Therapeutic focus - Sanofi snaps up rare unpartnered JAK-2 inhibitor

Sanofi-Aventis might be on the hunt for a big acquisition, but the French drug maker is also keeping busy snapping up the small fry. The acquisition of privately-held TargeGen last week, for an initial $75m and potential $560m in total, was struck for access to the company’s JAK2 kinase inhibitor, TG101348.

This is a class of drug that has been attracting a lot of attention over the last couple of years but the structure of the deal, heavily linked to the success of TG101348, no doubt reflects the fact that as yet, none have successfully completed a pivotal study. Still, as the table below shows, the move means Sanofi has gained access to one of the few remaining unpartnered JAK2 inhibitors, placing it in a strong position should this class begin to demonstrate robust efficacy.

Sanofi will pay further milestones to TargeGen’s owners as TG101348 moves through the clinic. The US company raised $40m in a series D financing round back in mid-2007, and as such has gathered a wide array of venture capital backers over the years which will have to share the spoils.

With further studies planned to start later this year, the next significant payment could be a couple of years away.

Blood disorders

Like most of the other JAK2 inhibitors in development, TG101348 is primarily being developed for myelofibrosis (MF). This is a life threatening, progressive condition whereby scar tissue develops in the bone marrow, reducing a person’s ability to produce sufficient blood cells. Consequently, more blood cells are made in other organs, such as the liver and spleen, which are not as efficient at blood cell production as the bone marrow. As such, MF causes an enlarged spleen and worsening anaemia.

The condition is classified as a myeloproliferative disease, which also includes polycythemia vera (PV) and essential thrombocythemia (ET), other areas of research for these drugs.

Current therapies for MF are mostly palliative in nature. While the actual cause of the disease is unknown, the JAK2 gene has been implicated in the development of this condition.

Furthest along

The furthest JAK2 along is Incyte’s INCB18424, which has completed a number of phase II trials in autoimmune disorders and blood cancers.

Partnered with Novartis, two phase III studies called Comfort I and Comfort-II were started last year in myelofibrosis, in 240 and 150 patients in the US and Europe respectively. The drug will be pitted against “best available therapy” in the eyes of the physician, highlighting the lack of specific options to treat this group of patients. The primary endpoint is reduction is spleen volume and results could be due next year, an event that will be of interest to all the companies mentioned in the table below.

Novartis paid $210m upfront for ex-US rights last year, suggesting hopes are high for a positive read out ([inCYTE Scores Top Dollar Deal With Novartis for JAK Inhibitor](https://www.evaluate.co.uk/news/inCYTE-Scores-Top-Dollar-Deal-With-Novartis-for-JAK-Inhibitor-November-25-2009), November 25, 2009).

Moving along

The remainder of the clinical stage JAK2 pipeline is quite far behind, with only phase I/II studies having been conducted. However given the need for treatments the developers are no doubt hoping to move into phase III studies without substantial mid-stage data.

S*Bio announced earlier this month that enrolment has been completed in two single-arm phase II trials for SB1518, a compound which has demonstrated potency against both the wild-type JAK2 kinase, and the kinase carrying a mutation known as V617F. Around half of patients with MF are thought to carry this mutation.
Onyx has the option to sign a full licensing deal for SB1518, and another JAK2 inhibitor still in pre-clinical development, at a predetermined but undisclosed stage of development. Should this be after proof-of-concept at phase II, the results from these two ongoing trials, due next year, will be an important event for the Singapore company.

YM BioSciences gained its JAK2, CYT387, through the acquisition of Cytopia. The company is also pursuing MF, and announced in March that an ongoing phase I/II trial would be expanded and should mean results become available early next year, six months earlier than anticipated. The company is hoping to push straight on into phase III studies should data be positive.

AstraZeneca’s candidate, AZD1480, should produce further phase II data in mid-2011.

**Picking a winner**

TargeGen meanwhile completed dose-ranging phase I/II trials last year and presented the results at the American Society of Hematology (ASH) Conference in New Orleans in December 2009. It is not clear whether the candidate is ready to begin pivotal studies, but it will be interesting to see which of the phase II pack makes it there next, following on the heels of Incyte and Novartis.

Analysts are already talking about blockbuster potential for INCB18424, should the drug show efficacy across all the myeloproliferative diseases. This market size suggests there will be room for a couple of competitors, but it seems unlikely they will all make it to the finish line.

It remains to be seen whether Sanofi has picked a winner.
<table>
<thead>
<tr>
<th>Status</th>
<th>Pharmacological Class</th>
<th>Product</th>
<th>Company</th>
<th>Originator</th>
<th>Indication Summary</th>
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<tr>
<td>Phase III</td>
<td>Janus kinase-2 (JAK-2) inhibitor</td>
<td>INCB18424</td>
<td>Novartis / Incyte</td>
<td>Incyte</td>
<td>Myelofibrosis [Phase III]; Polycythemia vera [Phase III]; Thrombocytopenia [Phase III]; Psoriasis [Phase II]; Leukaemia, acute myeloid (AML) [Phase II]</td>
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<td>Phase II</td>
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<td>INCB28050</td>
<td>Incyte (Eli Lilly for inflammatory &amp; autoimmune indications)</td>
<td>Incyte</td>
<td>Arthritis, rheumatoid [Phase II]; General cancer indications [Phase I]</td>
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<td>Janus kinase-2 (JAK-2) inhibitor</td>
<td>AZD1480</td>
<td>AstraZeneca</td>
<td>AstraZeneca</td>
<td>General blood malignancies [Phase II]; Solid tumour indications [Phase I]</td>
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<td>Janus kinase-2 (JAK-2) inhibitor</td>
<td>ONX 0803 (SB1518)</td>
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<td>S*BIO</td>
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<td>Janus kinase-1/2 (JAK-1/2) inhibitor</td>
<td>CYT387</td>
<td>YM BioSciences</td>
<td>Cytopia</td>
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<td>Janus kinase-2 (JAK-2) inhibitor</td>
<td>TG101348</td>
<td>Sanofi-Aventis</td>
<td>TargeGen</td>
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<td>Phase I</td>
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<td>Exelixis</td>
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<td>Syk kinase &amp; janus kinase (JAK) inhibitor</td>
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<td>Portola Pharmaceuticals</td>
<td>Portola Pharmaceuticals</td>
<td>Non-Hodgkin's lymphoma (NHL) [Phase I]; General cancer indications [Phase I]; Arthritis, rheumatoid [Phase I]; Systemic lupus erythematosus (SLE) [Phase I]</td>
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Source: EvaluatePharma