2. STUDY SYNOPSIS

<table>
<tr><td>NAME OF SPONSOR/COMPANY:
4SC AG</td><td rowspan="3">INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER

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<tr><td>NAME OF FINISHED PRODUCT:
resminostat mesilate (4SC-201)</td></tr>
<tr><td>NAME OF ACTIVE INGREDIENT(S):
resminostat (INN)</td></tr>
<tr><td colspan="3">Title of Study:
A proof-of-concept Phase II study to evaluate efficacy, safety and pharmacokinetics of 4SC-201 and the treatment combination of Sorafenib plus 4SC-201 in patients with hepatocellular carcinoma exhibiting progressive disease under Sorafenib treatment</td></tr>
<tr><td colspan="3">Protocol No.: 4SC-201-1-2009
EudraCT Number: 2009-010760-42</td></tr>
<tr><td colspan="3">Investigators:
Number of principal investigators: 15
Coordinating investigator:
• Prof. Dr. med. Michael Bitzer
Coordinating investigator in Italy:
• Prof. Edoardo Giovanni Giannini</td></tr>
<tr><td colspan="3">Study Centers:
Number of study sites:
• 15 sites: 8 sites in Germany and 7 sites in Italy
• Coordinating investigator Site:
Medizinische Universitätsklinik Tübingen Gastroenterologie, Hepatologie, Infektiologie, Tübingen, Germany</td></tr>
<tr><td colspan="3">Publication (Reference):
Based on the SHELTER study data several posters and abstracts have been presented at international congresses. These are presented in Section 16.1.12</td></tr>
<tr><td colspan="2">Study Period:
First Patient Consented: 20 July 2009
First Patient Dosed: 6 August 2009
Last patient completed treatment Week 20: 30 July 2012
Last patient last visit: 02 July 2013</td><td>Phase of development:
II</td></tr>
</table>

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Objectives:

Primary Objective

- To determine Progression Free Survival Rate (PFSR) after 12 weeks.

Secondary Objectives

- To establish the Maximum Tolerated Dose (MTD) of resminostat in combination with sorafenib;
- To investigate the safety and tolerability of repeated oral doses of resminostat and of the treatment combination of ascending repeated oral doses of resminostat and sorafenib;
- To investigate the Overall Response Rate (ORR) of repeated oral doses of resminostat and of the treatment combination of sorafenib plus resminostat (based on Response Evaluation Criteria In Solid Tumours [RECIST] and "2008 American Association for the Study of Liver Diseases [AASLD] Panel of Experts in HCC-Design Clinical Trials" criteria separately);
- To determine Time to Progression (TTP) of repeated oral doses of resminostat and of the treatment combination of sorafenib plus resminostat, including radiological and symptomatic progression;
- To assess Overall Survival (OS) in patients getting repeated oral doses of resminostat or the combination of sorafenib plus resminostat;
- To determine Progression Free Survival (PFS) of repeated oral doses of resminostat and of the treatment combination of sorafenib plus resminostat, including radiological and symptomatic progression;
- To determine PFSR after 6 weeks (C4D1 [Day 43]) and 20 weeks;
- To assess the Pharmacokinetics (PK) of resminostat and of the treatment combination of sorafenib plus resminostat;
- To investigate Alpha-fetoprotein (AFP) levels in patients under treatment;
- To investigate effects on Histone Deacetylase (HDAC) enzyme inhibition and histone acetylation in Peripheral Blood Mononuclear Cells (PBMC);
- To determine Vascular endothelial growth factor (VEGF) and Vascular endothelial growth factor receptor (VEGFR) levels;
- To investigate gene expression (Ribonucleic acid [RNA] profiling);
- To investigate biomarkers in tumour tissue samplings (only in German Amended Study Protocol, Version 4, 20 Apr 2011).

Methodology:

Multi-centre, open-label, uncontrolled, non-randomized, two-arm parallel group Phase II trial.

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Number of Patients (planned and analyzed):

Planned:

- Arm A Dose Escalation Phase (resminostat plus sorafenib): up to 24 patients
- Arm A Maintenance Phase (resminostat plus sorafenib): up to 25 patients
- Arm B (resminostat): up to 25 patients

Analyzed:

- Arm A Dose Escalation Phase (resminostat plus sorafenib): 18 patients:
  - 200 mg resminostat + 400 mg sorafenib: 3 patients;
  - 400 mg resminostat + 400 mg sorafenib: 3 patients;
  - 600 mg resminostat + 400 mg sorafenib: 6 patients;
  - 600 mg resminostat + 800 mg sorafenib: 6 patients.
- Arm A Maintenance Phase (600 mg resminostat + 400 mg sorafenib): 20 additional patients (total 26 patients at this dose level)
- Arm B (600 mg resminostat): 19 patients

Diagnosis and Main Criteria for Inclusion:

Patients aged ≥ 18, of both gender, with advanced stage hepatocellular carcinoma (HCC), Barcelona Clinic Liver Cancer (BCLC) classification class B or C, with either histologically proven HCC or clinical diagnosis of HCC by AASLD criteria, exhibiting progressive disease (PD) under sorafenib treatment as confirmed by an independent radiological review, Child-Pugh (CP) class A up to B7 without slight ascites or more than grade I hepatic encephalopathy, first-line daily sorafenib treatment with minimally 400 mg for 8 weeks (treatment interruptions shorter than 14 days), prior to treatment start no sorafenib treatment for at least 2 weeks but no more than than 10 weeks. For patients without cirrhosis, histological confirmation of HCC was mandatory.

Signed and dated written informed consent.

Test Product, Dose, Mode of Administration, and Batch No.:

Investigational product:

- Resminostat mesilate (laboratory code BYK408740)
- Nexavar® (sorafenib)

Total Daily Dose (TDD):

- Resminostat (as mesylate salt): 200 mg, 400 mg and 600 mg OD
- Sorafenib (as tosylate salt): 200 mg and 400 mg BID (total daily dose 400 mg and 800 mg)

Mode of administration: Oral (resminostat and sorafenib)

Batch numbers:

- Resminostat: 204630/02, 204630/05, 204630/07, 204630/08, 204630/10, 204630/17
- Sorafenib: BXF8DP3, BXFF293, BXG19P1, BXG19P2, BXG68G3

Duration of Treatment:

The main phase of the study consisted of 6 treatment cycles. Each cycle included repeated doses of resminostat for 5 consecutive days followed by a 9-day rest period without resminostat treatment. In Arm A (combination treatment), in addition to resminostat sorafenib was given continuously every day. Arm B consisted of mono-treatment of resminostat.

In the event of medical benefit after 6 treatment cycles (at least stable disease [SD]), patients had the option to be treated further on until PD. Study duration per patient was not limited.

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Criteria for evaluation:

Efficacy:

- A CT scan of the chest and an MRI scan of the abdomen and pelvis were performed as a baseline staging. Target lesions were further examined by MRI. During the treatment period chest X-Ray and chest CT scans were performed in an alternating manner for evaluation of lung metastases. In patients with lung metastases, CT scans were performed exclusively.

  Contrast-enhanced MRI including volumetric determination of vital tumour and necrosis in target lesions.

  In this clinical trial, RECIST and "2008 AASLD Panel of Experts in HCC-Design Clinical Trials" were used for evaluation of response (refer to Appendix A of the protocol in Section 16.1.1).

  Patients were examined for treatment response after 6, 12 and 20 weeks, i.e. 3, 6 and 10 treatment cycles.

Pharmacokinetics:

- Plasma concentrations (AUC_{0-6}, $AUC_{0-\infty}$, AUC_{last}, AUC_{tau}, C_{max}, t_{max}, $t_{1/2}$, CL/F) of resminostat and sorafenib.

Pharmacodynamics:

- HDAC enzyme inhibition, histone acetylation, RNA profile and effects on VEGF/VEGFR in blood, expression profiles of genes responsive to resminostat treatment or exploratory genes.
- Optionally: Exploratory protein and mRNA biomarkers as e.g. HDAC-3 protein and mRNA expression in already available paraffin embedded tumour tissue biopsies or resection specimens.

Safety and Tolerability:

- AEs, vital signs (blood pressure [BP], pulse rate), electrocardiogram (ECG), clinical laboratory parameters; ECOG Performance Status.

Statistical Methods:

The statistical methods to be used in the analyses are described in the Statistical Analysis Plan (SAP) Final Version 2 dated 18 July 2012.

All the statistical outputs were programmed using SAS® v 9.2 or higher.

Results:

Patient Disposition/Analysis Sets

A total of 71 patients were screened, of which 57 patients received study treatment. Most of the patients in the study were male (50 patients [87.7%]) and were white (56 patients [98.2%]). The mean age of the total study population was 64 years. Most patients presented with a Child-Pugh classification of A5 (28 patients; 49.1%) and A6 (18 patients [31.6%]) at screening. The demographic characteristics were comparable between all treatment groups. A higher proportion of patients with mild ascites was observed in the 600 mg resminostat monotherapy group than in the other treatment groups: 42.1% (8 patients) compared with 22.8% (13 patients) in the overall Safety/ITT population.

The majority of patients (47 patients, 82.5%) had BCLC class C (advanced stage) at study entry; the remaining 10 patients had BCLC class B. Most commonly reported in the medical history were

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gastrointestinal disorders (12 patients, 21.1%) and the most common current medical conditions reported concerned vascular disorders (37 patients, 64.9%).

Overall, all 57 (100%) patients received previous sorafenib treatment. Of these, 37 received 800 mg, 7 received 600 mg and 13 received 400 mg of sorafenib as last treatment prior to inclusion into the study.

The Safety/ Intention to Treat (ITT) Population included 57 treated patients; the Per Protocol (PP) population included 43 patients (75.4%). All of the patients excluded from the PP Population had major protocol deviations. Approximately half of the patients completed 6 cycles of treatment (29 patients, 50.9%), and 29.8% (17 patients) completed 10 cycles of treatment.

The great majority of patients was compliant with the prescribed dose of both study drugs and most had no dose reductions in both resminostat and sorafenib in Cycles 2 to 9.

Dose escalation

During the dose escalation phase, all planned dose levels were tested.
No Dose Limiting Toxicity (DLT) was observed in the patients that were treated at 200 mg resminostat + 400 mg sorafenib and 400 mg resminostat + 400 mg sorafenib.
One DLT was observed in the first 3 patients treated with 600 mg resminostat + 400 mg sorafenib: QTc prolongation in Patient 105. Therefore, the Data Safety Monitoring Board (DSMB) decided to recruit a further 3 patients at the same dose level (total: 6 patients). Assessment after these 3 patients had completed 1 treatment cycle concluded that this dose level was tolerated and it was decided to proceed to the next dose level of 600 mg resminostat + 800 mg sorafenib. This dose level was only administered to patients who tolerated an 800 mg dose of sorafenib in first-line treatment. No DLT was detected in the first 3 patients treated at the 600 mg resminostat + 800 mg sorafenib dose level and 3 additional patients were treated at this dose level (total: 6 patients). One DLT was detected in this dose cohort (total: 6 patients) based on AE documentation: patient 110 reported drug-related AEs of grade 3 (weakness on Day 3 and dehydration on Day 8). As this was the highest dose level planned, and DLT was detected in less than 2 out of 6 patients, no MTD could be defined.

The 600 mg resminostat + 400 mg sorafenib dosing regimen was selected for the Arm A maintenance phase. A considerable portion of patients did not tolerate the 800 mg sorafenib dose in the first-line treatment and it was considered clinical-practice-oriented to include these patients in a second-line treatment with a lower dose of sorafenib. An additional 20 patients were treated at this dose level, resulting in 26 patients treated at 600 mg resminostat + 400 mg sorafenib.

A total of 19 patients were treated in the Arm B monotherapy group at 600 mg resminostat.

Efficacy

The PFSR according to AASLD criteria (as determined by central assessment for patients with non-missing, evaluable PFS status) was 71.4% in the PP Population and 52.4% in the Safety/ITT Population for all patients receiving 600 mg resminostat + 400 mg sorafenib after 12 weeks. For 600 mg resminostat monotherapy group, PFSR was 16.7% in the PP Population and 14.3% for the Safety/ITT Population. At 6 and 20 weeks of treatment, PFSRs were also higher for the Arm A 600 mg resminostat + 400 mg sorafenib combination therapy group compared to resminostat monotherapy treatment.

ORR at 6, 12 and 20 weeks of treatment was assessed as a secondary objective. Only 2 patients (both in the 600 mg resminostat + 400 mg sorafenib group) classified as partial responders during the study according to the central AASLD assessment criteria. No patient had a complete response (CR) during the study.

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Median TTP was longest in the 600 mg resminostat + 400 mg sorafenib group at 197 days in both the PP and Safety/ITT Population. For the 600 mg resminostat monotherapy group, median TTP was 49 days in the PP Population and 55 days in the Safety/ITT Population. The Kaplan-Meier time to event plot (Safety/ITT population) showed that the proportion of patients without disease progression was higher in the combination therapy group (600 mg resminostat + 400 mg sorafenib group) than in the monotherapy group (600 mg resminostat) from 6 weeks of treatment onwards.

Median time to death (OS) was higher in the 600 mg resminostat + 400 mg sorafenib group: 242 days compared to 125 days in the 600 mg resminostat group (Safety/ITT population).

The Kaplan-Meier survival plot (Safety/ITT population) showed that OS was comparable between the 600 mg resminostat + 400 mg sorafenib group and the 600 mg resminostat monotherapy group up to about 12 weeks. From approximately 12 weeks to approximately 40 weeks, the OS was higher in the combination therapy group (600 mg resminostat + 400 mg sorafenib) than in the monotherapy group (600 mg resminostat). From 40 weeks onwards comparable overall survival was observed between both groups.

Median PFS was longest at 197.0 days in the 600 mg resminostat + 400 mg sorafenib group; in the 600 mg resminostat group, median PFS was 49.0 days (PP and Safety/ITT population). The Kaplan-Meier survival plot (Safety/ITT population) showed that from 6 weeks of treatment onwards, the proportion of patients without disease progression or death was higher in the combination therapy group (600 mg resminostat + 400 mg sorafenib) than in the monotherapy group (600 mg resminostat).

Pharmacokinetics

Maximum plasma concentrations, C_{max}, were obtained at 1.5 h for resminostat and 1.5-3 h for sorafenib (median), following multiple oral administration of the highest dose of 600 mg resminostat plus 800 mg sorafenib.

Geometric mean C_{max} ranged from 2.65 to 2.87 mg/L for resminostat and from 10.8 to 14.4 mg/L for sorafenib. Geometric mean AUC_{0-6h} ranged from 6.84 to 9.13 mg•h/L for resminostat and from 45.6 to 53.6 mg•h/L for sorafenib.

Geometric mean terminal plasma elimination half-life of resminostat remained constant in the range from 1.63 to 2.33 h at 400 and 600 mg dosing. Exposure (C_{max} and AUC_{0-6h}) to resminostat increased dose-proportionally at the dose range of 200 to 600 mg.

At C1D1 the following pharmacokinetic parameters were observed for resminostat:

Dose (mg)	C_{max} (mg/L)	t_{max} (h)	AUC_{0-6h} (mg×h/L)
200 mg resminostat + 400 mg sorafenib	0.937	1	2.29
400 mg resminostat + 400 mg sorafenib	2.57	1	4.86
600 mg resminostat + 400 mg sorafenib	3.69	1.5	8.42
600 mg resminostat + 800 mg sorafenib	3.41	1.25	8.75
600 mg resminostat	3.77	1	8.90

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No differences were detected between the resminostat exposures following single dose or multiple dosing. Consequently, no induction or inhibition of absorption or elimination of resminostat was detected following repeated dosing.

Exposure (C_{max} and AUC_{0-6h}) to sorafenib increased dose-proportionally between 400 and 800 mg total daily dose. The half-life of sorafenib is very long (25-48h), therefore, sampling up to 6 h time was not enough to accurately calculate $t_{1/2}$ and $AUC_{inf\ obs}$. Similarly, related pharmacokinetic parameters such as CL/F, Vz/F, λz, $AUMC_{inf\ obs}$, and $MRT_{inf\ obs}$ were unreliable.

Accumulation of plasma exposure of sorafenib (both C_{max} and AUC_{0-6h}) was apparent following oral administration of sorafenib for 5 consecutive days or 3 treatment cycles compared to single dose exposure on C1D1. The C1D5/C1D1 and C3D5/C1D1 geometric mean ratios of AUC_{0-6h} ranged from 2.34 to 9.19. The long elimination half-life of sorafenib and the short dosing regimen of twice daily were likely the cause of this accumulation.

Drug-Drug and Drug-Disease Interactions

Co-administration of sorafenib had apparently no impact on the exposure of resminostat. The AUC_{0-6h} values of resminostat ranged from 7.80 to 8.90 mg•h/L for 600 mg resminostat and from 6.84 to 9.13 mg•h/L for the combination 600 mg resminostat + 800 mg sorafenib.

Co-administration of 400 or 600 mg of resminostat had negligible impact on the exposure of sorafenib at 400 mg total daily dose. The AUC_{0-6h} values of sorafenib with 400/400 mg vs. 600/400 mg (resminostat/sorafenib) combination doses were 5.78 vs. 2.98 mg•h/L (C1D1), 15.9 vs 20.3 mg•h/L (C1D5) and 16.3 vs 23.3 mg•h/L (C3D5).

Pharmacodynamics and Pharmacogenetics

HDAC enzymatic activity, global H4 histone acetylation status, VEGF concentrations and changes in gene expression levels of a group of 13 selected genes were measured in peripheral blood cells or plasma from patients of all dose cohorts. Additionally, expression of putative biomarkers in tumour tissues of some patients were examined.

HDAC enzymatic activity

Inhibition of HDAC enzymatic activity was determined in 22 patients (11 patients in the 600 mg resminostat monotherapy and 11 patients in the 600 mg resminostat + 400 mg sorafenib combination group). In the other combination groups limited sampling in low patient numbers hampered evaluation. Maximum HDAC inhibition reached 94% (median) 2 h after dosing in both groups, occurring at peak plasma levels (t_{max}) of resminostat. Inhibition of HDAC enzyme activity was transient and returned to baseline activity 24 h post-dose following the plasma curve of resminostat. The inhibition of HDAC activity was not influenced by concomitant sorafenib treatment, which is in line with the pharmacokinetic evaluation.

Global H4 histone acetylation status

The global histone H4 acetylation status was analysed in 14 patients (5 patients in the 600 mg resminostat monotherapy and 9 patients in the 600 mg resminostat + 400 mg sorafenib combination group). Global histone H4 acetylation was increased 1.5 to 2.0-fold relative to baseline 2 h after resminostat dosing, independent of the dose group. Median H4 acetylation was restored to baseline levels 24 h post resminostat dose. Maximum individual acetylation increases up to 10.5-fold were observed. The global histone H4 acetylation status showed similar time profiles to HDAC inhibition and followed the plasma curve of resminostat. The acetylation status was not influenced by sorafenib treatment.

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VEGF concentrations

Quantification of VEGF baseline levels (pre-dose C1D1) in 40 patients revealed a correlation (p=0.0493) with overall survival (OS) when split at the 85th percentile (134 pg/ml VEGF), suggesting that VEGF baseline levels may have prognostic value. Lower VEGF levels at baseline correlated with longer overall survival.

The majority of patients treated with resminostat alone (10 out of 13) showed a VEGF reduction or at least stabilization, whereas the majority of patients treated with the combination of resminostat and sorafenib (15 out of 19) showed an increase in VEGF plasma levels between C3D5 and baseline (C1D1). The increase in median VEGF levels in the combination therapy groups was particularly prominent on C1D8 where only sorafenib was present; the increase was also dependent on dose and was associated with progressive disease as assessed after 6 cycles of treatment. The median change in VEGF concentration in the combination group was an increase of 79% for patients with PD and of 21% for patients with SD (p=0.08), showing a worse response (at C6) in patients with a greater VEGF increase at C3D5 compared to C1D1.

Pharmacogenetics

A set of 10 genes identified via initial chip microarray analysis and found to be responsive to resminostat treatment was analysed in peripheral blood cells.

Analysis of this gene set in peripheral blood cells of patients showed a clear correlation of changes in gene expression levels with resminostat plasma levels over time, with the strongest effects on transcription generally observed 5 h after dosing. The combination with sorafenib did not influence effects observed with resminostat alone.

When the baseline gene expression levels of the transcription factor ZFP64 were split into a high and low expression level group, a significant correlation of baseline ZFP64 expression with OS was seen: Patients with high baseline ZFP64 expression had a longer OS.

Biomarkers in tumour material

The tumour material used for biomarker expression evaluation was collected from 13 study patients at some point prior to treatment with resminostat and was not part of the SHELTER trial. The expression of 16 protein biomarkers was measured immunohistochemically and compared to each other. Some protein biomarker expressions showed clear or even strong and significant correlations ($p < 0.05$) to each other. These included HDAC1 to HDAC6, AcetylH3, and nuclear β-Cathenin; HDAC6 to HDAC3, STAT1 and p21; AcetylH3 to STAT1; STAT1 to p21; EZH2 to nuclear β-Cathenin; NEDD9 to Rad23B; CyclinD1 to p21 and ZFP64. Inverse correlations were observed in the combinations ZFP64 with NEDD9, CyclinD1 and Rad23B. The analysis of protein biomarker expression measured and evaluated here may give initial clues towards finding protein biomarkers for patients with hepatocellular cancer receiving HDAC inhibitor treatment.

Safety

The majority of patients in all treatment groups received the full, planned dose at each cycle.

Overall, 35.1% of the patients received at least 9 cycles of study treatment. The highest proportion of patients receiving 9 cycles of treatment was seen in the 400 mg resminostat + 400 mg sorafenib group (2 out of 3, 66.7%). Patients receiving 9 cycles of resminostat and sorafenib accounted for 46.2% of the patients in the 600 mg resminostat + 400 mg sorafenib group, and 16.7% of the patients in the 600 mg resminostat + 800 mg sorafenib group. In the monotherapy group, 26.3% of patients received 9 cycles of resminostat. No patient in the 200 mg resminostat + 400 mg sorafenib group received 9 cycles of treatment with resminostat or sorafenib, with 7 cycles of treatment (in 33.3% of

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the patients) being the highest in this group.

A total of 48 treated patients died during the study; the majority of whom died after their last cycle of treatment was returned (or was discontinued) and not while on treatment. One untreated patient died of progression of liver disease.

As expected for the study population, the majority of patients died due to disease progression/the underlying disease (35 patients). An additional 3 patients had the primary cause of death listed as another reason (liver and renal failure for 2 patients and anaemia for 1 patient) but death was considered to be related to disease progression. A total of 7 patients died of unknown causes after their treatment had ended. The remaining 3 patients each died of coronary failure, pneumonia, and myocardial infarction (all three of whom died after their last treatment was returned and not while on treatment).

There were a total of 53 treatment-emergent serious adverse events (SAEs) reported in 24 and 3 non-treatment-emergent SAEs in 2 patients. The majority of the SAEs were considered unrelated or unlikely related to the study drugs but 14 SAEs were considered at least possibly related to resminostat and 12 SAEs were considered at least possibly related to sorafenib. There were 9 SAEs considered at least possibly related to both drugs: deep vein thrombosis, ECG QT prolonged, cholangitis, pneumonia, fatigue, dehydration, hypophosphataemia, leukocytosis and thrombocythaemia. The SAEs considered at least possibly related to resminostat but not sorafenib were troponin I increased, ECG conduction disorder, dyspnoea, vomiting and nausea. The SAEs considered at least possibly related to sorafenib but not resminostat were myocardial ischaemia, rectal haemorrhage and hypophosphataemia.

A total of 28 AEs (15 of which were considered serious) led to discontinuation of treatment with resminostat, sorafenib or both in 16 patients (28.1%). Most of these were considered at least possibly related to one or both of the study drugs (16 AEs) and most led to discontinuation of both resminostat and sorefenib (17 AEs).

Resminostat and sorafenib doses were reduced due to AEs in 9 patients (15.8%) and 4 patients (7.0%), respectively. The highest proportion of patients having dose reductions due to AEs was observed in the 600 mg resminostat + 400 mg sorafenib group for both resminostat and sorafenib; however, the sample size was highest in this group.

The dose was temporarily interrupted due to AEs in 17 patients (29.8%) for resminostat and 14 patients (24.6%) for sorafenib. The greatest proportion of patients having doses temporarily interrupted was seen in the 600 mg monotherapy group (7 patients; 36.8%) for resminostat and in the 600 mg resminostat + 400 mg sorafenib group for sorafenib (12 patients; 46.2%).

All of the patients in the study (57 patients; 100.0%) experienced at least one treatment-emergent adverse event (TEAE) during the study.

Fifty-three (53) patients (93.0%) had a total of 370 TEAEs considered at least possibly related to resminostat during the study. The most common TEAEs related to resminostat were in the SOC gastrointestinal disorders (128 events experienced by 38 patients [66.7%]) and included nausea (35 events in 26 patients [45.6%]), vomiting (33 events in 20 patients [35.1%]) and diarrhoea (35 events in 19 patients [33.3%]).

Thirty-seven (37) patients (64.9%) had a total of 244 TEAEs considered at least possibly related to sorafenib during the study. The most common TEAEs related to sorafenib were in the SOC gastrointestinal disorders (87 events experienced by 31 patients [54.4%]) and included diarrhoea (29 events in 16 patients [28.1%]) and nausea (21 events in 16 patients [28.1%]).

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There was a higher proportion of patients with serious events in the 600 mg resminostat + 400 mg sorafenib treatment group (Arm A) than in the monotherapy treatment 600 mg resminostat (Arm B): 50.0% compared with 26.3%. There was also a higher proportion of patients with serious events related to resminostat in the 600 mg resminostat + 400 mg sorafenib group (19.2%) than in the 600 mg resminostat group (10.5%) and a higher incidence of withdrawals due to AEs: 9 patients (34.6%) in the 600 mg resminostat + 400 mg sorafenib group compared with 4 patients (21.1%) in the 600 mg resminostat group.

A total of 23 patients had clinically significant (CS) abnormal hematology values during the study. The most common CS abnormalities concerned platelet levels (15 patients), in most cases (13 patients), low platelet levels, which are linked with liver disease; and leukocytes (7 patients; 4 patients with low leukocyte levels and 3 patients with high leukocyte levels).

A total of 21 patients had CS abnormal clinical chemistry values during the study. The most common CS abnormal clinical chemistry values were >ULN bilirubin (7 patients), >ULN creatinine (6 patients) and out-of-range potassium (6 patients: 3 patients with >ULN values and 3 patients with <LLN values).

Only 2 patients had CS abnormal urinalysis values during the study.

Trends in vital signs over time showed an increase in both systolic and diastolic BP and a decrease in weight and body mass index (BMI) during the study.

CS ECG abnormalities were reported for 2 patients in the 600 mg resminostat + 400 mg sorafenib group and 2 patients in the 600 mg resminostat group. ECG findings as per the central analysis of ECG Data indicated that overall no signal for drug-induced prolongation of QTc was observed.

In general, treatment with resminostat monotherapy or in combination with sorafenib was safe and well tolerated at the tested dose levels.

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CONCLUSIONS

This was a multi-centre, open-label, uncontrolled, non-randomized two arm parallel group proof-of-concept Phase II study to evaluate the efficacy, safety, and pharmacokinetics of the HDAC inhibitor resminostat (4SC-201) and the treatment combination of sorafenib plus resminostat (4SC-201) in patients with HCC exhibiting progressive disease under sorafenib treatment.

Second line treatment with resminostat alone or in combination with sorafenib was safe and tolerated at all dose levels studied in patients with advanced HCC. Since only one DLT was detected out of 6 patients at the dose levels 600 mg resminostat + 400 mg sorafenib and 600 mg resminostat + 800 mg sorafenib, the MTD was not determined.But many second line patients do not tolerate the 800 mg sorafenib dose approved for first-line treatment, therefore the combination of 600 mg resminostat + 400 mg sorafenib was selected for the maintenance part of the study.

Inter-individual variability of PK parameters of resminostat and sorafenib analyzed in this study was low.

Effective modulation of pharmacodynamic biomarkers was observed in both treatment arms.

Clinical efficacy in terms of PFSR, Median TTP, and Median PFS was generally higher in the 600 mg resminostat + 400 mg sorafenib combination therapy group compared to the 600 mg resminostat monotherapy group. Thus, the primary efficacy endpoint PFSR at 12 weeks according to central assessment based on AASLD criteria was 71.4% in the 600 mg resminostat + 400 mg sorafenib combination therapy group and 16.7% in the 600 mg resminostat monotherapy group in the PP population.

Median time to death (OS) was higher in the 600 mg resminostat + 400 mg sorafenib group: 242 days compared to 125 days in the 600 mg resminostat group (Safety/ITT population).

The Kaplan-Meier survival plot showed that OS was comparable between the 600 mg resminostat + 400 mg sorafenib combination therapy group and the 600 mg resminostat monotherapy group up to about 12 weeks of treatment, whereas from approximately 12 weeks to 40 weeks the median OS was higher in the combination therapy group. From 40 weeks onwards comparable overall survival was observed between both groups.

No patient had a complete response during the study. Only 2 patients in the combination therapy group classified as partial responders according to the AASLD criteria applied by the central reader.

The pharmacodynamic investigations showed that the combination of resminostat and sorafenib did not affect the known pharmacodynamic characteristics of resminostat. Similarly, in the pharmacokinetic analysis sorafenib had negligible effect on the pharmacokinetics of resminostat.

A mutual dose-dependent interaction of both drugs with regard to VEGF protein regulation must be assumed.

In accordance with gene expression analysis in a previous clinical phase II study in advanced Hodgkin's lymphoma patients, baseline levels of the transcription factor ZFP64 correlated significantly with OS of advanced HCC patients treated with resminostat, indicating that ZFP64 may serve as a potential prognostic or even predictive marker for resminostat responsiveness.

No correlation of the degree of HDAC inhibition and H4 acetylation with clinical response to treatment could be detected.

Treatment with resminostat monotherapy or in combination with sorafenib was safe and well tolerated at the tested dose levels.

NAME OF SPONSOR/COMPANY: 4SC AG	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: resminostat mesilate (4SC-201)		
NAME OF ACTIVE INGREDIENT(S): resminostat (INN)		
Date of the report: Version 1.0, 23 Jul 2015		