Ascentage Pharma Group (6855 HK)

Pioneer in developing apoptosis pathway drug

- **Strong in-house R&D capability with global rights.** Ascentage Pharma is a globally-focused, clinical-stage biotech company developing novel small molecule drugs mainly for oncology. It develops an in-house eight drug candidates with global rights, targeting the apoptosis pathway and next generation tyrosine kinase inhibitors (TKIs). As of Jun 2019, Ascentage Pharma was conducting 28 phase I or II clinical trials in China, US and Australia.
- **Targeting key apoptosis pathways for cancer therapy with first or best in class potential small molecules.** Apoptosis is a process of programmed cell death and the major intrinsic apoptosis pathways include the Bcl-2, IAP and MDM2-p53. The global first-in-class Bcl-2 inhibitor, venetoclax, was developed by AbbVie (ABBV US) and approved by FDA in 2016. Frost & Sullivan (F&S) estimates that global market for apoptosis targeting therapies to grow from US$0.3bn in 2018 to US$4.9bn in 2023E, driven by indication expansion of venetoclax and new drug launches. Ascentage Pharma is the only company with active clinical programs targeting all three known classes of key apoptosis regulators.
- **HQP1351, a potential best-in-class third generation BCR-ABL TKI.** Ascentage Pharma also develops next-generation TKIs that focus on clinically validated and approved targets, including HQP-1351 (a third generation BCR-ABL/KIT inhibitor), HQP8361 (a selective c-Met inhibitor) and APG-2449 (a FAK/ALK/ROS1 inhibitor). HQP1351 is a third generation BCR-ABL/KIT inhibitor for drug resistance in current TKI treatments (imatinib, dasatinib and nilotinib). In Phase I trial, it showed comparable efficacy and improved safety profile than ponatinib. HQP1351 is under a pivotal phase II trial for CML in China and expected to receive approval from NMPA in 2021E.
- **Initiate BUY with TP of HK$45.8.** The most advanced drug is HQP1351 in Pivotal Phase II trial and may be approved by NMPA in 2021E. APG-2575, APG-1252, APG-115 and APG-1387 are in Phase I trials and expected to launch in 2023-24E. We forecast drug sales to start in 2022E and apply risk-adjusted revenue to those drugs with different probability of success (PoS). We derive our target price of HK$45.8 based on an 8-year DCF valuation (WACC: 10.98%, terminal growth 3%).
- **Catalysts:** 1) positive outcomes of clinical trials, 2) earlier-than-expected product launch. **Risk:** undesirable results from clinical trials.

Earnings Summary

(YE 31 Dec)	FY16A	FY17A	FY18A	FY19E	FY20E	FY21E
Revenue (RMB mn)	8	6	7	7	7	7
YoY growth (%)	N/A	(17)	8	0	0	0
Net profit (RMB mn)	(108)	(119)	(345)	(1,082)	(710)	(763)
EPS (RMB)	(0.55)	(0.61)	(1.77)	(5.18)	(3.40)	(3.75)
R&D expenses (RMB mn)	(103)	(119)	(250)	(550)	(600)	(600)
Capex (RMB mn)	3	(21)	(48)	(100)	(350)	(450)
Current ratio	6.0	5.2	9.4	3.3	0.3	0.1

Source: Company data, CMBIS estimates

BUY (Initiation)

Target Price	**HK$45.8**
Up/Downside	**+46.4%**
Current Price	**HK$31.30**

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Mkt. Cap. (HK$ mn)	6,539
Avg. 3mths t/o (HK$ mn)	N/A
52W High/Low (HK$)	53.60/29.70
Total Issued Shares (mn)	209

Source: Bloomberg

Shareholding Structure

Management	32.17%
Collected Mind (3SBio)	4.85%
Sino Biopharma	2.2%
Institution investors	26.28%
Free float	34.5%

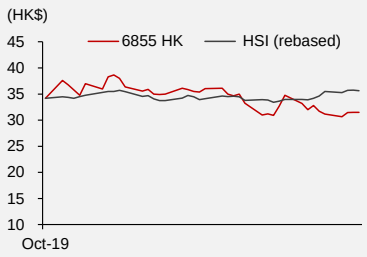
Source: Bloomberg

Share performance

	Absolute	Relative
1-mth	-12.7%	-16.5%
3-mth	N/A	N/A
6-mth	N/A	N/A

Source: Bloomberg

12-mth price performance



Source: Bloomberg

Auditor: Ernst & Young
Web-site: www.ascentagepharma.com

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Investment Thesis

Ascentage Pharma is a clinical-stage biotech company developing novel small molecule drugs mainly for oncology. It has strong R&D capability and develops in-house drug candidates with global rights. There are eight small molecule drugs in pipeline, targeting the apoptosis pathway and next generation tyrosine kinase inhibitors (TKIs), with the most advanced drug, HQP-1351, in Pivotal Phase II trial and projected two years to market and a number of key drug candidates (APG-2575, APG-1252, APG-115 and APG-1387, etc.) in Phase I trials. As of Jun 2019, Ascentage Pharma has conducted around 28 phase I or II clinical trials in US, Australia and China.

Tapping unmet demand in small molecule targeted drugs for cancer

F&S forecasts the global cancer drug market to increase from US$128.1bn in 2018 to US$216.7bn in 2023E, implying an 11.1% CAGR in 2018-23E. Small molecule targeted drugs accounted for 33.4% of total market and may bypass chemotherapy to be the Top 1 therapy for oncology by revenue in 2030E.

F&S forecasts China oncology market to grow from US$23.8bn in 2018 to US$47.9bn in 2023E, indicating a 15% CAGR in 2018-23E driven by higher adoption of early screening, acceleration of new drug approval, improving affordability and improving insurance coverage. China's oncology treatment lagged behind global market as chemotherapy still accounted for over 80% of oncology treatment market in 2018, based on F&S estimates. The current under-penetration of small molecule targeted drugs will lead to its faster growth in China going forwards.

Targeting key apoptosis pathways for cancer therapy with first or best in class potential small molecules

Apoptosis is a process of programmed cell death. The major intrinsic apoptosis pathways include the Bcl-2, IAP and MDM2-p53. The global first-in-class Bcl-2 inhibitor, venetoclax, was developed by AbbVie (ABBV US) and approved by FDA in Apr 2016. F&S estimates that global market for apoptosis targeting therapies to grow from US$0.3bn in 2018 to US$4.9bn in 2023E, driven by indication expansion of venetoclax and new drug launches.

APG-2575, a potential global second to market Bcl-2 inhibitor

APG-2575 is a novel Bcl-2 selective inhibitor for treatment of hematologic malignancies with Bcl-2 overexpression, including leukemia, lymphoma and multiple myeloma (MM). The first-in-class marketed Bcl-2 inhibitor (venetoclax) has validated the Bcl-2 pathway. EvaluatePharma predicted global sales of venetoclax to grow to US$2.8bn by 2024E given indication expansion. In pre-clinical trials, APG-2575 was almost as effective as venetoclax. Currently, Ascentage Pharma conducts two Phase I studies of APG-2575 in the US/Australia and in China, respectively. The Company plans to initiate combination trials with targeted agents, such as anti-CD20 mAbs, BTK inhibitors and PI3K inhibitors in AML, CLL, MM and NHL. We think APG-2575 may become the second-to-market Bcl-2 inhibitor worldwide, following venetoclax. We expect APG-2575 to be commercialized in 2023E.

APG-1252, a potential first/best-in-class Bcl-2/Bcl-xL inhibitor

APG-1252 is a novel small molecule drug targeting Bcl-2 and Bcl-xL for the treatment of SCLC, lymphoma and other solid tumors. APG-1252 significantly reduced platelet toxicity by design and has a favourable pharmacokinetic / pharmacodynamic (PK/PD) profile and may enjoy broader therapeutic window compared to navitoclax (ABT-263), the only other clinical stage Bcl-2/Bcl-xL inhibitor. APG-1252 is in Phase I trials in the US, Australia and China. We forecast APG-1252 targets to be commercialized in 2024E.

APG-115, a potent MDM2-p53 inhibitor

APG-115 is a MDM2-p53 inhibitor for the treatment of adenoid cystic carcinoma (ACC) and sarcomas. It is in Phase I clinical trials in China and the US in patients with sarcomas and other solid tumors and also in combination trial with Keytruda. As of Feb 2019, APG-115 was the only MDM2 inhibitor in clinical trials in China and had the potential to become the first-in-class MDM2 inhibitor in China. APG-115 may be best applied for the treatment of cancers harbouring wild-type p53, such as ACC, AML, MDS, liposarcoma, breast cancer, colorectal cancers, etc. Based on China Phase I trial results, APG-115 is welltolerated and with acceptable safety profile.

HQP1351, a potential best-in-class third generation BCR-ABL TKI

Global sales of Tyrosine-Kinase Inhibitors (TKI) grew from US$17.7bn in 2014 to US$22.5bn in 2018 driven by the sales of BCR-ABL and EGFR inhibitors, such as Gleevec (imatinib) and Tarceva (erlotinib). Global TKI market is expected to reach US$31.0bn in 2023E, driven by new drug launches, such as EGFR, ALK, ROS-1, c-Met and BTK inhibitors. Ascentage Pharma also develops next-generation TKIs that focus on clinically validated and approved targets, including HQP-1351 (a third generation BCR-ABL/KIT inhibitor), HQP8361 (a selective c-Met inhibitor) and APG-2449 (a FAK/ALK/ROS1 inhibitor).

HQP1351 is a third generation BCR-ABL/KIT inhibitor targeting BCR-ABL mutants for treatment of CML and ALL. It was designed to overcome T315I mutation and other drug resistance in current TKI treatments (imatinib, dasatinib and nilotinib). Ponatinib, the first-in-class third generation BCR-ABL TKI has been reported to cause severe thrombosis and is currently carrying a Black Box warning required by the US FDA. In Phase I trial, HQP1351 showed comparable efficacy and improved safety profile than ponatinib. HQP1351 is under pivotal phase II trials for CML in China and expected to receive approval from NMPA in 2021E. It is also in Phase Ib clinical trial in the US and expected to be approved by US FDA in 2022E. Based on the encouraging phase I data in China CML patients, HQP1351 could become a best-in-class drug for TKI resistant CML, in our view.

We forecast drug sales to start in 2022E and breakeven year to be 2024E

We forecast drug sales to start in 2022E and expect revenue of RMB91mn/ RMB1,161mn/ RMB2,599mn in FY2022E/23E/24E. The most advanced drug is HQP1351 in Phase II trial and may be approved by NMPA in 2021E. For other key candidates, APG-2575, APG-1252, APG-115 and APG-1387 in Phase I trials are expected to launch in 2023-24E. We apply risk-adjusted revenue to those drugs with different probability of success (PoS). We forecast a net loss of RMB1,082mn/ RMB710mn/ RMB783mn in FY2019E/20E/21E and expect net profit breakeven year to be 2024E.

Initiate BUY with TP of HK$45.8

As a pre-revenue biotechnology company, Ascentage Pharma relies on future cash flow of drug sales. We use DCF method to drive target price of HK$45.8 based on an 8-year DCF valuation (WACC: 10.98%, terminal growth: 3%).

Investment risks

1) Difficulty toin evaluating current business and predicting future performance;
2) Having incurred net losses in the past and will continue to incur losses for the foreseeable future;
3) Uncertain outcome and unpredictable results of studies and trials;
4) Failure in obtaining regulatory approval for drug candidates;
5) Substantial competition from peers with more competing and successful drugs;
6) Failure in protecting intellectual property rights throughout the world.

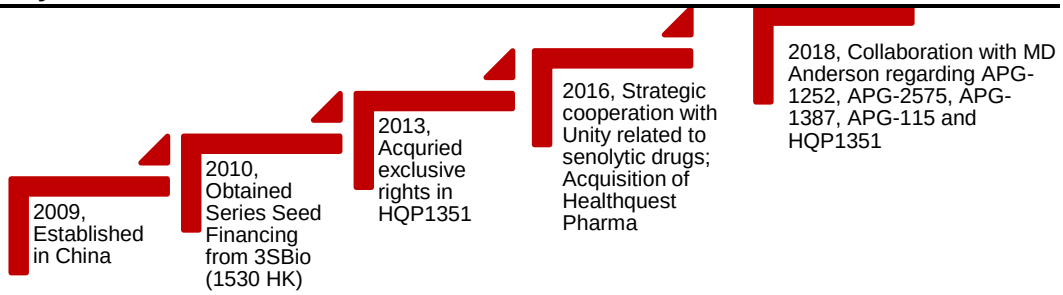
Pioneer in apoptosis-targeted drugs

Well established expertise in innovative drug development

Established in 2009, Ascentage Pharma is a globally-focused, clinical-stage biotech company developing novel small molecule therapies for cancers, hepatitis B virus and age-related diseases. Headquartered in Suzhou, China, Ascentage Pharma has R&D and manufacturing operations in China, US and Australia. Ascentage Pharma develops a robust pipeline of eight clinical stage small molecule drug candidates and it is the only company with active clinical programs targeting all three known classes of key apoptosis regulators.

By 30 Jun 2019, Ascentage Pharma had 358 employees while 293 of which (or 81.8%) were R&D staff. Management of the Company has accumulated rich experiences in apoptosis area. Dr. Yang, Dr. Wang and Dr. Guo are co-founders of Ascentage Pharma. The Company currently leases an around 4,480 sq m facility for R&D and manufacturing in Taizhou, China and plans to complete the construction of a 10,000 sq m facility for R&D and manufacturing in Suzhou by 2019E.

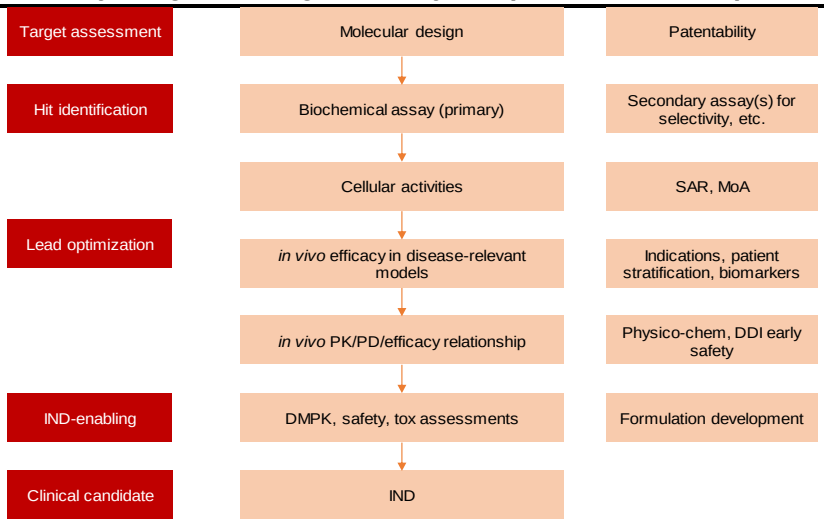
Figure 1: Key milestones



Source: Company data, CMBIS

The Company has built up fully integrated discovery and preclinical development capabilities covering processes including new target initiatives or target assessment, hit identification, lead generation, lead optimization, Investigational New Drug (IND)-enabling studies and clinical candidate selection.

Figure 2: Internal, fully integrated drug discovery and preclinical development capabilities



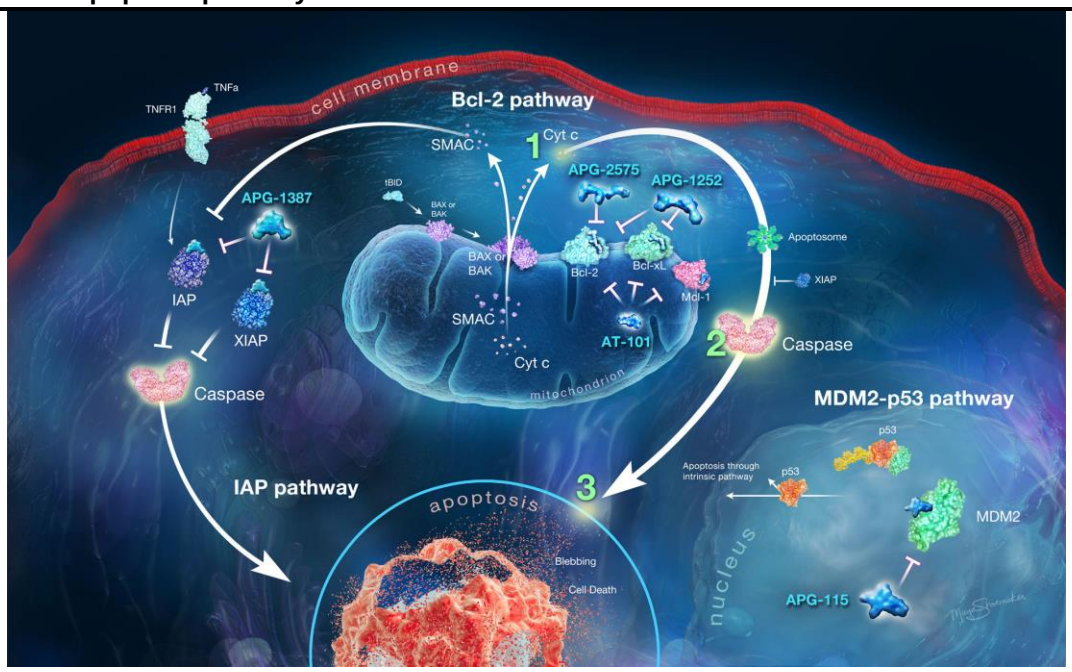
Source: Company data, CMBIS

Global-leading apoptosis drug development company

Apoptosis is a process of programmed cell death in which a series of specific biochemical events operating in a controlled sequence ultimately leads to the destruction of the cell. The normal apoptosis process is disrupted in many types of cancers and diseases. Thus, selective targeting of certain PPIs in the apoptosis pathways represents a new therapeutic approach to the treatment of cancers and other diseases that stem from the dysregulation of the apoptosis process.

The major intrinsic apoptosis pathways include the Bcl-2, IAP and MDM2-p53 pathways. Apoptosis targeting therapies, can potentially be used to treat a variety of diseases, such as cancer. According to F&S, more than 90% of lung cancer could be potentially treated with apoptosis targeting therapies, especially small cell lung cancer (SCLC).

Figure 3: Apoptotic pathways



1. ***BCL-2 Pathway****: APG-1252 (Bcl-2/Bcl-xL dual inhibitor) or APG-2575 (Bcl-2 selective inhibitor) can compete for the binding of pro-death proteins with Bcl-2 or Bcl-xL (dual inhibitor only), thus triggering the downstream cascade of BAX/BAK oligomerization, cytochrome c (Cyt c)/SMAC release from mitochondria and caspase activation, leading to cancer cell death (apoptosis). AT-101 is a pan Bcl-2, Bcl-xL and Mcl-1 inhibitor which can neutralize the anti-apoptotic function of these proteins and trigger the downstream cascade of BAX/BAK oligomerization, Cyt c/SMAC release from mitochondria and caspase activation, leading to cancer cell death (apoptosis).*
2. ***IAP Pathway****: APG-1387 is a SMAC mimetic which can antagonize the function of cIAP or XIAP, which triggers caspase activation and leads to apoptosis.*
3. ***MDM2-p53 Pathway****: APG-115 is a second generation MDM2 inhibitor that can block the interaction of MDM2-p53, thus stabilizing the p53 protein and allowing it to resume its transcriptional regulation function for the cell cycle and apoptosis.*

Source: Company data, CMBIS

Ascentage Pharma is the only company with active clinical programs targeting all three known classes of key apoptosis regulators. The Company has three compounds in clinical development targeting the Bcl-2 family proteins: APG-1252 in Phase I, APG-2575 in Phase I and AT-101 in Phase II. Ascentage also has two apoptosis targeting compounds: APG-1387 (a pan-IAP inhibitor) in Phase I and APG-115 (an MDM2-p53 inhibitor) in Phase I. Besides the above-mentioned candidates for treatment of cancers, Ascentage Pharma is evaluating APG-1387 in a Phase I clinical trial in China for the treatment of HBV.

Tyrosine kinases play an integral role in regulating cellular functions. Ascentage Pharma has a few TKIs in the pipeline, including HQP1351 (a third generation BCR-ABL inhibitor) in pivotal phase II, HQP8361 in phase I and APG-2449 in phase I.

The Company has a robust pipeline of eight clinical stage small molecule drug candidates. Its pipeline consists of novel drug candidates that disrupt complex and difficult-to-target protein-protein interactions, or PPIs, and next generation tyrosine kinase inhibitors, or TKIs. As of Jun 2019, Ascentage Pharma had conducted 28 phase I or II clinical trials in US, Australia and China.

Figure 4: Pipeline of Ascentage Pharma (as of 30 Jun 2019)

Candidate	Target	Lead indications	Preclinical	Phase I	Phase II	Market rights
Apoptosis targeted compounds						
APG-1252	Bcl-2/Bcl-xL	Cancer (SCLC, lymphoma)				Global
APG-2575	Bcl-2 Selective	Blood cancer				
AT-101	Bcl-2/Bcl-xL/Mcl-1	CLL				
APG-1387	IAP Dimer	Solid tumors				
		IO combo				
		Hepatitis B				
APG-115	MDM2-p53	Solid tumors				
		Chemotherapy combo (Salivary Gland Carcinoma)				
		IO combo				
		Dry AMD				
Next-generation kinase inhibitors						
HQP1351	BCR-ABL Mutant	Resistant CML				Global
	KIT	GIST				
HQP8361	c-Met Selective	Cancer (c-Met+)				Australia, Japan, Greater China
APG-2449	FAK	Cancer (FAK, ALK, Ros)				Global
Age-related diseases						
Bcl-2 related			The Company has a strategic relationship with Unity related to Unity's development of senolytic drugs			JV in Greater China

Source: Company data, CMBIS
Note: 1) AT-101 was in-licensed from University of Michigan in 2015. 2) In Dec 2010, the Company entered into a license agreement with the University of Michigan, as amended, covering certain of its patent rights relating to Bcl-2/Bcl-xL, IAP and MDM2-p53 inhibitors. 3) HQP8361 (also known as MK-8033) was in-licensed from MSD.

In addition to strong in-house R&D capability, Ascentage Pharma has established global collaboration relationships with leading biotechnology and pharmaceutical companies and academic institutions, such as the University of Michigan, Unity (UBX US), MD Anderson, Junshi Biosciences (1877 HK), Henlius Biotech (2696 HK), etc.

Figure 5: Established strategic cooperation with biotech companies and academic institutions

Partner of cooperation	Date of agreement	Details
University of Michigan	Dec 2010	Obtained an exclusive worldwide license to patent rights covering Bcl-2/Bcl-xL, IAP and MDM2-p53 inhibitors
MSD	Apr 2013	Obtained exclusive right in HQP8361 (MK-8033) in Australia, Japan and the PRC
GIBH	Jun 2013	Obtained patents and technology knowhow relating to HQP1351
Unity	Feb 2016	Unity to develop molecules in Company's library of Bcl-2/Bcl-xL/McL-1 inhibitors for the treatment of age-related diseases
	Jan 2019	Granted Unity exclusive development and commercialization rights and non-exclusive manufacturing rights to APG-1197 for all non-oncology indications outside of Greater China
MD Anderson	Oct 2018	MD Anderson will conduct preclinical and clinical studies on APG-1252, APG-2575, APG-1387, APG-115, HQP1351 and other compounds developed by Ascentage Pharma
Junshi Biosciences	Apr 2019	Explored synergies of APG-1387 and toripalimab (anti PD-1 mAb) in clinical trials in solid and hematological tumors in China
Henlius Biotech	Nov 2019	Co-developed the combination therapy between APG-2575 and Hanlikang (Rituximab) for CLL in China

Source: Company data, CMBIS

HQP1351, a potential best-in-class third generation BCR-ABL TKI

HQP1351 is one of the core products of Ascentage Pharma. It is a third generation BCR-ABL/KIT inhibitor targeting BCR-ABL mutants, including those with the T315I mutation. The T315I mutation is found in 4-15% of patients with resistance to the first generation TKI, imatinib. To overcome the drug resistance to first generation TKIs, second generation BCR-ABL kinase inhibitors, such as dasatinib and nilotinib, has been developed. Nevertheless, patients carrying the T315I mutation do not respond to the second generation TKIs. HQP1351 was designed to overcome T315I mutation and other drug resistance in current TKI treatments.

HQP1351 is under a pivotal phase II trial for treatment of patients with TKI resistant chronic myeloid leukemia (CML) in China. In Dec 2018, China's Center For Drug Devaluation (CDE) confirmed that the revised pivotal phase II clinical trial protocol of HQP1351 was accepted. By Sep 2019, patient enrollment was completed for the two pivotal phase II trials of CP CML and AP CML. We expect HQP1351 to receive approval from NMPA in 2021E assuming satisfactory clinical data.

In Jul 2019, the US FDA allowed Ascentage Pharma to initiate a Phase Ib clinical trial of HQP1351 for the treatment of TKI-resistant CML in the US. This clinical study is a bridging Phase Ib clinical trial with three dose cohorts (30mg, 40mg and 50mg), which is more efficient than the traditional 3+3 dose-escalation study and is expected to accelerate the progress of this clinical trial. It is designed to evaluate the safety, tolerability, and pharmacokinetic (PK) of HQP1351 in CML patients who are resistant or intolerant to at least second-line TKIs and to confirm the recommended Phase II dose (RP2D). We expect HQP1351 to receive approval from US FDA in 2022E assuming satisfactory clinical data.

Since HQP1351 is also a potent inhibitor of the KIT receptor tyrosine kinase, it is under a phase I trial for treatment of patients with gastrointestinal stromal tumors (GIST) in China.

Tap the unmet need in TKI resistant CML

Imatinib is the first approved TKI and also a BCR-ABL inhibitor, which has transformed CML into a manageable chronic disease. Nilotinib and dasatinib are the second generation BCR-ABL inhibitors which tackle a proportion of patients resistant to imatinib. The current Standard of Care (SoC) treatment for CML is imatinib followed by other TKIs once recurs. There's unmet clinical need for patients with T315I mutations who generally fail to respond to the first and second generation TKIs due to drug resistance.

The first third generation BCR-ABL TKI, ponatinib (brand name ICLUSIG) was developed by Ariad Pharmaceuticals which was acquired by Takeda. Ponatinib received approval from the FDA in 2012. As of Jul 2019, ponatinib had received FDA approval for treatment of 1) CML or Ph+ ALL when no other TKI therapy is indicated and 2) T315I-positive CML or T315I-positive Ph+ ALL. Patent of ponatinib will be valid till Jan 2027. Ponatinib is on the list of "urgently needed medicine" issued by NMPA and National Health Commission in China, which qualifies it for expedited approval program in China. We notice that Ponatinib already received IND approval from the NMPA in Aug 2019.

To date, ponatinib is the only commercialized third generation TKI addressing patients with T315I mutation. Another late-stage third generation BCR-ABL inhibitor is Asciminib being developed by Novartis. Asciminib is currently in a phase III clinical trial evaluating against bosutinib for CML patients without T315I or V299L mutations.

We believe besides ponatinib which is already commercialized, HQP1351 is the only late-stage third generation BCR-ABL inhibitor worldwide targeting T315I mutation.

Figure 6: Summary of TKI drugs

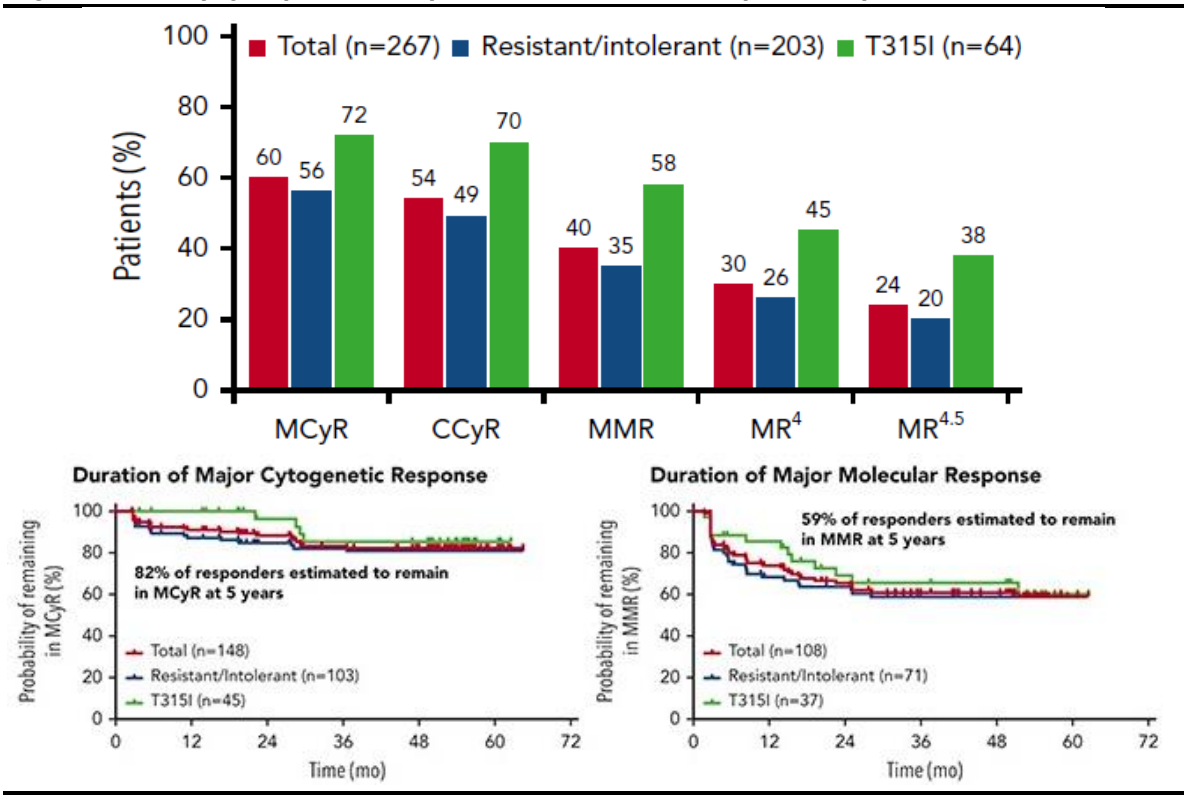
Generation	Drug	Company	Indications	Latest stage
The first generation	Gleevec (imatininb)	Novartis	CML, GIST	Marketed (2001)
The second generation	Sprycel (dasatinib)	Bristol Myers Squibb	CML, ALL	Marketed (2006)
	Tasigna (nilotinib)	Novartis	CML	Marketed (2007)
	Bosulif (bosutinib)	Pfizer	CP-CML	Marketed (2012)
The third generation	Iclusig (ponatinib)	Takeda	R CML, ALL	Marketed (2012)
	Asciminib (ABL001)	Novartis	CML	Phase III
	HQP1351	**Ascentage Pharma**	**R CML, GIST**	**Pivotal phase II**

Source: Company data, CMBIS

Ponatinib, the only available TKI for T315I mutation, has serious safety concerns

In 2018, ponatinib published its 5-year efficacy and safety data of the phase II PACE trial. The pivotal phase II Ponatinib Ph+ ALL and CML Evaluation (PACE) trial evaluated efficacy and safety of ponatinib at a starting dose of 45mg once daily in 449 patients with CML or Ph+ ALL resistant/ intolerant to dasatinib or nilotinib, or with T315I mutation. This analysis focuses on chronic-phase CML (CP-CML) patients (n = 270) with 56.8-month median follow-up. Among 267 heavily pre-treated CP-CML patients, 60% achieved major cytogenetic response (MCyR), 40% major molecular response (MMR), and 24% achieved 4.5-log molecular response. Among CP-CML patients, responses were durable, with 82% and 59% of those who achieved MCyR by 12 months and MMR at any time, respectively, estimated to maintain these responses at five years.

Figure 7: Final (5-year) results of ponatinib PACE trial: response to ponatinib in CP-CML



Source: Blood, CMBIS

Drug discontinuation was common. For CP-CML patients, 11% discontinued treatment due to disease progression, 21% due to adverse event, 11% due to patient request, 6% due to lack of efficiency.

TEAEs occurred in above 20% of all patients. The most common grade 3/4 TEAEs in CP-CML patients treated by ponatinib were thrombocytopenia (35%), neutropenia (17%), hypertension (14%), increased lipase (13%), abdominal pain (10%), and anemia (10%). Individual serious AEs reported ≥5% of CP-CML patients were pancreatitis (7%), atrial fibrillation (6%), pneumonia (6%), and angina pectoris (5%).

Figure 8: Treatment-emergent AEs of ponatinib

	CP-CML, n = 270		AP-CML, n = 85		BP-CML, n = 62		Ph+ ALL, n = 32		Total, N = 449	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Nonhematologic AEs, n (%)										
Abdominal pain	125 (46)	28 (10)	36 (42)	7 (8)	21 (34)	5 (8)	10 (31)	2 (6)	192 (43)	42 (9)
Rash	127 (47)	10 (4)	32 (38)	4 (5)	22 (35)	3 (5)	7 (22)	1 (3)	188 (42)	18 (4)
Constipation	112 (41)	7 (3)	25 (29)	2 (2)	17 (27)	0	17 (53)	1 (3)	171 (38)	10 (2)
Headache	116 (43)	9 (3)	26 (31)	1 (1)	19 (31)	2 (3)	8 (25)	0	169 (38)	12 (3)
Dry skin	114 (42)	9 (3)	27 (32)	1 (1)	16 (26)	1 (2)	8 (25)	0	165 (37)	11 (2)
Fatigue	81 (30)	6 (2)	32 (38)	4 (5)	16 (26)	3 (5)	9 (28)	0	138 (31)	13 (3)
Hypertension	99 (37)	37 (14)	22 (26)	9 (11)	13 (21)	5 (8)	8 (25)	3 (9)	142 (32)	54 (12)
Pyrexia	70 (26)	3 (1)	34 (40)	6 (7)	23 (37)	2 (3)	8 (25)	0	135 (30)	11 (2)
Arthralgia	90 (33)	8 (3)	29 (34)	2 (2)	12 (19)	0	4 (13)	0	135 (30)	10 (2)
Nausea	79 (29)	2 (<1)	27 (32)	0	21 (34)	1 (2)	7 (22)	0	134 (30)	3 (<1)
Diarrhea	54 (20)	2 (<1)	25 (29)	2 (2)	15 (24)	2 (3)	4 (13)	1 (3)	98 (22)	7 (2)
Increased lipase	73 (27)	34 (13)	13 (15)	11 (13)	9 (15)	8 (13)	3 (9)	2 (6)	98 (22)	55 (12)
Vomiting	50 (19)	4 (1)	23 (27)	0	17 (27)	1 (2)	8 (25)	0	98 (22)	5 (1)
Myalgia	65 (24)	3 (1)	18 (21)	0	11 (18)	0	2 (6)	0	96 (21)	3 (<1)
Pain in extremity	65 (24)	8 (3)	17 (20)	0	8 (13)	0	4 (13)	0	94 (21)	8 (2)
Hematologic AEs, n (%)										
Thrombocytopenia	123 (46)	95 (35)	45 (53)	37 (44)	23 (37)	22 (35)	7 (22)	6 (19)	198 (44)	160 (36)
Neutropenia	53 (20)	45 (17)	31 (37)	31 (37)	22 (35)	18 (29)	8 (25)	7 (22)	114 (25)	101 (22)
Anemia	53 (20)	28 (10)	31 (37)	19 (22)	21 (34)	20 (32)	8 (25)	6 (19)	113 (25)	73 (16)

Source: Blood, CMBIS

Arterial occlusion is a common and serious side effect of ponatinib. The cumulative incidence of arterial occlusive events (AOEs) in CP-CML patients increased over time to 31%. In the total population, five patients had grade 5 AOEs. The cumulative incidence of AOEs continued to increase over time. Among 111 total patients who had at least one AOE, the median time to initial onset of an AOE was 13.4 months (0.1-59.7 months). Meanwhile, the cumulative incidence of venous thromboembolic events (VTEs) in CP-CML patients was 6%.

Figure 9: Ponatinib's cumulative and exposure-adjusted incidences of treatment-emergent AOEs and VTEs

	CP-CML, N = 270		Total, N = 449	
	AE	SAE	AE	SAE
AOEs, n (%)	84 (31)	69 (26)	111 (25)	90 (20)
Cardiovascular	42 (16)	33 (12)	59 (13)	44 (10)
Cerebrovascular	35 (13)	28 (10)	41 (9)	33 (7)
Peripheral vascular	38 (14)	31 (11)	48 (11)	38 (8)
Exposure-adjusted AOEs, no. of patients with events per 100 patient-years	14.1	10.9	13.8	10.6
VTEs, n (%)	15 (6)	13 (5)	27 (6)	23 (5)
Exposure-adjusted VTEs, no. of patients with events per 100 patient-years	2.1	1.8	2.8	2.4

Source: Blood, CMBIS

According to US FDA label of ponatinib, the drug can cause hepatotoxicity, including liver failure and death. With 48 months follow-up, 11% (50/449) of ponatinib-treated patients experienced Grade 3 or 4 hepatotoxicity in the Phase 2 trial. The most common forms of hepatotoxicity were elevations of aspartate aminotransferase (AST) or alanine aminotransferase (ALT), bilirubin, and alkaline phosphatase. The incidence of AST or ALT elevation was 54% (all Grades) and 8% (Grade 3 or 4). Hepatotoxic events were observed in 29% of patients. The median time to onset of hepatotoxicity event was 3 months (<1 to 47 months).

In FY2018 (Apr 2018 – Mar 2019), ponatinib recorded JPY28.7bn (or US$271mn) sales worldwide, up 24% YoY. In the first half of FY2019, worldwide sales of ponatinib increased to JPY14.6bn (or US$134mn), up 3% YoY. The unsatisfying sales performance of ponatinib was due to severe safety issues. Ponatinib has been reported to cause severe thrombosis and is currently carrying a Black Box warning required by the US FDA. Severe side effects caused by ponatinib include arterial occlusion, venous thromboembolism, heart failure and hepatotoxicity.

The safety issues have limited the clinical use of ponatinib while HQP1351 is a potential best-in-class third generation TKI with potent efficacy and significantly better safety than ponatinib.

HQP1351 significantly improves tolerability and demonstrates comaparable potency with ponatinib

Based on the encouraging phase I data in China CML patients, HQP1351 could become a best-in-class drug for TKI resistant CML, in our view.

Ascentage Pharma released the topline tolerability and efficacy data from phase I dose-escalation trial in CML patients at the annual meeting of American Society of Hematology (ASH) in Dec 2018. The preliminary data showed that HQP1351 was effective in the treatment of first and second generation TKI-resistant CML, especially the highly resistant CML with T315I mutation, with improved safety profile compared to other agents in the same class. This result demonstrates HQP1351's best-in-class potential for treating TKI-resistant CML.

In ASH 2019, Ascentage Pharma updated the results of phase 1 study of HQP1351 in Chinese CML patients. From 26 Oct 2016 to 27 May 2019, 101 CML patients including 87 with chronic-phase CML (CP-CML) patients and 14 accelerated-phase CML (AP-CML) patients were enrolled in this study. Median duration of follow-up was 12.8 (range, 1.2-31.5) months.

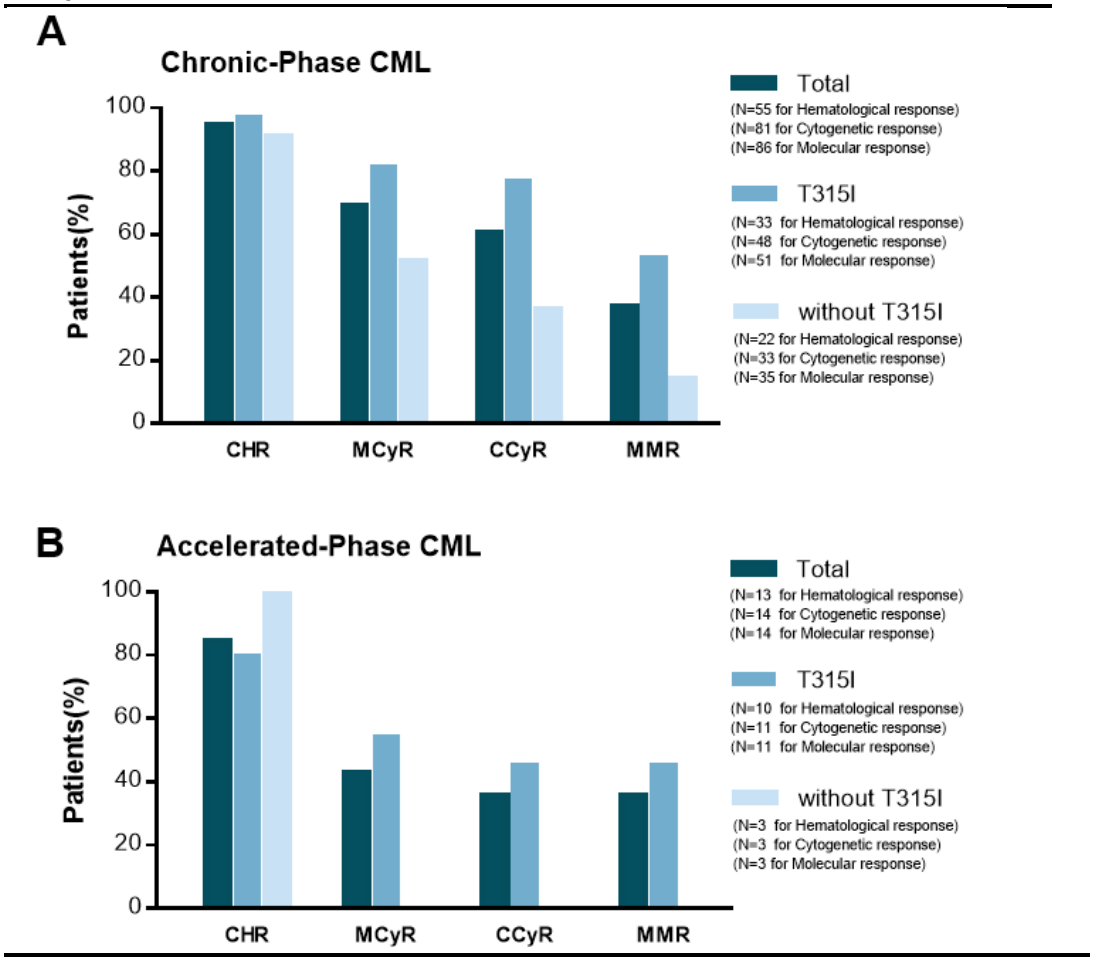
As of 27 May 2019, of the evaluable patients with CP-CML, 95% of evaluable patients had a complete hematologic response (CHR), 69% had a major cytogenetic response (MCyR), 61% had a complete cytogenetic response (CCyR) and 37% had a major or complete molecular response (MMR). Of the evaluable CP-CML patients with T315I mutation, 97% had a CHR, 82% had a MCyR, and 52% had an MMR. For the evaluable patients with AP-CML, 85% had a CHR, 43% had a MCyR, 36% had a CCyR and 36% had an MMR. HQP1351 showed highly efficacious in the patients with T315I mutation.

Figure 10: Efficacy summary of HQP1351 Phase I trial in CML in China (as of 27 May 2019)

Variable	CP-CML patients			AP-CML patients		
	All patients	With T315I mutation	Without T315I mutation	All patients	With T315I mutation	Without T315I mutation
Hematological response						
No. of evaluable subjects -n	55	33	22	13	10	3
Complete hematological response -n(%)	52 (94.5%)	32 (97.0%)	20 (90.9%)	11 (84.6%)	8 (80.0%)	3 (100.0%)
Cytogenetic response						
No. of evaluable subjects -n	81	48	33	14	11	3
Major cytogenetic response -n(%)	56 (69.1%)	39 (81.3%)	17 (51.5%)	6 (42.9%)	6 (54.5%)	0
Complete cytogenetic response -n(%)	49 (60.5%)	37 (77.1%)	11 (33.3%)	5 (35.7%)	5 (45.5%)	0
Molecular response						
No. of evaluable subjects -n	86	51	35	14	11	3
Major/ Complete molecular response -n(%)	32 (37.2%)	27 (52.9%)	5 (14.3%)	5 (35.7%)	5 (45.5%)	0

Source: ASH 2019, CMBIS

Figure 11: Efficacy results of phase 1 trial of HQP1351 in China (as of 27 May 2019)

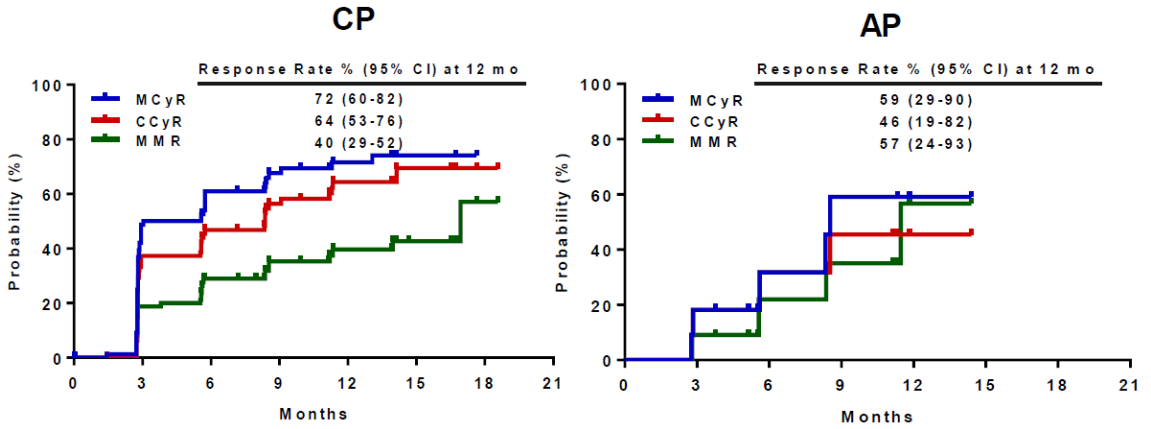


Source: ASH 2019, CMBIS

The probability and the depth of response increased with prolonged treatment period. For CP-CML patients, MCyR response rate was 72% at 12 months, CCyR response rate was 64% at 12 months

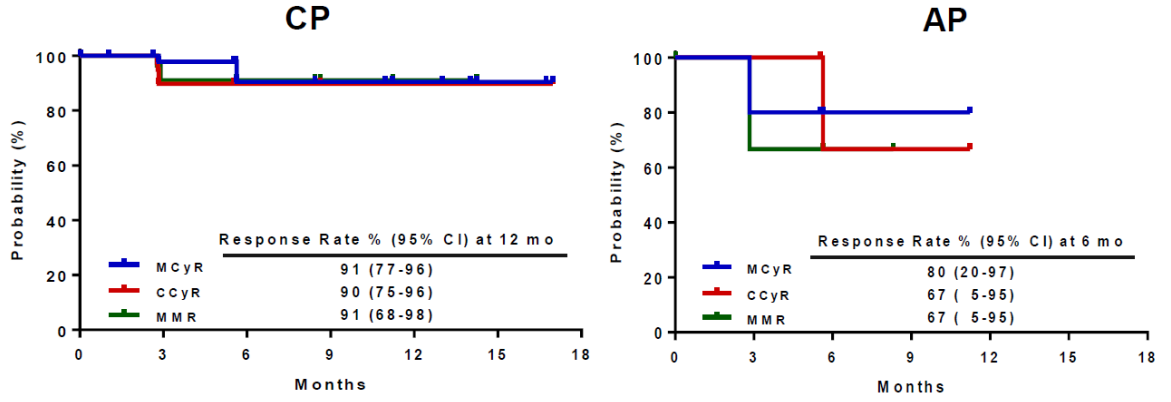
and MMR response rate was 40% at 12 months. Duration of response is quite long for CP-CML patients.

Figure 12: Cumulative incidence of achieving responses (≥30mg cohorts, as of 27 May 2019)



Source: ASH 2019, CMBIS

Figure 13: Duration of responses (≥30mg cohorts, as of 27 May 2019)



Source: ASH 2019, CMBIS

HQP1351 was well tolerated. As of 27 May 2019, 92 out of 101 patients were still receiving treatment, with the longest treatment duration of 31 months. Nine patients (5 CP and 4 AP) were withdrawn from the study, including progression to AP or BP (n=5), intolerant AEs (n=2), consent withdrawal (n=1), and newly diagnosis of breast cancer (n=1). The progression free survival (PFS) rate at 18-month was 94% in the CP patients and 61% in the AP patients.

There has been no cardiovascular, or peripheral vascular thrombosis reported in HQP1351 treated patients at any dose level, compared to serious arterial thrombosis cases reported in 16% of patients treated with ponatinib in clinical trials. The liver toxicity of HQP1351 was moderate in severity, compared to ALT or AST elevation observed in 56% (all grade) and 8% (grade 3 or 4) of patients treated with ponatinib. The most common hematologic TRAE of grade 3/4 was thrombocytopenia (49.5%). The frequency of grade 3 or 4 thrombocytopenia reported in HQP1351 treated patients was consistent with that of ponatinib treated patients. No death and grade 5 AEs occurred.

Figure 14: Treatment related AE of phase 1 trial of HQP1351 (as of 27 May 2019)

	Treated Population (N=101)		
	Any Grade	Grade 3/4	Serious
	number of patients (percent)		
Non hematological AEs			
Skin pigmentation	79 (78.2%)	0	0
Hypertriglyceridaemia	55 (54.5%)	8 (7.9%)	0
AST elevation	37 (36.6%)	3 (3.0%)	0
Proteinuria	35 (34.7%)	5 (5.0%)	0
ALT elevation	34 (33.7%)	2 (2.0%)	0
Bilirubin elevation	34 (33.7%)	1 (1.0%)	0
Hypocalcaemia	34 (33.7%)	0	0
GGT elevation	24 (23.8%)	0	0
Hyponatraemia	23 (22.8%)	0	0
Hyperglycaemia	21 (20.8%)	0	0
Myalgia	21 (20.8%)	0	0
CPK elevation	20 (19.8%)	2 (2.0%)	0
Hypokalaemia	20 (19.8%)	0	0
Pyrexia	18 (17.8%)	7 (6.9%)	1 (1.0%)
Rash	15 (14.9%)	2 (2.0%)	0
Skin mass	10 (9.9%)	1 (1.0%)	0
Hematological AEs			
Thrombocytopenia	76 (75.2%)	50 (49.5%)	6 (5.9%)
Anemia	25 (24.8%)	12 (11.9%)	2 (2.0%)
Leukopenia	21 (20.8%)	20 (19.8%)	0

Source: ASH 2019, CMBIS

Expect RMB1.7bn risk-adjusted peak sales from HQP1351

CML is a rare cancer of the white blood characterized by increased and unregulated growth of myeloid cells originating in the bone marrow that invade the blood and potentially other organs. CML is divided into three phases: chronic, accelerated and blast crisis. Most patients with CML are diagnosed at chronic phase. CML accounts for 15% of all leukemia in adults. According to F&S, the global resistance and relapse rate of CML is 55.1% among all new cases in 2018. F&S estimates that there were approximately 33,300 new cases of CML worldwide in 2018 and the global prevalence of CML were around 135,600 in 2018. In China, the prevalence of resistant CML reached 21,400 in 2018 and may reach 38,500 by 2030E, according to F&S. Globally, the prevalence of resistant CML reached 74,700 in 2018 and may reach 110,900 by 2030E. F&S estimates that the market size of BCR-ABL inhibitors for the treatment of resistant CML was US$3.1bn in 2018.

We expect HQP1351 to realize RMB1.7bn peak sales from CML indication and RMB1.0bn peak sales from ALL indication. We apply 70% probability of success for CML indication and 50% probability of ALL indication, we forecast RMB1.7bn risk-adjusted peak sales from HQP1351. We estimate that Ascentage Pharma will pay c.3% sales royalties to GIBH (中国科学研广州生物医药与健康研究院) and the attributable risk-adjusted peak sales from HQP1351 will be RMB1.6bn.

Figure 15: HQP1351 sales forecasts in CML indication

	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
HQP1351-CML in US									
Prevalence of CML in US (people)	61,067	62,289	63,534	64,805	66,101	67,423	68,772	70,147	71,550
Rate of relapse or drug resistance	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*
New relapse or drug resistance CML patients in US (people)	12,213	12,458	12,707	12,961	13,220	13,485	13,754	14,029	14,310
% of drug resistant patients with T315I mutation	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*
Patients with T315I mutation (people)	2,027	2,055	2,083	2111	2140	2170	2200	2231	2262
Penetration of HQP1351 in addressable CML patients in US	-	*30%*	*50%*	*55%*	*60%*	*63%*	*66%*	*69%*	*72%*
Patients treated with HQP1351 (people)	-	616	1,041	1,161	1,284	1,367	1,452	1,539	1,628
Ex-factory price of HQP1351 in US (US$ per month)	-	11,900	11,781	11,663	11,547	11,431	11,317	11,204	11,092
Average period of treatment (month)	-	12	12	12	12	12	12	12	12
HQP1351 sales in US CML market (US$ mn)	**-**	**88**	**147**	**163**	**178**	**188**	**197**	**207**	**217**
HQP1351 sales in US CML market (RMB mn)	**-**	**616**	**1,031**	**1,138**	**1,246**	**1,313**	**1,380**	**1,448**	**1,517**
HQP1351-CML in China									
Incidence of CML in China (people)	6,757	6,825	6,893	6,962	7,031	7,102	7,173	7,244	7,317
Average survival period in China (years)	6	6	6	6	6	7	7	7	7
Prevalence of CML in China (people)	37,839	39,583	41,357	43,163	45,001	46,871	48,774	50,711	52,681
Rate of relapse or drug resistance	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*
New relapse or drug resistance CML patients in China (people)	7,568	7,917	8,271	8,633	9,000	9,374	9,755	10,142	10,536
% of drug resistant patients with T315I mutation	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*
Patients with T315I mutation (people)	1,361	1,400	1,441	1,481	1,523	1,565	1,608	1,652	1,696
Penetration of HQP1351 in addressable patients in China	*30%*	*40%*	*45%*	*50%*	*55%*	*58%*	*61%*	*64%*	*67%*
Patients treated with HQP1351 (people)	408	560	648	741	838	908	981	1,057	1,136
Ex-factory price of HQP1351 in China (RMB per month)	15,719	15,405	15,096	14,795	14,499	14,209	13,924	13,646	13,373
Average period of treatment (month)	12	12	12	12	12	12	12	12	12
HQP1351 sales in China CML market (RMB mn)	**77**	**104**	**117**	**132**	**146**	**155**	**164**	**173**	**182**
Total HQP1351 sales in CML market (RMB mn)	**77**	**720**	**1,148**	**1,269**	**1,391**	**1,467**	**1,544**	**1,622**	**1,700**

Source: Company data, CMBIS estimates

Figure 16: HQP1351 sales forecasts in Ph+ ALL indication

	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
HQP1351-ALL in US									
Incidence of ALL in US (people)	6,019	6,049	6,080	6,110	6,141	6,171	6,202	6,233	6,264
Ph+ ALL as % of total ALL patients	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
Incidence of Ph+ ALL in China (people)	1,806	1,815	1,824	1,833	1,842	1,851	1,861	1,870	1,879
Average survival period of Ph+ ALL patients in China (years)	4	4	4	4	4	4	4	4	4
Prevalence of Ph+ ALL in China (people)	7,223	7,259	7,296	7332	7369	7406	7443	7480	7517
Rate of relapse or drug resistance	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*
New relapse or drug resistance Ph+ ALL patients in China (people)	1,445	1,452	1,459	1,466	1,474	1,481	1,489	1,496	1,503
% of drug resistant patients with T315I mutation	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*
Ph+ ALL patients with T315I mutation (people)	1,138	1,143	1,149	1,155	1,161	1,166	1,172	1,178	1,184
Penetration of HQP1351 in addressable ALL patients in China	-	*30%*	*50%*	*55%*	*60%*	*63%*	*66%*	*69%*	*72%*
Patients treated with HQP1351 (people)	-	343	575	635	696	735	774	813	852
Ex-factory price of HQP1351 in China (RMB per month)	-	11,900	11,781	11,663	11,547	11,431	11,317	11,204	11,092
Average period of treatment (month)	-	12	12	12	12	12	12	12	12
HQP1351 sales in US ALL market (US$ mn)	**-**	**49**	**81**	**89**	**96**	**101**	**105**	**109**	**113**
HQP1351 sales in US ALL market (RMB mn)	**-**	**343**	**569**	**622**	**675**	**706**	**735**	**765**	**794**
HQP1351-ALL in China									
Incidence of ALL in China (people)	9,920	10,019	10,119	10,220	10,323	10,426	10,530	10,635	10,742
Ph+ ALL as % of total ALL patients	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
Incidence of Ph+ ALL in China (people)	2,976	3,006	3,036	3,066	3,097	3,128	3,159	3,191	3,223
Average survival period of Ph+ ALL patients in China (years)	3	3	4	4	4	4	4	4	4
Prevalence of Ph+ ALL in China (people)	9,821	10,219	10,625	11,038	11,458	11,885	12,320	12,763	13,212
Rate of relapse or drug resistance	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*	*20%*
New relapse or drug resistance Ph+ ALL patients in China (people)	1,964	2,044	2,125	2,208	2,292	2,377	2,464	2,553	2,642
% of drug resistant patients with T315I mutation	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*
Ph+ ALL patients with T315I mutation (people)	1,729	1,767	1,806	1,846	1,886	1,927	1,968	2,010	2,053
Penetration of HQP1351 in addressable ALL patients in China	*20%*	*35%*	*40%*	*45%*	*50%*	*53%*	*56%*	*59%*	*62%*
Patients treated with HQP1351 (people)	346	619	723	831	943	1,021	1,102	1,186	1,273
Ex-factory price of HQP1351 in China (RMB per month)	15,719	15,405	15,096	14,795	14,499	14,209	13,924	13,646	13,373
Average period of treatment (month)	12	12	12	12	12	12	12	12	12
HQP1351 sales in China ALL market (RMB mn)	**65**	**114**	**131**	**147**	**164**	**174**	**184**	**194**	**204**
Total HQP1351 sales in ALL market (RMB mn)	**65**	**457**	**699**	**770**	**839**	**880**	**920**	**959**	**998**

Source: Company data, CMBIS estimates

Figure 17: Risk-adjusted HQP1351 sales forecasts

	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
HQP1351 sales in CML (RMB mn)	77	720	1,148	1,269	1,391	1,467	1,544	1,622	1,700
Probability of success for CML	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*
HQP1351 sales in ALL (RMB mn)	65	457	699	770	839	880	920	959	998
Probability of success for ALL	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*
Risk-adjustedHQP1351 sales (RMB mn)	**87**	**732**	**1,153**	**1,273**	**1,394**	**1,467**	**1,541**	**1,615**	**1,689**
% of royalties paid to GIBH	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*
Attributable risk-adjustedHQP1351 sales (RMB mn)	**84**	**710**	**1,119**	**1,235**	**1,352**	**1,423**	**1,494**	**1,566**	**1,638**

Source: Company data, CMBIS estimates

GIST is another potential indication

GIST can occur anywhere along the gastrointestinal tract, but most often is found in the stomach or small intestine. Imatinib is the standard front-line treatment for advanced KIT+ GIST. For imatinib resistant patients, sunitinib is usually administered, followed by regorafenib if further relapse happens. There is unmet clinical need for patients who do not respond to the currently approved TKIs.

In preclinical studies, HQP1351 inhibits not only BCL-ABL but also KIT and PDGFR. We believe HQP1351 is a potential treatment for GIST patients resistant to currently available TKIs.

F&S estimates that in 2018, there were 96,500 new cases of GIST worldwide, and it is estimated that the number of new cases will increase to 125,000 by 2030E. F&S forecasts the global GIST drug market to increase from US$0.35bn in 2018 to US$1.1bn in 2030E with a CAGR of 10%.

Figure 18: BCL-ABL TKIs

Drug candidate	Company	Unit price in the US	Monthly cost in the US
HQP1351	Ascentage Pharma	NA	NA
Gleevec (imatinib)	Novartis	~US$8,700/90 tablets of 100mg (for generic drug, the lowest price for the same specification is ~US$630)	~US$11,600 per month for Gleevec
Sutent (sunitinib)	Pfizer	~US$18,200/28 capsules of 50mg	~US$13,000 per month
Stivarga (regorafenib)	Bayer	~US$17,500/84 tablets of 40mg	~US$18750 per month

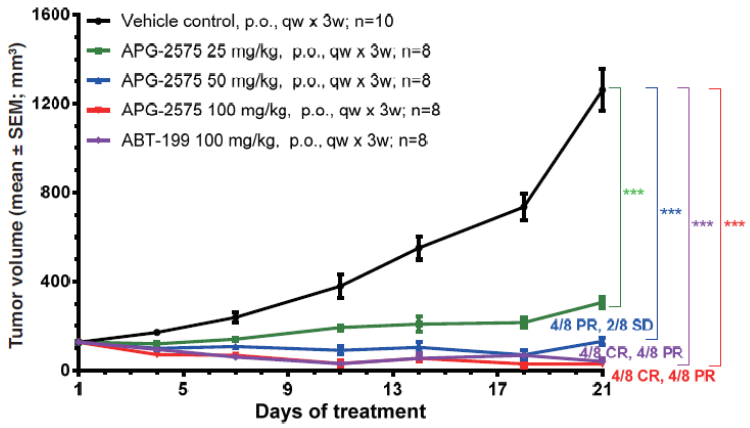
Source: Company data, CMBIS

APG-2575, a potential global second to market Bcl-2 inhibitor

APG-2575 is a novel, orally administered Bcl-2 selective inhibitor for treatment of hematologic malignancies with Bcl-2 overexpression, including leukemia, lymphoma and multiple myeloma (MM). In preclinical studies, APG-2575 has demonstrated antitumor activity as a single agent and in combination with APG-115 (an MDM2-p53 inhibitor), Bruton's tyrosine kinase (BTK) inhibitors, anti-CD20 monoclonal antibodies, phosphoinositide 3-kinase (PI3K) inhibitors, in various types of B cell malignancies.

As a single agent, APG-2575 has shown substantial time and dose-dependent anti-tumor activity in human ALL xenograft mice using various dosing schedules, including once daily, once every three days, and once weekly. The antitumor activity of APG-2575 is comparable with that of venetoclax in human ALL xenograft mice.

Figure 19: Antitumor activity of APG-2575 in a RS4; 11 Human ALL Xenograft Model



Source: Company data, CMBIS
Note: APG-2575, ABT-199 (venetoclax), or vehicles used for dissolving the drugs (control) was orally (p.o.) administered once-weekly (qw) for 3 weeks (3w). Eight or ten animals were enrolled into each group (n=8 or n=10). SD, stable disease; PR, partial (tumor) regression; CR, complete (tumor) regression. ***p<0.001 SEM, standard error of the mean.

Ascentage Pharma initiated a multi-center Phase I dose-escalation study of APG-2575 as a single agent in multiple hematologic malignancies in the US and Australia in Aug 2018. The first patient was dosed in Oct 2018 and a total of 90 patients are expected to be enrolled. The current dose level is 600mg.

As of 13 Aug 2019, of the six evaluable patients with hematologic malignancies, two had SDs. Three CLL patients in the 400mg dose cohort had not yet completed the two treatment cycles necessary for fully evaluating efficacy, but had already showed a significant response to APG-2575 by the end of the first treatment cycle and the absolute lymphocyte counts of these three patients reached the criteria for CR. In addition, an assessment of one patient in the 50mg dose cohort found that the size of this patient's lymph nodes at the end of cycle 6 had reduced by more than 60% compared to baseline, which met the criteria for PR.

APG-2575 was well tolerated in all five dose cohorts tested, no DLT has been reported and the MTD has not been reached. During the 28-day DLT observation period (cycle 1), there were no clinically significant changes in vital signs, including platelet counts. There was no laboratory TLS or TLS observed. All of the TRAEs were grade 1 or 2. There were no grade 3 or 4 events.

The Company obtained IND approval from NMPA for APG-2575 in hematologic malignancies in Oct 2018. The first patient in China was dosed in Jun 2019. As of 13 Aug 2019, two patients with

hematologic malignancies have completed the first cycle of treatment with APG-2575 at 20mg dose level.

In addition to the two Phase I trials in which APG-2575 is administrated as a single agent, the Company plans to initiate combination trials with targeted agents, such as anti-CD20 mAbs, BTK inhibitors and PI3K inhibitors in blood cancers, including AML, CLL, MM, WM and NHL. In Nov 2019, Ascentage Pharma entered into an agreement with Henlius Biotech (2696 HK) to co-develop the combination therapy between APG-2575 and Hanlikang (Rituximab) for CLL patients in China.

Competitive landscape of Bcl-2 inhibitors is favourable worldwide due to the difficulties of development. Novartis' BCL-201 (S-55746) is in Phase I clinical trial. Beigene (BGNE US)'s BGB-11417 has completed IND-enabling studies and may start clinical trials in 1H20E. We think APG-2575 has the potential to become a second-to-market Bcl-2 inhibitor worldwide. Given the successful experiences of venetoclax (the first-in-class Bcl-2 inhibitor), we expect APG-2575 to follow the clinical strategy of venetoclax.

Bcl-2 is a promising target with high entry barrier

The Bcl-2 family proteins function as important gatekeepers of intrinsic apoptosis pathways. The members of the Bcl-2 family proteins can be classified into three functional groups: anti-apoptotic proteins (Bcl-2, Bcl-xL), pro-apoptotic effectors, and pro-apoptotic activators.

The overexpression of Bcl-2 has been found in many tumor types. For solid tumors, Bcl-2 overexpression has been observed in tumors such as prostate, breast and small cell and non-small cell lung cancers. Moreover, Bcl-2 overexpression may also relate to hematologic malignancies, such as leukemia and lymphoma.

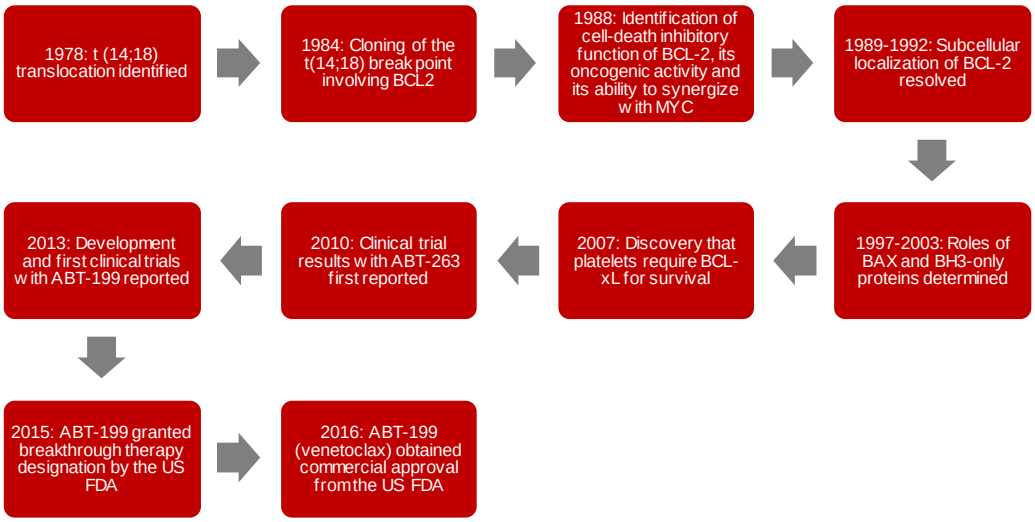
Development of Bcl-2 targeted drug is very difficult. The intracellular localization of the Bcl-2 family proteins on the mitochondrial membrane prevents the use of antibodies and other large molecules to target these anti-death Bcl-2 family proteins. Moreover, the very large and hydrophobic interfaces involved in Bcl-2 PPIs makes Bcl-2 family proteins difficult targets for small molecule drugs.

Over 30 years have passed since the cloning of t(14;18) chromosomal break point in human follicular lymphoma, and the naming of BCL-2. The discovery of Bcl-2 started with the association of t(14;18) chromosomal translocations with human follicular lymphoma by Fukuhara and Rowley in 1978. This enabled others to clone the chromosomal break point, and subsequently the cDNA, of a gene on chromosome 18, which was termed B cell leukemia or lymphoma gene number 2 (BCL2).

ABT-737 was the first small molecule targeting Bcl-2 family proteins that has entered into clinical phase. Nevertheless, ABT-737 can only be administered via injection. Abbott Laboratories has ceased the development of ABT-737. ABT-263 (navitoclax) is a successor of ABT-737 and can be orally administered. ABT-263 started clinical trials in 2006 but was found to cause severe thrombocytopenia which limits the dosing of ABT-263. This was because Bcl-xL is crucial for the survival of platelets.

ABT-199 (venetoclax), developed by AbbVie (ABBV US) and Genetech, only targets Bcl-2 but not Bcl-xL and is therefore better tolerated than ABT-263. In 2016, venetoclax became the firstly approved Bcl-2 inhibitor worldwide. To date, venetoclax has received five breakthrough designations from the US FDA.

Figure 20: Timeline of key discoveries related to Bcl-2 family members



Source: "30 years of Bcl-2: translating cell death discoveries into novel cancer therapies" published at Nature, 29 Jan 2016, CMBIS

In addition to Bcl-2 inhibitors developed by Ascentage Pharma, there are only a small number of Bcl-2 targeting agents in active clinical development, including navitoclax (ABT-263) developed by AbbVie and BCL-201 developed by Novartis. Beigene (BGNE US)'s BGB-11417 has completed IND-enabling studies and may start clinical trials in 1H20E.

Ascentage Pharma has three Bcl-2 targeting agents in clinical development: APG-1252 (a Bcl-2/Bcl-xL dual inhibitor), APG-2575 (a Bcl-2 selective inhibitor) and AT-101 (a pan-Bcl-2 inhibitor).

Figure 21: Clinical Bcl-2 inhibitor programs

Drug candidate	Target	Progress	Target indication	Company
APG-1252	**Bcl-2/Bcl-xL**	**Phase I**	**SCLC, Lymphoma**	**Ascentage Pharma**
APG-2575	**Bcl-2**	**Phase I**	**Blood cancer**	**Ascentage Pharma**
AT-101	**Pan-Bcl-2**	**Phase II**	**CLL**	**Ascentage Pharma**
Navitoclax / ABT-263	Bcl-2/Bcl-xL	Phase II	MF, Ovarian cancer	Abbvie
Navitoclax / ABT-263	Bcl-2/Bcl-xL	Phase I/II	SCLC	Abbvie
Navitoclax / ABT-263	Bcl-2/Bcl-xL	Phase I	ALL, etc.	Abbvie
Venetoclax / ABT-199	Bcl-2	Marketed	CLL, AML, MM, MCL, etc.	Abbvie
BCl-201 (S-55746)	Bcl-2	Phase I	MCL, FL, AML, MDS	Novartis

Source: F&S, CMBIS

Bcl-2 inhibitor shows excellent efficacy, especially in combo therapies

To date, venetoclax (brand name Venclexta) is the only approved Bcl-2 selective inhibitor globally. Venetoclax was firstly approved by the US FDA in Apr 2016 as a second line therapy for CLL with 17p deletion. As of Jul 2019, venetoclax has expanded its approved indication to 1) in combination with obinutuzumab as a first-line treatment of CLL/SLL and 2) in combination with azacytidine or decitabine or low-dose cytarabine as a first-line treatment of newly-diagnosed AML in adults who aged 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

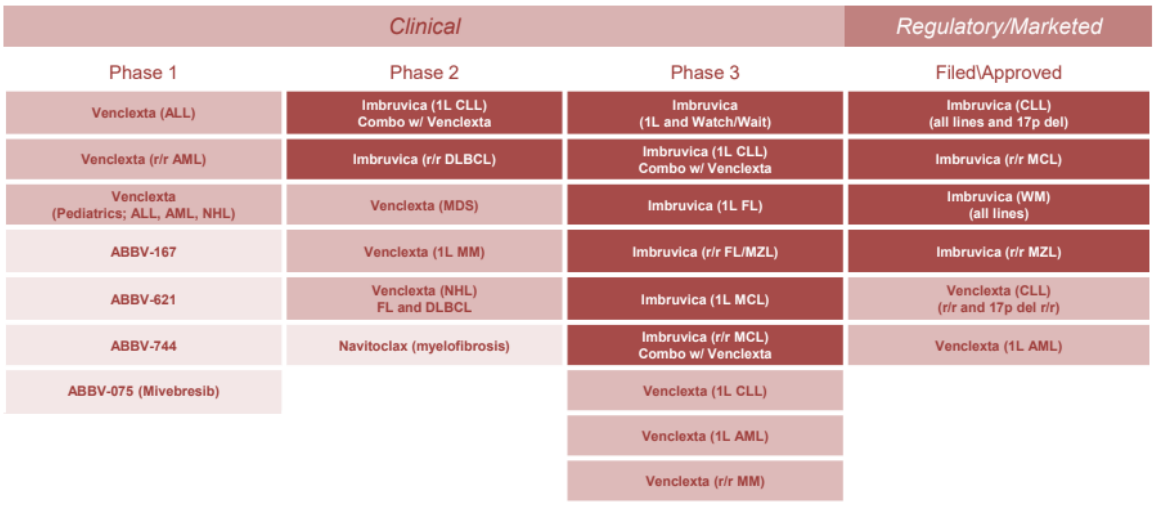
Figure 22: Venetoclax had indication expansion in past years

Date of FDA approval	Indications approved by FDA
2016-04-11	2nd line treatment of CLL with 17p deletion
2018-08-06	2nd line treatment of CLL/SLL, with or without 17p deletion
2018-11-21	1) 2nd line treatment of CLL/SLL, with or without 17p deletion 2) In combination with azacitidine or decitabine or low-dose cytarabine as 1st line therapy for AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy
2019-05-15	1) In combination with obinutuzumab as a 1st line treatment of CLL/SLL 2) In combination with azacitidine or decitabine or low-dose cytarabine as 1st line therapy for AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy

Source: FDA, CMBIS

There are currently more than 80 ongoing clinical trials of venetoclax. Ongoing trials cover major hematologic oncology indications, such as CLL/SLL, AML, MM, MDS, NHL (FL and DLBCL), ALL, etc. We expect venetoclax to expand indications to major hematologic cancer types in the future.

Figure 23: Venetoclax plays an important role in AbbVie's hematologic oncology pipeline



Source: AbbVie, CMBIS

Venetoclax has shown strong efficacy in combination with ibrutinib (BTK inhibitor) and obinutuzumab (anti-CD20 antibody). These combination therapies achieve very high rates of complete response and high rates of minimal residual disease-negativity.

Bcl-2 inhibitor in combination with anti-CD20 antibody:

In Jun 2019, AbbVie announced results from the Phase III CLL14 trial, evaluating efficacy and safety of venetoclax plus obinutuzumab versus obinutuzumab plus chlorambucil in previously untreated patients with CLL, which demonstrated that venetoclax plus obinutuzumab prolonged progression-free survival and achieved higher rates of complete response and minimal residual disease-negativity compared to commonly used standard of care obinutuzumab plus chlorambucil. The results were presented in an oral presentation at the American Society of Clinical Oncology (ASCO) Annual Meeting in Jun 2019.

Complete response rates were significantly higher with venetoclax plus obinutuzumab than with chlorambucil plus obinutuzumab (49.5% versus 23.1%, P<0.001). Higher rates of MRD-negativity were observed with venetoclax plus obinutuzumab compared to obinutuzumab plus chlorambucil in both peripheral blood (75.5% versus 35.2%, P<0.001) and bone marrow (56.9% versus 17.1%, P<0.001) three months after treatment completion.

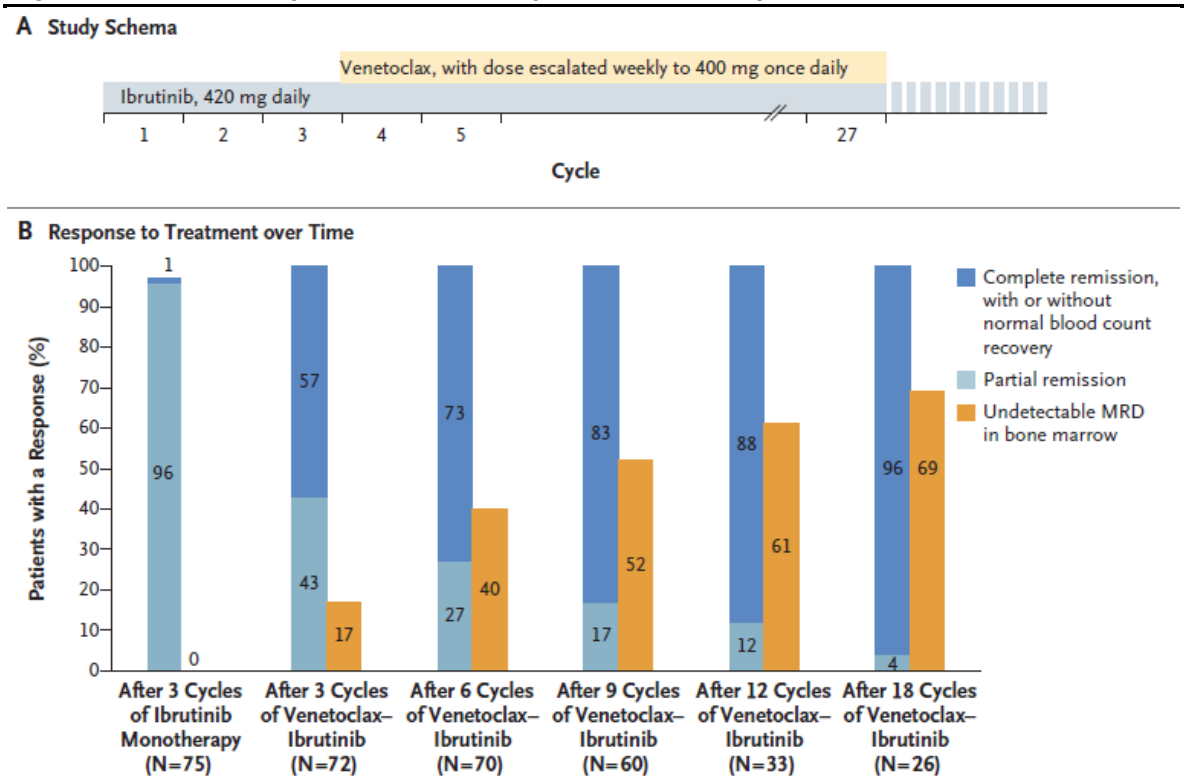
Bcl-2 inhibitor in combination with BTK inhibitor (oral regimen):

In a phase II study (NCT02756897), venetoclax and ibrutinib are orally administered for first-line treatment of CLL. Combined therapy was administered for 24 cycles. The median follow-up was 14.8 months.

Of the total 80 patients enrolled, 59 (74%) had complete remission or complete remission with incomplete count recovery as their best response. After 12 cycles of combined treatment, 88% of the patients had complete remission or complete remission with incomplete count recovery, and 61% had remission with undetectable minimal residual disease. After 18 cycles of the combination, 96% were in complete with incomplete count recovery, with 69% having remission with undetectable minimal residual disease in bone marrow. Three patients completed 24 cycles of combined therapy; all had complete remission or complete remission with incomplete count recovery, with undetectable minimal residual disease in bone marrow.

Especially, we would like to highlight that, after the initial three cycles of ibrutinib monotherapy, most responses were partial. After the addition of venetoclax, the proportions of patients who had complete remission or complete remission with incomplete count recovery and remission with undetectable minimal residual disease in bone marrow increased over time.

Figure 24: Venetoclax plus ibrutinib: study schema and response to treatment



Source: "Ibrutinib and Venetoclax for First-Line Treatment of CLL" published at N Engl J Med 2019; 380:2095-2103, CMBIS
Note: Panel A shows the study schema. Patients received ibrutinib monotherapy (420 mg once daily) for three cycles (each cycle was 28 days), and then venetoclax was added. The dose of venetoclax was escalated weekly to a target dose of 400 mg once daily. Combined ibrutinib and venetoclax were administered for a total of 24 cycles. Patients who remained positive for minimal residual disease (MRD) in bone marrow at the end of combined treatment could continue ibrutinib alone until disease progression or unacceptable toxic effects. Clinical responses and MRD were measured after three cycles of ibrutinib monotherapy and then after every three cycles for the first 12 cycles of the combination and every six cycles for cycles 13 to 24 of the combination. Panel B shows response to treatment over time. Responses (complete remission, with or without normal blood count recovery; partial remission; and undetectable MRD in bone marrow) are shown for patients after three cycles of ibrutinib monotherapy and at different time points for the combination therapy.

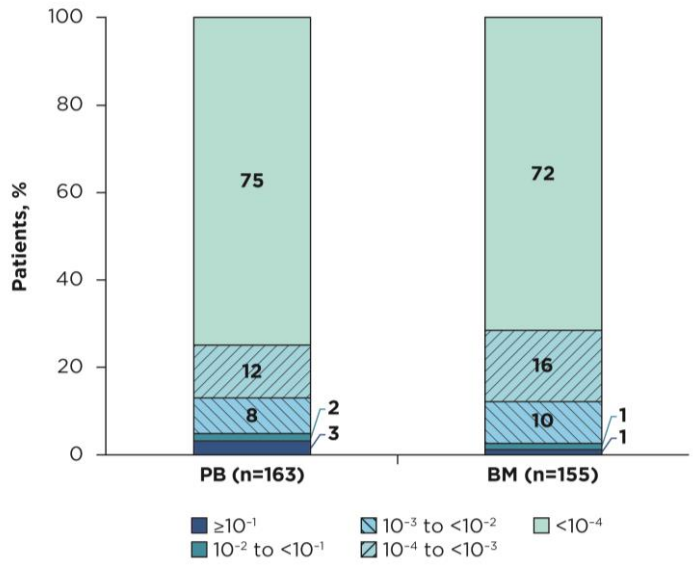
In ASH 2019, Abbvie announced the results of phase 2 CAPTIVATE study (NCT02910583) for first-line treatment of CLL/SLL. In the study, treatment naïve CLL/SLL patients received single-agent Ibrutinib lead in for three cycles followed by Ibritinib + Venetoclax for 12 cycles. A total of 164 patients were enrolled and 151 patients (92%) completed Ibrutinib lead-in and all 12 cycles of Ibrutinib + Venetoclax.

Undetectable minimal residual disease (uMRD) was achieved at any time after baseline in 75% of patients (122/163) in peripheral blood (PB) and 72% (111/155) in bone marrow (BM). The proportion of patients who had uMRD in PB increased over time from 57% after six cycles, 68% after nine cycles, and 73% after 12 cycles of Ibrutinib + Venetoclax.

With median follow-up of 14.7 months, no patients developed clinical TLS. AEs leading to discontinuation were infrequent, occurring in 7% patients overall (Ibrutinib 5%, Venetoclax 4%).

We think the results further proved that the oral Ibritinib + Venetoclax regimen is highly effective and tolerable. This trial provides the evidence to support a time-limited treatment option with a fixed duration regimen of 12 cycles of Ibrutinib + Venetoclax in untreated CLL/SLL patients.

Figure 25: MRD response of phase 2 CAPTIVATE study in first line CLL/SLL patients



Source: ASH 2019, CMBIS

In comparison, ibrutinib monotherapy can reach 87% ORR with a median follow-up of five years while most responses were partial with persistent disease typically in the bone marrow and complete remission was uncommon.

We believe the oral combination of Bcl-2 inhibitor and BTK inhibitor could potentially become the golden standard for first-line treatment of CLL given the excellent efficacy of the combination therapy.

Figure 26: Comparison of efficacy between different therapies for CLL

CLL/SLL	Venetoclax + Ibrutinib	Venetoclax + Ibrutinib	Venetoclax + Obinutuzumab	Obinutuzumab + chlorambucil	Ibrutinib + Rituximab	Venetoclax	Ibrutinib	
Source	ASH 2019	NEJM	ASCO 2019	ASCO 2019	NEJM	NEJM	Blood Journal	
Trial registration No.	NCT02910583	NCT02756897	NCT02242942	NCT02242942	NCT02048813	NCT01328626	NCT01105247, NCT01109069	
Administration	Oral	Oral	Oral + Intravenous	Oral + Intravenous	Oral + Intravenous	Oral	Oral	
Trial phase	Phase II	Phase II	Phase III	Phase III	Phase III	Phase I	NA	
Line of treatment	1st line	1st line	1st line	1st line	1st line	2nd line	1st line	2nd line
Median follow-up (mo)	14.7 mos	14.8 mos	28.1 mos	28.1 mos	33.6 mos	17 mos	5-year	5-year
n	164	80	216	216	354	116	31	101
MRD-negativity in bone marrow	72%	69% (after 18 cycles of combo)	56.90%	17.10%	NA	5%	NA	NA
CR		74%	49.50%	23.10%	17.2%	20%	29%	10%
ORR		100%	84.70%	71.30%	95.8%	79%	87%	89%

Source: ASH, The New England Journal of Medicine (NEJM), ASCO, Blood Journal, CMBIS

Expect RMB2.0bn risk-adjusted peak sales from APG-2575

Venetoclax worldwide sales was US$541mn in 1H19, up 146% YoY. Sales surge of venetoclax was mainly driven by new indication approvals. F&S forecasts Bcl-2 inhibitors may reach US$13.2bn revenue worldwide by 2030E.

F&S estimates that there were 0.44mn leukemia patients worldwide in 2018 while the prevalence may increase to 0.55mn by 2030E. Meanwhile, global sales for drugs to treat leukemia may grow from US$11.5bn in 2018 to US$50.5bn by 2030E. According to F&S, there were 0.14mn new cases of AML worldwide in 2018. The global AML market may grow from US$0.4bn in 2018 to US$18.0bn in 2030E. CLL is a slowly progressing blood cancer that causes an excess of white blood cells in the bone marrow, blood, liver and spleen. F&S estimates 0.11mn new cases of CLL worldwide in 2018 with a global prevalence of 0.51mn. CLL drug sales may grow from US$4.2bn in 2018 to US$10.2bn in 2030E.

We expect APG-2575 to realize RMB5.6bn peak sales from CLL indication, RMB836mn peak sales from AML indication and RMB1.0bn peak sales from MM indication. We apply 30% probability of success for CLL and AML indication and 15% probability for MM indication, we forecast RMB2.0bn risk-adjusted peak sales from AGP-2575.

Figure 27: APG2575 sales forecasts in CLL/SLL indication

	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
APG2575 -CLL/SLL in US								
Incidence of CLL/SLL in US (people)	21,561	21,777	21,995	22,215	22,437	22,661	22,888	23,117
Penetration of Bcl-2 inhibitor as first-line treatment of CLL/SLL	*19%*	*22%*	*25%*	*28%*	*31%*	*34%*	*37%*	*40%*
CLL/SLL patients receiving Bcl-2 inhibitor as first-line treatment (people)	4,097	4,791	5,499	6,220	6,955	7,705	8,468	9,247
Prevalence of CLL/SLL in US (people)	197,781	200,748	203,759	206,815	209,918	213,066	216,262	219,506
Rate of relapse or drug resistance	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*
Penetration of Bcl-2 inhibitor as second-line treatment of CLL/SLL	*35%*	*38%*	*41%*	*44%*	*47%*	*50%*	*53%*	*56%*
CLL/SLL patients receiving Bcl-2 inhibitor as second-line treatment (people)	5,538	6,103	6,683	7,280	7,893	8,523	9,170	9,834
Market share of APG-2575 in Bcl-2 market in US	*10%*	*14%*	*17%*	*18%*	*22%*	*23%*	*24%*	*25%*
CLL/SLL patients receiving APG-2575 (people)	963	1,525	2,071	2,430	3,267	3,732	4,233	4,770
Ex-factory price of APG-2575 in US (US$ per month)	8,400	8,316	8,233	8,151	8,069	7,988	7,908	7,829
Average period of treatment (month)	20	20	20	20	20	20	20	20
APG-2575 sales in US CLL/SLL patients (US$ mn)	**162**	**254**	**341**	**396**	**527**	**596**	**670**	**747**
APG-2575 sales in US CLL/SLL market (RMB mn)	**1,133**	**1,776**	**2,387**	**2,773**	**3,690**	**4,174**	**4,687**	**5,229**
APG2575-CLL/SLL in China								
Incidence of CLL/SLL in China (people)	4,174	4,258	4,343	4,430	4,518	4,609	4,701	4,795
Penetration of Bcl-2 inhibitor as first-line treatment of CLL/SLL	*5%*	*9%*	*13%*	*17%*	*20%*	*22%*	*24%*	*26%*
CLL/SLL patients receiving Bcl-2 inhibitor as first-line treatment (people)	209	383	565	753	904	1,014	1,128	1,247
Average survival period in China (years)	8	8	8	8	8	9	9	9
Prevalence of CLL/SLL in China (people)	31,723	33,209	34,742	36,323	37,953	39,634	41,366	43,153
Rate of relapse or drug resistance	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*	*8%*
Penetration of Bcl-2 inhibitor as second-line treatment of CLL/SLL	*10%*	*15%*	*20%*	*25%*	*30%*	*32%*	*34%*	*36%*
CLL/SLL patients receiving Bcl-2 inhibitor as second-line treatment (people)	254	399	556	726	911	1,015	1,125	1,243
Market share of APG-2575 in Bcl-2 market in China	*50%*	*55%*	*56%*	*57%*	*58%*	*59%*	*60%*	*61%*
CLL/SLL patients receiving APG-2575 (people)	231	430	627	843	1,052	1,197	1,352	1,519
Ex-factory price of APG-2575 in China (RMB per month)	13,870	13,592	13,320	13,054	12,793	12,537	12,286	12,041
Average period of treatment (month)	20	20	20	20	20	20	20	20
APG-2575 sales in China CLL/SLL market (RMB mn)	**64**	**117**	**167**	**220**	**269**	**300**	**332**	**366**
Total APG-2575 sales in CLL/SLL patients (RMB mn)	**1,197**	**1,892**	**2,554**	**2,993**	**3,959**	**4,474**	**5,019**	**5,594**

Source: Company data, CMBIS estimates

Figure 28: APG2575 sales forecasts in AML indication

	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
APG2575-AML in US								
Incidence of AML in US (people)	21,882	21,992	22,102	22,212	22,323	22,435	22,547	22,660
Penetration of Bcl-2 inhibitor as first-line treatment among adult AML patients	*21%*	*23%*	*25%*	*26%*	*27%*	*28%*	*29%*	*30%*
Market share of APG-2575 in Bcl-2 market in US	*10%*	*14%*	*17%*	*18%*	*22%*	*23%*	*24%*	*25%*
AML patients receiving APG-2575 as first-line treatment (people)	460	708	939	1,040	1,326	1,445	1,569	1,699
Ex-factory price of APG-2575 in US (US$ per month)	8,400	8,316	8,233	8,151	8,069	7,988	7,908	7,829
Average period of treatment (month)	5	5	5	5	5	5	5	5
APG-2575 sales in US AML market (US$ mn)	**19**	**29**	**39**	**42**	**53**	**58**	**62**	**67**
APG-2575 sales in US AML market (RMB mn)	**135**	**206**	**271**	**297**	**374**	**404**	**434**	**466**
APG2575-AML in China								
Incidence of Leukemia in China (people)	88,226	89,990	91,790	93,626	95,499	97,409	99,357	101,344
Adult AML as % of total leukemia incidence in China (people)	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*
Penetration of Bcl-2 inhibitor as first-line treatment among adult AML patients	*5%*	*9%*	*13%*	*17%*	*20%*	*22%*	*24%*	*25%*
Market share of APG-2575 in Bcl-2 market in China	*50%*	*55%*	*56%*	*57%*	*58%*	*59%*	*60%*	*61%*
AML patients receiving APG-2575 as first-line treatment (people)	878	1,773	2,660	3,611	4,410	5,033	5,695	6,152
Ex-factory price of APG-2575 in China (RMB per month)	13,870	13,592	13,320	13,054	12,793	12,537	12,286	12,041
Average period of treatment (month)	5	5	5	5	5	5	5	5
APG-2575 sales in China AML market (RMB mn)	**61**	**121**	**177**	**236**	**282**	**315**	**350**	**370**
Total APG-2575 sales in AML market (RMB mn)	**196**	**327**	**448**	**532**	**657**	**719**	**784**	**836**

Source: Company data, CMBIS estimates

Figure 29: APG2575 sales forecasts in MM indication

	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
APG2575-MM in US								
Prevalence of multiple myeloma (MM) in US (people)	136,060	136,741	137,424	138,111	138,802	139,496	140,193	140,894
Rate of relapse or drug resistance	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*
New replase or drug resistance MM patients in US (people)	20,409	20,511	20,614	20,717	20,820	20,924	21,029	21,134
Penetration of Bcl-2 inhibitor as second-line treatment among r/r MM patients	*10%*	*14%*	*18%*	*21%*	*22%*	*23%*	*24%*	*25%*
Market share of APG-2575 in Bcl-2 market in US	*10%*	*14%*	*17%*	*18%*	*22%*	*23%*	*24%*	*25%*
MM patients receiving APG-2575 as second-line treatment (people)	204	402	631	783	1,008	1,107	1,211	1,321
Ex-factory price of APG-2575 in US (US$ per month)	8,400	8,316	8,233	8,151	8,069	7,988	7,908	7,829
Average period of treatment (month)	12	12	12	12	12	12	12	12
APG-2575 sales in US MM market (US$ mn)	**21**	**40**	**62**	**77**	**98**	**106**	**115**	**124**
APG-2575 sales in US MM market (RMB mn)	**144**	**281**	**436**	**536**	**683**	**743**	**805**	**869**
APG2575-MM in China								
Incidence of MM in China (people)	15,104	15,406	15,714	16,029	16,349	16,676	17,010	17,350
Average survival period of MM in China (years)	3	3	3	3	3	3	3	3
Prevalence of multiple myeloma (MM) in China (people)	45,312	46,218	47,143	48,086	49,047	50,028	51,029	52,049
Rate of relapse or drug resistance	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*
New replase or drug resistance MM patients in China (people)	6,797	6,933	7,071	7,213	7,357	7,504	7,654	7,807
Penetration of Bcl-2 inhibitor as second-line treatment among r/r MM patients	*5%*	*9%*	*11%*	*13%*	*15%*	*17%*	*19%*	*20%*
Market share of APG-2575 in Bcl-2 market in China	*50%*	*55%*	*56%*	*57%*	*58%*	*59%*	*60%*	*61%*
MM patients receiving APG-2575 as second-line treatment (people)	170	343	436	534	640	753	873	953
Ex-factory price of APG-2575 in China (RMB per month)	13,870	13,592	13,320	13,054	12,793	12,537	12,286	12,041
Average period of treatment (month)	12	12	12	12	12	12	12	12
APG-2575 sales in China MM market (RMB mn)	**28**	**56**	**70**	**84**	**98**	**113**	**129**	**138**
Total APG-2575 sales in MM market (RMB mn)	**172**	**337**	**506**	**620**	**781**	**856**	**933**	**1,006**

Source: Company data, CMBIS estimates

Figure 30: Risk-adjusted APG-2575 sales forecasts

	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
APG-2575 sales in CLL/SLL (RMB mn)	1,197	1,892	2,554	2,993	3,959	4,474	5,019	5,594
Probability of success for CLL/SLL	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
APG-2575 sales in AML (RMB mn)	196	327	448	532	657	719	784	836
Probability of success for AML	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
APG-2575 sales in MM (RMB mn)	172	337	506	620	781	856	933	1,006
Probability of success for MM	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*
Risk-adjustedAPG-2575 sales (RMB mn)	**444**	**716**	**976**	**1,151**	**1,502**	**1,686**	**1,881**	**2,080**

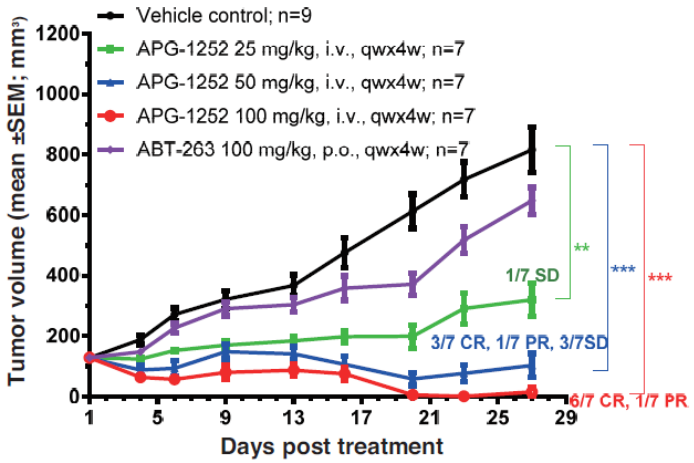
Source: Company data, CMBIS estimates

APG-1252, a potential best/first-in-class Bcl-2/Bcl-xL inhibitor

APG-1252 is a novel, highly potent, small molecule drug targeting Bcl-2 and Bcl-xL for the treatment of SCLC, lymphoma and other solid tumors. In the pre-clinical tumor models treated with APG-1252, antitumor activities were observed in a broad range of tumor types, including SCLC, lymphoma, colorectal cancer (CRC), metastatic breast cancer (mBC), etc. With high potency and sub-nanomolar binding affinity to Bcl-2 family proteins, APG-1252 minimizes platelet toxicity by design and has a favourable pharmacokinetic / pharmacodynamic (PK/PD) profile. Thus, APG-1252 could have a potentially wide therapeutic window compared to navitoclax (ABT-263) developed by Abbvie, the only other Bcl-2/Bcl-xL inhibitor in clinical development.

APG-1252 has shown strong, schedule- and dose-dependent antitumor activity in multiple human cancer xenograft models. In one preclinical xenograft study, APG-1252 administered intravenously on a weekly dosing schedule achieved complete tumor regression, or CR. This result was not achieved with administration of navitoclax on the same dosing schedule.

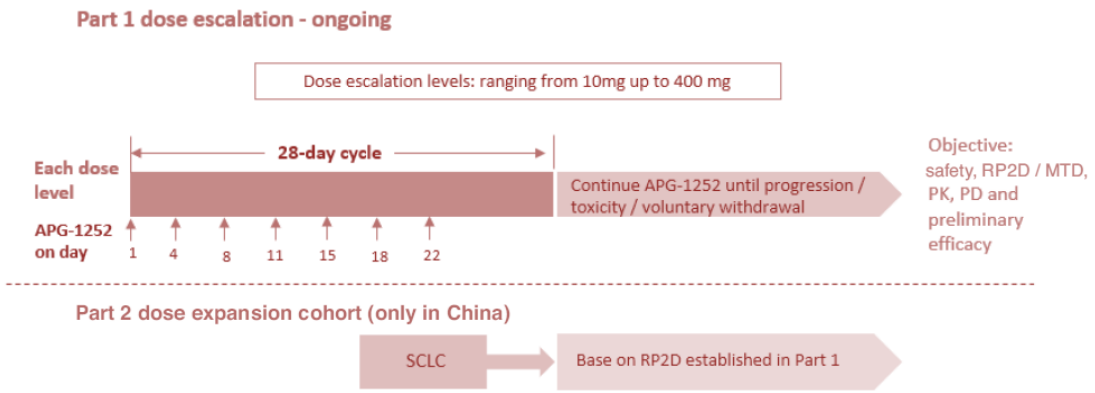
Figure 31: Antitumor activity of APG-1252 in SCLC Xenograft model



Source: Company data, CMBIS
Note: Antitumor activity of APG-1252 administered intravenously (i.v.) using a weekly (qw) dosing schedule for 4 weeks (4w) in a xenograft tumor model of human SCLC (NCI-H146) in mice. ABT-263 (navitoclax) was administered orally (p.o.) for comparison. The vehicles used for both APG-1252 and ABT-263 were administered to animals in the control group. Seven or nine mice were enrolled into each treatment group (n=7 or n=9). SD, stable disease; PR, partial (tumor) regression; CR, complete (tumor) regression. **p<0.01, ***p<0.001. In statistical hypothesis testing, the p-value is the probability for a given statistical model that, when the null hypothesis is true, the statistical summary would be the same as, or of greater magnitude than, the actual observed results. SEM, standard error of the mean.

APG-1252 is going through two Phase I dose-escalation trials in patients with advanced cancers in the US and Australia. In parallel, APG-1252 is under a Phase I dose-escalation/expansion trial as a monotherapy in SCLC patients in China. In current Phase I trials, APG-1252 is administered intravenously, twice a week on a three week on and one week off schedule. The current dose level being explored is 320mg, twice weekly.

Figure 32: Study design of APG-1252 Phase I trials



Source: Company data, CMBIS
Note: Study design for illustrative purpose only: actual clinical trial design may deviate from this illustrative chart.

As of 10 Aug 2019, 65 patients have been treated with APG-1252. The current dose level being explored is 400mg twice weekly and weekly. As of 10 Aug 2019, of 29 evaluable SCLC patients, one patient with relapsed progressive SCLC has confirmed PR at a dose level of 40mg. Four patients from China at the 80mg and 160mg dose levels had SD. Also, five SDs were observed in the clinical trial in Australia in other tumor types.

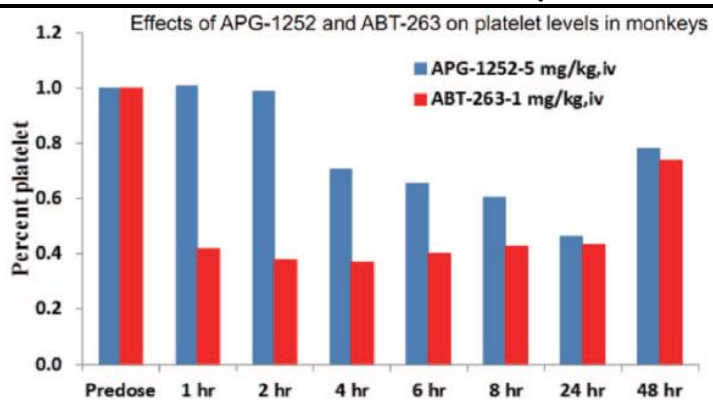
Pending Phase I results, a potential registration-enabling Phase II trial in r/r SCLC is planned in the US and China in 2019E and 2020E.

APG-1252 shows better safety than first-generation Bcl-xL inhibitor

One major safety concern for Bcl-xL targeting inhibitor is decrease in platelet count. APG-1252 has potential to become best-in-class Bcl-2/Bcl-xL inhibitor because it significantly decreases platelet toxicity compared with navitoclax/ABT-263 (the first generation Bcl-2/Bcl-xL inhibitor). APG-1252 is designed with modified cellular permeability and contains a negatively charged phosphate group, which greatly reduces its platelet permeability when administered intravenously.

Since navitoclax/ABT-263 requires a daily oral regimen to be effective, it has been found to constantly supress platelet counts in patients, which has prevented its further clinical development as a single agent for cancer treatment. Pre-clinical data implies that APG-1252 triggered significantly less platelet toxicity than navitoclax, even at 5-10 times higher dosage, in rats, dogs and monkeys.

Figure 33: Effects of APG-1252 and ABT-263 on platelet levels in monkeys



Source: Company data, CMBIS
Note: Significantly reduced platelet toxicity (thrombocytopenia) of APG-1252 in comparison with ABT-263 (navitoclax). Either APG-1252 or ABT-263 at the indicated doses was administered intravenously (iv) once to monkeys, a well-known species commonly used in non-clinical research. Platelet counts were measured at various time points post-dosing. Percent platelet represents the platelet levels after the treatment.

APG-1252 shows good tolerability in Phase I trial in China. As of 10 Aug 2019, no AEs leading to drug discontinuation have been reported. The most common Grade 3/4 AEs were: thrombocytopenia (7.7%), increased ALT (4.6%), increased AST (3.1%) hyponatremia (3.1%) and increased lipase (3.1%).

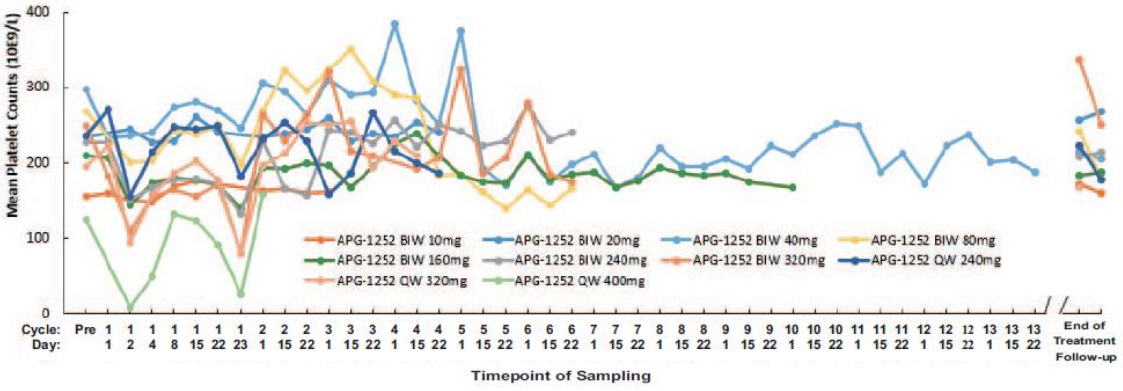
Figure 34: Safety overview of drug related clinically significant events

Drug related clinically significant events	n (patients)	% (n=65 patients)
Patients with any grade 3-4 AE	14	21.5
Patients with any grade SAE	4	6.2
Patients with any AE leading to permanent treatment discontinuation	0	0
Patients with any AE leading to death	0	0

Source: Company data, CMBIS

Two patients receiving APG-1252 at 400mg with twice weekly dosing experienced a grade 4 SAE consisting of decreased platelet count. The reduction in platelet count was transient and improved to grade 1 within 72 hours, with one dose interruption then reduced to 320mg.

Figure 35: APG-1252's phase I trial shows no significant decrease in platelet count



Source: Company data, CMBIS

Expect RMB1.3bn risk-adjusted peak sales from APG-1252

Ascentage Pharma is planning a Phase II trial in relapsed/ refractory SCLC (r/r SCLC) in the US and China. The Company also targets to pursue clinical development of APG-1252 in combination with standard of care (SoC) for treatment of SCLC, lymphoma and other solid tumors.

SCLC is the most aggressive and lethal sub-type of lung cancer, representing about 15% of all lung cancer cases worldwide. Currently, patients with advanced SCLC are treated with systemic chemotherapy as there's short to innovative therapies for this disease. Most SCLC patients relapse within a year on chemotherapy and the disease progress rapidly, with a five-year survival rate of less than 10%. According to F&S, there were about 0.31mn new cases of SCLC worldwide in 2017 while the number may rise to 0.44mn by 2030E. F&S forecasts the global SCLC drug market will grow from US$1.5bn in 2017 to US$10.9bn in 2030E due to the significant unmet need and the launch of new targeted therapies.

In addition to SCLC, Ascentage Pharma is conducting a phase Ib trial assessing APG-1252 plus osimertinib (AZD9291) in EGFR TKI resistant NSCLC patients in China (NCT04001777). The trial started in Jul 2019 with a targeted enrollment of 60 patients.

Ascentage Pharma also intends to develop APG-1252 for the treatment of lymphoma. Lymphoma is a blood cancer that affects immune system cells. Lymphoma had an estimated global incidence of 0.59mn cases in 2018 and the number may increase to 0.76mn n 2030E, according to F&S. The most common type of lymphoma is NHL. B-cell lymphomas is the most common type of NHL. According to F&S, approximately 77% of patients with lymphoma have B-cell lymphoma. The most aggressive forms of NHL, such as DLBCL and MCL, account for 36% of B cell lymphomas. Currently, the SoC of NHL is rituximab plus chemotherapy. BTK inhibitors such as ibrutinib and acalabrutinib, PI3K inhibitors such as copanlisib are new treatment options for NHL. F&S estimate global NHL drug market to grow from US$9.5bn in 2018 to US$26.9bn by 2030E.

We expect APG-1252 to realize RMB3.3bn peak sales from SCLC indication and RMB2.3bn peak sales from NSCLC indication. We apply 30% probability of success for SCLC and 15% probability of for NSCLC indication, and forecast RMB1.3bn risk-adjusted peak sales from AGP-1252. We estimate that Ascentage Pharma will pay c.5% sales royalties to University of Michigan and the attributable risk-adjusted peak sales from APG-1252 will be RMB1.3bn.

Figure 36: APG1252 sales forecast in SCLC indication

	2024E	2025E	2026E	2027E	2028E	2029E	2030E
APG1252 - SCLC in US							
Incidence of lung cancer in US ('000 people)	228	228	228	228	228	228	228
SCLC as % of total lung cancer incidence	*13%*	*13%*	*13%*	*13%*	*13%*	*13%*	*13%*
Incidence of SCLC in US ('000 people)	30	30	30	30	30	30	30
Penetration of APG1252 in US SCLC patients	*5%*	*8%*	*11%*	*12%*	*13%*	*14%*	*15%*
SCLC patients receiving APG-1252 ('000 people)	1	2	3	4	4	4	4
Ex-factory price of APG-1252 in US (US$ per month)	10,500	10,395	10,291	10,188	10,086	9,985	9,886
Average period of treatment (month)	6	6	6	6	6	6	6
APG-1252 sales in US SCLC patients (US$ mn)	**93**	**148**	**201**	**218**	**233**	**249**	**264**
APG-1252 sales in US SCLC market (RMB mn)	**654**	**1,036**	**1,410**	**1,523**	**1,633**	**1,741**	**1,847**
APG1252 - SCLC in China							
Incidence of lung cancer in China ('000 people)	876	894	912	930	949	968	987
SCLC as % of total lung cancer incidence	*13%*	*13%*	*13%*	*13%*	*13%*	*13%*	*13%*
Incidence of SCLC in China ('000 people)	114	116	119	121	123	126	128
Penetration of APG1252 in China SCLC patients	*5%*	*8%*	*11%*	*12%*	*13%*	*14%*	*15%*
SCLC patients receiving APG-1252 ('000 people)	6	9	13	15	16	18	19
Ex-factory price of APG-1252 in China (RMB per month)	13,870	13,592	13,320	13,054	12,793	12,537	12,286
Average period of treatment (month)	6	6	6	6	6	6	6
APG-1252 sales in China SCLC market (RMB mn)	**474**	**758**	**1,042**	**1,136**	**1,231**	**1,325**	**1,419**
Total APG-1252 sales in SCLC market (RMB mn)	**1,128**	**1,794**	**2,452**	**2,659**	**2,864**	**3,066**	**3,266**

Source: Company data, CMBIS estimates

Figure 37: APG1252 sales forecast in NSCLC indication

	2024E	2025E	2026E	2027E	2028E	2029E	2030E
APG1252 - NSCLC in US							
Incidence of lung cancer in US ('000 people)	228	228	228	228	228	228	228
NSCLC as % of total lung cancer incidence	*87%*	*87%*	*87%*	*87%*	*87%*	*87%*	*87%*
Incidence of NSCLC in US ('000 people)	198	198	198	198	198	198	198
% of EGFR mutation among NSCLC patients in US	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*
NSCLC patients with EGFR mutation ('000 people)	20	20	20	20	20	20	20
% of r/r EGFR TKI resistant NSCLC patients	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*
r/r EGFR TKI resistant NSCLC patients in US ('000 people)	10	10	10	10	10	10	10
Penetration of APG1252 in US EGFR TKI resistant NSCLC patients	*5%*	*8%*	*11%*	*12%*	*13%*	*14%*	*15%*
NSCLC patients receiving APG-1252 ('000 people)	0	1	1	1	1	1	1
Ex-factory price of APG-1252 in US (US$ per month)	10,500	10,395	10,291	10,188	10,086	9,985	9,886
Average period of treatment (month)	6	6	6	6	6	6	6
APG-1252 sales in US NSCLC patients (US$ mn)	**31**	**50**	**67**	**73**	**78**	**83**	**88**
APG-1252 sales in US NSCLC market (RMB mn)	**219**	**347**	**472**	**510**	**547**	**583**	**618**
APG1252 - NSCLC in China							
Incidence of lung cancer in China ('000 people)	876	894	912	930	949	968	987
NSCLC as % of total lung cancer incidence	*87%*	*87%*	*87%*	*87%*	*87%*	*87%*	*87%*
Incidence of NSCLC in China ('000 people)	762	778	793	809	825	842	859
% of EGFR mutation among NSCLC patients in China	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*	*35%*
NSCLC patients with EGFR mutation ('000 people)	267	272	278	283	289	295	301
% of r/r EGFR TKI resistant NSCLC patients	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*
r/r EGFR TKI resistant NSCLC patients in China ('000 people)	133	136	139	142	144	147	150
Penetration of APG1252 in China EGFR TKI resistant NSCLC patients	*5%*	*8%*	*11%*	*12%*	*13%*	*14%*	*15%*
NSCLC patients receiving APG-1252 ('000 people)	7	11	15	17	19	21	23
Ex-factory price of APG-1252 in China (RMB per month)	13,870	13,592	13,320	13,054	12,793	12,537	12,286
Average period of treatment (month)	6	6	6	6	6	6	6
APG-1252 sales in China NSCLC market (RMB mn)	**555**	**888**	**1,220**	**1,331**	**1,441**	**1,551**	**1,662**
Total APG-1252 sales in NSCLC market (RMB mn)	**774**	**1,235**	**1,692**	**1,840**	**1,988**	**2,134**	**2,280**

Source: Company data, CMBIS estimates

Figure 38: Risk-adjusted APG-1252 sales forecasts

	2024E	2025E	2026E	2027E	2028E	2029E	2030E
APG-1252 sales in SCLC (RMB mn)	1,128	1,794	2,452	2,659	2,864	3,066	3,266
Probability of success for SCLC	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
APG-1252 sales in NSCLC (RMB mn)	774	1,235	1,692	1,840	1,988	2,134	2,280
Probability of success for NSCLC	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*
Risk-adjusted APG-1252 sales (RMB mn)	**455**	**723**	**989**	**1,074**	**1,157**	**1,240**	**1,322**
% of royalties paid to University of Michigan	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*
Attributable risk-adjusted APG-1252 sales (RMB mn)	**432**	**687**	**940**	**1,020**	**1,099**	**1,178**	**1,256**

Source: Company data, CMBIS estimates

APG-115, a potent MDM2-p53 inhibitor

APG-115 is an oral small molecule inhibitor of the MDM2-p53 PPI. APG-115 could act as a single agent for adenoid cystic carcinoma (ACC) and sarcomas and in combination with IO, chemotherapeutic or targeted therapies for treatment of solid tumors or hematologic malignancies. As a second generation MDM2 inhibitor, APG-115 has stable chemical structure, high cell permeability and a favourable PK profile. These characteristics allow for every other day dosing schedule.

Ascentage Pharma is conducting two Phase I clinical trials of APG-115 as a monotherapy in the US and China for patients with advanced solid tumors or lymphoma. Preliminary Phase I data shows that APG-115 is well tolerated. As of 7 Aug 2019, a total of 63 patients were treated with APG-115 at various doses. In the trial in US, the most common grade 3 or 4 TRAEs were decreased neutrophil count and thrombocytopenia. In the trial in China, the most common grade 3 or above AEs were vomiting and hematologic toxicities. One partial response was observed in a liposarcoma patient with MDM2-amplification and TP53-wild type at the 150mg cohort. Six patients (4 STSs and 2 ACCs) had SD as the best overall response in the trial in China. In the trial in US, 14 patients achieved SD among 24 response evaluable patients and 62% (8/13) of the patients at the MTD cohort achieved SD.

In addition, a Phase Ib/II trial of APG-115 in combination with pembrolizumab (Keytruda, anti-PD-1 mAb) in patients with unresectable or metastatic melanomas in the US was initiated in Sep 2018. As of 7 Aug 2019, 19 patients have been treated with APG-115 plus pembrolizumab up to the third

cohort at 200mg. One confirmed CR and two PRs were observed in 14 patients who were evaluable for efficacy, and six patients had SD at the best response. One patient with ovarian cancer treated at 100mg has confirmed CR. The Company received IND approval from the US FDA to start a Phase Ib/II trial of APG-115 for patients with rare cancer disease, salivary gland carcinoma (SGC) in Dec 2018. The Company also plans to file IND for Phase Ib/II clinical trials for treatment of patients with AML in China and the US in 2019E.

MDM2-p53 pathway

The transcription factor p53 is a tumor suppressor that is activated by cellular stress, such as low nutrients or DNA damage. A number of hematologic cancers and some solid tumors involve p53 dysfunction resulting from abnormal activity of certain p53 regulatory proteins, including MDM2. Preclinical data have shown that inhibiting MDM2-53 binding may induce apoptosis in both MDM2-overexpressing and wild-type tumor cell lines.

MDM2 is amplified in approximately 7% of all human cancers, but has been found to be amplified with higher frequency in specific tumor types, such as liposarcomas (over 80%), soft tissue tumors (20%), osteosarcomas (16%), and esophageal carcinomas (13%). In addition, MDM2 amplification have been implicated in hyper-progression in patients receiving PD-1/PD-L1 blockade IO therapy. Several drugs targeting MDM2-p53 pathway are in clinical development while idasanutlin (RG7388) could potentially become the first-to-market MDM2 inhibitor in the world. Idasanutlin is going through a Phase 3 trial combined with cytarabine for treatment of r/r AML.

Figure 39: Summary of MDM2-p53 inhibitors in clinical trials

Drug candidate	Target	Progress	Target indication	Company
APG-115	**MDM2-p53**	**Phase I/II**	**Cancers, Malignant Salivary Gland Cancer**	**Ascentage Pharma**
Idasanutlin/ RG7388	MDM2-p53	Phase III	AML, Polycythemia Vera, NHL, Solid tumors	Roche
RO-6839921	MDM2-p53	Phase I	AML, Neoplasms	Roche
HDM201	MDM2-p53	Phase I/II	Solid tumors; Hematological tumors	Novartis
CGM097	MDM2-p53	Phase I	Solid tumors	Novartis
AMG232	MDM2-p53	Phase I/II	AML; Solid tumors	Amgen
DS-3032	MDM2-p53	Phase I	AML; MM	Daichi-Sankyo
ALRN-6924	MDM2-p53; MDMX	Phase I/II	PTCL, AML, MDS, Solid tumors	Aileron Therapeutics
UBX0101	MDM2-p53	Phase I	Osteoarthritis	Unity

Source: F&S, CMBIS

As of Feb 2019, there is no approved MDM2 inhibitor in the world and APG-115 was the only MDM2 inhibitor under clinical trials in China. APG-115 has the potential to become the first-in-class MDM2 inhibitor in China. APG-115 may be best applied for the treatment of cancers harbouring wild-type p53, such as ACC, AML, MDS, liposarcoma, breast cancer and colorectal cancers.

Expect RMB0.7bn risk-adjusted peak sales from APG-115

According to F&S, there were around 9.6 thousand new cases of ACC worldwide in 2017 while the incidence may rise to approximately 12.7 thousand in 2030E. ACC drug sales were US$0.3bn in 2017 and may grow to US$1.6bn in 2030E. F&S estimates 0.37mn new cases of MDS globally in 2017 and expects the number to reach 0.39mn in 2022E. Global sales of MDS drugs were US$1.2bn in 2017 and may rise to US$1.8bn in 2022E.

We expect APG-115 to realize RMB1.4bn peak sales from AML indication, RMB464mn peak sales from liposarcoma indication, RMB310mn peak sales from ACC indication and RMB488mn peak sales from ovarian cancer indication. We apply 30% probability of success for AML, liposarcoma and ACC, respectively, and 15% probability for ovarian cancer indication, we forecast RMB730mn risk-

adjusted peak sales from AGP-115. We estimate that Ascentage Pharma will pay c.5% sales royalties to University of Michigan and the attributable risk-adjusted peak sales from APG-115 will be RMB694mn.

Figure 40: APG-115 sales forecasts in AML indication

	2024E	2025E	2026E	2027E	2028E	2029E	2030E
APG115-AML in US							
Prevalence of AML in US (people)	63,533	63,851	64,170	64,491	64,813	65,137	65,463
% of refractory AML patients	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
New refractory AML patients (people)	19,060	19,155	19,251	19,347	19,444	19,541	19,639
Penetration of APG-115 among r/r AML patients	*5%*	*10%*	*13%*	*16%*	*18%*	*19%*	*20%*
r/r AML patients receiving APG-115 (people)	953	1,916	2,503	3,096	3,500	3,713	3,928
Ex-factory price of APG-115 in US (US$ per month)	7,000	6,930	6,861	6,792	6,724	6,657	6,590
Average period of treatment (month)	6	6	6	6	6	6	6
APG-115 sales in US AML market (US$ mn)	40	80	103	126	141	148	155
APG-115 sales in US AML market (RMB mn)	280	558	721	883	988	1,038	1,087
APG115-AML in China							
Incidence of Leukemia in China (people)	89,990	91,790	93,626	95,499	97,409	99,357	101,344
Adult AML as % of total leukemia incidence in China (people)	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*	*40%*
Incidence of AML in China (people)	35,822	36,539	37,269	38,015	38,775	39,551	40,342
Prevalence of AML in China (people)	99,506	101,496	103,526	105,597	107,708	109,863	112,060
% of refractory AML patients	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
Penetration of APG-115 among r/r AML patients	0	*10%*	*13%*	*16%*	*18%*	*19%*	*20%*
r/r AML patients receiving APG-115 (people)	1,493	3,045	4,038	5,069	5,816	6,262	6,724
Ex-factory price of APG-115 in China (RMB per month)	9,246	9,061	8,880	8,703	8,529	8,358	8,191
Average period of treatment (month)	6	6	6	6	6	6	6
APG-115 sales in China AML market (RMB mn)	83	166	215	265	298	314	330
Total APG-115 sales in AML market (RMB mn)	**363**	**723**	**936**	**1,148**	**1,286**	**1,352**	**1,418**

Source: Company data, CMBIS estimates

Figure 41: APG-115- Liposarcoma sales forecasts

	2024E	2025E	2026E	2027E	2028E	2029E	2030E
APG115- Liposarcoma in US							
Incidence of soft tissue sarcoma in US (people)	13,072	13,137	13,203	13,269	13,335	13,402	13,469
Liposarcomas as % of all soft tissue sarcomas	*18%*	*19%*	*19%*	*19%*	*19%*	*19%*	*19%*
New incidence of liposarcomas (people)	2,412	2,437	2,461	2,486	2,511	2,536	2,561
Penetration of APG-115 among liposarcoma patients	*5%*	*10%*	*15%*	*20%*	*23%*	*24%*	*25%*
liposarcoma patients receiving APG-115 (people)	121	244	369	497	577	609	640
Ex-factory price of APG-115 in US (US$ per month)	7,000	6,930	6,861	6,792	6,724	6,657	6,590
Average period of treatment (month)	12	12	12	12	12	12	12
APG-115 sales in US liposarcoma market (US$ mn)	10	20	30	41	47	49	51
APG-115 sales in US liposarcoma market (RMB mn)	71	142	213	284	326	340	354
APG115- Liposarcomain China							
New incidence of liposarcomas (people)	4,060	4,121	4,183	4,246	4,310	4,375	4,440
Penetration of APG-115 among liposarcoma patients	*5%*	*10%*	*15%*	*20%*	*23%*	*24%*	*25%*
liposarcoma patients receiving APG-115 (people)	203	412	627	849	991	1,050	1,110
Ex-factory price of APG-115 in China (RMB per month)	9,246	9,061	8,880	8,703	8,529	8,358	8,191
Average period of treatment (month)	12	12	12	12	12	12	12
APG-115 sales in China liposarcoma market (RMB mn)	23	45	67	89	101	105	109
Total APG-115 sales in liposarcoma market (RMB mn)	**93**	**187**	**280**	**372**	**428**	**446**	**464**

Source: Company data, CMBIS estimates

Figure 42: APG-115- ACC sales forecasts

	2024E	2025E	2026E	2027E	2028E	2029E	2030E
APG115- ACC in US							
Incidence of Adenoid Cystic Carcinoma (ACC) in US (people)	228	228	228	228	228	228	228
Penetration of APG-115 among ACC patients	*5%*	*10%*	*15%*	*20%*	*23%*	*24%*	*25%*
ACC patients receiving APG-115 (people)	60	120	180	240	276	288	300
Ex-factory price of APG-115 in US (US$ per month)	7,000	6,930	6,861	6,792	6,724	6,657	6,590
Average period of treatment (month)	12	12	12	12	12	12	12
APG-115 sales in US ACC market (US$ mn)	5	10	15	20	22	23	24
APG-115 sales in US ACC market (RMB mn)	35	70	104	137	156	161	166
APG115- ACC in China							
Incidence of ACC in China (people)	5,500	5,555	5,610	5,666	5,723	5,780	5,838
Penetration of APG-115 among ACC patients	*5%*	*10%*	*15%*	*20%*	*23%*	*24%*	*25%*
liposarcoma patients receiving APG-115 (people)	275	555	842	1,133	1,316	1,387	1,459
Ex-factory price of APG-115 in China (RMB per month)	9,246	9,061	8,880	8,703	8,529	8,358	8,191
Average period of treatment (month)	12	12	12	12	12	12	12
APG-115 sales in China ACC market (RMB mn)	31	60	90	118	135	139	143
Total APG-115 sales in ACC market (RMB mn)	**66**	**130**	**193**	**255**	**291**	**300**	**310**

Source: Company data, CMBIS estimates

Figure 43: APG-115- Ovarian cancer sales forecasts

	2024E	2025E	2026E	2027E	2028E	2029E	2030E
APG115- Ovarian cancer in US							
Incidence of ovarian cancer in US (people)	21,972	21,862	21,753	21,644	21,536	21,429	21,321
Prevalence of ovarian cancer in US (people)	220,839	219,735	218,636	217,543	216,456	215,373	214,296
% of refractory ovarian cancer patients	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*
New refractory ovarian cancer patients (people)	22,084	21,974	21,864	21,754	21,646	21,537	21,430
Penetration of APG-115+PD-1 for refractory ovarian cancer patients	*0%*	*1%*	*1%*	*2%*	*2%*	*3%*	*3%*
Refractory ovarian cancer patients receiving APG-115+PD-1	-	110	219	326	433	538	643
Ex-factory price of APG-115 in US (US$ per month)	-	6,930	6,861	6,792	6,724	6,657	6,590
APG-115 sales in US ovarian cancer market (US$ mn)	-	9	18	27	35	43	51
APG-115 sales in US ovarian cancer market (RMB mn)	-	64	126	186	245	301	356
APG115- Ovarian cancer in China							
Incidence of ovarian cancer in China (people)	54,492	54,764	55,038	55,313	55,590	55,868	56,147
Prevalence of ovarian cancer in China (people)	435,936	438,115	440,306	442,507	444,720	446,943	449,178
% of refractory ovarian cancer patients	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*
New refractory ovarian cancer patients (people)	43,594	43,812	44,031	44,251	44,472	44,694	44,918
Penetration of APG-115+PD-1 for refractory ovarian cancer patients	*0%*	*1%*	*1%*	*2%*	*2%*	*3%*	*3%*
Refractory ovarian cancer patients receiving APG-115+PD-1	-	219	440	664	889	1,117	1,348
Ex-factory price of APG-115 in China (RMB per month)	-	9,061	8,880	8,703	8,529	8,358	8,191
APG-115 sales in China ovarian cancer market (RMB mn)	-	24	47	69	91	112	132
Total APG-115 sales in ovarian cancer market (RMB mn)	**-**	**88**	**173**	**255**	**336**	**413**	**488**

Source: Company data, CMBIS estimates

Figure 44: Risk-adjusted APG-115 sales forecasts

	2024E	2025E	2026E	2027E	2028E	2029E	2030E
APG-115 sales in AML (RMB mn)	363	723	936	1,148	1,286	1,352	1,418
Probability of success for AML	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
APG-115 sales in liposarcoma (RMB mn)	93	187	280	372	428	446	464
Probability of success for liposarcoma	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
APG-115 sales in ACC (RMB mn)	66	130	193	255	291	300	310
Probability of success for ACC	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
APG-115 sales in ovarian cancer (RMB mn)	-	88	173	255	336	413	488
Probability of success for ovarian cancer	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*
Total risk-adjusted APG-115 sales (RMB mn)	**157**	**325**	**449**	**571**	**652**	**691**	**730**
% of royalties paid to University of Michigan	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*
Attributable risk-adjusted APG-115 sales (RMB mn)	**149**	**309**	**426**	**542**	**619**	**657**	**694**

Source: Company data, CMBIS estimates

APG-1387, a potential best-in-class IAP inhibitor

APG-1387 is a novel, small molecule inhibitor targeting IAP proteins for treatment of advances solid tumors and chronic HBV infection. High expression of IAP is related to many types of cancers, including lung, head and neck, breast, gastrointestinal cancers and MM.

The inhibitors of apoptosis proteins (IAPs) are a family of proteins that act to block apoptosis and regulate various cellular processes, including cell death and immune and inflammatory responses. Most IAP family inhibitors have been indicated to be correlated to the tumor grade and advanced tumor stage in human tumor tissues. We found five drugs targeting IAPs in clinical trials, with most in the early stage of development.

Figure 45: Summary of IAP inhibitors in clinical trials

Drug candidate	Target	Progress	Target indication	Company
APG-1387	**IAP Dimer**	**Phase I/II**	**Cancers; HBV**	**Ascentage Pharma**
Debio 1143	IAP Monomer	Phase I	NSCLC; Solid tumors	Debio Pharma
LCL161	IAP Monomer	Phase II	MM; Solid tumors	Novartis
ASTX660	IAP Monomer	Phase I/II	Solid tumors, Lymphoma	Astex Pharmaceuticals
Birinapant	IAP Dimer	Phase II	Solid tumors	Medivir

Source: F&S, CMBIS

APG-1387 is designed to bind to IAP protein dimers, unlike other IAP inhibitors in development that bind only to IAP monomers. This dual inhibition approach may lead to improved activity in a wide range of diseases, either as monotherapy or in combination with other targeted agents such as TKIs or IO therapies.

APG-1387 is the first IAP-targeting drug to enter clinical trials in China. On a weekly intravenous dosing regimen, APG-1387 has the potential to have broad anti-cancer activity. The drug has completed two Phase I clinical trials as a single agent in solid tumors in Australia and China, respectively. The Company is also conducting a Phase I clinical trial in the US, evaluating combination of APG-1387 with pembrolizumab in solid tumors.

As of 10 Aug 2019, a total of 74 patients with doses ranging from 0.075mg to 60mg were treated in these three clinical trials. In the US, a total of 39 patients were enrolled in these studies. 27 patients were treated with doses ranging from 30mg to 60mg in the single-agent dose-escalation stage of the study in the US and 12 patients have been treated with APG-1387 plus pembrolizumab. 23 of 39 patients experienced at least one TEAE. The most common TEAEs were nausea, fatigue and decreased appetite. In the clinical trial in China, no APG-1387 related SAEs have been reported. No

cytokine release syndrome (CRS) have been reported, as compared to CRS cases observed in patients treated with LCL161 (an IAP monomer inhibitor).

Figure 46: Safety overview of drug related clinically significant events

Drug related clinically significant events	n (patients)	% (n=74 patients)
Patients with any grade 3-4 AE	3	4.1
Patients with any grade SAE	0	0
Patients with any AE leading to permanent treatment discontinuation	3	4.1
Patients with any AE leading to death	0	0

Source: Company data, CMBIS

For APG-1387 as monotherapy, four out of 13 mPC patients achieved SD and one of them has been treated for over 11 cycles with confirmed SD. This preliminary result is worth mentioning, because mPC patients in general have only 3-6 months survival time, and overall survival rate of one year is 8.8%. Currently there is no effective treatment for mPC.

A total of 12 patients, who were treated with APG-1387 in combination with pembrolizumab, had no DLT observed during the first cycle. Among 10 evaluable patients, one had a confirmed PR and three SDs were observed. One patient with advanced breast cancer who previously had been treated and was refractory to multiple lines of treatment has shown a confirmed PR after six cycles of treatment, with treatment ongoing.

The pre-clinical data indicates that APG-1387 treatment is safe to clear chronic HBV infection in various mouse models via inducing the apoptosis of HBV-infected hepatocytes preferentially. A Phase I trial of APG-1387 as a single-agent in HBV patients is ongoing in China. As of 31 Mar 2019, 12 patients were treated with dose ranging from 7mg to 20mg. No APG-1387 related SAEs have been reported. When compared to baseline values, 10 out of 12 patients' HBV DNA levels declined and eight out of 12 patients' HBsAg levels declined after completion of four treatments. Among them, six patients' HBV DNA levels and HBsAg levels were declined together. Among six patients who completed D112 follow-up period in 7mg and 12mg cohorts, two patients' ALT values were declined to normal range. The preliminary data have demonstrated antiviral and immune modulatory activities of APG-1387 in patients and the potential for a functional cure of these patients.

Existing therapies can hardly achieve clinical cure for chronic HBV patients. In 2018, there were 96.5mn HBV infected patients in China, and 1.0mn newly infected HBV patients. According to China's guideline for HBV (2015 version), there are about 20mn chronic HBV patients in China.

F&S forecasts the global prevalence of HBV infection to increase from 267mn infected patients in 2018 to 296mn in 2030E. The global market for hepatitis B virus (HBV) contains several types of drugs, including nucleoside analogues, interferons and immunomodulators. According to F&S, global sales of HBV therapeutic drugs reached US$3.5bn in 2018 and will grow to US$5.9bn by 2030E. Meanwhile, China HBV market will increase from US$1.4bn in 2018, representing 40% of the global HBV drug sales.

Expect RMB0.6bn risk-adjusted peak sales from APG-1387

We expect APG-1387 to realize RMB1.4bn peak sales from pancreatic cancer indication and RMB3.8bn peak sales from HBV indication. We apply 15% probability of success for pancreatic cancer and 10% probability for HBV, and forecast RMB587mn risk-adjusted peak sales from AGP-1387. We estimate that Ascentage Pharma will pay c.5% sales royalties to University of Michigan and the attributable risk-adjusted peak sales from APG-1387 will be RMB557mn.

Figure 47: APG-1387 sales forecasts in Pancreatic cancer

	2024E	2025E	2026E	2027E	2028E	2029E	2030E
APG-1387- Pancreatic cancer in US							
Incidence of metastatic pancreatic cancer in US (people)	34,630	34,630	34,630	34,630	34,630	34,630	34,630
Penetration of APG-1387 among metastatic pancreatic cancer patients	*5%*	*8%*	*10%*	*12%*	*14%*	*16%*	*18%*
Pancreatic cancer patients receiving APG-1387 (people)	1,731	2,770	3,463	4,156	4,848	5,541	6,233
Ex-factory price of APG-1387 in US (US$ per month)	7,000	7,000	7,000	7,000	7,000	7,000	7,000
Average period of treatment (month)	4	4	4	4	4	4	4
APG-1387 sales in US pancreatic cancer market (US$ mn)	**48**	**78**	**97**	**116**	**136**	**155**	**175**
APG-1387 sales in US pancreatic cancer market (RMB mn)	**339**	**543**	**679**	**814**	**950**	**1,086**	**1,222**
APG-1387- Pancreatic cancer China							
Incidence of metastatic pancreatic cancer in China (people)	78,833	79,621	80,417	81,222	82,034	82,854	83,683
Penetration of APG-1387 among metastatic pancreatic cancer patients	*5%*	*8%*	*10%*	*12%*	*14%*	*16%*	*18%*
Pancreatic cancer patients receiving APG-1387 (people)	197	510	804	1,170	1,608	2,121	2,711
Ex-factory price of APG-1387 in China (RMB per month)	13,870	13,592	13,320	13,054	12,793	12,537	12,286
Average period of treatment (month)	4	4	4	4	4	4	4
APG-1387 sales in China pancreatic cancer market (RMB mn)	**11**	**28**	**43**	**61**	**82**	**106**	**133**
Total APG-1387 sales in pancreatic cancer market (RMB mn)	**350**	**571**	**722**	**876**	**1,033**	**1,192**	**1,355**

Source: Company data, CMBIS estimates

Figure 48: APG-1387 sales forecasts in HBV

	2024E	2025E	2026E	2027E	2028E	2029E	2030E
APG-1387 - HBV in China							
Prevalence of chronic HBV patients ('000 people)	20,000	20,000	20,000	20,000	20,000	20,000	20,000
% of chronic HBV patients receiving treatment	*20%*	*21%*	*22%*	*23%*	*24%*	*25%*	*26%*
Penetration of APG-1387 among chronic HBV patients	*0%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*
Chronic HBV patients receiving APG-1387 ('000 people)	16	21	26	32	38	45	52
Ex-factory price of APG-1387 in China (RMB per month)	13,870	13,592	13,320	13,054	12,793	12,537	12,286
Average period of treatment (month)	6	6	6	6	6	6	6
APG-1387 sales in China HBV market (RMB mn)	**1,331**	**1,713**	**2,110**	**2,522**	**2,947**	**3,385**	**3,833**

Source: Company data, CMBIS estimates

Figure 49: Risk-adjusted APG-1387 sales forecasts

	2024E	2025E	2026E	2027E	2028E	2029E	2030E
APG-1387 sales in pancreatic cancer (RMB mn)	350	571	722	876	1,033	1,192	1,355
Probability of success for pancreatic cancer	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*
APG-1387 sales in HBV (RMB mn)	1,331	1,713	2,110	2,522	2,947	3,385	3,833
Probability of success for HBV	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*
Risk-adjustedAPG-1387 sales (RMB mn)	**186**	**257**	**319**	**384**	**450**	**517**	**587**
% of royalties paid to University of Michigan	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*
Attributable risk-adjustedAPG-1387 sales (RMB mn)	**176**	**244**	**303**	**364**	**427**	**491**	**557**

Source: Company data, CMBIS estimates

Other innovative small molecules

APG-2449, a FAK inhibitor

APG-2449 is an oral inhibitor of FAK, ROS1 and ALK kinases for treatment of cancer. Preclinical studies have shown that APG-2449 overcomes the drug resistance to the first generation ALK inhibitors, and exhibits synergistic effects with EGFR inhibitors in an EGFR-T790M mutant NSCLC xenograft tumor model. APG-2449 entered phase I study in China in Feb 2019.

Extensive studies in cultured cells and conditional FAK knockout mouse models have shown that FAK plays a key role in angiogenesis during cancer progression. More recent studies have also revealed kinase-independent functions for FAK in endothelial cells and fibroblasts. Increased expression and/or activation of FAK is found in a variety of human cancers.

Figure 50: Most FAK inhibitors in development are in early stage clinical trials

Drug candidate	Target	Progress	Target indication	Company
GSK2256098	FAK	Phase II	Solid tumors	GSK
Defactinib	FAK	Phase II	NSCLC, Ovarian cancer	Verastem
BI 853520	FAK	Phase I	Solid tumors	iPharma
APG-2449	**FAK**	**Phase I**	**Cancers**	**Ascentage Pharma**

Source: F&S, CMBIS

AT-101, a pan Bcl-2 inhibitor

AT-101 is a pan Bcl-2 inhibitor which blocks Bcl-2, Bcl-xL, Bcl-w and Mcl-1 proteins. Since 2005, 14 Phase I and II clinical trials for AT-101 have been conducted in the US, Russia and Ukraine. More than 700 patients with various types of cancers were enrolled in these trials.

Ascentage Pharma is conducting a Phase II trial for AT-101 in combination with lenalidomide or rituximab in patients with r/r CLL in China. We expect the release of topline data from the trial by 2021E. The Company is also coordinating an investigator-initiated Phase I/II trial in the US to evaluate the efficacy and safety of AT-101 in patients with r/r CLL or r/r MM. Given that relative patents of AT-101 will expire in 2025, we do not view AT-101 as a potential blockbuster.

HQP8361, a novel c-Met inhibitor for NSCLC

HQP8361 is a second-generation c-Met inhibitor that is in development for the treatment of gastric cancer, NSCLC and liver cancer. In 2013, Ascentage Pharma licensed in Asia Pacific market rights for HQP8361 from MSD.

The drug has completed a Phase I trial in the US with a total of 47 patients enrolled. One PR with a long duration of 846 days (endometrial cancer) and seven SD (including two NSCLC) were reported. HQP8361 was well tolerated with no significant toxicity issues found.

Another Phase I trial in China in patients with advanced solid tumors was also finished. As of 31 Dec 2018, 22 patients have received HQP8361 monotherapy. No PR or CR was observed across all dose cohorts, and best response was SD in six patients. The limited antitumor activity of HQP8361 could be few patients with c-Met alteration involved in the study.

Ascentage Pharma plans to initiate a Phase II trial for HQP8361 as a monotherapy in c-Met amplified solid tumors such as NSCLC, gastric cancer and hepatocellular cancer, as well as Phase II combination trials with an EGFR inhibitor in EGFR TKI resistant NSCLC patients.

Crizotinib and cabozantinib which inhibit c-Met kinases have been approved by the FDA for treating NSCLC, HCC, MTC and RCC, etc. According to F&S, in 2018, the global sales of crizotinib and

cabozantinib reached US$524mn and US$794mn, respectively. Crizotinib is the only approved c-Met inhibitor in China. Several other c-Met inhibitor candidates are in clinical development.

Figure 51: Clinical stages of c-Met inhibitors

Drug candidate	Target	Progress	Target indication	Company
Crizotinib	HGFR; c-Met; ROS1; ALK	Phase II for c-Met (Marketed for ALK+ NSCLC)	Gastric, RMM (refractory multiple myeloma), NSCLC, etc.	Sugen
Cabozantinib	HGFR; c-Met; VEGFR; Axl; SCFR; c-Kit	Phase II for c-Met (Marketed for MTC)	HCC, RCC, RMM, etc.	BMS; Takeda
Capmatinib	HGFR; c-Met	Phase II for c-Met (Phase III)	HCC, NSCLC, mCRC, etc.	Incyte; Novartis
Savolitinib	c-Met	Phase II for c-Met (Phase III)	RCC, NSCLC, mCRC, etc.	Hutchison Chi-Med; AstraZeneca
HQP8361	**c-Met**	**Phase I completed for c-Met (Phase I)**	**c-Met positive cancers**	**Ascentage Pharma**

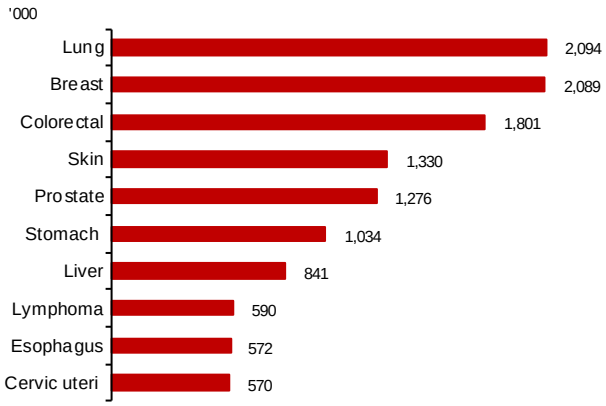
Source: Company data, CMBIS

Tapping unmet demand in oncology

Small molecule targeted drugs to play significant role in global oncology market

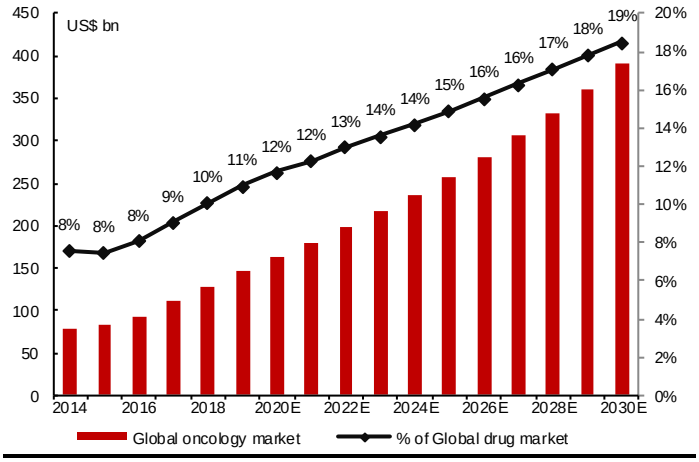
According to F&S, there were 18.1mn new cancer cases globally in 2018 and the number will rise to 24.1mn by 2030E, indicating a 2.4% CAGR between 2018 and 2030E.

Figure 52: New cases of global major cancer types, 2018



Source: F&S, CMBIS

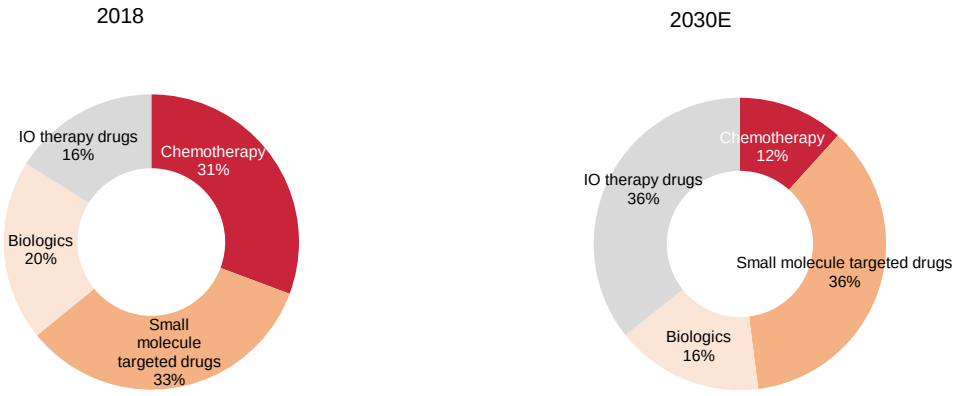
Figure 53: Global oncology drug market (2014-30E)



Source: F&S, CMBIS

F&S forecasts the global market for cancer drugs to increase from US$128.1bn in 2018 to US$216.7bn in 2023E, implying an 11.1% CAGR during 2018 and 2023E. The growth will be mainly driven by aging population, rapid evolution in treatment of cancer and rich pipeline of new oncology drugs. According to F&S, small molecule targeted drugs became the leading type of cancer treatment of sales in 2018, with global sales of US$42.8bn, accounting for 33.4% of the global oncology market. By 2030E, small molecule targeted drugs may reach US$141.7bn global sales, representing 36.3% of global oncology market.

Figure 54: Breakdown of global oncology drug market in 2018 and 2030E by rough estimate

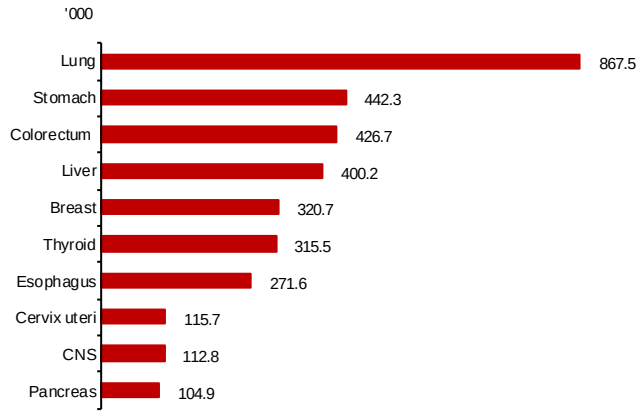


Source: F&S, CMBIS estimates
Note: Biologics excludes immune checkpoint inhibitors, such as PD-1/ PD-L1/ CTLA-4 mAbs. Immunotherapy (IO) includes immune checkpoint inhibitors and CAR-T, etc.

China oncology market to grow fast

F&S estimates cancer incidence in China to be 4.3mn in 2018, representing 23.7% of global cancer incidence. In 2023E, the number of new cancer cases will reach 4.9mn. According to F&S, the top 5 most commonly diagnosed cancers are lung, stomach, colorectum, liver and breast cancers, which in aggregated accounted for about 60% of all cancer incidence.

Figure 55: New cases for Top 10 cancers in China, 2018



Source: F&S, CMBIS

F&S forecasts China oncology market to grow from US$23.8bn in 2018 to US$47.9bn in 2023E, indicating a CAGR of 15.0% between 2018 and 2023E. The growth will be mainly driven by higher adoption of early screening, acceleration of new drug approval, improving affordability and access and improving insurance coverage.

From 2013 to 2017, NDAs approved by the NMPA increased from six to 29 while INDs reached 227 in 2017. Among all INDs, oncology drug candidates accounted for 41.7% which is the largest proportion.

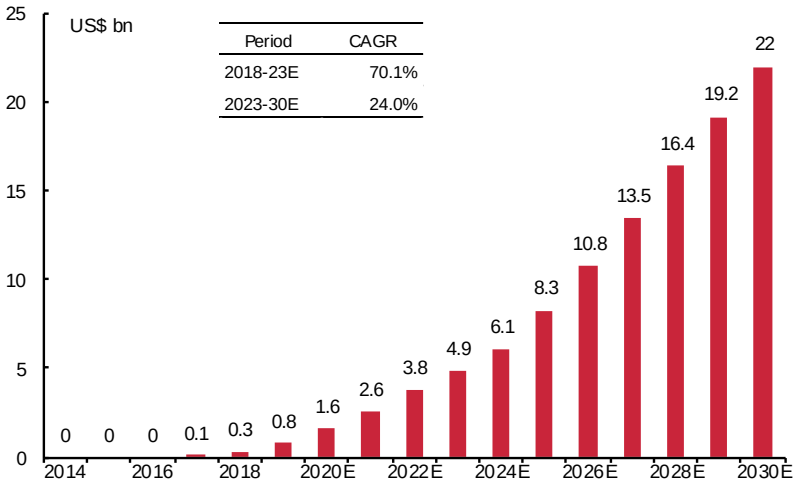
Chinese government has increased the frequency of National Reimbursement Drug List (NRDL) updates which allows more new drugs to receive reimbursement coverage. National Healthcare Security Administration (NHSA) announced the plan abut revising the NRDL in Apr 2019. According to the plan, drugs with reasonable prices will be added into the NRDL directly while some high-cost exclusive drugs will need to go through price negotiations to be included into the list. Drugs obtained approval after end-2018 will not be considered for this round of NDRL inclusion. NHSA released the new NRDL in Aug 2019 and aims to release the negotiated drug reimbursement list by end-2019.

China's fast-growing medical insurance revenue also has promoted the improving reimbursement coverage for oncology drugs. F&S estimates China urban medical insurance revenue to increase from US$222.7bn in 2017 to US$404.8bn in 2022E, representing a CAGR of 12.7% from 2017 to 2022E.

Promising outlook for apoptosis targeting therapies

According to F&S, the global market for apoptosis targeting therapies was US$0.3bn in 2018 and may rise significantly to US$4.9bn in 2023E, mainly driven by indication expansion of venetoclax and new drug launches.

Figure 56: Global apoptosis targeting therapy market (2014-30E)

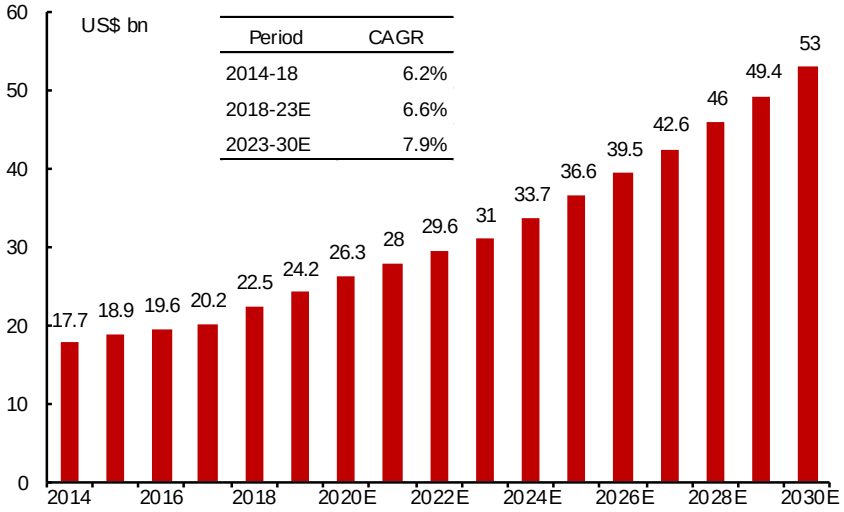


Source: F&S, CMBIS
Note: Apoptosis targeting therapy contains small molecule targeted therapies directly targeting at intrinsic apoptosis pathways such as Bcl-2/ IAP/ MDM2 proteins.

Fast growing tyrosine-kinase inhibitors market

The abnormal expression of tyrosine kinases is associated with numerous diseases, including cancers. Key tyrosine pathways include the BCR-ABL, KIT, c-Met, FAK, etc. According to F&S, the global sales of TKI drugs reached US$22.5bn in 2018. With launch of new generation inhibitors which address the drug resistance to some of the previous generation TKIs and act on new targets, the global TKI drug sales may grow to US$31.0bn in 2023E, with a CAGR of 6.6% from 2018 to 2023E.

Figure 57: Global drug sales of tyrosine-kinase inhibitors (2014-30E)



Source: F&S, CMBIS estimates

Risks

Difficulty in evaluating current business and predicting future performance

Ascentage Pharma is a globally-focused, clinical-stage biotechnology company formed in May 2009, focusing on the discovery and development of novel therapies for cancers, hepatitis B and age-related diseases. To date, it has no products approved for commercial sale, and has not yet demonstrated an ability to successfully obtain regulatory approvals, manufacture a commercial scale drug or conduct sales.

Having incurred net losses in the past and will continue to incur losses for the foreseeable future

Ascentage Pharma incurred losses of RMB107.8mn/ RMB118.5mn/ RMB345.3mn in FY16/FY17/FY18 due mainly to the cost devoted in R&D and general administrative expenses. Ascentage Pharma will continue to incur substantial and increasing losses for the foreseeable future.

Uncertain outcome and unpredictable results of studies and trials

Clinical study is time-consuming and expensive with uncertainty outcome. Failure can occur at any time during the whole clinical process. Despite positive results in preclinical studies and early clinical trials, drug candidates in later clinical trial stages may fail to show desired safety and efficacy traits, due to changes in trial procedures, differences in the size and type of patient population and the rate of dropout among clinical trial participants.

Failure in obtaining regulatory approval for drug candidates

The time required to obtain approval by the FDA, CNDA, EMA and other comparable regulatory authorities is unpredictable but typically takes many years. In addition, the related policies in each jurisdiction may change and vary during the course of a drug candidate's clinical development Ascentage Pharma may fail to receive regulatory approval from regulatory authorities, due to unsatisfactory with the design, the results and the insufficient data of clinical trials.

Competition from peers with more competing drugs

The development and commercialization of new drugs is highly competitive. Ascentage Pharma faces fierce competition worldwide. Ascentage Pharma currently mainly focus on developing oncology drugs, which is a highly evolving and competitive field. Some of these competitive drugs and therapies are based on scientific approaches that are the same as or similar to Ascentage's approach, and others are based on entirely different approaches.

Failure in protecting intellectual property rights throughout the world

Ascentage Pharma has sought to protect proprietary position by filing patent applications in the US, the PRC and other countries related to novel technologies and drug candidates. But, they may not be able to prevent third parties from practicing its inventions in countries outside or in the US and the PRC.

Financial Analysis

We estimate drugs sales to start from 2022E

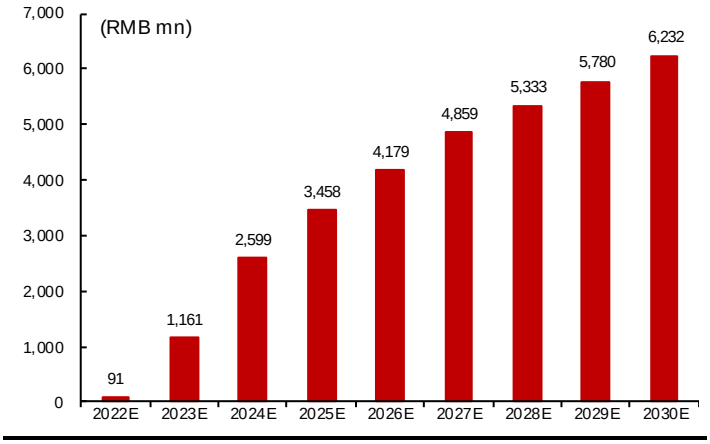
We forecast drug sales to start from 2022E. The most advanced drug is HQP1351 in Phase II trial and may be approved by NMPA in 2021E and start commercialization from 2022E. For other key candidates, APG-2575, APG-1252, APG-115 and APG-1387 in Phase I trials are expected to launch in 2023-24E. We apply risk-adjusted revenue to those drugs with different probability of success (PoS). We forecast total risk-adjusted revenue to be RMB91mn/ RMB1,161mn/ RMB2,599mn in FY22E/23E/24E.

Figure 58: Revenue forecasts and key assumptions

	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
HQP1351 sales in CML (RMB mn)	77	720	1,148	1,269	1,391	1,467	1,544	1,622	1,700
Probability of success for CML	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*	*70%*
HQP1351 sales in ALL (RMB mn)	65	457	699	770	839	880	920	959	998
Probability of success for ALL	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*	*50%*
Risk-adjusted HQP1351 sales (RMB mn)	87	732	1,153	1,273	1,394	1,467	1,541	1,615	1,689
% of royalties paid to GIBH	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*	*3%*
Attributable risk-adjusted HQP1351 sales (RMB mn)	**84**	**710**	**1,119**	**1,235**	**1,352**	**1,423**	**1,494**	**1,566**	**1,638**
APG-2575 sales in CLL/SLL (RMB mn)		1,197	1,892	2,554	2,993	3,959	4,474	5,019	5,594
Probability of success for CLL/SLL		*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
APG-2575 sales in AML (RMB mn)		196	327	448	532	657	719	784	836
Probability of success for AML		*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
APG-2575 sales in MM (RMB mn)		172	337	506	620	781	856	933	1,006
Probability of success for MM		*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*
Risk-adjusted APG-2575 sales (RMB mn)		**444**	**716**	**976**	**1,151**	**1,502**	**1,686**	**1,881**	**2,080**
APG-1252 sales in SCLC (RMB mn)			1,128	1,794	2,452	2,659	2,864	3,066	3,266
Probability of success for SCLC			*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
APG-1252 sales in NSCLC (RMB mn)			774	1,235	1,692	1,840	1,988	2,134	2,280
Probability of success for NSCLC			*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*
Risk-adjusted APG-1252 sales (RMB mn)			455	723	989	1,074	1,157	1,240	1,322
% of royalties paid to University of Michigan			*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*
Attributable risk-adjusted APG-1252 sales (RMB mn)			**432**	**687**	**940**	**1,020**	**1,099**	**1,178**	**1,256**
APG-115 sales in AML (RMB mn)			363	723	936	1,148	1,286	1,352	1,418
Probability of success for AML			*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
APG-115 sales in Liposarcoma (RMB mn)			93	187	280	372	428	446	464
Probability of success for liposarcoma			*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
APG-115 sales in ACC (RMB mn)			66	130	193	255	291	300	310
Probability of success for ACC			*30%*	*30%*	*30%*	*30%*	*30%*	*30%*	*30%*
APG-115 sales in Ovarian cancer (RMB mn)			-	88	173	255	336	413	488
Probability of success for ovarian cancer			*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*
Total risk-adjusted APG-115 sales (RMB mn)			157	325	449	571	652	691	730
% of royalties paid to University of Michigan			*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*
Attributable risk-adjusted APG-115 sales (RMB mn)			**149**	**309**	**426**	**542**	**619**	**657**	**694**
APG-1387 sales in pancreatic cancer (RMB mn)			350	571	722	876	1,033	1,192	1,355
Probability of success for pancreatic cancer			*15%*	*15%*	*15%*	*15%*	*15%*	*15%*	*15%*
APG-1387 sales in HBV (RMB mn)			1,331	1,713	2,110	2,522	2,947	3,385	3,833
Probability of success for HBV			*10%*	*10%*	*10%*	*10%*	*10%*	*10%*	*10%*
Risk-adjusted APG-1387 sales (RMB mn)			186	257	319	384	450	517	587
% of royalties paid to University of Michigan			*5%*	*5%*	*5%*	*5%*	*5%*	*5%*	*5%*
Attributable risk-adjusted APG-1387 sales (RMB mn)			**176**	**244**	**303**	**364**	**427**	**491**	**557**
Total drug sales (RMB mn)	**84**	**1,154**	**2,592**	**3,452**	**4,172**	**4,852**	**5,327**	**5,773**	**6,225**
License fee income	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
Provision of R&D services	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**
Total sales (RMB mn)	**91**	**1,161**	**2,599**	**3,458**	**4,179**	**4,859**	**5,333**	**5,780**	**6,232**

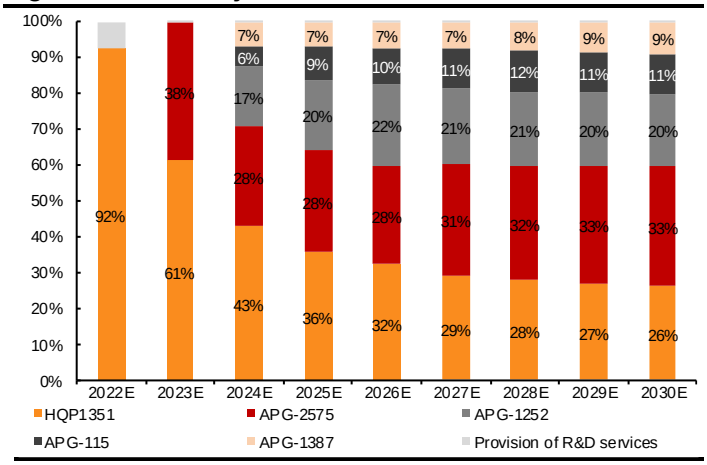
Source: Company data, CMBIS estimates

Figure 59: Risk-adjusted revenue forecasts



Source: Company data, CMBIS estimates

Figure 60: Risk-adjusted revenue forecast breakdown



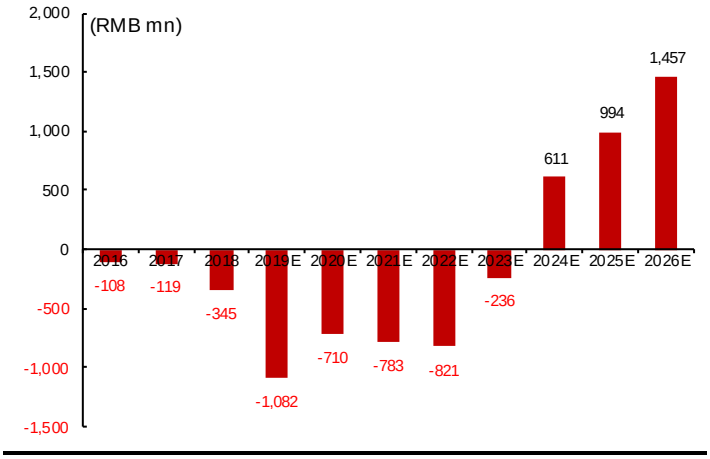
Source: Company data, CMBIS estimates

Net profit breakeven in 2024E

We forecast a net loss of RMB1,082mn/ RMB710mn/ RMB783mn in FY19E/20E/21E and expect breakeven year to be 2024E.

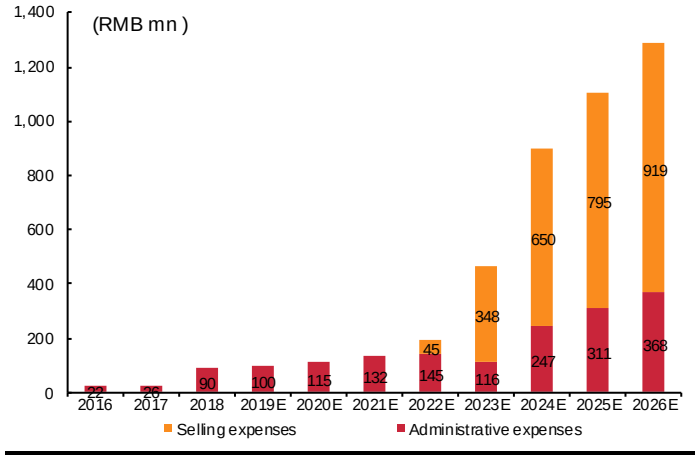
We forecast admin expenses to be RMB100mn/ RMB115mn/ RMB132mn in FY19E/20E/21E. Selling expenses is forecasted to be incurred from 2022E.

Figure 61: Expect to reach breakeven in 2024E



Source: Company data, CMBIS estimates

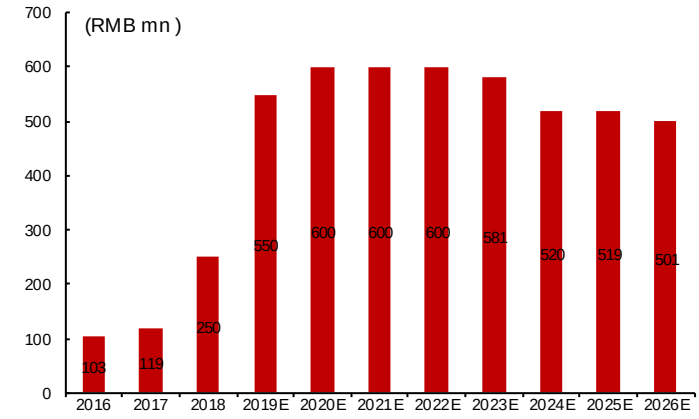
Figure 62: SG&A expenses forecasts



Source: Company data, CMBIS estimates

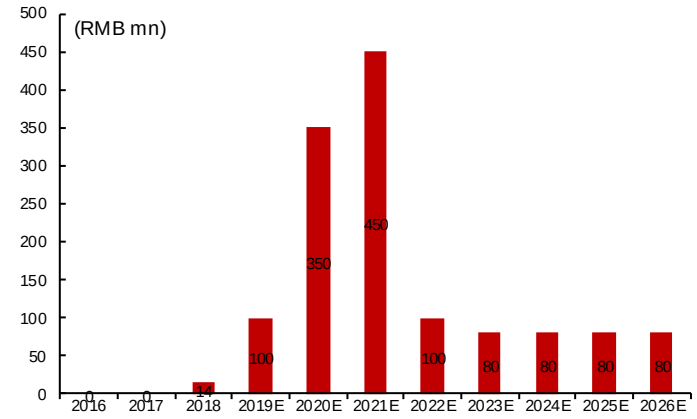
Ascentage Pharma recorded R&D spending of RMB103mn/ RMB119mn/ RMB250mn in FY16/FY17/FY18. Given that the pipeline drugs will enter late stage trials, we forecast its R&D spending will rise to RMB550mn/ RMB600mn/ RMB600mn in FY19E/20E/21E. The Company plans to complete the construction of a 10,000 sq m facility for R&D and manufacturing in Suzhou by 2019E. Given the factory construction plan, we forecast capex of RMB100mn/RMB350mn/RMB450mn in FY19E/ 20E/21E.

Figure 63: R&D cost forecasts



Source: Company data, CMBIS estimates

Figure 64: CAPEX forecasts



Source: Company data, CMBIS estimates

Financial Statments

Income statement

YE 31 Dec (RMB mn)	FY17A	FY18A	FY19E	FY20E	FY21E
Revenue	**6**	**7**	**7**	**7**	**7**
License fee income	0	0	0	0	0
Provision of R&D services	6	7	7	7	7
Cost of sales	0	0	0	0	0
Gross profit	**6**	**7**	**7**	**7**	**7**
Other income	77	61	19	19	19
Selling & distribution expenses	0	0	0	0	0
Administrative expenses	(26)	(90)	(100)	(115)	(132)
R&D expenses	(119)	(250)	(550)	(600)	(600)
Operating profit	**(62)**	**(272)**	**(625)**	**(690)**	**(707)**
Other expenses	(0)	(38)	(455)	0	0
Finance costs, net	(58)	(37)	(3)	(20)	(56)
Pre-tax profit	**(120)**	**(347)**	**(1,082)**	**(710)**	**(763)**
Income tax	2	2	0	0	0
Minority interests	0	0	0	0	0
Net profit (Net loss)	**(119)**	**(345)**	**(1,082)**	**(710)**	**(763)**

Cash flow summary

YE 31 Dec (RMB mn)	FY17A	FY18A	FY19E	FY20E	FY21E
Profit before tax	**(120)**	**(347)**	**(1,082)**	**(710)**	**(783)**
D&A	13	18	20	32	81
Change in working capital	11	27	(5)	0	0
Tax paid	0	0	0	0	0
Others	(11)	64	353	20	56
Net cash from operating	**(108)**	**(238)**	**(715)**	**(658)**	**(646)**
Capex	(21)	(48)	(100)	(350)	(450)
Purchase of financial assets	(210)	376	0	0	0
Other investing activities	0	(35)	(5)	(5)	(5)
Net cash from investing	**(230)**	**293**	**(105)**	**(355)**	**(455)**
Net proceeds from shares issued	61	911	329	0	0
Bank borrowing	0	35	70	800	1,000
Capital repurchase	0	(76)	0	0	0
Interests paid	(0)	(2)	(3)	(20)	(56)
Net cash from financing	**58**	**860**	**396**	**780**	**944**
FX changes	0	27	0	0	0
Net change in cash	**(280)**	**915**	**(424)**	**(233)**	**(157)**
Cash at the beginning year	295	15	957	533	300
Cash at the end	**15**	**957**	**533**	**300**	**144**

Balance sheet

YE 31 Dec (RMB mn)	FY17A	FY18A	FY19E	FY20E	FY21E
Non-current assets	**167**	**239**	**325**	**648**	**1,021**
PP&E	20	27	121	453	835
Right-of-use assets	5	40	37	34	31
Other intangible assets	81	75	69	63	58
Goodwill	25	25	25	25	25
Equity investment measured at FVTPL	30	60	60	60	60
Others	6	12	12	12	12
Current assets	**415**	**990**	**566**	**334**	**177**
Inventories	0	0	0	0	0
Trade receivables	0	0	0	0	0
Prepayments & other receivables	16	19	19	19	19
Other financial assets	384	14	14	14	14
Cash and bank balances	15	957	533	300	144
Current liabilities	**80**	**105**	**170**	**970**	**1,970**
Bank loans	2	38	108	908	1,908
Trade payables	4	5	0	0	0
Other payables & accruals	74	63	63	63	63
Contract liabilities	0	0	0	0	0
Non-current liabilities	**634**	**2,136**	**2,486**	**2,486**	**2,486**
Bank loans	3	4	4	4	4
Deferred tax liabilities	20	19	19	19	19
Preferred shares	0	2,076	2,426	2,426	2,426
Other non-current liabilities	589	0	0	0	0
Others	22	37	37	37	37
Total net assets	(132)	(1,012)	(1,765)	(2,475)	(3,258)
Minority interest	0	0	0	0	0
Shareholders' equity	(132)	(1,012)	(1,765)	(2,475)	(3,258)

Key ratios

YE 31 Dec	FY17A	FY18A	FY19E	FY20E	FY21E
Sales mix (%)					
License fee income	1	1	1	1	1
Provision of R&D services	99	99	99	99	99
Total	100	100	100	100	100
Profit & loss ratios (%)					
Gross margin	100	100	100	100	100
EBITDA margin	N/A	N/A	N/A	N/A	N/A
Pre-tax margin	N/A	N/A	N/A	N/A	N/A
Net margin	N/A	N/A	N/A	N/A	N/A
Effective tax rate (%)	1	0	0	0	0
Balance sheet ratios					
Current ratio (x)	5	9	3	0	0
Trade receivables turnover days	N/A	N/A	N/A	N/A	N/A
Trade payables turnover days	N/A	N/A	N/A	N/A	N/A
Net debt to total equity ratio (%)	N/A	N/A	N/A	N/A	N/A
Total debt to asset ratio (%)	123	182	298	352	372
Returns (%)					
ROE	N/A	N/A	N/A	N/A	N/A
ROA	N/A	N/A	N/A	N/A	N/A
Per share data					
EPS (RMB)	(0.61)	(1.77)	(5.18)	(3.40)	(3.75)
DPS (RMB)	0.00	0.00	0.00	0.00	0.00
BVPS (RMB)	N/A	N/A	N/A	2.93	8.47

Source: Company data, CMBIS estimates

Valuation

Ascentage Pharma is a pre-revenue biotech company and relies on the successful commercialization of its pipeline drugs in the future. Therefore, we use DCF method to value the Company and we derive TP of HK$45.80 based on 8-year risk-adjusted DCF model (WACC: 10.98%, terminal growth rate: 3.0%). We employed a WACC of 10.98%, which is higher than that of HK listed peers due to higher risk, and terminal growth rate of 3%, which is also higher than that of Chinese pharma companies.

Figure 65: Base case valuation on risk-adjusted DCF valuation

DCF Valuation (in RMB mn)		2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E
EBIT		(710)	(783)	(821)	(236)	611	1,170	1,714	2,041
Tax rate		0%	0%	0%	0%	0%	15%	15%	15%
EBIT*(1-tax rate)		(710)	(783)	(821)	(236)	611	994	1,457	1,735
+ D&A		32	81	138	134	127	122	117	113
- Change in working capital		0	0	(18)	(230)	(320)	(194)	(166)	(151)
- Capx		(355)	(455)	(105)	(85)	(85)	(85)	(85)	(85)
FCFF		**(1,033)**	**(1,157)**	**(806)**	**(417)**	**333**	**838**	**1,323**	**1,611**
Terminal value									**20,800**
FCF + Terminal value		(1,033)	(1,157)	(806)	(417)	333	838	1,323	22,411
Discount factor		1.0	0.9	0.8	0.7	0.7	0.6	0.5	0.5
PV of FCF		**(1,033)**	**(1,042)**	**(654)**	**(305)**	**220**	**497**	**708**	**10,808**
Present value of enterprise (RMB mn)	9,199								
Net debt (RMB mn)	612								
Equity value (RMB mn)	8,587								
Equity value (HK$ mn)	9,573								
No. of shares outstanding	208,901,727								
DCF per share (HK$)	**45.8**								
Terminal growth rate	**3.0%**								
WACC	**10.98%**								
Cost of Equity	13.5%								
Cost of Debt	6.0%								
Equity Beta	1.0								
Risk Free Rate	3.0%								
Market Risk Premium	10.5%								
Target Debt to Asset ratio	30.0%								
Effective Corporate Tax Rate	15.0%								

Source: CMBIS estimates

Figure 66: Sensitivity analysis

		WACC				
		9.98%	**10.48%**	**10.98%**	**11.48%**	**11.98%**
Terminal growth rate	**2.0%**	49.3	44.0	39.4	35.3	31.7
	2.5%	53.3	47.5	42.4	37.9	34.0
	3.0%	58.0	51.5	**45.8**	40.9	36.5
	3.5%	63.4	56.0	49.7	44.2	39.4
	4.0%	69.6	61.2	54.1	47.9	42.6

Source: CMBIS estimates

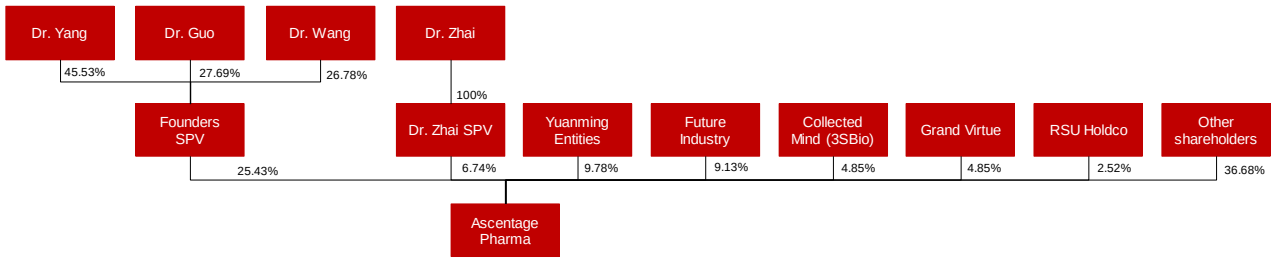
Appendix: Company Profile

Figure 67: Key board members and management of Ascentage Pharma

Management	Age	Position	Date of joining	Experiences
Dr. Yang Dajun	56	Chairman, Executive Director and CEO	2009	Dr. Yang was an associate professor and senior investigator of the Lombardi Cancer Center at the medical center of Georgetown University; Co-founded Ascenta Therapeutics Inc., which was dissolved in 2017
Dr. Wang Shaomeng	55	Co-founder, Non-executive Director and Chairman of scientific advisory board	2009	Dr. Wang was an associate professor in Georgetown University Medical Center and now serves as a tenured faculty of the University of Michigan
Dr. Tian Yuan	65	Non-executive Director	2016	Dr. Tian is the founding partner of YuanMing Capital
Mr. Zhao Qun	44	Non-executive Director	2016	Dr. Zhao is a partner of SIP Oriza Seed Fund Management Co., Ltd.
Dr. Lu Simon Dazhong	50	Non-executive Director	2016	Dr. Lu is a managing director and partner of SDIC Fund Management Company Ltd.
Mr. Liu Qian	47	Non-executive Director	2018	Mr. Liu is the chief investment officer of Prudence Investment Management (Hong Kong) Limited
Dr. Guo Edward Ming	62	Co-founder, Chief operating officer	2009	Dr. Guo served in various technical and managerial roles at Pfizer Inc. and worked at Ascenta Therapeutics, Inc. as vice president of pharmaceutical sciences and manufacturing
Dr. Zhai Yifan	57	Chief medical officer	2013	Dr. Zhai is the spouse of Dr. Yang. Dr. Zhai served as scientists at Human Genome Sciences Inc., (now GSK), Bayer Pharmaceuticals Corp., Exelixis Inc., HealthQuest Inc., Oncomax Acquisition Corp., etc. She joined Healthquest Pharma as President and CEO in 2012.
Mr. Raymond Jeffrey Kmetz	61	Chief business officer	2019	Mr. Kmetz was associate director of oncology marketing at Berlex Laboratories, director of global strategic marketing and hematlogy franchise head of Bayer Healthcare, director of marketing at Alexion Pharmaceuticals, senior director in marketing and head of commercial development at Pharmacyclics LLC.
Mr. Thomas Joseph Knapp	67	Senior Vice President, General counsel	2018	Mr. Knapp was executive vice president, chief legal officer and corporate secretary of Sucampo Pharmaceuticals, Inc., interim general consel and corporate secretary at Galena Biopharma, Inc., consultant at SELLAS Life Sciences Group, Inc.

Source: Company data, CMBIS

Figure 68: Shareholder structure as of 13 Oct 2019



Source: Company data, CMBIS

Figure 69: Number of employees by function, as of 30 Jun 2019

Function	Number of Employees	% of total
Research and development	293	81.8%
Administrative	65	18.2%
Total	**358**	**100.0%**

Source: Company data, CMBIS

Figure 70: Awards

Award date	Name of award/recognition	Awarding authority
2017.02	2016 Bio-Industry Innovation Breakthrough Enterprise (2016 生物产业创新突破企业)	Enmore Healthcare (易贸医疗) and 17 Talk (易企说)
2017.04	Biomedical Year 2016 Best Investment Case (2016 生物医药年度最佳投资案例)	Haoyue Capital (浩悦资本)
2017.05	Jiangsu Province Innovation Team Award (江苏省创新争先团队奖)	• Jiangsu Provincial Department of Human Resources and Social Security (江苏省人力资源和社会保障厅) • Jiangsu Science and Technology Association (江苏省科学技术协会) • Jiangsu Science and Technology Department (江苏省科技厅) • State-owned Assets Supervision and Administration Commission of Jiangsu Province (江苏省国有资产监督管理委员会)
2017.11	2017 R&D Achievement Award (2017 年度研发成就奖)	The BayHelix Group (百花协会)
2017.11	2017 Deloitte China Medicine Health Star of Tomorrow (2017 德勤中国医药健康明日之星)	Deloitte China (德勤中国)
2018.01	2017 Life Sciences “Most innovative” Enterprise (2017 年度生命科学领域最具创新力企业)	biodiscover.com (生物探索)
2018.06	Suzhou “Major Innovation Team in 2018” (苏州 2018 重大创新团队)	Suzhou Government (苏州市政府)
2018.06	Unicorn Breeding Company (独角兽培育企业)	Suzhou Industrial Park District Government (苏州市工业园区区政府)

Source: Company data, CMBIS

Disclosures & Disclaimers

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NOT RATED	: Stock is not rated by CMBIS
OUTPERFORM	: Industry expected to outperform the relevant broad market benchmark over next 12 months
MARKET-PERFORM	: Industry expected to perform in-line with the relevant broad market benchmark over next 12 months
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