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OVERVIEW

We are an innovative, commercial-stage biopharmaceutical company based in China aiming to become a global leader in the discovery, development and commercialization of targeted therapies and immunotherapies for the treatment of cancer and immunological diseases. Our mission is to leverage the highly specialized expertise of our fully integrated drug discovery division, known as our Innovation Platform, to develop and expand our drug candidate portfolio for the global market while also building on our first-mover advantage in the development and launch of novel cancer drugs in China. We also operate well-established and profitable Prescription Drug and Consumer Health businesses in China, known together as our Commercial Platform. Our commercial footprint in China gives us extensive infrastructure and know-how to market pharmaceutical products in the complex healthcare system in China.

Innovation Platform

Focusing on both the global innovation and China oncology markets, our Innovation Platform is led by a team of over 420 scientists and staff. This team has an established track record of highly productive drug development over the last 17 years. Currently, we have eight self-discovered drug candidates in clinical trials, five of which are either in or about to start global clinical development. We plan to further establish and leverage this platform to produce and commercialize a stream of novel drug candidates with global potential.

Our Innovation Platform achieved an important milestone in its China oncology drug development with the commercial launch in late November 2018 of our self-discovered and developed drug fruquintinib, sold under the brand name Elunate, for the treatment of metastatic colorectal cancer. Fruquintinib is the first ever China-discovered and developed targeted oncology therapy to have received unconditional approval and be subsequently commercialized.

Our core research and development philosophy is to take a holistic approach to the treatment of cancer and immunological diseases, through multiple modalities and mechanisms, including targeted therapies, immunotherapies and other pathways. Our initial focus has been to design uniquely selective small molecule tyrosine kinase inhibitors deliberately engineered to improve drug efficacy and reduce known off-target toxicities. We recognized early on in our research and development that high selectivity is crucial in effectively treating patients with monotherapies as well as with combination therapies which we believe are needed to significantly improve treatment outcomes. We are designing these highly selective tyrosine kinase inhibitors against various targets with applications across multiple cancer and immunological indications.

We believe that our long track record of research and development in China will enable us to take advantage of the significant market opportunities in that country, which have been buoyed by the PRC government's recent policy reforms aimed at accelerating domestic innovative drug development and the expansion of access to world-class medicines for the people of China. The PRC government has enacted a series of policies to shorten the review and approval time for innovative drugs that address urgent medical needs and support innovative drug development by both domestic and multinational companies. In addition, national-, city- and provincial-level medical insurance reimbursement has been expanding rapidly, thereby reducing out-of-pocket treatment cost for patients. With these reforms, more advanced cancer treatments are being approved at an expedited pace and more patients will be able to afford such treatments. As a result, the China oncology market is expected to grow at a CAGR of 15.0% between 2018 and 2023 and 11.1% between 2023 and 2030.

Global Clinical Drug Development

We believe our drug candidates in global development, savolitinib, fruquintinib, surufatinib (previously named sulfatinib), HMPL-523 and HMPL-689, are uniquely selective and/or differentiated and have the potential to be global first-in-class and/or best-in-class therapies.

The following table summarizes the status of our global clinical drug portfolio's development as of the Latest Practicable Date.

Our Global Clinical Development Pipeline

Program	Treatment	Indication	Target patient	Study name	Sites	Dose finding / safety run-in	Proof-of-concept	Registration
Savolitinib MET	**Savolitinib** + Tagrisso	NSCLC	2L/3L EGFRm; Tagrisso ref.; MET+	SAVANNAH	Global			†
	Savolitinib + Tagrisso	NSCLC	2L EGFRm; EGFR TKI ref.; MET+	TATTON	Global			
	Savolitinib + Imfinzi (PD-L1)	Papillary RCC	All	CALYPSO	UK/Spain			
	Savolitinib + Imfinzi (PD-L1)	Clear cell RCC	VEGFR TKI refractory	CALYPSO	UK/Spain			
	Savolitinib	Gastric cancer	MET+	VIKTORY	South Korea			
	Savolitinib + Taxotere	Gastric cancer	MET+	VIKTORY	South Korea	*		
	Savolitinib + Taxotere	Gastric cancer	MET over expression	VIKTORY	South Korea	*		
	Savolitinib	Prostate cancer	MET+	CCGT 1234B	Canada			
Fruquintinib VEGFR 1/2/3	**Fruquintinib**	Colorectal cancer	3L/4L; Stivarga/Lonsurf ref./intol.		US			
	Fruquintinib + Tyvyt (PD-1)	Solid tumors	1L		US	**		
Surufatinib VEGFR 1/2/3; FGFR1; CSF-1R	**Surufatinib**	Pancreatic NET	2L; Sutent/Afinitor refractory		US			
	Surufatinib + Tuoyi (PD-1)	Solid tumors				**		
HMPL-523 Syk	**HMPL-523**	Indolent NHL			Australia			
	HMPL-523	Indolent NHL			US	**		
HMPL-689 PI3Kδ	**HMPL-689**	Healthy volunteers			Australia			
	HMPL-689	Indolent NHL			US	**		

Notes: Dose finding/safety run-in = Phase I/Ia studies; Proof-of-concept = Phase Ib, Ib/II or II studies; Registration = Phase II, II/III or III registration intent studies; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; NHL = Non-Hodgkin's Lymphoma; * Further patient enrolment directed to savolitinib monotherapy arm due to the high efficacy observed; ** In planning; and † Phase II registration intent study subject to regulatory discussions.

Over the next several years, we intend to accelerate development of our global clinical drug portfolio through existing partnerships such as that with AstraZeneca, as well as increasingly through our own clinical and regulatory operations in the United States and Europe.

- *Savolitinib – potential first-in-class selective MET inhibitor in late-stage clinical development as a monotherapy and in combination therapies in partnership with AstraZeneca*

Savolitinib is a potent and selective inhibitor of the mesenchymal epithelial transition factor, or MET, receptor tyrosine kinase, an enzyme which has been shown to function abnormally in many types of solid tumors. We designed savolitinib through chemical structure modification to specifically address kidney toxicity, the primary issue that halted development of several other selective MET inhibitors. In clinical trials to date in over 900 patients globally, savolitinib has shown promising signs of clinical efficacy in patients with MET gene alterations in lung cancer, kidney cancer, gastric cancer and prostate cancer with an acceptable safety profile.

We are currently testing savolitinib in global partnership with AstraZeneca, both as a monotherapy and in combination with immunotherapy, targeted therapy and chemotherapy drugs. Specifically, we are currently progressing a global Phase II study, known as the SAVANNAH study, on savolitinib in combination with Tagrisso for treating epidermal growth factor receptor mutation, or EGFRm, non-small cell lung cancer with MET amplification, or MET+. We expect the primary data from the SAVANNAH study to become available in 2021 and are hopeful that such data will be enough to support regulatory approval for this combination therapy. We also anticipate announcing plans for further Phase II/III studies on savolitinib in lung cancer during 2019. Furthermore, proof-of-concept studies of savolitinib in kidney cancer (as a monotherapy as well as in combinations with programmed death-ligand 1, or PD-L1, inhibitors) and gastric cancer (as a monotherapy as well as in combinations with chemotherapy) are expected to be submitted for publication or presentation at scientific conferences in 2019 and, if the results of such studies are positive, they may lead to subsequent clinical development.

- *Fruquintinib – potential best-in-class selective VEGFR 1, 2 and 3 inhibitor*

Fruquintinib is a highly selective and potent oral inhibitor of three vascular endothelial growth factor receptors, known as VEGFR 1, 2 and 3. We believe that fruquintinib has the potential to become the global best-in-class selective small molecule VEGFR 1, 2 and 3 inhibitor for many types of solid tumors, and we are currently studying fruquintinib in colorectal cancer, gastric cancer and lung cancer. Based on pre-clinical and clinical data to date, fruquintinib's kinase selectivity has been shown to reduce off-target toxicity. This allows for drug exposure that is able to fully inhibit VEGFR, a receptor tyrosine kinase which contributes to angiogenesis, the buildup of new blood vessels around a tumor, thereby contributing to the growth of tumors. Such selectivity

also facilitates use in potential combinations with immunotherapy, targeted therapy and chemotherapy drugs. Fruquintinib has been approved for the treatment of third-line metastatic colorectal cancer in China.

Building on the data collected from our successful Phase III trial in China, known as the FRESCO study, which supported fruquintinib's approval in China, and the ongoing Phase Ib dose finding study of fruquintinib in the United States, we are planning to initiate a registration study of fruquintinib in the United States and Europe as a third/fourth-line treatment for metastatic colorectal cancer patients. We also intend to conduct global combination studies of fruquintinib with Tyvyt, a programmed cell death protein 1, or PD-1, monoclonal antibody developed by Innovent Biologics (Suzhou) Co. Ltd., or Innovent, and recently approved for clinical development.

- *Surufatinib – unique angio-immuno kinase inhibitor*

Surufatinib is an oral small molecule inhibitor targeting VEGFR, fibroblast growth factor receptor 1, or FGFR 1, and colony stimulating factor-1 receptor, or CSF-1R, kinases that could simultaneously block tumor angiogenesis and immune evasion. This unique angio-immuno kinase profile seems to support surufatinib as an attractive candidate for exploration of possible combinations with checkpoint inhibitors against various cancers. Surufatinib is the first oncology candidate that we have taken through proof-of-concept in China and expanded globally ourselves.

We currently have various clinical trials of surufatinib ongoing as a single agent in patients with neuroendocrine tumors and biliary tract cancer and in combination with checkpoint inhibitors. The encouraging data from our Phase II study of surufatinib in pancreatic neuroendocrine tumor patients in China and the ongoing Phase Ib study in the United States of surufatinib in pancreatic neuroendocrine tumor patients is guiding our planning for a registration study in the United States and Europe in patients who have progressed on Sutent or Afinitor. Similar to fruquintinib, we intend to conduct a combination study of surufatinib with Tuoyi, a PD-1 monoclonal antibody being developed by Shanghai Junshi Biosciences Co. Ltd., or Junshi, in both China, where we are currently enrolling a Phase I study, and the United States, where a Phase I study is in planning. We believe surufatinib has potential in a number of other tumor types such as breast cancer with FGFR 1 activation.

- *HMPL-523 – potential first-in-class selective Syk inhibitor for oncology*

HMPL-523 is a highly selective oral inhibitor targeting the spleen tyrosine kinase, or Syk, for the treatment of hematological cancers and certain chronic immune diseases, such as rheumatoid arthritis. HMPL-523 has a unique pharmacokinetic profile which provides for higher drug exposure in the tissue where rheumatoid arthritis and hematological cancer occur, rather than on a whole blood level.

We currently have various clinical trials of HMPL-523 ongoing. Based on emerging Phase I/Ib proof-of-concept clinical data in China and Australia on HMPL-523, we plan to initiate development in the United States and Europe in 2019, focusing on multiple sub-categories of indolent non-Hodgkin's lymphoma.

- *HMPL-689 – potential best-in-class selective PI3Kδ inhibitor*

HMPL-689 is a novel, highly selective and potent small molecule inhibitor targeting the isoform PI3Kδ. We have designed HMPL-689 with superior PI3Kδ isoform selectivity, in particular to not inhibit other kinases so as to minimize the risk of serious infection caused by immune suppression. Its selectivity also makes it well suited for use in potential combination therapies. HMPL-689's strong potency, particularly at the whole blood level, also allows for reduced daily doses to minimize compound related toxicity.

We have early stage clinical trials of HMPL-689 ongoing. Based on emerging Phase I/Ib proof-of-concept clinical data in China and Australia on HMPL-689, we plan to initiate development of this drug candidate in the United States and Europe in 2019, focusing on multiple sub-categories of indolent non-Hodgkin's lymphoma.

In line with our strategy to expand clinical activities globally, we commenced operation of our U.S. subsidiary, Hutchison MediPharma (US) Inc., at our new office in New Jersey in early 2018. While we have been involved in clinical and non-clinical development in North America and Europe for over a decade, the activities conducted by this new U.S. office will support our growth strategy outside of China and significantly broaden and scale our non-Asian clinical development and international operations. We also intend to significantly expand our U.S. clinical team to support our increasing clinical activities in the United States, Europe and other parts of the world.

China Oncology Drug Development

The Chinese oncology market, which comprises approximately a quarter of the global oncology patient population, represents a substantial and fast-growing market opportunity. Strong market growth is expected to be driven by gradually improving affordability for world-class novel oncology drugs and the PRC government's increasing emphasis on innovation combined with rapidly reforming regulatory infrastructure. We believe our established presence in China, combined with our ability to deliver global-quality innovation, positions us well to address the major unmet medical needs in the China oncology market.

With a deep and risk-balanced drug development pipeline focusing on both validated targets and novel targets, we currently have eight drug candidates in clinical development covering a dozen cancer targets, including savolitinib and surufatinib which are in late-stage development in China. Our other drug candidates are also uniquely selective and/or differentiated and have the potential to be first-in-class and/or best-in-class oncology therapies in China.

As the first mover to bring a self-discovered and developed innovative targeted cancer treatment to market in China with the launch of Elunate, we believe we are well positioned to take advantage of this significant market opportunity.

Driven by our strong expertise in molecular-targeted drugs and commitment to combination therapies of our tyrosine kinase inhibitors with various immunotherapies, we recently entered into multiple global and China-only collaboration agreements with Innovent, Junshi, Genor Biopharma Co. Ltd., or Genor, and Taizhou Hanzhong Pharmaceuticals, Inc., or Hanzhong, to evaluate the safety, tolerability and efficacy of fruquintinib and surufatinib in combination with various PD-1 inhibitors, which are important additions to our ongoing studies combining savolitinib with AstraZeneca's PD-L1 inhibitor Imfinzi.

The following table summarizes the status of our China clinical programs as of the Latest Practicable Date.

Our China Clinical Development Pipeline

Program	Treatment	Indication	Target patient	Study name	Sites	Dose finding / safety run-in	Proof-of-concept	Registration
Savolitinib MET	**Savolitinib**	NSCLC	MET Exon 14 deletion		China			
	Savolitinib + Iressa	NSCLC	2L EGFRm; Iressa ref.; MET+		China			
	Savolitinib	Gastric cancer	MET+		China			
Fruquintinib VEGFR 1/2/3	**Fruquintinib**	Colorectal cancer	≥3L; chemotherapy refractory	FRESCO	China			
	Fruquintinib + Taxol	Gastric cancer	2L	FRUTIGA	China			
	Fruquintinib	NSCLC	3L; chemotherapy refractory	FALUCA	China			
	Fruquintinib + Iressa	NSCLC	1L EGFRm		China			
	Fruquintinib + genolimzumab (PD-1)	Solid tumors			China	*		
	Fruquintinib + Tyvyt (PD-1)	Solid tumors			China	*		
Surufatinib VEGFR 1/2/3; FGFR1; CSF-1R	**Surufatinib**	Pancreatic NET	All	SANET-p	China			
	Surufatinib	Non-Pancreatic NET	All	SANET-ep	China			
	Surufatinib	Biliary Tract cancer	2L; chemotherapy refractory		China			
	Surufatinib + Tuoyi (PD-1)	Solid tumors			China			
	Surufatinib + HX008 (PD-1)	Solid tumors			China	*		
HMPL-523 Syk	**HMPL-523** + azacitidine	Acute Myeloid Leuke.	1L		China			
	HMPL-523	B-cell malignancies	All		China			
	HMPL-523	ITP	All		China	*		
HMPL-689 PI3Kδ	**HMPL-689**	Indolent NHL			China			
Epitinib EGFR	**Epitinib**	NSCLC	EGFRm with brain metastasis		China			
	Epitinib	Glioblastoma	EGFR gene amplified		China			
Theliatinib EGFR wt	**Theliatinib**	Esophageal cancer	EGFR over expression		China	**		
HMPL-453 FGFR 1/2/3	**HMPL-453**	Solid tumors			China			

Notes: Dose finding/safety run-in = Phase I/Ia studies; Proof-of-concept = Phase Ib, Ib/II or II studies; Registration = Phase II, II/III or III registration intent studies; acute myeloid leuke. = acute myeloid leukemia; NSCLC = non-small cell lung cancer; NET = neuroendocrine tumors; NHL = non-Hodgkin's lymphoma; ref. or refractory = resistant to prior treatment; MET+ = MET-amplification; * in planning; and ** discontinued.

- *Savolitinib – potential first-in-class selective MET inhibitor in China*

We are currently conducting a Phase II registration study in China of savolitinib in non-small cell lung cancer patients with MET Exon 14 mutation/deletion who have failed prior systemic therapy, or are unwilling or unable to receive chemotherapy, which is expected to complete enrollment in late 2019. If the results from this study are positive, we hope this would be sufficient to support an NDA submission in China. We believe MET Exon 14 mutation/deletion non-small cell lung cancer in China has the potential to be the first savolitinib indication approved.

- *Fruquintinib – commercially launched in colorectal cancer in November 2018*

In November 2018, we commenced commercial sales of Elunate, the brand name of fruquintinib capsules, targeting the more than 55,000 metastatic colorectal cancer third-line patients in China each year as of 2018. In addition to this commercial launch, we have made progress with fruquintinib in partnership with Eli Lilly in various other cancer indications, including the initiation of the FRUTIGA study in China, a pivotal Phase III study to evaluate the efficacy and safety of fruquintinib in combination with Taxol compared with Taxol monotherapy for second-line treatment of advanced gastric cancer in patients who had failed first-line chemotherapy. We have also completed enrollment of a Phase II study in China of fruquintinib in combination with Iressa in first-line EGFR activating mutation non-small cell lung cancer, from which preliminary data has shown encouraging efficacy and safety profile and further development is being considered. Moreover, in addition to our global collaboration to evaluate the combination of fruquintinib with Innovent's PD-1 monoclonal antibody Tyvyt, we have entered into a collaboration in China to evaluate the combination of fruquintinib with genolimzumab, a PD-1 monoclonal antibody being developed by Genor.

Fruquintinib is currently our most advanced asset in China, and as a result we place high importance on gaining decision-making responsibilities in the life cycle development of fruquintinib. We believe that fruquintinib is a best-in-class VEGFR 1, 2 and 3 inhibitor and could be considered for development in China in many solid tumor indications in which VEGFR inhibitors have been approved globally. To this end, we recently amended our collaboration agreement with Eli Lilly with respect to fruquintinib, which gives us, among others, all planning, execution and decision-making responsibilities for life cycle indication development of fruquintinib in China. For further details, see *"– Overview of Our Collaborations – Eli Lilly Agreement*."

- *Surufatinib – potential first-in-class inhibitor for all neuroendocrine tumors*

Our two most advanced Phase III studies of surufatinib in neuroendocrine tumor patients in China are set for interim analyses in mid- and late-2019. Subject to clinical outcome, we are hopeful that these interim analyses could support NDA submission during 2020. Based on encouraging Phase Ib data, a third registration study on surufatinib, a Phase IIb/III study in biliary tract cancer, has also recently begun enrollment in China. In addition to our global collaboration to evaluate the combination of surufatinib with Junshi's PD-1 monoclonal antibody Tuoyi, we have entered into a collaboration in China to evaluate the combination of surufatinib with HX008, a PD-1 monoclonal antibody being developed by Hanzhong.

- *HMPL-523 – highly selective Syk inhibitor with potential in hematological cancer and immunological diseases*

Data from an extensive Phase I/Ib dose escalation and expansion study (covering more than 110 patients) on HMPL-523 has encouraged us to initiate exploratory studies in China on multiple indolent non-Hodgkin's lymphoma sub-categories, including chronic lymphocytic leukemia/small lymphocytic lymphoma, follicular lymphoma, marginal zone lymphoma, Waldenstrom's macroglobulinemia and mantle cell lymphoma. We plan to initiate registration studies in China late in 2019 in several of these indolent non-Hodgkin's lymphoma sub-categories.

Furthermore, we have initiated a Phase I study of HMPL-523, in combination with Vidaza, an approved hypomethylating agent, in elderly patients with acute myeloid leukemia in China. We are also considering immunology applications for HMPL-523 including for the treatment of immune thrombocytopenia in China.

- *HMPL-689 – highly selective PI3Kδ inhibitor with potential in hematological cancer*

Our Phase I dose escalation study on HMPL-689 in China is close to completion and expected to proceed into Phase Ib proof-of-concept expansion studies in 2019 in multiple sub-categories of indolent non-Hodgkin's lymphoma.

- *Epitinib, theliatinib and HMPL-453 – clinical-stage drug candidates for which we aim to establish proof-of-concept by 2021*

We have initiated a Phase Ib/II trial in China to study epitinib, our unique EGFR inhibitor that has demonstrated the ability to penetrate the blood-brain barrier, for the treatment of glioblastoma, a primary brain cancer that harbors high levels of EGFR gene amplification. We aim to establish proof-of-concept for epitinib as well as theliatinib, targeting EGFR wild-type, and HMPL-453, targeting FGFR 1, 2 and 3, by 2021.

Global-facing Discovery Engine

Leveraging the extensive and well-established drug discovery resources of our Innovation Platform, we are invested in continuing to create differentiated novel oncology and immunology treatments. These novel drug candidates reflect our core research and development philosophy in treating cancer and immunological diseases through multiple modalities and mechanisms. These include furthering our other pre-clinical programs for therapies addressing aberrant genetic drivers, inactivated T-cell response and insufficient T-cell response.

Commercial Platform

In addition to our Innovation Platform, we have established a profitable Commercial Platform in China. Many of the drugs sold by our Commercial Platform are household-name brands and/or have significant market share.

Our Commercial Platform has grown to a significant scale, with extensive manufacturing, marketing and distribution capabilities for prescription drugs and consumer health products. Our Commercial Platform has provided us the infrastructure and know-how in operating and marketing pharmaceutical products in the complex and evolving healthcare system in China. Additionally, cash flow from our Commercial Platform has provided an important source of funding for our Innovation Platform since our inception.

Our Prescription Drugs business joint ventures with Shanghai Pharma and Sinopharm operate a network of approximately 2,500 prescription drugs sales representatives covering over 24,900 hospitals in over 320 cities and towns in China as of December 31, 2018. Leveraging this extensive network, these joint ventures, Shanghai Hutchison Pharmaceuticals and Hutchison Sinopharm, own or have distribution rights to a number of important prescription drugs in China, including She Xiang Bao Xin Pill, a nationally known oral vasodilator and pro-angiogenesis drug, Seroquel (quetiapine tablets), a leading anti-psychotic therapy, and Concor (Bisoprolol tablets), one of the leading cardiac beta-1 receptor blockers in China.

Over the next several years, we will combine the marketing and sales experience and hospital access gained from our Commercial Platform's operations with our growing dedicated oncology-focused sales team to support the launch of products from our Innovation Platform if and when they are approved for use in China. Concurrent with this commercial team expansion, we also plan to increase our manufacturing capacity with a fully integrated active pharmaceutical ingredients or formulation manufacturing facility that is capable of supporting the manufacturing of our current and future commercial-stage oncology drugs.

OUR STRENGTHS

We believe the following strengths have contributed to our success and differentiate us from our competitors:

Fully integrated biopharmaceutical company with an established risk-balanced research and development approach to discovering and developing next-generation therapies for the treatment of cancer and immunological diseases.

We are a fully integrated biopharmaceutical company with capabilities spanning drug discovery, development, registration and commercialization. Our company has over 17 years of experience in drug discovery and development. Each of our eight clinical-stage drug candidates was discovered and developed in-house by our research and development team. Our dedicated research and development team comprises over 420 scientists and staff with offices in Shanghai, Suzhou and New Jersey. This represents a fully integrated drug discovery and development organization covering chemistry, biology, pharmacology, toxicology, chemistry and manufacturing controls, clinical and regulatory and other functions, all of which work seamlessly together. With the NMPA's approval of fruquintinib, sold under the brand name Elunate, in 2018, we became the first Chinese biopharmaceutical company to bring a targeted oncology therapy from discovery through unconditional approval and commercialization in China.

Leveraging our fully integrated platform, our research and development strategy has focused on developing drug candidates to treat significant unmet medical needs such as lung cancer, colorectal cancer and gastric cancer. We balance risk in our research and development activities by focusing on both novel targets, including MET and Syk, and validated targets, including VEGFR and PI3Kδ. A primary objective of our research efforts has been to develop next generation tyrosine kinase inhibitors and immunotherapies, which has allowed us to develop drug candidates with:

- unique selectivity to limit target-based toxicity,
- high potency to optimize the dose selection with the objective to lower the required dose and thereby limit compound-based toxicity,
- chemical structures deliberately engineered to improve drug exposure in the targeted tissue, and
- ability to be combined with other therapeutic agents, including tyrosine kinase inhibitors, immunotherapies and chemotherapies.

This approach has led to favorable clinical outcomes in clinical trials to date. As a result, we believe our research and development team has the potential to discover candidates that are global first-in-class or best-in-class therapies in their respective categories and are well suited for combination therapies.

Our Innovation Platform is complemented by our sales and marketing infrastructure in China as well as our in-house manufacturing capabilities, including our new GMP-certified formulation facility in Suzhou which produces commercial supplies of fruquintinib.

Robust pipeline of drug candidates in global development with high-potential for use in innovative combination therapies.

We believe we have one of the broadest global clinical pipelines among China-based oncology and immunology focused biotechnology companies, with five drug candidates in clinical development. A key benefit of our research and development team's focus on developing drugs with high selectivity and superior safety profile is that they have the potential to be effectively paired with other oncology and immunology therapies at their maximum dosages without intolerable side effects. Cancer is a resilient and extremely heterogeneous disease, and a major area of focus in the oncology field worldwide in recent years is the use of two or more treatments concurrently. Such combination therapies can be more efficacious than a single treatment as they can treat the cancer from multiple angles at the same time and potentially decrease the likelihood that the cancer will develop a resistance to the treatment which can be a significant problem for monotherapies.

We have been conducting clinical studies of a number of our drug candidates in combination therapies. For example, preliminary data from Phase II clinical trials of fruquintinib in combination with Iressa, AstraZeneca's approved EGFR inhibitor, have shown promising efficacy and an acceptable safety profile when used for the treatment of lung cancer. We have also entered into collaboration agreements with Innovent, Junshi, Genor and Hanzhong to evaluate the safety, tolerability and efficacy of fruquintinib and surufatinib in combination with various PD-1 inhibitors. In addition, we are currently testing savolitinib in combination with AstraZeneca's Tagrisso and Imfinzi as well as Taxotere in global studies. We believe our broad pipeline of highly selective drug candidates presents opportunities for further studies of combination therapies in a variety of indications.

First mover in China to bring a self-discovered innovative targeted cancer drug to market and well positioned to capture lucrative growth opportunities.

Established in 2000, we strategically chose to locate our operations in China to address the unmet medical needs of this very large and underserved market. In our view, the China oncology market, which comprises approximately a quarter of the global oncology patient population, represents a substantial and fast-growing market opportunity.

Unlike the global oncology market, China's oncology market is still dominated by traditional chemotherapies and, until recently, many advanced molecularly targeted therapies were not yet broadly available in China. As a result, cancer patients in China have had significantly lower five-year overall survival rate as compared to patients in the United States where more advanced therapies have been available for longer. Recognizing this significant medical need, the PRC government in recent years has placed an increasing emphasis on innovation and has enacted a number of initiatives to shorten the review and approval time for innovative drugs that address urgent unmet medical needs.

In addition, both the increase in disposable income and the expansion of medical reimbursement coverage are expected to make oncology treatments more affordable in China, thereby increasing the market for oncology drugs. The PRC government has announced a plan to give every person in China access to basic healthcare by 2020. To this end, the PRC government has expanded its National Medical Insurance Program. According to the PRC National Bureau of Statistics, as of December 31, 2018, approximately 770 million people in China were enrolled in the National Medical Insurance Program for urban employees and residents, compared to only 223 million people as of December 31, 2007. Moreover, the PRC government has recently taken steps to expand the coverage of the National Medical Insurance Program to include novel oncology drugs, including adding 32 novel oncology drugs to the National Reimbursement Drug List in 2017 and 2018. While manufacturers and the PRC government commonly negotiate price discounts in return for inclusion in the National Reimbursement Drug List, inclusion typically results in materially broader patient access and consequently higher sales volume. A separate National Medical Insurance Program covers an additional approximately 430 million rural people in China; however, drug reimbursement under the rural scheme is limited.

In addition, the NMPA has reduced the time for new clinical trial application approvals to 60 working days, which is equivalent to the United States, and eliminated import taxes on imported oncology drugs. The NMPA has also created a Priority Review system for drugs which meet urgent clinical need or rare diseases. Benefiting from this new system, fruquintinib was approved and launched under the Priority Review approval process. We intend to seek Priority Review for our other drug candidates, surufatinib, savolitinib, HMPL-523, HMPL-689, epitinib, theliatinib and HMPL-453 in due course. We currently have eight drug candidates in clinical development in China covering a dozen cancer targets, including savolitinib and surufatinib which are in late-stage development. Our other drug candidates are also uniquely selective and/or differentiated and have the potential to be first-in-class and/or best-in-class oncology therapies in China.

Proven and profitable Commercial Platform providing us with local experience and commercial capabilities in China.

Since 2001, we have developed a profitable Commercial Platform in China, which encompasses two businesses: our Prescription Drugs business and our Consumer Health business. Many of the drugs sold by our Commercial Platform are household-name brands and/or have significant or leading market shares. Our Commercial Platform serves a dual purpose as both an extensive prescription drug sales network with deep know-how in marketing and selling drugs within the complex medical system in China and an ongoing source of cash to fund our research and development activities.

Our Commercial Platform has advanced to a significant scale, with our Prescription Drugs business operating a network of approximately 2,500 prescription drugs sales representatives covering over 24,900 hospitals in over 320 cities and towns in China as of December 31, 2018. The infrastructure of our Prescription Drugs business, particularly in commercial operations management, manufacturing and distribution, and regulatory and reimbursement coverage, is well established in our therapeutic specialty areas of cardiovascular and central nervous system treatments. Our infrastructure in China gives us a nationwide platform through which we intend to bring our new oncology and immunology drug innovations to market if we receive regulatory approval for them.

Net income attributable to our company from the continuing operations of our Commercial Platform totaled over $150.0 million for the three years ended December 31, 2016, 2017 and 2018 in the aggregate. Since inception, we have received dividends from the Commercial Platform totaling approximately US$200.0 million which has been reinvested in our Innovation Platform.

Validated business development and execution capabilities with world-class partnerships and strategic collaborations, while retaining flexibility with respect to our unpartnered drug candidates.

We believe our business development and execution capabilities have been validated by our ability to secure and effectively manage world-class partnerships and strategic collaborations with leading global pharmaceutical companies. In particular, our partnerships with AstraZeneca with respect to savolitinib and Eli Lilly with respect to fruquintinib have brought us clinical and regulatory support, which have accelerated the development of our drug candidates and have been a source of funding. For instance, we believe that AstraZeneca's portfolio of proprietary targeted therapies is well suited to be used in combinations with savolitinib, and we are studying combinations of savolitinib with AstraZeneca's Iressa (EGFRm+), Tagrisso (T790M+) and Imfinzi (PD-L1). These combinations of multiple global first-in-class compounds are difficult to replicate, and we believe represent a significant opportunity for us and AstraZeneca. Additionally, in partnership with Eli Lilly in China, we have been able to accelerate and broaden the development of fruquintinib as well as leverage its global technical expertise in manufacturing and quality to help us establish fruquintinib's GMP-certified formulation facility in China.

Now as our drug candidate pipeline has further developed, we have taken steps to retain more flexibility with respect to our partnered drug candidates. Specifically, we recently amended our collaboration agreement with Eli Lilly with respect to fruquintinib, which gives us, among other things, all planning, execution and decision making responsibilities for life cycle indication development of fruquintinib in China. With the added flexibility in our Eli Lilly agreement, we recently entered into strategic global and China-only collaboration agreements on a cost-sharing basis with Innovent and Genor, respectively, to evaluate combination therapies of fruquintinib with their PD-1 inhibitors.

Experienced and stable management team with proven track record in drug discovery development and commercialization.

We are led by an experienced and stable management team of seasoned industry executives, including many with senior level experience at leading pharmaceutical companies such as Pfizer, Bristol-Myers Squibb, Sanofi, Eli Lilly, Roche and Gilead. Christian Hogg, our Chief Executive Officer, joined our company in 2000 as its first employee. Mr. Hogg has since led all aspects of the creation, implementation and management of our strategy, business and listings, including the establishment of both our Innovation and Commercial Platforms.

Led by our Chief Scientific Officer, Dr. Wei-guo Su, our research and development management team has extensive relevant experience. All team members have worked at multinational pharmaceutical and biotechnology companies and have participated in the discovery or development of global blockbuster drugs, including Alimta, Erbitux, Gemzar, Incivek, Sutent, Verzenio and Zithromax. Together, they have systematically built a productive research and development team of over 420 scientists and staff based in China, of which 232 had advanced technical degrees including 27 M.D.s and 53 doctorate degrees as of the Latest Practicable Date. This team has a proven track record in internal discovery, with our current eight self-discovered drug candidates having all advanced into the clinic in the past ten years.

OUR STRATEGY

Our vision is to become a leading global science-focused biopharmaceutical company. Key elements of our strategy are to:

Continue to leverage our expertise in discovering and designing highly selective small molecules while advancing our early-stage biologic drug candidates.

We believe our world-class drug discovery engine is our key competitive advantage. We aim to retain and grow our team of skilled scientists and provide them a stable and well-funded Innovation Platform, with a clear strategic focus and long-term purpose to deliver global first-in-class and best-in-class medicines to patients.

Our core research and development philosophy is to take a balanced, multipronged approach to the treatment of cancer and immunological diseases using targeted therapies, immunotherapies and other pathways. A primary objective of our drug discovery team's efforts has been, and will continue to be, to use our expertise in advanced medicinal chemistry to develop next-generation tyrosine kinase inhibitors that have both high selectivity and superior pharmacokinetic properties. We believe these characteristics are crucial to maximizing effectiveness, such as in inhibiting targeted genetic drivers of cancer cell proliferation and angiogenesis. Equally importantly, we will continue to design drug candidates with profiles that enable them to be used in innovative combinations with other selective inhibitors, chemotherapy agents and immunotherapies. Such combination therapies enable treatment of cancer via multiple pathways and modalities simultaneously, which has the potential to significantly improve treatment outcomes.

We further plan to enrich our global pipeline of self-discovered drug candidates by advancing a broad range of early-stage drug candidates, which include biologics addressing novel targets designed for use in combination with our small molecules as well as potentially a broad range of third-party therapies.

Advance the global clinical programs of our multiple potential first-in-class and best-in-class drug candidates.

Over the next several years, we plan to accelerate global development of our four unpartnered drug candidates: fruquintinib (ex-China), surufatinib, HMPL-523 and HMPL-689. We are planning to initiate global registration studies on fruquintinib in colorectal cancer and surufatinib in neuroendocrine tumors. We also plan to explore combination treatment opportunities for fruquintinib and surufatinib with developers of leading PD-1 monoclonal antibodies. In addition, we will look to advance both HMPL-523 and HMPL-689 into proof-of-concept studies in hematological cancer patients in the United States and Europe, both as monotherapies as well as potentially in innovative combinations with other tyrosine kinase inhibitors.

Together with AstraZeneca, we intend to advance global development of savolitinib. In particular, we are hopeful that data from our ongoing SAVANNAH study, if successful, will demonstrate the efficacy of savolitinib in combination with Tagrisso as a second/third-line treatment for EGFRm MET+ non-small cell lung cancer patients who have progressed on first/second-line Tagrisso. Furthermore, we anticipate announcing plans for further studies on savolitinib in lung cancer during 2019 as well as potential further development activities in both kidney cancer and gastric cancer in either monotherapy or combination regimens.

To broaden and scale our international operations and support our increasing clinical activities in the United States and Europe, we also plan to significantly expand our newly established U.S. clinical team.

Capitalize on regulatory reforms currently underway in China aimed at addressing existing major unmet medical needs and improving the health of its people.

The oncology drug market in China is poised to continue its rapid growth as a result of important government reforms that are underway. We intend to capitalize on this market opportunity by leveraging and expanding our large and well-established drug discovery platform in China.

Historically, cumbersome pharmaceutical registration regulations led to limited availability of advanced therapies in China and high prices for those that were available. This led to surgery and chemotherapy being the standard of care for most Chinese residents. During the past decade, the PRC government has endeavored to foster an innovative biopharmaceutical ecosystem, and in the last three years, the pace of reforms has accelerated with a clear focus on providing Chinese patients access to world-class oncology therapies through expanded insurance reimbursement and reduced time for clinical trial and drug approvals.

Having invested in drug innovation in China for over 17 years, beginning at a time when almost no other domestic companies were involved in innovative oncology research, we believe we are well positioned to capture this market opportunity. Supported by China's improving regulatory environment, we intend to rapidly advance our eight clinical-stage drug candidates to meet the country's significant unmet medical needs. For instance, we expect that our Phase II study of savolitinib in non-small cell lung cancer patients with MET Exon 14 mutation/deletion and our Phase III studies of surufatinib in neuroendocrine tumors would, if successful, be sufficient to support NDA submissions for these drugs in China potentially as soon as 2020. In addition, we aim to advance our other highly differentiated drug candidates, including surufatinib, HMPL-523 and HMPL-689, to build our leading position in the China oncology market.

We aspire to have the largest and most productive oncology drug discovery platform in China, with the goal of advancing novel drug candidates into development on a regular basis.

Leverage expertise and know-how of our commercial infrastructure in China to support commercialization of our innovative drug candidates.

While we will continue to focus the majority of our resources and available capital on our Innovation Platform, we are likely to continue to expand our Commercial Platform and its sales and marketing infrastructure which stood at over 3,500 total sales staff for prescription drugs and over-the-counter products at the end of 2018. We will particularly look to further build an oncology-focused sales team within our Prescription Drugs business to commercialize drugs developed by our Innovation Platform if they are approved for sale in China. We expect to significantly grow such a team over the next several years to capture the attractive market opportunity in China for targeted therapies that address significant unmet medical needs. Outside of China, we intend to commercialize our products, if approved, in the United States, Europe and other major markets on our own and/or through partnerships with leading biopharmaceutical companies.

Identify global business development and strategic acquisition opportunities to complement our internal research and development activities, while continuing to adapt existing collaborations as necessary.

We expect to further expand our portfolio of drug candidates in oncological and immunological therapeutic areas by pursuing business development opportunities with other biopharmaceutical companies both in China and globally. In addition, we may explore opportunities to acquire rights to complementary drug candidates and/or interests in other biopharmaceutical companies to supplement our in-house research and development capabilities and to enhance our current drug candidate pipeline.

We will also continue to work with our partners, AstraZeneca and Eli Lilly, to develop our partnered drug candidates savolitinib (global) and fruquintinib (in China) and seek to optimize the terms of these collaborations in the future to the extent possible in order to foster the further development of such drugs. For example, the amendments to our collaborations for savolitinib in 2016 and fruquintinib in 2018 have enabled acceleration of the clinical studies of such drugs and expanded our share of the economic value of these assets, in return for our increased investment in development.

OUR CLINICAL PIPELINE

The following table summarizes the status of our clinical programs as of the Latest Practicable Date:

Program	Treatment	Indication	Target Patient	Study Name	Sites	Dose Finding / Safety Run-in	Proof-of-concept	Registration
Savolitinib MET	**Savolitinib** + Tagrisso	NSCLC	2L/3L EGFRm; Tagrisso ref.; MET+	SAVANNAH	Global			†
	Savolitinib + Tagrisso	NSCLC	2L EGFRm; EGFR TKI ref.; MET+	TATTON	Global			
	Savolitinib + Imfinzi (PD-L1)	Papillary RCC	All	CALYPSO	UK/Spain			
	Savolitinib + Imfinzi (PD-L1)	Clear cell RCC	VEGFR TKI refractory	CALYPSO	UK/Spain			
	Savolitinib	Gastric cancer	MET+	VIKTORY	S. Korea			
	Savolitinib + Taxotere	Gastric cancer	MET+	VIKTORY	S. Korea	*		
	Savolitinib + Taxotere	Gastric cancer	MET over expression	VIKTORY	S. Korea	*		
	Savolitinib	Prostate cancer	MET+	CCGT 1234B	Canada			
	Savolitinib	NSCLC	MET Exon 14 deletion		China			
	Savolitinib + Iressa	NSCLC	2L EGFRm; Iressa ref.; MET+		China			
	Savolitinib	Gastric cancer	MET+		China			
Fruquintinib VEGFR 1/2/3	**Fruquintinib**	Colorectal cancer	3L/4L; Stivarga/Lonsurf ref./intol.		US			
	Fruquintinib + Tyvyt (PD-1)	Solid tumors	1L		US	**		
	Fruquintinib	Colorectal cancer	≥3L; chemotherapy refractory	FRESCO	China			
	Fruquintinib + Taxol	Gastric cancer	2L	FRUTIGA	China			
	Fruquintinib	NSCLC	3L; chemotherapy refractory	FALUCA	China			
	Fruquintinib + Iressa	NSCLC	1L EGFRm		China			
	Fruquintinib + genolimzumab (PD-1)	Solid tumors			China	**		
	Fruquintinib + Tyvyt (PD-1)	Solid tumors			China	**		
Surufatinib VEGFR 1/2/3; FGFR1; CSF-1R	**Surufatinib**	Pancreatic NET	2L; Sutent/Afinitor refractory		US			
	Surufatinib + Tuoyi (PD-1)	Solid tumors				**		
	Surufatinib	Pancreatic NET	All	SANET-p	China			
	Surufatinib	Non-Pancreatic NET	All	SANET-ep	China			
	Surufatinib	Biliary Tract cancer	2L; chemotherapy refractory		China			
	Surufatinib + Tuoyi (PD-1)	Solid tumors			China			
	Surufatinib + HX008 (PD-1)	Solid tumors			China	**		
HMPL-523 Syk	**HMPL-523**	Indolent NHL			Australia			
	HMPL-523	Indolent NHL			US	**		
	HMPL-523 + azacitidine	AML	1L		China			
	HMPL-523	B-cell malignancies	All		China			
	HMPL-523	ITP	All		China	**		
HMPL-689 PI3Kδ	**HMPL-689**	Healthy volunteers			Australia			
	HMPL-689	Indolent NHL			US	**		
	HMPL-689	Indolent NHL			China			
Epitinib EGFR	**Epitinib**	NSCLC	EGFRm with brain metastasis		China			
	Epitinib	Glioblastoma	EGFR gene amplified		China			
Theliatinib EGFR wt	**Theliatinib**	Esophageal cancer	EGFR over expression		China	***		
HMPL-453 FGFR 1/2/3	**HMPL-453**	Solid tumors			China			

Global China

Notes: Dose finding/safety run-in = Phase I/Ia studies; Proof-of-concept = Phase Ib, Ib/II or II studies; Registration = Phase II, II/III or III registration intent studies; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; NHL = Non-Hodgkin's Lymphoma; AML = acute myeloid leukemia; * Further patient enrolment directed to savolitinib monotherapy arm due to the high efficacy observed; ** In planning; *** Discontinued; and † Phase II registration intent study subject to regulatory discussion.

The following is a summary of the clinical pipeline for our drug candidates, many of which are being investigated against multiple indications.

1. Savolitinib MET Inhibitor

Savolitinib is a potent and selective inhibitor of MET, an enzyme which has been shown to function abnormally in many types of solid tumors. We designed savolitinib to address human metabolite-related renal toxicity, the primary issue that halted development of several other selective MET inhibitors. In clinical trials to date, savolitinib has shown promising signs of clinical efficacy in patients with MET gene alterations in non-small cell lung cancer, papillary renal cell carcinoma, colorectal cancer, gastric cancer and prostate cancer with an acceptable safety profile. We are currently testing savolitinib in partnership with AstraZeneca, both as a monotherapy and in combinations. For more information regarding our partnership with AstraZeneca, see "– *Overview of Our Collaborations – AstraZeneca Agreement.*"

Mechanism of Action

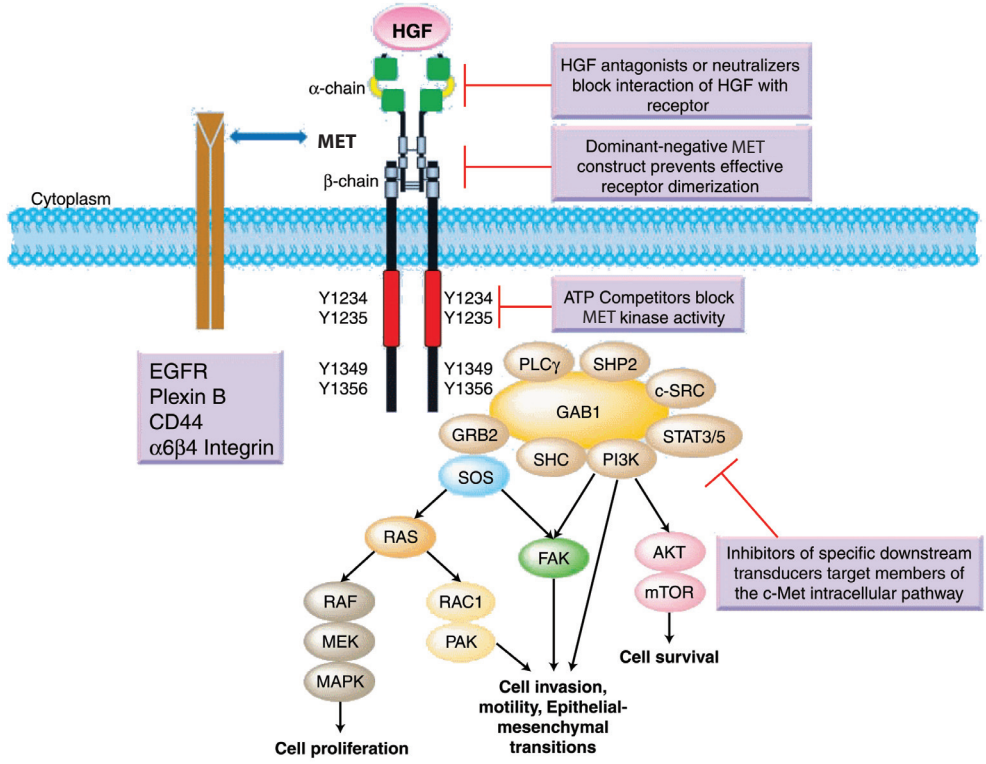
MET is a signaling pathway that has specific roles in normal mammalian growth and development. However, the MET pathway has also been shown to function abnormally in a range of different cancers, primarily through MET gene amplification, overexpressed and gene mutations.

The aberrant activation of MET has been demonstrated to be highly correlated in many cancer indications, including kidney, lung, gastric, colorectal, esophageal and brain cancer. It plays a major role in cancer pathogenesis (i.e., the development of the cancer), including tumor growth, survival, invasions, metastasis, the suppression of cell death as well as tumor angiogenesis.

MET also plays a role in drug resistance in many tumor types. For instance, MET gene amplification has been found in non-small cell lung cancer and colorectal cancer following anti-EGFR treatment, leading to drug resistance. Furthermore, MET overexpression has been found to emerge in renal cell carcinoma following anti-VEGFR treatment.

As a result, MET has become a widely investigated oncology target in recent years although no selective MET inhibitor has received regulatory approval to date.

The MET Signaling Pathway



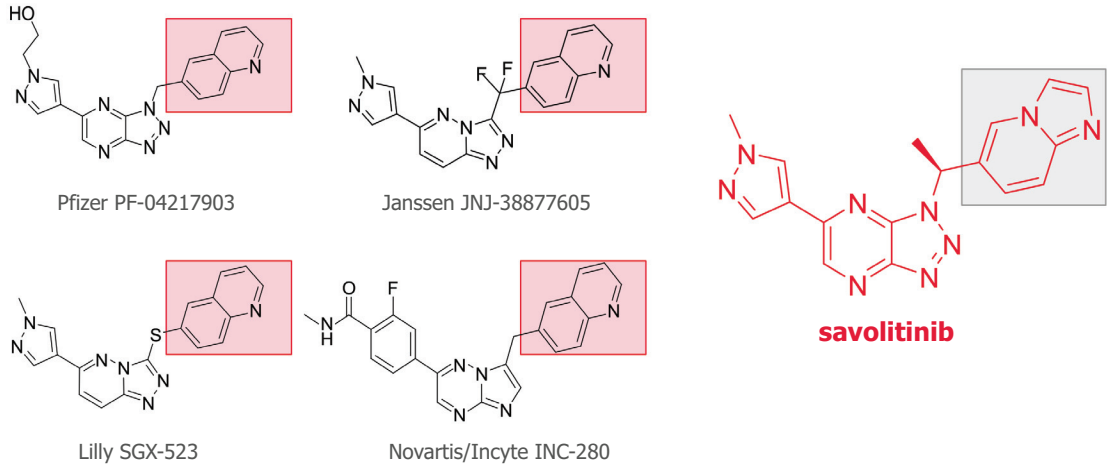
Notes: This graphic is a highly simplified representation of the two main MET signaling pathways, which are each composed of a signaling cascade of the multiple kinases indicated in the graphic. Signaling from the MET receptor through the cascade triggers tumor cell growth, survival, invasion, metastasis and inhibition of apoptosis (cell death).

Source: Joseph Paul Eder, et al, Novel Therapeutic Inhibitors of the MET Signaling Pathway in Cancer, ClinCancer Res 2009;15(7).

Savolitinib Research Background

Selective MET compounds previously discovered by multinational pharmaceutical companies had positive pre-clinical data that supported their high MET selectivity and pharmacokinetic and toxicity profiles, but did not progress very far due to kidney toxicity. The issue appeared to be that certain metabolites of earlier compounds had dramatically reduced solubility and appeared to crystalize in the kidney, resulting in obstructive toxicity. With this understanding, we designed our compound, savolitinib (also known as AZD6094 and HMPL-504, formerly known as volitinib), differently while preserving high MET selective properties. Savolitinib has not shown any renal toxicity to date and does not appear to carry the same metabolite problems as the earlier selective MET compounds.

Chemical Structures of Selective MET Inhibitors Versus Savolitinib Chemical Structure, Showing Replacement of the Quinoline Group



Sources: Zou H, et al., 99th Annual Meeting for American Association for Cancer Research (AACR); 12 – 16 April 2008; San Diego, USA; Perera T, et al., 99th Annual Meeting for American Association for Cancer Research (AACR); 12 – 16 April 2008; San Diego, USA; Bounaud, et al., WO 2008/051808 A2; Liu X, et al., 99th Annual Meeting for American Association for Cancer Research (AACR); 12 – 16 April 2008; San Diego, USA; Su W, et al., 105th AACR; April 2014; San Diego, USA; Diamond S, et al., Species-specific metabolism of SGX523 by aldehyde oxidase, Drug Metabolism and Disposition, 2010, 38, 1277-85.

Savolitinib Pre-clinical Evidence

In vitro biological profile

In pre-clinical trials, savolitinib demonstrated strong in vitro activity against MET, affecting its downstream signaling targets and thus blocking the related cellular functions effectively, including proliferation, migration, invasion, scattering and the secretion of vascular endothelial growth factor, or VEGF, that plays a pivotal role in tumor angiogenesis.

One of our key areas of focus in our pre-clinical trials is to achieve superior selectivity on a number of kinases. A commonly used quantitative measure of selectivity is through comparing enzyme IC_{50}, which represents the concentration of a drug that is required for 50% inhibition of the target kinase in vitro and the plasma concentration required for obtaining 50% of a maximum effect in vivo. High selectivity is achieved with a very low IC_{50} for the target cells, and a very high IC_{50} for the healthy cells (approximately 100 times higher than for the target cells). IC_{50} is measured in nM (nano-mole, a microscopic unit of measurement for the number of small molecules required to deliver the desired inhibitory effect).

In the MET enzymatic assay, savolitinib showed potent activity with IC_{50} of 5 nM. In a kinase selectivity screening with 274 kinases, savolitinib had potent activity against the MET Y1268T mutant (comparable to the wild-type), weaker activity against other MET mutants and almost no activity against all other kinases. Savolitinib was found to be approximately 1,000 times more potent to MET than the next non-MET kinase. Similarly, in cell-based assays

measuring activity against MET phosphorylation, savolitinib demonstrated potent activity in both ligand-independent (gene amplified) and ligand-dependent (overexpressed) cells with IC_{50}s at low nanomolar levels. In target related tumor cell function assays, savolitinib showed high potency with IC_{50} of less than 10 nM. Furthermore, savolitinib demonstrated cytotoxicity only on tumor cells that were MET gene amplified or MET overexpressed. In other cells, inhibition measurements demonstrated that IC_{50} amounts were over 30,000 nM, which is thousands of times higher than the IC_{50} on MET tumor cells.

The data above suggest that (i) savolitinib has potent activity against tumor cell lines with MET gene amplification in the absence of HGF, indicating that there is HGF-independent MET activation in these cells; (ii) savolitinib has potent activity in tumor cell lines with MET overexpressed, but only in the presence of HGF, indicating HGF-dependent MET activation; and (iii) savolitinib has no activity in tumor cell lines with low MET overexpressed/gene amplification, suggesting that savolitinib has strong kinase selectivity.

In vivo efficacy

We tested the in vivo activity of savolitinib on different human tumor xenograft models, a technique where human tumor cells are transplanted into various animal models. For example, in a gastric cancer MET gene amplification model, savolitinib was found to inhibit tumor growth potently with good dose response at a 2.5 mg/kg (kg weight of the animal), suggesting potent anti-tumor activity. Moreover, the anti-tumor activity appeared to correlate well with the inhibition of MET phosphorylation and activation. Similarly in a non-small lung cancer MET gene amplified xenograft model, savolitinib also showed significant anti-tumor efficacy.

Savolitinib showed strong synergistic effects with other oncology therapies in certain xenograft models, including a model which has high MET gene amplification and originally derived from a non-small cell cancer cell line that is highly sensitive to EGFR inhibitors. The combination of savolitinib with the EGFR inhibitor Iressa demonstrated strong synergistic effect, suggesting targeting multiple pathways simultaneously may provide a viable approach for the treatment of tumors with activation of multiple pathways. These data suggest that there is a strong rationale for patients whose disease progressed after EGFR tyrosine kinase inhibitor treatment with MET gene amplification to use a combination therapy including savolitinib. We also studied in several subcutaneous xenograft models the anti-tumor effect of savolitinib in combination with Taxotere, a commonly used chemotherapy in gastric cancer treatment. In our studies, the combination produced additive or synergistic anti-tumor effect, and no significant additive or synergistic toxicity between the two drugs was found.

Savolitinib First-in-human Studies

We conducted the first-in-human Phase I study of savolitinib in patients with advanced solid tumors starting in 2012 in Australia. The study was conducted to determine the maximum tolerated dose or recommended Phase II dose, dose-limiting toxicities, pharmacokinetics profile and preliminary anti-tumor activity of savolitinib. The first patient was enrolled in February 2012, and enrollment of a total of 47 patients was completed in June 2015.

The data of 35 patients in the dose escalation stage of this Phase I study were presented at the 2014 annual meeting of the American Society of Clinical Oncology. Grade ≥3 adverse events with greater than 5% incidence, based on the National Cancer Institute's Common Terminology Criteria for Adverse Event, or CTC, which is a set of criteria for the standardized classification of adverse effects of drugs used in cancer therapy (with 1 and 2 being relatively mild and higher numbers (up to 5) being more severe), associated with savolitinib treatment were fatigue (9%) and shortness of breath, or dyspnea (6%). Four patients reported five incidences of dose-limiting toxicities, including one CTC grade 3 incidence of elevated alanine transaminase (600 mg once daily), one incidence of CTC grade 3 fatigue (800 mg once daily), two incidences of CTC grade 3 fatigue and one incidence of CTC grade 3 headache (1,000 mg once daily). Notably, no obstructive kidney toxicity was seen in this study.

A pharmacokinetics analysis showed savolitinib was rapidly absorbed with a half-life of approximately five hours, and drug exposure increased in a dose-proportional manner and with no obvious accumulation. This study showed that savolitinib was well tolerated at doses of up to 800 mg once daily.

In 2013, we initiated a Phase I dose escalation study of savolitinib in China. A total of 41 patients were enrolled across the dose escalation and dose expansion stages of the study. We concluded that the data from this China Phase I study were consistent with the Australian Phase I study discussed above and that savolitinib was well tolerated at doses up to 800 mg once daily or 600 mg twice daily. The complete Phase I study results, combining data from Australia and China, were presented at the American Society of Clinical Oncology's annual meeting in 2015.

Savolitinib Clinical Development

As discussed below, we have tested, and are currently testing, savolitinib in partnership with AstraZeneca in multiple indications, both as a monotherapy and in combination with other targeted therapies.

Non-small Cell Lung Cancer

MET is an increasingly important target in non-small cell lung cancer. The table below shows a summary of the clinical trials that we have recently completed and underway for savolitinib in non-small cell lung cancer patients.

Clinical Trials of Savolitinib in Non-small Cell Lung Cancer

Treatment	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Savolitinib and Tagrisso	TATTON: 2L/3L EGFRm+; EGFR TKI refractory; MET+	Global	Ib/II	Completed enrollment; preliminary data presented at AACR 2019	NCT02143466
Savolitinib and Tagrisso	SAVANNAH: 2L/3L EGFRm+; Tagrisso refractory; MET+	Global	II	Initiated in Dec 2018	NCT03778229
Savolitinib and Iressa	2L EGFRm; Iressa refractory MET+	China	Ib/II	Completed	NCT02374645
Savolitinib	MET Exon 14 deletion	China	II Registration	Target enrollment completion in end 2019	NCT02897479

Notes: Global = >2 countries; AACR = American Association for Cancer Research Annual Meeting; and refractory = resistant to prior treatment.

Savolitinib and Tagrisso Combination

In 2015, AstraZeneca received FDA approval for Tagrisso, its drug for the treatment of T790M+ EGFRm+, tyrosine kinase inhibitor-resistant non-small cell lung cancer. A drug with this type of activity is known as a third-generation EGFR inhibitor. In 2018, Tagrisso's label was expanded to include previously untreated patients with EGFRm+ non-small cell lung cancer. Tagrisso sales in 2018, only the third year since its launch, were US$1.9 billion. Tagrisso has been established as a new standard of care in the treatment of EGFRm+ non-small cell lung cancer and has now been approved in over 80 countries. Understanding the mechanism of acquired resistance following Tagrisso treatment is a key clinical question to inform the next treatment choice. A portion of EGFRm+ tyrosine kinase inhibitor-resistant patients and a portion of T790M+ EGFRm+ tyrosine kinase inhibitor-resistant patients progress because of MET gene amplification.

At the European Society of Medical Oncology Congress in 2018, AstraZeneca presented the first results on the acquired resistance spectrum detected in patient plasma after progression in the first-line (FLAURA) and second-line T790M (AURA3) Phase III studies. MET amplification was among the most frequent mechanisms of acquired resistance to Tagrisso, with 15% of patients in the FLAURA study and 19% of patients in the AURA3 study exhibiting MET amplification after treatment with Tagrisso. Ongoing research with tissue (biopsy) samples will further elucidate the incidence of MET and other mechanisms in the development of resistance to EGFR inhibitors.

Data presented in June 2017 at the American Society of Clinical Oncology by Harvard Medical School and Massachusetts General Hospital Cancer Center showed that about 30% (7/23 patients) of Tagrisso-resistant third-line non-small cell lung cancer patients harbor MET

gene amplification based on analysis of tissue samples. This third-line patient population is generally heavily pre-treated and highly complex from a molecular analysis standpoint, with the study showing that more than half of the MET gene amplification patients also harbored additional genetic alterations, including EGFR gene amplification and K-Ras mutations.

As discussed in more detail below, we and AstraZeneca are studying savolitinib in combination with Tagrisso as a treatment choice for patients who have developed a resistance to tyrosine kinase inhibitors (primarily Tagrisso). The acceptance and uptake of Tagrisso indicates that the market potential for savolitinib in Tagrisso resistant, non-small cell lung cancer could be material.

TATTON study (Part A); Phase I dose finding study of savolitinib in combination with Tagrisso in non-small cell lung cancer (Status: completed; NCT02143466)

The primary objective of the TATTON study (Part A) Phase I study was to establish safe and effective combination doses of Tagrisso plus a number of potential new medicines, including savolitinib. All patients were tested for their T790M status (+/–) and screened for MET gene amplification status for entry into the savolitinib arms, if sufficient tissue samples were available, although patients of all tumor types were admitted to the trial regardless of status. A total of 12 patients were dosed with either 600 mg or 800 mg of savolitinib in combination with 80 mg of Tagrisso once daily. It was found that both 600 mg and 800 mg once daily could be combined with 80 mg of Tagrisso once daily with a safety profile consistent with single agent use. Furthermore, of the 11 evaluable patients in the study, six confirmed partial responses were observed. This resulted in an objective response rate of 55% and contributed to a disease control rate of 100%. None of the adverse effects in the 600 mg dose were CTC grade ≥3, and only two in the 800 mg dose were CTC grade ≥3. These were nausea (8%) and decreased white blood cell count (8%). The results were presented in 2015 at the American Society of Clinical Oncology Annual Meeting.

This novel combination of two well-tolerated therapies, albeit a small sample size, delivered significant objective response rate levels. As a result, we expanded the TATTON Phase Ib study to demonstrate broader proof-of-concept.

TATTON study (Part B) and TATTON study (Part D); Phase Ib/II expansion studies of savolitinib in combination with Tagrisso in non-small cell lung cancer EGFRm+ inhibitor refractory patients (Status: completed; NCT02143466)

In 2016, the savolitinib arms of the global Phase Ib/II TATTON study (Part B) expansion began, aiming to recruit sufficient MET gene amplified patients who had progressed after prior treatment with EGFR inhibitors to support a decision on global Phase II/III registration strategy.

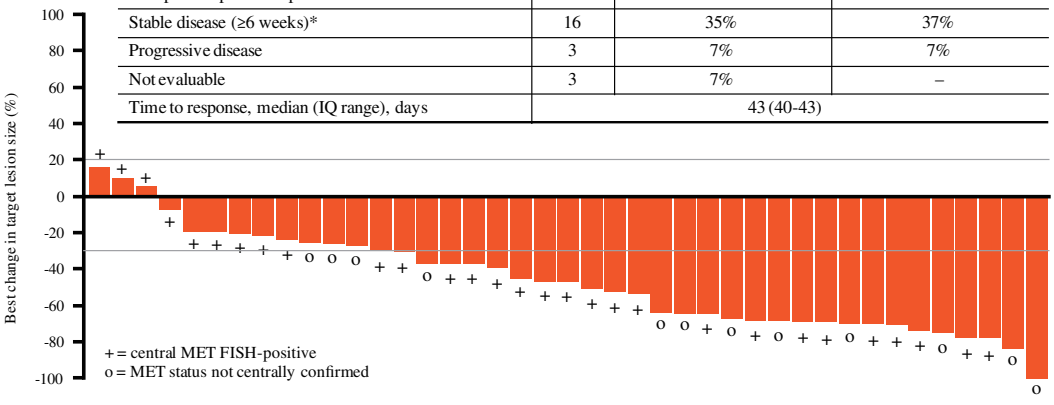
First and second-generation EGFRm+ inhibitor refractory patients with acquired resistance driven by MET amplification

Preliminary data (cut-off on August 31, 2017) from TATTON (Part B) in 34 evaluable patients who had not previously received a third-generation EGFR inhibitor, were presented at the 2017 World Conference on Lung Cancer and showed confirmed partial responses in 20/34 (59%) of patients regardless of T790M mutation status. Among the 23 evaluable patients who were T790M−, 14/23 (61%) patients had a response. Among the 11 evaluable T790M+ patients, confirmed partial responses were seen in 6/11 (55%) patients. These data are consistent with the TATTON study (Part A).

More recent preliminary data which added an additional 20 evaluable patients, for a total of 43 evaluable patients (46 total patients), who were T790M− and who had not previously received a third-generation EGFR inhibitor were presented at the 2019 American Association for Cancer Research Annual Meeting. There were 24 confirmed responses (56% of efficacy evaluable patients), four unconfirmed responses, 12 others with stable disease, for a total of 40 patients who experienced disease control (93% of efficacy evaluable patients). These results are generally consistent with the preliminary data presented at the 2017 World Conference on Lung Cancer. The median duration of response was 7.1 months, with an interquartile range from 4.1 months to 10.7 months. CTC grade ≥3 adverse events with greater than 5% incidence independent of causality were increased aspartate aminotransferase (8%), increased neutrophil count (8%), fatigue (7%) and pain (7%).

Preliminary Data from TATTON Study (Part B Expansion) – Patients Whose Disease Progressed on a First-or Second-Generation EGFR Inhibitor and were T790M− and MET+

Best response after treatment with Tagrisso and savolitinib	# pts	% Enrolled (n=46)	% Efficacy Evaluable (n=43)
Complete or partial response	24	52%	56%
Stable disease (≥6 weeks)*	16	35%	37%
Progressive disease	3	7%	7%
Not evaluable	3	7%	–
Time to response, median (IQ range), days	43 (40-43)		



Notes: * Includes four patients with unconfirmed partial responses; Waterfall plot of the best percentage change in target lesion size, assessed in the safety analysis set. Best change in target lesion size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction; and IQ = interquartile.

In late 2017, the TATTON study (Part D) was initiated to study Tagrisso combined with a lower savolitinib dose (300 mg once daily) in the context of maximizing long-term tolerability of the combination for patients who could be in poor condition and/or on the combination for long periods of time. Enrollment of the TATTON study (Part B expansion) and the TATTON study (Part D) has now been completed, patients continue to be treated and clinical data continues to mature. Finalization of the registration study dose of Tagrisso and savolitinib is close to complete.

Tagrisso or another experimental third-generation EGFRm tyrosine kinase inhibitor refractory patients with acquired resistance driven by MET amplification

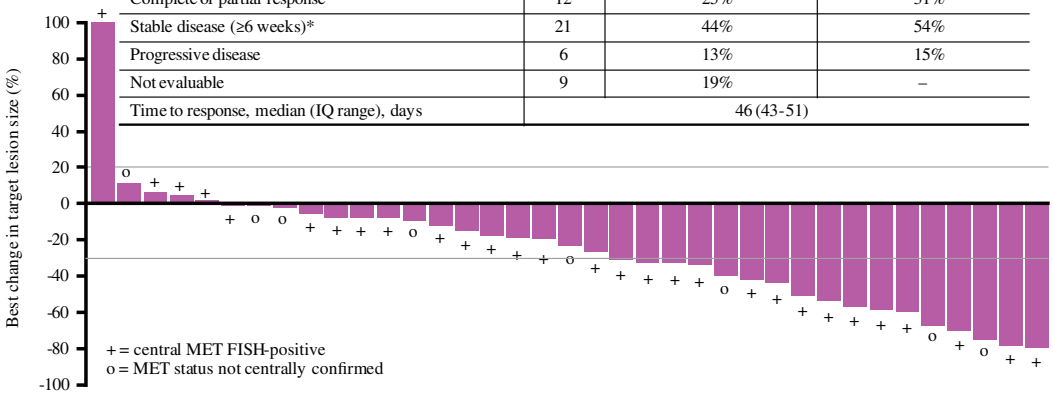
The TATTON study (Part B) also enrolled non-small cell lung cancer patients that had progressed after treatment with a third-generation EGFR inhibitor as a result of MET gene amplification acquired resistance. These patients were recruited prior to the April 2018 FDA approval of Tagrisso as a first-line treatment and the January 2019 update to the National Comprehensive Cancer Network guidelines that state that Tagrisso is the preferred first-line treatment for patients with EGFR mutation regardless of pre-treatment T790M mutation status.

Preliminary data (cut-off on August 31, 2017) in 30 evaluable patients previously treated with third-generation T790M-directed EGFR inhibitors, primarily Tagrisso, which was presented at the 2017 World Conference on Lung Cancer. Confirmed partial responses were observed in 10/30 (33% objective response rate) of these patients, and while this is lower than the 55%-61% objective response rate in patients refractory to first- or second-generation EGFR inhibitors, it was as expected given the additional driver genes at work post-Tagrisso monotherapy failure.

More recent preliminary data added an additional 11 evaluable patients for a total of 39 evaluable patients were presented at the 2019 American Association for Cancer Research Annual Meeting, with results generally consistent with the initial 30 evaluable patient data. There were 12 confirmed responses (31% of evaluable patients), five unconfirmed responses and 16 other patients with stable disease, totaling 33 patients who experienced disease control (85% of efficacy evaluable patients). These median duration of response was 9.7 months, with an interquartile range from 5.5 months to an incalculable higher figure at the time of data cut-off.

Preliminary Data from TATTON Study (Part B expansion) – Patients whose Disease Progressed on a Third-generation EGFR Inhibitor and were MET Positive

Best response after treatment with Tagrisso and savolitinib	# pts	% Enrolled (n=48)	% Efficacy Evaluable (n=39)
Complete or partial response	12	25%	31%
Stable disease (≥6 weeks)*	21	44%	54%
Progressive disease	6	13%	15%
Not evaluable	9	19%	–
Time to response, median (IQ range), days	46 (43-51)		



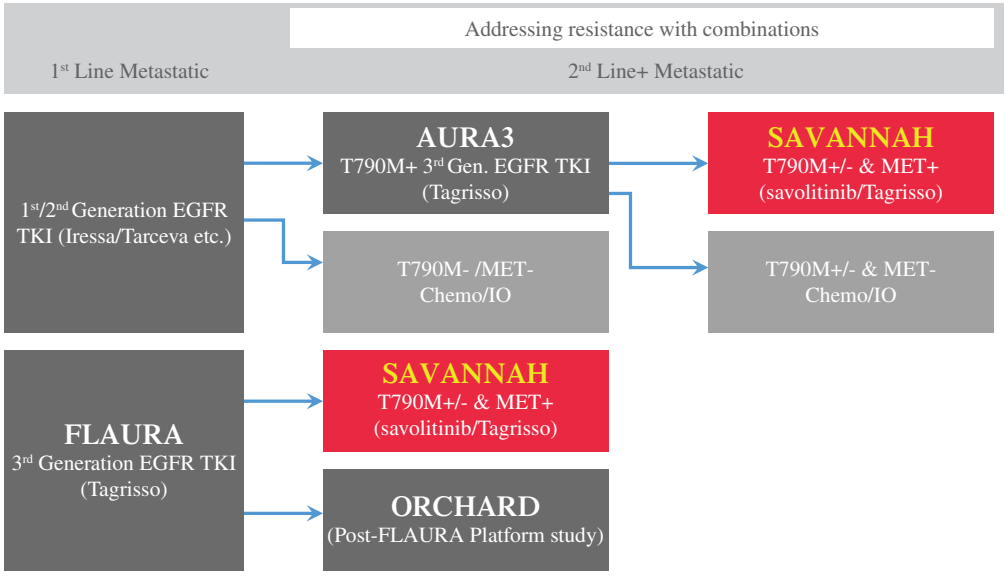
Notes: * Includes five patients with unconfirmed partial response; Waterfall plot of the best percentage change in target lesion size, assessed in the safety analysis set. Best change in target lesion size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction; and IQ = interquartile.

Overall the combination regimen of savolitinib and Tagrisso was tolerable. The only CTC grade ≥3 adverse event with greater than 5% incidence independent of causality was decreased appetite (6%).

SAVANNAH study; Phase II study of savolitinib in combination with Tagrisso in non-small cell lung cancer Tagrisso-refractory EGFRm+ patients (Status: initiated in December 2018; NCT03778229)

Based on the encouraging results of the multiple TATTON studies, we and AstraZeneca have initiated a global Phase II study of savolitinib in combination with Tagrisso in EGFRm+ non-small cell lung cancer patients with MET gene amplification who have progressed following first or second-line Tagrisso therapy. The SAVANNAH study is a single-arm study, in North and South America, Europe and Asia. Subject to positive clinical outcomes and regulatory interactions, the SAVANNAH study is designed to support potential NDA submission for savolitinib. The primary data completion is anticipated in 2021.

The SAVANNAH Study Design: Addressing Tagrisso Resistance Through Combination Therapies



Notes: 2nd line+ = second line and above; Chemo = chemotherapy; and IO = immunotherapy.

Source: Company.

Savolitinib and Iressa Combination

In 2003, AstraZeneca received FDA approval for Iressa, a drug for the treatment of EGFRm+ tyrosine kinase inhibitor-resistant non-small cell lung cancer. Iressa is used in the treatment of patients with advanced EGFRm+ non-small cell lung cancer, and has been approved in over 64 countries. A portion of EGFRm+ tyrosine kinase inhibitor-resistant patients progress because of MET gene amplification. As discussed in more detail below, we and AstraZeneca are studying savolitinib in combination with Iressa as a second- and third-line treatment choice for patients who have developed a resistance to Iressa. We will continue to evaluate this opportunity during 2019 in the context of the evolving treatment paradigm for EGFRm+ non-small cell lung cancer.

Phase Ib study of savolitinib in combination with Iressa in non-small cell lung cancer (second-line) EGFR inhibitor-refractory patients (Status: completed; NCT02374645)

At the 2017 World Conference on Lung Cancer, we presented Phase Ib proof-of-concept data assessing savolitinib (600 mg once daily) in combination with Iressa in patients in China with EGFRm+ advanced non-small cell lung cancer with centrally confirmed MET gene amplification who had progressed following first-generation EGFR inhibitor therapy. Preliminary results showed confirmed partial responses in 12 of 23 T790M– patients (52% objective response rate), as well as confirmed partial responses in two of 23 T790M+ patients (9% objective response rate). The 52% objective response rate in T790M– patients was as expected and similar to that recorded in the TATTON study (Part B) for this target patient

population, indicating that for these patients Iressa might be the most cost-efficient combination partner for savolitinib. The low 9% objective response rate in T790M+ patients was also as expected, as Iressa does not effectively address T790M mutants. In terms of safety, the savolitinib plus Iressa combination dose was safe and well tolerated. We and AstraZeneca will continue to evaluate this opportunity during 2019.

Savolitinib Monotherapy

It is estimated that 2-3% of newly diagnosed non-small cell lung cancer patients have a specific genetic mutation, known as MET Exon 14 deletion, where exon 14 of the MET gene is either deleted or not functional, resulting in MET overexpression, which is believed to play a role in cancer development as discussed above in the mechanism of action section. This equates to approximately 10,000 new patients per year in China.

Phase II study of savolitinib monotherapy in non-small cell lung cancer patients with MET Exon 14 deletion (Status: recruitment ongoing; NCT02897479)

A registration intent Phase II study of savolitinib as a monotherapy is currently enrolling in China for non-small cell lung cancer patients with MET Exon 14 deletion who have progressed following prior systemic therapy, or are unwilling or unable to receive chemotherapy.

During the 2019 American Association for Cancer Research Annual Meeting, early mid-trial interim data were presented on 41 treated patients, of which only 31 patients were efficacy evaluable. The overall data was encouraging and supported the continuation of the study as originally planned. Treatment emergent CTC grade ≥3 adverse events with greater than 5% incidence related to savolitinib treatment were increased aspartate aminotransferase (7%) and increased alanine aminotransferase (7%).

We currently expect to complete enrollment in 2019, and if results are sufficiently positive, this has the potential to be savolitinib's first NDA.

Kidney Cancer

The table below shows a summary of the clinical trials that we have recently completed or underway for savolitinib in kidney cancer patients.

Clinical Trials of Savolitinib in Kidney Cancer

Treatment	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Savolitinib monotherapy	PRCC	Global	II	Completed	NCT02127710
Savolitinib monotherapy	SAVOIR: MET+ PRCC	Global	III	Enrol. suspended	NCT03091192
Savolitinib monotherapy	CALYPSO: Clear cell RCC; VEGFR-TKI refractory	U.K./ Spain	II	Discontinued (focus on PD-L1 combos)	NCT02819596
Savolitinib and Imfinzi	CALYPSO: PRCC	U.K./ Spain	II	Interim-Presented at ASCO GU 2019	NCT02819596
Savolitinib and Imfinzi	CALYPSO: Clear cell RCC; VEGFR-TKI refractory	U.K./ Spain	II	Enrolling-Data late 2019/2020	NCT02819596

Notes: PRCC = papillary renal cell carcinoma; RCC = renal cell carcinoma; Enrol. = enrollment; ASCO GU 2019 = the American Society of Clinical Oncology's 2019 Genitourinary Cancers Symposium; VEGFR-TKI refractory = resistant to prior VEGFR tyrosine kinase inhibitor treatment; and Global = >2 countries.

Papillary renal cell carcinoma is the most common of the non-clear cell renal cell carcinomas representing about 14% of kidney cancer. Approximately 403,300 new cases of kidney cancer were diagnosed globally in 2018, equating to about 56,500 cases of papillary renal cell carcinoma, with approximately half harboring MET driven disease. No targeted therapies have been approved specifically for papillary renal cell carcinoma, although modest efficacy in non-clear cell renal cell carcinoma has been reported in sub-group analyses of broader renal cell carcinoma studies of VEGFR (e.g., Sutent) and mammalian target of rapamycin (e.g., Afinitor) tyrosine kinase inhibitors, with objective response rates of <10% and median progression-free survival in first-line setting of four to six months and second-line setting of only one to three months (ESPN study, Tannir N. M. et al.).

During an Australian Phase I study, our investigators noted positive outcomes among papillary renal cell carcinoma patients with a strong correlation to MET gene amplification status. Out of a total of eight papillary renal cell carcinoma patients in our Australia Phase I study who were treated with various doses of savolitinib, three achieved confirmed partial response (tumor measurement reduction of greater than 30%). A further three of these eight papillary renal cell carcinoma patients achieved stable disease, which means patients without partial response but with a tumor measurement increase of less than 20%. This aggregate objective response rate (the percentage of patients in the study who show either partial response or complete response) of 38% was very encouraging for papillary renal cell carcinoma, which has no effective approved treatments. These responses were also durable as demonstrated by a patient who has been on the therapy for over 30 months and had tumor measurement reduction of greater than 85%. Importantly, the level of tumor response among these papillary renal cell carcinoma patients correlated closely with the level of MET gene amplification. The patients with consistent MET gene amplification across the whole tumor responded most to savolitinib, and with those patients with the highest level of MET gene amplification responding most to the treatment.

Recent data have emerged to show that papillary renal cell carcinoma responds to immunotherapy such as inhibitors of an immune checkpoint known as programmed cell death 1, or PD-1, used by cancer cells to avoid being attacked by the immune system. Preliminary data from the KEYNOTE-427 study (Cohort B) as presented by Merck & Co at the American Society of Clinical Oncology's 2019 Genitourinary Cancers Symposium showed objective response in treatment naïve papillary renal cell carcinoma patients treated with the PD-1 inhibitor Keytruda was 25%. In the broader kidney cancer setting, combinations of PD-1 or PD-L1, with targeted therapies that demonstrated single agent effect have demonstrated additive benefits.

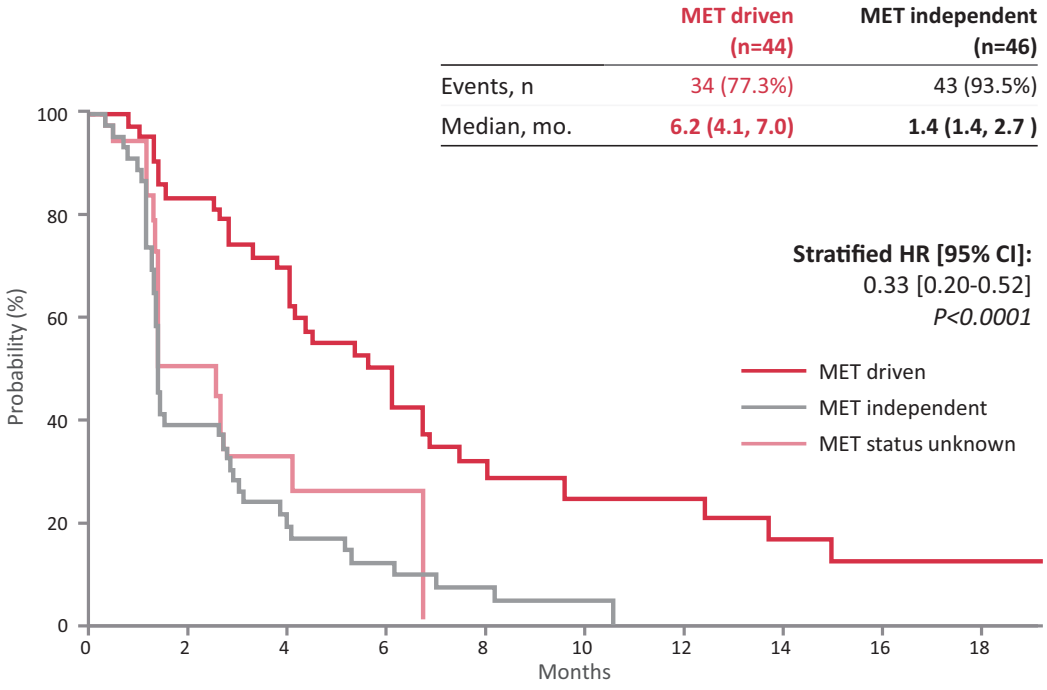
Savolitinib Monotherapy

Phase II study of savolitinib monotherapy in papillary renal cell carcinoma (Status: completed; NCT02127710)

In early 2017, we presented the results of our global Phase II study in papillary renal cell carcinoma at the American Society of Clinical Oncology's Genitourinary Cancers Symposium and subsequently published these results in the Journal of Clinical Oncology. This Phase II study, conducted in the United States, Canada and Europe, was the largest and most comprehensive clinical study in papillary renal cell carcinoma ever conducted. Of 109 patients treated with savolitinib, papillary renal cell carcinoma was MET driven in 44 patients (40%), MET independent in 46 patients (42%) and MET status unknown in 19 patients (17%). The objective response rate based on confirmed partial responses in all patients was 7% (8/109). MET driven papillary renal cell carcinoma was strongly associated with encouragingly durable response to savolitinib with an objective response rate in the MET driven group of 18% (8/44) as compared to 0% (0/46) in the MET independent group (p=0.002). P-value is a measure of the probability of obtaining the observed sample results, with a lower value indicating a higher degree of statistical confidence in these studies. Median progression-free survival for patients

with MET driven and MET independent papillary renal cell carcinoma patients was 6.2 months (95% confidence interval: 4.1-7.0) and 1.4 months (95% confidence interval: 1.4-2.7), respectively (hazard ratio=0.33; 95% confidence interval: 0.20-0.52; p<0.0001). A 95% confidence interval means that there is a 95% chance that the results will be within the stated range. Hazard ratio is the probability of an event (such as disease progression or death) occurring in the treatment arm divided by the probability of the event occurring in the control arm of a study, with a ratio of less than one indicating a lower probability of an event occurring for patients in the treatment arm. Savolitinib was well tolerated, with no reported treatment related CTC grade ≥3 adverse events with greater than 5% incidence. Total aggregate savolitinib treatment-related CTC grade ≥3 adverse events occurred in just 19% of patients.

Phase II Study of Savolitinib Monotherapy in Papillary Renal Cell Carcinoma in the United States, Canada and Europe. This Study Clearly Demonstrated MET Driven Patients had Better Progression-free Survival Compared to MET Independent Patients.



Notes: n = number of patients; mo. = months; 95% CI = 95% confidence interval; and HR = hazard ratio.

Source: Company.

SAVOIR study; Phase III study of savolitinib monotherapy in papillary renal cell carcinoma (Status: enrollment suspended; NCT03091192)

Based on the Phase II results we presented in early 2017, we initiated the SAVOIR study in June 2017. The SAVOIR study was designed to be a global Phase III, open-label, randomized, controlled trial evaluating the efficacy and safety of savolitinib (600 mg once daily) compared with Sutent in patients with MET driven, unresectable, locally advanced or metastatic papillary renal cell carcinoma. MET status was confirmed by the novel targeted next-generation sequencing assay developed for savolitinib. Patients were randomized in a 1:1 ratio to receive either treatment with savolitinib, or treatment with Sutent. The primary endpoint for efficacy in the SAVOIR study was median progression-free survival, with secondary endpoints of overall survival, objective response rate, duration of response, best percentage change in tumor size, disease control rate, and safety and tolerability. Furthermore, to further understand the role of MET driven disease in papillary renal cell carcinoma, we conducted a global molecular epidemiology study, which screened, using our companion diagnostic, archived tissue samples from papillary renal cell carcinoma patients to identify MET driven disease. Historical medical records from these patients were then used to determine if MET driven disease is predictive of worse outcome, in terms of progression-free survival and overall survival, in papillary renal cell carcinoma patients.

Based on the molecular epidemiology study, the Phase II study and the first section of SAVOIR enrollment, we concluded that savolitinib would provide significant benefit only in second-line patients who are resistant to prior Sutent therapy. As a result, in late 2018 Chi-Med, AstraZeneca and our investigators suspended enrollment of savolitinib monotherapy in MET-positive papillary renal cell carcinoma patients, including savolitinib enrollment for the SAVOIR Phase III study, in order to reassess the strategy for papillary renal cell carcinoma in favor of potential combinations of savolitinib and immunotherapy as discussed below.

Savolitinib and Immunotherapy Combinations

Immunotherapy combinations are rapidly changing the treatment landscape in kidney cancer. Immune checkpoints such as PD-L1 are sometimes used by cancer cells to avoid being attacked by the immune system. As such, drugs that target these checkpoints are being developed or marketed as cancer treatments. Imfinzi is an anti-PD-L1 antibody owned by AstraZeneca. Anti-PD-L1 antibodies have been associated with clinical benefits in metastatic renal cell carcinoma, and MET dysregulation has been considered to play an important role in papillary renal cell carcinoma pathogenesis (including in our savolitinib Phase I and Phase II monotherapy studies) and is a mechanism of resistance against kinase inhibitors in clear cell renal cell carcinoma. Moreover, it is believed that the MET signaling pathway has a complex interplay with the immune system, including correlation with PD-L1 expression, immune suppression through angiogenesis and many other facets of the immune system. Our CALYPSO study discussed below aims to explore and potentially confirm this interplay.

CALYPSO study; Phase Ib study of savolitinib in combination with Imfinzi in renal cell carcinoma (Status: completed: NCT02819596)

A Phase Ib dose escalation study in the United Kingdom sponsored and led by the Barts Cancer Institute of Queen Mary University of London was conducted to determine the recommended Phase II dose of savolitinib and Imfinzi when given in combination. Six evaluable patients were enrolled, and none reported dose-limiting toxicities. Adverse events were in line with the established safety profiles of each drug as monotherapies. In 2016, 600 mg once daily of savolitinib and 1,500 mg once every four weeks of Imfinzi was selected as the recommended Phase II dose for the expansion phase of the CALYPSO study, which is discussed in more detail below.

CALYPSO study; Phase II study of savolitinib in combination with Imfinzi in both papillary renal cell carcinoma and clear cell renal cell carcinoma patients (status: dose expansion ongoing; NCT02819596)

As detailed above, the CALYPSO study completed a Phase Ib dose finding study to assess safety/tolerability of savolitinib and Imfinzi combination therapy in several MET driven kidney cancer patient populations. In 2017, the study moved on to the Phase II expansion stage in papillary renal cell carcinoma and clear cell renal cell carcinoma patients in the United Kingdom and Spain to further explore efficacy.

Interim results of the papillary renal cell carcinoma cohort of the CALYPSO Phase II study were presented at the 2019 American Society of Clinical Oncology's Genitourinary Cancers Symposium showing encouraging efficacy across all patients, both MET+ and MET-. The interim CALYPSO data reported an objective response rate of 27% (11/41), while median progression-free survival was 5.3 months (95% confidence interval: 1.5-12.0 months). Median overall survival was immature/not reached. For the study's 28 previously untreated patients, the objective response rate was 32% (9/28). There were 13 treatment related CTC grade $\geq$3 adverse events that occurred in more than three patients, with edema (10%), nausea (5%) and transaminitis (5%) being most frequent. The investigators concluded that the Imfinzi-savolitinib combination is associated with durable responses in papillary renal cell carcinoma and that both progression-free survival and overall survival data were immature but encouraging. This compares favorably to the results of the Phase II study of savolitinib as a monotherapy, which reported a 7% objective response rate in all papillary renal cell carcinoma patients (18% ORR in MET+; and 0% in MET-).

Data on the clear cell renal cell carcinoma cohort are expected to be submitted for presentation in late 2019 or early 2020.

Gastric Cancer

We have multiple Phase II studies in Asia to test savolitinib in MET-driven gastric cancer patients. The table below shows a summary of our clinical trials for savolitinib in gastric cancer patients.

Clinical Trials of Savolitinib in Gastric Cancer

Treatment	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Savolitinib monotherapy	Gastric cancer (MET amplification) and VIKTORY	China & South Korea	Ib/II	Enrolling in China; VIKTORY complete, to publish 2019	NCT01985555 NCT02449551
Savolitinib and Taxotere	VIKTORY: Gastric cancer (MET amplification)	South Korea	II	Enrollment stopped (patients directed to savo mono due to high efficacy observed)	NCT02447406
Savolitinib and Taxotere	VIKTORY: Gastric cancer (MET overexpression)	South Korea	II	Enrollment stopped (patients directed to savo mono due to high efficacy observed)	NCT02447380

Note: savo mono = savolitinib monotherapy trial.

Phase II gastric cancer studies have been completed in China and in South Korea. A total of over 1,000 gastric cancer patients had been screened in these studies and those patients with confirmed MET-driven disease were treated.

Phase Ib/II study of savolitinib monotherapy in MET amplified gastric cancer in China (Status: enrolling; NCT01985555)

Preliminary results of the China study were presented at the 2017 Chinese Society of Clinical Oncology for the efficacy evaluable MET gene amplified patients. Based on confirmed and unconfirmed partial responses, the objective response rate was 43% (3/7) and disease control rate was 86% (6/7), with objective response rate of 14% (3/22) and disease control rate of 41% (9/22) among the overall efficacy evaluable aberrant MET set of patients with MET amplification (n=7) and MET overexpression (n=15). As of data cut-off, the longest duration of treatment was in excess of two years. Savolitinib monotherapy was determined to be safe and well tolerated in patients with advanced gastric cancer. CTC grade 3 treatment emergent adverse events with greater than 5% incidence included abnormal hepatic function in 13% (4/31), gastrointestinal bleeding or decreased appetite in 10% (3/31 each), and diarrhea or gastrointestinal perforation in 6% (2/31 each). This China study concluded that savolitinib monotherapy demonstrated promising anti-tumor efficacy in gastric cancer patients with MET gene amplification, and that the potential benefit to these patients warranted further exploration, with enrollment continuing.

VIKTORY Phase II study of savolitinib monotherapy in MET amplified gastric cancer in South Korea (Status: completed; NCT02449551)

The South Korean study is known as the VIKTORY study and is an umbrella study run and sponsored by the Samsung Medical Center in South Korea.

The VIKTORY trial is a biomarker-based, Phase II umbrella trial in gastric cancer conducted by the Samsung Medical Center. Patients were allocated to one of 12 biomarker-driven arms, based on a master screening protocol with tissue-based molecular analyses. Patients that tested positive for MET amplification or overexpression were treated with either savolitinib monotherapy or a combination of savolitinib and Taxotere. The primary endpoint was objective response rate for each arm. Between 2014 and 2018, over 700 advanced gastric cancer patients were entered into molecular screening. We believe that the VIKTORY study is first and largest study to use an umbrella trial design with pre-planned genomic biomarker analyses to assign patients to molecularly matched therapies in advanced gastric cancer.

The VIKTORY Phase II study is now complete in MET gene amplified patients, and the full data is expected to be published in a scientific journal in 2019.

VIKTORY; Phase II studies of savolitinib in combination with Taxotere in MET amplified or overexpression gastric cancer in South Korea (Status: completed; NCT02447406/ NCT02447380)

In a Phase I dose-finding trial, 17 patients were enrolled including seven gastric cancer patients, five melanoma patients, three sarcoma patients and two rectal cancer patients. Most of the patients (14 of 17) were heavily pretreated (≥third line or greater lines of treatment). One gastric cancer patient with both MET overexpression and MET amplification achieved a durable partial response for 297 days, and another MET amplified gastric cancer patient achieved stable disease for 86 days. The combination therapy demonstrated promising antitumor activity with durable responses in MET amplified gastric cancer patients.

As stated above, the VIKTORY Phase II trial commenced to assess safety and tolerability of savolitinib in combination with Taxotere along with the preliminary efficacy of the combination therapy in both MET amplified patients and the cancer patients who harbor MET overexpression.

While the savolitinib and Taxotere combination was well tolerated, the VIKTORY study investigators decided to stop enrollment in the two combination cohorts in order to direct patients to the above higher priority savolitinib monotherapy arm of the VIKTORY study.

Prostate cancer

The table below shows a summary of the clinical study that is underway for savolitinib in prostate cancer patients.

Clinical Trials of Savolitinib in Prostate Cancer

Treatment	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Savolitinib monotherapy	Metastatic Castration-Resistant Prostate Cancer	Canada	II	Enrolling	NCT03385655

Phase II study of savolitinib monotherapy in metastatic castration-resistant prostate cancer (Status: enrolling; NCT03385655)

A Phase II study sponsored by the Canadian Cancer Trials Group is enrolling patients to determine the effect of savolitinib on prostate-specific antigen decline and time to prostate-specific antigen progression. The study will assess the objective response rate as determined by Response Evaluation Criteria in Solid Tumors, or RECIST, revision version 1.1, a set of published rules that define when tumors improve, stay the same or worsen during treatment. It will also evaluate the safety and toxicity profile of savolitinib in metastatic castration-resistant prostate cancer patients and identify potential predictive and prognostic factors. The umbrella study targets to enroll around 500 patients into four treatment arms based on molecular status, with one treatment arm being patients with MET-driven disease receiving savolitinib. High levels of MET overexpression can be prevalent in prostate cancer patients.

Partnership with AstraZeneca

In December 2011, we entered into a global licensing, co-development, and commercialization agreement for savolitinib with AstraZeneca. As noted above, given the complexity of many of the signal transduction pathways and resistance mechanisms in oncology, the industry is increasingly studying combinations of targeted therapies (tyrosine kinase inhibitors, monoclonal antibodies and immunotherapies) and chemotherapy as potentially the best approach to treating this complex and constantly mutating disease. Based on savolitinib showing early clinical benefit as a highly selective MET inhibitor in a number of cancers, in August 2016 we and AstraZeneca amended our global licensing, co-development, and commercialization agreement for savolitinib. We believe that AstraZeneca's portfolio of proprietary targeted therapies is well suited to be used in combinations with savolitinib, and we are studying combinations with Iressa (EGFRm+), Tagrisso (T790M+) and Imfinzi (PD-L1). These combinations of multiple global first-in-class compounds are difficult to replicate, and we believe represent a significant opportunity for us and AstraZeneca.

For more information regarding our partnership with AstraZeneca, see "*– Overview of Our Collaborations – AstraZeneca Agreement.*"

2. Fruquintinib VEGFR 1, 2 and 3 Inhibitor

Fruquintinib (also known as HMPL-013) is a VEGFR inhibitor that we believe is highly differentiated due to its superior kinase selectivity compared to other small molecule VEGFR inhibitors, which can be prone to excessive off-target toxicities. Fruquintinib's selectivity on VEGFR 1, 2 and 3 results in fewer off-target toxicities, thereby allowing for better target coverage, as well as possible use in combination with other agents such as chemotherapies, targeted therapies and immunotherapies.

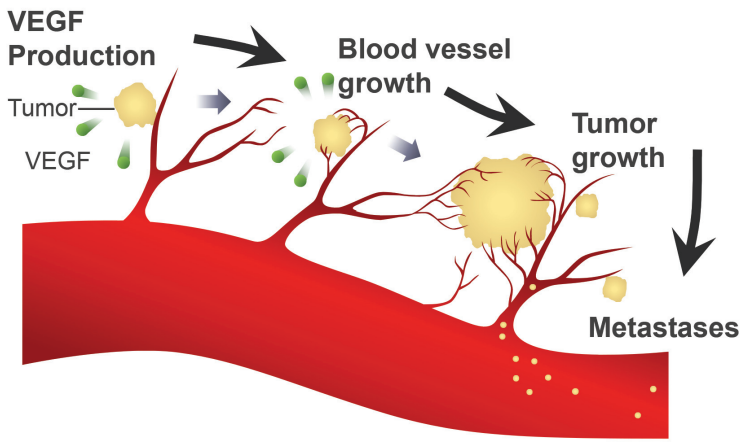
We believe these are meaningful points of differentiation compared to other approved small molecule VEGFR inhibitors such as Sutent, Nexavar and Stivarga, and can potentially significantly expand the use and market potential of fruquintinib. Consequently, we believe that fruquintinib has the potential to become the global best-in-class selective small molecule VEGFR inhibitor for many types of solid tumors.

We received full approval for launch of fruquintinib (under the brand name Elunate) in colorectal cancer in September 2018, including GMP certification of our manufacturing facility in Suzhou. In partnership with Eli Lilly, we launched fruquintinib in China in late November 2018 in a series of national launch meetings across China. Elunate is indicated for the treatment of patients with metastatic colorectal cancer that have been previously treated with fluoropyrimidine, oxaliplatin and irinotecan, including those who have previously received anti-VEGF therapy and/or anti-EGFR therapy (Ras wild type). For more information regarding the Elunate product launch, see "– *Overview of Elunate Commercial Launch*."

Mechanism of Action

During the development of cancer, tumors at an advanced stage can secrete large amounts of VEGF, a protein ligand, to stimulate formation of excessive vasculature (angiogenesis) around the tumor in order to provide greater blood flow, oxygen, and nutrients to fuel the rapid growth of the tumor. Since essentially all solid tumors require angiogenesis to progress beyond a few millimeters in diameter, antiangiogenesis drugs have demonstrated benefits in a wide variety of tumor types.

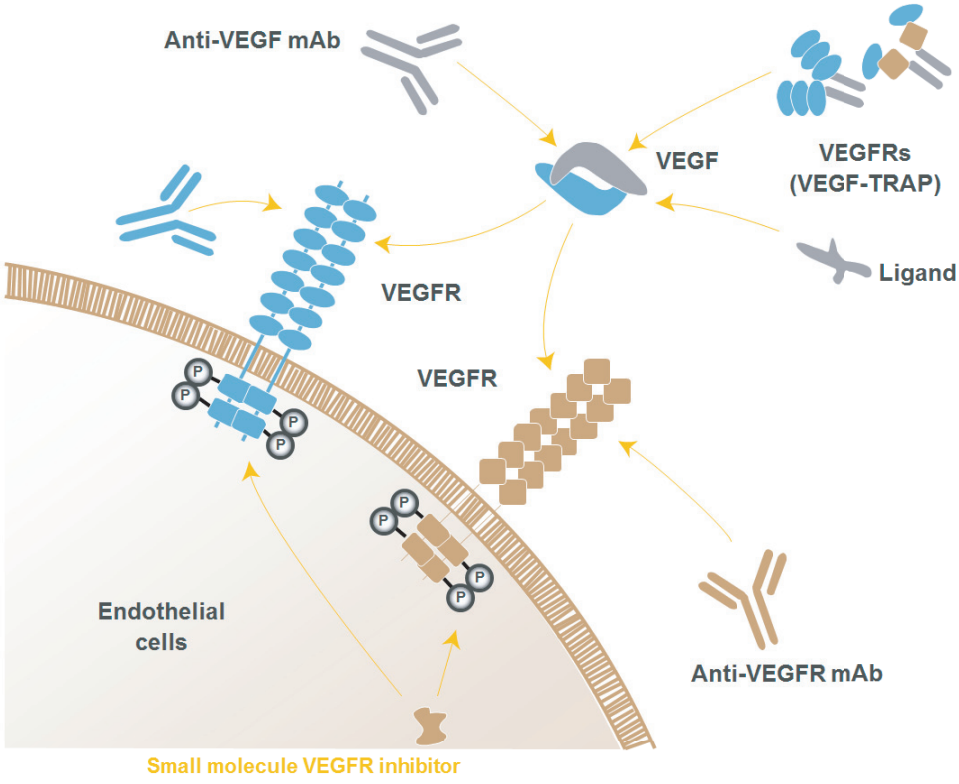
VEGF Production Plays a Role in Angiogenesis



Source: Company.

The global market for antiangiogenesis therapies was estimated at over US$16 billion in 2018, including both monoclonal antibodies and small molecules approved in around 30 tumor settings. VEGF and other ligands can bind to three VEGF receptors, VEGFR 1, 2 and 3, each of which has been shown to play a role in angiogenesis. Therefore, inhibition of the VEGF/VEGFR signaling pathway can act to stop the growth of the vasculature around the tumor and thereby starve the tumor of the nutrients and oxygen it needs to grow rapidly.

VEGFR Inhibitors Block Downstream Signaling Activation



Note: mAb = monoclonal antibody.

Source: *Company.*

This therapeutic strategy has been well validated with several first-generation VEGF inhibitors having been approved globally since 2005 and 2006. These include both small molecule multi-kinase inhibitor drugs such as Nexavar and Sutent as well as monoclonal antibodies such as Avastin. The success of these drugs validated VEGFR inhibition as a new class of therapy for the treatment of cancer.

Fruquintinib Pre-clinical Evidence

Potency and Selectivity

Pre-clinical trials have demonstrated that fruquintinib is a highly selective VEGFR 1, 2 and 3 inhibitor with high potency and low cell toxicity at the enzymatic and cellular levels. Fruquintinib has been studied in nude mice models bearing various human tumors and has shown significant inhibition of tumor growth, with human gastric cancer showing the strongest sensitivity. A daily dose of 2 mg/kg was found to almost completely inhibit tumor growth in mice models.

As a result of off-target side effects, existing VEGFR inhibitors are often unable to be dosed high enough to completely inhibit VEGFR, the intended target. In addition, the complex off-target toxicities resulting from inhibition of multiple signaling pathways are often difficult to be managed in clinical practice. Combining such drugs with chemotherapy can lead to severe toxicities that can cause more harm than benefit to patients. To date, the first generation VEGFR tyrosine kinase inhibitors have been rarely used in combination with other therapies, thereby limiting their potential. Because of the potency and selectivity of fruquintinib, we believe that it has the potential to be safely combined with other oncology drugs, which could significantly expand its clinical potential.

The pharmacokinetic properties of fruquintinib in patients have also been found to have high drug exposures at the optimal 5 mg daily dose of approximately 6,000 h*ng/mL (i.e., hours multiplied by nanogram per milliliter, which is a measurement of drug exposure over time), well above the exposure of 898 h*ng/mL required to cover the VEGFR target to EC_{50} levels in mouse models, suggesting potentially strong target coverage in humans at this dose. At this dose, we expect fruquintinib to fully inhibit VEGFR for an entire day through a single oral dose based on modeling using pre-clinical data. In contrast, Sutent achieved a drug exposure of only 592 h*ng/mL at the maximum tolerated dose of 50 mg per day, which is well below the drug exposures required for target inhibition determined in its pre-clinical models of 2,058 h*ng/mL, suggesting insufficient target coverage in humans.

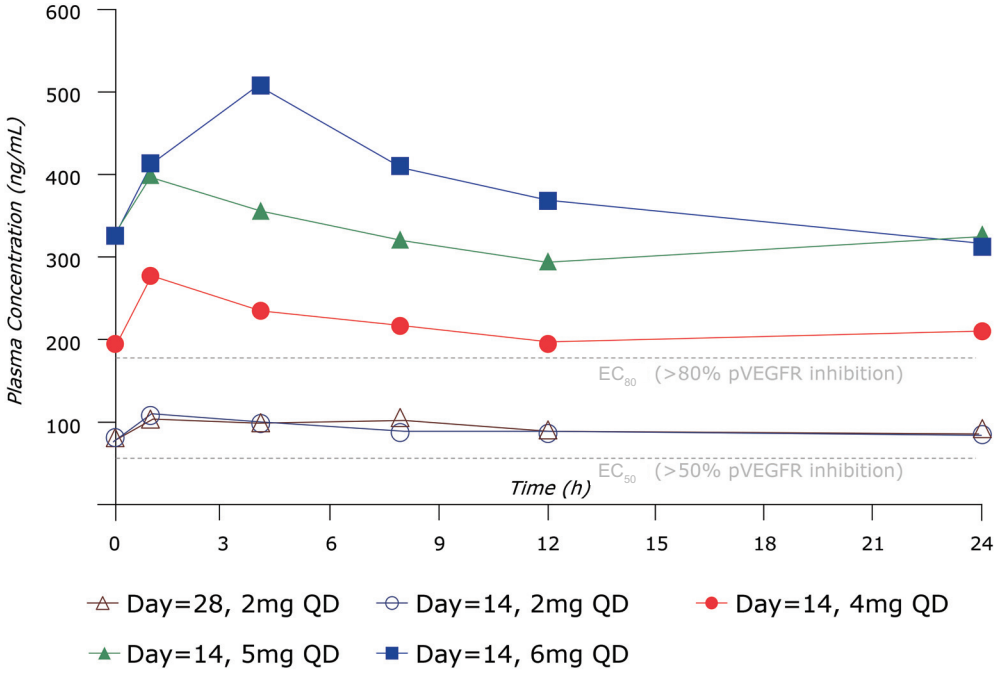
Fruquintinib First-in-human Studies

A Phase I dose escalation study in patients with advanced solid tumors in China was initiated in January 2011, and results were presented at the American Association for Cancer Research's meeting in 2013 and subsequently published in Cancer Chemotherapy and Pharmacology in August 2016. A total of 40 subjects with advanced solid tumors were enrolled in this clinical study. The primary endpoint was evaluation of safety during the first 28-day cycle of therapy following the initiation of multiple dosing of fruquintinib. The safety variables evaluated in this study were adverse events, physical examinations, vital signs (specifically including blood pressure), clinical laboratory evaluations including serum chemistry, hematology, urinalysis (with detailed sediment analysis, proteinuria, and 24-hour urine for collection of protein), and electrocardiograms.

Most adverse events were considered mild and graded as CTC grade 1 or 2. Adverse events CTC grade ≥3 with greater than 5% incidence related to fruquintinib treatment were hypertension (18%), hand-foot syndrome (18%), thrombocytopenia (13%), diarrhea (8%), fatigue (8%) and proteinuria (5%).

Furthermore, the Phase I study validated in humans the pre-clinical pharmacokinetic animal model findings of fruquintinib's ability to provide strong target coverage. The chart below shows that fruquintinib fully inhibits VEGFR in humans for the entire day at the optimal 5 mg daily dose level.

Fruquintinib Plasma Concentration in Humans Following Once Daily Dosing in Comparison to Effective Concentrations (EC) of Fruquintinib Required for VEGFR2 Phosphorylation (Activation) Inhibition in Mice



Notes: EC_{50} = concentration of a drug that gives 50% of maximal response; EC_{80} = concentration of a drug that gives 80% of maximal response; and QD = once daily.

Source: Company's Phase I study data for fruquintinib.

Tumor response and progression were evaluated using the RECIST 1.0. In terms of efficacy, in the entire intent-to-treat population of 40 subjects, 14 had confirmed partial response, 14 had stable disease, 6 had progressed disease, and 6 were not evaluable. The objective response rate was 41% in the 34 evaluable patients and 35% in the entire intent-to-treat population of 40 patients, and the disease control rate was 82% among evaluable patients and 70% in the intent-to-treat population. Out of the 34 evaluable patients, only six patients had tumor growth, with the rest experiencing substantial tumor shrinkage.

In this Phase I study, clear tumor response was observed in multiple tumor types, consistent with the fact that angiogenesis, driven by VEGFR activation, accelerates the growth of tumors in many settings. The highest objective response rate in this Phase I study was achieved in non-small cell lung cancer and gastric cancer patients with objective response rates of over 50%. However, we also observed objective response rates of approximately 30% in colorectal and breast cancer patients.

As a result of this study, we determined that either 4 mg once daily or 5 mg once daily on a 3-weeks-on/1-week-off basis was safe and tolerable. This study also found that doses above 4 mg once daily achieved drug exposures well above EC80 (the concentration that leads to an 80% maximal response) of the VEGFR phosphorylation inhibition over a 24-hour time period.

In December 2017, we initiated a multi-center, open-label, Phase I clinical study to evaluate the safety, tolerability and pharmacokinetics of fruquintinib in U.S. patients with advanced solid tumors. In 2018, the U.S. recommended Phase II dose for fruquintinib was determined to be the same as that in China, 5 mg once daily on a 3-weeks-on/1-week-off regimen.

Fruquintinib Clinical Trials

Studies in Colorectal Cancer

The table below shows a summary of the clinical trials we have recently completed, are underway or are in planning for fruquintinib in colorectal cancer patients. We have one additional trial in planning for fruquintinib in colorectal cancer in combination with a checkpoint inhibitor as discussed in more detail below under "– *Fruquintinib Combinations with Checkpoint Inhibitors*."

Clinical Trials of Fruquintinib in Colorectal Cancer

Treatment	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Fruquintinib monotherapy	≥3L metastatic CRC	China	Ib/II	Completed	NCT01975077 NCT01645215 NCT02196688
Fruquintinib monotherapy	FRESCO: ≥3L CRC; chemotherapy refractory	China	III	Approved and launched	NCT02314819
Fruquintinib monotherapy	3L/4L CRC; Stivarga/Lonsurf ref./intol.	US/EU	II/III	US/EU registration study in planning	TBD

Notes: CRC = colorectal cancer; ref. or refractory = resistant to prior treatment; intol. = intolerant to prior treatment; and TBD = to be determined.

Phase Ib and II studies of fruquintinib monotherapy in third-line or above metastatic colorectal cancer patients (Status: completed; NCT01975077/NCT01645215/NCT02196688)

In 2012, we initiated a Phase Ib study in China in patients with advanced colorectal cancer to compare the safety and tolerability of a 5 mg once daily 3-weeks-on/1-week-off regimen versus a 4 mg continuous once daily regimen. The study was divided into a randomized comparison study with 20 patients taking each regimen. The primary endpoint was the incidence of adverse effects, including significant adverse events, CTC grades 3 or 4 adverse effects and adverse effects that lead to dose interruption or dose discontinuation. In this study, both dose regimens demonstrated similar clinical efficacy and safety profile with the 5 mg once daily 3-weeks-on/1-week-off regimen showing slightly more favorable results. An additional 22 patients were subsequently enrolled into the 5 mg once daily 3-weeks-on/1-week-off regimen to further confirm the safety and tolerability of this regimen. As a result of this study, we determined the recommended Phase II dose regimen to be 5 mg, once daily, on a 3-weeks-on/1-week-off basis. Full results of this study were presented at the American Society of Clinical Oncology's annual meeting in 2014.

In late 2014, we completed enrollment for a Phase II, double-blind, placebo-controlled, multi-center study in China in just over four months to test fruquintinib as a monotherapy among third-line metastatic colorectal cancer patients, using the 5 mg daily, 3-weeks-on/1-week-off dose regimen determined from our Phase I study discussed above. The goal of this study was to compare the efficacy, including progression-free survival, of fruquintinib versus placebo in metastatic colorectal cancer patients who failed at least two prior lines of treatment, including fluorouracil, oxaliplatin and irinotecan. A total of 71 patients were enrolled, with 47 in the fruquintinib arm and 24 in the placebo arm, respectively. Patient baseline characteristics were similar between the two treatment arms.

Fruquintinib demonstrated strong anti-tumor activity in this study. Median progression-free survival was 4.7 months in the fruquintinib arm compared to median progression-free survival of 1.0 month in the placebo arm (hazard ratio = 0.30 ($p<0.001$)). The disease control rate in the fruquintinib arm was 68% compared with 21% in the placebo arm ($p<0.001$). The interim median overall survival rate was 7.6 months and 5.5 months in the fruquintinib arm and the placebo arm, respectively. In this study, fruquintinib has not shown any major unexpected safety issues and clearly met its primary endpoint of progression-free survival. The result of 4.7 months in median progression-free survival compares favorably with results recorded to date in third-line colorectal cancer in trials involving VEGFR tyrosine kinase inhibitors. The safety profile in this study was also consistent with our Phase Ib trial for fruquintinib in third-line metastatic colorectal cancer patients. The full results of this study were presented at the European Cancer Congress in 2015.

FRESCO study; Phase III study of fruquintinib monotherapy in third-line colorectal cancer (Status: completed and product launched in November 2018; NCT02314819)

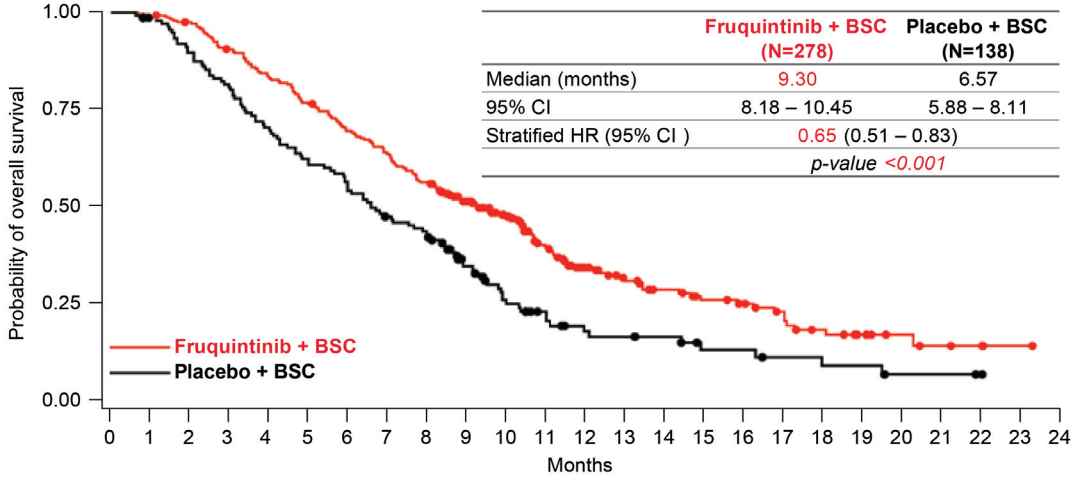
In 2014, we initiated the FRESCO study, which is a randomized, double-blind, placebo-controlled, multi-center, Phase III pivotal trial in China in patients with locally advanced or metastatic colorectal cancer who have failed at least two prior systemic antineoplastic therapies, including fluoropyrimidine, Eloxatin and Camptosar. No drugs had been approved in third-line colorectal cancer in China with best supportive care being the general standard of care.

Enrollment was completed in May 2016, and 519 patients were screened. The intent-to-treat population of 416 patients was randomized at a 2:1 ratio to receive either: 5 mg of fruquintinib orally once daily, on a three-weeks-on/one-week-off cycle, plus best supportive care (278 patients) or placebo plus best supportive care (138 patients). Randomization was stratified for prior anti-VEGF therapy and K-RAS gene status. The trial concluded in January 2017.

In June 2017, we presented the results of the FRESCO study in an oral presentation during the American Society of Clinical Oncology Annual Meeting. Results showed that FRESCO met all primary and secondary endpoints including significant improvements in overall survival and progression-free survival with a manageable safety profile and lower off-target toxicities compared to other targeted therapies.

The primary endpoint of median overall survival was 9.30 months (95% confidence interval: 8.18-10.45) in the fruquintinib group versus 6.57 months (95% confidence interval: 5.88-8.11) in the placebo group, with a hazard ratio of 0.65 (95% confidence interval: 0.51-0.83; two-sided p<0.001).

Phase III Study in China of Fruquintinib Monotherapy in Third-line Colorectal Cancer. FRESCO Clearly Succeeded in Meeting the Primary Efficacy Endpoint of Overall Survival.

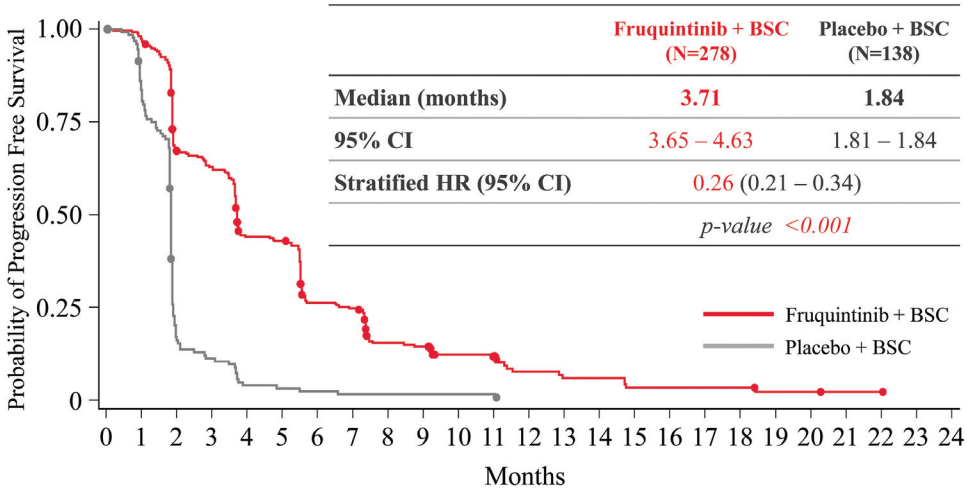


Notes: N = number of patients; BSC = best supportive care; 95% CI = 95% confidence interval; and HR = hazard ratio.

Source: Company.

The secondary endpoint of median progression-free survival was 3.71 months (95% confidence interval: 3.65-4.63) in the fruquintinib group versus 1.84 months (95% confidence interval: 1.81-1.84) in the placebo group, with a hazard ratio of 0.26 (95% confidence interval: 0.21-0.34; two-sided p<0.001). Significant benefits were also seen in other secondary endpoints. The disease control rate in the fruquintinib group was 62% versus 12% for placebo (p<0.001), while the objective response rate based on confirmed responses was 5% versus 0% for placebo (p=0.012).

FRESCO Clearly Succeeded in Meeting Endpoint of Progression-free Survival



	Fruquintinib + BSC (N=278)	Placebo + BSC (N=138)
Median (months)	**3.71**	**1.84**
95% CI	3.65 – 4.63	1.81 – 1.84
Stratified HR (95% CI)	0.26 (0.21 – 0.34)	
	p-value <0.001	

Notes: CI = confidence interval; HR = hazard ratio; N = number of patients; BSC = best supportive care; and p-value = probability value.

Source: Company.

In terms of safety, results showed that fruquintinib had a manageable safety profile with lower off-target toxicities compared to other VEGFR tyrosine kinase inhibitors. Of particular interest was that the CTC grade ≥3 hepatotoxicity was similar for the fruquintinib group as compared to the placebo group, which is in contrast to Stivarga which was markedly worse and often difficult to manage in this patient population in the CONCUR study, a Phase IV study of Stivarga monotherapy in colorectal cancer. The most frequently reported fruquintinib-related CTC grade ≥3 adverse events included hypertension (21%), hand-foot skin reaction (11%), proteinuria (3%) and diarrhea (3%), all possibly associated with VEGFR inhibition. No other CTC grade ≥3 adverse events exceeded 2% in the fruquintinib population, including hepatic function adverse events such as elevations in bilirubin (1%), alanine aminotransferase (<1%) or aspartate aminotransferase (<1%).

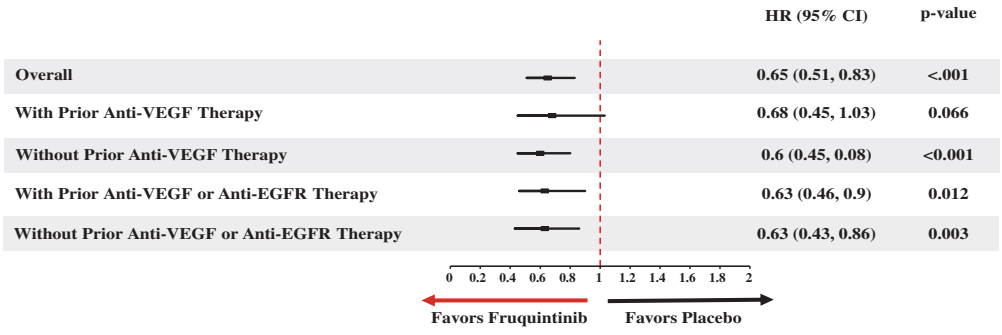
In terms of tolerability, dose interruptions or reductions occurred in only 35% and 24% of patients in the fruquintinib arm, respectively, and only 15% of patients discontinued treatment of fruquintinib due to adverse events versus 6% for placebo. The FRESCO study was published in the Journal of the American Medical Association in June 2018.

Subgroup analysis

In June 2018, a further subgroup analysis of data from the FRESCO Phase III study was presented during the American Society of Clinical Oncology Annual Meeting. This analysis explored possible effects of prior target therapy on the efficacy and safety of fruquintinib by analyzing the subgroups of patients with prior target therapy and those without prior target therapy.

Results showed that the benefits of fruquintinib were generally consistent across all subgroups. Among a total of 278 fruquintinib-treated patients, 111 had received prior target therapy while 55 of the 138 placebo-treated patients had received prior target therapy. In the prior target therapy subgroup, fruquintinib significantly prolonged overall survival and progression-free survival. Median overall survival was 7.69 months for patients treated with fruquintinib and 5.98 months for placebo (hazard ratio = 0.63; p = 0.023). Median progression-free survival was 3.65 months for patients treated with fruquintinib and 1.84 months for placebo (hazard ratio = 0.24; p < 0.001).

Overall Survival Subgroup Analysis by Prior Treatment



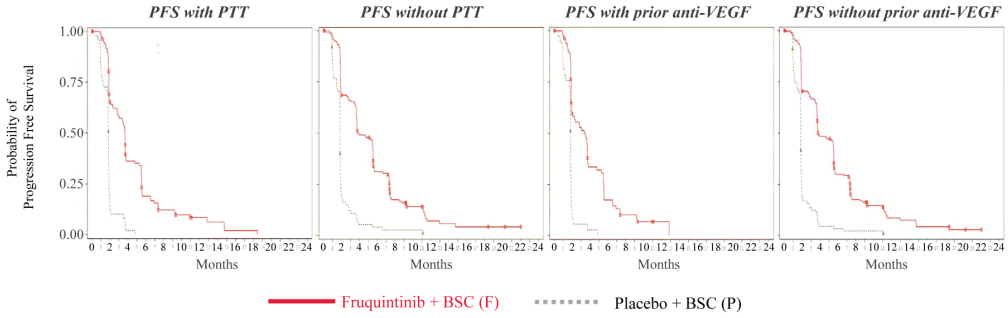
Notes: CI = confidence interval; and HR = hazard ratio.

Source: Company.

Among these 278 patients, the results showed that a subgroup of 84 patients who had received prior anti-VEGF treatment also benefited from fruquintinib. In this subgroup, the median overall survival was 7.20 months for fruquintinib and 5.91 months for placebo (hazard ratio = 0.68; p=0.066) and the median progression-free survival was 3.48 months for fruquintinib and 1.84 months for placebo (hazard ratio = 0.24; p < 0.001).

In the subgroup of 250 patients without prior target therapy, the median overall survival was 10.35 months for 167 patients treated with fruquintinib and 6.93 months for 83 patients treated with placebo (hazard ratio = 0.63; p = 0.01), and the median progression-free survival for patients treated with fruquintinib was 3.81 months versus 1.84 months for placebo (hazard ratio = 0.28; p < 0.001).

Progression-free Survival by Prior Therapy



	F (N=111)	P (N=55)	F (N=167)	P (N=83)	F (N=84)	P (N=41)	F (N=194)	P (N=97)
Median, months (95% CI)	3.65 (2.83, 3.71)	1.84 (1.81, 1.84)	3.81 (3.68, 5.49)	1.84 (1.84, 1.87)	3.48 (1.94, 3.71)	1.84 (1.81, 1.84)	3.81 (3.68, 5.49)	1.84 (1.81, 1.87)
HR (95% CI)	0.24 (0.16, 0.35)		0.28 (0.21, 0.37)		0.24 (0.15, 0.38)		0.26 (0.20, 0.35)	
P-value	*<0.001*		*<0.001*		*<0.001*		*<0.001*	

Notes: PFS = progression-free survival; BSC = best supportive care; CI = confidence interval; HR = hazard ratio; OS = overall survival; N = number of patients; PBO = placebo; and PTT= prior target therapy (prior anti-VEGFR therapy or anti-EGFR therapy or both).

Source: Company.

Additional data showed that there were no observed accumulative CTC grade ≥3 treatment-emergent adverse events in the subgroup of patients with prior target therapy. The CTC grade ≥3 treatment-emergent adverse event rates of fruquintinib were similar in the subgroups with prior target therapy (61.3%) and without prior target therapy (61.1%). This subgroup analysis is consistent with the previously reported results from the FRESCO study's intent-to-treat population.

The results of this analysis showed that fruquintinib had clinically meaningful benefits in third-line metastatic colorectal cancer patients regardless of prior target therapy without observed accumulative toxicity.

Quality-adjusted survival analysis

At the 2018 American Society of Clinical Oncology Annual Meeting, an analysis was presented that aimed to compare the quality-adjusted survival between the two arms of the FRESCO study using quality-adjusted time without symptoms or toxicity, or Q-TWiST, methodology and to investigate the Q-TWiST benefit of fruquintinib treatment among subgroups. Q-TWiST is a tool to evaluate relative clinical benefit-risk from patient's perspective and has been widely used in oncology treatment assessment. The survival time for each patient was divided into three portions: time with CTC grade ≥ 3 toxicity before progression, time without symptoms or CTC grade ≥ 3 toxicity, and time from progression or relapse until death or end of follow-up.

Patients treated with fruquintinib had longer Q-TWiST periods compared to patients treated with placebo. Q-TWiST benefits were observed regardless of prior lines of chemotherapy and prior anti-VEGF or anti-EGFR targeted therapy. The relative improvement of Q-TWiST with fruquintinib represents a clinically important quality-of-life benefit for metastatic colorectal cancer patients.

Supported by data from the successful FRESCO study, we submitted an NDA for fruquintinib in June 2017. Fruquintinib was subsequently awarded priority review status by the NMPA in view of its clinical value in September 2017, and in September 2018, the NMPA approved fruquintinib for the treatment of patients with advanced colorectal cancer and was launched in November 2018. For more information regarding the Elunate product launch, see "*– Overview of Elunate Commercial Launch.*"

Phase II/III study of fruquintinib monotherapy in third- or fourth-line metastatic colorectal cancer (Status: in planning)

We have begun planning for a Phase II/III registration study in the United States and Europe in third or fourth-line metastatic colorectal cancer patients who are resistant to or intolerant of prior Stivarga or Lonsurf treatment.

Gastric Cancer

Advanced gastric cancer is a major medical need, particularly in Asian populations, with limited treatment options for patients who have failed first-line standard chemotherapy with 5-fluorouracil and platinum doublets. There were approximately 442,300 new cases of gastric cancer in China in 2018. The table below shows a summary of the clinical study we have underway for fruquintinib in gastric cancer patients.

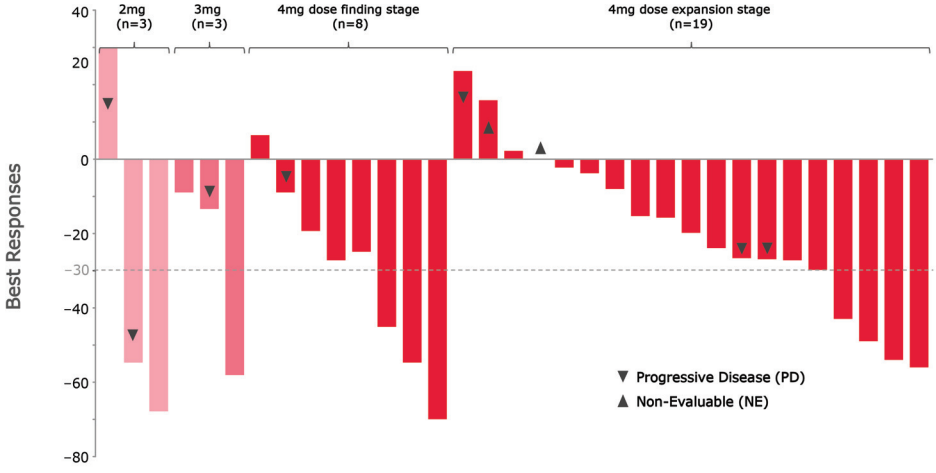
Clinical Trials of Fruquintinib in Gastric Cancer

Treatment	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Fruquintinib and Taxol	2L gastric cancer	China	Ib	Completed	NCT02415023
Fruquintinib and Taxol	FRUTIGA: 2L gastric cancer	China	III	Enrolling; Interim analysis conducted early 2019	NCT03223376

Phase Ib study of fruquintinib in combination with Taxol in second-line gastric cancer patients (Status: completed; NCT 02415023)

In early 2017, we completed an open label, multi-center Phase Ib dose finding/expansion study of fruquintinib in combination with Taxol in second-line gastric cancer and presented the results during the American Society of Clinical Oncology's 2017 Gastrointestinal Cancers Symposium. As of September 10, 2016, a total of 32 patients were enrolled in the study and the recommended dose was determined to be 4 mg once daily on a 3-weeks-on/1-week-off schedule in combination with a weekly dose of 80 mg/m^2 of Taxol. A total of 28 out of the 32 patients were efficacy evaluable with an objective response rate of 36% (10/28, based on confirmed partial responses) and a disease control rate of 68% (19/28). At the recommended dose, progression-free survival of ≥16 weeks was 50% of and overall survival of ≥7 months was 50%. Tolerability of the recommended dose combination was as expected. In the drug expansion stage, CTC grade ≥3 adverse events with greater than 5% incidence related to the treatment were neutropenia (58%), leukopenia (21%), hypertension (11%), decreased platelet count (5%), anemia (5%), hand-foot skin reaction (5%), mucositis oral (5%), hepatic disorder (5%), and upper gastrointestinal hemorrhage (5%), while neutropenia and leukopenia are common Taxol adverse events. The combination regime resulted in an approximately 30% increase in Taxol exposure in patients indicating the potential to decrease the required dose of Taxol in future development. In October 2017, based on the Phase Ib data, we initiated FRUTIGA, a pivotal Phase III clinical trial of fruquintinib in combination with Taxol in second-line gastric cancer.

Phase Ib Study of Fruquintinib Combined with Taxol in Gastric Cancer. Phase III Initiation Made on the Basis of these Encouraging Efficacy Data



Notes: As of November 30, 2016; and n = number of patients.

Source: Company.

FRUTIGA study; Phase III study of fruquintinib in combination with Taxol in gastric cancer (second-line) (Status: interim analysis reported; NCT03223376)

In October 2017, we initiated the FRUTIGA study, a pivotal Phase III clinical trial of fruquintinib in combination with Taxol for the treatment in advanced gastric or gastroesophageal junction adenocarcinoma patients in China. This randomized, double-blind, placebo-controlled, multi-center trial is being conducted in patients with advanced gastric cancer who have progressed after first-line standard chemotherapy. Over 500 patients are expected to be enrolled in the FRUTIGA study to evaluate the efficacy and safety of fruquintinib combined with paclitaxel compared with paclitaxel monotherapy for second-line treatment of advanced gastric or gastroesophageal junction adenocarcinoma. The trial will enroll patients with disease that has been confirmed through histology or cytology and who did not respond to first-line standard chemotherapy containing platinum and fluorouracil. All subjects will receive fruquintinib or placebo combined with paclitaxel. Patients will be randomized at a 1:1 ratio and stratified according to factors such as stomach versus gastroesophageal junction tumors and ECOG performance status, a scale established by the Eastern Cooperative Oncology Group which determines ability of patient to tolerate therapies in serious illness, specifically for chemotherapy.

The primary efficacy endpoint is overall survival. Secondary efficacy endpoints include progression-free survival, objective response rate, disease control rate, duration of response and quality-of-life score (EORTC QLQ-C30, version 3.0). Biomarkers related to the antitumor activity of fruquintinib will also be explored.

In April 2019, we conducted an interim analysis of the FRUTIGA study for futility. The analysis evaluated progression-free survival and overall survival trends after six months of therapy for the first 100 patients recruited into the study. The independent data monitoring committee recommended to continue the study without changes.

Non-small Cell Lung Cancer

The table below shows a summary of the clinical trials we have recently completed and underway for fruquintinib in non-small cell lung cancer patients. We have one additional trial in planning for fruquintinib in non-small cell lung cancer in combination with a checkpoint inhibitor as discussed in more detail below under "– *Fruquintinib Combinations with Checkpoint Inhibitors*."

Clinical Trials of Fruquintinib in Non-small Cell Lung Cancer

Treatment	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Fruquintinib monotherapy	3L NSCLC; chemotherapy refractory	China	II	Completed	NCT02590965
Fruquintinib monotherapy	FALUCA: 3L NSCLC; chemotherapy refractory	China	III	Announced top-line results	NCT02691299
Fruquintinib and Iressa	1L NSCLC; EGFRm	China	II	Enrollment completed	NCT02976116

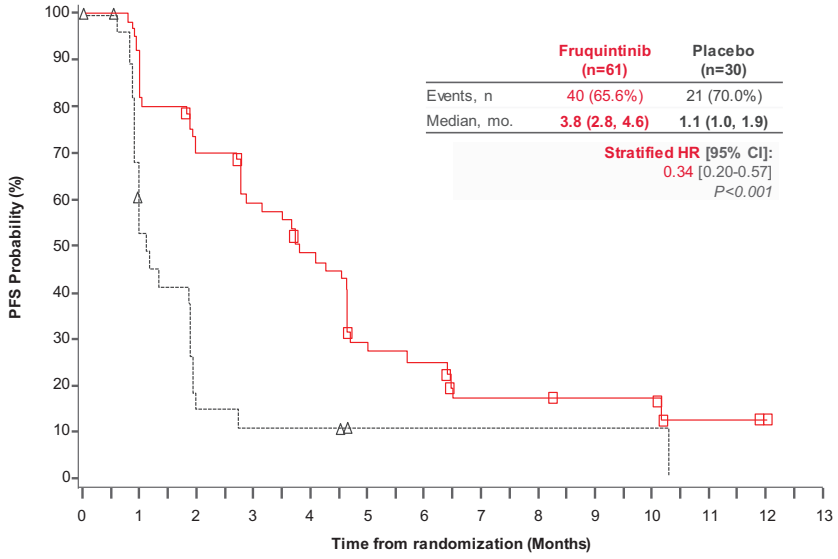
Notes: NSCLC = non-small cell lung cancer; and chemotherapy refractory = resistant to prior chemotherapy treatment.

Phase II study of fruquintinib monotherapy in third-line non-small cell lung cancer (Status: completed; NCT02590965)

In 2014, we initiated a Phase II randomized, double-blind, placebo-controlled, multi-center study of fruquintinib versus placebo among patients with advanced non-squamous non-small cell lung cancer who failed two lines of chemotherapy in China. By early March 2015, enrollment had been completed with a total of 91 patients randomized to 5 mg of fruquintinib orally once per day, on a 3-weeks-on/1-week-off regimen plus best supportive care, or placebo plus best supportive care at a 2:1 ratio.

In 2015, we reported that fruquintinib had clearly met its primary endpoint of superior median progression-free survival versus placebo in this study, and in December 2016, we reported the full data from this study at the 2016 World Conference on Lung Cancer, which showed median progression-free survival of 3.8 months for the fruquintinib group compared with 1.1 months for the placebo group (hazard ratio=0.34; 95% confidence interval: 0.20-0.57; $p<0.001$), an objective response rate based on confirmed partial responses of 13% for the fruquintinib group compared with 0% for the placebo group ($p=0.041$), and a 48% increase in disease control rate for the fruquintinib group compared with the placebo group ($p<0.001$). All were assessed by blinded independent clinical review. Fruquintinib was well tolerated with treatment related CTC grade ≥ 3 adverse events with greater than 5% incidence being hypertension (8%).

Phase II Study in China of Fruquintinib Monotherapy in Third-line Non-small Cell Lung Cancer. This Study Clearly Met the Median Progression-Free Survival Primary Endpoint.



Notes: N = number of patients; mo. = months; PFS = progression-free survival; 95% CI = 95% confidence interval; and HR = hazard ratio.

Source: Company.

FALUCA study; Phase III study of fruquintinib monotherapy in third-line non-small cell lung cancer (Status: topline results announced; NCT02691299)

Following a positive Phase II study comparing fruquintinib with placebo in advanced non-squamous non-small cell lung cancer patients who have failed two prior systemic chemotherapies, or third-line non-small cell lung cancer, we initiated a Phase III registration study, the FALUCA study, in late 2015. In February 2018, we completed enrollment of the FALUCA study in China, in which a total of 527 patients were randomized at a 2:1 ratio to receive either 5 mg of fruquintinib orally once daily, on a 3-weeks-on/1-week-off cycle plus best supportive care, or placebo plus best supportive care. In November 2018, we announced that the trial did not meet the primary endpoint to demonstrate a statistically significant increase in overall survival compared to placebo. However, fruquintinib demonstrated a statistically significant improvement in all secondary endpoints including progression-free survival, objective response rate, disease control rate and duration of response as compared to the placebo. The safety profile of the trial was in line with that observed in prior clinical trials. We intend to submit a full analysis of the study/presentation at a scientific conference in 2019.

Fruquintinib and EGFR Inhibitor Combinations

Fruquintinib's unique safety and tolerability profile, resulting from its high kinase selectivity, combined with better flexibility to manage treatment emergent toxicities due to its shorter half-life than monoclonal antibody antiangiogenesis therapies, makes it a suitable potential combination partner for EGFR tyrosine kinase inhibitors.

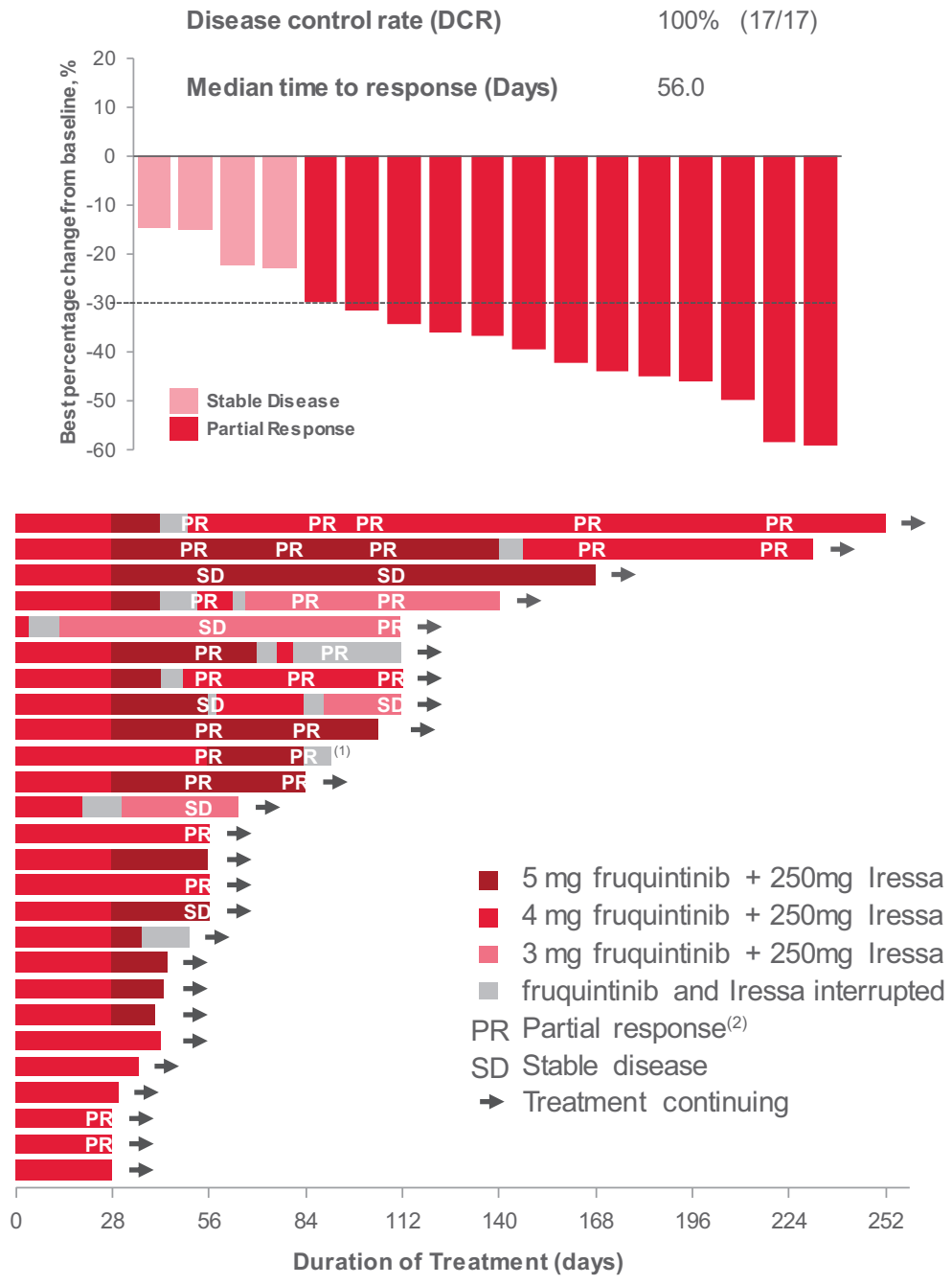
Phase II study of fruquintinib in combination with Iressa in first-line non-small cell lung cancer (Status: enrollment complete; NCT02976116)

In early 2017, we initiated a multi-center, single-arm, open-label, dose-finding Phase II study of fruquintinib in combination with Iressa in China in the first-line setting for patients with advanced or metastatic non-small cell lung cancer with EGFR activating mutations. We have enrolled about 50 patients in this study with the objective of evaluating the safety and tolerability as well as the efficacy of the combination therapy. Preliminary data was presented in 2017 at the World Conference on Lung Cancer, showing an encouraging response and safety profile.

There were eight (31%) CTC grade ≥3 treatment emergent adverse events being increased alanine aminotransferase (19%), increased aspartate aminotransferase (4%), proteinuria (4%) and hypertension (4%). There were no serious adverse events or those that lead to death. Preliminary results in 17 efficacy evaluable patients showed an objective response rate of 76% (13/17), including nine confirmed and four unconfirmed partial responses at the time of data cut-off, as well as a disease control rate of 100% (17/17).

The primary objective of this exploratory study is to determine the safety and tolerability and median progression-free survival of the fruquintinib and Iressa combination. Primary data completion is anticipated in late 2019.

Phase II Study of Fruquintinib Combined with Iressa in Non-small Cell Lung Cancer. Preliminary Data Showed Promising Efficacy in the First-line Setting.



Notes: Data as of October 2017; (1) Drug discontinuation due to CTC Grade 3 proteinuria and CTC Grade 3 QTc prolonged; and (2) Four partial responses not yet confirmed at the time of data cut-off date.

Source: *Lu, S., et al, "A Phase II study of fruquintinib in combination with gefitinib in stage IIIb/IV NSCLC patients harboring EGFR activating mutations", ID 10907 IASLC 18th World Conference on Lung Cancer, Yokohama, Japan, October 15-18, 2017.*

Fruquintinib Combinations with Checkpoint Inhibitors

The table below shows a summary of the clinical trials we have in planning for fruquintinib in combination with checkpoint inhibitors.

Clinical Trials of Fruquintinib with Checkpoint Inhibitors

Treatment	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Fruquintinib and genolimzumab (PD-1)	Solid tumors	China	I	Safety run-in in planning	TBD
Fruquintinib and Tyvyt (PD-1)	Solid tumors	China	I	Safety run-in in planning	TBD
Fruquintinib and Tyvyt (PD-1)	Solid tumors	U.S.	I	In planning	TBD

Note: TBD = to be determined.

In November 2018, we entered into two collaboration agreements to evaluate the safety, tolerability and efficacy of fruquintinib in combination with checkpoint inhibitors. These include a global collaboration with Innovent to evaluate the combination of fruquintinib with Innovent's Tyvyt (IBI308), a PD-1 monoclonal antibody approved in China in late 2018 and a collaboration in China with Genor to evaluate the fruquintinib combination with genolimzumab, a PD-1 monoclonal antibody being developed by Genor. Safety run-in studies are currently underway/in planning to establish the safe and effective dose regimens for the fruquintinib combinations with either Tyvyt or genolimzumab.

Overview of Elunate Commercial Launch

Fruquintinib capsules, sold under the brand name Elunate, were approved for marketing in China by the NMPA in September 2018 and commercially launched in late November 2018. Elunate is for the treatment of patients with metastatic colorectal cancer that have been previously treated with fluoropyrimidine, oxaliplatin and irinotecan, including those who have previously received anti-VEGF therapy and/or anti-EGFR therapy (RAS wild type).

Working closely with our commercial partner Eli Lilly, we were able to secure Elunate's inclusion on certain city-level reimbursement lists in early 2019. We believe this will give us a sense for the longer-term market potential for Elunate in third-line colorectal cancer patients. Aside from these cities, all sales are currently paid for out of pocket by patients, but we aim for Elunate eventually to be included in China's National Reimbursement Drug List. To broaden access to Elunate, Eli Lilly has implemented a means-based patient access program, whereby patients pay for three 28-day cycles of Elunate (cycles one, two and five) at the full price. Outside of these three paid-for cycles, Elunate will be provided for free.

Partnership with Eli Lilly

In October 2013, we entered into a license and collaboration agreement with Eli Lilly in order to accelerate and broaden our fruquintinib development program in China. As a result, we were able to quickly expand the clinical development of fruquintinib in three indications with major unmet medical needs in China: colorectal cancer, non-small cell lung cancer and gastric cancer, as discussed above. We recently amended our license and collaboration agreement with Eli Lilly. This amendment gives us, among other things, all planning, execution and decision making responsibilities for life cycle indication development of fruquintinib in China. It also gives us the promotion and distribution rights for fruquintinib in provinces that represent 30% (or 40% if certain additional criteria are met) of sales of fruquintinib in China upon the achievement of a non-fruquintinib related Eli Lilly commercial action. Support from Eli Lilly has also helped us to establish our own manufacturing (formulation) facility in Suzhou, China, which now produces clinical and commercial supplies of fruquintinib.

For more information regarding our partnership with Eli Lilly, see "*– Overview of Our Collaborations – Eli Lilly Agreement*."

3. Surufatinib VEGFR 1, 2 and 3, FGFR1 and CSF-1R Inhibitor

As with fruquintinib, surufatinib (also known as HMPL-012) was created as part of our initial research goals to develop better, more selective inhibitors than what was under late-stage development at the time, including inhibitors targeting VEGFR and FGFR, two tyrosine kinase receptors associated with angiogenesis and tumor growth. In early 2008, we declared our first small molecule oncology drug candidate, surufatinib, and it was subsequently the first new compound IND application to be submitted, reviewed and approved by the NMPA under its "green channel" fast-track approval process.

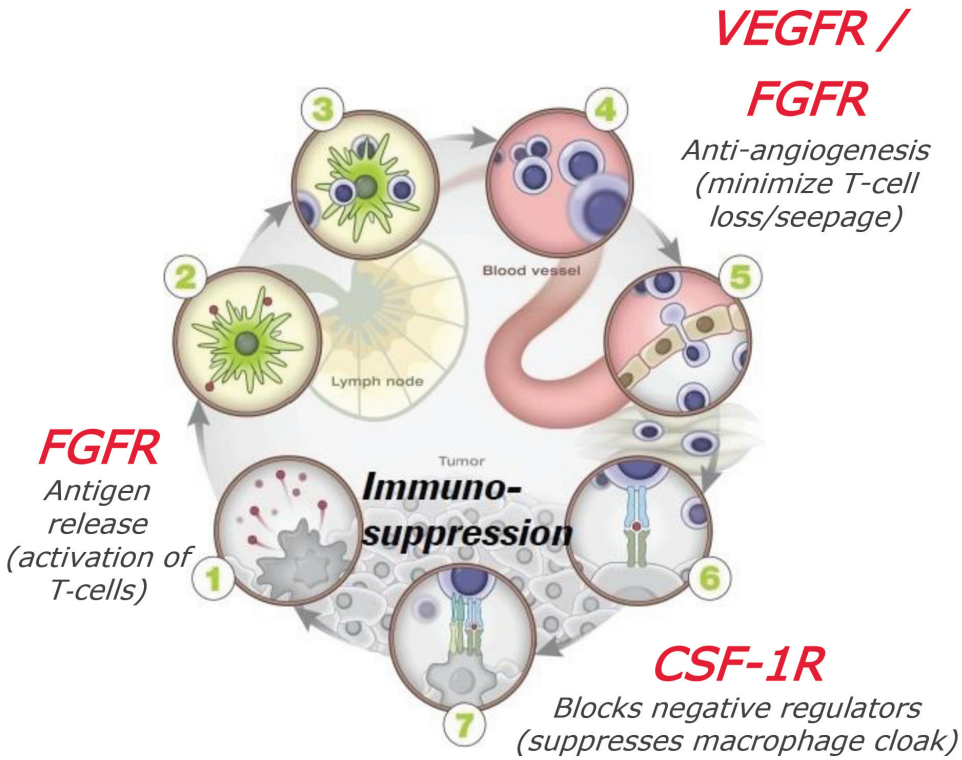
Surufatinib is an oral small molecule angio-immuno kinase inhibitor targeting VEGFR 1, 2 and 3, FGFR1 and CSF-1R, kinases that could simultaneously block tumor angiogenesis and immune evasion. Its unique angio-immuno kinase profile seems to support surufatinib as an attractive candidate for exploration of possible combinations with checkpoint inhibitors against various cancers. Surufatinib is currently in development as a single agent for neuroendocrine tumors and biliary tract cancer. It also has potential in other tumor types such as breast cancer with FGFR1 activation.

Surufatinib is the first oncology candidate that we have taken through proof-of-concept in China and expanded globally ourselves. Surufatinib is in proof-of-concept clinical trials in the United States and late-stage clinical trials in China as a monotherapy.

Mechanism of Action

Both VEGFR and FGFR signaling pathways can mediate tumor angiogenesis. CSF-1R plays an important role in the functions of macrophages. Recently, the roles in increasing tumor immune evasion of VEGFR, FGFR in regulation of T cells, tumor-associated macrophages and myeloid-derived suppressor cells have been demonstrated. Therefore, blockade of tumor angiogenesis and tumor immune evasion by simultaneously targeting VEGFR 1, 2 and 3, FGFR1 and CSF-1R kinases may represent a promising approach for oncology therapy.

Surufatinib's Unique Mechanism of Action Targets VEGFR 1, 2 and 3, FGFR1 and CSF-1R



Source: Company.

For more information on the VEGF mechanism of action, see "– *Our Clinical Pipeline – 2. Fruquintinib VEGFR 1, 2 and 3 Inhibitor – Mechanism of Action*."

Surufatinib Pre-clinical Evidence

Surufatinib inhibited VEGFR 1, 2, and 3, FGFR1 and CSF-1R kinases with IC_{50} in a range of 1 nM to 24 nM. It also strongly blocked VEGF-induced VEGFR2 phosphorylation in HEK293 cells and CSF-1R phosphorylation in RAW264.7 cells with an IC_{50} of 2 nM and 79 nM, respectively. Surufatinib also reduced VEGF- or FGF-stimulated human umbilical vein endothelial cell proliferation with an IC50 < 50 nM. In animal studies, a single oral dose of

surufatinib inhibited VEGF-stimulated VEGFR2 phosphorylation in lung tissues of nude mice in an exposure-dependent manner. Furthermore, elevation of FGF23 levels in plasma 24 hours post dosing suggested suppression of FGFR signaling.

Surufatinib demonstrated potent tumor growth inhibition in multiple human xenograft models and decreased cluster of differentiation 31 expression remarkably, suggesting strong inhibition on angiogenesis through VEGFR and FGFR signaling. In a syngeneic murine colon cancer model, surufatinib demonstrated moderate tumor growth inhibition after single-agent treatment. Flow cytometry and immunohistochemistry analysis revealed an increase of certain T cells and a significant reduction in certain tumor-associated macrophages, including CSF-1R mutation positive tumor-associated macrophages in tumor tissue, indicating surufatinib has a strong effect on CSF-1R. Interestingly, a combination of surufatinib with a PD-L1 antibody resulted in enhanced anti-tumor effect. These results suggested that surufatinib has a strong effect in modulating angiogenesis and cancer immunity.

Surufatinib First-in-human Studies

The multi-center, open-label, dose escalation, first-in-human Phase I study of surufatinib was initiated in China in 2010. Its primary objective was to study the safety and tolerability and determine the maximum tolerated dose or the recommended Phase II dose of surufatinib in patients with advanced malignant solid tumors. Secondary endpoints included pharmacokinetic properties and clinical efficacy. The study consisted of a dose escalation period and dose expansion period. The initial surufatinib dose was 50 mg, once daily. By 2014, 12 dose groups of 50-350 mg surufatinib per day had completed the dose escalation study. The maximum tolerated dose was not reached. However, the drug exposures appeared to stop increasing in proportion to dose from 300 mg to 350 mg. In addition, encouraging activity was seen both at 300 mg and 350 mg doses. A dose expansion study was conducted at the 300 mg and 350 mg dose levels to further investigate the safety, tolerability and pharmacokinetic profile, and preliminary efficacy of surufatinib. Final results as of 2015 were published in Oncotarget in February 2017.

A total of 77 patients were enrolled in the study. The first 43 patients were enrolled in surufatinib, formulation 1, in 50 mg, 75 mg, 110 mg, 150 mg, 200 mg, 265 mg and 300 mg once daily, as well as 125 mg and 150 mg twice daily dose cohorts. As the study progressed, a new milled formulation, formulation 2, was developed with an improved pharmacokinetic profile to replace formulation 1 and was used in the remaining study. There was no subject treated with surufatinib cross-over by formulations (i.e., no subject receiving formulation 1 had crossed over to formulation 2 during study treatment). A total of 34 patients were enrolled and treated with surufatinib formulation 2. 23 of the patients were enrolled in the formulation 2 dose escalation study in dose cohorts of 200 mg, 300 mg and 350 mg once daily, and a further 11 were enrolled in an expansion study in dose cohorts of 300 mg and 350 mg once daily. All 34 patients on formulation 2 completed the safety and pharmacokinetic evaluation. The maximum tolerated dose was also not reached in this formulation.

CTC grade ≥3 adverse events observed in formulation 2 patients with greater than 5% incidence include proteinuria (15%), hypertension (9%), increased aspartate aminotransferase (6%), diarrhea (6%), decreased hemoglobin (6%), decreased platelet count (6%) and hypophosphatemia (6%). No dose-limiting toxicity was observed, and maximum tolerated dose has not been determined. Overall, in this Phase I dose escalation study, surufatinib showed a safety profile that is comparable to the other drugs in the same class and that, as a single agent, it was well tolerated in patients with advanced solid tumors.

Pharmacokinetic analyses showed that the inter- and intra-individual variability in drug concentration was optimized and the exposures in terms of Cmax, or the maximum concentration that a drug achieves in a specified test area of the body after the drug has been administrated and prior to the administration of a second dose, and AUC were increased compared with formulation 1, indicating optimized oral absorption. Phase Ia pharmacokinetic profile of surufatinib in humans was consistent with pre-clinical findings in that surufatinib at the 300 mg Phase II dose provides for consistent and sustained target inhibition over 24 hours through an oral dose.

In terms of Phase Ia efficacy, among 34 patients treated with formulation 2, 28 patients were evaluable by RECIST 1.0 criteria, of which nine achieved confirmed partial response, including one patient with hepatocellular carcinoma receiving surufatinib 200 mg once daily, and eight with neuroendocrine tumors receiving surufatinib 300 or 350 mg once daily. There were 15 patients with stable disease (10 with neuroendocrine tumors, three with hepatocellular carcinoma, one with gastrointestinal stromal tumors, and one with an abdominal malignancy) and four patients with progressive disease. Based on confirmed responses, the objective response rate amongst all patients treated with surufatinib formulation 2 was 27% (9/34) and the disease control rate was 71% (24/34), or an objective response rate of 32% (9/28) and a disease control rate was 86% (24/28) amongst efficacy evaluable formulation 2 patients. The recommended Phase II dose was determined to be 300 mg once daily based on overall safety, tolerability and early clinical efficacy results.

Favorable clinical efficacy has been seen with surufatinib in patients with neuroendocrine tumors. The formulation 2 expansion study was conducted in neuroendocrine tumor patients who were given 300 mg or 350 mg once daily. Including dose escalation patients, a total of 21 neuroendocrine tumor patients were treated with formulation 2. There were eight confirmed partial response patients, 10 stable disease patients, and three patients were not evaluable for response. This yielded an objective response rate of 44% in the 18 evaluable neuroendocrine tumor patients and 38% in the entire intent-to-treat population of 21 neuroendocrine tumor formulation 2 patients (compared to an objective response rate of less than 10% for competing products, Sutent and Afinitor). The tumor origins of the eight neuroendocrine tumor patients with partial responses include pancreas (3 patients), duodenum (1 patient), rectum (1 patient) and thymus (1 patient), with the remaining two patients' tumors of unknown origin. Furthermore, neuroendocrine tumor responses to surufatinib have been observed to improve gradually with time.

This early preliminary clinical efficacy of surufatinib compared favorably to existing drugs approved for the treatment of neuroendocrine tumors. As shown below, however, approved therapies for neuroendocrine tumors are very limited with Afinitor and Sutent approved only for pancreatic neuroendocrine tumors (representing less than 10% of total neuroendocrine tumors) and showing an objective response rate of less than 10%. The somatostatin analogues octreotide and lanreotide are also approved for narrow subsets of gastrointestinal neuroendocrine tumors, but their objective response rate is less than 5%. In January 2018, the FDA approved Lutathera (lutetium Lu 177 dotatate) injection, a radiolabeled somatostatin analog which, like octreotide and lanreotide, is indicated for the treatment of somatostatin receptor-positive neuroendocrine tumors (gastroenteropancreatic in the case of Lutathera), and has a half-life of less than seven days.

Surufatinib Clinical Trials

We currently have various clinical trials of surufatinib ongoing or expected to begin in the near term in patients with neuroendocrine tumors and biliary tract cancer and in combination with checkpoint inhibitors.

Neuroendocrine tumors

The table below shows a summary of the clinical trials that we have completed underway for surufatinib in neuroendocrine cancer patients.

Clinical Trials of Surufatinib in Neuroendocrine Tumors

Treatment	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Surufatinib monotherapy	Pancreatic NET	China	Ib/II	Completed	NCT02267967
Surufatinib monotherapy	SANET-p: Pancreatic NET	China	III	Interim analysis end 2019; Est. enrolled early 2020	NCT02589821
Surufatinib monotherapy	2L Pancreatic NET; Sutent/Afinitor refractory	US/EU	Ib	US/EU registration study in planning	NCT02549937
Surufatinib monotherapy	SANET-ep: Non-pancreatic NET	China	III	Interim analysis mid-2019 Est. enrolled 2019/2020	NCT02588170

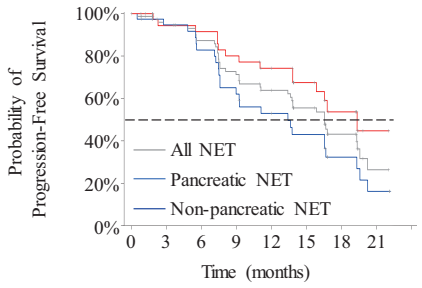
Notes: Sutent/Afinitor refractory = resistant to previous Sutent or Afinitor therapy; NET = neuroendocrine tumor; and Est. = estimated.

Phase Ib/II study of surufatinib monotherapy in neuroendocrine tumors (Status: completed; NCT02267967)

In 2015, we began a 30-patient, 300 mg daily, Phase Ib study in China in broad spectrum neuroendocrine tumor patients (pancreatic, gastrointestinal, liver, lymph and lung, among others) which, due to the major unmet medical need and strong efficacy of surufatinib, was expanded to over 65 patients, and enrollment was completed in August 2015. We then amended the protocol from a Phase Ib study to a single arm Phase II study for which enrollment of 81 patients (41 with pancreatic neuroendocrine tumors and 40 with extra-pancreatic neuroendocrine tumors) was completed in December 2015.

The majority of the patients enrolled in this Phase II study had grade 2 diseases (79%) and had failed previous systemic treatments (65%). We reported the results of this Phase II study at the 2017 European Neuroendocrine Tumor Society conference. As of January 2017, 13 patients had confirmed partial response and 61 patients had stable disease corresponding to an overall objective response rate of 16%, with 17% in pancreatic neuroendocrine tumors and 15% in extra-pancreatic neuroendocrine tumors, and an overall disease control rate of 91%. Median overall progression-free survival has not been reached, but is estimated to be 16.6 months, with as-expected, longer median progression-free survival in pancreatic neuroendocrine tumors estimated to be 19.4 months and shorter median progression-free survival in extra-pancreatic neuroendocrine tumors estimated to be 13.4 months. Importantly, in the context of our potential global development strategy, there were 14 patients who had progressed after treatment with systemic therapies (Sutent and Afinitor) and all benefited from the surufatinib treatment (four patients with partial response and 10 patients with stable disease). Surufatinib was well tolerated with adverse events CTC grade ≥3 with greater than 5% incidence being hypertension (31%), proteinuria (14%), hyperuricemia (10%), hypertriglyceridemia (9%), diarrhea (7%) and alanine aminotransferase increase (6%). Based on this promising efficacy data and tolerability in patients with advanced pancreatic neuroendocrine tumors, two randomized Phase III trials, SANET-p and SANET-ep, have been initiated, as discussed below.

Phase II Study in China of Surufatinib Monotherapy in Neuroendocrine Tumors. Interim Data Demonstrates Promising Efficacy.



	Median PFS (months)	PD or Deaths (% pts)
All NET (n=81)	**16.6m** (13.4, 19.4)	51.9% (42/81)
P-NET (n=41)	**19.4m** (13.8, 22.1)	39.0% (16/41)
Non-P NET (n=40)	**13.4m** (7.6, 16.7)	65.0% (26/40)

Notes: NET = neuroendocrine tumors; P-NET = pancreatic neuroendocrine tumors; Non-P NET = non-pancreatic neuroendocrine tumors; PD = progressive disease; % pts = percentage of patients; PFS = progression-free survival; n = number of patients; and m = months.

Source: *European Neuroendocrine Tumour Society Annual Conference 2017. Data cut-off as of January 20, 2017.*

SANET-p study; Phase III study of surufatinib monotherapy in pancreatic neuroendocrine tumors (Status: enrolling; NCT02589821)

In 2016, we initiated the SANET-p study, which is a Phase III study in China in patients with low- or intermediate-grade, advanced pancreatic neuroendocrine tumors. In this study, patients are randomized at a 2:1 ratio to receive either an oral dose of 300 mg of surufatinib or a placebo once daily on a 28-day treatment cycle. The primary endpoint is progression-free survival, with secondary endpoints including objective response rate, disease control rate, time to response, duration of response, overall survival, safety and tolerability.

We expect to deliver an interim analysis in late 2019 and complete enrollment in early 2020. If the SANET-p Phase III data is consistent with the 17% objective response rate and estimated 19.4 month median progression-free survival reported in the above-mentioned Phase Ib/II study, we believe the benefits of surufatinib as a monotherapy to the approximately 3,200 new patients with pancreatic neuroendocrine tumors in China could be significant as compared to the treatment alternatives currently available to them.

Phase Ib/IIa study of surufatinib monotherapy in second-line pancreatic neuroendocrine tumors (Status: enrolling; NCT02549937)

In 2015, we initiated a multi-center, open-label, Phase I clinical study to evaluate the safety, tolerability and pharmacokinetics of surufatinib in U.S. patients with advanced solid tumors, which established the U.S. recommended Phase II dose to be the same as that in China. The encouraging data from the Phase II study of surufatinib in pancreatic neuroendocrine tumor patients in China discussed above has led us to expand enrollment in the United States into pancreatic neuroendocrine tumor patients. In addition, we have decided to proceed with planning for a U.S. and Europe registration study of surufatinib in patients with pancreatic neuroendocrine tumors who have progressed on Sutent or Afinitor.

SANET-ep study; Phase III study of surufatinib monotherapy in extra-pancreatic neuroendocrine tumors (Status: enrolling; NCT02588170)

In 2015, we initiated the SANET-ep study, which is a Phase III study in China in patients with low- or intermediate-grade advanced extra-pancreatic neuroendocrine tumors. In this study, patients are randomized at a 2:1 ratio to receive either an oral dose of 300 mg of surufatinib or a placebo once daily on a 28-day treatment cycle. The primary endpoint is progression-free survival, with secondary endpoints including objective response rate, disease control rate, time to response, duration of response, overall survival, safety and tolerability.

We expect to deliver an interim analysis in mid-2019 and complete enrollment in 2020. If the SANET-ep Phase III data is consistent with the 15% objective response rate and estimated 13.4 month median progression-free survival reported in the above-mentioned Phase II study, we believe the benefit of surufatinib as a monotherapy to patients with extrapancreatic neuroendocrine tumors in China could be significant as compared to the minimal treatment alternatives currently available to them.

Biliary Tract Cancer

Biliary tract cancer (also known as cholangiocarcinoma) is a heterogeneous group of rare malignancies arising from the biliary tract epithelia. Gemzar, a type of chemotherapy, is the currently approved first-line therapy for biliary tract cancer patients, with median survival of less than 12 months for patients with unresectable or metastatic disease at diagnosis. As a result, this is a major unmet medical need for patients who have progressed on chemotherapy. There is currently no standard of care for these patients. Surufatinib may offer a new targeted treatment option in this tumor type. The table below shows a summary of the clinical study that we have underway for surufatinib in biliary tract cancer patients.

Clinical Trial of Surufatinib in Biliary Tract Cancer

Treatment	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Surufatinib monotherapy	Chemotherapy refractory BTC	China	Ib/II	Enrollment complete	NCT02966821
Surufatinib monotherapy	Chemotherapy refractory BTC	China	II/III	Enrolling	NCT03873532

Note: BTC = biliary tract cancer.

Phase II/Ib surufatinib monotherapy in chemotherapy refractory biliary tract cancer – China (Status: enrollment complete; NCT02966821)

In early 2017, we began a Phase Ib/II proof-of-concept study in patients with biliary tract cancer and expect to submit the results of this study for publication during 2019. We have dosed the first patient in the open-label Phase II/III study of surufatinib in second-line biliary tract cancer patients in comparison to capecitabine in China.

Surufatinib Combinations with Checkpoint Inhibitors

The table below shows a summary of the clinical trials that we have in planning for surufatinib combination with checkpoint inhibitors.

Clinical Trials of Surufatinib with Checkpoint Inhibitors

Treatment	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Surufatinib and Tuoyi (PD-1)	Solid tumors	China	I	Enrolling	NCT03879057
Surufatinib and Tuoyi (PD-1)	Solid tumors	U.S.	I	In planning	TBD
Surufatinib and HX008 (PD-1)	Solid tumors	China	I	Safety run-in in planning	TBD

Note: TBD = to be determined.

In November 2018, we entered into two collaboration agreements to evaluate the safety, tolerability and efficacy of surufatinib in combination with checkpoint inhibitors. These include a global collaboration with Junshi to evaluate the combination of surufatinib with Junshi's Tuoyi, a PD-1 monoclonal antibody approved in China in late 2018, and a collaboration in China with Hanzhong to evaluate the combination of surufatinib with HX008, a PD-1 monoclonal antibody being developed by Hanzhong. A Phase I safety run-in study of savolitinib in combination with Tuoyi in China is enrolling. Two other safety run-in studies are currently in planning.

4. HMPL-523 Syk Inhibitor

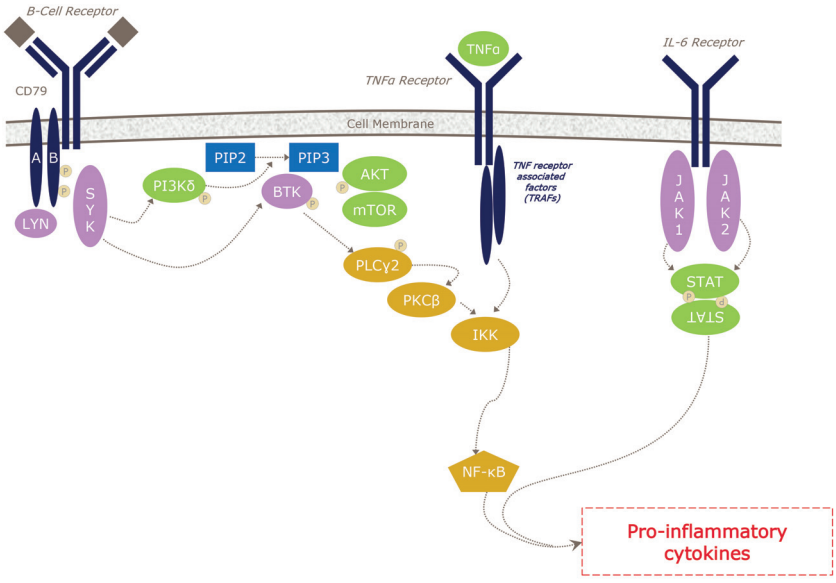
The result of our over six-year program of discovery and pre-clinical work against Syk is HMPL-523, a highly selective Syk inhibitor with a unique pharmacokinetic profile which provides for higher drug exposure in the tissue than on a whole blood level. We designed HMPL-523 intentionally to have high tissue distribution because it is in the tissue that the B-cell activation associated with rheumatoid arthritis and lupus occurs most often. Furthermore, and somewhat counter intuitively, in hematological cancer the vast majority of cancer cells nest in tissue, with a small proportion of cancer cells releasing and circulating in the blood where they cannot survive for long. In both rheumatoid arthritis and hematological cancer, we assessed that an effective small molecule Syk inhibitor would need to have superior tissue distribution.

However, many pharmaceutical and biotechnology companies had experienced difficulties in developing a safe and efficacious Syk-targeted drug. For example, the development of the Syk inhibitor Tavalisse for rheumatoid arthritis was one such failed program, although clear efficacy was observed in Phase II and Phase III trials. The main problem was off-target toxicities associated with poor kinase selectivity, such as hypertension and severe diarrhea. Therefore, we believe that kinase selectivity is critical to a successful Syk inhibitor. In addition, Tavalisse was designed as a prodrug in order to improve solubility and oral absorption. A prodrug is medication administered in a pharmacologically inactive form which is converted to an active form once absorbed into circulation. The rate of the metabolism required to release the active form can vary from patient to patient, resulting in large variation in active drug exposures that can impact efficacy. We believe HMPL-523 offers important advantages over intravenous monoclonal antibody immune modulators in rheumatoid arthritis in that small molecule compounds clear the system faster, thereby reducing the risk of infections from sustained suppression of the immune system.

Mechanism of Action

Targeting the B-cell signaling pathway is emerging as a potential means to treat both hematological cancer and immunological diseases. Inhibiting PI3Kδ and BTK, two kinases found along the B-cell signaling pathway, has proven to have clinical efficacy in hematological cancers, with three breakthrough therapies having been recently approved by the FDA. Syk is a key kinase upstream to PI3Kδ and BTK within the B-cell signaling pathway and therefore thought to be an important target for modulating B-cell signaling.

The B-cell Signaling Pathway



Notes: This graphic is a highly simplified representation of the B-cell signaling pathways, which are each composed of a signaling cascade of the multiple kinases indicated in the graphic. Signaling from the B-cell receptor (BCR) through the cascade, in simple terms, triggers an immune response, including tumor cell activation, proliferation, survival and migration.

Source: Company.

Syk, a target for oncology

In hematological cancer, we believe Syk is a high potential target. In hematopoietic cells, Syk is recruited to the intracellular membrane by activated membrane receptors like B-cell receptors or another receptor called Fc and then binds to the intracellular domain of the receptors. Syk is activated after being phosphorylated by certain kinases and then further induces downstream intracellular signals including B-cell linker, PI3Kδ, BTK and Phospholipase Cγ2 to regulate B-cell proliferation, growth, differentiation, homing, survival, maturation, and immune responses. Syk not only involves the regulation of lymphatic cells but also signal transduction of non-lymphatic cells such as mast cells, macrophages, and basophils, resulting in different immunological functions such as degranulation to release immune active substances, leading to immunological reaction and disease. Therefore, regulating B-cell signal pathways through Syk is expected to be effective for treating lymphoma.

The high efficacy and successful approvals of both Imbruvica (developed by AbbVie Inc.), a BTK inhibitor, and Zydelig (developed by Gilead), a PI3Kδ inhibitor, are evidence that modulation of the B-cell signaling pathway is critical for the effective treatment of B-cell malignancies. Syk is upstream of both BTK and PI3Kδ, and we believe it could deliver the same outcome as Imbruvica and Zydelig, assuming no unintentional toxicities are derived from Syk inhibition. Entospletinib (GS-9973), a Syk inhibitor developed by Gilead, reported promising Phase II study results in late 2015 with a nodal response rate of 65% observed in

chronic lymphocytic leukemia and small lymphocytic lymphoma. Nodal response is defined as a greater than 50% decrease from baseline in the sum of lymph node diameters. Gilead has also reported that entospletinib demonstrated a nodal response rate of 44% in an exploratory clinical study in chronic lymphocytic leukemia patients previously treated with Imbruvica and Zydelig, thereby indicating that Syk inhibition has the potential to overcome resistance to Imbruvica and Zydelig. Takeda reported similarly strong signs of efficacy for their TAK-659 Phase I dose escalation study in lymphoma, which was also published in late 2015.

Syk, a target for immunological diseases

The central role of Syk in signaling processes is not only in cells of immune responses but also in cell types known to be involved in the expression of tissue pathology in autoimmune, inflammatory and allergic diseases. Therefore, interfering with Syk could represent a possible therapeutic approach for treating these disorders. Indeed, several studies have highlighted Syk as a key player in the pathogenesis of a multitude of diseases, including rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis.

HMPL-523 Research Background

The threshold of safety for a Syk inhibitor in chronic disease is extremely high, with no room for material toxicity. The failure of Tavalisse in a global Phase III registration study in rheumatoid arthritis provided important insights for us in the area of toxicity. While Tavalisse clearly showed patient benefit in rheumatoid arthritis, a critical proof-of-concept for Syk modulation, it also caused high levels of hypertension which is widely believed to be due to the high levels of off-target KDR inhibition. In addition, Tavalisse has also been shown to strongly inhibit the Ret kinase, and in pre-clinical trials it was demonstrated that inhibition of the Ret kinase was associated with developmental and reproductive toxicities.

The requirement for Syk kinase activity in inflammatory responses was first evaluated with Tavalisse, which was co-developed by AstraZeneca/Rigel Pharmaceuticals, Inc. (also called R788, a prodrug of an active Syk inhibitor R406). In 2013, AstraZeneca announced results from pivotal Phase III clinical trials that Tavalisse statistically significantly improved ACR20 (a 20% improvement from baseline based on the study criteria) response rates of patients inadequately responding to conventional disease-modifying anti-rheumatic drugs and a single anti-TNFα (a key pro-inflammatory cytokine involved in rheumatoid arthritis pathogenesis) antagonist at 24 weeks, but failed to demonstrate statistical significance in comparison to placebo at 24 weeks. As a result, AstraZeneca decided not to proceed.

Tavalisse was also in trials for B-cell lymphoma and T-cell lymphoma. It demonstrated some clinical efficacy in diffused large B-cell lymphoma patients with an objective response rate of 22%. Entospletinib, a Syk inhibitor developed by Gilead, has features of high potency and good selectivity toward kinases. However, while the Phase II study discussed above showed that it had significant efficacy in patients with chronic lymphocytic leukemia and small lymphocytic lymphoma, its poor solubility and permeability into intestinal epithelial cells resulted in unsatisfactory oral absorption and a great variation of individual drug exposure. In

addition, entospletinib shows some inhibition of the CYP3A4, CYP2D6, and CYP1A2 enzymes involved in the metabolism of certain drugs, and therefore their inhibition could increase the risk of drug-to-drug interaction when used in combined therapy.

HMPL-523 Pre-clinical Evidence

The safety profile of HMPL-523 was evaluated in multiple in vitro and in vivo pre-clinical trials under good laboratory practice guidelines and found to be well tolerated following single dose oral administration. Toxic findings were seen in repeat dose animal safety evaluations in rats and dogs at higher doses and found to be reversible. These findings can be readily monitored in the clinical trials and fully recoverable upon drug withdrawal. The starting dose in humans was suggested to be 5 mg. This dose level is approximately 5% of the human equivalent dose extrapolated from the pre-clinical "no observed adverse event levels", which is below the 10% threshold recommended by FDA guidelines.

In vitro Pharmacology

HMPL-523 is a highly selective Syk inhibitor with an IC_{50} of 24 ± 4 nM (n=7) in a Syk kinase enzymatic assay. HMPL-523 has been evaluated in a kinase selectivity panel of 287 kinases and a broad pharmacological panel of 79 targets. We believe, as shown in the chart below, HMPL-523's lack of KDR inhibition will mean a much lower risk of hypertension, which is a major off-target toxicity of R406 in clinical trials.

HMPL-523 Kinase Selectivity in Comparison to R406 (The Syk Inhibitor, Metabolite of Tavalisse). R406 is Shown Below to be as Potent in Inhibiting KDR as it is in Inhibiting Syk, and Significantly More Potent in Inhibiting FLT3 and Ret.

Selectivity	**HMPL-523 IC_{50} (nM)**	**Tavalisse IC_{50} (nM)**
Syk enzyme	25 ± 5 (n=10)*	54 ± 16 (n=10)*
JAK 1,2,3 enzyme	>300, >300, >300*	120, 30, 480*
FGFR 1,2,3	>3,000, >3,000, >3,000	89, 22, 32*
FLT3 enzyme	63*	9*
LYN enzyme	921*	160*
Ret enzyme	>3,000*	5**
KDR enzyme	390 ± 38 (n=3)*	61 ± 2 (n=3)*
KDR cell	5,501 ± 1,607 (n=3)*	422 ± 126 (n=3)*

*Sources: * Chi-Med, Eun-ho Lee et al., 2011 American College of Rheumatology; and ** S. P. McAdoo and F. W. Tam, Drugs Future, 2011, 36(4), PP273-283.*

In vivo Pharmacology

HMPL-523 blocked B-cell activation in mouse whole blood and rat whole blood *ex vivo* challenge with an EC_{50} of 1301 ng/mL (ED_{50} of 2.9 mg/kg) and 332.8~471.7 ng/mL (ED_{50} of 4.1~5.2 mg/kg) at 2 hours after dosing, respectively. The maximum inhibition was observed at 2 hours after oral dosing, while the significant inhibition was maintained for up to 4 hours. In collagen-induced rheumatoid arthritis in mice and rats, HMPL-523 treatment significantly reduced disease severity in a dose dependent manner. HMPL-523 not only halted disease progression, but also reversed aspects of the disease such as paw swelling and bone resorption to normal levels at higher doses in rat collagen-induced arthritis therapeutic models. HMPL-523 dose delivered similar efficacy to both Tavalisse, at a significantly higher dosage, and Enbrel (an approved monoclonal antibody from Amgen/Pfizer/Takeda).

In lupus-prone mice, HMPL-523 significantly blocked skin lesions, delayed the onset of proteinuria (the presence of abnormal quantities of proteins in urine which may indicate kidney damage) and reduced the immune organs to body weight ratios and suppressed production of anti-dsDNA antibodies (a group of anti-nuclear antibodies that act against certain DNA).

Anti-tumor activity and combination synergy with other therapies

In *in vitro* B-cell lymphoma cell lines with Syk/BCR dysregulation, HMPL-523 was found to block phosphorylation of B-cell linker protein as well as inhibit cell viability by inhibiting cell survival and increasing apoptotic rate. HMPL-523 also showed synergistic anti-tumor activity on human diffused large B-cell lymphoma cells, in combination with other drugs such as PI3Kδ inhibitors, B-cell lymphoma 2 family inhibitors, or chemotherapies. Potent anti-tumor activity was also demonstrated in nude mice bearing B-cell lymphoma xenograft tumors with Syk/B-cell receptor dysregulation

HMPL-523 First-in-human Studies

Phase I study of HMPL-523 in healthy volunteers in Australia and China (Status: complete; NCT02105129)

In 2016, we reported results of the Phase I dose-escalation study on HMPL-523 in healthy volunteers in Australia, in which a total of 118 adult male healthy subjects were enrolled at baseline and 114 (97%) subjects completed the study. The Phase I study showed HMPL-523 exhibited a tolerable safety profile. A total of 83 treatment emergent adverse events were reported, with 39% in the HMPL-523 groups and 32% in the placebo groups, respectively. Two serious adverse events were reported in the Phase I study and when HMPL-523 was discontinued in those subjects the serious adverse events were resolved. Off-target toxicities such as diarrhea and hypertension, seen with the first-generation Syk inhibitor Tavalisse, were not observed.

In an ex-vivo human whole blood pharmacodynamic assay, HMPL-523 inhibited anti-IgE-induced basophil activation (CD63+) in a concentration-dependent manner with an estimated half maximal effective concentration of 47.70mg/mL. Systemic exposure of HMPL-523 was increased up to 1.5 fold when administered in a fed condition compared to a fasted condition, indicating that food consumption increases the relative bioavailability of HMPL-523. Human pharmacokinetic exposures at 200 mg once daily and above can be expected to provide the target coverage required for clinical efficacy based on the pre-clinical human pharmacokinetic/pharmacodynamics analysis and as a result, a multiple-dose regimen of 300 mg or less of HMPL-523, administered once daily, is the recommended Phase II dose for clinical trials in immunological diseases. HMPL-523 demonstrated a dose dependent suppression of B-cell activation. The data were presented at the annual meeting of the American College of Rheumatology/Association of Rheumatology Health Professionals in 2016. We have submitted IND applications for immunological diseases and expect, pending the imminent submission of additional data requested by the FDA, to progress into a Phase II proof-of-concept study in immunology in 2019.

HMPL-523 Clinical Trials

As discussed below, we currently have various clinical trials of HMPL-523 ongoing or expected to begin in the near term in Australia, the United States, Europe and China as a monotherapy and in combination with Vidaza. The table below shows a summary of the clinical trials that we have underway for HMPL-523.

Clinical Trials of HMPL-523

Treatment	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
HMPL-523 monotherapy	Indolent NHL	Australia	Ib	Enrolling	NCT02503033
HMPL-523 monotherapy	Multiple subtypes of B cell malignancies	China	Ib	Enrolling	NCT02857998
HMPL-523 monotherapy	Indolent NHL	US/EU	I	In planning	NCT03779113
HMPL-523 and Vidaza	AML	China	I	Enrolling	NCT03483948
HMPL-523 monotherapy	Immune thrombocytopenia	China	I/Ib	In planning	TBD

Notes: NHL = non-Hodgkin's lymphoma; AML = acute myeloid leukemia; and TBD = to be determined.

Phase Ib studies of HMPL-523 in indolent non-Hodgkin's lymphoma and multiple subtypes of B cell malignancies (Status: enrolling; NCT02503033/NCT02857998)

In early 2016, we initiated a Phase I dose escalation study of HMPL-523 in Australia in hematological cancer patients and have completed seven dose cohorts. A Phase I study in China began in early 2017 and has now completed five dose cohorts. In both Australia and China, we have established both efficacious once daily and twice daily dose regimens. Since early 2018, we have been increasing the number of active clinical sites, now totaling 18, in Australia and China to support a large dose expansion program in a broad range of hematological cancers. We intend to use safety and efficacy data from these Phase I/Ib dose escalation/expansion studies in B-cell malignancies to guide registration strategy in China during late 2019.

Phase I study of HMPL-523 in indolent non-Hodgkin's lymphoma (Status: in planning; NCT03779113)

Our U.S. IND application for HMPL-523 was cleared by the FDA in mid-2018, and we are now planning to start a Phase I/Ib study in indolent non-Hodgkin's lymphoma patients in the U.S. and Europe in the first half of 2019.

Phase I study of HMPL-523 in combination with Vidaza in acute myeloid leukemia (Status: Enrolling; NCT03483948)

In October 2018, we initiated a Phase I study of HMPL-523 in combination with Vidaza, an approved hypomethylating agent, in elderly patients with acute myeloid leukemia in China. This is a Phase I, open-label, multicenter study to evaluate the safety, pharmacokinetics and preliminary efficacy of the combination in previously untreated elderly patients with acute myeloid leukemia. The primary outcome measure is safety with a secondary endpoint of efficacy. The two-stage study will have a dose escalation and dose expansion stage.

Phase I/Ib study of HMPL-523 in patients with immune thrombocytopenia (Status: in planning)

We are also considering immunology applications for HMPL-523 including immune thrombocytopenia in China. Immune thrombocytopenia purpura is an autoimmune disorder characterized by low platelet count and an increased bleeding risk. Despite availability of several treatments with differing mechanisms of action, a significant proportion of patients develop resistance to treatment and are prone to relapse. In addition, there is a significant population of patients who have limited sensitivity to currently available agents and are in need of a new approach to treatment.

5. HMPL-689 PI3Kδ Inhibitor

HMPL-689 is a novel, highly selective and potent small molecule inhibitor targeting the isoform PI3Kδ, a key component in the B-cell receptor signaling pathway. We have designed HMPL-689 with superior PI3Kδ isoform selectivity, in particular to not inhibit PI3Kγ (gamma), offering advantages over Zydelig to minimize the risk of serious infection caused by

immune suppression. HMPL-689's strong potency, particularly at the whole blood level, also allows for reduced daily doses to minimize compound related toxicity, such as the high level of liver toxicity observed with the first-generation PI3Kδ inhibitor Zydelig. HMPL-689's pharmacokinetic properties have been found to be favorable with good oral absorption, moderate tissue distribution and low clearance in pre-clinical pharmacokinetic studies. We also expect that HMPL-689 will have low risk of drug accumulation and drug-to-drug interaction.

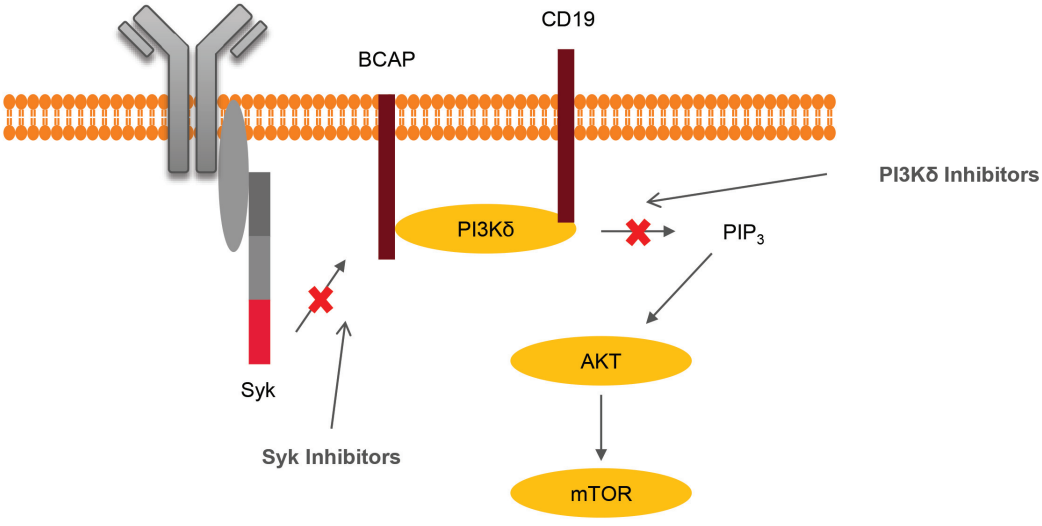
Mechanism of Action

Class I phosphatidylinositide-3-kinases, or PI3Ks, are lipid kinases that, through a series of intermediate processes, control the activation of several important signaling proteins including the serine/threonine kinase AKT. In most cells, AKT is a key PI3K effector that regulates cell proliferation, carbohydrate metabolism, cell motility and apoptosis, and other cellular processes.

There are multiple sub-families of PI3K kinases, and PI3Kδ is a lipid kinase that, through a series of intermediate processes, controls the activation of several important signaling proteins, including the serine/threonine kinase AKT. In most cells, AKT is a key PI3Kδ affector that regulates cell proliferation, carbohydrate metabolism, cell motility and apoptosis and other cellular processes. Upon an antigen binding to B-cell receptors, PI3Kδ can be activated through the Lyn and Syk signaling cascade.

Aberrant B-cell function has been observed in multiple immunological diseases and B-cell mediated malignancies. Therefore, PI3Kδ is considered to be a promising target for drugs that aim to prevent or treat hematologic cancer, autoimmunity and transplant organ rejection and other related inflammation diseases.

Mechanism of Action of PI3Kδ Inhibitors



Source: Frost & Sullivan.

HMPL-689 Pre-clinical Evidence

Compared to other PI3Kδ inhibitors, HMPL-689 shows higher potency and selectivity.

Enzyme Selectivity (IC_{50}, in nM) of HMPL-689 Versus Competing PI3Kδ Inhibitors; this Shows HMPL-689 is Approximately Five-fold More Potent than Zydelig on Whole Blood Level and, unlike Copiktra, does not Inhibit PI3Kγ.

Enzyme IC_{50} (nM)	HMPL-689	Zydelig	Copiktra	Aliqopa
PI3Kδ	0.8 (n = 3)	2	1	0.7
PI3Kγ (fold vs. PI3Kδ)	114 (142x)	104 (52x)	2 (2x)	6.4 (9x)
PI3Kα (fold vs. PI3Kδ)	>1,000 (>1,250x)	866 (433x)	143 (143x)	0.5 (1x)
PI3Kδ human whole blood CD63+	3	14	15	n/a
PI3Kβ (fold vs. PI3Kδ)	87 (109x)	293 (147x)	8 (8x)	3.7 (5x)

Source: Company.

HMPL-689 First-in-human Studies

In 2016, we completed a Phase I, first-in-human, dose escalation study in healthy adult volunteers in Australia to evaluate the pharmacokinetics and safety profile following single oral dosing HMPL-689 (NCT02631642). Results were as expected with linear pharmacokinetics properties and good safety profile.

We subsequently received IND clearance in China and then initiated a Phase I dose escalation and expansion study in patients with hematologic malignancies in August 2017 (NCT03128164). We will aim to complete dose escalation and begin dose expansion in China in 2019.

We have received IND clearance for HMPL-689 in the United States and Europe. We plan to start a Phase I/Ib study in indolent NHL in the U.S. and Europe in the first half of 2019 (NCT03786926).

6. Epitinib EGFR Inhibitor

Epitinib (also known as HMPL-813) is a potent and highly selective oral EGFR inhibitor designed to optimize brain penetration. A significant portion of patients with non-small cell lung cancer go on to develop brain metastasis. Patients with brain metastasis suffer from poor prognosis and low quality of life with limited treatment options. Epitinib is a potent and highly selective oral EGFR inhibitor which has demonstrated brain penetration and efficacy in pre-clinical and now clinical trials. EGFR inhibitors have revolutionized the treatment of

non-small cell lung cancer with EGFR activating mutations. However, approved EGFR inhibitors such as Iressa and Tarceva cannot penetrate the blood-brain barrier effectively, leaving the majority of patients with brain metastasis without an effective targeted therapy.

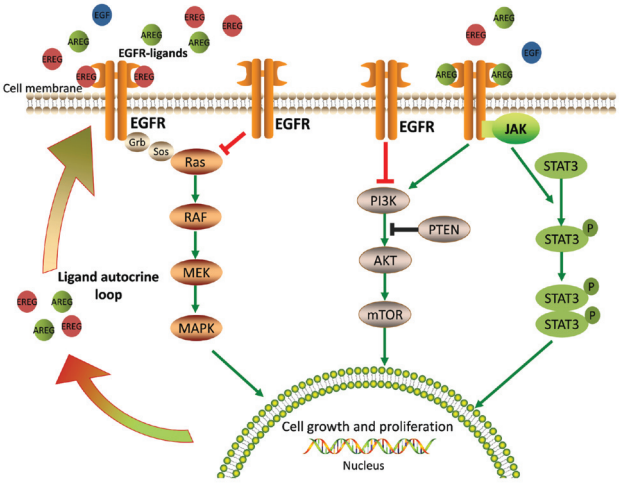
Our strategy has been to create targeted therapies in the EGFR area that would go beyond the already approved EGFRm+ non-small cell lung cancer patient population to address certain areas of unmet medical needs that represent significant market opportunities, including: (i) brain metastasis and/or primary brain tumors with EGFRm+, which we seek to address with epitinib; and (ii) tumors with EGFR gene amplification or EGFR overexpressed, which we seek to address with theliatinib as discussed below.

Mechanism of Action

EGFR is a protein that is a cell surface receptor tyrosine kinase for epidermal growth factor. Activation of EGFR can lead to a series of downstream signaling activities that activate tumor cell growth, survival, invasion, metastasis and inhibition of apoptosis. Tumor cell division can happen uncontrollably when the pathway is abnormally activated through EGFRm+, gene amplification of wild-type EGFR or overexpression of wild-type EGFR. Treatment strategies for certain cancers involve inhibiting EGFRs with small molecule tyrosine kinase inhibitors. Once the tyrosine kinase is disabled, it cannot activate the EGFR pathway and trigger downstream signaling activities, thereby suppressing cancer cell growth.

Outside of non-small cell lung cancer, EGFRm+ also occurs in glioblastoma, a common type of malignant primary brain tumor.

The EGFR Signaling Pathway



Notes: This graphic is a highly simplified representation of the two main EGFR signaling pathways, which are each composed of a signaling cascade of the multiple kinases indicated in the graphic. Signaling from the EGFR receptor through the cascade triggers tumor cell growth, survival, invasion, metastasis and inhibition of apoptosis (cell death).

Source: Company.

Epitinib Pre-clinical Evidence

Pre-clinical trials and orthotopic brain tumor models have shown that epitinib demonstrated brain penetration and efficacy superior to that of current globally marketed EGFRm+ inhibitors such as Iressa and Tarceva. In orthotopic brain tumor models, epitinib demonstrated good brain penetration, efficacy and pharmacokinetic properties as well as a favorable safety profile.

Epitinib First-in-human Studies

A first-in-human study was conducted in China to assess the maximum tolerated dose and dose-limiting toxicity, safety and tolerability, pharmacokinetics, and preliminary anti-tumor activity of epitinib. 36 patients were enrolled in seven cohorts (20 mg, 40 mg, 80 mg, 120 mg, 160 mg, 200 mg and 240 mg). This study found that the safety and tolerability of epitinib was acceptable. No dose-limiting toxicity was observed, and the maximum tolerated dose was not reached. The recommended dose from this study was 160 mg once daily based on pharmacokinetics data and safety data.

Epitinib Clinical Development

The table below shows a summary of the clinical trials that we have recently completed and underway for epitinib.

Clinical Trials of Epitinib

Treatment	Name, Line, Patient Focus	Sites	Phase	Status/Plan	NCT #
Epitinib monotherapy	Glioblastoma	China	Ib/II	Enrolling	NCT03231501
Epitinib monotherapy	EGFR-mutation NSCLC with brain metastasis	China	Ib	Completed	NCT02590952

Note: NSCLC = non-small cell lung cancer.

Phase Ib/II epitinib monotherapy in glioblastoma (Status: enrolling; NCT03231501)

Glioblastoma is the most aggressive of the gliomas, which are tumors that arise from glial cells or their precursors within the central nervous system. Glioblastoma is classified as grade IV under the World Health Organization grading of central nervous system tumors, and is the most common brain and central nervous system malignancy, accounting for about half of such tumors according to the Cancer Genome Atlas Research Network. The standard of care for treatment is surgery, followed by radiotherapy and chemotherapy. Median survival is approximately 15 months, and the five-year overall survival rate is 6%. There are currently no target therapies approved for glioblastoma.

Epitinib is a highly differentiated EGFR inhibitor designed for optimal blood-brain barrier penetration. EGFR gene amplification has been identified in about half of glioblastoma patients, according to The Cancer Genome Atlas Research Network, and hence is a potential therapeutic target in glioblastoma.

In March 2018, we initiated a Phase Ib/II proof-of-concept study of epitinib in glioblastoma patients with EGFR gene amplification in China. This Phase Ib/II study will be a multi-center, single-arm, open-label study to evaluate the efficacy and safety of epitinib as a monotherapy in patients with EGFR gene amplified, histologically confirmed glioblastoma.

Phase Ib epitinib monotherapy in non-small cell lung cancer, EGFRm+ with brain metastasis-China (Status: Completed; NCT02590952)

In this Phase Ib study, a total of 33 non-small cell lung cancer patients, of which 12 had previously received EGFR tyrosine kinase inhibitor treatment and 21 were EGFR tyrosine kinase inhibitor treatment naïve, were efficacy evaluable with an objective response rate of 39%, including 10 confirmed and 3 unconfirmed partial responses. Patients were treated with epitinib at a 160 mg once daily dose. All responses occurred in EGFR tyrosine kinase inhibitor treatment naïve patients resulting in an objective response rate of 62% and in the 11 EGFR tyrosine kinase inhibitor naïve patients who also had measurable brain metastasis (lesion diameter>10 mm per RECIST 1.1) with a 64% objective response rate. Furthermore, when patients with MET gene amplification were excluded, epitinib's objective response rate increased to 68% in the EGFR tyrosine kinase inhibitor treatment naïve patients and 70% of those patients who also had measurable brain metastasis. Epitinib was well tolerated with treatment related adverse events in the dose expansion stage CTC grade ≥3 with greater than 10% incidence were elevations in alanine transaminase (19%), elevations in gamma-glutamyltransferase (11%), and aspartate transaminase (11%).

In late 2016 we presented this encouraging efficacy data at the World Conference on Lung Cancer.

In 2017 and 2018, we worked to finalize epitinib dose regimen while planning our Phase III registration study. During this time, the EGFR tyrosine kinase inhibitor treatment landscape has evolved rapidly. First, Tagrisso, a third-generation EGFR tyrosine kinase inhibitor with blood-brain barrier penetration, was launched with accessible pricing in China and was subsequently included in the National Reimbursement Drug List. Second, generic versions of first-generation EGFR tyrosine kinase inhibitors (Iressa and Tarceva) were launched in China at approximately one-quarter of their previous National Reimbursement Drug List prices. We are studying the impact of the above two factors on epitinib's market potential and Phase III investment case in EGFRm+ non-small cell lung cancer with brain metastasis in China.

7. Theliatinib EGFR Inhibitor

Like epitinib, theliatinib (also known as HMPL-309) is a novel small molecule EGFR inhibitor. Tumors with wild-type EGFR activation, for instance, through gene amplification or protein over-expression, are less sensitive to EGFR tyrosine kinase inhibitors such as Iressa and Tarceva due to sub-optimal binding affinity. Theliatinib was designed with strong affinity to the wild-type EGFR kinase and has demonstrated five to ten times the potency than Tarceva in pre-clinical trials. This holds importance because tumors with wild-type EGFR activation have been found to be less sensitive to current EGFR inhibitors and is notable in certain cancer types such as esophageal cancer, where 15-28% have EGFR gene amplification and 50-70% have EGFR overexpressed. As a result, we believe that theliatinib could potentially be more effective than existing EGFR tyrosine kinase inhibitor products and benefit patients with tumor types with a high incidence of wild-type EGFR activation. We currently retain all rights to theliatinib worldwide.

Mechanism of Action

Unlike MET, where targeted therapies have yet to be approved in the patient population with MET overexpressed, there are successful examples of clinical efficacy among patients with EGFR overexpressed in tumor types such as colorectal cancer and head and neck cancer. The most successful targeted therapy in the patient population with EGFR overexpressed is the monoclonal antibody Erbitux (from Bristol Myers Squibb/Merck Serono), which is indicated for head and neck cancer and colorectal cancer. Importantly, there remain many tumor types with high levels of EGFR overexpression for which no targeted therapies have been approved. In addition, in patients with EGFR gene amplification, there are no approved targeted therapies despite high levels of EGFR gene amplification occurring in many of the above EGFR overexpressed tumor types.

Theliatinib Pre-clinical Evidence

EGFR is overexpressed in a significant proportion of epithelium-derived carcinomas, which are cancers that begin in a tissue that lines the inner or outer surfaces of the body. Theliatinib inhibits the epidermal growth factor-dependent proliferation of cells at nanomolar concentrations. Of most interest is the strong binding affinity to wild-type EGFR enzyme demonstrated by theliatinib. The data indicated that upon withdrawal of the drug, the EGFR phosphorylation rapidly returns to higher levels for Iressa and Tarceva, while EGFR phosphorylation remained low for theliatinib after drug withdrawal, suggesting theliatinib may demonstrate a sustained target occupancy or "slow-off" characteristic due to strong binding.

Theliatinib First-in-human Studies

In 2012, we initiated the first-in-human Phase I, open-label, dose escalation study in China of theliatinib administered orally to patients with wild-type EGFR gene amplification or EGFR overexpressed solid tumors who have failed standard therapy. The primary objectives of the study were to evaluate its safety and tolerability in patients with advanced solid tumors and to determine the maximum tolerated dose. The study also evaluated efficacy against non-small cell lung cancer, esophageal cancer and head and neck squamous cell lung cancer, determined the pharmacokinetics of theliatinib under single dose and repeat doses, and explored the relationship between theliatinib's activity and certain biomarkers.

Theliatinib Clinical Development

In September 2017, new clinical data were presented at the Annual Meeting of the Chinese Society of Clinical Oncology. Results showed that doses up to 500 mg once daily were determined to be safe and well-tolerated, with no dose-limiting toxicities and no clear maximum tolerated dose. Pharmacokinetic exposure increased with dose, with a 300 mg once daily or more considered to be sufficient to inhibit EGFR phosphorylation. Among the 21 patients that received 120 mg to 500 mg once daily, there were only four treatment-emergent adverse events of grade ≥3: gastrointestinal bleeding, decreased white blood cell count, anemia or decreased platelet count (1/21 = 5% each). There were no incidences of grade ≥3 rash or diarrhea. Among seven esophageal cancer patients, five had measurable lesions and could be evaluated for response. All five had stable disease. Of the efficacy evaluable patients in the 120 mg to 500 mg cohorts, 44% (8/18) had stable disease after 12 weeks.

Although we observed efficacy, primarily in the form of stable disease or short duration response, we have decided that it does not warrant continued development of theliatinib monotherapy in esophageal cancer at this time. We now plan to look at alternative uses of theliatinib and could consider the potential for use in combinations with immunotherapy.

8. HMPL-453 FGFR Inhibitor

Mechanism of Action

FGFR belongs to a subfamily of receptor tyrosine kinases, or RTKs. Four different FGFRs (FGFR1-4) and at least 18 ligand FGFs constitute the FGF/FGFR signaling system. Activation of the FGFR pathway through the phosphorylation of various downstream molecules ultimately leads to increased cell proliferation, migration and survival. FGF/FGFR signaling regulates a wide range of basic biological processes, including tissue development, angiogenesis, and tissue regeneration. Given the inherent complexity and critical roles in physiological processes, dysfunction in the FGF/FGFR signaling leads to a number of developmental disorders and is consistently found to be a driving force in cancer. Deregulation of the FGFR can take many forms, including receptor amplification, activating mutations, gene fusions, and receptor isoform switching, and the molecular alterations are found at relatively low frequencies in most tumors. The incidence of FGFR aberrance in various cancer types is listed in the figure below.

Common FGFR Alterations in Certain Tumor Types

	Gene amplification	Gene translocation	Gene mutation
FGFR1	Lung squamous (7-15%) H&N squamous (10-17%) Esophageal squamous (9%) Breast (10-15%)	Lung squamous (n/a) Glioblastoma (n/a) Myeloproliferative syndrome (n/a) Breast (n/a)	Gastric (4%) Pilocytic astrocytoma (5-8%)
FGFR2	Gastric (5-10%) Breast (5-10%)	Intra-hepatic biliary tract cancer (14%) Breast (n/a)	Endometrial (12-14%) Lung squamous (5%)
FGFR3	Bladder (3%) Salivary adenoid cystic (n/a) Breast (1%)	Bladder (3-6%) Lung squamous (3%) Glioblastoma (3-7%) Myeloma (15-20%)	Bladder (60-80% NMIBC; 15-20% MIBC) Cervical (5%)

Notes: H&N = head and neck; NMIBC = non-muscle invasive bladder cancer; MIBC = muscle invasive bladder cancer; and n/a = data not available.

Source: M. Touat et al., "Targeting FGFR Signaling in Cancer," Clinical Cancer Research (2015); 21(12); 2684-94

HMPL-453 Research Background

We noted a growing body of evidence has demonstrated the oncogenic potential of FGFR aberrations in driving tumor growth, promoting angiogenesis, and conferring resistance mechanisms to oncology therapies. Targeting the FGF/FGFR signaling pathway has therefore attracted attention from biopharmaceutical companies and has become an important exploratory target for new anti-tumor target therapies.

Currently, FGFR monoclonal antibodies, FGF ligand traps and small molecule FGFR tyrosine kinase inhibitors are being evaluated in clinical trials. BGJ-398 (Novartis) and AZD4547 (AstraZeneca) are the leading FGFR selective tyrosine kinase inhibitors, and their clinical trials provided substantial proof-of-concept with regard to anti-tumor efficacy and pharmacodynamic markers of effective FGFR pathway inhibition. Balversa was recently approved in the United States for the treatment of bladder cancer.

The main FGFR on-target toxicities observed to date in these compounds are all mild and manageable, including hyperphosphatemia, nail and mucosal disorder, and reversible retinal pigmented epithelial detachment. However, there are still many challenges in the development of FGFR-directed therapies. Uncertainties include the screening and stratifying of patients who are most likely to benefit from FGFR targeted therapy. Intra-tumor heterogeneity observed in FGFR amplified cancer may compromise the anti-tumor activity. In addition, the low frequency of specific FGFR molecular aberrance in each cancer type may hinder clinical trial enrollment.

HMPL-453 Pre-clinical Evidence

HMPL-453 is a potential best-in-class, highly selective and potent, small molecule that targets FGFR 1/2/3 with an IC_{50} in the low nanomolar range. Its good selectivity was revealed in the screening against 292 kinases. HMPL-453 exhibited strong anti-tumor activity that correlated with target inhibition in tumor models with abnormal FGFR activation.

HMPL-453 has good pharmacokinetic properties characterized by rapid absorption following oral dosing, good bioavailability, moderate tissue distribution and moderate clearance in all pre-clinical animal species. HMPL-453 was found to have little inhibitory effect on major cytochrome P450 enzymes, indicating low likelihood of drug-to-drug interaction issues.

HMPL-453 First-in-human Studies

In late 2016, we received clinical trial clearance in Australia and China. In June 2017, we initiated a Phase I/II clinical trial of HMPL-453 in China (NCT03160833). This Phase I/II study is a multi-center, single-arm, open-label, two-stage study to evaluate safety, tolerability, pharmacokinetics and preliminary efficacy of HMPL-453 monotherapy in patients with solid tumors harboring FGFR genetic alterations. The dose-escalation stage will enroll patients with locally advanced or metastatic solid tumors, for whom standard therapy either does not exist or has proven to be ineffective or intolerable, regardless genetic status, to determine the maximum tolerated dose and recommended Phase II dose. The dose-escalation stage is currently enrolling patients to further evaluate safety, tolerability and pharmacokinetics as well as preliminary anti-tumor efficacy at the recommended Phase II dose. This stage will enroll primarily cancer patients harboring FGFR dysregulated tumors, including those with advanced bladder cancer, advanced cholangiocarcinoma and other solid tumors. For this second stage, the primary endpoint is objective response rate, with secondary endpoints including duration of response, disease control rate, progression-free survival, overall survival and safety.

We had also initiated a first-in-human Phase I clinical trial in Australia. However, in July 2018, we discontinued the Australian Phase I study due to the emergence of certain serious, though non-life threatening, FGFR target-related toxicities.

OUR RESEARCH AND DEVELOPMENT APPROACH

Our core research and development philosophy is to take a holistic approach to the treatment of cancer and immunological diseases, through multiple modalities and mechanisms, including targeted therapies, immunotherapies and other pathways. A primary objective of our research efforts has been to develop next generation tyrosine kinase inhibitors and immunotherapies, which has allowed us to develop drug candidates with:

- unique selectivity to limit target-based toxicity;
- high potency to optimize the dose selection with the objective to lower the required dose and thereby limit compound-based toxicity;
- chemical structures deliberately engineered to improve drug exposure in the targeted tissue; and
- ability to be combined with other therapeutic agents, including tyrosine kinase inhibitors, immunotherapies and chemotherapies.

We believe our ability to successfully develop innovative drug candidates through our Innovation Platform will be the primary factor affecting our long-term competitiveness, as well as our future growth and development. Creating high quality global first-in-class or best-in-class drug candidates requires a significant investment of resources over a prolonged period of time, and a core part of our strategy is to continue making sustained investments in this area. As a result of this commitment, our pipeline of drug candidates has been steadily advancing and expanding, with eight clinical-stage drug candidates, five of which are either in or about to start global clinical development. See "– *Our Clinical Pipeline*" for more details.

All of the drug candidates of our Innovation Platform, other than fruquintinib for one indication in China, are still in development, and we have incurred and will continue to incur significant research and development costs for pre-clinical trials and clinical trials. We expect that our research and development expenses will significantly increase in future periods in line with the advance and expansion of the development of our drug candidates.

We and our collaboration partners have invested about US$650 million in our Innovation Platform as of December 31, 2018, with almost all of these funds used for research and development expenses for the development of our drug candidates. Innovation Platform expenses include:

- employee compensation related expenses, including salaries, benefits and equity compensation expense;

- expenses incurred for payments to CROs, investigators and clinical trial sites that conduct our clinical trials;
- the cost of acquiring, developing, and manufacturing clinical study materials;
- facilities, depreciation, and other expenses, which include office leases and other overhead expenses; and
- costs associated with pre-clinical activities and regulatory operations.

See "*Financial Information*" for further details of our research and development costs incurred by our Innovation Platform.

As of the Latest Practicable Date, our Innovation Platform had approximately over 420 scientists and staff, of which 80 have M.D. or Ph.D. degrees. We staff our research and development teams for each project based on employees' experience, education, and availability. Our research and development team operates primarily in two major facilities in Shanghai totalling approximately 11,000 square meters, a formulation facility in Suzhou as well as our new office in New Jersey.

OVERVIEW OF OUR COLLABORATIONS

Collaborations and joint ventures with corporate partners have provided us with significant funding and access to our partners' scientific, development, regulatory and commercial capabilities. Our current oncology collaborations focus on savolitinib (collaboration with AstraZeneca) and fruquintinib (collaboration with Eli Lilly). We also have a joint venture with Nestlé Health Science, S.A. or Nestlé Health Science, which has been focused on developing drugs for gastrointestinal indications. Our collaboration partners fund a significant portion of our research and development costs for drug candidates developed in collaboration with them. In addition, we receive upfront payments upon our entry into these collaboration arrangements and upon the achievement of certain development milestones for the relevant drug candidate. We and Nutrition Science Partners, in the aggregate, have received upfront payments, equity contributions and milestone payments totaling approximately US$158.5 million mainly from our collaborations with AstraZeneca, Eli Lilly, Nestlé Health Science as of December 31, 2018. In return, our collaboration partners are entitled to a significant proportion of any future revenue from our drug candidates developed in collaboration with them, as well as a degree of influence over the clinical development process for such drug candidates.

AstraZeneca Agreement

In December 2011, we entered into an agreement with AstraZeneca under which we granted to AstraZeneca co-exclusive, worldwide rights to develop, and exclusive worldwide rights to manufacture and commercialize savolitinib for all diagnostic, prophylactic and therapeutic uses. We refer to this agreement as the AstraZeneca Agreement. AstraZeneca paid US$20.0 million upon execution of the AstraZeneca Agreement and agreed to pay royalties and

additional amounts upon the achievement of development and sales milestones. Under the original terms of the AstraZeneca Agreement, we and AstraZeneca agreed to share the development costs for savolitinib in China, with AstraZeneca being responsible for the development costs for savolitinib in the rest of the world. Based on savolitinib showing early clinical benefit as a highly selective MET inhibitor in a number of cancers, in August 2016 we and AstraZeneca amended our global licensing, co-development, and commercialization agreement for savolitinib whereby we agreed to contribute up to US$50.0 million, spread primarily over three years, to the joint development costs of the global pivotal Phase III study in patients with MET driven papillary renal cell carcinoma. As of December 31, 2018, we had received US$24.9 million in milestone payments in addition to approximately US$25.2 million in reimbursements for certain development costs. We may potentially receive future clinical development and first sales milestones payments for clinical development and initial sales of savolitinib, plus significant further milestone payments based on sales. AstraZeneca also reimburses us for certain development costs. Subject to approval of savolitinib in papillary renal cell carcinoma, under the amended AstraZeneca Agreement, AstraZeneca is obligated to pay us increased tiered royalties from 14% to 18% annually on all sales made of any product outside of China, which represents a five percentage point increase over the original terms. After total aggregate sales of savolitinib have reached US$5 billion, this royalty will step down over a two year period, to an ongoing royalty rate of 10.5% to 14.5%. AstraZeneca is also obligated to pay us a fixed royalty of 30% on all sales made of any product in China.

Development and collaboration under this agreement are overseen by a joint steering committee that is comprised of three of our senior representatives as well as three senior representatives from AstraZeneca. AstraZeneca is responsible for the development of savolitinib and all regulatory matters related to this agreement in all countries and territories other than China, and we are responsible for the development of savolitinib and all regulatory matters related to this agreement in China.

Subject to earlier termination, the AstraZeneca Agreement will continue in full force and effect on a country-by-country basis as long as any collaboration product is being developed or commercialized. The AstraZeneca Agreement is terminable by either party upon a breach that is uncured, upon the occurrence of bankruptcy or insolvency of either party, or by mutual agreement of the parties. The AstraZeneca Agreement may also be terminated by AstraZeneca for convenience with 180 days' prior written notice. Termination for cause by us or AstraZeneca or for convenience by AstraZeneca will have the effect of, among other things, terminating the applicable licenses granted by us. Termination for convenience by AstraZeneca will have the effect of obligating AstraZeneca to grant to us all of its rights to regulatory approvals and other rights necessary to commercialize savolitinib. Termination by AstraZeneca for convenience will not have the effect of terminating any license granted by AstraZeneca to us.

Eli Lilly Agreement

In October 2013, we entered into an agreement with Eli Lilly whereby we granted Eli Lilly an exclusive license to develop and commercialize fruquintinib for all uses in China and Hong Kong. In December 2018, following the commercial launch of fruquintinib in China, we and Eli Lilly amended the terms of the original agreement. We refer to this agreement, including the amendments thereto, as the Eli Lilly Agreement.

Eli Lilly paid a US$6.5 million upfront fee following the 2013 execution of the Eli Lilly Agreement, and agreed to pay royalties and additional amounts upon the achievement of development and regulatory approval milestones. As of December 31, 2018, Eli Lilly had paid us US$37.2 million in milestone payments in addition to approximately US$47.4 million in reimbursements for certain development costs.

We could potentially receive future milestone payments for the achievement of development and regulatory approval milestones in China. Additionally, Eli Lilly is obligated to pay us tiered royalties from 15% to 20% annually on sales made of fruquintinib in China and Hong Kong, the rate to be determined based upon the dollar amount of sales made for all products in that year. Upon the first commercial launch of fruquintinib in China in a new life cycle indication, these tiered royalties will increase to 15% to 29% under the terms of our 2018 amendment.

Development, collaboration and manufacture of products under this agreement are overseen by a joint steering committee comprised of equal numbers of representatives from each party. Under the terms of our 2018 amendment, we are now responsible for all development activities and costs for fruquintinib in China in new life cycle indications, and we have the liberty to collaborate with third parties to explore combination therapies of fruquintinib with various immunotherapy agents.

Once development is complete, Eli Lilly is obligated to use commercially reasonable efforts to commercialize products and bears all the costs and expenses incurred in such commercialization efforts until the achievement of a non-fruquintinib related Eli Lilly commercial action. If this milestone is achieved, we will be given promotion and distribution rights for fruquintinib in provinces that represent 30% (or 40% if certain additional criteria are met) of sales of fruquintinib in China.

We are responsible in consultation with Eli Lilly for the supply of, and have the right to supply, all clinical and commercial supplies for fruquintinib pursuant to an agreed strategy for manufacturing. For the term of the Eli Lilly Agreement, such supplies will be provided by us at a transfer price that accounts for our cost of goods sold.

The Eli Lilly Agreement is terminable by either party for breach that is uncured. The Eli Lilly Agreement is also terminable by Eli Lilly for convenience with 120 days' prior written notice or if there is a major unexpected safety issue with respect to a product. Termination by either us or Eli Lilly for any reason will have the effect of, among other things, terminating the applicable licenses granted by us, and will obligate Eli Lilly to transfer to us all regulatory materials necessary for us to continue development efforts for fruquintinib.

PD-1 Collaboration Agreements

In 2018, we entered into non-exclusive global collaboration agreements with Junshi and Innovent and non-exclusive China-only collaboration agreements with Genor and Hanzhong to conduct safety run-in studies to evaluate the safety of fruquintinib or surufatinib in combination with PD-1 monoclonal antibodies being developed by Junshi (Tuoyi), Innovent (Tyvyt), Genor (genolimzumab) and Hanzhong (HX008), respectively. We refer to these collaboration agreements, collectively, as the PD-1 Agreements.

Development activities conducted under the PD-1 Agreements are overseen, in each case, by a joint development committee comprised of three representatives from each party. Under the global PD-1 Agreement with Junshi, we are responsible for leading development of, and bearing all costs related to, the initial development of the surufatinib and Tuoyi combination in China. Junshi is responsible for leading development of, and bearing all costs related to, initial global development of the combination. Under our PD-1 Agreements with Genor and Hanzhong, they are responsible for leading the initial development of the combination therapies in China. Genor and Hanzhong are responsible for all costs associated with such initial development activities. We and Innovent will share all initial development costs equally.

The PD-1 Agreements may be terminated for material breach or insolvency of the other party. In addition, there are certain rights to terminate the development activities if: (i) the responsible party does not commence activities under an initial development plan within one year of approval of such plan by the joint development committee; (ii) serious safety issues arise as a result of the development activities; (iii) data from the development activities will not to support regulatory approval; or (iv) in the case of the Genor and Hanzhong PD-1 Agreements, if the joint development committee has not approved a subsequent development plan within six months of completion of initial development activities. The PD-1 Agreements with Junshi and Innovent may also be terminated by either party in the event that no election to begin subsequent development has been made within 12 months of completion of the initial development plan. Either party may terminate the Innovent PD-1 Agreement for convenience upon 60 days' notice.

Nestlé Health Science Agreement

In 2012, we entered into a joint venture agreement with Nestlé Health Science to form Nutrition Science Partners, a joint venture whose shares are owned in equal portions by us and Nestlé Health Science. The objective of Nutrition Science Partners was to develop, manufacture and commercialize certain botanical drug candidates for the treatment of ulcerative colitis and Crohn's Disease and to identify, develop, manufacture and commercialize products in gastrointestinal indications.

In 2018, we and Nestlé Health Science reviewed the status of this program and, after due consideration of the timeline and further investments required to complete clinical trials and reach the commercialization stage for these drug candidates, we and Nestlé Health Science decided to explore alternative strategic options. In light of this, Nutrition Science Partners recorded a full impairment provision of its US$30.0 million intangible asset in the year ended December 31, 2018. The portion attributable to our Company was US$15.0 million.

OUR COMMERCIAL PLATFORM

Since 2001, we have also developed a profitable Commercial Platform in China, which encompasses two businesses: our strategically important Prescription Drugs business and our Consumer Health business. Our Commercial Platform has grown strongly and provided an important source of funding for our Innovation Platform since inception. In total, net income attributable to our company from the continuing operations of our Commercial Platform was US$70.3 million, US$40.0 million and US$41.4 million for the years ended December 31, 2016, 2017 and 2018, respectively. Net income attributable to our company from our Commercial Platform included one-time gains of US$40.4 million, US$2.5 million and nil in the years ended December 31, 2016, 2017 and 2018, respectively, net of tax, from land compensation and other government subsidies paid to Shanghai Hutchison Pharmaceuticals by the Shanghai government.

Additionally, our Commercial Platform has provided us the infrastructure and know-how in operating and marketing pharmaceutical products in the complex and evolving healthcare system in China. The infrastructure of our Commercial Platform, particularly in commercial operations management, manufacturing and distribution, regulatory and reimbursement coverage, is well established in our therapeutic specialty areas such as cardiovascular and central nervous system health. Over the next several years, we will combine the marketing and sales experience and hospital access gained from our Commercial Platform's operations with our growing dedicated oncology-focused sales team to support the launch of products from our Innovation Platform if and when they are approved for use in China. Concurrent with this team expansion, we also plan to increase our manufacturing capacity with a fully integrated active pharmaceutical ingredients or formulation manufacturing facility that is capable of supporting the manufacturing of our current and future commercial-stage oncology drugs.

Prescription Drugs Business

Our Prescription Drugs division is conducted through the following two joint ventures in which we nominate management and run the day-to-day operations:

- **Shanghai Hutchison Pharmaceuticals**, which primarily manufactures, markets and distributes prescription drug products originally contributed by our joint venture partner, as well as third-party prescription drugs. 50% of this joint venture is owned by us and 50% by Shanghai Traditional Chinese Medicine Co., Ltd., a subsidiary of Shanghai Pharmaceuticals, a leading pharmaceutical company in China listed on the Shanghai Stock Exchange and the Hong Kong Stock Exchange. Shanghai Hutchison Pharmaceuticals is a non-consolidated joint venture of our Company; and

- **Hutchison Sinopharm**, which focuses on providing logistics services to, and distributing and marketing prescription drugs manufactured by, third-party pharmaceutical companies in China. 51% of this joint venture is owned by us and 49% is owned by Sinopharm, a leading distributor of pharmaceutical and healthcare products and a leading supply chain service provider in China listed on the Hong Kong Stock Exchange. Hutchison Sinopharm is a consolidated joint venture of our Company.

Our Prescription Drugs business employs a physician-targeted marketing model that is focused on promoting its products by providing physicians and hospitals with information on the benefits and differentiating clinical aspects of our products. In collaboration with our partners, we have built our joint ventures' extensive prescription drug sales and distribution network across China, with approximately 2,500 prescription drugs sales representatives as of December 31, 2018. These sales representatives covered over 24,900 hospitals in over 320 cities and towns in China as of December 31, 2018. Approximately 66% of these sales representatives cover eastern and central-southern China. Of the remaining medical sale representatives, approximately 25% cover northern China and approximately 9% cover western and south-western China.

Shanghai Hutchison Pharmaceuticals *– manufacturing, marketing and distributing proprietary and licensed prescription drugs*

Shanghai Hutchison Pharmaceuticals primarily engages in the manufacture and sale of prescription drug products originally contributed by our joint venture partner, as well as third-party prescription drugs with a focus on cardiovascular medicine. Shanghai Hutchison Pharmaceuticals' proprietary products are sold under the "Shang Yao" brand, literally meaning "Shanghai pharmaceuticals," a trademark that has been used for over 35 years in the pharmaceutical retail market, primarily in Eastern China. As of December 31, 2018, Shanghai Hutchison Pharmaceuticals held 74 registered drug licenses in China, of which 31 are included in the National Reimbursement Drug List. In addition, 17 of Shanghai Hutchison Pharmaceuticals' products are represented on China's National Essential Medicines List, of which three are in active production.

Its key product is She Xiang Bao Xin pills, a vasodilator for the long-term treatment of coronary artery and heart disease and for rapid control and prevention of acute angina pectoris, a form of chest pain, which is listed on China's low price drug list, or LPDL, and fully reimbursed in all provinces in China. She Xiang Bao Xin pills' sales represented 85% of all Shanghai Hutchison Pharmaceuticals sales in 2018. There are over one million deaths due to coronary artery disease per year in China, with this number set to rise due to an aging population with high levels of smoking (28% of adults), increasing levels of obesity (30% of adults are overweight) and hypertension (25% of adults). She Xiang Bao Xin pill is the third largest botanical prescription drug in this indication in China, with a market share of 17% nationally and 48% in Shanghai in 2018. The average daily cost of She Xiang Bao Xin pills is RMB4.4, or approximately US$0.66.

She Xiang Bao Xin pills were first approved in 1983 and subsequently enjoyed 23 proprietary commercial protections under the prevailing regulatory system in China. In 2005, Shanghai Hutchison Pharmaceuticals was able to attain "Confidential State Secret Technology" status protection, as certified by China's Ministry of Science and Technology and State Secrecy Bureau, which extended proprietary protection in China until late 2016, and it is in the process of renewing this protection. Shanghai Hutchison Pharmaceuticals holds an invention patent in China covering its formulation, which extends proprietary protection through 2029.

Shanghai Hutchison Pharmaceuticals manufactures its products at its GMP-certified 78,000 square meter production facility located in Feng Pu district outside the center of Shanghai. This factory, completed construction in 2017, has approximately tripled Shanghai Hutchison Pharmaceuticals' capacity relative to its prior factory.

Shanghai Hutchison Pharmaceuticals, through its GSP-certified subsidiary, also markets and sells third-party prescription drugs in collaboration with Hutchison Sinopharm. As discussed below, in early 2015, Hutchison Sinopharm signed an agreement with AstraZeneca to provide marketing services for AstraZeneca's Seroquel (a drug for the treatment of various psychiatric disorders) to market and distribute such drug in China. In connection with Hutchison Sinopharm's agreement with AstraZeneca, Hutchison Sinopharm entered into an agreement with Shanghai Hutchison Pharmaceuticals to provide certain promotion and marketing services within China for this drug. Under this agreement, Shanghai Hutchison Pharmaceuticals manages marketing and is paid a fee for its services provided. Hutchison Sinopharm manages distribution and logistics for this product and is paid a fee for its services provided.

Shanghai Hutchison Pharmaceuticals is the exclusive co-promoter of Merck Serono's bisoprolol fumarate tablets, sold under the Concor trademark, in nine provinces, markets that contain about 600 million people. Concor is the number two beta-blocker in China with an approximately 24% national market share in China's beta-blocker drug market and 63% of China's generic bisoprolol market in 2018. Shanghai Hutchison Pharmaceuticals' cardiovascular sales team provides detailing for Concor alongside its She Xiang Bao Xin pills on a fee-for-service basis.

Shanghai Hutchison Pharmaceuticals, through its GSP-certified subsidiary, sells its products and its third-party licensed prescription drugs directly to distributors who on-sell such products to hospitals and clinics, pharmacies and other retail outlets in their respective areas, as well as to other local distributors. In early 2018, as a result of the two-invoice system, Shanghai Hutchison Pharmaceuticals was required to restructure its distribution and logistics network. Prior to the two-invoice system, Shanghai Hutchison Pharmaceuticals employed a group of approximately 200 primary distributors to cover China. These primary distributors in turn used over 1,600 secondary distributors to work directly with hospitals, on a local level, to manage logistics and collection. The two-invoice system required Shanghai Hutchison Pharmaceuticals to eliminate one layer of distributors and, as a result, a new system with approximately 800 primary distributors was established in early 2018 to work directly with hospitals. This included the original approximately 200 primary distributors in addition to approximately 600 new primary distributors. Shanghai Hutchison Pharmaceuticals' own prescription drugs sales representatives promote its products to doctors and purchasing managers in hospitals, clinics and pharmacies as part of its marketing efforts. As of December 31, 2018, Shanghai Hutchison Pharmaceuticals had approximately 2,500 prescription drugs sales representatives and about 540 manufacturing employees across China. See "– *Sales and Marketing*" for further information relating to sales through our distributors.

Hutchison Sinopharm *– providing logistics services and marketing and distribution primarily for prescription drugs manufactured by third parties*

In 2014, we commenced operating Hutchison Sinopharm, a consolidated joint venture in collaboration with Sinopharm. Based in Shanghai, Hutchison Sinopharm is a GSP-certified company focused on providing logistics services to, and distributing and marketing prescription drugs manufactured by, third-party pharmaceutical companies in China. Hutchison Sinopharm also distributes certain products from Hutchison Healthcare's Zhi Ling Tong infant nutrition brand. Hutchison Sinopharm also continues to operate its legacy business which was primarily focused on providing logistics and distribution services, primarily within Shanghai, to third-party pharmaceutical companies.

We intend to increasingly focus on expanding Hutchison Sinopharm to operate as a full-service, third-party prescription drug commercialization company in China.

Its primary product is Seroquel. Since 2015, Hutchison Sinopharm has been the exclusive first-tier distributor to distribute and market AstraZeneca's quetiapine tablets, under the Seroquel trademark in China. Seroquel is a first-line antipsychotic medicine for the treatment of schizophrenia and bipolar disorder, which was launched in China in 2001. Seroquel holds a 6% market share in China's approximately US$0.9 billion atypical anti-psychotic prescription drug market and 48% of China's generic quetiapine market, primarily as a result of being the first-mover and original patent holder on quetiapine. Seroquel is the only brand in China to have an extended release formulation, which in 2017 was included on China's National Reimbursement Drug List, thereby providing us with major competitive advantage over quetiapine generics. Subject to Hutchison Sinopharm's continued delivery of pre-specified annual sales targets, which required 22% sales growth in 2018 and would require

approximately 15% sales growth per year thereafter, we can continue to retain exclusive commercial rights to Seroquel in China until 2025. In June 2018, AstraZeneca sold and licensed its rights to Seroquel to Luye Pharma Group, Ltd., including its rights in China. The terms of our agreement with AstraZeneca were assigned to Luye Pharma Hong Kong Ltd. and remain unchanged following this transaction. We believe that we met the 2018 sales growth targets, but, despite this, we cannot rule out the possibility that Luye may try to take back Seroquel rights in China. We will use all available resources to protect our rights under the current agreement.

As of December 31, 2018, Shanghai Hutchison Pharmaceuticals had a dedicated medical sales team of about 110 people to support Hutchison Sinopharm's commercialization of Seroquel. Historically, our consolidated revenues reflected total gross sales of Seroquel, but this began to shift to a fee-for-service model in October 2017 when China started implementing a new regulatory two-invoice system on a province-by-province basis. In principle, the purpose of the two-invoice system is to restrict the number of layers in the drug distribution system in China, in order to improve transparency, compliant business conduct and efficiency. As a result of this shift to a fee-for-service model, the top-line revenue that Hutchison Sinopharm was and will be able to record from sales of Seroquel, as well as many of our other third-party customers, was reduced in provinces which had adopted the two-invoice system. Importantly however, this drop in reported sales will have no material impact on profitability and will have limited impact to our commercial team operations and expansion plans.

The substantial portion of Hutchison Sinopharm's sales are made directly to hospitals and clinics, with the remaining sales being made through distributors. As of December 31, 2018, Hutchison Sinopharm had approximately 400 customers of which approximately 20% of these customers are distributors and the revenue generated from these distributors accounted for approximately 30% of the revenue of Hutchison Sinopharm for the financial year ended December 31, 2018. As a result of the two-invoice system referred to above, we expect the downward trend in the revenue generated from distributors to continue. See "– *Sales and Marketing*" for further information relating to sales through our distributors.

In 2018, China enacted another regulatory reform initiative known as the 4+7 Quality Consistency Evaluation bidding process, or 4+7 QCE, in a several cities. The 4+7 QCE initiative is aimed at driving consolidation in the fragmented generic prescription drug market in China. Under this pilot program, major cities bulk-buy certain generic drugs together, forcing companies to bid for contracts and driving down prices. The 4+7 QCE system is expected to gradually expand to cover more cities and drugs over the coming years. In the short term, we expect that the 4+7 QCE system may reduce Hutchison Sinopharm's product portfolio as some of our third-party generic drug partners may fail to win 4+7 QCE bids. In the mid- to long-term, we believe that the 4+7 QCE system will benefit us by allowing increased numbers of innovative drugs to be included in the National Reimbursement Drug List. During 2017 and 2018, 32 innovative oncology drugs were added to the National Reimbursement Drug List, a trend that we believe could ultimately benefit our Innovation Platform drug candidates.

Consumer Health Business

Our Consumer Health business is a profitable business, focusing primarily on the manufacture, marketing and distribution of over-the-counter pharmaceutical products and other natural and organic consumer products in China. Our Consumer Health products business includes:

- **Hutchison Baiyunshan**, a joint venture established in 2005 which focuses primarily on the manufacture, marketing and distribution of proprietary over-the-counter pharmaceutical products. 50% of this joint venture is owned by us and 50% by Guangzhou Baiyunshan, a leading China-based pharmaceutical company listed on the Shanghai Stock Exchange and the Hong Kong Stock Exchange. Hutchison Baiyunshan is a non-consolidated joint venture of our Company,

- **Hutchison Hain Organic**, a joint venture which was established in 2009 and has rights to market and distribute a broad range of natural and organic consumer products under brands owned by Hain Celestial in nine Asian territories. 50% of this joint venture is owned by us and 50% by Hain Celestial, which is a Nasdaq-listed, natural and organic food and personal care products company. Hutchison Hain Organic is a consolidated joint venture of our Company,

- **Hutchison Healthcare**, a wholly owned subsidiary which was established in 2001 and manufactures and sells health supplements and licenses its infant nutrition products to Hutchison Sinopharm for distribution, and

- **Hutchison Consumer Products**, a wholly owned subsidiary which was established in 2007 that distributes and markets certain third-party consumer products.

Hutchison Baiyunshan *– manufacturing, marketing and distributing proprietary over-the-counter pharmaceutical products*

Hutchison Baiyunshan primarily engages in the manufacture, marketing and distribution of proprietary over-the-counter pharmaceutical products. Its "Bai Yun Shan" brand is a market-leading household-name, established over 30 years ago and is known by the majority of Chinese consumers. As of the Latest Practicable Date, Hutchison Baiyunshan held 145 registered drug licenses in China, of which 76 are included in the National Reimbursement Drug List. In addition, 31 of Hutchison Baiyunshan's products are represented on China's National Essential Medicines List, of which 11 are in active production. As of the end of 2018, substantially all pharmaceutical products manufactured and sold by Hutchison Baiyunshan in 2018 were capable of being reimbursed under the National Reimbursement Drug List.

Hutchison Baiyunshan's key products are two generic over-the-counter therapies both of which are each listed on the LPDL:

- **Fu Fang Dan Shen tablets** – generic over-the-counter drug for the treatment of chest congestion and angina pectoris to promote blood circulation and relieve pain, with a leadership market share in China of 38%. It represented approximately 26% of the sales of Hutchison Baiyunshan in 2018; and

- **Banlangen granules** – generic over-the-counter drug for the treatment of viral flu, fever, and respiratory tract infections, with a leadership market share in China of 54%. It represented approximately 29% of the sales of Hutchison Baiyunshan in 2018.

Hutchison Baiyunshan's products are mainly manufactured in-house at its GMP-certified facilities in Guangzhou, Guangdong province and Bozhou, Anhui province. Third-party contract manufacturers are also used. Hutchison Baiyunshan is also in the process of negotiating the return of its land use rights for the approximately 30,000 square meter unused plot of land in Guangzhou, which has been listed for sale as part of the Guangzhou municipal government's urban redevelopment scheme plan since 2016. The date of this public auction will be determined by the Guangzhou government. While we are actively working to facilitate this transaction, changes in government policy continue to delay the process.

Hutchison Baiyunshan sells its products directly to regional distributors across China who on-sell to local distributors, hospitals and clinics, pharmacies and other retailers, and employs its own sales representatives at a local level to market its products and promote over-the-counter sales to retailers. See "– *Sales and Marketing*" for further information relating to sales through our distributors.

In September 2017, Hutchison Baiyunshan divested its 60% shareholding in Nanyang Baiyunshan Hutchison Whampoa Guanbao Pharmaceutical Company Limited, a primarily third-party over-the-counter logistics business which we had determined was not strategically important to our business, for consideration approximately equal to its carrying value.

As of December 31, 2018, Hutchison Baiyunshan had approximately 950 sales representatives and about 1,000 manufacturing employees across China.

Hutchison Hain Organic *– marketing and distributing Hain Celestial-licensed natural and organic food and personal care products*

Hutchison Hain Organic is a joint venture with Hain Celestial, a Nasdaq-listed, natural and organic food and personal care products company. Hutchison Hain Organic distributes a broad range of over 500 imported organic and natural products.

Pursuant to its joint venture agreement, Hutchison Hain Organic has rights to market and distribute Hain Celestial's products within nine Asian territories. We believe the key strategic product for Hutchison Hain Organic is Earth's Best organic baby products, a leading brand in the United States. Hutchison Hain Organic's other products are distributed to hypermarkets, specialty stores and other retail outlets in Hong Kong, China and across seven other territories in Asia mainly through third-party local distributors, including retail chains owned by affiliates of CK Hutchison.

Hutchison Healthcare *– manufacturing, marketing and distributing health supplements*

Hutchison Healthcare is our wholly owned subsidiary and is primarily engaged in the manufacture and sale of health supplements. Hutchison Healthcare's major product is Zhi Ling Tong DHA capsules, a health supplement made from algae DHA oil for the promotion of brain and retinal development in babies and young children, which is distributed by Hutchison Sinopharm.

The majority of Hutchison Healthcare's products are contract manufactured at a dedicated and certified manufacturing facility operated by a third party and sold to Hutchison Sinopharm, which distributes such products to hospital pharmacies, specialty stores and drugstore chains.

Hutchison Consumer Products *– distribution of consumer products*

Hutchison Consumer Products is our wholly owned subsidiary that is primarily engaged in the distribution of third-party consumer products to hypermarkets, specialty stores and other retail outlets in Asia.

PATENTS AND OTHER INTELLECTUAL PROPERTY

Our commercial success depends in part on our ability to obtain and maintain proprietary or intellectual property protection for our Innovation Platform's drug candidates, our Commercial Platform's products and other know-how. Our policy is to seek to protect our proprietary and intellectual property position by, among other methods, filing patent applications in various jurisdictions related to our proprietary technology, inventions and improvements that are important to the development and implementation of our business. We also rely on trade secrets, know-how and continuing technological innovation to develop and maintain our proprietary and intellectual property position.

Patents

We and our joint ventures file patent applications directed to our Innovation Platform's drug candidates and our Commercial Platform's products in an effort to establish intellectual property positions with regard to new small molecule compounds and/or extracts of natural herbs, their compositions as well as their medical uses in the treatment of diseases. In relation to our Innovation Platform, we also file patent applications directed to crystalline forms, formulations, processes, key intermediates, and secondary uses as clinical trials for our drug

candidates evolve. We file such patent applications in major market jurisdictions, including the United States, Europe, Japan and China as well as Argentina, Australia, Brazil, Canada, Chile, India, Indonesia, Israel, Mexico, Malaysia, New Zealand, Peru, the Philippines, Singapore, South Korea, Ukraine and South Africa. We do not currently in-license any patents except to the extent necessary to ensure our drug candidate fruquintinib has freedom to operate as discussed below.

Our Innovation Platform Patents

As of December 31, 2018, we had 176 issued patents, including 18 Chinese patents, 20 U.S. patents and nine European patents, 130 patent applications pending in the above major market jurisdictions, and six pending Patent Cooperation Treaty, or PCT, patent applications relating to the drug candidates of our Innovation Platform. The intellectual property portfolios for our most advanced drug candidates are summarized below. Some of these portfolios, such as HMPL-453 and HMPL-689, are in very early stages of development. With respect to most of the pending patent applications covering our drug candidates, prosecution has yet to commence. Prosecution is a lengthy process, during which the scope of the claims initially submitted for examination by the relevant patent office is often significantly narrowed by the time when they issue, if they issue at all. We expect this to be the case for our pending patent applications referred to below.

Savolitinib – The intellectual property portfolio for savolitinib contains two patent families.

The first patent family for savolitinib is directed to novel small molecule compounds as well as methods of treating cancers with such compounds. As of December 31, 2018, we owned 31 patents in this family, including patents in China, the United States, Europe and Japan, and we had 22 patent applications pending in various other jurisdictions. Our European patent is also registered in Hong Kong. Our issued patents will expire in 2030. We are aware that Chinese Patent No. ZL201510906993.3, or the 993 Patent, was granted to Shanghai Xuanchuang Biotechnology Co. Ltd, or Xuanchuang, in September 2018 claiming a crystalline form of savolitinib. Our PRC legal advisor as to intellectual property matters has advised us that there are substantial deficiencies in the 993 Patent. Accordingly, as of the date of the filing of this prospectus we believe that the 993 Patent will not present a material obstacle to our further development of savolitinib. See "*Risk Factors – Risks Relating to Intellectual Property – We, our joint ventures and our collaboration partners may not be able to effectively enforce our intellectual property rights throughout the world.*"

The second patent family was filed in 2018 and is subject to confidential review by the patent authorities. This patent family is co-owned by us and AstraZeneca.

Our collaboration partner AstraZeneca is responsible for maintaining and enforcing the intellectual property portfolio for savolitinib.

Fruquintinib – The intellectual property portfolio for fruquintinib contains four patent families.

The first patent family for fruquintinib is directed to novel small molecule compounds as well as methods of treating tumor angiogenesis-related disorders with such compounds. As of December 31, 2018, we owned three U.S. patents, one Chinese patent and one Taiwanese patent in this family, each of which will expire in 2028. We also owned patents in Europe and 14 other jurisdictions expiring in 2029 and had one patent application pending in Brazil.

The second patent family is directed to crystalline forms of fruquintinib as well as methods of treating tumor angiogenesis-related disorders with such forms. As of December 31, 2018, we had one patent application pending in China in this family, which, if issued, would have an expiration date in 2034. We own one patent in Australia expiring on 2035 and had 22 patent applications pending in other various jurisdictions, including China, the United States, Europe and Taiwan, each of which, if issued, will each have expiration dates in 2035.

The third patent family is directed to the method of preparing one of the critical intermediates used in the manufacturing process of fruquintinib. With respect to this patent family, we have one patent application pending in China, which, if issued, will have an expiration date in 2034.

The fourth patent family was filed in 2018 and is subject to confidential review by the patent authorities.

We also in-license certain freedom-to-operate rights from AstraZeneca, which grant us non-exclusive rights within China and Hong Kong to develop and commercialize pharmaceutical compounds used in fruquintinib which are covered by one of its patents.

Surufatinib – The intellectual property portfolio for surufatinib contains four patent families.

The first patent family for surufatinib is directed to novel small molecule compounds as well as methods of treating tumor angiogenesis-related disorders with such compounds. As of December 31, 2018, in this patent family we owned one Chinese patent expiring in 2027 and 12 patents in various other jurisdictions, including the United States expiring in 2031, and Europe and Japan, each expiring in 2028. As of December 31, 2018, we also had one patent application pending in Brazil.

The second patent family is directed to the crystalline forms of surufatinib as well as methods of treating tumor angiogenesis-related disorders with such forms. As of December 31, 2018, in this patent family we owned two patents in China expiring in 2029 and 2030, respectively, and we owned 14 patents in other countries, including the United States which will expire in 2031 and Europe which will expire in 2030. As of December 31, 2018, we also had two patent applications pending in other jurisdictions.

The third patent family is directed to the formulation of a micronized active pharmaceutical ingredient used in surufatinib as well as methods of treating tumor angiogenesis-related disorders with such formulation. With respect to this patent family, we have 18 patent applications pending in various jurisdictions, including China, the U.S. and Europe.

The fourth patent family is directed to clinical indications of surufatinib. With respect to this patent family, we have a PCT application pending, which was filed in 2016.

HMPL-523 Syk Inhibitor – The intellectual property portfolio for HMPL-523 contains two patent families.

The first patent family is directed to novel small molecule compounds as well as methods of treating cancers, inflammatory diseases, allergic diseases, cell-proliferative diseases, and immunological diseases with such compounds. As of December 31, 2018, we owned 19 patents in this family in various jurisdictions, including the United States, China and South Korea, each of which will expire in 2032. As of December 31, 2018, we also had six patent applications in this family pending in other jurisdictions.

The second patent family was filed in 2017 and is subject to confidential review by the patent authorities.

HMPL-689 – The intellectual property portfolio for HMPL-689 contains two patent families.

The first patent family is directed to novel small molecule compounds as well as uses of such compounds. As of December 31, 2018, we owned four patents in this family in various jurisdictions, including Australia and Japan, each of which will expire in 2035. As of December 31, 2018, we also had 24 patent applications pending in this family in other various jurisdictions.

The second patent family was filed in 2018 and is subject to confidential review by the patent authorities.

Epitinib – The intellectual property portfolio for epitinib contains three patent families.

The first patent family is directed to novel small molecule compounds as well as methods of treating cancers with such compounds. As of December 31, 2018, we owned patents in China and Taiwan expiring in 2028, one patent in the United States expiring in 2031 and 12 patents in other jurisdictions, including Europe, each expiring in 2029. As of December 31, 2018, we also had two patent applications in this family pending in other jurisdictions.

The second patent family is directed to the salts and solvates of epitinib and crystalline forms thereof, as well as methods of treating cancers with such forms. As of December 2018, we had one patent application pending in China in this family, which, if issued, would have an expiration date in 2037. We have also filed PCT and Taiwan patent applications in this family, which, if issued, will each have expiration dates in 2038.

The third patent family was filed in 2017 and is subject to confidential review by the patent authorities.

Theliatinib – The intellectual property portfolio for theliatinib contains four patent families.

The first patent family is directed to novel small molecule compounds as well as methods of treating cancers with such compounds. As of December 31, 2018, we owned 16 patents in this family in various jurisdictions, including China and Japan, each of which will expire in 2031. As of December 31, 2018, we also had three patent applications in this family pending in various jurisdictions. Our Chinese patent was also registered in Hong Kong and Macau.

The second patent family is directed to the crystalline forms of theliatinib as well as methods of treating cancers with such forms. As of December 31, 2018, we have filed PCT and Taiwan patent applications in this family, which, if issued, will each have expiration dates in 2037.

The third patent family was filed in 2017 and is subject to confidential review by the patent authorities.

The fourth patent family was filed in 2018 and is subject to confidential review by the patent authorities.

HMPL-453 – The intellectual property portfolio for HMPL-453 contains patent applications directed to novel small molecule compounds as well as methods of treating cancers with the compounds. As of December 31, 2018, we owned 15 patents in this family in various jurisdictions, including China, Europe, Japan and the United States, each of which will expire in 2034. As of December 31, 2018, we had 18 patent applications pending in other various jurisdictions.

Our Commercial Platform Patents

Prescription Drugs Patents

As of the Latest Practicable Date, our Prescription Drugs joint venture Shanghai Hutchison Pharmaceuticals had 48 issued patents and 14 pending patent applications in China, including patents for its key prescription products described below.

She Xiang Bao Xin Pills. As of December 31, 2018, Shanghai Hutchison Pharmaceuticals held an invention patent in China directed to the formulation of the She Xiang Bao Xin pill. Under PRC law, invention patents are granted for new technical innovations with respect to products or processes. Invention patents in China have a maximum term of 20 years. This patent will expire in 2029. The "Confidential State Secret Technology" status protection on the She Xiang Bao Xin pill technology held by Shanghai Hutchison Pharmaceuticals, as certified by China's Ministry of Science and Technology and State Secrecy Bureau, has expired, and as of December 31, 2018, Shanghai Hutchison Pharmaceuticals was in the process of renewing such protection status, and we believe our status remains unchanged during this process.

Danning Tablets. As of December 31, 2018, Shanghai Hutchison Pharmaceuticals also held an invention patent in China directed to the formulation of the Danning tablet. This patent will expire in 2027.

Consumer Health Patents

Many of the products sold by our Consumer Health Products joint venture Hutchison Baiyunshan, including its Banlangen granules and Fu Fang Dan Shen tablets, are generic, over-the-counter products for which Hutchison Baiyunshan does not hold patents. As of the Latest Practicable Date, Hutchison Baiyunshan had 75 issued patents in China, two PCT patents and one in Australia.

Patent Term

The term of a patent depends upon the laws of the country in which it is issued. In most jurisdictions, a patent term is 20 years from the earliest filing date of a non-provisional patent application. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the USPTO in examining and granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier filed patent. The term of a patent that covers a drug or biological product may also be eligible for patent term extension when FDA approval is granted, provided statutory and regulatory requirements are met. In the future, if and when our drug candidates receive approval by the FDA or other regulatory authorities, we expect to apply for patent term extensions on issued patents covering those drugs, depending upon the length of the clinical trials for each drug and other factors. There can be no assurance that any of our pending patent applications will be issued or that we will benefit from any patent term extension.

As with other pharmaceutical companies, our or our joint ventures' ability to maintain and solidify our proprietary and intellectual property position for our drug candidates or our or their Commercial Platform products and technologies will depend on our or our joint ventures' success in obtaining effective patent claims and enforcing those claims if granted. However, our or our joint ventures' pending patent applications and any patent applications that we or they may in the future file or license from third parties may not result in the issuance of patents. We also cannot predict the breadth of claims that may be allowed or enforced in our or our joint ventures' patents. Any issued patents that we may receive in the future may be challenged, invalidated or circumvented. For example, we cannot be certain of the priority of filing covered by pending third-party patent applications. If third parties prepare and file patent applications in the United States, China or other markets that also claim technology or therapeutics to which we or our joint ventures have rights, we or our joint ventures may have to participate in interference proceedings, which could result in substantial costs to us, even if the eventual outcome is favorable to us, which is highly unpredictable. In addition, because of the extensive time required for clinical development and regulatory review of a drug candidate we may develop, it is possible that, before any of our drug candidates can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thereby limiting protection such patent would afford the respective product and any competitive advantage such patent may provide.

Trade Secrets

In addition to patents, we and our joint ventures rely upon unpatented trade secrets and know-how and continuing technological innovation to develop and maintain our or their competitive position. We and our joint ventures seek to protect our proprietary information, in part, by executing confidentiality agreements with our collaborators and scientific advisors, and non-competition, non-solicitation, confidentiality, and invention assignment agreements with our employees and consultants. We and our joint ventures have also executed agreements requiring assignment of inventions with selected scientific advisors and collaborators. The confidentiality agreements we and our joint ventures enter into are designed to protect our or our joint ventures' proprietary information and the agreements or clauses requiring assignment of inventions to us or our joint ventures, as applicable, are designed to grant us or our joint ventures, as applicable, ownership of technologies that are developed through our or their relationship with the respective counterpart. We cannot guarantee, however, that these agreements will afford us or our joint ventures adequate protection of our or their intellectual property and proprietary information rights.

Trademarks and Domain Names

We conduct our business using trademarks with various forms of the "Hutchison," "Chi-Med" and "China-MediTech" brands, as well as domain names incorporating some or all of these trademarks. In April 2006, we entered into a brand license agreement with Hutchison Whampoa Enterprises Limited, an indirect wholly owned subsidiary of CK Hutchison, pursuant to which we have been granted a non-exclusive, non-transferrable, royalty-free right to use such trademarks, domain names and other intellectual property rights owned by the CK Hutchison group in connection with the operation of our business worldwide. See *"Connected Transactions"* for further details.

In addition, our joint ventures seek trademark protection in China for their Commercial Platform products. As of the Latest Practicable Date, our joint ventures Shanghai Hutchison Pharmaceuticals and Hutchison Baiyunshan owned a total of 245 trademarks in the aggregate related to products sold by them. For example, the name "Shang Yao" is a registered trademark of Shanghai Hutchison Pharmaceuticals in China for certain uses including pharmaceutical preparations. In addition, our joint venture Hutchison Baiyunshan has been granted a royal-free license to use the registered trademark "Bai Yun Shan" for a term equal to its operational period of the joint venture by Guangzhou Baiyunshan.

RAW MATERIALS AND SUPPLIES

Raw materials and supplies are ordered based on our or our joint ventures' respective sales plans and reasonable order forecasts and are generally available from our or our joint ventures' own cultivation operations and various third-party suppliers in quantities adequate to meet our needs. We typically order raw materials on short-term contract or purchase order basis and do not enter into long-term dedicated capacity or minimum supply arrangements.

For our Innovation Platform, the active pharmaceutical ingredient, drug product and drug substance used in our drug candidates are supplied to us from third-party vendors. Our ability to successfully develop our drug candidates, and to ultimately supply our commercial drugs in quantities sufficient to meet the market demand, depends in part on our ability to obtain the active pharmaceutical ingredient, drug product and drug substance for these drugs in accordance with regulatory requirements and in sufficient quantities for commercialization and clinical testing.

While we generally aim to identify and qualify multiple manufacturers to provide such active pharmaceutical ingredient, drug product and drug substance prior to submission of an NDA to the FDA and/or NMPA, we contract with a single supplier to manufacture and supply us with the active pharmaceutical ingredient for fruquintinib for commercial purposes. We do not currently have arrangements in place for a redundant or second-source supply of the active pharmaceutical ingredient for fruquintinib or any other active pharmaceutical ingredients, drug product or drug substance used in our drug candidates in the event any of our current suppliers of such active pharmaceutical ingredient, drug product and drug substance cease their operations for any reason, which may lead to an interruption in our production. However, to

date, while we have experienced price fluctuations associated with our raw materials, we have not experienced any material disruptions in the supply of this active pharmaceutical ingredient or the other raw materials we and our joint venture partners use. See "*Risk Factors – Risks Relating to Our Commercial Platform and Sales of Our Commercial-stage Drug Candidates – Our Commercial Platform's principal products involve the cultivation or sourcing of key raw materials including botanical products, and any quality control or supply failure or price fluctuations could adversely affect our Commercial Platform's ability to manufacture our products and/or could materially and adversely affect our operating results.*" and *"Risk Factors – Risks Relating to Our Dependence on Third Parties – The third-party vendors upon whom we rely for the supply of the active pharmaceutical ingredient, drug product and drug substance used in our drug candidates are our sole source of supply, and the loss of any of these suppliers could significantly harm our business.*"

CROs

Although we or our collaboration partners design the clinical trials for our drug candidates, CROs conduct most of the clinical trials. Our agreements with CROs are usually structured as master service agreements which set out the services to be performed, payment schedule, term and confirmation that all intellectual rights arising out of or made in performance of the services are owned by us. We and our collaboration partners work with the major global and Chinese CROs.

PRODUCTION

Our and our joint ventures' manufacturing operations consist of bulk manufacturing and formulation, fill, and finishing activities that produce products and drug candidates for both clinical and commercial purposes. Our and our joint ventures' manufacturing capabilities have a large operation scale for our own-brand products. We and our joint ventures manufacture and sell about 4.8 billion doses of medicines a year, in the aggregate, through our well-established GMP manufacturing base. See *"– Our Commercial Platform – Prescription Drugs Business – Shanghai Hutchison Pharmaceuticals – manufacturing, marketing and distributing proprietary and licensed prescription drugs"* and *"– Our Commercial Platform – Consumer Health Business – Hutchison Baiyunshan – manufacturing, marketing and distributing proprietary over-the-counter pharmaceutical products"* for more details on our manufacturing operations.

Additionally, we rent and operate a 2,107 square meter production facility for fruquintinib in Suzhou, Jiangsu Province in Eastern China.

Manufacturing is subject to extensive regulations that impose various procedural and documentation requirements governing recordkeeping, manufacturing processes and controls, personnel, quality control and quality assurance, among others. Our manufacturing facilities and the contract manufacturing organizations we use to manufacture our drugs and drug candidates operate under cGMP conditions. cGMP are regulatory requirements for the production of pharmaceuticals that will be used in humans.

CUSTOMERS AND SUPPLIERS

For the financial years ended December 31, 2016, 2017 and 2018, revenue from our five largest customers represented approximately 26%, 27% and 35% of our total revenue, respectively, and revenue from our largest customer in those periods represented approximately 6%, 8% and 11% of our revenue in the same periods, respectively. Save for Sinopharm, Shanghai Hutchison Pharmaceuticals and Nutrition Science Partners, our five largest customers were independent third parties and none of our Directors or their close associates or, to the knowledge of our Directors, any Shareholder who owned more than 5% of our issued Shares had any interest in any of our five largest customers as of the Latest Practicable Date.

For the financial years ended December 31, 2016, 2017 and 2018, our purchases from our five largest suppliers represented less than 30% of our total purchases. Save for Sinopharm and Hain Celestial, all of our five largest suppliers were independent third parties and none of our Directors or their close associates or, to the knowledge of our Directors, any Shareholder who owned more than 5% of our issued Shares had any interest in any of our five largest suppliers as of the Latest Practicable Date.

During the Track Record Period, Sinopharm, which is a connected person of the Company, was one of our five largest customers as well as one of our five largest suppliers. Sales to Sinopharm contributed 15%, 14% and 12% of the Group's revenue in 2016, 2017 and 2018, respectively. Purchases from Sinopharm contributed 4%, 3% and less than 1% of the Group's total operating expenses in 2016, 2017 and 2018, respectively. See "*Connected Transactions*" for details of historical transaction amounts of our transactions with Sinopharm.

QUALITY CONTROL AND ASSURANCE

We have our own independent quality control system and devote significant attention to quality control for the designing, manufacturing and testing of our products. We have established a strict quality control system in accordance with NMPA regulations. Our laboratories fully comply with the Chinese GMP guidelines and are staffed with highly educated and skilled technicians to ensure quality of all batches of product release. We monitor in real time our operations throughout the entire production process, from inspection of raw and auxiliary materials, manufacture, delivery of finished products, clinical testing at hospitals, to ethical sales tactics. Our quality assurance team is also responsible for ensuring that we are in compliance with all applicable regulations, standards and internal policies. Our senior management team is actively involved in setting quality policies and managing internal and external quality performance of our company and our joint ventures, Shanghai Hutchison Pharmaceuticals and Hutchison Baiyunshan.

CERTIFICATES AND PERMITS

We are required to obtain and renew certain certificates and permits for our business operations. See *"Appendix IV – Regulatory Overview and Taxation"* for more information.

Hutchison MediPharma (Suzhou) Limited holds a pharmaceutical manufacturing permit issued by its local regulatory authority expiring on December 31, 2020. It also holds a GMP certificate issued by its local regulatory authority expiring on September 16, 2023.

Hutchison Sinopharm holds a GSP certificate issued by its local regulatory authority expiring on October 22, 2019. It also holds a pharmaceutical trading license issued by its local regulatory authority expiring on August 24, 2019.

Shanghai Hutchison Pharmaceuticals holds a pharmaceutical manufacturing permit from its local regulatory authorities expiring on December 31, 2020. Shanghai Hutchison Pharmaceuticals also holds three GMP certificates issued by its local regulatory authority and the NMPA. The three GMP certificates will expire on August 14, 2021, November 16, 2021 and December 3, 2022, respectively.

Shanghai Shangyao Hutchison Whampoa GSP Company Limited, a subsidiary of Shanghai Hutchison Pharmaceuticals, holds a pharmaceutical trading license from its local regulatory authority expiring on December 29, 2019. It also holds a GSP certificate issued by its local regulatory authority expiring on April 21, 2020.

Hutchison Baiyunshan holds a pharmaceutical manufacturing permit issued by its local regulatory authority expiring on December 31, 2020. Hutchison Baiyunshan holds three GMP certificates issued by its local regulatory authority expiring on March 18, 2020, December 21, 2020 and December 11, 2023, respectively.

Hutchison Whampoa Guangzhou Baiyunshan Pharmaceuticals Limited, a subsidiary of Hutchison Baiyunshan, holds a GSP certificate issued by its local regulatory authority expiring on January 15, 2020. It also holds a pharmaceutical trading license issued by its local regulatory authority expiring on November 12, 2019 and a food trading license issued by its local regulatory authority expiring on September 26, 2021.

Hutchison Whampoa Guangzhou Baiyunshan Chinese Medicine (Bozhou) Company Limited, a subsidiary of Hutchison Baiyunshan, holds a GMP certificate issued by its local regulatory authority expiring on January 18, 2022. It also holds a pharmaceutical manufacturing license issued by its local regulatory authority expiring on December 31, 2020.

Hutchison Whampoa Baiyunshan Lai Da Pharmaceutical (Shan Tou) Company Limited, a subsidiary of Hutchison Baiyunshan, holds a GMP certificate issued by its local regulatory authority expiring on February 28, 2021. It also holds a pharmaceutical manufacturing license issued by its local regulatory authority expiring on December 31, 2020.

During the Track Record Period and up to the Latest Practicable Date, we had obtained all requisite certificates, permits and approvals that are material for our operations, and all of such certificates, permits and approvals were within their respective effective periods. We did not experience any material difficulty in renewing such certificates, permits and licenses during the Track Record Period and up to the Latest Practicable Date, and we currently do not expect to have any material difficulty in renewing them when they expire, if applicable. During the Track Record Period and up to the Latest Practicable Date, we had not been penalized by any government authorities for any non-compliance relating to maintenance and renewal of our material licenses, permits and approvals.

EMPLOYEES

As of December 31, 2016, 2017 and 2018, we had 563, 590 and 714 full-time employees, respectively. None of our employees are represented by labor unions or covered by collective bargaining agreements. The number of employees by function as of the end of the period for our financial years ended December 31, 2016, 2017 and 2018 was as follows:

	2016	2017	2018
By Function:			
Innovation Platform	329	358	418
Commercial Platform	209	205	267
Corporate Head Office	25	27	29
Total	563	590	714

Additionally, our Commercial Platform joint venture Shanghai Hutchison Pharmaceuticals employed a total of 3,093 full-time employees, and Hutchison Baiyunshan employed a total of 1,702 full-time employees and 3,499 outsourced contract staff, who are mostly sales representatives and manufacturing employees as of December 31, 2018. Their employees are represented by labor unions and covered by collective bargaining agreements.

As of the Latest Practicable Date, neither Shanghai Hutchison Pharmaceuticals nor Hutchison Baiyunshan has experienced any strikes, labor disputes or industrial actions which had a material effect on their business, and consider their relations with the union and our employees to be good.

PROPERTY, PLANT AND EQUIPMENT

We are headquartered in Hong Kong where we have our main administrative offices.

Our non-consolidated joint ventures, Shanghai Hutchison Pharmaceuticals and Hutchison Baiyunshan, operate two large-scale research and development and manufacturing facilities for which they have obtained land use rights and property ownership certificates.

Shanghai Hutchison Pharmaceuticals relocated to its current facility outside of Shanghai in September 2016, and it has an aggregate site area of approximately 78,000 square meters (compared to approximately 58,000 square meters for its old facility located in Shanghai). Shanghai Hutchison Pharmaceuticals agreed to surrender its land use rights for the property where its old production facility was located to the Shanghai government for cash consideration. The total cash and subsidies paid by the Shanghai government to Shanghai Hutchison Pharmaceuticals was approximately US$113 million, including approximately US$101 million for land compensation and US$12 million in government subsidies related to research and development projects.

Hutchison Baiyunshan's facility is in Guangzhou and has an aggregate site area of approximately 90,000 square meters. Hutchison Baiyunshan plans to sell its land use rights for an unused portion of its Guangzhou property to the local government for cash consideration. In December 2016, its subsidiary completed construction of new production facilities in Bozhou and production commenced in 2017.

See "*– Our Commercial Platform – Prescription Drugs Business – Shanghai Hutchison Pharmaceuticals – manufacturing, marketing and distributing proprietary and licensed prescription drugs*" and "*– Our Commercial Platform – Consumer Health Business – Hutchison Baiyunshan – manufacturing, marketing and distributing proprietary over-the-counter pharmaceutical products*" for more details on the new facilities of Shanghai Hutchison Pharmaceuticals and Hutchison Baiyunshan mentioned above.

Additionally, we rent and operate a 2,107 square meter manufacturing facility for fruquintinib in Suzhou, Jiangsu Province in Eastern China, and own a 5,024 square meter facility in Shanghai which houses research and development operations. We also lease 907 square meters of office space in Shanghai which houses Hutchison MediPharma's management and staff. In 2017, we entered into a new lease for a 6,129 square meter combined office and lab space in Shanghai to accommodate the anticipated growth of Hutchison MediPharma's management and staff and for an approximately 209 square meter facility in Florham Park, New Jersey where we house clinical and regulatory management and staff. In January 2019, we leased an additional approximately 420 square meters of office space to accommodate the planned expansion of our New Jersey clinical and regulatory operations.

As none of our properties had a carrying amount of 15% or more of our consolidated total assets, we are not required to include a property valuation report in this prospectus.

SALES AND MARKETING

Our in-house sales and marketing team as well as sales representatives of our Prescription Drugs division joint ventures, being Shanghai Hutchison Pharmaceuticals and Hutchison Sinopharm, directly market and promote prescription drugs and other products to hospitals, clinics, pharmacies and other customers. As of December 31, 2018, Shanghai Hutchison Pharmaceuticals and Hutchison Sinopharm operated a network of approximately 2,500 prescription drugs sales representatives covering over 24,900 hospitals in over 320 cities and towns in China.

As is common in the PRC pharmaceutical industry, sales of prescription drugs and other products are carried out through third party distributors. Shanghai Hutchison Pharmaceutical and Hutchison Baiyunshan, both of which are non-consolidated joint ventures of our Company, primarily conduct sales of their products through third party distributors, while Hutchison Sinopharm, a consolidated joint venture of our Company, relies primarily on direct sales to hospitals and clinics and to a lesser extent on third party distributors.

We select our distributors based on their business qualifications and marketing capabilities, such as distribution network, customer portfolio, number of sales personnel, credit record, financial strength, market position, logistics, compliance standard and past performance. We also check the qualification of our distributors to ensure that they have obtained the necessary permits, licenses and certifications for the distribution of relevant products, including drug operation permits and GSP certifications.

Our relationship with our distributors is that of seller and buyer and not principal and agent. Legal title to the products as well as all significant risks and rewards associated with the products are transferred to the distributors upon sale. We have no ownership or management control over our distributors.

We enter into distribution agreements with our distributors. While specific terms vary from distributor to distributor, in summary, the key terms of our typical distribution agreements are as follows:

Duration:	Typical term of 12 months, subject to termination by us in certain circumstances, such as breach of applicable law by the distributor.
Rights and obligations of parties involved and geographic or other exclusivity:	The distributor is generally authorized to sell the specified products only within the designated geographical area set out in the distribution agreement and is prohibited from selling the products outside the designated geographical area without our prior consent.

Sales and pricing policies:	The distributor is typically required to sell the products at a price which is not less than the price set out in the price list. Consistent with pharmaceutical industry practice, we offer a discount or rebate if certain sales targets are achieved.
Obsolete stock and products return arrangements:	The distributor is generally not permitted to return products to us unless the products are defective.
Minimum purchase amounts/sales targets:	The distributor is generally not required to purchase a minimum amount of the products but the distribution agreement will generally set out sales targets to be achieved by the distributor.
Sales and inventory reports and estimates:	The distributor is generally required to provide us with monthly reports on sales volumes and inventory levels of the products.
Payment and credit terms:	The distributor is typically required to pay for the products at the time the order is made. We may extend a credit period of up to 90 days for some distributors.

To the best of our knowledge, during the Track Record Period, we did not experience any material non-compliance by our distributors with respect to the terms and conditions of our distribution agreements.

We actively monitor the performance of our distributors, and our distributors are generally required to provide us with periodic market information related to our products that they distribute. Sales returns are only accepted with the requisite approvals from relevant departmental managers. We regularly monitor the inventory level of our distributors in order to identify any unusual inventory levels and the volume of relevant products the distributor resells to hospitals and other medical institutions, which allows us to manage the risk of channel stuffing. Our sales representatives regularly communicate with target hospitals and retail pharmacies as part of our efforts to assess the performance of our distributors. Our distributors generally may not return any unsold products (except for defective products). We regularly monitor the level of sales returns in order to identify and investigate any unusual or material issues. During the Track Record Period, sales returns were immaterial and accounted for less than 0.3% of the revenue generated by our Commercial Platform. We consider that these internal control measures are sufficient to mitigate the risk of channel stuffing for our distributors.

See "*Risk Factors – Risks Relating to Our Dependence on Third Parties – We and our joint ventures rely on our distributors for logistics and distribution services for our Commercial Platform business.*"

In China, prices of pharmaceutical products are regulated by the government to ensure that drugs are offered at affordable prices. In June 2015, the Chinese government abolished the 15-year-old government-led pricing system for drugs, and lifted the maximum retail price requirement for most drugs, including drugs reimbursed by government medical insurance funds, patented drugs, and some other drugs. The government regulates prices mainly by establishing a consolidated procurement mechanism, restructuring medical insurance reimbursement standards and strengthening regulation of medical and pricing practices.

In China, our commercial products need to go through the centralized procurement process in the form of public tenders operated by provincial-level government agencies, in order to be commercially available at public medical institutions owned by the government or owned by state-owned or controlled enterprises. Assessment of the bids takes a number of factors into consideration, including but not limited to bid price, product quality, clinical effectiveness, product safety, level of technology, qualifications and reputation of the manufacturer, after-sale services and innovation. As a result, the prices of our commercial products are affected by the bidding process. In addition, in order for our commercial products to be included in the National Reimbursement Drug List and critical illness insurance reimbursement listings, we are subject to price negotiation with the Ministry of Human Resources and Social Security and the relevant authorities at provincial level.

INSURANCE

We maintain insurance policies that we consider to be in line with market practice and adequate for our business. Our principal insurance policies cover product liability for fruquintinib, property loss due to accidents or natural disasters and adverse events in clinical trials. We do not maintain product liability insurance for products or drug candidates other than fruquintinib. We also do not maintain "key person" insurance. See "*Risk Factors – Other Risks and Risks Relating to Doing Business in China – Product liability claims or lawsuits could cause us or our joint ventures to incur substantial liabilities*" and "*Risk Factors – Risks Relating to Our Innovation Platform and Development of Our Drug Candidates – Our future success depends on our ability to retain key executives and to attract, retain and motivate qualified personnel.*"

INTERNAL CONTROL AND RISK MANAGEMENT

We have established and maintained risk management and internal control policies and procedures that we consider to be appropriate for our business operations, and we are dedicated to continuously improving these policies and procedures. We have adopted and implemented comprehensive risk management policies in various aspects.

Financial Reporting Risk Management

As a public company in the United States, we are subject to the Sarbanes-Oxley Act, together with rules implemented by the SEC, and applicable market regulators. The Sarbanes-Oxley Act requires, among other things, that we maintain effective internal control for financial reporting and disclosure controls and procedures. Our internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of consolidated financial statements in accordance with U.S. GAAP. Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Projections of any evaluation of effectiveness of our internal control over financial reporting to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate. Our management, with the participation of our Chief Executive Officer and Chief Financial Officer, assesses the effectiveness of our internal control over financial reporting based on the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in Internal Control-Integrated Framework (2013 Framework) in order to report on the effectiveness of our internal control over financial reporting and describe any material weakness in internal control over financial reporting, as required by Section 404 of the Sarbanes-Oxley Act. The effectiveness of our internal control over financial reporting is also tested by our independent registered public accounting firm on an annual basis.

Audit Committee Oversight

Our Audit Committee reviews the effectiveness of our internal control and financial reporting risk management and reviews the policies and procedures for the identification, assessment and reporting of financial and non-financial risks and our management of those risks in accordance with the requirements of the Sarbanes-Oxley Act and other applicable laws, rules and regulations and the applicable requirements of any stock exchange.

Information Security Policy

Our Board has adopted an information security policy to define and help communicate the common policies for information confidentiality, integrity and availability to be applied to us and our joint ventures. The purpose of the information security policy is to ensure business continuity by preventing and minimizing the impact of security risks within our company and our joint ventures. Our information security policy applies to all of our and our joint ventures' business entities across all countries. It applies to the creation, communication, storage, transmission and destruction of all different types of information. It applies to all forms of information, including but not limited to electronic copies, hardcopy, and verbal disclosures whether in person, over the telephone, or by other means.

During the Track Record Period and up to the Latest Practicable Date, we do not believe that we have experienced any material information leakage or loss of sensitive data.

Human Resources Risk Management

We provide regular and specialized training tailored to the needs of our employees in different departments. We regularly organize internal training sessions conducted by senior employees or outside consultants on topics of interest. Our long term goal is to further increase the number of trainings available to all employees as well as measure the success of the trainings.

Our Board has adopted a Code of Ethics to set standards for our directors, officers and employees as are reasonably necessary to promote (i) honest and ethical conduct, including the ethical handling of actual or apparent conflicts of interest between personal and professional relationships; (ii) full, fair, accurate, timely and understandable disclosure in the reports and documents that we file or submit to the applicable stock exchanges, and in any other public communications; (iii) compliance with applicable governmental and regulatory laws, rules, codes and regulations; (iv) prompt internal reporting of any violations of the code of ethics; and (v) accountability for adherence to the code of ethics.

We also have in place an Anti-Bribery and Anti-Corruption Policy to safeguard against any corruption within our Company. The policy explains potential corrupt conduct and our anti-corruption measures. Our Board has also adopted Complaints Procedures for the confidential receipt, retention, and treatment of complaints from, or concerns raised by, employees regarding accounting, internal accounting controls and auditing matters as well as illegal or unethical matters. The complaint procedures are reviewed by the Audit Committee from time to time as warranted to ensure their continuing compliance with applicable laws and listing standards as well as their effectiveness.

Ongoing Measures to Monitor the Implementation of Risk Management Policies

Our Board and management together monitor the implementation of our risk management policies on an ongoing basis to ensure our policies and implementation are effective and sufficient.

ENVIRONMENTAL, WORKPLACE, HEALTH AND SAFETY MATTERS

We and our joint ventures are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We and our joint ventures are therefore subject to PRC laws and regulations concerning the discharge of waste water, gaseous waste and solid waste during our manufacturing processes. We and our joint ventures are required to establish and maintain facilities to dispose of waste and report the volume of waste to the relevant government authorities, which conduct scheduled or unscheduled inspections of our facilities and treatment of such discharge. We and our joint ventures generally contract with third parties for the disposal of these materials and wastes. See "*Risk Factors – Other Risks and*

Risks Relating to Doing Business in China – If we or our joint ventures fail to comply with environmental, health and safety laws and regulations, we or they could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business."

During the Track Record Period and up to the Latest Practicable Date, we have not had any material non-compliance with health, safety or environmental regulations.

LEGAL AND REGULATORY MATTERS AND COMPLIANCE

Legal Proceedings

From time to time, we may become subject to legal proceedings and claims in the ordinary course of our business, including claims of alleged infringement of patents and other intellectual property rights. As of the Latest Practicable Date, there were no legal or arbitration proceedings pending or, to our knowledge, threatened against us that could have a material adverse effect on our financial condition or results of operations.

Relevant Key Laws and Regulations

A summary of the relevant key laws and regulations in the PRC and the United States which are applicable to our business is set out in "*Appendix IV – Regulatory Overview and Taxation.*"

Compliance with Laws and Regulations

During the Track Record Period and up to the Latest Practicable Date, we did not have any non-compliance incidents which our Directors believe would, individually or in the aggregate, have a material adverse effect on our financial condition or results of operations.

Risks Relating to Doing Business in China – If we or our joint ventures fail to comply with environmental, health and safety laws and regulations, we or they could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business."

During the Track Record Period and up to the Latest Practicable Date, we have not had any material non-compliance with health, safety or environmental regulations.

LEGAL AND REGULATORY MATTERS AND COMPLIANCE

Legal Proceedings

From time to time, we may become subject to legal proceedings and claims in the ordinary course of our business, including claims of alleged infringement of patents and other intellectual property rights. As of the Latest Practicable Date, there were no legal or arbitration proceedings pending or, to our knowledge, threatened against us that could have a material adverse effect on our financial condition or results of operations.

Relevant Key Laws and Regulations

A summary of the relevant key laws and regulations in the PRC and the United States which are applicable to our business is set out in "*Appendix IV – Regulatory Overview and Taxation.*"

Compliance with Laws and Regulations

During the Track Record Period and up to the Latest Practicable Date, we did not have any non-compliance incidents which our Directors believe would, individually or in the aggregate, have a material adverse effect on our financial condition or results of operations.

In the Listing Application, the Company disclosed the following additional financial information:

Net Current Assets

The following table sets forth the Company's current net assets and current liabilities as of February 28, 2019:

	As of February 28, 2019
	US$'000
	(Unaudited)
Current assets:	
Cash and cash equivalents	69,893
Short-term investments	212,179
Accounts receivable—third parties	47,036
Accounts receivable—related parties	1,918
Other receivables, prepayments and deposits	14,797
Amounts due from related parties	1,123
Inventories	14,146
Total current assets	361,092
Current liabilities:	
Accounts payable	32,674
Other payables, accruals and advance receipts	55,335
Income tax payable	579
Deferred revenue	4,227
Amounts due to related parties	89
Lease liabilities	2,817
Total current liabilities	95,721
Net current assets	265,371

Our net current assets decreased from US$285.1 million as of December 31, 2018, as disclosed in our audited consolidated financial statements, to US$265.4 million as of February 28, 2019, primarily due to the continued investment in research and development activities.

Accounts Receivable Aging Analysis

The following table sets forth an aging analysis of our accounts receivable, gross, as of the dates indicated:

	As of December 31,		
	2016	2017	2018
		US$'000	
Not later than 3 months	37,560	34,874	37,326
3 months to 6 months	2,936	3,589	2,704
6 months to 1 year	608	205	61
Later than 1 year	2,428	-	126
Total	43,532	38,668	40,217

Accounts Payable Aging Analysis

The following table sets forth an aging analysis of our accounts payable as of the dates indicated:

	As of December 31,		
	2016	2017	2018
		US$'000	
Not later than 3 months	33,319	20,538	19,185
3 months to 6 months	1,967	3,262	5,584
6 months to 1 year	185	494	703
Later than 1 year	67	71	153
Total	35,538	24,365	25,625

Indebtedness

The table below sets forth a breakdown of our overall indebtedness as reported in the consolidated balance sheet, as of February 28, 2019. All amounts are unsecured and unguaranteed.

	As of February 28, 2019
	US$'000
	(Unaudited)
Non-current	
Bank borrowings	26,755
Loan from non-controlling shareholders of subsidiaries	579
Lease liabilities	3,104
Current	
Lease liabilities	2,817
Total indebtedness	**33,255**

The table below sets forth a maturity profile of our overall indebtedness as of February 28, 2019:

	As of February 28, 2019
	US$'000
Indebtedness repayable within:	(Unaudited)
Less than one year	2,992
One to two years	29,296
Two to five years	804
Five years or more	579
	33,671
Less: unamortized debt issuance costs and interest	(416)
Total indebtedness	**33,255**

The Company's independent registered public accounting firm has not audited, reviewed or performed any procedures with respect to the Company's financial data as of February 28, 2019 and accordingly does not express an opinion or any other form of assurance with respect thereto. This data could change as a result of further review.

Key Financial Ratios

The table below sets forth, as of the dates indicated, certain of the Company's key financial ratios:

	As of December 31,		
	2016	**2017**	**2018**
Current ratio[(1)]	176%	413%	433%
Quick ratio[(2)]	162%	402%	419%

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Notes:

(1) Current ratio is calculated as current assets divided by current liabilities, multiplied by 100%.
(2) Quick ratio is calculated as current assets minus inventories then divided by current liabilities, multiplied by 100%.

Current Ratio

Our current ratio increased from 176% as of December 31, 2016 to 413% as of December 31, 2017, primarily due to the increase in cash and cash equivalents and short-term investments after our follow-on offering on the Nasdaq Global Select Market in October 2017. Our current ratio then increased slightly to 433% as of December 31, 2018.

Quick Ratio

Our quick ratio increased from 162% as of December 31, 2016 to 402% as of December 31, 2017, primarily due to the increase in cash and cash equivalents and short-term investments after our follow-on offering on the Nasdaq Global Select Market in October 2017. Our quick ratio then increased to 419% as of December 31, 2018.

Customers and Suppliers

For the financial years ended December 31, 2016, 2017 and 2018, revenue from our five largest customers represented approximately 26%, 27% and 35% of our total revenue, respectively, and revenue from our largest customer in those periods represented approximately 6%, 8% and 11% of our revenue in the same periods, respectively. Save for Sinopharm Group Co., Ltd. ("Sinopharm"), our joint venture partner, and our joint ventures, Shanghai Hutchison Pharmaceuticals Limited and Nutrition Science Partners Limited, our five largest customers were independent third parties pursuant to the rules of the SEHK, and none of our directors or their close associates or, to the knowledge of our directors, any shareholder who owned more than 5% of our issued shares had any interest in any of our five largest customers as of April 5, 2019.

For the financial years ended December 31, 2016, 2017 and 2018, our purchases from our five largest suppliers represented less than 30% of our total purchases. Save for our joint venture partners, Sinopharm and The Hain Celestial Group, Inc., all of our five largest suppliers were independent third parties pursuant to the rules of the SEHK, and none of our directors or their close associates or, to the knowledge of our directors, any shareholder who owned more than 5% of our issued shares had any interest in any of our five largest suppliers as of April 5, 2019.

Five Highest Paid Individuals

In the Listing Application, the Company disclosed the following information about the compensation of the Company's five highest paid individuals:

For 2016, two of the five highest paid individuals were directors. The aggregate amount of the salaries, housing allowances, other allowances, benefits in kind (including contributions to pension schemes), bonuses and share-based compensation borne by our group to the three remaining highest paid individuals were approximately US$4,296,410. For 2017 and 2018, three of the five highest paid individuals were directors. The aggregate amount of the salaries, housing allowances, other allowances, benefits in kind (including contributions to pension schemes), bonuses and share-based compensation borne by our group to the two remaining highest paid individuals were approximately US$2,268,577 and US$2,411,728, respectively.

Share Option Grants

In connection with the Listing, we intend to (a) implement a share split whereby one ordinary share will be sub-divided into 10 ordinary shares (the "Share Split") and (b) amend certain provisions of the Company's Articles of Association to reflect the requirements of the SEHK. Concurrent with the proposed share split, the American depositary share ("ADS") ratio will be changed from 1 ADS representing one-half Share to 1 ADS representing 5 Shares, so that the foregoing share split will not affect the trading price of our ADSs. The share split will, however, result in a reduction in the price of each Share trading on the AIM market such that, immediately following the share split, the price of each Share on AIM will be one-tenth of the price prior to the split. Further details will be provided to shareholders in due course and an extraordinary general meeting of the Company will be convened to obtain shareholders' approval for the share split and the amendments to the Company's Articles of Association.

In the Listing Application, the Company disclosed the following information about the options granted to senior management and other employees pursuant to our option schemes as of April 5, 2019 assuming the above mentioned Share Split has occurred on or before such date:

Grantee	Number of Shares under Options Granted and Outstanding	Exercise Price	Exercise Period
Grantees who are members of senior management			
May Wang	1,000,000[(1)]	GBP1.97	15.6.2016 to 19.12.2023
Zhenping Wu	1,000,000[(1)]	GBP1.97	15.6.2016 to 19.12.2023
Mark Lee	936,860[(1)]	GBP1.97	15.6.2016 to 19.12.2023
Marek Kania	375,000[(1)]	GBP4.86	06.8.2018 to 05.8.2028
Enrico Magnanelli	255,000[(1)]	GBP4.86	06.8.2018 to 05.8.2028
	3,566,860		
Other grantees			
Employees in the aggregate	750,000[(2)]	GBP0.44	24.06.2011 to 23.06.2021
	1,095,180[(2)]	GBP0.61	20.12.2013 to 19.12.2023
	7,148,100[(1)]	GBP4.65	20.04.2018 to 19.04.2028
	369,360[(1)]	GBP4.17	06.06.2018 to 05.06.2028
	50,000[(1)]	GBP4.86	06.08.2018 to 05.08.2028
	430,000[(1)]	GBP4.61	19.10.2018 to 18.10.2028
	9,842,640		

Notes: (1) Share options granted under the 2015 Chi-Med Option Scheme.

(2) Share options granted under the 2005 Chi-Med Option Scheme.

In the Listing Application, the Company disclosed the following supplemental risk factors:

We may be restricted from transferring our scientific data abroad.

On March 17, 2018, the General Office of the State Council promulgated the Measures for the Management of Scientific Data, or the Scientific Data Measures, which provides a broad definition of scientific data and relevant rules for the management of scientific data. According to the Scientific Data Measures, enterprises in China must seek governmental approval before any scientific data involving a state secret may be transferred abroad or to foreign parties. Further, any researcher conducting research funded at least in part by the Chinese government is required to submit relevant scientific data for management by the entity to which such researcher is affiliated before such data may be published in any foreign academic journal. Given the term state secret is not clearly defined in the Scientific Data Measures, if and to the extent our research and development of drug candidates will be subject to the Scientific Data Measures and any subsequent laws as required by the relevant government authorities, we cannot assure you that we can always obtain relevant approvals for sending scientific data (such as the results of our pre-clinical studies or clinical trials conducted within China) abroad or to our foreign partners in China. If we are unable to obtain necessary approvals in a timely manner, or at all, our research and development of drug candidates may be hindered, which may materially and adversely affect our business, results of operations, financial conditions and prospects. If the relevant government authorities consider the transmission of our scientific data to be in violation of the requirements under the Scientific Data Measures, we may be subject to fines and other administrative penalties imposed by those government authorities.

We may be involved in litigation, legal disputes, claims or administrative proceedings which could be costly and time-consuming to resolve.

We may become subject, from time to time, to legal proceedings and claims that arise in the ordinary course of business or pursuant to governmental or regulatory enforcement activity. Any litigation or proceeding to which we become a party might result in substantial costs and divert management's attention and resources. Furthermore, any litigation, legal disputes, claims or administrative proceedings which are initially not of material importance may escalate and become important to us due to a variety of factors, such as changes in the facts and circumstances of the cases, the likelihood of loss, the monetary amount at stake and the parties involved. Our insurance might not cover claims brought against us, provide sufficient payments to financially cover all of the costs to resolve such claims or continue to be available on terms acceptable to us.

We are a Cayman Islands company. Because judicial precedent regarding the rights of shareholders is more limited under Cayman Islands law than under Hong Kong law, U.S. law or English law, shareholders may have different shareholder rights than they would have under Hong Kong law, U.S. law or English law and may face difficulties in protecting your interests.

We are an exempted company with limited liability incorporated in the Cayman Islands. Our corporate affairs are governed by our Articles of Association (as may be further amended from time to time), the Companies Law (as amended) of the Cayman Islands and the common law of the Cayman Islands. The rights of shareholders to take action against the Directors, actions by minority shareholders and the fiduciary responsibilities of our Directors are to a large extent governed by the common law of the Cayman Islands. This common law is derived in part from comparatively limited judicial precedent in the Cayman Islands as well as from English common law, which has persuasive, but not binding, authority on a court in the Cayman Islands. The rights of our shareholders and the fiduciary responsibilities of our Directors under Cayman Islands law are not as clearly established as they would be under statutes or judicial precedent in England,

Hong Kong and some jurisdictions in the United States. In particular, the Cayman Islands has a less developed body of securities law than Hong Kong, the United States or the United Kingdom. In addition, some states in the United States, such as Delaware, have more fully developed and judicially interpreted bodies of corporate law than the Cayman Islands.

In addition, as a Cayman Islands exempted company, our shareholders have no general rights under Cayman Islands law to inspect corporate records and accounts or to obtain copies of lists of shareholders of these companies with the exception that the shareholders may request a copy of the Articles of Association. Our Directors have discretion under our Articles of Association to determine whether or not, and under what conditions, our corporate records may be inspected by our shareholders, but are not obliged to make them available to our shareholders. This may make it more difficult for you to obtain the information needed to establish any facts necessary for a shareholder motion or to solicit proxies from other shareholders in connection with a proxy contest. As a Cayman Islands company, we may not have standing to initiate a derivative action in Hong Kong, U.S. federal courts or English courts. As a result, you may be limited in your ability to protect your interests if you are harmed in a manner that would otherwise enable you to sue in Hong Kong courts, U.S. federal courts or English courts. In addition, shareholders of Cayman Islands companies may not have standing to initiate a shareholder derivative action in Hong Kong, U.S. federal courts or English courts.

Some of our Directors and executive officers reside outside of Hong Kong and the United States and a substantial portion of their assets are located outside of Hong Kong and the United States. As a result, it may be difficult or impossible for you to bring an action against us or against these individuals in the Cayman Islands in the event that you believe that your rights have been infringed under the securities laws of Hong Kong, the United States or otherwise. In addition, some of our operating subsidiaries are incorporated in China. To the extent our Directors and executive officers reside in China or their assets are located in China, it may not be possible for investors to effect service of process upon us or our management inside China. Even if you are successful in bringing an action, the laws of the Cayman Islands and China may render you unable to enforce a judgment against our assets or the assets of our Directors and officers. There is no statutory recognition in the Cayman Islands of judgments obtained in the United States, Hong Kong or China, although the courts of the Cayman Islands will generally recognize and enforce a non-penal judgment of a foreign court of competent jurisdiction without retrial on the merits.

As a result of all of the above, public shareholders may have more difficulty in protecting their interests in the face of actions taken by management, members of the Board or controlling shareholders than they would as public shareholders of a Hong Kong company, an English company or a U.S. company.