ValiSeek Limited

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Reformulating a novel therapeutic for lung cancer

London-based ValiSeek is developing VAL401, a repurposed treatment for lung and other cancers that is now ready for partnering.

The outlook is grim for those suffering from the most common form of lung cancer. Most patients survive for only four to five months with palliative care, having been diagnosed too late for chemotherapy or targeted treatment, and those who do receive treatment often suffer from deleterious effects including nausea, wasting and delirium. There is clearly a high unmet need for a therapeutic that can help these people.

Enter ValiSeek's VAL401, a repurposed treatment for lung and other cancers that is poised to meet this challenge. With a unique mechanism of action, decades of data supporting its safe use, and preclinical proof of effectiveness, the drug is set to help patients with non-small-cell lung cancer (NSCLC) and address a multi-billion-dollar market.

VAL401 is a reformulation of Risperdal (risperidone), an antipsychotic used since 1993 as a first-line treatment for schizophrenia and bipolar disorder. Work carried out by scientists at Warwick University ultimately led to the discovery that Risperdal inhibits HSD10 (hydroxysteroid dehydrogenase type 10), an enzyme involved in the processing of steroids and fats. While normally located in the mitochondria, HSD10 is overexpressed (approximately tenfold) in cancer cells, where it is also accessible from the cytoplasm. Inhibition of HSD10 disrupts cancer energy metabolism, thereby breaking the cancer cell cycle.

Although Risperdal has no anticancer effects when administered alone, its anticancer activity is switched on when it is combined in a 1:1 ratio with rumenic acid (a nutritional supplement derived from safflower oil). "Acting as a functional excipient, rumenic acid is essential for delivery of risperidone into tumor cells for activity," said Suzanne Dilly, CEO of ValiSeek, which was established in 2014 to develop the novel cancer therapeutic.

ValiSeek has combined the ingredient risperidone and rumenic acid in a patent-protected gelatin-capsule formulation, VAL401, for oral delivery. The drug reduces cellular activity in many different cancer cell lines, including prostate, pancreatic, lung and breast adenocarcinomas. VAL401 has also demonstrated preclinical efficacy in lung, prostate and pancreatic models, slowing tumor growth by at least 50% and significantly improving survival. "VAL401 has a unique mechanism of action—different to that of current cancer treatments—so cross-resistance is unlikely," added Dilly, who is also the CEO of Tangent Reprofiling, which formed ValiSeek as a joint venture with ValiRx.

Having progressed VAL401 through preclinical development, ValiSeek is currently testing VAL401 in a small-scale phase 2b trial involving 20 patients with very late-stage NSCLC for whom chemotherapy has failed (**Fig 1**). The single-arm, open-label study is assessing progression-free survival, quality of life and overall survival of patients, as well as recording the pharmacokinetics, drug metabolism, safety and tolerability of the drug in comparison to historical clinical records for Risperdal.

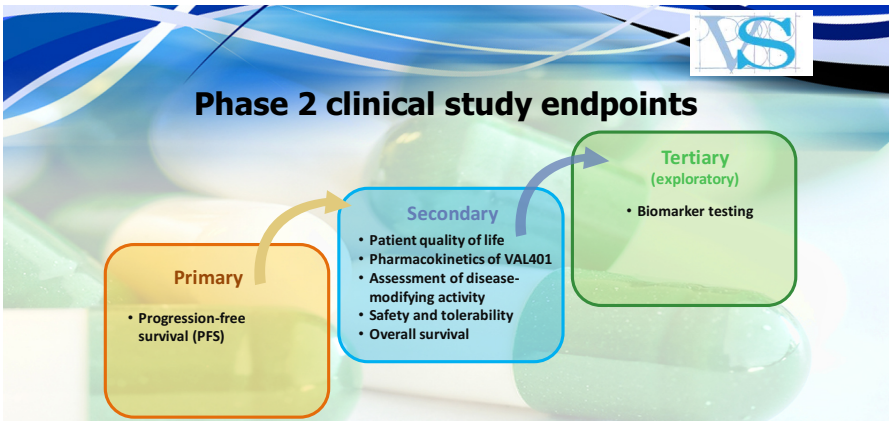

Figure 1: Diagram of the phase 2 clinical trial outcomes schemes.

Given Risperdal's record under its currently approved usage, treatment with VAL401 is expected to provide significant improvements in quality of life for cancer patients. Among these secondary benefits are the potential to counteract wasting, delirium caused by chemotherapy, and opioid-induced nausea. "One of the main measures we are looking at is quality of life; a meaningful improvement would be very attractive for these late-stage cancer patients," said Dilly.

Complete trial results are expected by the end of 2017. Pharmacokinetic data so far suggest no difference relative to conventional usage, and patients are tolerating the treatment well.

As an antipsychotic, Risperdal is typically taken for at least two years, and it has a well-established safety record derived from decades of clinical use. The equivalent dose of Risperdal in VAL401 (up to 10 mg daily) is within the range licensed as safe and tolerable for neural use with minimal side effects; preclinical toxicology has revealed no side effects beyond those expected from Risperdal, with preclinical pharmacokinetic data allowing for bridging from VAL401 to the historical full clinical data package on Risperdal. "VAL401 will provide a potential cancer treatment with a good safety profile, with a clear route to market supported scientifically by the extensive history of the drug's use, yet protected commercially by the detail of the reformulation," said Dilly.

Green light to partnering

With the active pharmaceutical ingredient readily available, manufacturing of VAL401 is relatively simple and, at $1,000 per patient per year, inexpensive. (Second-line therapeutics currently on the market for NSCLC sell for about $33,000 to $50,000 per annum.)

ValiSeek is keen to discuss acquisition proposals and is also looking for licensing partners with the resources to fully exploit VAL401 and move it through the clinic and quickly to market on a disease-specific and/or geographical basis. Advanced NSCLC—which accounts for over 80% of all lung cancer cases—is the lead indication, and represents a worldwide market projected to increase from $5.1 billion in 2013 to $7.9 billion in 2020. Although the drug was initially a second-line therapy, its label could potentially be expanded to include first-line, maintenance and combination therapies, further increasing the market.

Additional codevelopment opportunities are also available for any adenocarcinoma, particularly pancreatic and prostate cancers—markets worth around about $1.2 billion (2015) and $18.6 billion (2017), respectively, and for which there is also high unmet need. The historical data on Risperdal minimize the need for safety and tolerability clinical trials, and thus provide a swift path to efficacy trials in cancer patients.

"Our reformulation allows risperidone to access previously unexploited anticancer activity, offering patients treatment without devastating side effects," said Dilly. "VAL401 is safe and tolerable, has efficacy against various cancers, and is simple and cheap to manufacture with an abbreviated route to market."

contact
Suzanne Dilly, CEO
ValiSeek Limited
London, UK
Tel: +44 (0)7736 270615
Email: suzanne.dilly@valirx.com