歌礼
ascletis

Corporate Presentation

Ascletis Pharma Inc.

November 2021

Ascletis Overview

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

Through **Metabolic and Immune Modulation**, 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

歌礼 ascletis

Marketed Products in China

An all-oral regimen comprised of GANOVO® and ASCLEVIR® for HCV;
AND Pegasys® for HBV

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.

歌礼 ascletis

Pipeline Overview

4 targets, including 3 metabolic checkpoint targets and 1 immune checkpoint target

	Target	Candidate	Commercial rights	Pre-IND	IND	Phase I	Phase IIa	Phase IIb	Phase III / Pivotal
Metabolic Checkpoint	FASN	ASC40 (Oral small molecule)	Greater China	NASH					
				rGBM					
				Drug resistant Breast Cancer					
				KRAS mutant NSCLC					
				Acne					
		ASC60 (Oral small molecule)		Solid Tumor 1					
				Solid Tumor 2					
	THRβ	ASC41 (Oral small molecule)	Global	NASH					
	FXR	ASC42 (Oral small molecule)	Global	NASH					
				HBV functional cure					
				PBC					
	THRβ＋FXR	ASC43F (Oral FDC)	Global	NASH					
	FASN＋FXR	ASC44F (Oral FDC)	Global	NASH					
	FASN+THRβ	ASC45F (Oral FDC)	Global	NASH					
Immune Checkpoint	PD-L1	ASC22 (S.C mAb)	Greater China	HBV functional cure					
				HIV functional cure					
		ASC61 (Oral small molecule)	Global	Solid Tumor					
		ASC63 (Oral small molecule)		Solid Tumor					

NASH/PBC
Oncology
Viral Diseases
Exploratory Indications

歌礼 ascletis

Pipeline Overview

18 programs, 3 disease areas, actively expanding new indications with unmet medical needs

Viral Diseases

- Programs with novel targets for HBV functional cure, including 1 global leading immunotherapy candidate in phase IIb
- Global leading immunotherapy candidate for HIV functional cure

NASH/PBC

- Global leading NASH pipeline of 3 single agents and 3 fixed-dose combinations
- 1 NASH program in 52 weeks biopsy phase IIb
- 1 PBC program complete phase I, applying for phase II

Oncology

- Unique pipeline of cancer lipid metabolism and oral immune checkpoint inhibitors
- 1 candidate for recurrent glioblastoma (rGBM) in phase III

Exploratory Indications

- 1 candidate for acne in phase II

歌礼 ascletis

Viral Diseases

HBV (Functional Cure)

Target	Candidate	Commercial rights	Pre-IND	IND	Phase I	Phase IIa	Phase IIb	Phase III	Competitiveness
PD-L1	ASC22	Greater China[1]							• First-in-class candidate for HBV functional cure through blocking PD-1/PD-L1 pathway • 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	Greater China[1]							• Subcutaneous injection, easier administration

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

歌礼 ascletis

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 compare to other NASH candidates
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
FXR	ASC42 (PBC)	Global							• No pruritus • Applying for phase II

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 block de novo lipogenesis • Significantly improve PFS6 in Phase II
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
FASN	ASC60 (Oral)	Solid tumor 1	Greater China[1]						• FIC • Higher *in vitro* activities compare to ASC40
FASN	ASC60 (Oral)	Solid tumor 2	Greater China[1]						• FIC • Higher *in vitro* activities compare to ASC40
PD-L1	ASC61 (Oral small molecule)	Multiple tumors	Global						• Oral small molecule, easier administration • Comparable efficacy with antibody drug in animal model
PD-L1	ASC63 (Oral small molecule)	Multiple tumors	Global						• Oral small molecule, easier administration • Stronger effects on PD-L1 dimerization and internalization compare to competitor compound

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

歌礼 ascletis

Exploratory Indications

Acne

Target	Candidate	Commercial rights	Pre-IND	IND	Phase I	Phase II	Phase III	Competitiveness
FASN	ASC40	Greater China[1]						• FIC • Sebum production inhibited dose dependently in phase I study

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

歌礼 ascletis

Anticipated Key Milestone(s) in next 12 months*

Viral Diseases

- ASC22/HBV—**Top-line results** from **China phase IIb** study
- 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 the Company makes no guarantees for the achievement of the milestones.

歌礼 ascletis

Significant Market Potential

HBV

HBV (functional cure)

- 70 million hepatitis B virus carriers in China, and 1 million new cases reported every year recently;
- 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.

歌礼 ascletis

Significant Market Potential

rGBM

Recurrent Glioblastoma

- CN: GBM represents 46.1% of gliomas and has an incidence rate of 2.85-4.56/100,000 population per year, suggesting approximately 40,000 to 64,000 new cases of GBM per year ;
- US: GBM represents 56.6% of gliomas and has an incidence rate of approximately 3.21/100,000 population per year;
- More than 90% glioblastoma patients will relapse after surgery, radiation and chemotherapies;
- Bevacizumab is the only drug been approved for rGBM in China (PFS6 16%, 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.

Viral Diseases

HBV Functional cure

HBV functional cure

For at least 6 months after stop treatment:

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

70 million

hepatitis B virus carriers in China

1 million

new cases reported every year recently

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

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

HBV (Functional Cure)

Target	Candidate	Commercial rights	Pre-IND	IND	Phase I	Phase IIa	Phase IIb	Phase III	Competitiveness
PD-L1	ASC22	Greater China[1]							• First-in-class candidate for HBV functional cure through blocking PD-1/PD-L1 pathway • 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 exclusive rights in the Greater China.

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

歌礼 ascletis

MOA of PD-L1 Antibody Against Chronic Hepatitis B

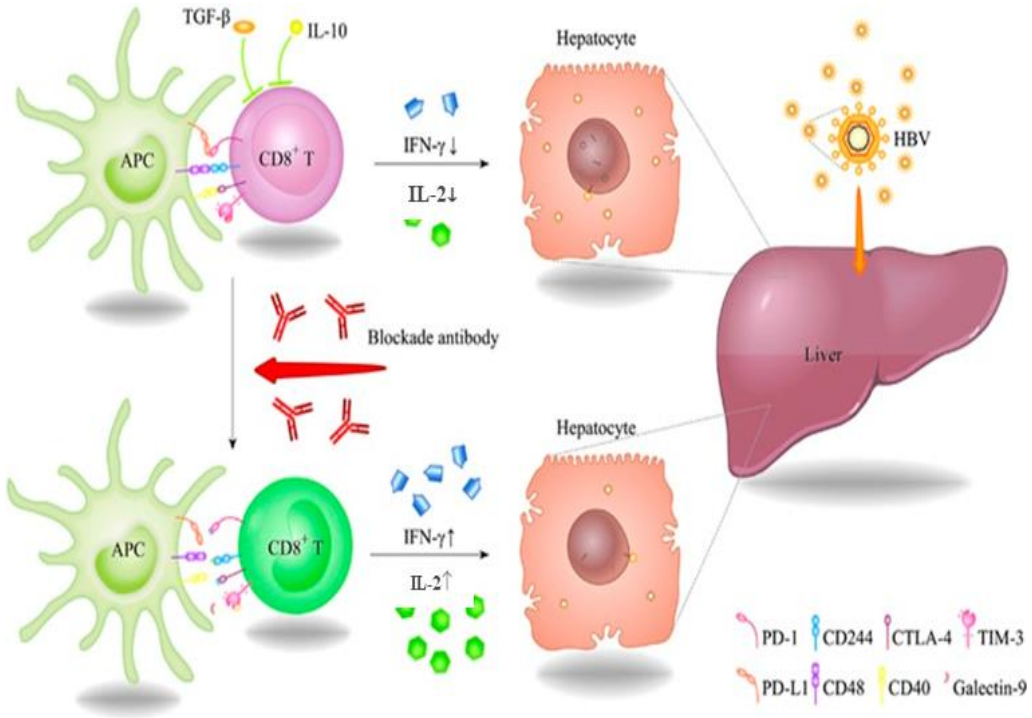
- ASC22 (KN035) can block the PD-1/PD-L1 pathway to restore T Cell immune function and eliminate HBV.

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.

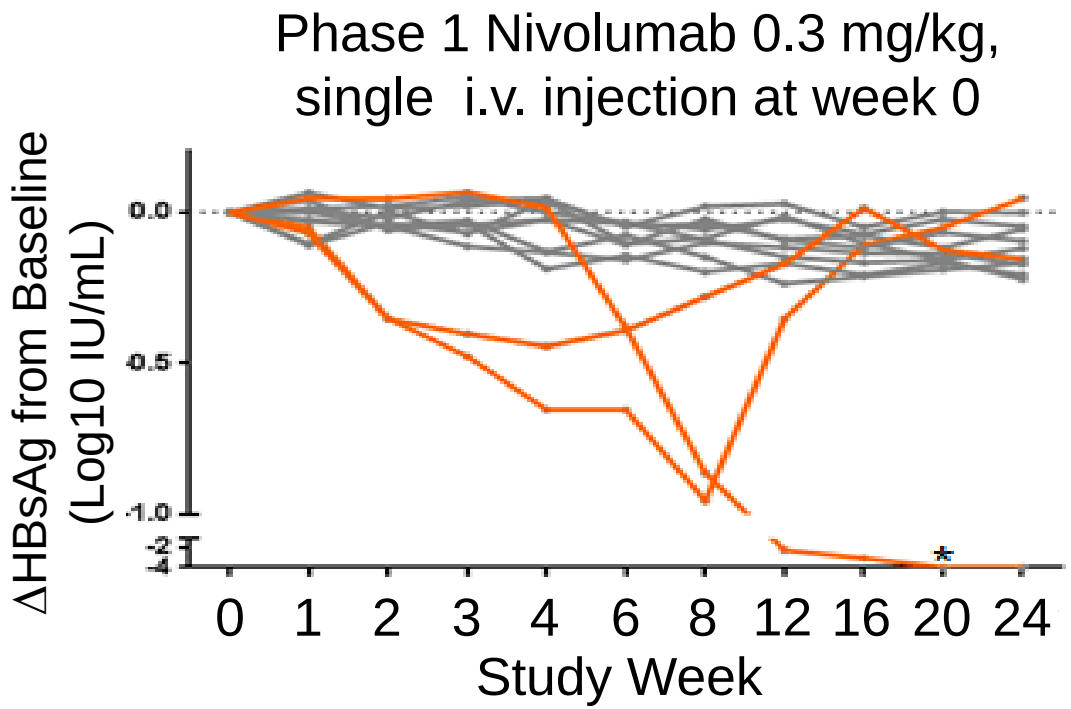
歌礼 ascletis

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.

Source: Gane, EASL 2017

歌礼 ascletis

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

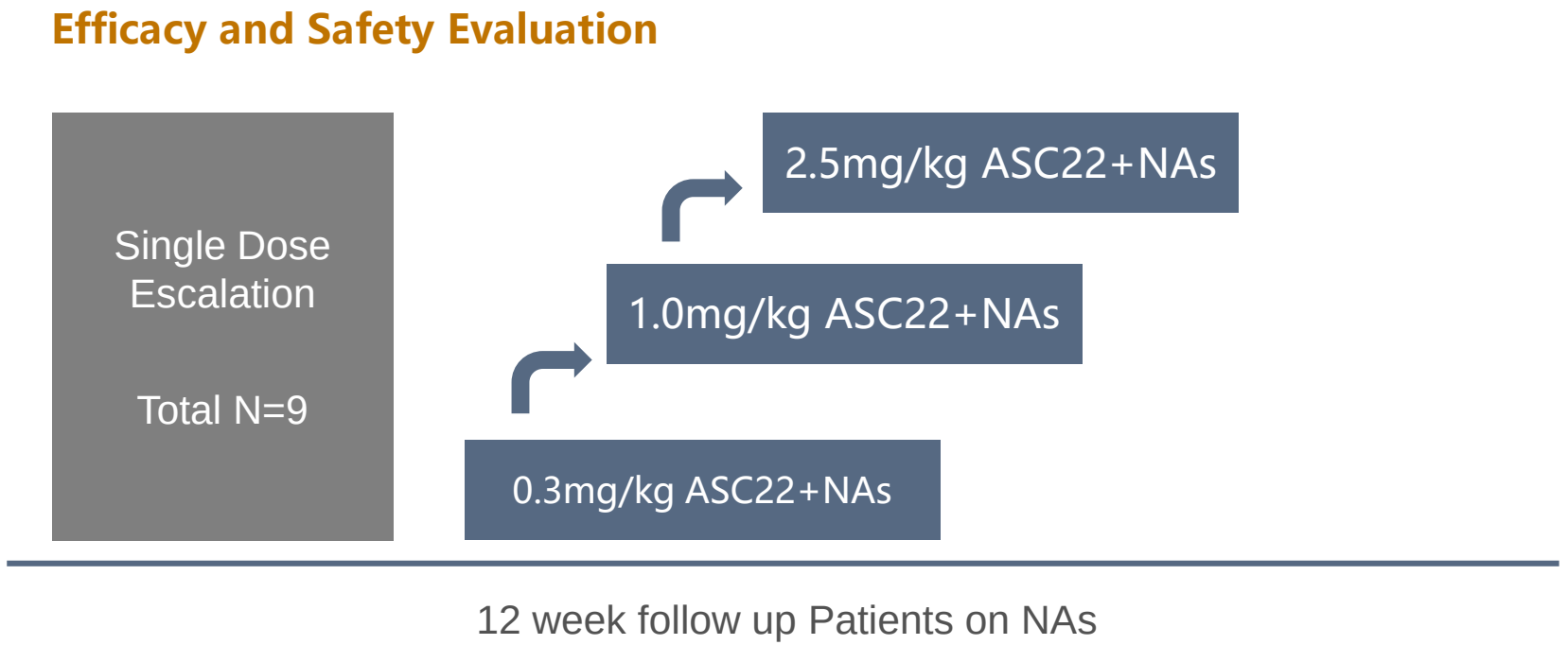
歌礼 ascletis

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 Chronic Hepatitis B Study Design for Functional Cure



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

歌礼 ascletis

Positive Efficacy 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.

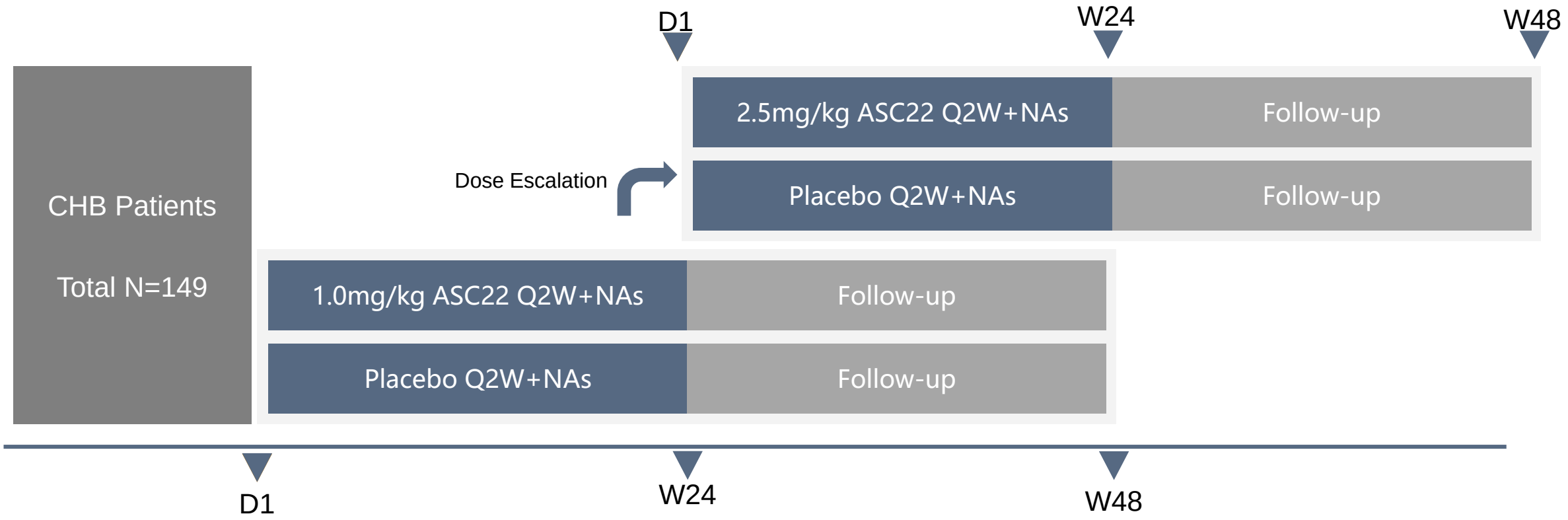
Source: Press Release on May 5, 2021

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.

Source: Press Release on May 5, 2021

ASC22 Phase IIb Chronic Hepatitis B Study Design for Functional Cure



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

歌礼 ascletis

Positive Interim Results of 149 Patient, Phase IIb Chronic Hepatitis B Study in China for PD-L1 Antibody ASC22 Plus NAs

- 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 HBsAg ≤ 500 IU/mL at baseline
  - No HBsAg reduction was observed for the placebo plus nucleos(t)ide analogs group
- Receptor occupancy after both 1 and 2.5 mg/kg dosing is predicted to be > 90% over one month, suggesting ASC22 has the potential to be given once monthly
- Patients treated with 1 mg/kg ASC22 plus nucleos(t)ide analogs had a comparable adverse event profile to the placebo plus nucleos(t)ide analogs

"I am delighted by the safety data so far for 1 mg/kg ASC22 Q2W plus NAs, which was comparable to that of placebo Q2W plus Nas, once-a-month dosing of PD-L1 antibody ASC22 will dramatically improve compliance and convenience of patients with CHB."

——————Guiqiang Wang, MD

Principal Investigator of the Phase IIb Study, Vice-President of Chinese Society of Physicians for Infectious Diseases and Director of Centre for Liver Diseases at Peking University First Hospital

歌礼 ascletis

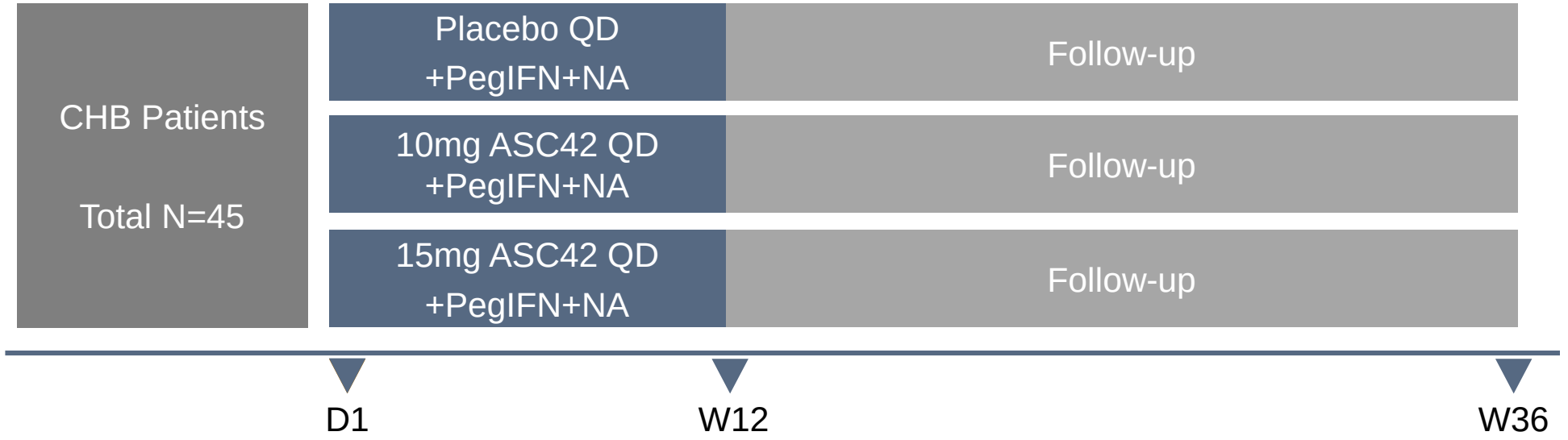
Safety Data as of July 20, 2021 from 149 Patient, Phase IIb Chronic Hepatitis B Study in China for PD-L1 Antibody ASC22 Plus NAs

- 1 mg/kg ASC22 Q2W plus NAs
  - 37% of patients (22/60) completed 24-week treatment per protocol
  - 35% of patients (21/60) completed 14 to 22-week treatment
  - 28% of patients (17/60) completed 1 to 12-week treatment
- 2.5 mg/kg ASC22 Q2W plus NAs
  - 7% of patients (4/59) completed 14 to 24-week treatment
  - 93% of patients (55/59) completed 1 to 12-week treatment
- 1 mg/kg ASC22 Q2W plus NAs had a rate of any adverse events of 75%, comparable to that (73%) of the placebo Q2W plus NAs group
  - The rate of grade 3 and 4 adverse events is 7% for both 1 mg/kg ASC22 Q2W plus NAs and placebo Q2W plus NAs
- 2.5mg/kg ASC22 plus NA was safe and well tolerated

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 for CHB Functional Cure



歌礼 ascletis

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.

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%

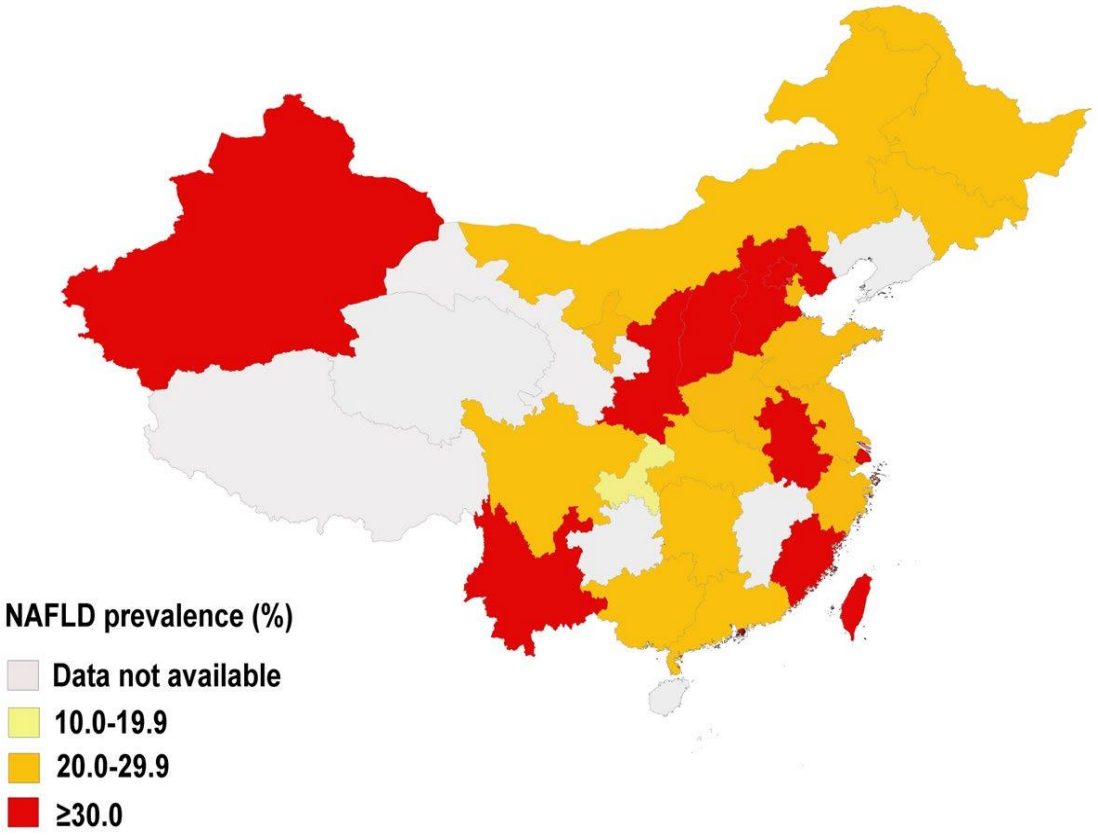
Obesity and Diabetes

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 in females over age 40
- Ursodeoxycholic acid (UDCA) is the only drug been approved in China with the effect of delaying disease progression. However, approximately 40% PBC patients have an inadequate response to UDCA or are unable to tolerate UDCA

US/EU

- The prevalence of PBC is 20-40 cases per 100,000 persons
- Obeticholic acid (Ocaliva) has been approved by US FDA for the indication of PBC in combination with UDCA in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA
- Significant side effects occurred with Ocaliva, including pruritus (63%) and fatigue (22%)

NASH/PBC Pipeline

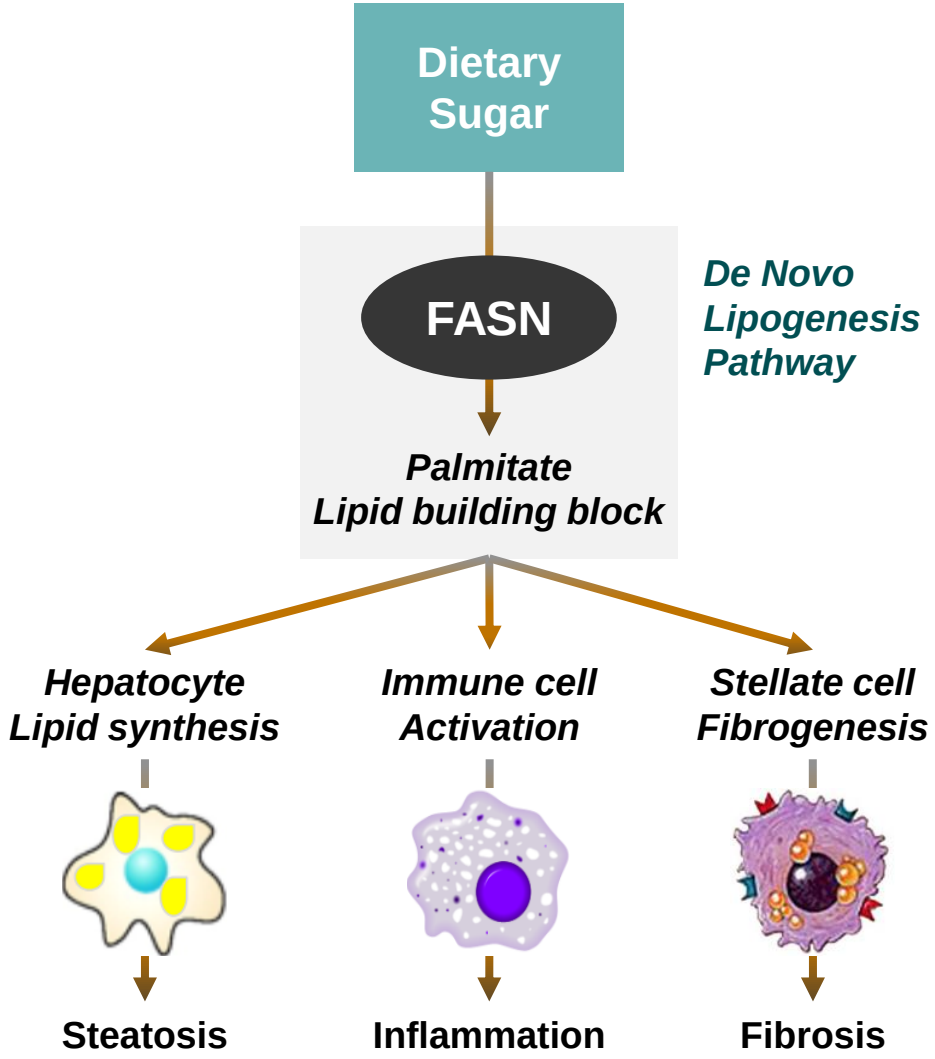
Target	Candidate	Commercial rights	Pre-IND	IND	Phase I	Phase IIa	Phase IIb	Phase III	Competitiveness
FASN	ASC40 (NASH)	Greater China[1]	***U.S. FDA Fast Track***						• First-in-class, inhibit de novo lipogenesis • US/CN phase II showed significant reduction of liver fat content, and minimal side effects compare to other NASH candidates
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
FXR	ASC42 (PBC)	Global							• No pruritus • Applying for phase II

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

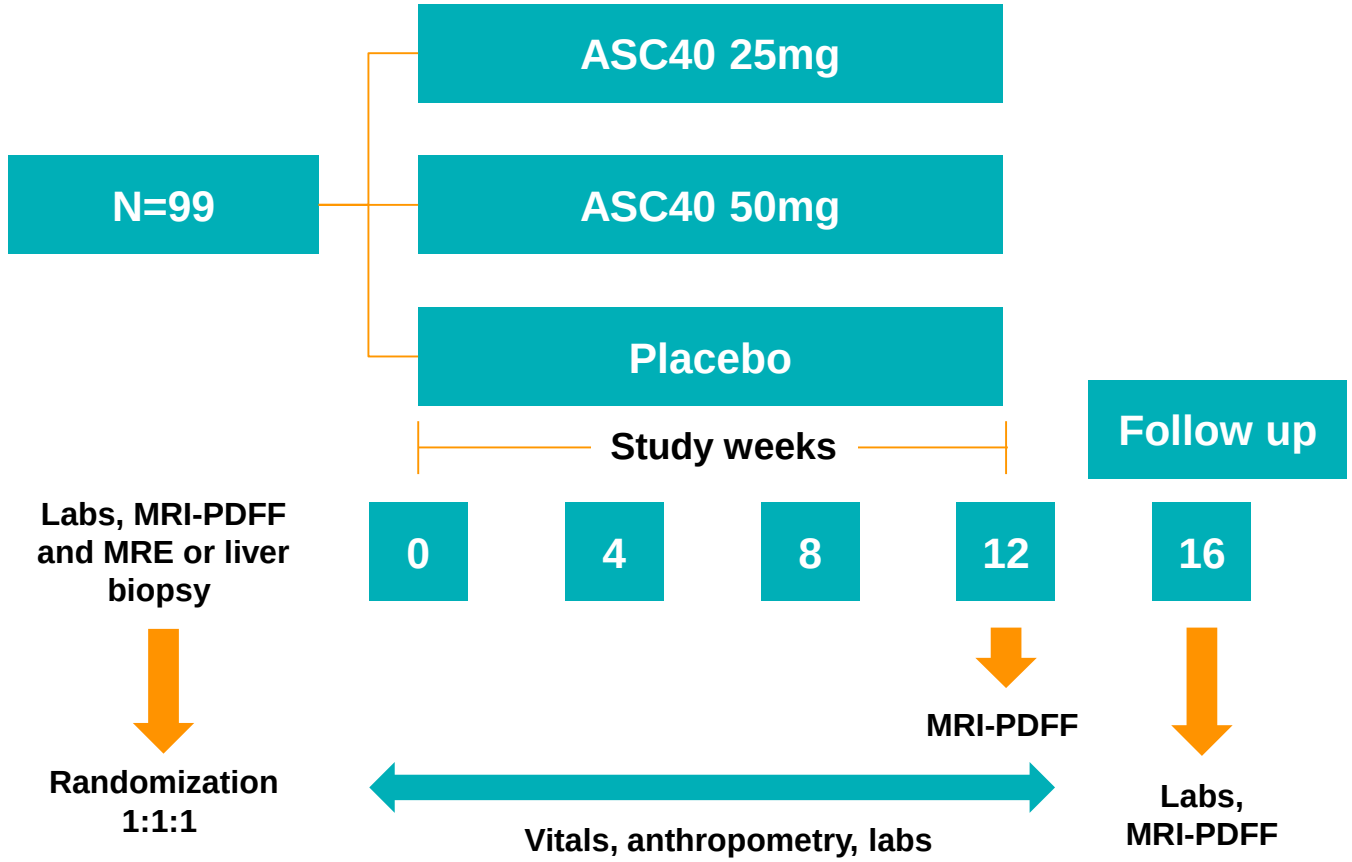
- Multicenter, randomized, placebo-controlled trial 1:1:1 25mg:50mg:placebo (N=99)

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

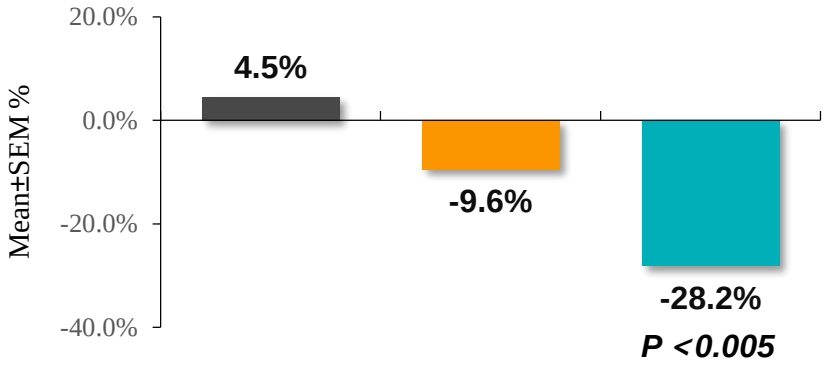


Source: Rohit Loomba et al. 2020,Hepatology 72;103.EASL 2020 Oral Presentation

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

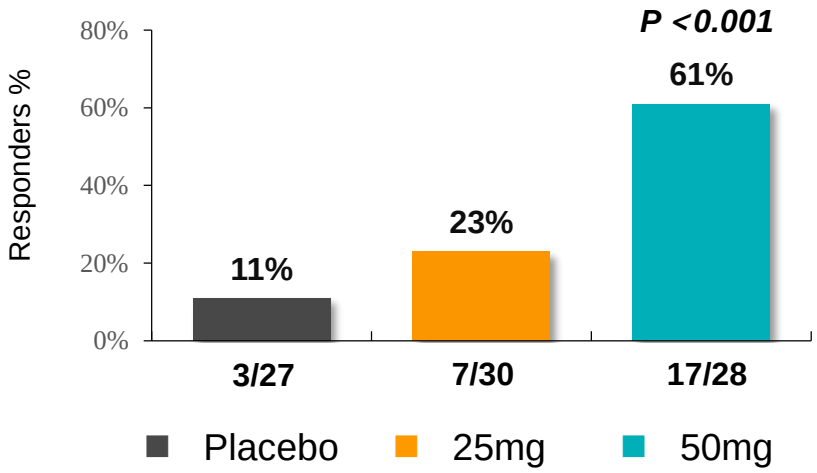
Mean relative liver fat reduction

MRI-PDFF at week 12

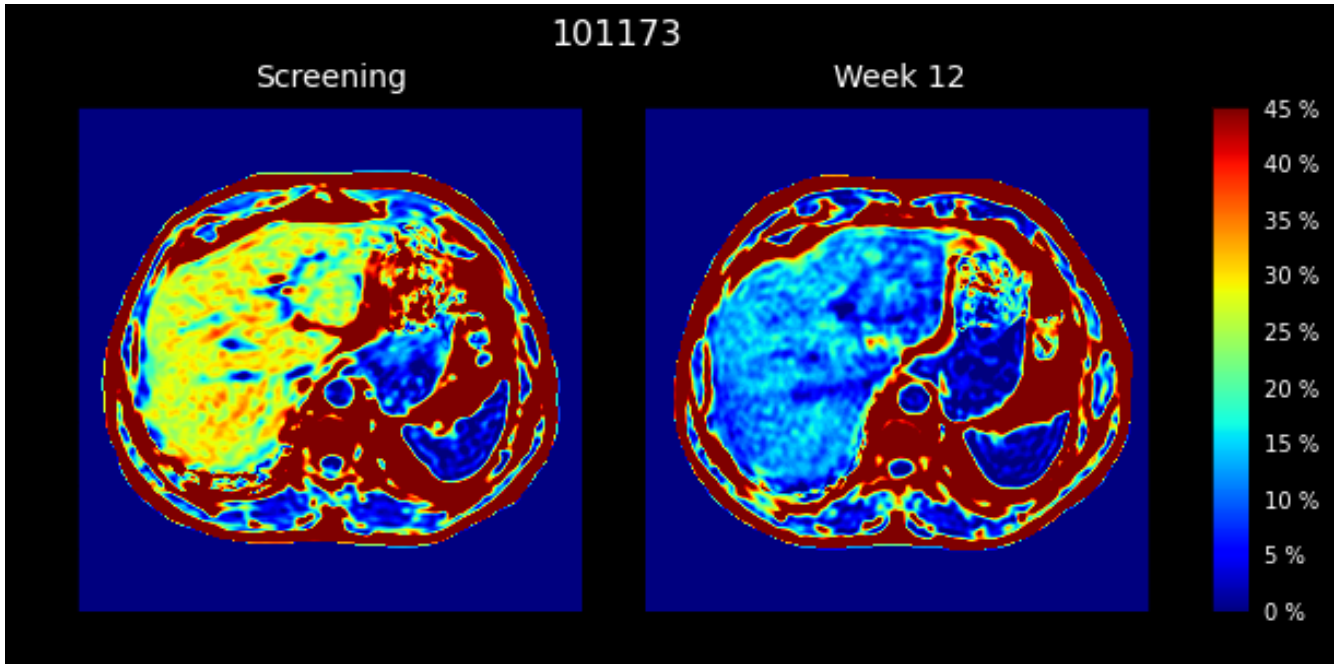


Responder frequency

Patients with ≥30% relative reduction



Significant reduction in liver fat content over 12 weeks of treatment

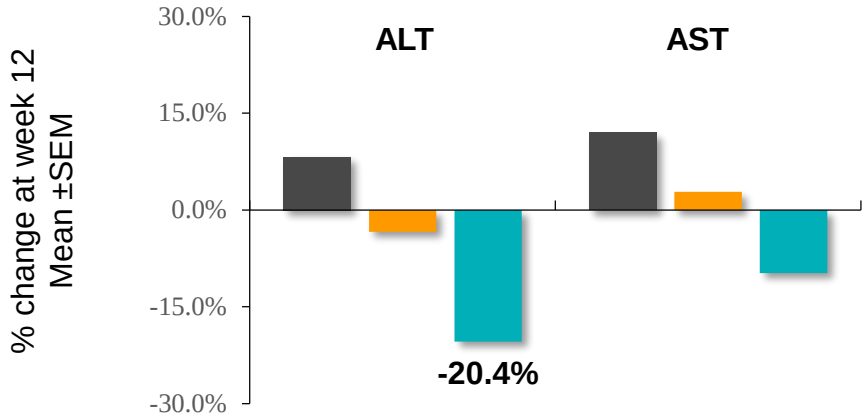


MRI-PDFF responders were defined as those with ≥ 30% MRI-PDFF decline relative to baseline

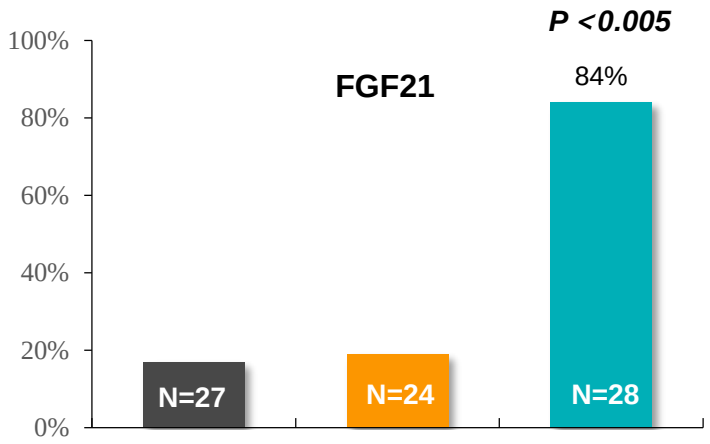
Source: Rohit Loomba et al. 2020, Gastroenterology & Hepatology 72;103AASLD 2020 Oral Presentation

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

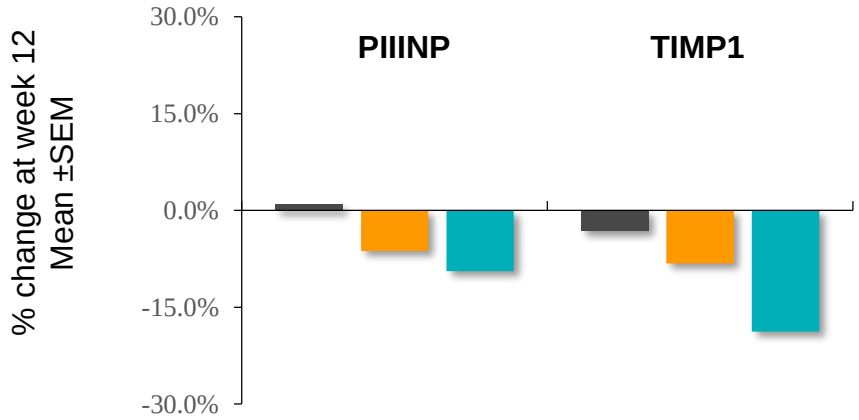
Dose-dependent response in reducing ALT/AST



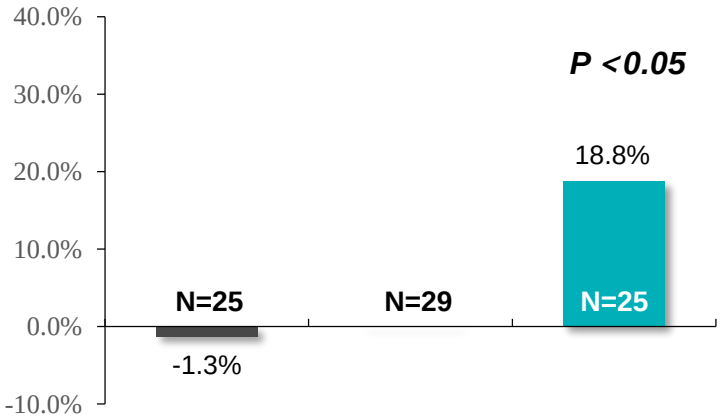
Improves markers of hepatic insunlin sensitivity



Decreases fibrosis markers



Adiponectin



■ Placebo ■ 25mg ■ 50mg

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

歌礼 ascletis GANNEX A Member of the Ascletis Group

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

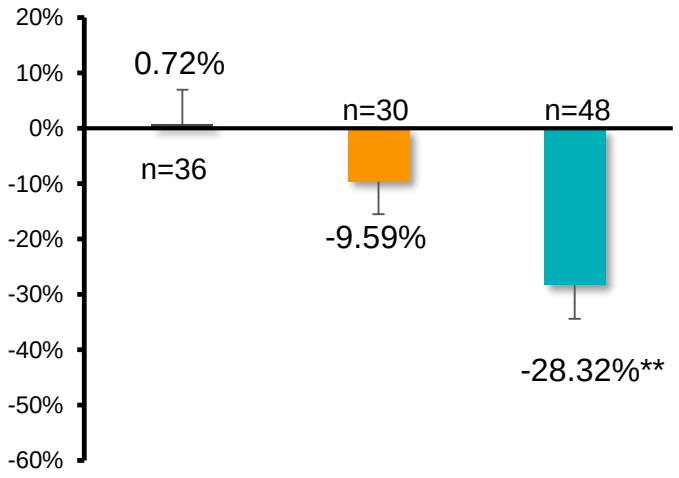
Non-head to head research

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

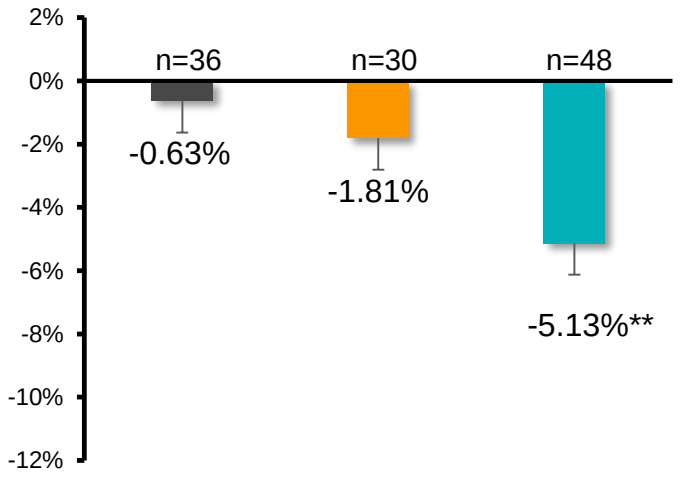
歌礼 ascletis GANNEX A Member of the Ascletis Group

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

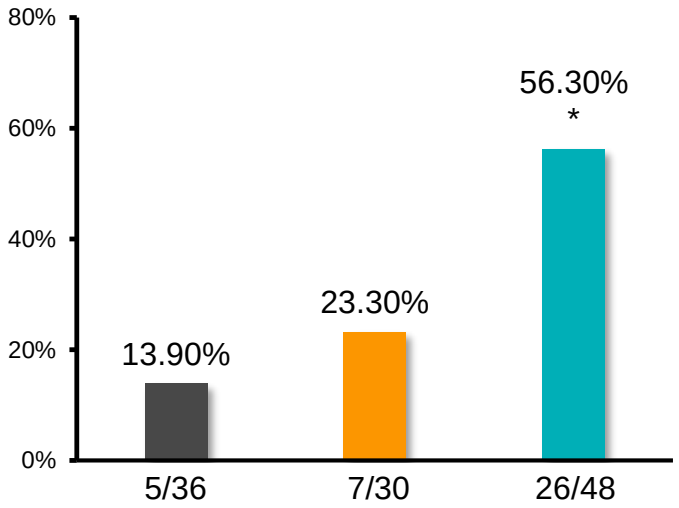
Mean relative liver fat reduction
MRI-PDFF at week 12



Mean absolute liver fat reduction
MRI-PDFF at week 12



Responder frequency
Patienct with ≥30% relative reduction

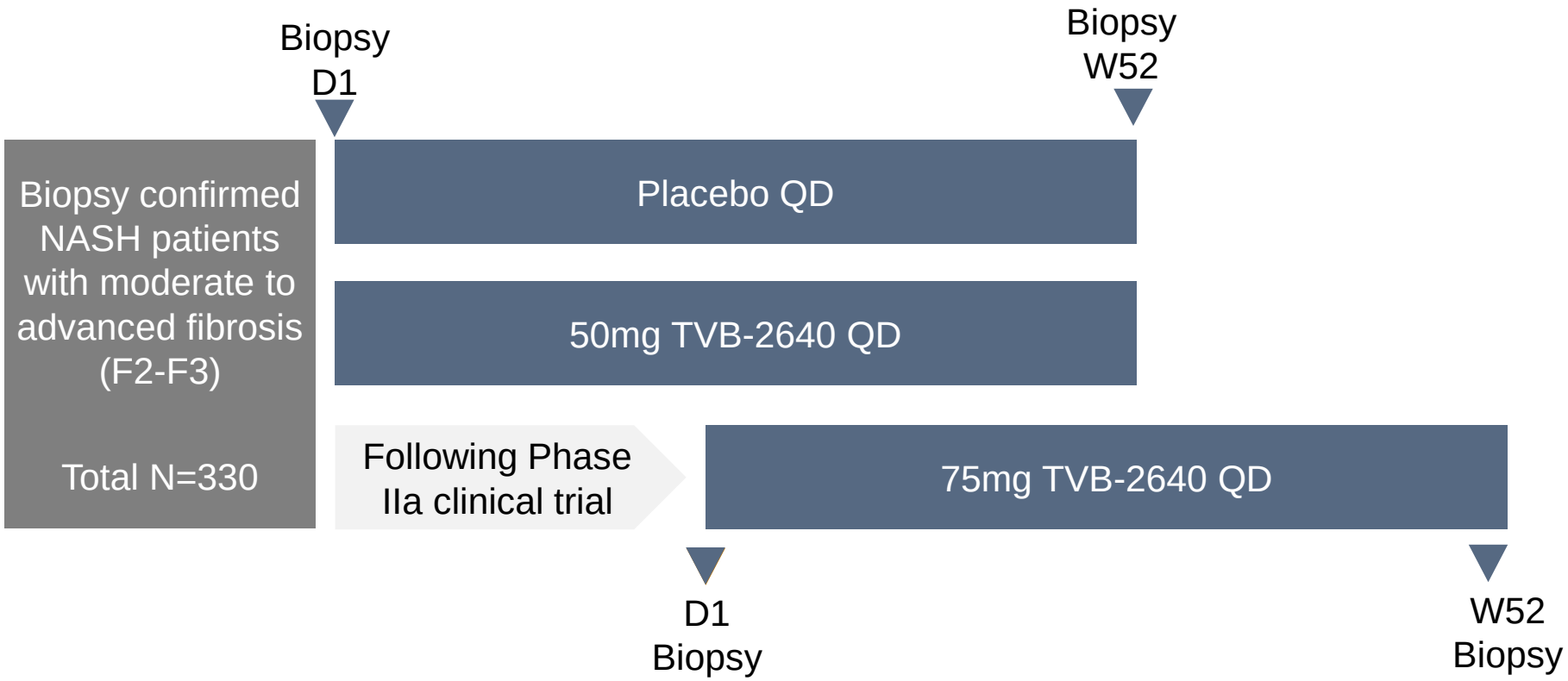


Placebo **25mg** **50mg**

Source: Gannex data
***p<0.001 Mean ± SEM LSM difference versus placebo for liver fat.Common risk difference for responder frequence*
**p=0.0002*

歌礼 ascletis GANNEX A Member of the Ascletis Group

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

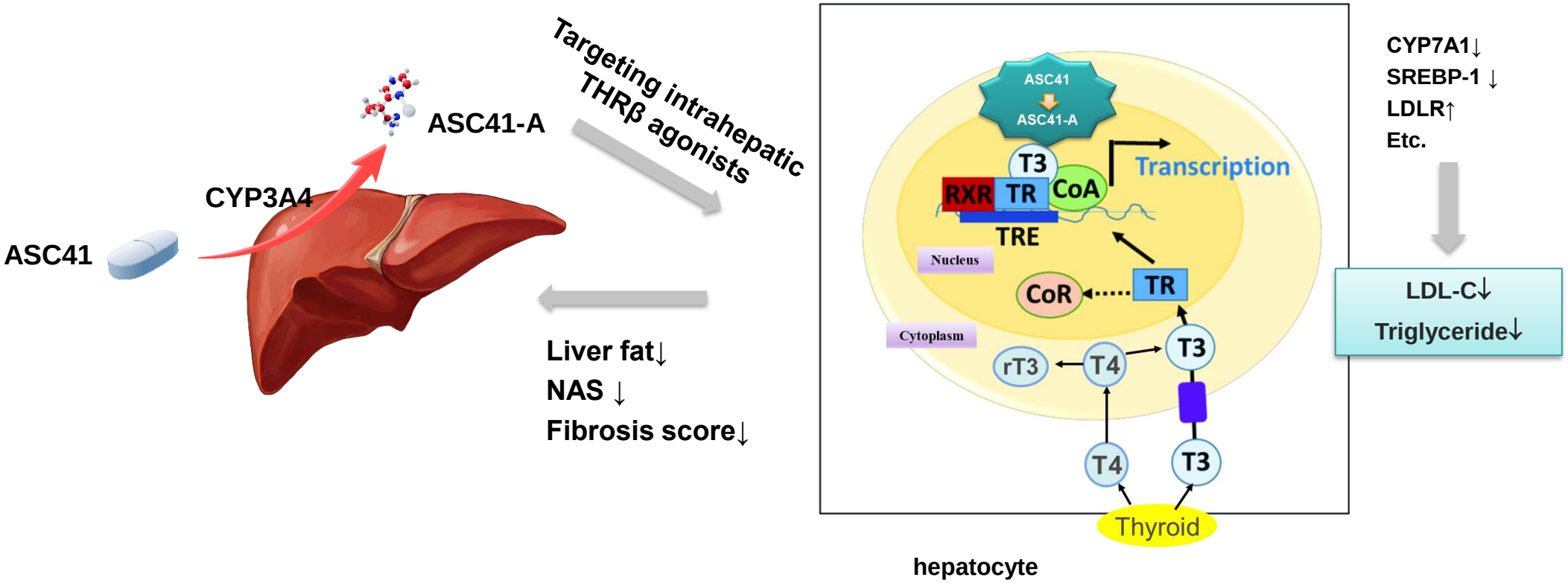


Primary efficacy endpoints:

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

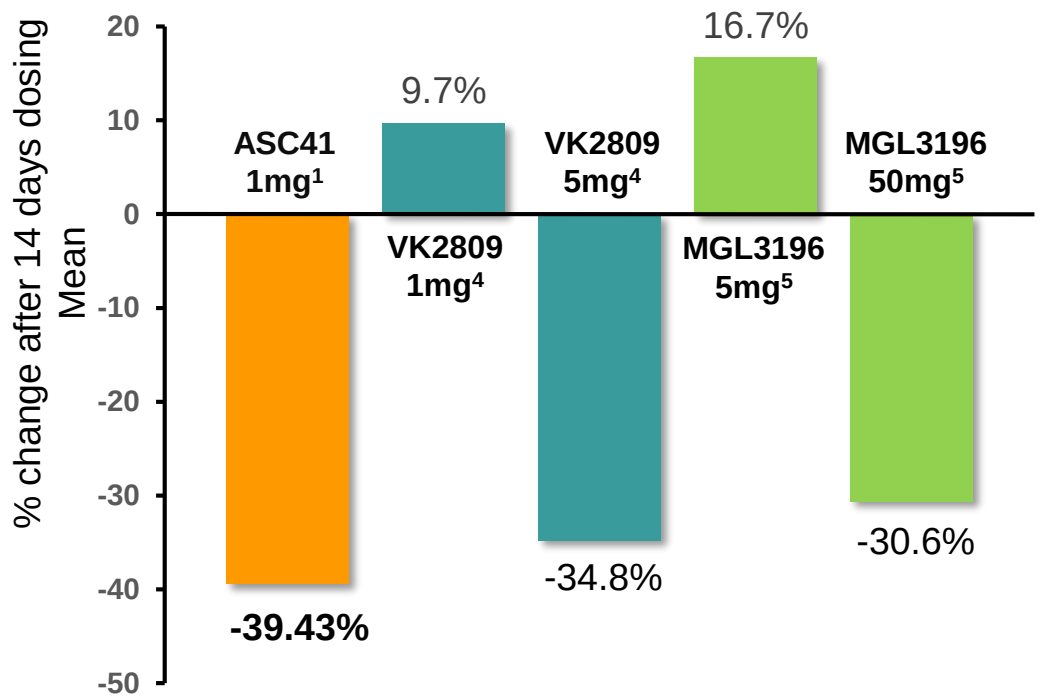
- In two NASH animal models, at 1/10th dose of MGL-3196, ASC41 demonstrated the same improvement in liver steatosis, inflammation and fibrosis.
- Commercially ready oral tablet formulation developed with in-house proprietary technology
- 2 Phase I studies completed
  - Single doses (1, 2, 5, 10, 20 mg) 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
- 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 showed that there was no significant drug-drug interactions between ASC41/ASC41-A and the most frequently used drugs of 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

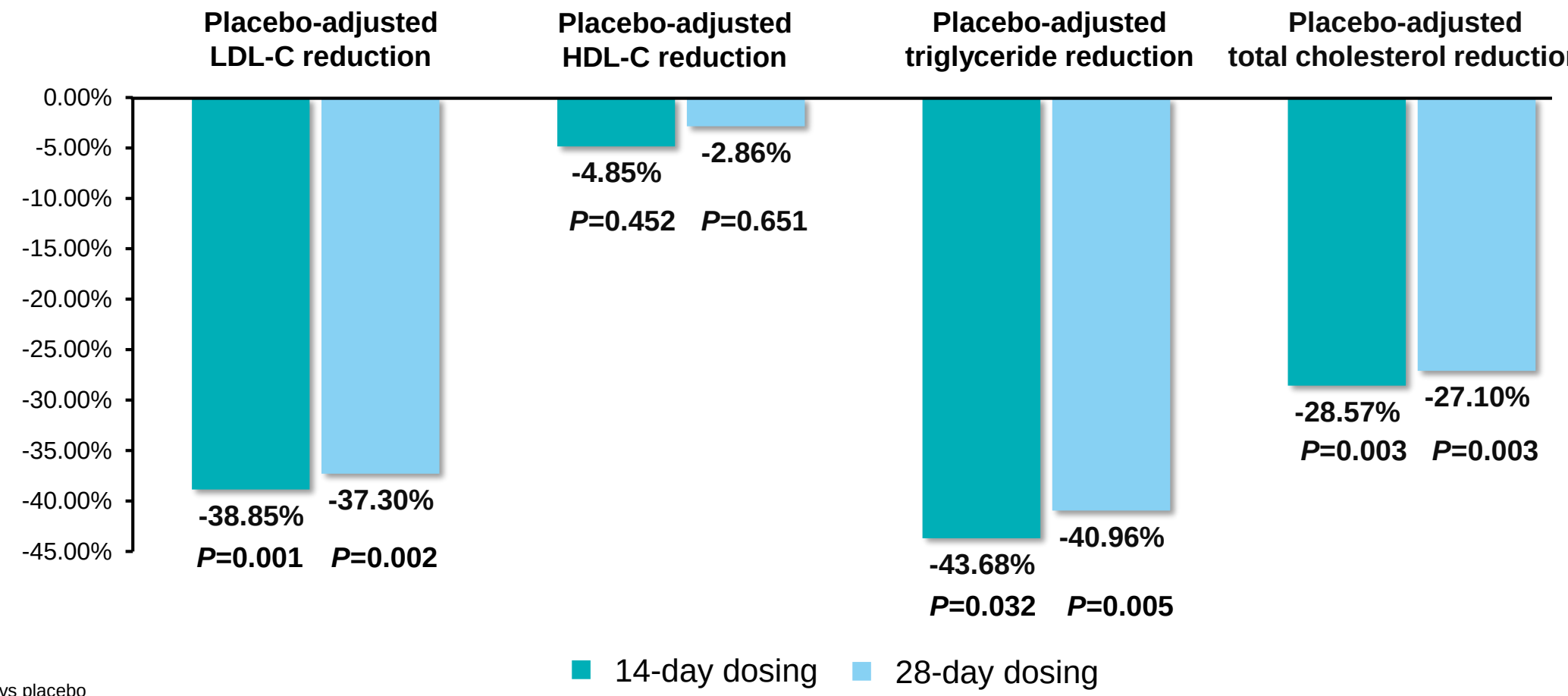


1.EASL 2021 Abstract No. PO-1851 2.EASL2020 Abstract No. AS073. 3.Stephen A Harrison et al. Resmetirom (MGL-3196) for the treatment of non-alcoholic steatohepatitis: a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. www.thelancet.com Published online November 11, 2019 https://doi.org/10.1016/S0140-6736(19)32517-6 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

歌礼 ascletis GANNEX A Member of the Ascletis Group

Positive Clinical Results in Overweight and Obese Subjects

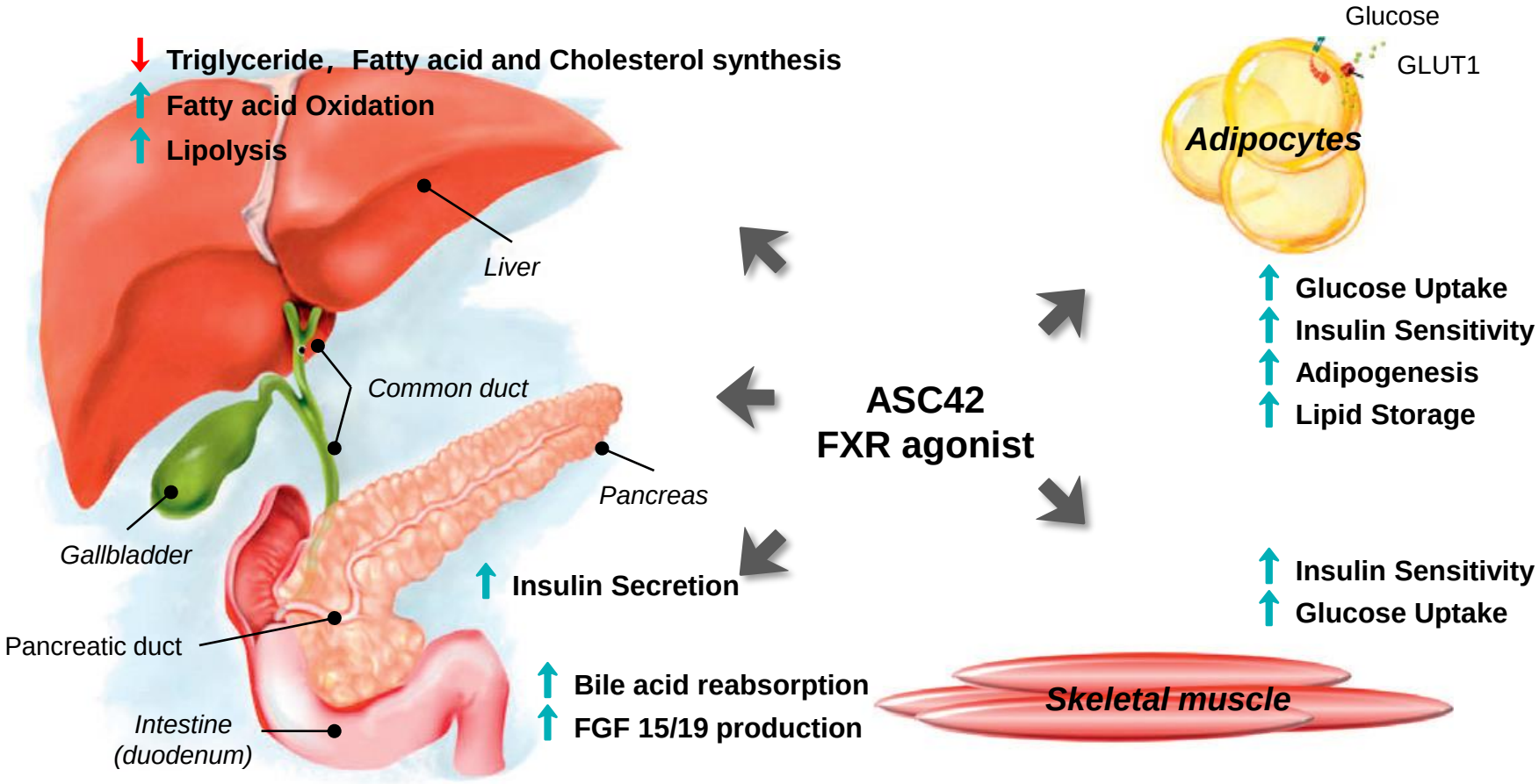
Placebo-adjusted relative change (mean) from baseline after 14 or 28 days of once daily oral dosing of 10 mg ASC41 tablets in overweight and obese subjects



P-value vs placebo

Source: 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

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
- 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

Source: Press Release on June 16, 2021

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		★★★		★★★		★★★

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 block de novo lipogenesis • Significantly improve PFS6 in Phase II
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
FASN	ASC60 (Oral)	Solid tumor 1	Greater China[1]						• FIC • Higher *in vitro* activities compare to ASC40
FASN	ASC60 (Oral)	Solid tumor 2	Greater China[1]						• FIC • Higher *in vitro* activities compare to ASC40
PD-L1	ASC61 (Oral small molecule)	Multiple tumors	Global						• Oral small molecule, easier administration • Comparable efficacy with antibody drug in animal model
PD-L1	ASC63 (Oral small molecule)	Multiple tumors	Global						• Oral small molecule, easier administration • Stronger effects on PD-L1 dimerization and internalization compare 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

歌礼 ascletis

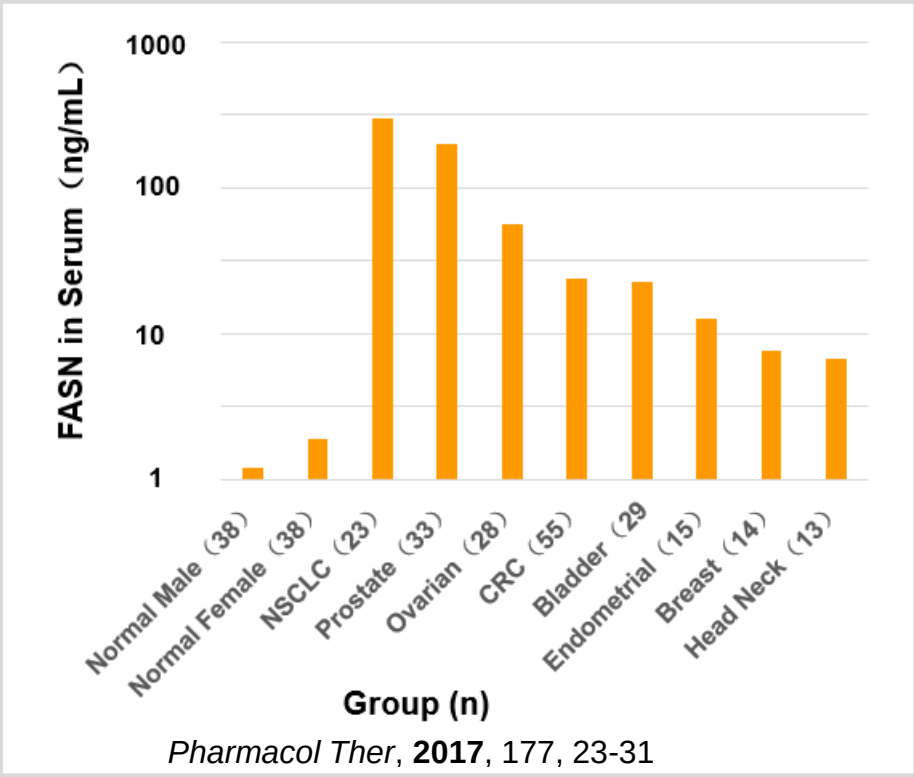
Cancer Metabolism: Approved Drugs and Clinical Stage Candidates

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)

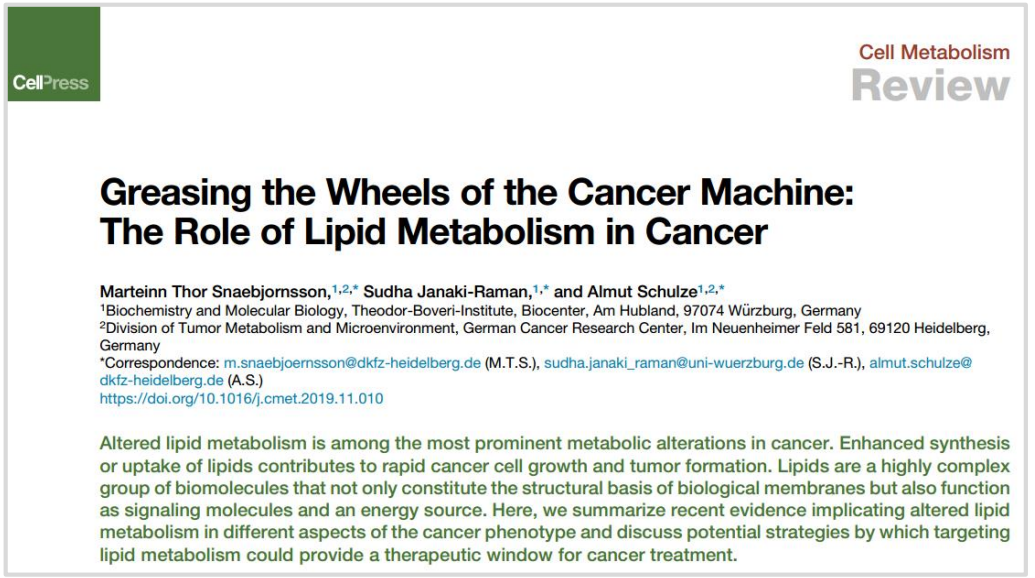
Fatty Acid Synthase, A Promising Cancer Drug Target

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

Marteinn Thor Snaebjornsson,[1,2,*] Sudha Janaki-Raman,[1,*] and Almut Schulze[1,2,*]
[1]Biochemistry and Molecular Biology, Theodor-Boveri-Institute, Biocenter, Am Hubland, 97074 Würzburg, Germany
[2]Division of Tumor Metabolism and Microenvironment, German Cancer Research Center, Im Neuenheimer Feld 581, 69120 Heidelberg, Germany
*Correspondence: m.snaebjoernsson@dkfz-heidelberg.de (M.T.S.), sudha.janaki_raman@uni-wuerzburg.de (S.J.-R.), almut.schulze@dkfz-heidelberg.de (A.S.)
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]

歌礼 ascletis

Glioblastoma

- In China, glioblastoma (GBM) represents 46.1% of gliomas and has an incidence rate of approximately 2.85 to 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 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 the historical Bevacizumab monotherapy PFS6 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

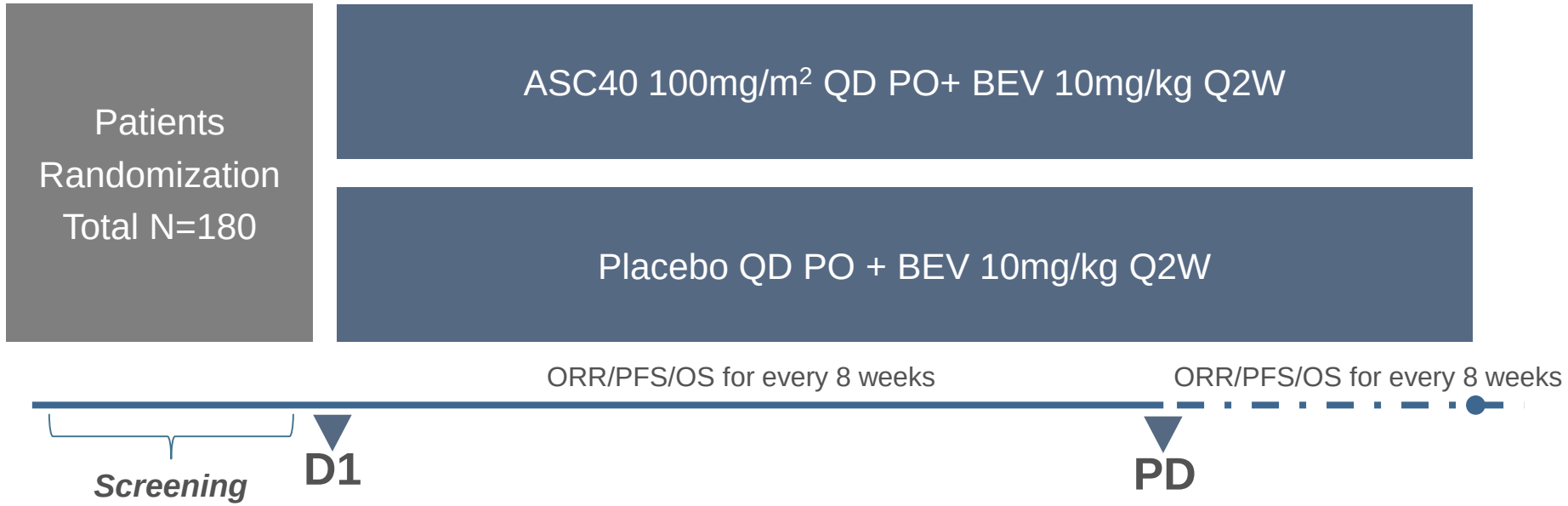
China NMPA Approved Phase III Clinical Trial of ASC40 Combined with Bevacizumab for Treatment of Patients with Recurrent Glioblastoma

- 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 for 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

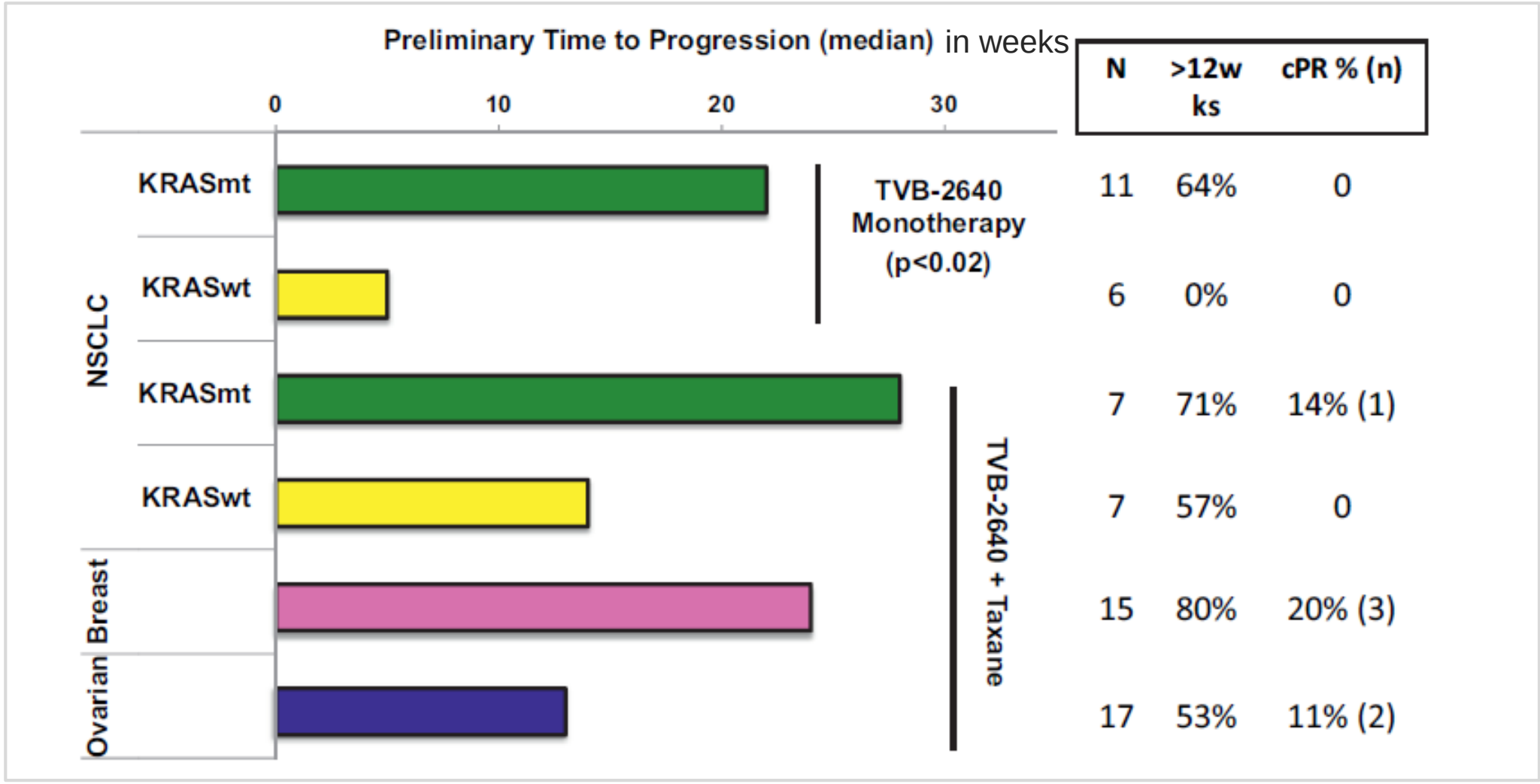


Primary endpoints: PFS and OS

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

PD: Progression disease

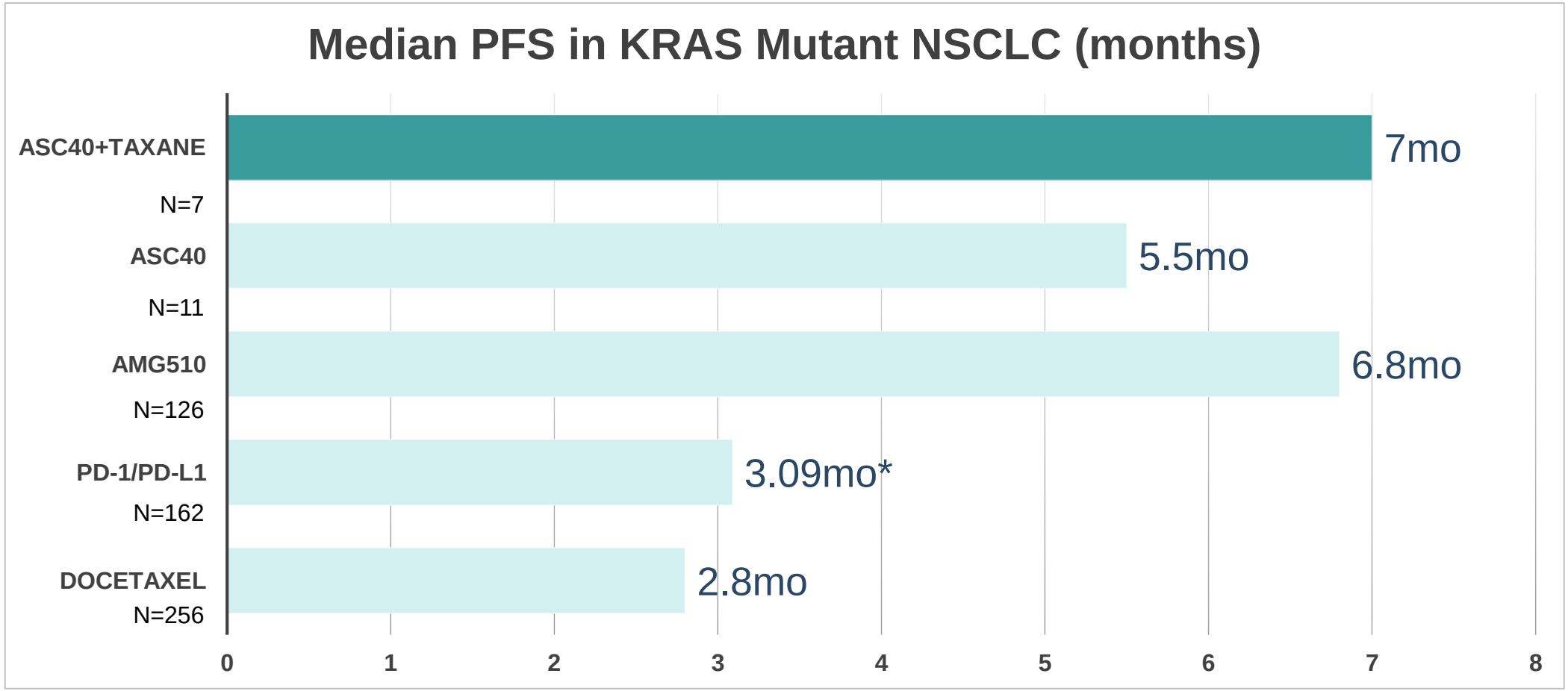
Phase I: Median time to progression of TVB-2640 alone and with a Taxane in patients with $KRAS^{MUT}$ versus $KRAS^{WT}$ non-small cell lung, breast, and ovarian cancer



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

歌礼 ascletis

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

歌礼 ascletis

Other Clinical Trials of ASC40 (TVB-2640)

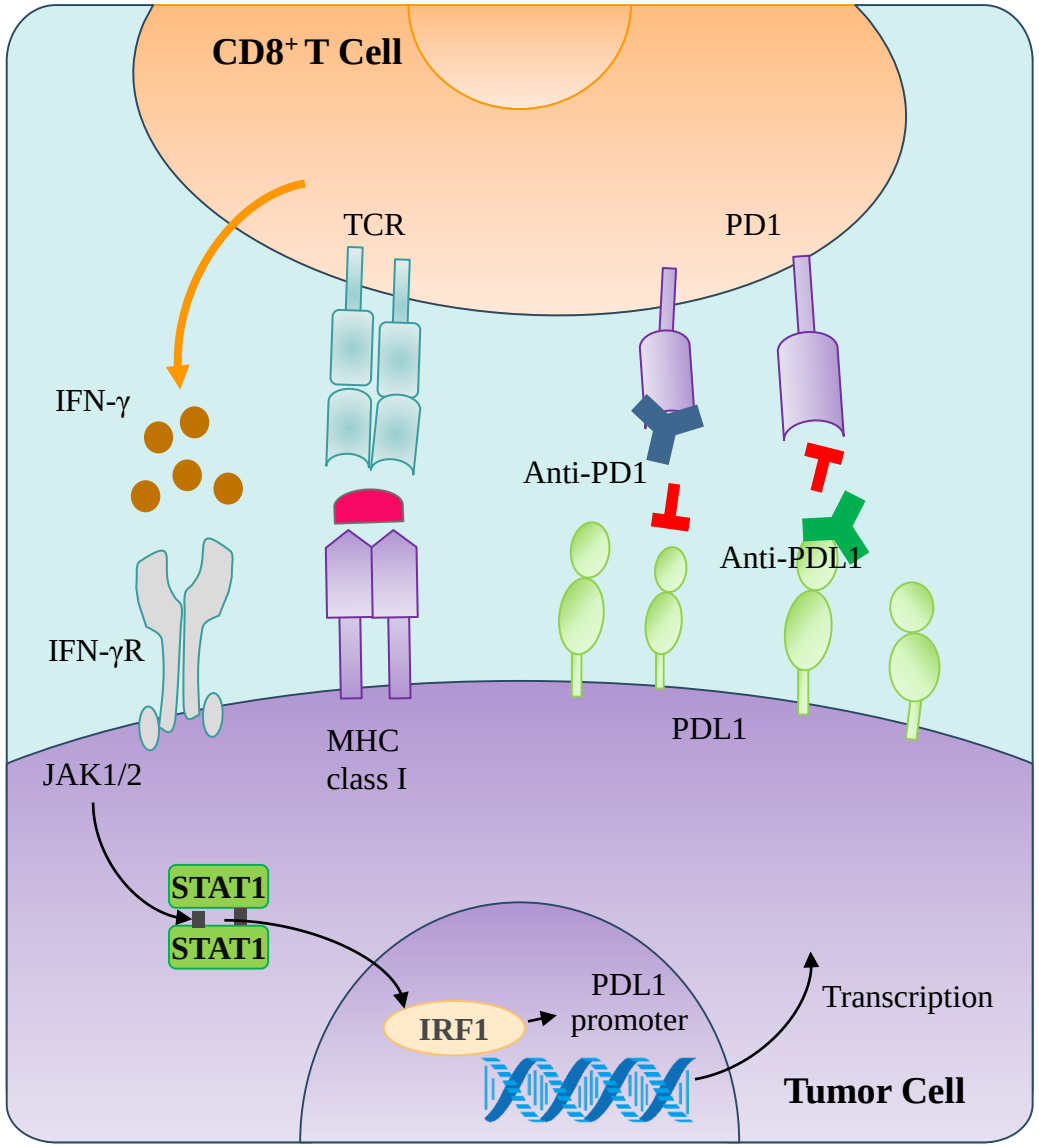
- Patients with KRAS mutatant non-small cell lung cancer (ClinicalTrials.gov Identifier: NCT03808558)
- Patients with breast cancer (ClinicalTrials.gov Identifier: NCT03179904)
- Patients with colon cancer/head and neck cancer (ClinicalTrials.gov Identifier: NCT02980029)

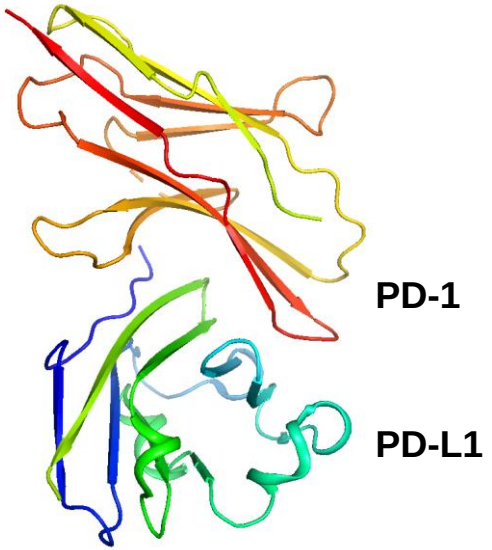
Oral Immune Checkpoint Inhibitors

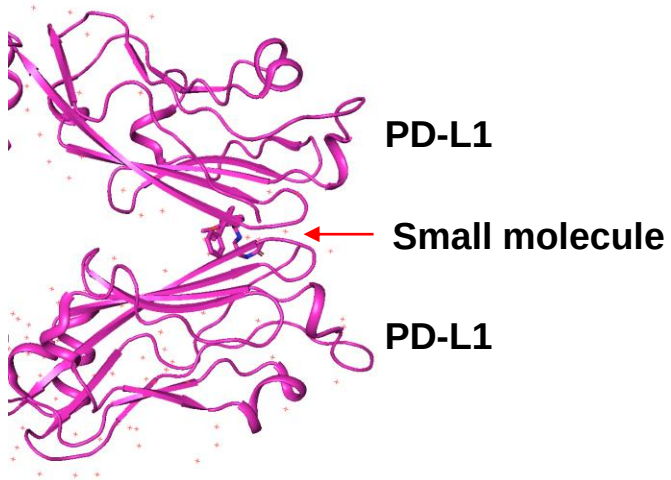
Immunotherapies: Great Success for mAb, It is Time for Oral Drugs

- 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 2020, Incyte announced its oral PD-L1 inhibitor INCB86550 was in Phase I for solid tumors

PD-L1 Small Molecule Inhibitors: Challenges and Opportunities



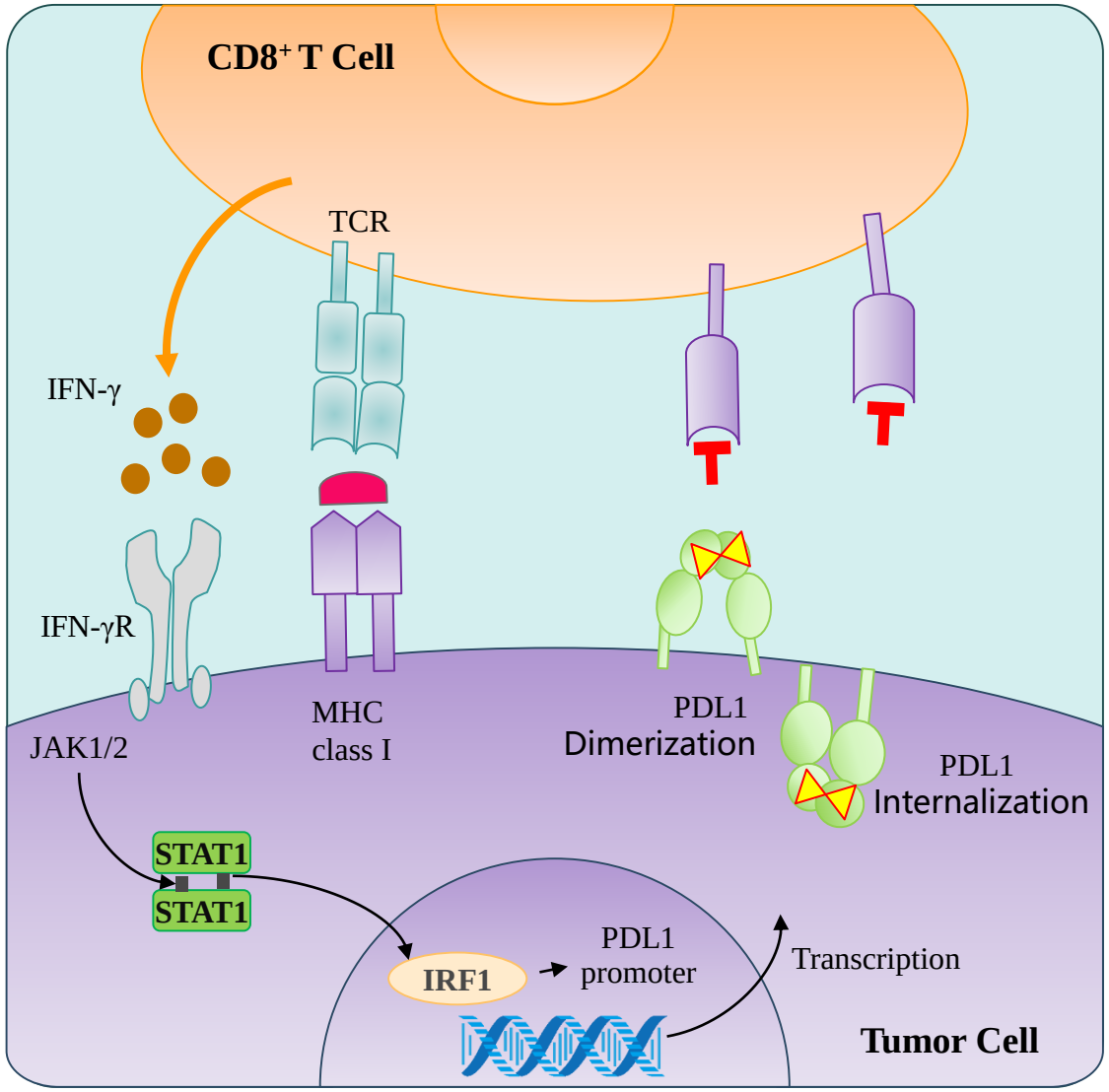


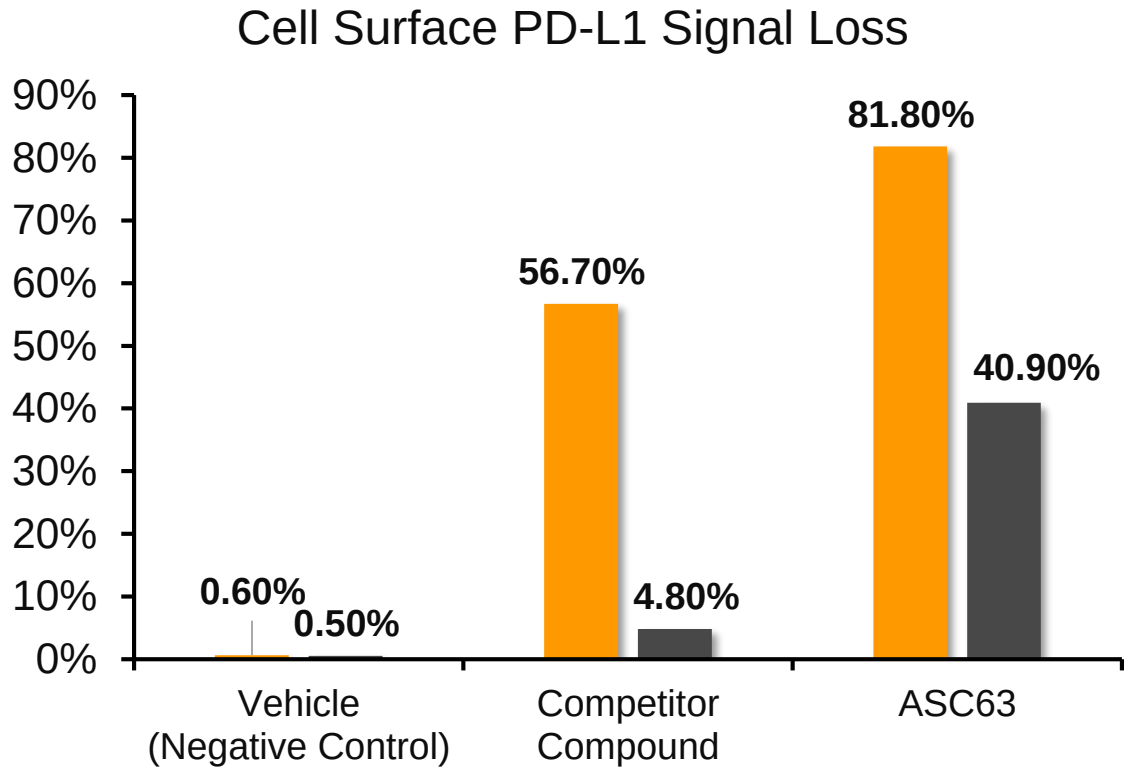


- Antibodies block PD-1/PD-L1 interface
- Traditional small molecules not good at inhibiting protein-protein interaction

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

ASC63: Induce PD-L1 Dimerization and Sustained Internalization



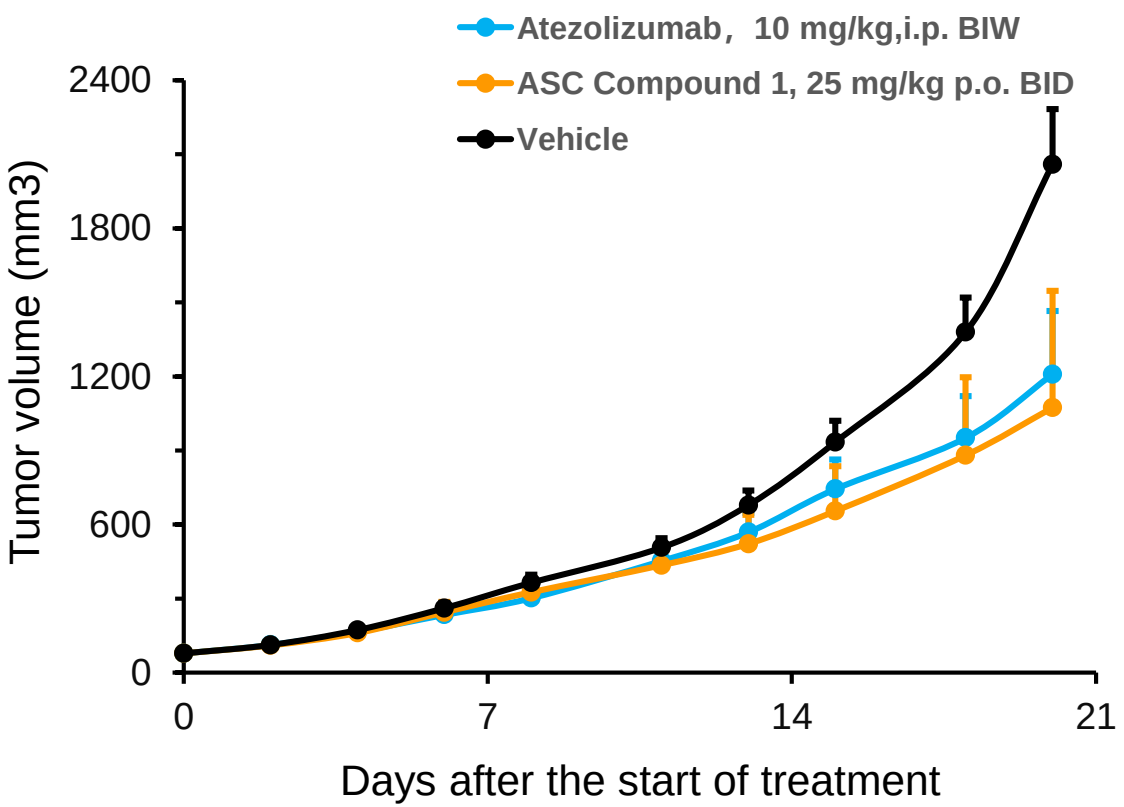


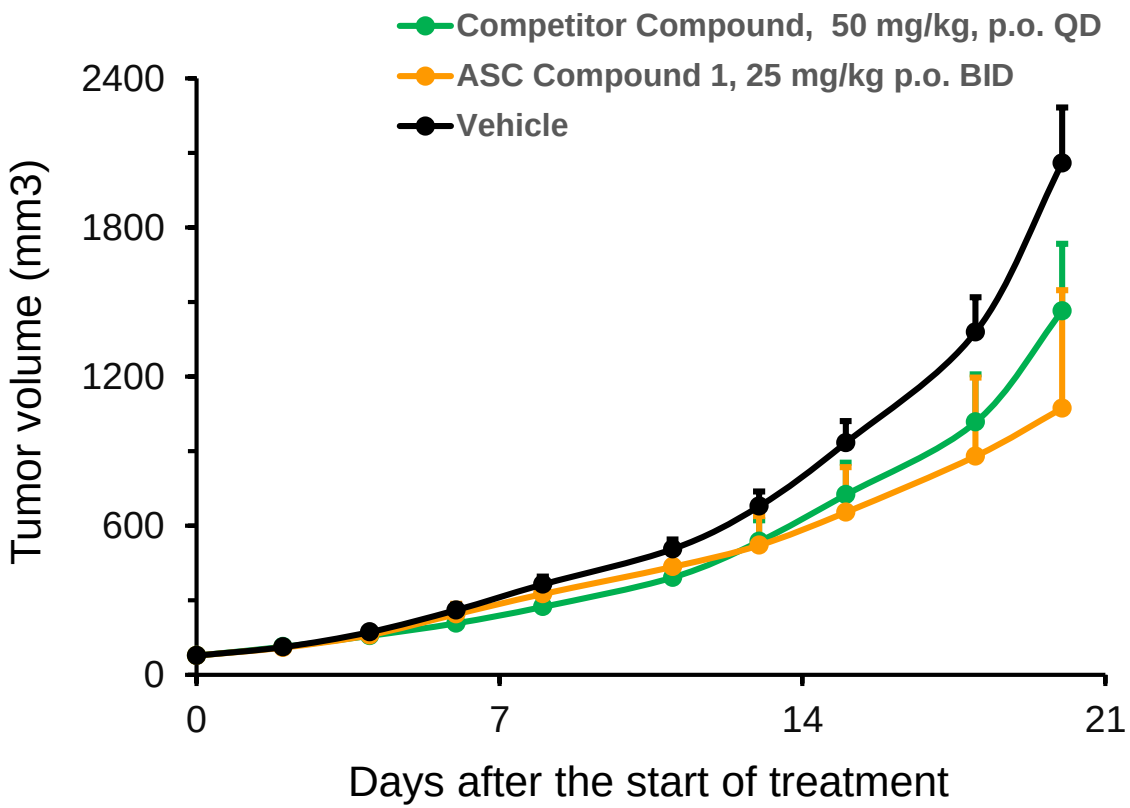
Ascletis' ASC63

- 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

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





Source: Ascletis data

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 • Sebum production inhibited dose dependently 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
  - However, acne can also persist into or dThe 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.
  - evelop 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

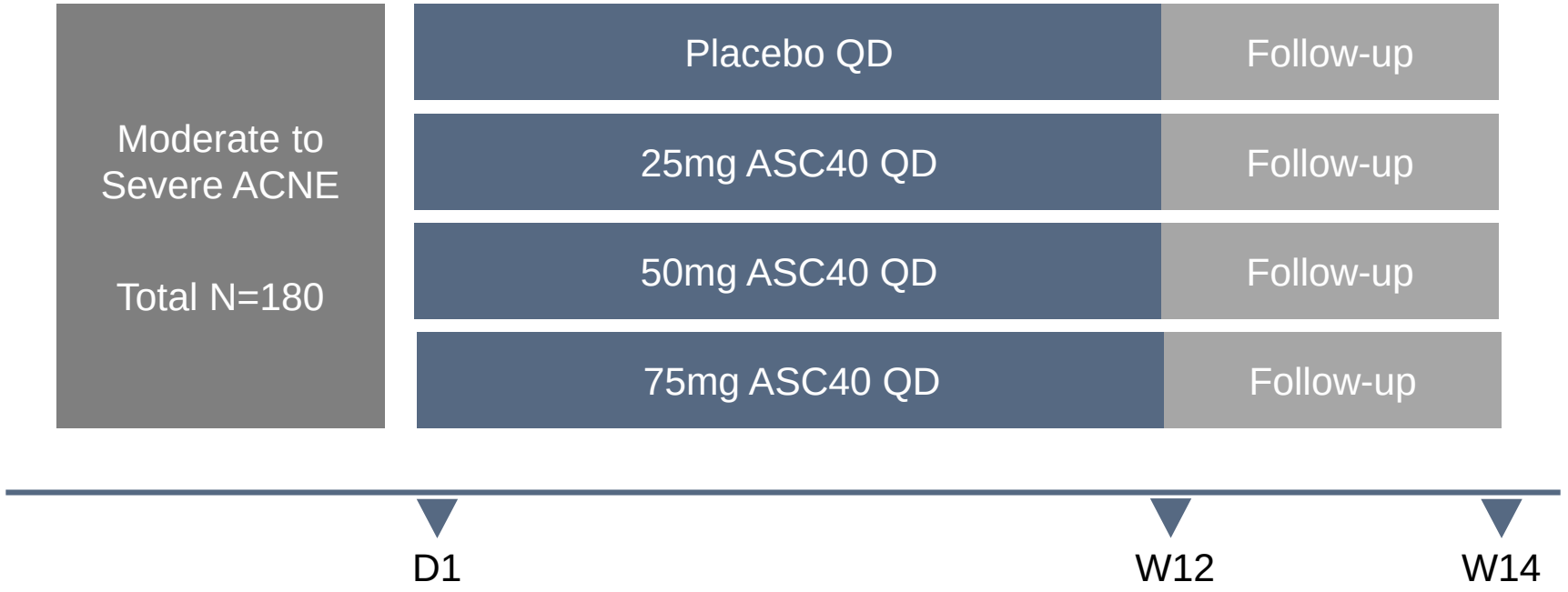
- Fatty acid synthase (FASN) is a key enzyme which regulates de novo lipogenesis.

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

- Clinical proof concept data

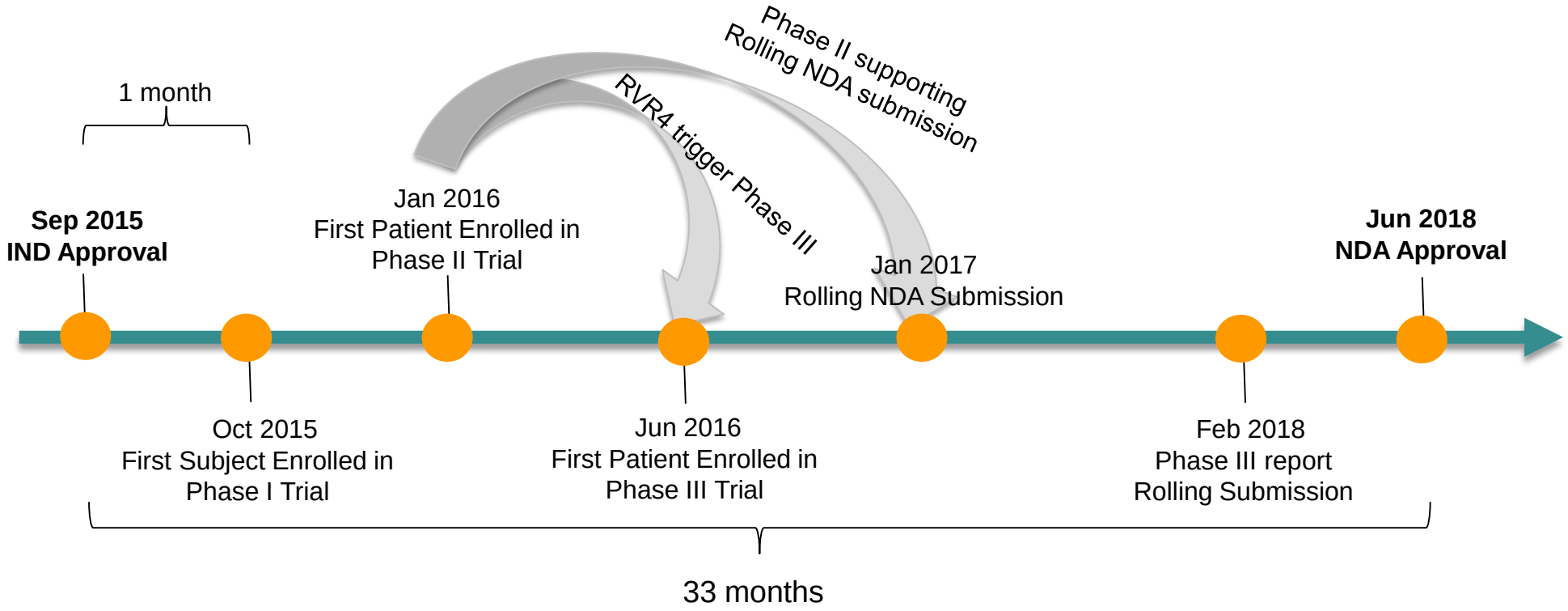
  ➢Clinical study indicated that sebum production was inhibited by ASC40 in a dose-dependent fashion

ASC40: China Phase II Study Design for Acne



R&D Execution Excellence
GMP Manufacturing Capacity
Commercialization Capability

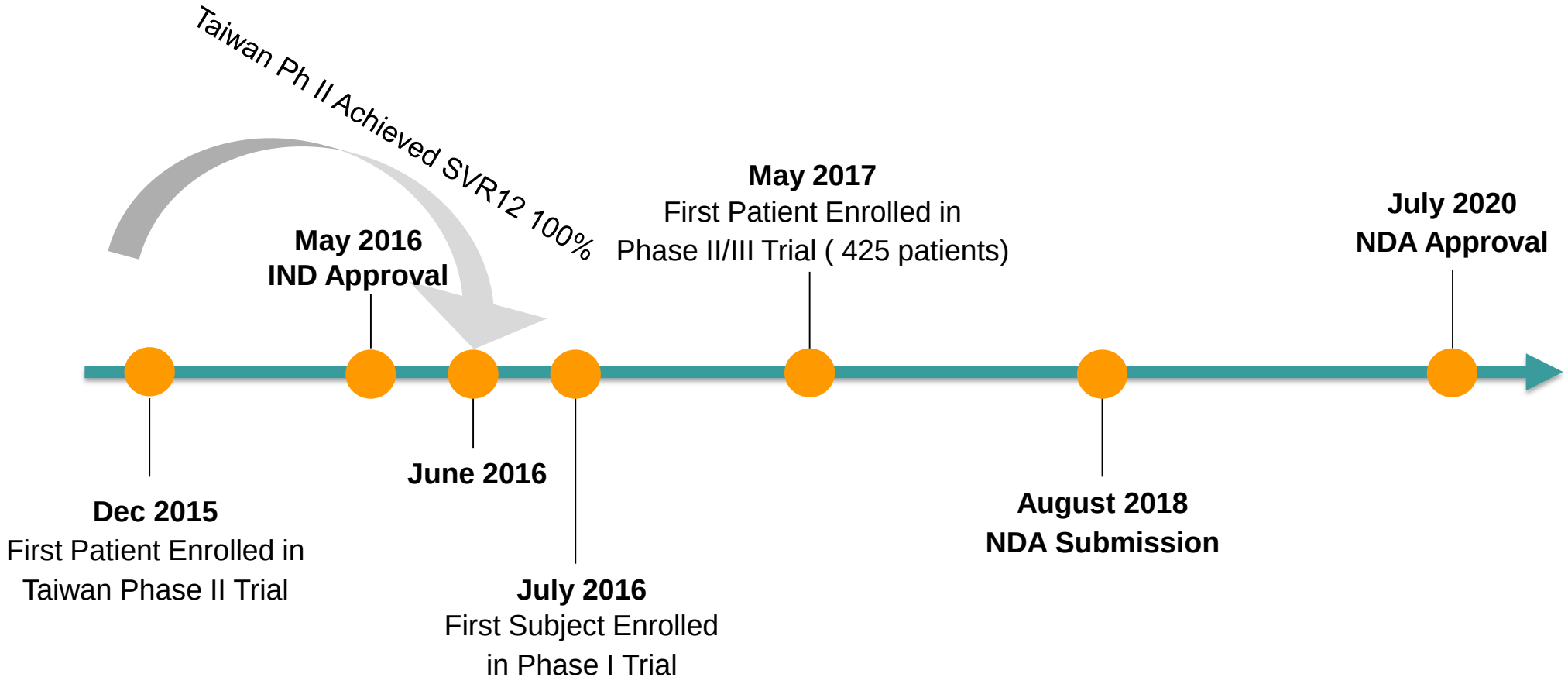
R&D Efficiency : GANOVO® from IND to NDA Approval: 33 months



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

歌礼 ascletis

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



歌礼 ascletis

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

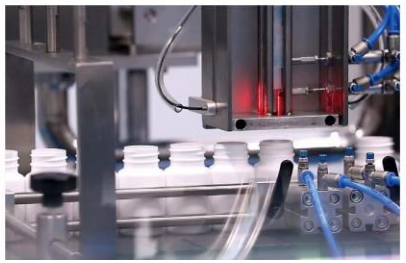
认证范围：片剂
Scope of Inspection: Tablets

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

歌礼 ascletis

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**

歌礼 ascletis

Global Business Development Strategy

Global Partnerships

Roche

janssen | PHARMACEUTICAL COMPANIES OF Johnson & Johnson

PRESIDIO

康宁杰瑞 ALPHAMAB

SAGIMET BIOSCIENCES

Galmed Pharmaceuticals

歌礼 ascletis

Global BD Strategy

2 License-Out

3 License-In

1 Co-Development

4 Strategic Investment

歌礼 ascletis

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

歌礼 ascletis

Thanks

Innovative cures liberate life to the fullest

Disclaimer

- The documents, opinions and materials presented and distributed in the presentation (collectively, the "Document"), which were prepared by Ascletis Pharma Inc. (the "Company") together with its subsidiaries and affiliates (collectively, the "Group"), are provided to you solely for your exclusive use and information in connection with a proposed investment and are not for public dissemination. The Document is not prepared by Morgan Stanley Asia Limited, Goldman Sachs (Asia) L.L.C. and China Merchants Securities (HK) Co., Limited (collectively, the "Joint Sponsors"), nor any of their respective affiliates, controlling persons, directors, officers, partners, employees, agents, advisors or representatives. You fully understand that the Document is being made available on a confidential basis and subject to the following provisions, to a limited number of recipients for the sole purpose of providing information to assist them in deciding whether they wish to proceed with a further investigation of the Company. The contents of this Document have not been reviewed by any regulatory authority in any jurisdiction. The distribution of this Document in certain jurisdictions may be restricted by law, and the recipients into whose possession this Document comes should inform themselves about, and observe such restrictions. By accessing this Document, you are agreeing (i) that you have read and agree to comply with the contents of this notice and disclaimer and (ii) to maintain absolute confidentiality regarding the information disclosed in this Document.
- This Document has not been independently verified and is not intended to form the basis of any investment decision. It does not constitute an offer or invitation to sell, or any solicitation of any offer to subscribe for or purchase any securities in any jurisdiction in which the making of such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of such jurisdiction or would not otherwise be in compliance with the laws and regulations of such jurisdiction, and nothing contained herein shall form the basis of any investment decision, contract or commitment whatsoever. Any decision to purchase securities of the Company in any public or private offering should be made solely on the basis of the prospectus and/or international offering circular to be prepared by the Company in relation to any such contemplated offering together with any supplementary pricing information. This Document contains no information or material which may result in it being deemed (1) to be a prospectus within the meaning of section 2(1) Companies (Winding Up and Miscellaneous Provisions) Ordinance (Chapter 32 of the Laws of Hong Kong) (the "Companies Ordinance"), or an advertisement in relation to a prospectus or proposed prospectus or extract from or abridged version of a prospectus within the meaning of section 38B of the Companies Ordinance or an advertisement, invitation or document containing an advertisement or invitation falling within the meaning of section 103 of the Securities and Futures Ordinance (Chapter 571 of the Laws of Hong Kong) (the "Securities and Futures Ordinance") or (2) in Hong Kong to have effected an offer to the public without compliance with the laws of Hong Kong or being able to invoke any exemption available under the laws of Hong Kong, and is subject to material change without notice.
- The securities of the Company have not been and will not be registered under the U.S. Securities Act 1933, as amended (the "U.S. Securities Act"), or under the laws of any state of the United States. This Document does not constitute or form a part of any offer or solicitation to purchase or subscribe for securities in the United States and is not for distribution and may not be distributed, directly or indirectly, in or into the United States (including its territories and possessions, any state of the United States and the District of Columbia). The securities of the Company will not be offered or sold in the United States except pursuant to an exemption from, or in a transaction not subject to the registration requirements of the U.S. Securities Act. There will be no public offer of the Company's securities in the United States.
- This Document and the information contained herein as well as information presented orally or otherwise are strictly confidential and must be treated as such. No part of this Document or its contents may be copied or reproduced, or redistributed or passed on, directly or indirectly, to any other person in any manner or published, in whole or in part, for any other purpose. By accessing this Document, you are deemed to represent to the Company and the Joint Sponsors and their respective affiliates, controlling persons, directors, offices, partners, employees, agents, advisors or representatives that you are, and any customers you represent are either (i) a "qualified institutional buyer" within the meaning of Rule 144A of the U.S. Securities Act, or (ii) outside the United States. You also represent that you are, and any customers you represent are "professional investors" described in Part I of Schedule 1 to the Securities and Futures Ordinance and any subsidiary legislation thereunder (including but not limited to the Securities and Futures (Professional Investor) Rules (Chapter 571D of the Laws of Hong Kong)).To the extent you purchase the securities of the Company, you will be doing so pursuant to either Rule 144A or Regulation S or another exemption from registration under the U.S. Securities Act. Neither this Document nor any copy of it may be taken or transmitted into or distributed, directly or indirectly, in the United States. Neither this Document nor any copy of it may be taken or transmitted into Canada or distributed or redistributed in Japan or to any resident thereof. Upon request, the recipient will promptly return this Document and all information made available in connection with the proposed investment, without retaining any copies.
- The information in this Document has been provided by the Company. This Document does not purport to be comprehensive or to contain all the information that a recipient may need in order to evaluate the Group. No representation, warranty or undertaking, express or implied, is given and, so far as is permitted by law, no responsibility or liability is accepted by any person (for the avoidance of doubt, including but not limited to, the Company and the Joint Sponsors and their respective affiliates, controlling persons, directors, officers, partners, employees, agents, advisors or representatives of any of the foregoing), with respect to the accuracy, reliability, correctness, fairness or completeness of this Document or its contents or any oral or written communication in connection with the proposed investment. In particular, but without limitation, no representation or warranty is given as to the achievement or reasonableness of, and no reliance should be placed on, any assumptions, projections, targets, estimates, forecasts or any forward-looking statements contained in this Document. Each of the Company and the Joint Sponsors and their respective affiliates, controlling persons, directors, officers, partners, employees, agents, advisors or representatives of any of the foregoing assumes no obligation to update or otherwise revise these forward-looking statements for new information, events or circumstances that occur subsequent to such dates. None of the Company and the Joint Sponsors and any of their respective affiliates, controlling persons, directors, officers, partners, employees, agents, advisors or representatives of any of the foregoing shall have any liability (in negligence or otherwise) in respect of the use of, or reliance upon, the information contained herein by you or any person to whom the information herein is disclosed.
- In furnishing this Document, the Company and the Joint Sponsors and their respective affiliates undertake no obligation to provide any additional information or to update this Document or any additional information or to correct any inaccuracies which may become apparent. This Document does not create an obligation on the Company or the Joint Sponsors or any of their respective affiliates to consider any offer. The provision of the information contained herein shall not be or be taken as any form of commitment on the Company, the Joint Sponsors, any of their respective affiliates or on you to proceed with the proposed placing or offering of securities in the Company.
- The Company reserves the right to negotiate with one or more prospective investors at any time and to enter into a definitive agreement for the sale for the financing of this transaction without prior notice to the other prospective investors. The Company, the Joint Sponsors and their respective affiliates each also reserves the right, without advance notice, to change the procedure or to terminate negotiations at any time prior to the entry into of any binding contract for the proposed investment.
- The Joint Sponsors or their affiliates are acting for the Company and not the recipient of this Document and the receipt of this Document by any recipient is not to be taken as constituting the giving of investment advice by the Joint Sponsors or their affiliates to that recipient, nor to constitute a customer or client relationship between the recipient and the Joint Sponsors or any of their affiliates. Accordingly, the Joint Sponsors or any of their affiliates will not be responsible to the recipient for providing protections afforded to their customers or clients or advising the recipient in relation to the proposed investment.
- You acknowledge and represent to the Company and the Joint Sponsors and their respective affiliates, controlling persons, directors, officers, partners, employees, agents, advisors or representatives that you are a professional investor, that you have the knowledge, experience and capability to conduct your own assessment of the Company and its securities and that you have conducted and will conduct your own investigation with respect to the Company and its securities and have obtained or will obtain your own independent advice relating to any investment in the securities of the Company.
- All enquiries or requests for additional information in connection with this Document should be submitted or directed to the Joint Sponsors. Management of the Company should not be contacted directly under any circumstances in connection with this Document and any unauthorized contact may result in termination of negotiations in relation to the proposed investment.

歌礼 ascletis