Efficacy, Safety and Tolerability of Vidofludimus in Patients with Inflammatory Bowel Disease: the ENTRANCE Study

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Introduction

Vidofludimus (4SC-101, SC12267) is a novel oral inhibitor of DHODH and interleukin-17 (IL-17) release. The primary objective of the study was to explore whether vidofludimus maintains remission in steroid-dependent IBD patients upon steroid weaning.

Vidofludimus is a small molecule drug candidate discovered and developed by 4SC AG (www.4sc.com).

Methods

The single-arm, open-label ENTRANCE Phase IIa study (ClinicalTrials NCT00820365) has been conducted at 13 study centres in Germany, Bulgaria and Romania.

34 steroid-dependent (defined according to ECCO guidelines) patients in remission with a confirmed diagnosis of Crohn’s disease (CD, n=18) or ulcerative colitis (UC, n=16) were treated with a 35 mg oral dose of vidofludimus once daily over a period of 12 weeks.

Simultaneously, prednisolone was tapered during the first eight weeks of the trial followed by a steroid-free treatment period of 4 weeks (figure 1).

Therefore, of the 34 patients enrolled 26 patients (CD=14, UC=12) were evaluable for the per protocol analysis (modified-ITT).

Response rates of vidofludimus as the primary efficacy endpoint of the trial are shown in figure 2. After completion of the 12 weeks study period, 14 of 26 (53.9%) patients were in remission without intake of any corticosteroids (complete responders).

Another 9 (34.6%) patients were in remission at a corticosteroid dose equal or lower than their individual threshold dose (partial responders). 3 patients (11.5%) were evaluated as non-responders.

In total, vidofludimus met the primary endpoint in 88.5% of patients (complete and partial response).

Results

The primary endpoint of the study was the number of patients with response to vidofludimus (complete and partial response).

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

The threshold dose is defined as the individual steroid dose at which a patient experienced a relapse in medical history.

Remission is defined as CDAI<150 (CD) or CAI<54 (UC), while a relapse is defined as CDAI>220 (CD) or CAI>46 (UC).

Secondary endpoints included CDAI/CAI at each visit, CRP, ESR, calprotectin, IL-17 and change of prednisolone threshold dose.

Response rates did not differ between Crohn’s disease and ulcerative colitis patients (table 2).

The development of prednisolone intake over the 12 weeks treatment period is shown in figure 3 (m-ITT, n=26). Median dose of prednisolone significantly (*p<0.001) decreased from 10 mg/day (10-26.5) to 0 mg/day (0-1.0) mg/day (± 2.7).

Safety & Tolerability

Vidofludimus was safe and well tolerated by all patients.

No clinically relevant changes for pulse rate, blood pressure, ECG, body temperature, hematology and biochemistry were recorded.

A total of 75 adverse events (AEs) were reported (53 mild, 18 moderate, 4 severe).

Two serious adverse events (SAEs) with hospital admission due to pre-existing renal calculi were reported in one patient after end of treatment: hydronephrosis and lithotripsy. Investigators judged these SAEs as not related to vidofludimus, therefore, no drug-related SAEs were reported.

19 AEs were judged by the investigators as “possibly” or “probably” drug-related including nesopharyngitis, abdominal pain, fatigue, insomnia, glucosuria, leucocyturia, microhematuria, musculoskeletal pain, myalgia, tachycardia, and dyspepsia (figure 5).

4 out of 6 reported cases of microhematuria based on dipstick tests by patients at home were not confirmed by laboratory analysis.

Conclusions

This trial provides first evidence of clinical efficacy of vidofludimus in patients with inflammatory bowel disease.

With a total response rate of 88.5% vidofludimus generated promising efficacy results in patients with both Crohn’s disease as well as ulcerative colitis.

Prednisolone consumption of all responders and steroid threshold doses of partial responders were significantly reduced during vidofludimus treatment.

Considering the favourable safety and tolerability profile vidofludimus may have the potential as a novel future remission maintenance therapy in IBD.

Randomized, placebo-controlled trials are planned to confirm the efficacy of vidofludimus observed in this exploratory study.

Figure 5: Treatment Emergent Adverse Events

Figure 4: Change of Prednisolone Threshold Doses of Partial Responders