Vidofludimus, a New IL-17 and DHODH Inhibitor for Treatment of Inflammatory and Autoimmune Diseases

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Introduction

Recently, clinical phase IIa ENTRANCE study of vidofludimus in patients suffering from ulcerative colitis and Crohn’s disease was completed. First evaluation of results demonstrating good tolerability and high clinical response rate in steroid dependent patients. Since levels of IL-17 in colon of IBD patients are correlated with the disease activity, the role of IL-17, which is presently considered one of the most important players in the aetiology of several inflammatory and autoimmune diseases, will be discussed.

Vidofludimus (4SC-101) was developed as a novel and potent inhibitor of human DHODH. Recently, we demonstrated, that vidofludimus is a potent inhibitor of IL-17 secretion in vitro and in vivo. Vidofludimus was examined in several relevant animal models showing beneficial effects and strong inhibition of IL-17 secretion. Preclinical and clinical data is presented.

Vidofludimus — in vitro

Chemical structure of Vidofludimus:

**Results:**

Readouts: Experimental design:

**Epidermal CD8+ T cells; dysregulation of keratin 6 typical for Psoriasis vulgaris**

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**Vidofludimus — Psoriasis**

Mice with ubiquitous LkRκ-deficiency develop an inflammation of the skin which is morphologically, immunohistochemically and regarding gene expression patterns similar to human Psoriasis vulgaris - model allows to study interaction between T cells and keratinocytes LkRκ-deficiency: scarring, parakeratosis, loss of Stratum Granulosum, intra-epidermal and subcorneal micro-abscesses, intra-epidermal CD8+ T cells, dermal infiltrates of neutrophilic granulocytes, macrophages and T-cells, dysregulation of keratin 6 typical for Psoriasis vulgaris

**Experimental design:** LkRκ-deficient mice typically treated with placebo or Vidofludimus creme (two doses: 3% and 5%) immediately after birth, once daily

Readouts: visual assessment, histology, immunohistochemistry, keratinocyte proliferation, analysis of inflammatory infiltrates

**Results:**

Wildtype control without symptoms, untreated after 7 days, 40x zoom

Placebo control: LkRκ ubiquitous knock-out mouse, treated with placebo, after 7 days, 40x zoom

**Vidofludimus — Arthritis**

Rat model:

Female Lewis rats are immunized with collagen II followed by a booster injection on day 8, dosing once daily po, from day 0–28. 8 animals per dose group; total observation period 28 days

**Results:**

Vidofludimus attenuated weight loss in a dose dependent manner and showed dose dependent effects on disease scores; histopathology confirms disease scores.

**Mouse model (Vidofludimus + Methotrexate):**

DBA/1J mice (male, 7-8 weeks) immunized with bovine collagen II, followed by a booster injection on day 21, dosing once daily po, from day 0–14; 10 animals per dose group; total observation period 28 days

**Results:**

Combination of Vidofludimus and Methotrexate is much more effective than the single agents.

**Clinical Phase II study:**

Vidofludimus + MTX versus Placebo + MTX ongoing.

**Results expected in Q2 2011.**

**Vidofludimus — Lupus**

Systemic Lupus Erythematosus mouse model:

MPL-Faspr-/ mice; dosing once daily po for 10 weeks; 11 animals per dose group (7 for cytokopharmacology)

**Results:**

Vidofludimus shows a dose-dependent protective effect on tissue damage of skin, lung and kidney.

Vidofludimus has a dose-dependent effect on the proliferation of autoreactive T and B cells.

Compared to cytokopharmacide, Vidofludimus shows no myelotoxicity.

**Vidofludimus — IBD**

TNBS colitis mouse model:

Balb/c mice (female, ~10 weeks), TNBS in 50% ethanol administered by intracolonic enema; dosing once daily po, from day 1–6

**Results:**

TNBS-treated animals lost significant body weight compared to control treatment with Vidofludimus significantly prevented TNBS-induced loss of body weight

Summary:

Vidofludimus is capable of significantly reducing typical symptoms equivalent to human Psoriasis vulgaris in a topical murine model. Current results suggest that continuous treatment could completely abate inflammatory symptoms.

Cytokines from Vidofludimus treated groups reduced colonic damage.

**Reduction of IL-17 positive cells in Vidofludimus treated animals**

Vidofludimus completely ablates expression of IL-17 in colonic tissue.

Clinical Phase II Study — IBD

Single arm, open-label "ENTRANCE" Phase IIa study

Steroid-dependent patients with confirmed diagnosis of Crohn’s disease or ulcerative colitis treated with 35 mg oral dose of Vidofludimus once daily for 12 weeks.

Simultaneously, prednisone tapered during first eight weeks of trial followed by steroid-free treatment period of 4 weeks.

Primary endpoint: number of patients with response to Vidofludimus (complete and partial response).

Complete response defined as steroid-free clinical remission at week 12; partial response defined as being in remission at any steroid dose equal or lower than the individual threshold dose for relapse of the individual patient.

Threshold dose defined as individual steroid dose at which a patient experienced a relapse in medical history.

**Results:**

The exploratory, open-label, single-arm Phase IIa ENTRANCE study met its primary endpoint of significantly increasing the response rate in corticosteroid-dependent IBD patients (Crohn’s disease and ulcerative colitis) to 88.5% versus an average placebo response across published benchmark clinical trials of approximately 20%.

Following completion of a twelve week treatment phase with vidofludimus, disease remission was maintained in 14 out of 26 patients (53.8%) without intake of any corticosteroid (complete responders). A further 9 out of 24 patients (37.5%) remained in remission at the end of the study treatment period at a corticosteroid dose equal or below the patients’ individual threshold doses (partial responders) at which they experienced a documented disease relapse prior to entry into the study. Overall, vidofludimus significantly increased the number of patients with response (complete and partial responders — 88.5%) compared to the pre-defined placebo response rate (20%). Vidofludimus was well tolerated with no critical safety issues observed.

Conclusions

Vidofludimus is a potent inhibitor of human DHODH and of IL-17 secretion in vitro and in vivo. It was examined in several relevant animal models showing beneficial effects. Moreover, data from a clinical phase IIa study in patients suffering from ulcerative colitis and Crohn’s disease demonstrates good tolerability and high clinical response rate in steroid dependent patients.

Thus, vidofludimus promises to be a novel drug candidate broadly efficacious in inflammatory and autoimmune diseases. 4SC AG is planning to continue development of this compound in IBD, rheumatoid arthritis and other inflammatory and autoimmune diseases.

Collaborators (animal models):

*Prof. Rupec, Munich, Germany (Psoriasis)*
*Prof. Anders, Munich, Germany (SLE)*
*Prof. Fitzpatrick, Hershey, USA (IBD)*

Clinical study coordinator (IBD):
*Prof. Herrlinger, Stuttgart, Germany*