Highland Therapeutics
www.highlandtherapeutics.com

HIGHLAND THERAPEUTICS

Next-generation drug delivery targets early-morning release

Highland Therapeutics' novel drug delivery platform is designed to offer control over the timing of drug release and the duration of therapeutic exposure, enabling dosing at night for treatment effect starting the moment the patient wakes and lasting throughout the day.

Highland Therapeutics is an emerging pharmaceutical company that is leveraging a novel, oral, once-daily drug delivery technology designed to optimize the delivery of previously approved drug products. The proprietary DELEXIS drug delivery platform was specifically engineered to provide a consistent delay in the initial release of active drug after ingestion, followed by a period of extended release. This will enable drugs to be dosed at night to provide patients with the intended therapeutic effects immediately upon waking. The long absorption window extends these effects throughout the day.

DELEXIS uses a sophisticated microbead technology comprising two functional film coatings surrounding a drug-loaded core. The outer delayed-release (DR) layer comprises time- and pH-dependent polymers that provide a predictable delay in drug release. The inner extended-release (ER) layer comprises hydrophobic and pore-forming polymers that regulate permeability and tightly control the dissolution of the active ingredient.

"We have designed a combination of coatings that rely on different physiological phenomena to enable release of the active ingredient, which makes DELEXIS different from other modified-release products," said Bev Incledon, executive vice president of research and development at Highland Therapeutics. "By combining these different properties, we have been able to develop a product where the drug release rate is not dependent on any single factor, such as a pH trigger, site of release or gastrointestinal transit, which consequently minimizes inter- and intra-patient variability".

Highland Therapeutics was founded in 2008 by co-inventor of the technology and chief executive officer David Lickrish. Based in Toronto, Ontario, Canada, it operates through a wholly owned subsidiary, Ironshore Pharmaceuticals & Development, Inc. (Grand Cayman, Cayman Islands). The company's lead product candidates, HLD-200 and HLD-100, are novel formulations of the psychostimulants methylphenidate (MPH) and amphetamine, respectively and are being investigated for use in the treatment of children and adolescents diagnosed with attention-deficit/hyperactivity disorder (ADHD).

Extended delay and release

After ingestion, the DELEXIS capsule dissolves in the stomach and releases hundreds of beads into the digestive system. The DR layer is designed to remain intact until the beads reach the slightly alkaline ileum (pH 7.4), approximately six to eight hours after ingestion. The ratio of waxes and hydrophobic components in the DR layer and coat level—both of which affect wettability and the rate of erosion—also control the DR profile.

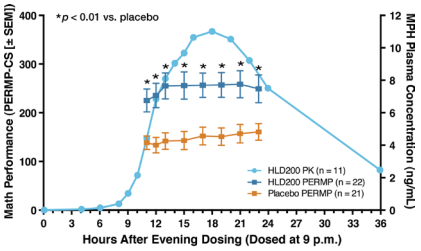

Figure 1: In an exploratory phase 3 trial, children aged 6–12 years with ADHD receiving HLD-200 had a statistically significant improvement over placebo in academic performance (PERMP) at all time points measured (between 8 a.m. and 8 p.m.)[3]. The improvement in PERMP, a mathematics-based test, coincides with the MPH release profile[1]. PERMP, Permanent Product Measure of Performance; PK, pharmacokinetics.

As the DR layer breaks down, pores start to form in the ER layer, enabling a slow release of dissolved active ingredient from the drug-loaded core of the bead. Again, the ratio of polymers and the coating level regulate the rate of film wetting and permeability. For example, a hydrophobic ER layer with few pores would enable a slow release of the drug, as moisture would enter the core slowly.

Data from a pharmacokinetic study in children and adolescents diagnosed with ADHD showed that after a single evening dose of HLD-200, the release profile of MPH was delayed by approximately eight hours[1]. The extended delay and release profile of DELEXIS is intended to allow for control of ADHD symptoms upon waking and throughout the day (**Fig. 1**).

Targeting a significant unmet need

Despite a range of existing stimulant medications, there remains a significant unmet need for clinically meaningful behavioral control of early-morning symptoms to enhance before-school functioning in children and adolescents with ADHD[2].

HLD-200 is the first MPH formulation designed for dosing before bedtime, and if it is approved by the US Food and Drug Administration (FDA), Highland Therapeutics believes that it may fundamentally change the way physicians treat ADHD. According to a recent physician survey commissioned by the company, an estimated 80% of physicians would inquire about symptoms during the morning routine upon FDA approval of HLD-200, and over 70% would likely prescribe the medication.

"By leveraging the advantages of DELEXIS specifically for ADHD, we seek to target the onset of drug release to coincide with the early morning, and provide effective treatment from the moment the patient wakes," said Incledon. "The controlled release of MPH is expected to continue throughout the day and into the evening period, giving all-day coverage."

Two pivotal phase 3 trials are under way to evaluate the safety and efficacy of evening treatment with HLD-200 in children diagnosed with ADHD, and a New Drug Application is planned for 2016.

"Few studies have attempted to assess behaviors and functioning in ADHD patients during the morning routine," said Lickrish. "The Before School Functioning Questionnaire, or BSFQ, provides physicians with a new tool for assessing patients during this critical time of day. We believe that, as awareness grows, physicians will start making questions about the morning routine a routine question, and adjust their treatment options accordingly."

The current trials were designed to build upon the results of an exploratory phase 3 trial (completed in 2014). In this study, subjects receiving evening dosing with HLD-200 showed improved control of ADHD symptoms compared to placebo, and the drug was well tolerated with a reported side-effect profile comparable to that of currently marketed stimulants[3].

Highland Therapeutics is developing a number of other drug candidates that utilize DELEXIS, including HLD-900 for binge eating disorder and two others (HLD-300 and HLD-400) for undisclosed indications. DELEXIS can also be applied to other therapeutic areas or drugs where there is a need for precise control over the onset and duration of drug release, site of drug absorption or therapeutic exposure.

1. Childress, A. *et al.*, poster presented at the American Professional Society of ADHD and Related Disorders Annual Meeting, Washington, D.C., USA, January 16–18, 2015.
2. Sallee, F.R. *J. Child Adolesc. Psychopharmacol.* **25**, 558–565 (2015).
3. McDonnell, M. *et al.*, poster presented at the 168th annual meeting of the American Psychiatric Association, Toronto, Ontario, Canada, May 16–20, 2015.

contact
David Lickrish, President & CEO
Highland Therapeutics
Toronto, Ontario, Canada
Tel: +1-345-749-8171
Email: ceo@ironshorepharma.com

ADVERTISER RETAINS SOLE RESPONSIBILITY FOR CONTENT