2. STUDY SYNOPSIS

NAME OF SPONSOR/COMPANY: 4SC AG NAME OF FINISHED PRODUCT: 4SC-201, resminostat (INN) NAME OF ACTIVE INGREDIENT(S): 4SC-201 as mesylate salt	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
Title of Study: A Phase 2 Proof of Concept Study to Evaluate the Efficacy, Safety and Pharmacokinetics of the HDAC Inhibitor 4SC-201 in Patients with Relapsed or Refractory Hodgkin's Lymphoma: The SAPHIRE Study		
Protocol No.: 4SC-201-2-2009 **EudraCT Number:** 2009-014699-24		
Investigators: Number of principal investigators: 10 Coordinating investigator: Prof. Jan A. Walewski, MD		
Publication (Reference):		
Study Centers: Number of study sites: 10 Coordinating investigator Site: Maria Sklodowska Curie Memorial Institute – Cancer Center ul. W.K. Roentgena 5, 02 781 Warszawa, Poland		
Study Period Reported: 17 Dec 2009 to 01 Oct 2012[1]		**Phase of development:** 2

Objectives:

Primary Objective

- To determine the best overall objective response rate (ORR) based on International Working Group (IWG) response criteria of 4SC-201 in subjects with relapsed or refractory Hodgkin's lymphoma (HL)

Secondary Objectives

- To investigate the safety and tolerability of repeated oral doses of 4SC-201
- To assess overall survival (OS) in subjects treated with repeated oral doses of 4SC-201
- To determine progression-free survival (PFS) in subjects treated with repeated oral doses of 4SC-201, including radiological and symptomatic progression
- To determine time to progression (TTP) in subjects treated with repeated oral doses of 4SC-201 including objective and symptomatic progression
- To determine duration of response (DOR) in subjects treated with repeated oral doses of 4SC-201
- To assess the pharmacokinetics (PK) of 4SC-201 after oral dosing

Exploratory Objectives

- To investigate effects on histone deacetylase (HDAC) enzyme inhibition in peripheral blood mononuclear cells (PBMC) from subjects treated with repeated oral doses of 4SC-201
- To investigate the effects on gene expression (ribonucleic acid [RNA] profiling) in PBMC from subjects treated with repeated oral doses of 4SC-201
- To investigate levels of CC thymus and activation-related chemokine (TARC, CCL17) in plasma from subjects treated with repeated oral doses of 4SC-201

[1] Data from extended OS observation period until 14 March 2013 are not reported here

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Methodology

This was an open-label, single-arm, Phase 2 study of 4SC-201 in subjects with relapsed or refractory HL after second- (salvage therapy) or subsequent-line therapy.

Eligible subjects were treated with 4SC-201 in repeating treatment cycles. Each treatment cycle was 14 days in duration. Within each treatment cycle, 4SC-201 was administered orally at 600 mg (original protocol) or 800 mg (protocol Amendment 1) once daily for 5 consecutive days, and directly thereafter no therapy was administered for the remaining 9 days of the treatment cycle.

The study was divided into 2 phases: a Main Phase and a Follow-Up Phase. The Main Phase consisted of the first 6 cycles of treatment, and the Follow-Up Phase, consisted of all subsequent treatment cycles for subjects who remained on treatment following Cycle 6 (applicable for subjects who did not show disease progression in Cycle 6 and continued on treatment with 4SC-201). Subjects could remain on treatment with 4SC-201 for up to 1 year.

Subjects eligible for efficacy analysis could not have a major protocol violation, had to have received ≥ 80% of all prescribed doses of 4SC-201 for at least 2 cycles, and had at least one assessment of extent of disease after screening (a follow-up disease assessment). Subjects identified as not eligible for efficacy analysis following treatment in Cycle 3 (first staging) were replaced. In addition, any subject who discontinued from the study prior to the first assessment of extent of disease (in Cycle 3) for reasons other than progressive disease was replaced.

Disease assessment had to be performed by a combination of positron emission tomography (PET) and computer tomography (CT) scanning in Cycles 3 and 6. For subjects who remained in the study after the Main Phase, disease assessments were to be conducted after every fourth treatment cycle. After completion of the first enrollment stage and at the conclusion of the study, scan results were to be centrally reviewed by an independent review committee (IRC) consisting of 3 nuclear medicine specialists for confirmation of local response assessments. During the second enrollment stage of the study, all subjects staged locally with progressive disease had their disease status to be confirmed by at least one member of the IRC due to the fact that in the first stage of the study some subjects were judged by the local radiologist as progressive disease (PD), however were assessed at least as stable according to IRC review. If, for a given subject, there was a discrepancy between the local and central assessments, or if there was a delay in receiving assessments, the decision regarding continuation of treatment (i.e., administration of the next treatment cycle) and participation in the study was to be made by the treating physician (i.e., investigator), who needed to consider the overall clinical condition of the subject in making such decisions. However, if, for a given subject PD was confirmed by IRC review, study treatment had to be discontinued and that subject had to be withdrawn from the study.

Subjects could remain on study treatment as long as they were tolerating it and did not demonstrate PD (i.e., progression of HL). Where possible, subjects who had to be discontinued from treatment with 4SC-201 continued to be followed for survival. Subjects for whom study treatment had to be discontinued for reasons other than disease progression were to be followed until progression, death, or any of the other criteria for study discontinuation as outlined in the protocol.

Toxicity severity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Subjects, who had experienced drug-related toxicity requiring interruption, delay, or reduction of the dose of 4SC-201 could continue participation in the study at a reduced dose of 4SC-201. Protocol-defined drug-related toxicities that could have led to dose interruption or reduction included the following: grade 4 neutropenia that persisted for 7 days or longer; febrile neutropenia; grade 4 platelet toxicity or grade 3 platelet toxicity with hemorrhage; confirmed QTc > 500 msec or an increase in QTc of ≥ 60 msec as compared to the corresponding baseline value (should have been confirmed by more than 1 electrocardiogram [ECG]); grade 2 neurotoxicity; grade 3 elevation in transaminase levels for 7 days or longer; and any other grade 3 or 4 nonhematologic toxicity other than inadequately treated nausea/vomiting or diarrhea.

Blood samples were to be obtained for PK and pharmacodynamic analyses. Safety was to be evaluated throughout a subject's participation in the study.

Number of Subjects (planned and analyzed)

Enrollment of 33 evaluable subjects from 10 centers was originally planned for the study. Forty-two subjects were screened from 5 sites (2 each in Poland and Romania and 1 site in Czech Republic); of which 37 subjects were in the Safety Analysis Set and 35 subjects were in the Efficacy Analysis Set.

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Diagnosis and Main Criteria for Inclusion

Enrolled subjects had relapsed HL after second or subsequent-line therapy or had refractory disease defined as non-CR after or PD during first-line therapy and PD following second-line (salvage) therapy. Subjects may also have undergone high-dose chemotherapy followed by autologous stem cell transplantation. Detailed inclusion and exclusion criteria were described in the protocol.

Test Treatment, Dose, Mode of Administration, and Batch No.

4SC-201 was orally administered as 3 (original protocol) or 4 (protocol Amendment 1) film-coated tablets, each containing 255 mg of 4SC-201 as mesylate salt, corresponding to active agent of 200 mg free base, for a total dose of 600 mg (original protocol) or 800 mg (protocol Amendment 1) active ingredient once daily for the first 5 consecutive days of a 14-day treatment cycle.

Duration of Treatment

Subjects were to be provided treatment with 4SC-201 for up to 1 year.

Assessments

Efficacy:

Efficacy evaluations included the following: HL staging and B symptoms, assessment of extent of disease by PET/CT scans, to determine response (complete or partial response) and disease stability/progression; Eastern Cooperative Oncology Group (ECOG) performance status and OS.

Pharmacodynamics:

Additionally, pharmacodynamic evaluations included the following (performed at some but not necessarily all study sites):

- HDAC activity in PBMC quantified directly by a cellular enzymatic HDAC assay ex vivo (i.e., using an artificial, cell-permeable HDAC substrate);
- quantification of specific RNA markers related to HDAC inhibition (to determine the effect of HDAC inhibition on gene transcription);
- plasma levels of TARC determined by enzyme-linked immunosorbent assay (ELISA);

Pharmacokinetics:

Pharmacokineticevaluation included determination of concentration of 4SC-201 in plasma by obtaining blood samples from subjects administered 4SC-201 at prescribed time points.

Safety:

Safety evaluations included the following: adverse events (AEs), physical examinations, vital signs, laboratory tests (including serum chemistry, complete blood count [CBC], urinalysis, pregnancy test [for females of childbearing potential], thyroid-stimulating hormone [TSH], and troponin), echocardiography, echocardiogram (ECG) assessments, and concomitant medications. Progressive neoplastic disease was not recorded as an AE, but as a part of the efficacy evaluation.

Statistical Methods

The study was conducted according to a Simon 2-stage Minimax design with $p_0 = 0.20$ and $p_1 = 0.40$ with $\alpha = 0.05$ and 80% power. In the first Simon stage, 18 subjects eligible for efficacy analysis were to be enrolled and the first stage analysis was to be performed when the eighteenth subject had a disease assessment following treatment in Cycle 3. If there would have been 4 or fewer responses, the study would have been discontinued for insufficient activity of 4SC-201, but with 5 or more responses enrollment would have continued until 33 evaluable subjects were enrolled. With 11 or more responses in both stages of the study, 4SC-201 would have been considered to be of interest in the treatment of relapsed/refractory HL. The estimated sample size was 22 if the true response rate was p_0; the probability of early stopping was considered to be 50%. For the purposes of this study, subjects who demonstrated stable disease by anatomical imaging using CT but showed improvement in functional PET imaging were included as (metabolic) responders.

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Results

Disposition of Subjects

Study 4SC-201-2009 was conducted between 17 Dec 2009 to 01 Oct 2012 at 5 study sites (2 in Poland, 2 in Romania, and 1 in the Czech Republic). The number of subjects planned for efficacy analysis was 33. A total of 42 subjects were screened of which 37 subjects received treatment with 4SC-201 and 35 subjects were eligible for efficacy analysis.

The Safety Analysis Set had 37 subjects, the PK Analysis Set had 33 subjects, and Efficacy Analysis Set had 35 subjects.

There were 19 male subjects (51.4%) and 18 female subjects (48.6%), and all were Caucasian (37 [100%]). Median age was 34.0 years (range: 19 to 71 years) and median BMI was 23.38 (range: 15.1 to 31.1). The demographic and baseline characteristics were comparable between the 600 mg and 800 mg treatment groups.

Overall, all 37 subjects (100%) reported previous HL treatments. The median number of previous HL treatments for all 37 subjects was 6; in the 600 mg group, subjects received on average 8 previous treatments and in the 800 mg group, subjects received on average 5 previous treatments. Individual subjects received from 2 to 14 previous HL treatments.

The most commonly reported medical history by body system was heart/cardiovascular (total of 10 [27%] subjects) and past surgeries (total of 12 [32.4%] subjects). Medical history was similar between the 2 treatment groups.

A total of 35 subjects were evaluable for tumor response, defined as those subjects who received at least 80% of all prescribed doses of 4SC-201 for at least 2 cycles and had at least one assessment of extent of disease after screening (a follow-up disease assessment). Two of the 37 subjects treated with 4SC-201 were not evaluable for tumor response: One subject discontinued due to a TEAE in Cycle 1 and did not have a follow-up disease assessment, and took less than 80% of the prescribed dose over the first 2 cycles. The second subject did not have a follow-up PET/CT disease assessment, (the subject died due to TEAEs not related to 4SC-201 [dyspnea, fever, pneumonia, and respiratory insufficiency] in Cycle 3).

Overall, 27 subjects (73.0%) developed PD; there were more subjects in the 600 mg treatment group (16 subjects [84.2%]) than in the 800 mg treatment group (11 subjects [61.1%]). Five subjects (13.5%) were discontinued from the study due to TEAEs/SAEs: one subject in the 600 mg group (requirement of more than 1 dose reduction was the primary reason for discontinuation) and 4 subjects (22.2%) in the 800 mg group. One subject (2.7%) in the 600 mg treatment group died during the study from TEAEs not related to 4SC-201 (dyspnea, fever, pneumonia, and respiratory insufficiency) that were considered related to disease progression.

Efficacy

The study was conducted according to a Simon 2-stage Minimax design. In the first stage, 18 evaluable subjects were enrolled, of which 5 responded, meeting the criteria for enrollment to the second stage. The Simon 2-stage design required an additional 15 subjects for a total of 33 evaluable subjects. In practice, enrollment was stopped after inclusion of an additional 18 subjects to avoid the study being delayed due to one of the final subjects not being evaluable and recruitment having to start up again. However, 17 of these 18 subjects fulfilled all protocol criteria giving a total of 35 evaluable subjects. Therefore, in the final Efficacy Analysis Set there were more subjects (35 subjects) than required to meet the Simon 2-stage design criteria. In terms of assessing whether the objective of the study, in relation to the Simon 2-stage design criteria was met, out of the first 33 subjects to become evaluable, 12 subjects were responders (1 subject with a complete remission and 11 subjects with a partial remission). Therefore, the criterion of seeing 11 responses over both stages of the study was met and 4SC-201 has been considered to be of interest in the treatment of relapsed/refractory HL.

For the Full Efficacy Analysis Set of 35 subjects, there were also 12 responders (1 subject with a complete remission and 11 subjects with a partial remission). Seven subjects had a best response of stable disease. The ORR was 34.3% with an exact 95% CI of 19.1, 52.2 and the overall disease control rate was 54.3% with an exact 95% CI of 36.6, 71.2. The response rate and disease control rate seen in the 800 mg group (41.2% and 58.8%, respectively) were slightly higher than those seen in the 600 mg group (27.8% and 50.0%, respectively).

The median DOR in total was 8.36 weeks, with a 95% CI of 4.71, 18.86. The median DOR in the 800 mg group was 8.71 weeks and 8.00 weeks in the 600 mg group. The 25th percentile for DOR in total was 6.93 weeks, with a 95% CI of 3.29, 8.00 and the 75th percentile for DOR was 17.93 weeks with a 95% CI of 8.00, not defined.

The median PFS for all subjects was 10.00 weeks, with a 95% CI of 5.71, 14.14. The minimum PFS for all subjects was 5.0 weeks and maximum was 78.1 weeks (censored). The 25th percentile for PFS for all subjects was 5.43 weeks, with a 95% CI of 5.29, 6.14 and the 75th percentile for PFS was 18.86 weeks

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with a 95% CI of 12.14, 24.29. The median PFS in the 800 mg group (13.43 weeks) was higher than that seen in the 600 mg group (6.07 weeks).

The median OS across both treatment groups was 54.14 weeks (95% CI of 41.71, 81.00). The maximum observed OS was 135.6 weeks (censored). In the Efficacy Analysis Set, there was a total of 24 subjects (68.6%) who died during the OS observation period: 14 subjects (77.8%) in the 600 mg group (13 subjects died of causes related to disease progression; the death of 1 subject was not related to disease progression, but the cause of death was unknown) and 10 subjects (58.8%) in the 800 mg group (all deaths were related to disease progression).

Pharmacokinetics, Pharmacodynamics

Pharmacokinetic Results

The PK characteristics of 4SC-201 were assessed in 33 out of 37 subjects. These were the subjects who had received at least 80% of their prescribed doses of 4SC-201 up to and including Cycle 3 and for whom all PK samples had been obtained. Pharmacokinetic evaluation was performed on Day 1 (single dosing) and Day 5 of treatment in Cycle 1 and Day 5 of treatment in Cycle 3 (multiple dosing), i.e., C1D1, C1D5, and C3D5. Maximum plasma concentrations, C_{max}, were obtained between 0.5 to 6 hours (median value of 1.5 hours) after oral administration of 4SC-201. Geometric mean C_{max} values of 4000; 3870 and 3460 ng/mL and geometric mean AUC_{0-6h} values of 10600; 10100 and 9070 ng•h/mL were achieved at 600 mg on C1D1, C1D5 and C3D5, respectively. At 800 mg, geometric mean C_{max} values of 5060; 4700 and 4460 ng/mL and geometric mean AUC_{0-6h} values of 12200; 12300 and 11800 ng•h/mL were achieved on the same treatment days. Exposure (C_{max} and AUC_{0-6h}) to 4SC-201 increased roughly doseproportionately over the relatively narrow dose range of 600 and 800 mg. Geometric mean terminal plasma elimination half-lives for all doses and treatment days remained constant in the range from 1.67 to 2.23 hours at the dose levels administered.

No relevant differences were observed between the PK parameters of 4SC-201 after a single dose or multiple doses of 4SC-201. Consequently, no induction or inhibition of elimination processes of 4SC-201 was detected after repeated dosing. Correspondingly, there was no accumulation of 4SC-201 exposure (for both C_{max} and AUC_{0-6h}) after oral administration of 4SC-201 for 5 consecutive days or 3 treatment cycles as compared to exposure after a single dose on C1D1.

Taking into consideration that the PK characteristics of an oncological drug might become strongly affected by the disease state of the subject, concomitant medications and comorbidities, the overall PK assessment indicated that the inter-individual variability of PK parameters of 4SC-201 analyzed in this study was low.

Pharmacodynamic Results

Changes in histone deacetylase (HDAC) enzymatic activity, TARC/CCL17 plasma concentrations, and gene expression of a group of 10 selected genes were determined in peripheral blood cells or plasma from subjects of both dose groups. Histone deacetylase enzyme activity as assessed in 19 subjects (10 subjects from the 600 mg and 9 subjects from the 800 mg dose group) was effectively inhibited by a median of 85% and 93% at 2 hours after dosing in the 600 mg and 800 mg group, respectively, corresponding to peak plasma levels of 4SC-201. Similar to 4SC-201 plasma levels, inhibition of HDAC activity was transient and declined from 2 to 5 hours post dose. This decline appeared to be less pronounced in the 800 mg group.

The TARC/CCL17 measurements performed with plasma samples from 31 SAPHIRE subjects demonstrated very heterogeneous baseline concentrations ranging from 35 pg/ml to > 100,000 pg/ml. The TARC/CCL17 baselines values appeared to have some predictive value for clinical response to 4SC-201 as there was a statistical trend (p=0.03, excluding outliers) towards lower TARC/CCL17 baseline levels in subjects who had received a clinical benefit (response or disease stabilization) from 4SC-201 treatment. Changes of TARC/CCL17 plasma levels in response to 4SC-201 treatment was assessed in 27 subjects with median baseline concentrations of 8,400 pg/ml notably reduced in the majority of subjects (22) already after the first cycle of 4SC-201 treatment. At C3D5, a median plasma level of 2,800 pg/ml TARC/CCL17 was noted. Individual reductions of more than 50% with maximum reductions of 95% from baseline were observed in 12 subjects.

Subjects treated with 4SC-201 showed a clear correlation of gene expression levels with drug plasma levels over time, with strongest effects on transcription being generally observed 5 hours after dosing. In general, there was only a slight increase in the maximum change of expression levels for almost all genes in the 800 mg dose group (N=15) compared to the 600 mg dose group (N=17). The analysis of a potential correlation between expression levels of genes and clinical outcome in response to 4SC-201 treatment revealed that two genes, the transcription factor ZFP64 and the dipeptidyl-peptidase 3 (DPP3) exhibited different baseline expression levels in subjects with a clinical benefit compared to those who had progressed during treatment with 4SC-201. Further analysis compared the effect of 4SC-201 treatment on gene expression levels between Baseline and predose at C3D5 in each clinical response group, investigating a potential correlation of STAT6, showed a statistically significant decrease in expression in the clinical benefit group compared to the progressive disease group over the course of treatment,

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indicating its potential as a predictive biomarker.

Efficacy and Clinical Pharmacology Conclusions

Out of the first 33 subjects who were evaluable, 12 subjects were responders (1 subject had a complete remission and 11 subjects had partial remissions). The criterion of the Simon 2-stage design (11 or more responders in both stages of the study) was therefore met and 4SC-201 is considered to be of interest in the treatment of relapsed/refractory HL.

For the Full Efficacy Analysis Set of 35 subjects, the ORR was 34.3% and the disease control rate was 54.3%. The ORR and the disease control rate in the 800 mg group were slightly higher than those seen in the 600 mg group. The median DOR in total was 8.36 weeks and was similar for both dose groups. The median PFS for all subjects was 10.00 weeks, with a higher value in the 800 mg group (13.43 weeks) compared to the 600 mg group (6.07 weeks). The median OS across both treatment groups was 54.14 weeks. The maximum observed OS was 135.6 weeks (censored).

Maximum plasma concentrations were obtained at 1.5 hours after oral administration of 4SC-201. Exposure (C_{max} and $AUC_{0\text{-}6h}$) to 4SC-201 increased roughly dose-proportionally over the relatively narrow dose range of 600 and 800 mg. Terminal plasma elimination half-lives for all doses and treatment days remained constant in the range from 1.67 to 2.23 hours at the dose levels administered. No relevant differences were observed between the PK parameters of 4SC-201 after a single dose or multiple doses of 4SC-201.

Biomarker analyses performed in this study confirmed the usage of pharmacodynamic markers such as HDAC inhibition as a valuable tool to follow the activity of 4SC-201 in the body. Indication-specific markers such as TARC/CCL17 showed responsive behavior regardless of clinical outcome. The investigation of individual genes resulted in the identification of baseline levels of ZFP64 and DPP3 and reduced STAT6 levels during 4SC-201 treatment as potential indicators for clinical benefit.

Safety

During the study, 37 subjects were exposed to 4SC-201 (600 mg [19 subjects] and 800 mg [18 subjects]), with a mean treatment duration of 72.1 days. These subjects were included in the Safety Analysis Set.

A total of 11 subjects (29.7%) had dose delays in both treatment groups: 4 subjects (21.1%) in the 600 mg group and 7 subjects (38.9%) in the 800 mg group. A total of 5 subjects (13.5%) had dose reductions: 3 subjects (15.8%) in the 600 mg group and 2 subjects (11.1%) in the 800 mg group. Two subjects (5.4%) had dose omissions; 1 subject (5.3%) in the 600 mg group and 1 subject (5.6%) in the 800 mg group. There were more dose reductions and delays due to abnormal laboratory values in the 800 mg treatment group than in the 600 mg treatment group.

No 4SC-201 treatment-related deaths occurred during the study. One subject (2.7%) in the Safety Analysis Set died from TEAEs not related to 4SC-201 (dyspnea, fever, pneumonia, and respiratory insufficiency) that were considered related to disease progression. During the observation period for survival in the Efficacy Analysis Set, a total of 24 subjects (68.6%) died: 14 subjects (77.8%) in the 600 mg group (13 subjects died due to causes related to disease progression and death of 1 subject was not related to disease progression but the cause of death is unknown) and 10 subjects (58.8%) in the 800 mg group (all deaths were related to disease progression).

Ten subjects (27.0%) had treatment-emergent SAEs that were reported for 6 subjects (31.6%) in the 600 mg group and 4 subjects (22.2%) in the 800 mg group. Seven subjects (18.9%) had SAEs that were assessed by the investigator as treatment-related (4 subjects in the 600 mg group and 3 subjects in the 800 mg group). The most frequently reported treatment-emergent SAE was anemia in 4 subjects (21.1%) in the 600 mg group and 3 subjects (16.7%) in the 800 mg group. One should note that in Poland blood transfusion always requires hospitalization of the subject and therefore automatically results in an SAE report. The rates of treatment-emergent SAEs and related treatment-emergent SAEs were comparable between the treatment groups.

Five subjects (13.5%) were discontinued from the study due to a TEAE/SAE: 1 subject in 600 mg group (required more than 1 dose reduction was the primary reason for discontinuation) and 4 subjects in the 800 mg group. Adverse events leading to study discontinuation were of grade 2 and 3 severity. Notably only 2 subjects were discontinued due to hematological TEAEs, in both cases, the event leading to discontinuation was thrombocytopenia. No subject was discontinued due to gastrointestinal disorders. It is also interesting to note that 3 of 5 subjects who discontinued due to TEAEs were from the same site (23)

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and that the dose of 4SC-201 was not reduced prior to the investigator making the decision to discontinue the subjects.

Overall, a total of 35 subjects (94.6%) experienced at least one TEAE: 17 subjects (89.5%) in the 600 mg treatment group and 18 subjects (100%) in the 800 mg group. The number of TEAEs was higher in the 800 mg group than in the 600 mg group. However, one should consider that treatment in the 800 mg group had a longer duration than the 600 mg group (81.9 days versus 62.8 days, respectively). Overall, most TEAEs were mild to moderate in severity. However, most subjects experienced at least one moderate or severe TEAE. Only one subject (2.7%) experienced a grade 4 TEAE and one subject (2.7%) died from grade 5 TEAEs (assessed as not-related to 4SC-201, but related to disease progression).

The most common TEAEs across all subjects treated with 4SC-201 included nausea (62.2%; n=23), vomiting (56.8%; n=21), anemia (40.5%, n =15), and thrombocytopenia (27.0%, n=10), all assessed by the investigator in most cases as related, and pyrexia (32.4%, n=12) in most cases assessed by the investigator as not related to 4SC-201. Less common TEAEs (reported for > 4 subjects) included asthenia, diarrhea, fatigue, insomnia, cough, and ALT increased. Related TEAEs were reported for 12 subjects (63.2%) in the 600 mg treatment group and 18 subjects (100%) in the 800 mg group. The number of related TEAEs was higher in the 800 mg group as in the 600 mg group.

Clinically significant abnormalities of the laboratory values were rare. Less than 20% of the subjects reported abnormalities in liver function tests and electrolyte imbalances. Only a few subjects showed mostly mild to moderate changes in the alkaline phosphatase, albumin and liver transaminases during the treatment period. Changes in the electrolytes (mainly potassium) were observed in some subjects, especially those with previous hypokalemia at baseline.

In general, hematological values were lower during the study than at Baseline, which were attributed to the underlying disease. For some parameters (platelets, white blood cells, neutrophils and lymphocytes), the levels were particularly low on Day 5 of each cycle, which seemed to indicate some hematological toxicity of 4SC-201.

No clear pattern was identified in the changes seen on the coagulation parameters (prothrombin time and international normalized ratio) during the study.

According to investigators assessment clinically there were no relevant changes to vital signs or physical examinations that were observed, secondary to study drug administration..

The number of subjects suffering from B symptoms at the Final Visit was 21.9%, whereas the number of subjects with B symptoms at screening was 45.9%.

Very careful monitoring of cardiac function was implemented for all subjects on study. Electrocardiograms were recorded repeatedly on 6 study days (C1D1, C1D5, C2D1, C2D5, C3D1 and C3D5) to capture eventual effect of high plasma levels of 4SC-201 on cardiac function. For the 37 subjects in the Safety Analysis Set, more than 1200 ECGs were recorded during the study. All observed ECG abnormalities were assessed by investigators as not clinically significant. Sinus tachycardia was the most frequently reported abnormality and occurred already at screening as well as during the course of the study. According to central ECG assessment sinus tachycardia was present more often in the 600 mg as compared to the 800 mg treatment group. Two subjects had tracing showing an old infarct at screening as noted by investigators. Non-clinically significant ECG changes were observed for these subjects during the treatment period which indicate that the study medication was well tolerated and did not induce any serious ECG changes even in subjects with prior conduction abnormality.

Consistent with ECG findings there were no troponin elevations during the 4SC-201 treatment.

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Safety Conclusions

There were no deaths related to the study drug. One subject died during the study (prior to first staging and thus not part of the Efficacy Analysis Set) due to cardiorespiratory arrest and respiratory insufficiency related to disease progression (not related to treatment with 4SC-201). In the Efficacy Analysis Set, a total of 24 subjects (68.6%) died during the OS observation period, 14 subjects (77.8%) in the 600 mg group and 10 subjects (58.8%) in the 800 mg group. All deaths were considered related to disease progression except for one with unknown cause.

- Ten subjects had treatment-emergent SAEs that were reported during the study: 7 subjects had events that were related to study treatment and 3 subjects had events that were not related to study treatment.
- The majority of the TEAEs were of mild to moderate severity.
- Overall, 5 subjects discontinued study treatment or discontinued from the study due to AEs/SAEs or more than 1 dose reduction required (600 mg dose group). Adverse events leading to study discontinuation were of grade 2 and 3 severity.
- Shifts in vital signs and physical examination results were generally small and not clinically significant.
- A substantial improvement of the HL-related B symptoms was observed at the Final Visit. The number of subjects suffering from B symptoms at the Final Visit was 21.9 %, whereas the number of subjects with B symptoms at screening was 45.9%.
- No signals indicating an influence of 4SC-201 on cardiac parameters were observed.

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CONCLUSIONS

This was a multicenter, open-label, single-arm, Phase 2 study to evaluate the efficacy, safety, and PK of the HDAC inhibitor 4SC-201 in subjects with relapsed or refractory HL.

Efficacy data revealed substantial anti-tumor activity of 4SC-201 in heavily pre-treated HL subjects as demonstrated by objective responses including 11 partial remissions and 1 complete remission.

The pre-defined statistical criterion of the Simon 2-stage design was met, therefore, 4SC-201 was considered to provide clinical benefit in the treatment of relapsed or refractory HL.

Nausea and vomiting, anemia and thrombocytopenia were the most frequently reported AEs related to 4SC-201. As expected for this subject population, infections, pyrexia, pain, and respiratory disorders were commonly reported. The majority of AEs were of mild or moderate severity. Grade 3 AEs were reported for 12 subjects with a higher proportion in the 800 mg group. Only one subject experienced a grade 4 hematological AE. Overall, the number of TEAEs was higher in the 800 mg group compared to the 600 mg group. However, also mean treatment duration in the 800 mg group was longer in comparison with the 600 mg group (80.9 days versus 61.8 days, respectively).

In conclusion, this study demonstrated promising single-agent activity of 4SC-201 in subjects with relapsed or refractory HL. Of particular note is the very favorable safety profile of 4SC-201, which allows the oral administration of up to 800 mg once daily in a 5+9 day treatment schedule without significant toxicities but a slightly improved efficacy compared to the 600 mg dose. There were no safety concerns including no clinically significant cardiac influences as confirmed by central ECG analyses.

Histone deacetylase inhibitors have demonstrated multiple synergistic effects with other chemotherapeutics and targeted therapies in the past and thus further development of 4SC-201 in HL could also envision its combination with other treatments to leverage mechanistic synergisms and potential prevention of drug resistance development.

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