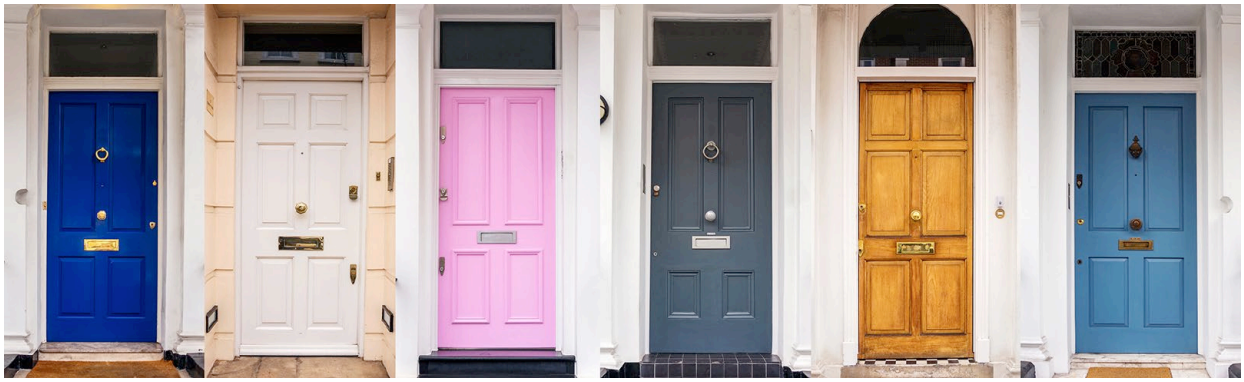
BioCentury
REPRINT FROM FEBRUARY 4, 2019



GEORGECLERK/ISTOCK/GETTY IMAGES

PRODUCT DEVELOPMENT

YEAR OF THE LION

BY ALLISON JOHNSON, STAFF WRITER

With three data readouts coming in 2019, Aslan Pharmaceuticals Ltd. is hoping this will be the year it starts to reap the benefits of its 2012 strategy rethink, giving the biotech more options for advancing its therapies. A key opportunity will be commercializing lead compound varlitinib on its own, pending a pivotal trial readout in biliary tract cancer.

Launched in 2010, Aslan's founding strategy was to in-license neglected, early stage compounds, take them through Phase II proof-of-concept testing, then find a partner for late-stage development and commercialization. Aslan leverages its Asia location to enable lower development costs, higher clinical trial recruitment rates and shorter timelines to trial starts than are typical in the U.S. or Europe (see "Aslan: A Bridge to Phase III").

Of its three clinical compounds, two stand to be first-in-class in their respective indications, and the other could be best-in-class.

The value proposition of those therapies led Aslan to begin rethinking its business strategy as early as 2012, Co-founder and CEO Carl Firth told BioCentury.

"As we were taking these drugs further and further along, we recognized that if all we did was partner them out, we would give up a very significant chunk of value of these assets," Firth said.

Aslan went back to the companies it had licensed the programs from and restructured its deals to add late-stage development and commercialization rights for select indications where it made sense to go it alone. Now Aslan has the option to take two of the compounds to market itself.

The first chance could come from pan-HER inhibitor varlitinib. Aslan is planning parallel submissions in the U.S. and China, while hoping to find partners for other geographies. Firth said Aslan had anticipated finding a commercial partner in China until recent regulatory and drug pricing changes in the country made it possible for a small biotech like itself to go it alone.

But taking on additional development and commercial activities requires more capital, and Aslan found itself needing to shore up its resources. As of Sept. 30, 2018, it reported $34.8 million in cash and an average quarterly burn rate of $10.4 million in the first three quarters of the year.

On Jan. 29, Aslan announced a restructuring that reduced headcount by 30% and cut operating costs in half.

The added runway will take the biotech through 2H20, Firth said.

The biotech has already had one clinical failure this year, but is awaiting at least three more data milestones that could turn things around.

TAKING CONTROL

Firth said the outcome of Aslan's 2011 deal with Bristol-Myers Squibb Co. reaffirmed its decision to commercialize its own drugs.

Under the original agreement, which was made prior to Aslan's strategy shift, Aslan gained development and commercialization rights in Asia to ASLAN002 and the pharma had the option to reacquire the compound. ASLAN002 is a dual inhibitor of c-MET (MET; HGFR; c-Met proto-oncogene) and macrophage stimulating 1 receptor c-Met-related tyrosine kinase (MST1R; RON; CD136; CDw136).

No targeted therapies are approved for biliary tract cancer. At least three candidates are ahead of varlitinib in Phase III or pivotal studies in the indication, but none target the HER family, according to BioCentury's BCIQ database.

ASLAN003 is the most advanced DHODH inhibitor in any cancer indication, according to BCIQ. Marketed therapies against the target are indicated for inflammatory diseases.

In contrast to varlitinib and ASLAN003, Aslan does not intend to renegotiate rights to its third clinical candidate, the Phase I compound ASLAN004. The therapy is a potentially best-in-class mAb against the IL-4 receptor (IL-4R; IL-4RA; CD124) that, if approved, would compete with Sanofi's marketed product Dupixent dupilumab in atopic

"WE RECOGNIZED THAT IF ALL WE DID WAS PARTNER THEM OUT, WE WOULD GIVE UP A VERY SIGNIFICANT CHUNK OF VALUE OF THESE ASSETS."

CARL FIRTH, ASLAN PHARMACEUTICALS LTD.

BMS exercised the option in 2016, earlier than Aslan had expected. The compound had only completed Phase I testing.

Firth said the $10 million upfront from the reacquisition was "far in excess of what we spent to develop the drug, so it was a project with a max return." Aslan also is eligible for milestones and royalties, he said. Still, Firth noted Aslan's upside and its return to investors would have been greater if it had taken the therapy further.

"We know that doing deals like that is not the sort of thing that is going to get investors terribly excited," said Firth.

Earlier in 2016, Aslan updated its agreement with Almirall S.A. to include full rights for dihydroorotate dehydrogenase (DHODH) inhibitor ASLAN003 in oncology indications, in addition to the rheumatoid arthritis rights it already had.

The therapy is in Phase II testing for acute myelogenous leukemia (AML). Aslan expects data from part one of the trial this half.

In January 2018, Aslan amended its 2011 deal with Array BioPharma Inc. to obtain commercial rights to varlitinib. It had already started the pivotal Phase II/III TreeTopp study testing the therapy in second line biliary tract cancer. Under the original agreement, Aslan was responsible for finding a Phase III partner.

Aslan expects data from TreeTopp next half.

Both compounds are poised to become first-in-class therapies for their respective indications.

dermatitis. Aslan's license to the therapy from CSL Ltd. does not include commercial rights.

"I think to play in that arena, you need to have the backing of a big pharma. So with 004, it's always been our intention to develop it to a certain stage and then partner it with a pharma company."

Aslan expects Phase I data from ASLAN004 this half.

CHARTING VARLITINIB'S COURSE

Aslan was initially developing varlitinib for a variety of cancer indications, eventually opting for gastric cancer where another HER family antibody was already approved and biliary cancer where the disease biology was less well understood.

In gastric cancer, Aslan saw an opportunity to expand the number of patients treatable with a HER family targeted therapy. The only approved HER family agent for gastric cancer, the anti-HER2 mAb Herceptin trastuzumab, is indicated for HER2-amplified patients. Firth had hoped varlitinib, a pan-HER inhibitor, could be effective for patients co-expressing EGFR and HER2 at lower levels, corresponding to about 40% of gastric cancer patients.

But last month the biotech reported that varlitinib plus mFOLFOX6 missed the primary endpoint of a Phase II study vs. mFOLFOX6. The miss precipitated the Jan. 29 restructuring, which included R&D personnel from gastric cancer areas.

The company's hypothesis in biliary cancer is based on expression data and previous clinical trials by other groups.

"We do know that there is a lot of HER family expression in biliary tract cancer, particularly of HER4 [EGFR4]," he said.

Firth thinks the ability of varlitinib to inhibit EGFR4 in addition to EGFR and HER2 gives it a better likelihood of success over EGFR-specific antibodies like Erbitux cetuximab.

He pointed to results from an exploratory, investigator-led Phase II study of Erbitux plus gemcitabine and capecitabine in patients with inoperable biliary tract cancer. The combination led to a median progression-free survival (PFS) of 34.3 weeks and median overall survival (OS) of 62.8 weeks among 34 patients with a median follow-up of 15.4 months. There was no control arm; other studies in the literature show biliary cancer patients treated with gemcitabine-based chemotherapy combos live about 47.9 weeks.

> "THINGS ARE CHANGING VERY QUICKLY AND MAKING CHINA A MUCH MORE ATTRACTIVE PLACE TO BUILD YOUR OWN COMMERCIAL ORGANIZATION."
>
> CARL FIRTH, ASLAN PHARMACEUTICALS LTD.

"While they didn't show an effect sufficient for approval, they actually did show an effect," that supports a role for the HER family in biliary tract cancer, he said.

Results from a Phase I/II study of varlitinib in combination with gemcitabine and cisplatin in first-line biliary tract cancer showed the regimen led to an overall response rate (ORR) of 43.8% among 16 evaluable patients across two cohorts.

TreeTopp's readout next half will be its first. If the data look good, Firth said Aslan will start preparing regulatory applications immediately.

COMMERCIALIZING IN CHINA

Due to recent changes in regulatory and drug pricing policies, Aslan is no longer shying away from commercializing varlitinib in China.

"Back in 2013, we decided we needed to have a commercial strategy but our feelings on China at that stage were unclear," Firth said. "I think there may have been a time that we would have considered going in with a partner," but the company's resolve to go it alone in China has since solidified, he added.

Two changes that tipped the scales are the ability to submit international data for Chinese approvals and more rapid reimbursement of newly approved drugs in the county.

Whereas Chinese regulators previously required data from at least 200 Chinese patients from a bridging study or a global Phase III study, Firth said, now data from the 127-patient, global TreeTopp trial could be sufficient for approval thanks to regulatory changes set in motion in 2015 (see "Opening the Gates in China"). Firth declined to disclose the number of Chinese patients in TreeTopp.

As part of last month's restructuring, Aslan closed a single-arm Chinese trial testing varlitinib for biliary tract cancer in the second line because the trial was scheduled to readout after TreeTopp.

Firth said historically it took several years to get reimbursement for a new therapy in China, pointing to an eight-year gap between 2009 and 2017 where the country's reimbursement list did not get updated.

"Now, the idea is that you launch your drug and in six to 12 months you could get reimbursement," he said. "Things are changing very quickly and making China a much more attractive place to build your own commercial organization if you have that experience."

Last year, Aslan hired Stephen Doyle to head its commercial operations as VP of commercial and head of China. Since 2010, Doyle has held VP roles in sales and marketing in China at Boehringer Ingelheim GmbH and Sanofi.

Assuming Aslan gets positive results from TreeTopp, it plans to hire an initial sales team of about 30-40 people for the 150,000 biliary tract cancer patients in China, and about 20-25 people for the 12,000 U.S. patients, Firth said.

BEYOND VARLITINIB

Aslan thinks its second program ASLAN003 is attractive for cancer because the compound's target, DHODH, catalyzes the synthesis of pyrimidine, a building block of DNA base pairs, which cancer cells rely on to rapidly divide.

Firth said the first class of DHODH inhibitors approved for inflammatory conditions are not potent enough to be effective in cancer. Aslan's inhibitor is about 100-fold more potent than those agents, he said, giving the biotech the option to develop ASLAN003 in either disease area.

A 2016 *Cell* paper solidified the company's interest in pursuing cancer, said Firth. In the study, a group from Harvard University designed an small molecule screen to identify compounds that enabled leukemic cell differentiation. Eleven of the 12 most potent anti-tumor compounds identified were DHODH inhibitors.

Since the *Cell* paper, which included authors from Bayer AG, at least two other companies have disclosed cancer programs against DHODH: Bayer's BAY 2402234 is in Phase I testing for hematologic malignancies including AML, and Agios Pharmaceuticals Inc. submitted an IND in October for its DHODH inhibitor AG-636 to treat hematologic malignancies.

Aslan reported preliminary Phase II data from ASLAN003 at the 2018 American Society of Hematology (ASH) meeting showed the therapy was "very well tolerated" and led to stable disease for more than three months in four of eight evaluable patients.

Firth thinks the Phase I data from ASLAN004 in healthy volunteers could show it outperforms Dupixent on three measures: time to efficacy, dosing frequency and safety.

Dupixent also targets the IL-4/IL-13 receptor complex, only via IL-13 receptor α 1 (IL-13RA1; IL-13Ra; CD213A1) instead of IL-4R.

Aslan's Phase I study is measuring the ability of ASLAN004 to modulate the biomarker STAT6, which lies downstream of the IL-4/IL-13 receptor complex, and will compare the result to historical data from Dupixent on

STAT6. The results will give Aslan an idea of what differences in efficacy to expect moving forward, Firth said.

Dupixent is dosed every two weeks. Firth said Aslan is aiming to dose every four weeks.

"Dupilumab does take some time to be effective — we think we can be quicker," Firth said.

ASLAN004 also could have a safety advantage with respect to conjunctivitis. he said. "With dupilumab, we see a large number of patients developing conjunctivitis. We've now treated enough patients to get a good sense of where we will stand in comparison." bc

COMPANIES AND INSTITUTIONS MENTIONED

Agios Pharmaceuticals Inc. (NASDAQ:AGIO), Cambridge, Mass.
Almirall S.A. (Madrid:ALM), Barcelona, Spain
Array BioPharma Inc. (NASDAQ:ARRY), Boulder, Colo.
Aslan Pharmaceuticals Ltd. (TPEx:6497; NASDAQ:ASLN), Singapore, Singapore
Bayer AG (Xetra:BAYN), Leverkusen, Germany
Boehringer Ingelheim GmbH, Ingelheim, Germany
Bristol-Myers Squibb Co. (NYSE:BMY), New York, N.Y.
CSL Ltd. (ASX:CSL), Parkville, Australia
Sanofi (Euronext:SAN; NASDAQ:SNY), Paris, France

BIOCENTURY INC.

NEWSROOM
pressreleases@biocentury.com

SAN CARLOS, CA
+1 650-595-5333; Fax: +1 650-595-5589

CHICAGO
+1 312-755-0798; Fax: +1 650-595-5589

WASHINGTON, DC
+1 202-462-9582; Fax: +1 202-667-2922

UNITED KINGDOM
+44 (0)1865-512184; Fax: +1 650-595-5589

BioCentury™

BIOCENTURY INC.

NEWSROOM
pressreleases@biocentury.com

SAN CARLOS, CA
+1 650-595-5333; Fax: +1 650-595-5589

CHICAGO
+1 312-755-0798; Fax: +1 650-595-5589

WASHINGTON, DC
+1 202-462-9582; Fax: +1 202-667-2922

UNITED KINGDOM
+44 (0)1865-512184; Fax: +1 650-595-5589