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Preliminary review of RhuDex[®] as a potential Surge Dose[®] candidate

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IM 04-10-01

Preliminary review of RhuDex[®] as a potential Surge Dose[®] candidate

Table of Contents

| | | |
|-----|---|---|
| 1 | BACKGROUND..... | 1 |
| 2 | PHYSICOCHEMICAL PROPERTIES AND PERMEABILITY..... | 1 |
| 3 | PHARMACOKINETICS (PK)..... | 2 |
| 3.1 | Absorption, metabolism and elimination..... | 2 |
| 3.2 | Formulations..... | 4 |
| 4 | PHARMACODYNAMICS (PD)..... | 5 |
| 4.1 | Mechanism of action | 5 |
| 4.2 | Efficacy..... | 6 |
| 5 | PATENTS | 6 |
| 6 | POTENTIAL OF RHUDEX [®] AS SURGE DOSE [®] CANDIDATE | 6 |

IM 04-10-01

Preliminary review of RhuDex[®] as a potential Surge Dose[®] candidate

1 Background

Avidex Ltd in Abingdon, UK <Avidex> was founded in 1999 with the aim of becoming the world's leading T- cell receptor company based on a series of patents which protect its novel technologies to produce soluble and stable T-cell proteins used for the development of new chemical entities that act on T-cell receptors and that would be useful in the treatment of autoimmune diseases.

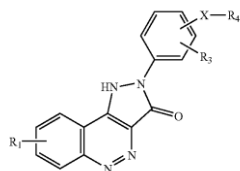
Avidex was acquired by MediGene AG, a Frankfurt listed biotechnology company, in October 2006. In 2008 a new company, Immunocore was spun out based on the Avidex technology. In 2002 Active Biotech a Swedish company and Avidex had signed a licensing agreement covering its patented small molecule CD80 antagonists that inhibit T- cell stimulation including RhuDex[®] or AV1142742 the development of which is being progressed through the Active Biotech – MediGene partnership as a promising therapy for rheumatoid arthritis.

The agreement gives MediGene exclusive right to evaluate the CD80 antagonists, and to develop and market products incorporating them or their derivatives. These novel compounds suppress the inappropriate immune responses in autoimmune diseases. If MediGene successfully develops the CD80 antagonists, Active Biotech will receive pre-agreed milestone payments worth up to GBP 6 million as well as low single digit royalties on future sales.

2 Physicochemical properties and permeability

The exact chemical formula or structure of RhuDex[®] has not been found. However patents on CD80 antagonists with priority going back to 2004 indicate an acidic structure for this group of compounds such as shown in Figure 1 where R4 is a carboxylic acid group¹.

Figure 1 General chemical structure of CD80 antagonists



A study on a group of CD80 antagonists by Avidex identifies the lead compound as that shown in Figure 2 which may well be RhuDex^{®2}. This is an acidic molecule which is likely

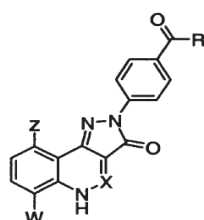
¹ US 7,932,253 Immunomodulating oxopyrrazolocinnolines as CD80 inhibitors

IM 04-10-01

Preliminary review of RhuDex[®] as a potential Surge Dose[®] candidate

to have higher solubility under alkaline conditions, with minimal aqueous solubility under acidic conditions such as occur in the fasted stomach.

Figure 2 Possible structure for RhuDex[®]



where R = OH, W = F, Z = H and X = CH

3 Pharmacokinetics (PK)

3.1 Absorption, metabolism and elimination

Only very limited published PK data have been on RhuDex[®] (AV1142742) in 5 healthy subjects³. RhuDex[®] was administered alone at 1.5 mg/kg in fasted subjects compared with administration after ranitidine, a H₂-receptor antagonist that inhibits gastric acid production or after the alkaline buffer meglumine which neutralises gastric acid. Dosing was repeated in fed subjects after administration of ranitidine. Repeat dosing over 5 days was evaluated with twice daily dosing taken with ranitidine and normal diet. Twelve hour plasma profiles were recorded. No description is given of the dosage form tested.

The terminal half life of elimination was around 15 hours and geometric mean peak plasma concentrations are summarized in Table 1. No statistical data were included to assess the variability of results in this very small population. All regimes were well tolerated.

Table 1 Summary of PK data for RhuDex[®] (AV1142742) in 5 healthy subjects

| Dosing regime 1.5 mg/kg | Geometric mean C _{max} (ng/mL) | T _{max} (h) |
|-------------------------------|--|----------------------|
| AV1142742 alone fasted | 376 | - |
| AV1142742 + meglumine fasted | 5667 | - |
| AV1142742 + ranitidine fasted | 2139 | 1 |
| AV1142742 + ranitidine fed | 1148 | 6 |

² Huxley P, Sutton DH, Debnam P, Matthews IR, Brewer JE, Rose J, Trickett M, Williams D, Andersen B, Classon BJ. High-affinity molecule inhibitors of T-cell co-stimulation: compounds for immunotherapy. Chem Biol (2004) 11:1651-8

³ MacKenzie NM, Phase I studies of AV1142742: A novel oral inhibitor of CD80 mediated co-stimulation of T-cells. American College of Rheumatology 2006 Annual Scientific Meeting. Presentation L14

IM 04-10-01

Preliminary review of RhuDex[®] as a potential Surge Dose[®] candidate

The highest peak plasma concentrations were seen when AV1142742 was administered after meglumine which would have an immediate effect in neutralising gastric acid and providing a higher gastric pH to solubilise the drug. Ranitidine administration resulted in an intermediate peak plasma concentration which is consistent with delayed absorption as oral ranitidine will take some time to be absorbed and inhibit gastric acid production sufficiently to increase gastric pH in a single dose study.

Although food reduced peak plasma concentrations and delayed absorption, there was no change in total exposure (total AUC) indicating a broad peak as a result of slow absorption. Extended delays in C_{max} from 1 to 6 hours after food suggests slow dissolution of the drug formulation in any co-administered liquid, with the dosage form caught up with food in the stomach delaying its transfer to the small intestine. The extended T_{max} may be a result of multiple peaks as aliquots of the drug progressively reach the small intestine in solution for absorption, in some ways behaving like a delayed release product.

At steady state with twice daily dosing and normal diet, trough and peak plasma concentrations were around 1,200 and 2,000 ng/mL respectively with C_{max} values consistent with single dose studies. These compare with pre-clinical models of rheumatoid arthritis and delayed type hypersensitivity, where drug concentrations above 1,500 ng/mL were reported to inhibit T-cell activation and reduce inflammation. Such levels were only achieved when gastric acid was neutralized in fasted subjects.

Based on these results a placebo controlled cross over dose escalation phase II study was proposed in 35 patients with rheumatoid arthritis, measuring clinical symptoms. However no publication of these results has been found.

Study CT5002⁴ details a follow-up dose ranging PK study of a tablet formulation of RhuDex[®] with a fixed amount of the base meglumine, an amino sugar derived from sorbitol, as the most effective buffer to increase absorption under fed and fasted conditions as well as with the co-administration of the proton pump inhibitor pantoprazole. Four doses were to be evaluated in 12 healthy subjects, 31.65, 63.33, 126.63 and 253.26 mg RhuDex[®] with twice daily dosing for 7 days in the final stage. Scheduled to run from May – August 2008, this study was suspended in July 2008, following the death of a trial participant from myocardial infarction several days after taking the new tablet formulation. The autopsy revealed severe impairment of cardiac function deemed to be present prior to the trial.

Following an investigation by the UK medicines agency, MHRA and a series of in vitro studies, no potentially harmful interactions were found between RhuDex[®] and

⁴ <http://clinicaltrials.gov/ct2/show/NCT00704119>

IM 04-10-01

Preliminary review of RhuDex[®] as a potential Surge Dose[®] candidate

atherosclerotic blood vessels, platelets or endothelial cells. In July 2009, the MHRA agreed to continuation of the clinical development of RhuDex[®] without requesting any further in vitro or ex vivo data. In October 2011, the MHRA authorized the RapidFACT[™] trial (Rapid Formulation Development and Clinical Testing) to determine an optimized formulation for the chronic treatment of rheumatoid arthritis⁵. MediGene flagged the importance to have an improved formulation and patient-friendly dosage form to facilitate therapeutically ideal release of the drug with data from this Phase I study to provide the foundation for a clinical Phase II trial in patients with rheumatoid arthritis.

The primary objectives of this latest PK study⁶ scheduled for completion in July 2012 were to compare the PK profiles of two novel oral formulations of RhuDex[®] and optimize the lead formulation which meets the target PK profile and shows acceptable safety and tolerability. The target optimal plasma PK profile is defined by plasma $C_{max} < 5,000$ ng/mL, elimination half-life > 8 h and $C_{(last)} (24h)$ of around 800-1,000 ng/mL. The lead formulation will explicitly not be selected based on determinations of C_{max} or $AUC_{(0-inf)}$ alone. The study protocol includes an optional arm for IV administration of a microtracer of [¹⁴C] RhuDex[®] to determine the oral bioavailability of this drug. Blood samples were scheduled pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48 and 72 hours after dosing.

3.2 Formulations

The second part of the study allows for the evaluation of 4 different compositions based on the lead formulation to optimize drug delivery.

One of the test formulations is based on Labrafac[®]/Gelucire[®] (A) and the other Labrafac[®]/Aerosil[®] (B). Based on the nature of these three excipients and their general use, it is possible that one or both of these formulations is a soft gelatin capsule containing a solubilized dispersion of the drug:

- Labrafac[®] (Gattefosse) is a range of medium chain fatty acid triglycerides used as solvents for lipophilic drugs to achieve improved oral absorption. They are an oily vehicle that can be adsorbed onto a powder carrier for use in tablets or as an oily phase for self-emulsifying lipid formulations such as contained in soft gelatin formulations. Given the low solubility of RhuDex[®], this could be used as the primary solubilizing agent for this drug.

⁵ <http://www.bioportfolio.com/news/article/844812/Medigene-Receives-Authorization-For-The-Clinical-Formulation-Study-Of-Rhudex.html>

⁶ <http://clinicaltrials.gov/ct2/show/NCT01500122> An Open-label, Non Randomized Monocentric Phase I Study Evaluation the Pharmacokinetic Profile of Novel Formulations of RHUDEX[®]

IM 04-10-01

Preliminary review of RhuDex[®] as a potential Surge Dose[®] candidate

- The Gelucire[®] (Gattefosse) range is based on mixtures of polyethylene glycol (PEG) glycerides with different compositions that can be matched with a given drug to improve its solubility and/or modify its release. They are used in oral dosage forms of disperse phase systems.
- The Aerosil[®] range (Evonik Industries) is based on fumed silica available as different grades with applications in solid dosage forms as well as liquid phase products such as liquid filled capsules

4 Pharmacodynamics (PD)

4.1 Mechanism of action

The immune system controls homeostasis between activation and inactivation of T-lymphocytes where some mechanisms specifically inhibit or end an immune response. When an antigen is presented to a T-cell receptor, activation will only occur in the presence of additional co-stimulatory signals. In the absence of such accessory signals, lymphocytes are not activated inducing either functional inactivation (anergy or tolerance) or cell death (apoptosis). A co-stimulatory signal essential for full T-cell activation involves the interaction of CD80 on specialized antigen-presenting cells with CD28 on T-cells^{7,8,9,10}.

A group of compounds from Avidex with average MW 424 ± 75 demonstrate specific binding to CD80 with low nanomolar affinity antagonizing CD28 and CTLA-4. The lead compound described in this study could be RhuDex^{®11}. This is described as an orally administered CD80 inhibitor which binds to CD80 and so inhibits its interaction with CD28 preventing T-cell activation¹². Thus RhuDex[®] blocks undesired activation of T-cells demonstrating immune-modulating and anti-inflammatory effects.

⁷ Lenschow DJ, Walunas TL, Bluestone JA. CD28/B7 system of T-cell co-stimulation. *Annu Rev Immunol* (1996) 14:233-58

⁸ Uvebrant K, da Graca Thrige D, Rosén A, Åkesson M, Berg H, Walse B, Björk P. Discovery of Selective Small-Molecule CD80 Inhibitors. *J Biomol Screen* (2007) 12:464-72

⁹ Sørensen, Kussmann M, Rosén A, Bennett KL, da Graca Thrige D, Uvebrant K, Walse B, Roepstorff P, Björk P. Identification of Protein-Protein Interfaces Implicated in CD80-CD28 Co-stimulatory Signaling. *J Immunol* (2004) 172:6803-9

¹⁰ Debnam P, Huxley P, da Graca Thrige D, Aberly J. Blocking T-cell activation in rheumatoid arthritis. Biacore/Avidex article for CDD Dec 03

¹¹ Huxley P, Sutton DH, Debnam P, Matthews IR, Brewer JE, Rose J, Trickett M, Williams D, Andersen B, Classon BJ. High-affinity molecule inhibitors of T-cell co-stimulation: compounds for immunotherapy. *Chem Biol* (2004) 11:1651-8

¹² MacKenzie NM. New therapeutics that threat rheumatoid arthritis by blocking T-cell activation. *Drug Discov Today* (2006) 11: 952-6

IM 04-10-01

Preliminary review of RhuDex[®] as a potential Surge Dose[®] candidate

4.2 Efficacy

The reactivity of RhuDex[®] with Rhesus monkey lymphocytes has been demonstrated in vitro, inhibiting pro-inflammatory cytokine release and cellular proliferation with micromolar potency¹³. Systemic administration to Rhesus monkeys significantly inhibited the delayed type hypersensitivity (DTH) response suggesting the potential use of RhuDex[®] for the inhibition of autoimmune mediated inflammatory processes with CD80 up-regulation.

A Phase IIa trial in 29 patients is reported to have demonstrated first indications of biological activity for RhuDex[®] in rheumatoid arthritis but no publication has been found.

5 Patents

Several patents cover CD80 antagonists with MediGene as the assignee and Richard Ian Matthews as the inventor:

- US 7,816,361 (WO 2005/046629) with priority 04 Nov 2003 covers immune inhibitory pyrazolone compounds
- US 7,932,253 based on the PCT filed on 09 Aug 04 covers immunomodulating oxopyrrazolocinnolines as CD80 inhibitors has been extended by 379 days under 35 U.S.C.154(b) to compensate for delays in examination
- US 2009/0312334 with priority dates of 14 Mar 2003 and 19 Aug 2003 covers immunomodulating heterocyclic compounds
- US 2012/0004237 covers salts of CD 80 antagonists with a priority of 22 Feb 2006

6 Potential of RhuDex[®] as Surge Dose[®] candidate

Based on limited published data available in 5 subjects, RhuDex[®] would appear to be a poorly soluble acidic drug which at the proposed therapeutic doses demonstrates solubility limited absorption. As an acidic drug, its solubility will be lower at low pH such as the acidic conditions in the fasted stomach. If the gastric pH is increased then C_{max} values in the order of 10 times higher can be achieved. In the fed state following administration of ranitidine to maintain increased gastric pH, C_{max} values exceed those found for RhuDex[®] alone in fasted subjects, although they are less than those when administered with ranitidine in the fasted state. Following ranitidine administration, food increases T_{max} from 1 hour to 6 hours which is consistent with slow absorption providing a prolonged stream of dissolved drug to the small intestine for absorption. It also highlights retention of undissolved drug with the food so that absorption is heavily influenced by gastric emptying

¹³ Haanstra KG, Endell J, Estevao D, Kondova I, Jonker M. Blocking T-cell co-stimulation using a CD80 blocking small molecule reduces delayed type hypersensitivity responses in rhesus monkeys. Clin Exp Immunol (2009) 158(1):91-8

IM 04-10-01

Preliminary review of RhuDex[®] as a potential Surge Dose[®] candidate

after food. T_{max} values of 1 hour in the fasted state indicate that dissolved drug is freely absorbed once it reaches the small intestine.

Surge Dose[®] formulations are specifically designed for each drug to achieve rapid dissolution independent of gastric pH. In the case of RhuDex[®], the customized Surge Dose[®] pH modulating agent is likely to contain 400 – 600 mg sodium bicarbonate with 25 – 100 mg of a pharmaceutically acceptable organic acid. This will increase the local pH and hence drug solubility in the microenvironment of the dissolving drug particles to provide fast activated dissolution independent of gastric pH. Surge Dose[®] formulations of acidic drugs typically achieve at least 50 % dissolution in 5 minutes in 900 mL 0.0033 M HCl at 30 rpm and 37 °C. The pH modulating agent will be sufficient to neutralize gastric pH so that once the drug is dissolved it will remain in solution. Once the dissolved drug reaches the small intestine, the higher pH will favour solubility and dissolved drug will drive faster absorption.

Based on the proposed twice daily dosage regimen for RhuDex[®], a Surge Dose[®] formulation will allow more consistent absorption as the formulation provides pH control that favours solubility in the microenvironment of the dissolving drug particles independent of the bulk pH in the stomach. Dissolved drug will rapidly drain from the stomach allowing fast absorption. Results similar to those achieved with Surge Dose[®] lornoxicam would be expected where T_{max} was 30 minutes compared with 1 hour for the conventional tablet, with 75 % of subjects reaching T_{max} within 30 minutes compared with only 8 %. C_{max} levels were around 40 % higher with the Surge Dose[®] lornoxicam.

Clearly MediGene is aware of the solubility limitations of this drug, and recognizes that neutralization of gastric acid is one means of improving its bioavailability, albeit that co-administration with materials to increase gastric pH is not desirable. The current formulation strategy being evaluated by MediGene appears to involve solubilization of the drug with medium chain fatty acid triglycerides (Labrafac[®]). Two formulations are being evaluated at least one of which could be a liquid filled soft capsule. The other could be a tablet in which the solubilized drug is adsorbed onto the fumed silica, thus providing a dry powder or granule for compression. Alternatively it could be another soft capsule.

A liquid filled soft capsule will have a lag time associated with release of its contents which is generally slowed significantly by food. Also although the drug is dissolved, there is no component to modify the gastric pH so that re-precipitation may occur with resultant slow and variable absorption. Similar for any tablet formulation where although dissolved drug may be incorporated it will be subject to pH induced re-precipitation under acidic conditions. Therefore the current formulations under evaluation may not produce the desired result of improved bioavailability and consistent absorption.