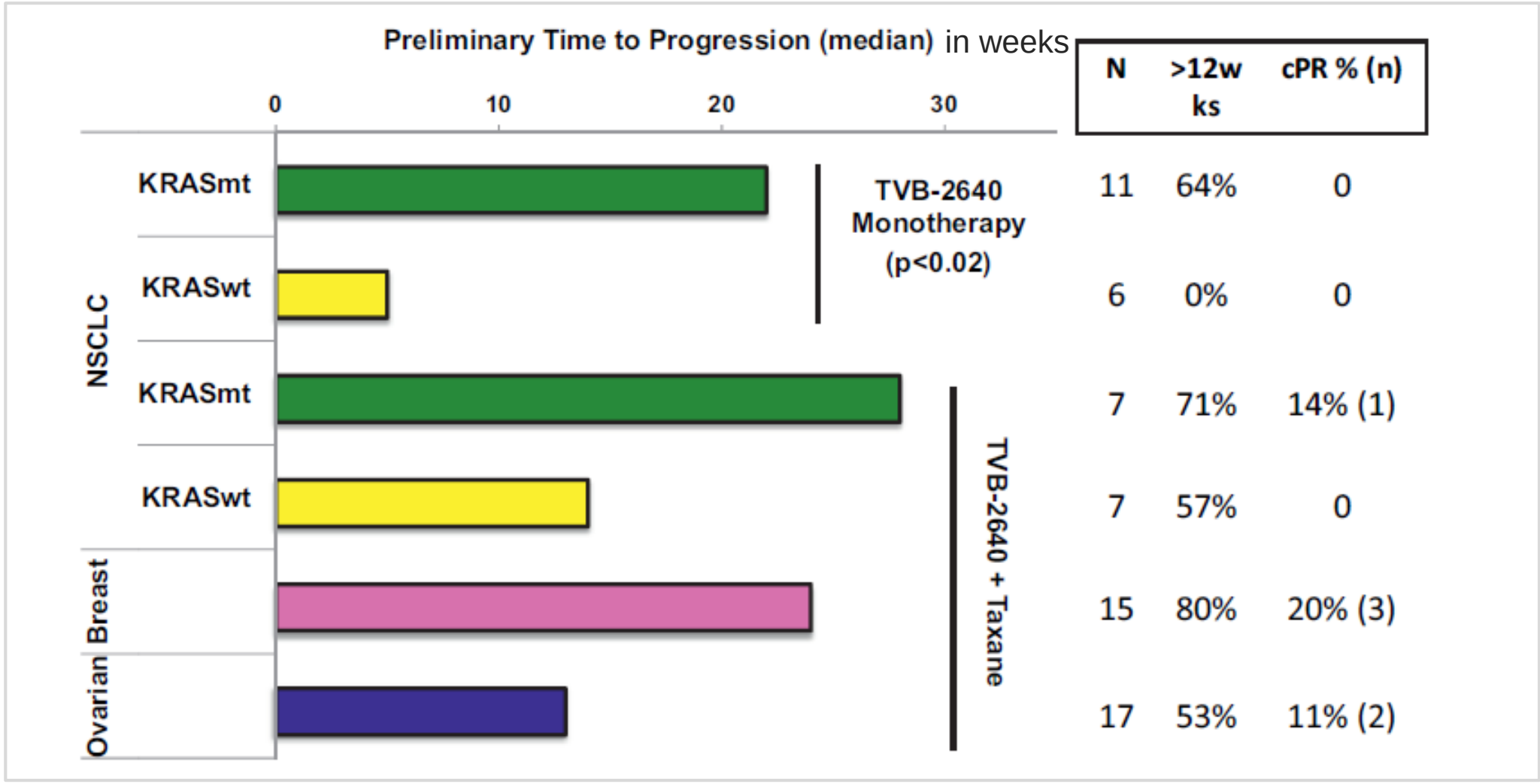


Primary endpoints: PFS and OS

Source: William Kelly et,al. TVB-2640 with Bevacizumab in Relapsed High-grade Astrocytoma. ESMO 2020

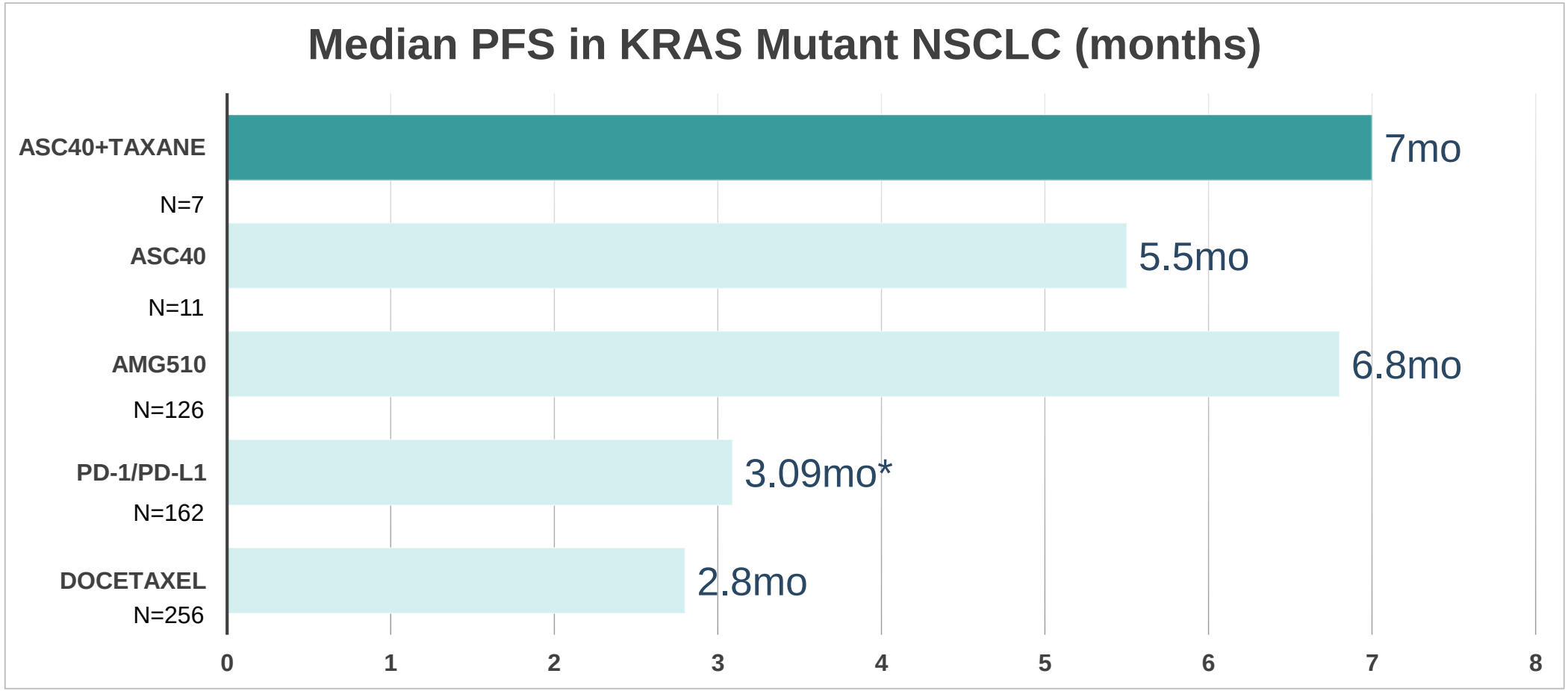
PD: Progression disease

Phase I: Median time to progression of TVB-2640 alone and with a Taxane in patients with $KRAS^{MUT}$ versus $KRAS^{WT}$ non-small cell lung, breast, and ovarian cancer



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

ASC40 Shows Competitive Efficacy in KRAS Mutant NSCLC



*: represents mean PFS (range 2.36-3.82 months) instead of median PFS

Ref: EClinicalMedicine, 34 (2021), 100797; N Engl J Med; 384(25):2371-2381; Journal of Thoracic Oncology; 14(6): 1095-1101; JAMA; 317(18): 1844-1853

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Other Clinical Trials of ASC40 (TVB-2640)

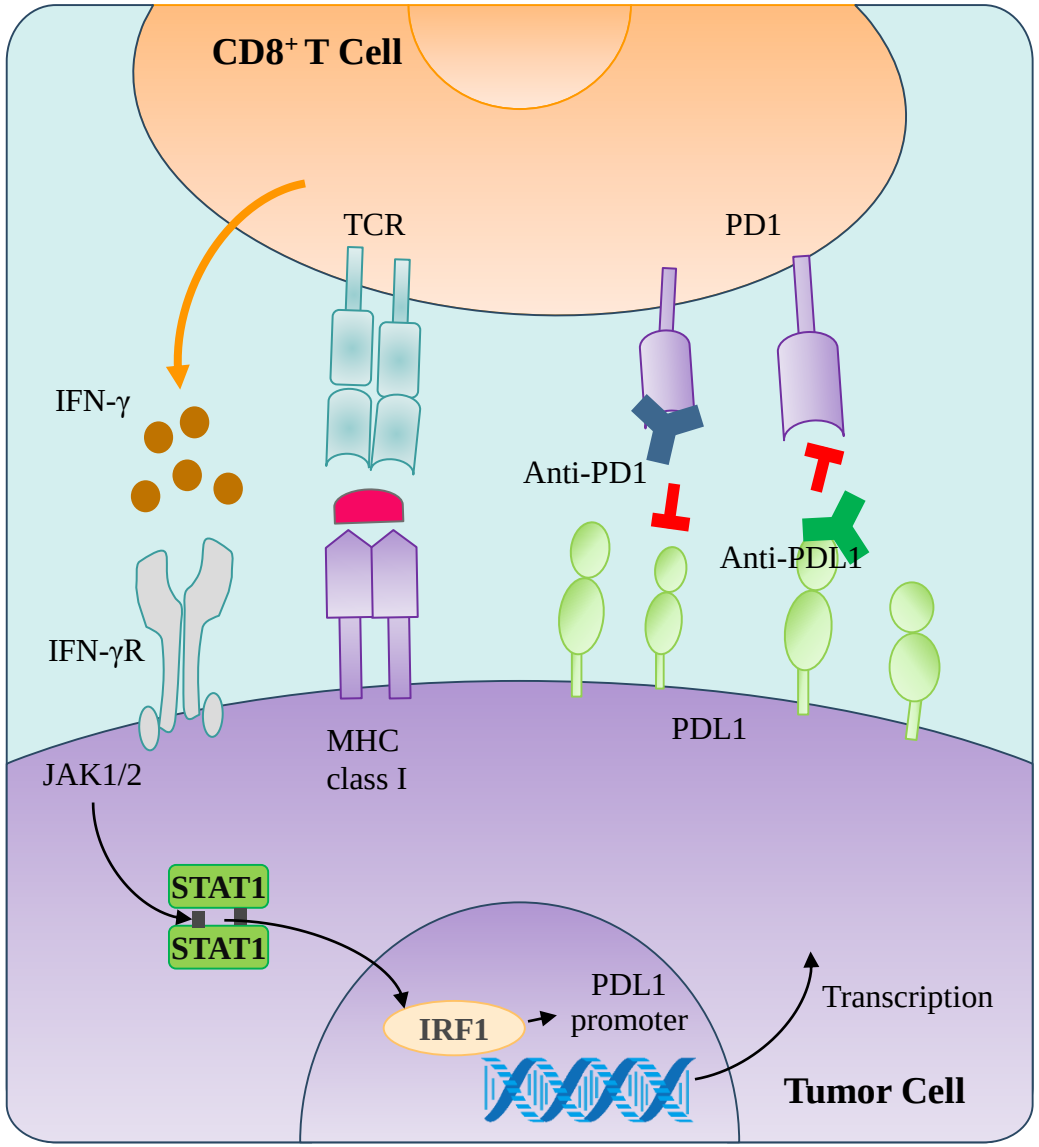
- Patients with KRAS mutatant non-small cell lung cancer (ClinicalTrials.gov Identifier: NCT03808558)
- Patients with breast cancer (ClinicalTrials.gov Identifier: NCT03179904)
- Patients with colon cancer/head and neck cancer (ClinicalTrials.gov Identifier: NCT02980029)

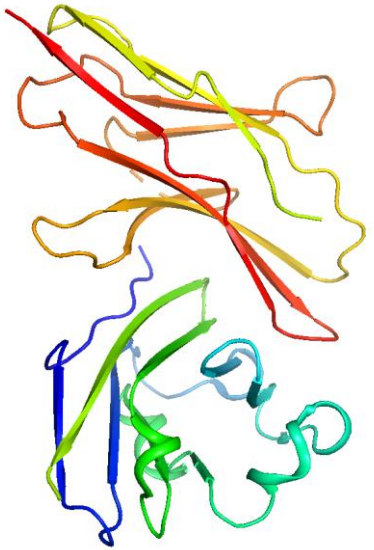
Oral Immune Checkpoint Inhibitors

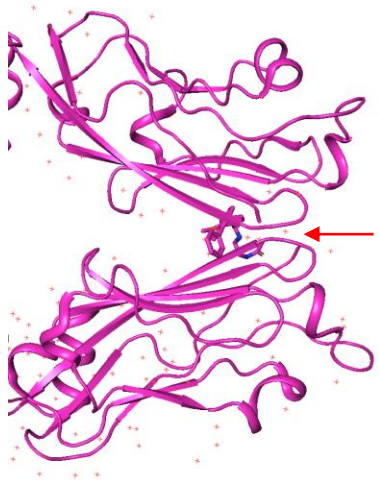
Immunotherapies: Great Success for mAb, It is Time for Oral Drugs

- 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 2021, Incyte unveiled the preliminary results of the Phase I study of its oral small-molecule inhibitor,INCB86550, which showed promising pharmacodynamic. All fatal TEAEs were considered unrelated to study drug. Preliminary efficacy of INCB086550 is encouraging and a Phase II study has been launched

PD-L1 Small Molecule Inhibitors: Challenges and Opportunities



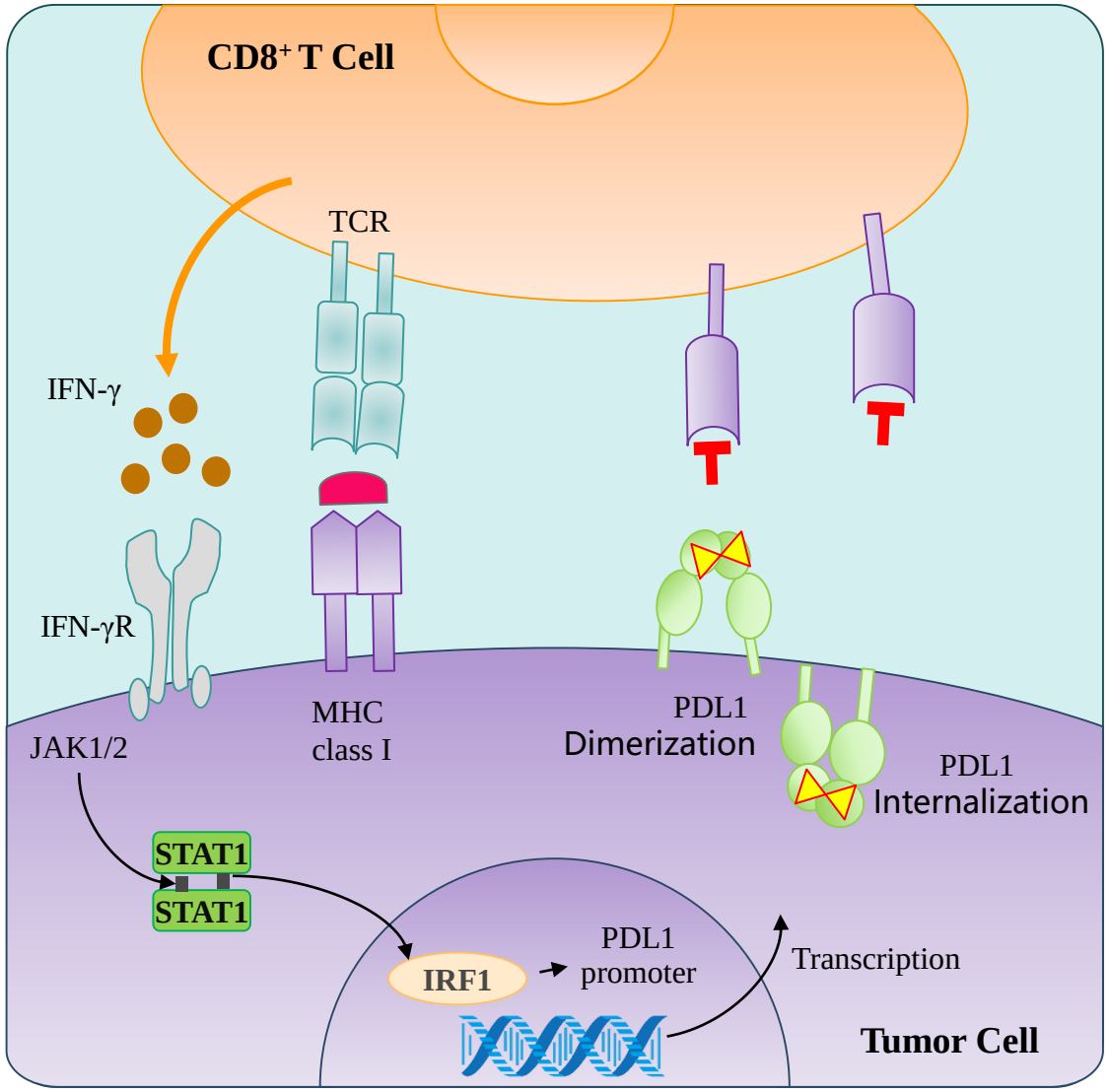


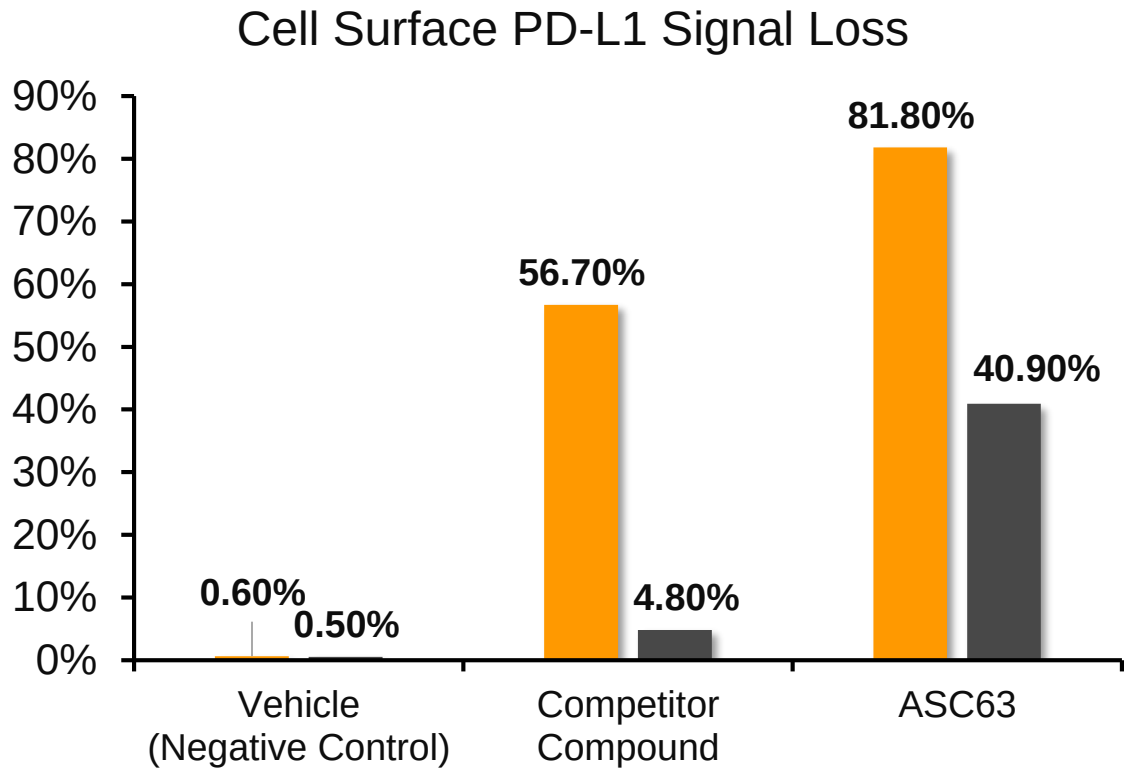


- Antibodies block PD-1/PD-L1 interface
- Traditional small molecules not good at inhibiting protein-protein interaction

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

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)

Source: Ascletis data

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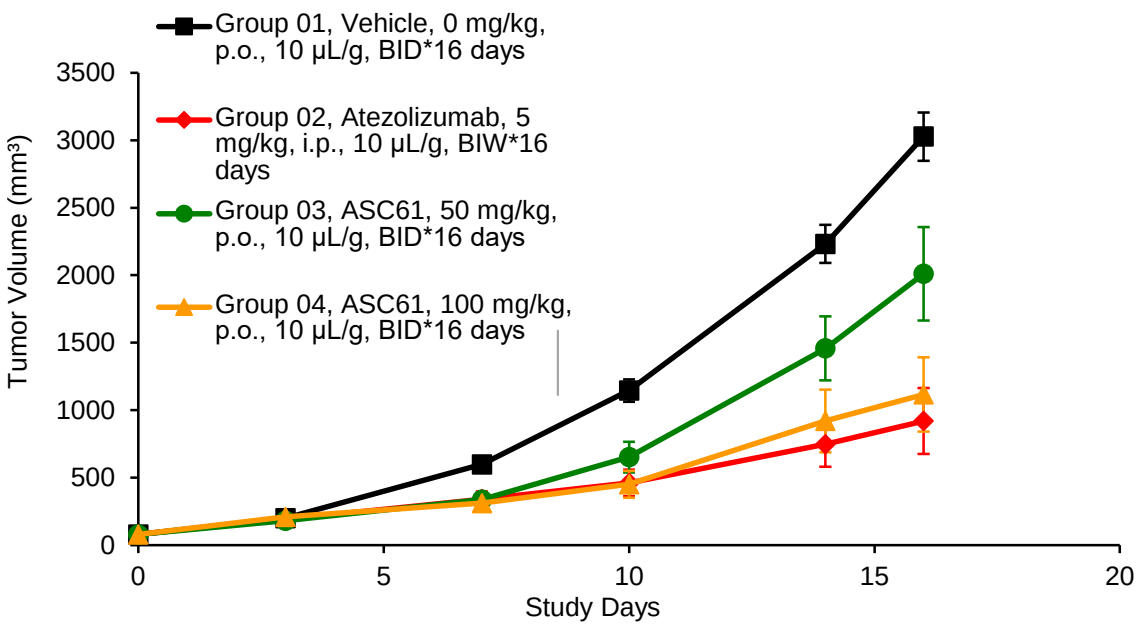
ASC61 showed comparable antitumor activities as the FDA- approved PD-L1 antibody, Atezolizumab, in mouse tumor models



Note: PD-1/PD-L1 dKI HuGEMM mice with human PD-1 and PD-L1 gene double knock-in are an ideal model for testing human-specific PD-1/PD-L1 immune checkpoint inhibitor drugs.

Description	Tumor Size (mm^3) [a] on day 16	T/C (%) on day 16 [b]	TGI (%) on day 16	p value compare with G1[c]	p value compare with G2[d]
Vehicle, p.o., 10 μL/g, p.o., BID*3 weeks	3027.54±179.16	-	-	-	-
Atezolizumab, 5 mg/kg, i.p., BIW*3 weeks	919.73±244.00	30.38	69.62	<0.001	-
ASC61, 50 mg/kg, p.o., BID*3 weeks	2009.72±346.48	66.38	33.62	0.0954	0.0362
ASC61, 100 mg/kg, p.o., BID*3 weeks	1115.61±275.17	36.85	63.15	<0.001	0.954

Note: a. Mean ± SEM; b. tumor volume treatment/control; c. compared with group 1 tumor volume on day 16 using Tukey's HSD test; d. compared with group 2 tumor volume on day 16 using Tukey's HSD test.

■ Oral administration of ASC61 resulted in significant tumor growth inhibitions in mouse tumor models. Antitumor activity of ASC61 was shown to be dose-dependent.

■ No significant difference of body weight was observed among all groups during studies, indicating that ASC61 was generally well-tolerated in mice.

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Exploratory Indications

Exploratory Indications

Acne

Target	Candidate	Commercial rights	Pre-IND	IND	Phase I	Phase II	Phase III	Competitiveness
FASN	ASC40	Greater China[1]						• FIC • Reduced sebum production in a dose-dependent manner in phase I study

1. ASC40 is licensed from Sagimet Biosciences Inc. for the exclusive rights in the Greater China.

Acne

- Eighth most prevalent disease in the world and affects more than 640 million people globally
  - The onset of acne often coincides with pubertal hormonal changes, and the condition affects approximately 85% of adolescents and young adults aged 12 to 25 years.
  - However, acne can also persist into or develop during adulthood.
- A report recently published by Allied Market Research indicated that the global acne medication market size was US$11.86 billion in 2019, and is projected to reach US$13.35 billion by 2027.
  - Current first-line treatments for acne include topical creams such as topical retinoids and androgen receptor inhibitor, oral isotretinoin, and antibiotics.

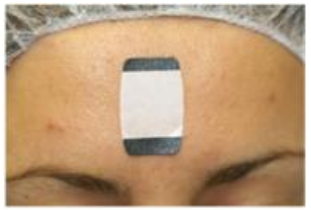
ASC40: A first-in-class drug with novel mechanism of action for Acne

- Fatty acid synthase (FASN) is a key enzyme which regulates de novo lipogenesis.

  ➢Human sebum production requires de novo lipogenesis, which is increased in acne and suppressed by the FASN inhibitor ASC40.

- Clinical proof concept data

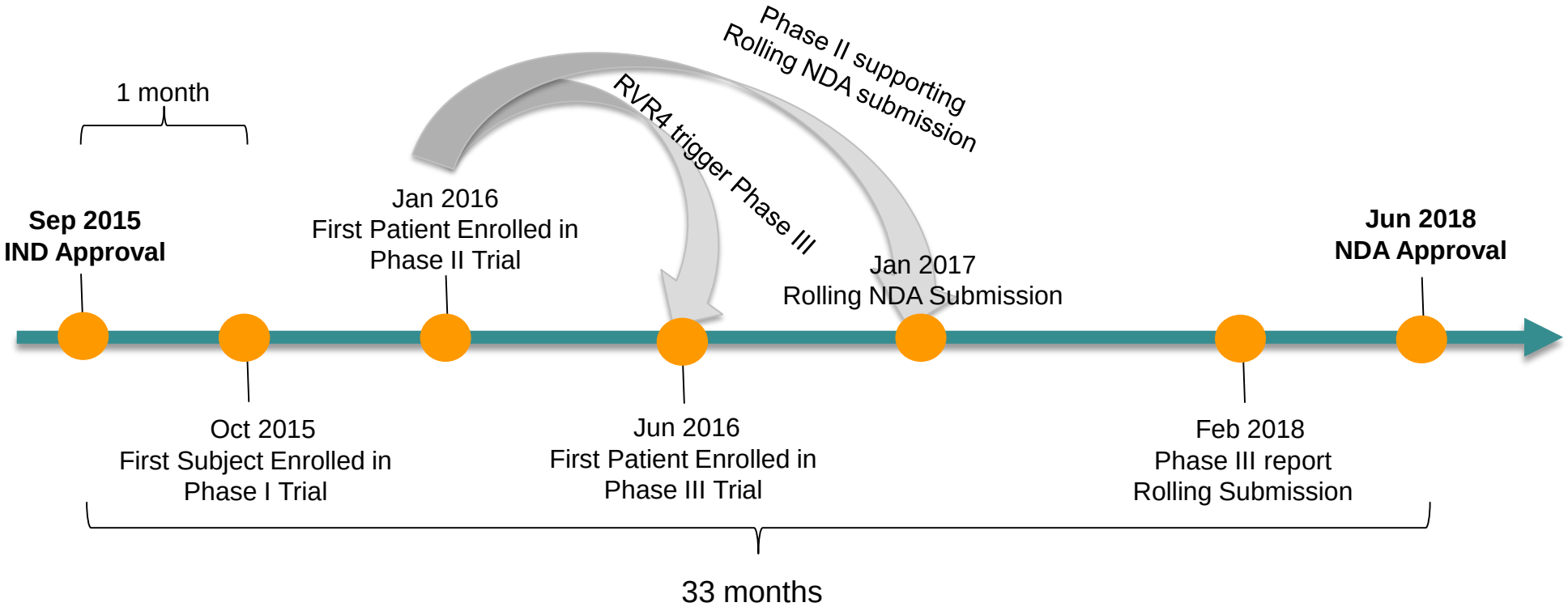
  ➢Clinical study indicated that sebum production was inhibited by ASC40 in a dose-dependent fashion



ASC40: China Phase II Study Design for Acne

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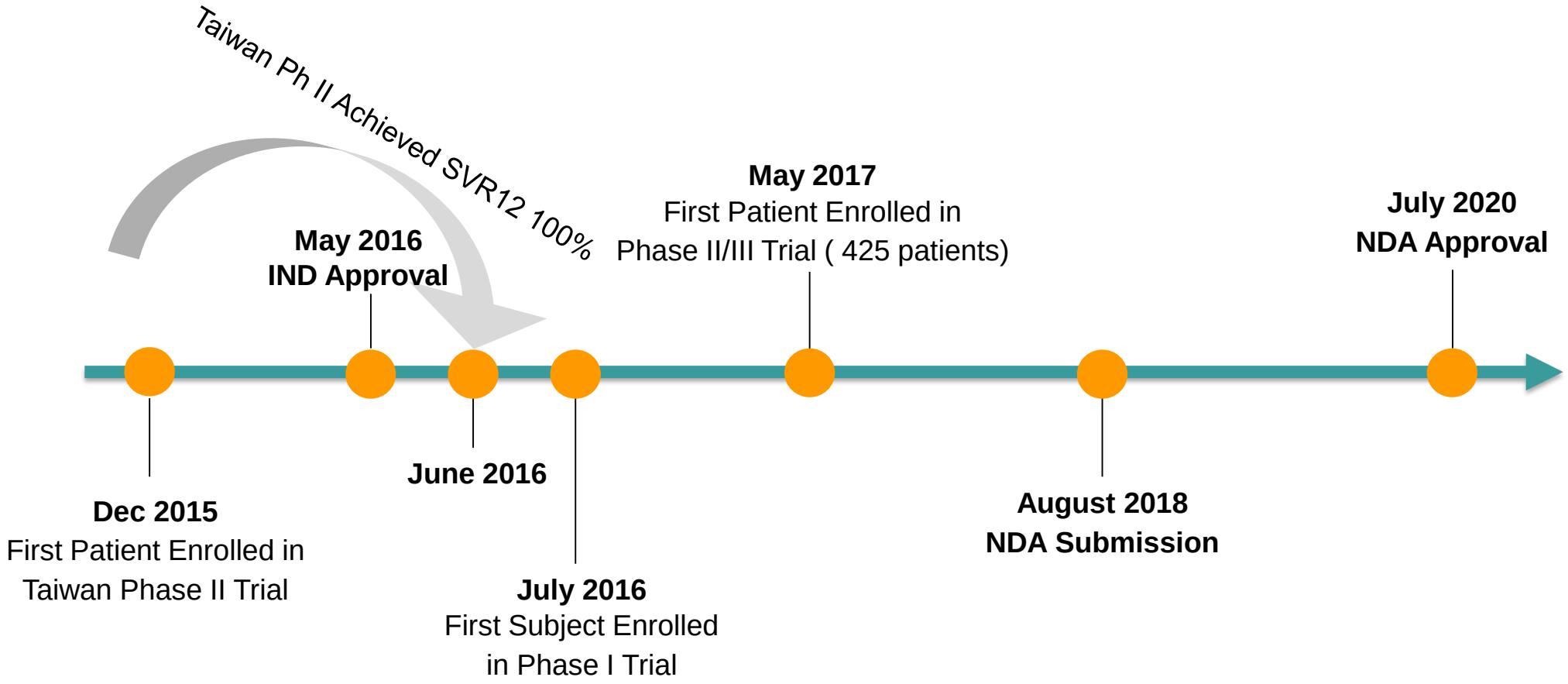
R&D Efficiency: ASCLEVIR® from IND to NDA Approval: 50 months



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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

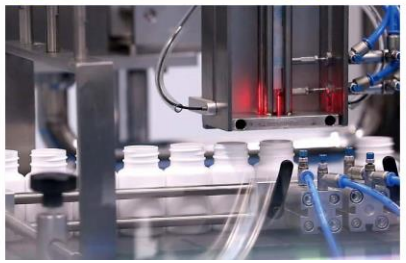
发证机关：

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 **June 8** → GMP Certified **June 14** → Inaugural Sales **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 (THRβ) + 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 (THRβ)
- ASC42 (FXR)

HBV

Oncology

License-In: Areas of Interest

HBV

Oncology

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Thanks

Innovative cures liberate life to the fullest