1 Synopsis

Title of the study: Exploratory, open-label study to demonstrate efficacy, safety, and tolerability of SC12267 (35 mg) in patients with inflammatory bowel disease (Crohn's disease and ulcerative colitis) ("ENTRANCE")

Note: Protocol Version 2.0 extended the indication from Crohn's disease to inflammatory bowel disease and allowed enrollment of patients with ulcerative colitis. Efficacy assessments as well as inclusion and exclusion criteria were adjusted accordingly and the updated information will be reported throughout this synopsis.

Principal investigators and study centers: A total of 13 centers and investigators: 8 centers in Germany, 2 centers in Romania, and 3 centers in Bulgaria

Coordinating investigator: Prof. Dr. med. Klaus Herrlinger, Klinik für Innere Medizin I, Robert Bosch Krankenhaus, Auerbachstr. 110, D-70376 Stuttgart

Publication (reference): Herrlinger et al., *J Crohns Colitis* 2011; 5(1):S100-101

Studied period: 26-Mar-2009 (first patient in) to 01-Nov-2010 (last patient out)

Clinical phase: II

Objectives:

Primary objective

The primary objective of this study was to explore the efficacy of SC12267 at a dose of 35 mg once daily in patients with inflammatory bowel disease (IBD) after a 12-week therapy as measured by the number of patients with complete or partial response.

Secondary objectives

The secondary objective of this study was to evaluate the safety and tolerability of SC12267 at a dose of 35 mg once daily in patients with IBD and to explore plasma levels (trough values) of SC12267.

Methodology:

This was an exploratory, open-label, non-controlled, multi-center, multi-national[3] study in patients with IBD. All patients received 35 mg SC12267 once daily for 12 weeks and commercially available prednisolone. Prednisolone was administered once daily (20 mg to

[3] Changed from national to multi-national in protocol Version 3.0.

40 mg)[4] during screening and Week 1 and was then gradually tapered down weekly by 10 mg, 5 mg, or 2.5 mg until Week 8 or relapse. Patients were evaluated at screening, at Weeks 1, 2, 4, 8, and 12 during the treatment period and at a follow-up visit at Week 16 (four weeks after study drug discontinuation) or earlier in case of relapse during the follow-up period. Telephone contacts were made at Weeks 6 and 10 during the treatment period to collect safety information and to assess the patient's current prednisolone dose. Additional telephone contacts at Weeks 20 and 36[5] after start of study medication were made to evaluate if the patient had relapsed. Data collected during the two additional telephone contacts will be presented in an addendum to this report.

Number of patients planned as per study protocol and analyzed:

- planned: 21 patients evaluable for primary efficacy assessment (modified intention-to-treat [mITT])
- analyzed: intention-to-treat (ITT) set: 34 patients; mITT set: 26 patients

Diagnosis and criteria for inclusion:

Criteria regarding Crohn´s disease

1. Established diagnosis of Crohn's disease (CD), confirmed by standard criteria (e.g. endoscopy, ultrasound, x-ray)
2. Patients had to be in clinical remission (Crohn's Disease Activity Index [CDAI] <150 points) on steroid therapy for at least two weeks
3. Confirmed steroid-dependency of CD:
   Patients who were either
   - unable to taper steroids completely within three months of starting steroids without recurrent active disease, or
   - who had a relapse within two months of stopping steroids
4. Individual threshold dose of previous relapses was to be less than 20 mg/day prednisolone or equivalent steroid dose
5. Patients with stable glucocorticosteroid therapy between 20 and 40 mg/day[4] prednisolone or equivalent steroid dose for the previous week

[4] Changed from "40 mg daily" to "20 mg to 40 mg daily" in protocol Version 2.0.

[5] Telephone contacts at Weeks 20 and 36 were added in Addendum 1 (dated 02-Oct-2009) to protocol Version 2.0.

Criteria regarding ulcerative colitis

6. Established diagnosis of ulcerative colitis (UC), confirmed by standard criteria (e.g. endoscopy, ultrasound, x-ray)
7. Patients had to be in clinical remission (Clinical Activity Index [CAI] <4 points) on steroid therapy for at least two weeks
8. Confirmed steroid-dependency of UC:
   Patients who were either
   - unable to taper steroids completely within three months of starting steroids without recurrent active disease, or
   - who had a relapse within two months of stopping steroids
9. Individual threshold dose of previous relapses was to be less than 20 mg/day prednisolone or equivalent steroid dose.
10. Patients with stable glucocorticosteroid therapy between 20 and 40 mg/day prednisolone or equivalent steroid dose for the previous week

Criteria regarding general requirements

11. Men and women, 18 to 70 years of age
12. Written informed consent
13. Negative pregnancy test at screening in females of child-bearing potential
14. Males willing to use condoms or to be sexually abstinent
15. Use of appropriate contraceptive methods for females of childbearing potential one month before, throughout the course of the study, and one month after study termination. This had to be a combination of the following:
    - a highly effective method of first choice = a method with a low failure rate (i.e. less than 1% per year) like sexual abstinence, combined oral contraceptives, implants, injectables, some intrauterine devices, vasectomized partner
      together with
    - a method of second choice like condom, diaphragm, or cup pessary

For the complete list of exclusion criteria refer to Section 9.3.2.

Test product, dose, mode of administration, batch number:

SC12267 tablets 35 mg, once daily, oral administration, batch number(s): 85841G001, 88047G003, 88048G004, 90292G005

Background steroid therapy:

Commercially available prednisolone tablets (5 mg, 10 mg or 20 mg), once daily, oral administration. Prednisolone was administered once daily starting with 20 mg to 40 mg[6] and was then gradually tapered down weekly by 10 mg, 5 mg, or 2.5 mg according to a tapering schedule until Week 8 or relapse.

Duration of treatment: 12 weeks

Criteria for evaluation:

Efficacy

Primary endpoint

- Number of patients with response (complete or partial). Complete response was defined as steroid-free remission at Week 12 and partial response as being in remission at any glucocorticoid dose equal or lower than the threshold dose for relapse of the individual patient. For CD patients, remission was defined as CDAI <150 and relapse as CDAI >220. For UC patients, remission was defined as CAI <4 and relapse as CAI >6.

Secondary endpoints

- CDAI or CAI at each visit
- C-reactive protein (CRP)
- erythrocyte sedimentation rate (ESR)
- calprotectin
- steroid dose at Week 12
- lowest steroid dose the patient received during the course of the study without experiencing a relapse for at least 7 days
- serum levels of IL-17[7]

Safety endpoints

- vital signs (blood pressure, pulse)
- 12-lead electrocardiogram (ECG)
- safety laboratory (hematology, coagulation, clinical chemistry, urinalysis)
- adverse events (AEs)
- patient´s global assessment of tolerability
- physician´s global assessment of tolerability

[6] Changed from "40 mg daily" to "20 mg to 40 mg daily" in protocol Version 2.0.

[7] Serum levels of IL-17 were defined as a secondary efficacy endpoint in the statistical analysis plan.

Other endpoints

- plasma levels of SC12267

Statistical methods:

The primary endpoint, response, was evaluated as the percentage of patients with complete or partial response. A 1-sample binomial test was used to compare the response rate achieved with SC12267 against a historical placebo rate of 20%. A 1-sided test hypothesis was used at a 5% level of significance. The primary endpoint was analyzed for the mITT set which included all patients of the ITT set (all enrolled patients) who were evaluable for the primary efficacy endpoint and compliant regarding the study medication. Analysis of the primary efficacy endpoint using the mITT set was considered confirmatory. In addition, the primary endpoint was also analyzed for the ITT set without being considered confirmatory.

All other analyses were exploratory and were based on the ITT set. CDAI or CAI, CRP, ESR, and calprotectin levels were analyzed descriptively and the change from baseline (Day 1) to each visit was calculated. Steroid doses were analyzed descriptively for Week 12 and all study visits. The lowest possible steroid dose per patient throughout the study was calculated as the lowest dose without experiencing a relapse for at least seven days. The lowest possible steroid dose of all study patients, as well as plasma levels of SC12267 and serum levels of IL-17 were analyzed descriptively. AEs, laboratory parameters, vital signs, ECG findings, as well as the patient's and the physician's global assessments of tolerability were summarized descriptively.

Subgroup analyses of CDAI, CAI, ESR, CRP, calprotectin, and steroid doses were performed post-hoc for the following groups: complete responders, partial responders, or patients who were neither complete nor partial responders (for mITT: non-responders, for ITT: non-responders and patients who dropped out and response could not be determined). Demographic data and response were also analyzed stratified by indication (CD or UC).

SUMMARY - CONCLUSIONS

Disposition of patients and analysis sets:

Of the 38 patients screened, 34 patients were enrolled, received treatment and were part of the ITT population (all enrolled patients). Eight patients were excluded from the ITT population due to various reasons, e.g. non-compliance, intake of prohibited medication, or incorrect inclusion, forming the mITT population (N = 26).

Demography and screening characteristics:

Patients were almost equally distributed with regard to sex (16 male patients: 47.1%; 18 female patients: 52.9%). All patients were Caucasian, and the median age was 40.5 years. Within the study population 47.1% of patients had UC and 52.9% had CD. Extraintestinal

manifestations were present in 44.1% of patients. The median glucocorticosteroid threshold dose of previous relapses was 10 mg/day (10 mg/day in patients with CD and 15 mg/day in patients with UC).

Results - efficacy and pharmacokinetics:

Primary endpoint:

A response rate of 88.5% (23 of 26 patients) was observed in the mITT population, which was significantly higher than the assumed placebo response rate of 20% ($p < 0.0001$). Within the mITT population, 53.8% (14 of 26 patients) were complete responders, 34.6% (9 of 26 patients) were partial responders, and 11.5% (3 of 26 patients) were defined to be non-responders. Response rates did not differ between CD and UC patients.

Secondary endpoints:

In UC patients (N = 12), CAI scores remained stable over time, except at Visit 8, where the score had slightly increased (worsened). Partial responders (N = 5) showed a similar time course of CAI changes as in the overall population. CAI scores remained rather unchanged over time in complete responders (N = 6) with CAI scores far below 4.

In CD patients (N = 14), CDAI scores had slightly decreased at Visit 3, but had increased (worsened) at all later visits during the treatment period. However, the most pronounced increase was seen at post-treatment Visit 9. In partial responders (N = 4), CDAI scores had increased at each visit during the treatment and during follow-up. CDAI scores had decreased or remained almost unchanged at each visit during the treatment period in patients with complete response (N = 8) with CDAI scores far below 150. Again, CDAI scores increased at the post-treatment Visit 9 in this patient group.

Mean CRP values remained unchanged or relatively stable compared to baseline, except at Visits 6 and 8, where CRP values had slightly increased. Mean ESR and calprotectin values had increased at each visit, with peaks at Visits 6 and 8. Increases in CRP, ESR, and calprotectin values were generally more pronounced in partial responders.

There was only a low positive association between calprotectin levels and CAI as well as CDAI scores. IL-17 serum concentrations were below the limit of quantification for all tested patients except two patients, therefore, IL-17 data was not evaluated.

In both ITT and mITT patients, mean steroid dose of about 27 mg/day at screening was reduced to 1.0 mg/day at Week 12 (Visit 8). As expected, mean steroid dose at Week 12 was higher in partial responders compared with complete responders (2.8 versus 0.0 mg/day). Within the subgroup of partial responders, the lowest mean steroid dose the patients received

during the course of the study without experiencing a relapse for at least 7 days was 3.89 mg/day.

In the mITT population, the median threshold daily dose for relapse was 10 mg lower (range: -15.0 to -7.5 mg/day) than the threshold dose before study entry. Median threshold dose for relapse of partial responders dropped by 10 mg/day (range: -15.0 to -7.5 mg/day) compared with the threshold dose before study entry. Complete responders per definition do not have a steroid threshold dose anymore since these patients were in steroid-free remission at Week 12.

Trough plasma concentration levels of SC12267 were in a range between 4.17 and 5.49 µg/mL after 3, 4, 6, and 8 weeks during continuous daily treatment.

Results - safety:

A total of 75 AEs were reported by 23 patients (67.6%, ITT population). Of these, 19 AEs were judged to be related (possibly or probably) to the study medication. The most frequently reported AE was hematuria, followed by headache, which were experienced by 23.5% and 11.8% of patients, respectively. However, 4 out 6 cases of hematuria reported as possibly or probably related to the study medication were not confirmed by urine sediment analysis.

The majority of AEs was judged to be not related or unlikely related to the study medication. Most of the patients (58.8%) experienced AEs that were mild in intensity. Three patients (8.8%) experienced four severe AEs (dysuria, renal pain, and two cases of hematuria).

There was one SAE, hydronephrosis, which was judged to be moderate and not related to the study medication. The SAE completely resolved. One additional SAE (lithotripsy) in the same patient occurred one week after the end of the study. In the opinion of the investigator, the event was related to the previously experienced hydronephrosis. No patients died during this study.

Number of AEs	75	
Number of AEs related[a] to study treatment	19	
Number of SAEs	1[b]	
Number (%) of patients with AEs	23	(67.6)
Number (%)[c] of patients with AEs related[a] to study treatment	12[d]	(35.3)
Number (%) of patients with SAEs	1	(2.9)

[a] Possibly, probably, or definitely related to study treatment.
[b] There was one additional SAE (lithotripsy) in the same patient which occurred one week after the end of the study.
[c] Hand-calculated.
[d] One patient experienced two related AEs.
AE = adverse event, ITT = intention-to-treat, N = number of patients, SAE = serious adverse event.

No clinically meaningful changes in laboratory and physical examinations were observed and there were almost no changes in blood pressure and heart rate from screening to any of the study and follow-up visits.

Approximately one half of the patients as well as the physicians judged the tolerability of the study medication as good, the other half of the patients as well as the physicians judged the tolerability as very good.

Conclusions:

- SC12267 came out to be effective in the remission maintenance therapy of steroid dependent patients with CD and UC.
- A significantly higher response rate was observed with SC12267 compared to historical data of placebo control.
- More than 50% of the steroid dependent patients were in remission without intake of prednisolone at the end of the study.
- Mean steroid intake dropped from about 27 mg/day at screening to 1.0 mg/day at the end of the study.
- Additionally, more than 30% of the patients could reduce their prednisolone threshold dose of disease relapse markedly indicating a steroid-sparing effect of SC12267.
- SC12267 administered orally on a continuous once-daily dosing schedule for 12 weeks on a 35 mg dose level was safe and well tolerated.

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