

## SYNOPSIS

Name of sponsor/company: 4SC AG	Individual trial table referring to part of the dossier: Volume: Page:	(For national authority use only)
Name of finished product: Resminostat (4SC-201)		
Name of active ingredient: Resminostat mesilate (4SC-201)		
<b>Title of trial:</b> A multicenter, double blind, randomized, placebo controlled, Phase II trial to evaluate resminostat for maintenance treatment of patients with advanced stage (Stage IIB - IVB) mycosis fungoides (MF) or Sézary syndrome (SS) that have achieved disease control with systemic therapy.		
<b>Protocol No.:</b> 4SC-201-6-2015 <b>EudraCT Number:</b> 2016-000807-99 <b>NCT Number:</b> NCT02953301		
<b>Investigators:</b> Number of principal investigators: 84 Coordinating investigator: Prof. Dr. med. Rudolf Stadler		
<b>Trial center(s):</b> Number of trial sites opened: 69 (patient recruitment in: 55) Coordinating investigator site: Prof. Dr. med. Rudolf Stadler University-Clinic for Dermatology Johannes Wesling Klinikum Ruhr University Bochum Hans-Nolte-Str. 1 32429 Minden, Germany		
<b>Publication (reference):</b> Not applicable.		
<b>Studied period (years):</b> 8 First patient enrolled: 14-Dec-2016 Last patient randomized: 11-May-2022 Last patient completed: 08-Aug-2024	<b>Phase of development:</b> II	
<b>Objectives:</b> Primary objective: efficacy (based on the primary efficacy endpoint progression free survival (PFS)) Secondary objectives: efficacy (based on key secondary and additional efficacy parameters), safety, pharmacokinetic (PK), and exploratory analyses		
<b>Methodology:</b> <ul style="list-style-type: none"> <li>- Prospective multicenter, double-blind, randomized, placebo-controlled clinical trial</li> <li>- Randomization at a ratio of 1:1 to resminostat or placebo including stratification for current remission status (complete response (CR)/partial response (PR) versus stable disease (SD)) and disease stage (IIB/III/IVA1 versus IVA2/IVB) prior to last systemic treatment resulting in CR, PR or SD</li> <li>- Optional treatment for patients randomized to placebo: cross-over to open-label resminostat after disease progression</li> </ul>		
<b>Number of patients:</b> Planned: 200 (100 patients in each treatment arm) Screened: 234 Enrolled: 201 Analyzed: 201		
<b>Diagnosis and main eligibility criteria:</b> Patients with advanced stage MF or SS who had achieved disease control (CR, PR or SD) on a previous systemic therapy, fulfilling the following eligibility criteria: <u>Inclusion criteria:</u> <ol style="list-style-type: none"> <li>1. Patients with histologically confirmed MF (Stage IIB - IVB) or SS in an ongoing CR, PR or SD after at least one prior systemic therapy according to local standards (including but not limited to <math>\alpha</math>-interferon (<math>\alpha</math>-IFN), bexarotene, extracorporeal photopheresis (ECP), chemotherapy) or total skin electron beam (TSEB) irradiation. The most recent systemic therapy had to be completed as planned or stopped due to unacceptable toxicity 2 - 12 weeks prior to randomization, i.e. patients should not be withdrawn from a treatment from which they derived benefit</li> <li>2. Male or female <math>\geq</math> 18 years</li> </ol>		

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3. Written informed consent obtained prior to any trial specific procedure 4. Eastern Cooperative Oncology Group (ECOG) status score 0 - 2 5. Adequate hematological, hepatic and renal function, as demonstrated by: a) hemoglobin $\geq 9.0$ g/dl (International System [SI] of Units: 5.6 mmol/L) b) absolute neutrophil count $\geq 1,000/\text{mm}^3$ c) platelets $\geq 75 \times 10^9/\text{L}$ d) alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 2$ times upper limit of normal e) total bilirubin $\leq 2$ mg/dL (SI units: 34.2 $\mu\text{mol/L}$ ) (unless known Gilbert syndrome) f) serum creatinine $\leq 1.5$ mg/dL (SI units: 132 $\mu\text{mol/L}$ ) g) prothrombin time International Normalized Ratio $\leq 2.3$ 6. Women of childbearing potential (not post-menopausal for 1 year and not surgically sterile) and males with partners of childbearing potential had to be sexually abstinent (i.e. refraining from heterosexual intercourse) or had to use a highly effective contraception (at least one of the following: combined (oral, intravaginal or transdermal) or progestogen-only (oral, injectable or implantable) hormonal contraceptives, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomy of the partner) from the time of screening to 30 days (female patients) or 3 months (male patients) after the last dose of trial treatment 7. Adequate recovery from precedent non-hematological toxicities, excluding alopecia, to $\leq$ National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 8. Able to comply with all the requirements of the protocol <u>Exclusion criteria:</u> 1. Patients with progressive disease (PD) 2. Known central nervous system involvement 3. History and current cardiovascular complications, including unstable angina pectoris, uncontrolled hypertension, congestive heart failure (New York Heart Association [NYHA] Class III or IV) related to primary cardiac disease, a condition requiring anti-arrhythmic therapy, ischemic or severe valvular heart disease, or a myocardial infarction within 6 months prior to randomization 4. Baseline corrected QT (QTc) interval $> 500$ milliseconds [NOTE: QTcF is relevant] 5. History of additional risk factors for Torsade de Pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome) 6. Use of concomitant medications that are known to prolong the QT/QTc interval 7. Concurrent use of any other specific anti-tumor therapy including psoralen photo chemotherapy (PUVA), chemotherapy, immunotherapy, hormonal therapy, radiation therapy, or experimental medications 8. Previous or concurrent cancer that was distinct in primary site or histology from cutaneous T-cell lymphoma (CTCL), except curatively treated squamous-cell carcinoma of the skin stage 0-1 and curatively treated malignant melanoma stage 0-1A with a low risk of recurrence/metastasis as per assessment of the investigator, cervical carcinoma <i>in situ</i> , treated basal cell carcinoma, superficial bladder tumors (Ta, Tis and T1); any cancer curatively treated $> 3$ years prior to randomization was allowed 9. Current evidence of any uncontrolled clinically significant internal, psychiatric or neurologic disease 10. Altered mental status precluding understanding of the informed consent process and/or completion of the necessary trial procedures 11. Pregnant or breast-feeding women 12. History of allergic reactions attributed to compounds of similar chemical or biological composition to the trial drugs 13. Active alcohol and/or drug abuse 14. Any other acute or chronic condition that, in the investigator's opinion, would have limited the patient's ability to complete or participate in this trial 15. Patients with tumoral stage MF, presenting at baseline only with tumors (thereof at least one tumor $\geq 1$ cm in diameter), without current involvement of the skin by patches or plaques in conjunction with a modified severity weighted assessment tool (mSWAT) $> 0$ and $< 20$ (only applicable for Belgium) 16. Patients with a history of treatment with Vorinostat (only applicable for Japan)		
<b>Test product, dose and mode of administration, batch numbers:</b> Investigational product: resminostat Total Daily Dose (TDD): 600 mg (3 x 200 mg tablets)		

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Mode of administration: oral administration at once daily (QD), D1 - 5, every 2 weeks (q2w) Batch numbers: KH15/0023, KH16/0034, KH16/0034+, KH17/0062, KH17/0063, KH18/0209, KH18/0210, KH18/0212.		
<b>Reference therapy, dose and mode of administration, batch numbers:</b> Placebo: matching placebo tablet TDD: 3 x 1 placebo tablet (no active ingredient) Mode of administration: oral administration at QD, D1-5, q2w Batch numbers: KH15/0024, KH17/0054, KH22/0633+.		
<b>Duration of treatment:</b> Patients were treated with trial medication (resminostat or placebo) until disease progression or unacceptable toxicity. In case of disease progression, patients were unblinded after the blinded end of treatment (EOT) visit and patients on placebo were offered to roll-over into treatment with open-label resminostat for as long as they benefited in the opinion of the investigator or until unacceptable toxicity or withdrawal of consent.		
<b>Criteria for evaluation:</b> <u>Primary endpoint:</u> <ul style="list-style-type: none"> <li>- PFS</li> </ul> <u>Key secondary endpoint:</u> <ul style="list-style-type: none"> <li>- Time to Symptom Worsening (TTSW): pruritus</li> </ul> <u>Secondary endpoints:</u> <ul style="list-style-type: none"> <li>- Time to Progression (TTP)</li> <li>- Time to Next Treatment (TTNT)</li> <li>- PFS on the next treatment following trial therapy (PFS2)</li> <li>- PFS on the subsequent treatment (PFS3)</li> <li>- Overall Response Rate (ORR)</li> <li>- Duration of Response (DOR)</li> <li>- Overall Survival (OS)</li> <li>- Health-related Quality of Life (HrQoL) endpoints based on:               <ul style="list-style-type: none"> <li>o Visual Analogue Scale (VAS) for itching</li> <li>o Functional Assessment of Cancer Therapy - General (FACT-G) questionnaire</li> <li>o Skindex-29 questionnaire</li> </ul> </li> <li>- PK analysis of resminostat and metabolites</li> </ul> <p>Response was evaluated by the investigator according to the MF/SS Global Response Score (GRS) as recommended by the Consensus Statement of International Society for Cutaneous Lymphomas (ISCL), United States Cutaneous Lymphoma Consortium (USCLC) and European Organisation for Research and Treatment of Cancer (EORTC) (<a href="#">Olsen et al 2011</a>) and adapted to the maintenance setting of the trial.</p> <u>Safety endpoints:</u> <ul style="list-style-type: none"> <li>- Frequency and intensity of adverse events (AEs)</li> <li>- Vital signs, including body weight, temperature, systolic and diastolic blood pressure</li> <li>- 12-lead electrocardiogram (ECG) including heart rate, QRS, QT and QTc intervals</li> <li>- Laboratory analyses (hematology, coagulation, clinical chemistry)</li> </ul> <u>Exploratory endpoints:</u> <ul style="list-style-type: none"> <li>- Biomarker analysis:               <ul style="list-style-type: none"> <li>o immunohistochemistry (IHC)-based expression analysis of target proteins related to mode of action of resminostat in skin lesion biopsies</li> <li>o ribonucleic acid (RNA) expression analysis in skin lesion biopsies and peripheral blood cells</li> <li>o Concentration of circulating cytokines and chemokines in serum samples</li> </ul> </li> <li>- Other:               <ul style="list-style-type: none"> <li>o VAS itching score: changes from baseline over time and area under the curve (AUC) per time period</li> <li>o Changes in requirement of anti-itching treatment</li> <li>o Efficacy in maintenance of blinding (survey among patients and investigators at EOT)</li> </ul> </li> </ul> <u>Post-hoc analyses:</u> The following endpoints were defined post-hoc to further characterize effects of resminostat in CTCL: <ul style="list-style-type: none"> <li>- PFS from start of last prior systemic therapy to first PD (total PFS): based on intention-to-treat</li> </ul>		

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<p>(ITT) and per protocol (PP) populations and the subgroup of patients with prior systemic drug therapy (ITT-PSDT; excluding ECP and TSEB as relevant last prior systemic therapy)</p> <ul style="list-style-type: none"> <li>- Effect of treatment on mSWAT changes from baseline</li> <li>- Time to development or worsening of skin tumors, the time to tumor event (TTTE) based on ITT population and the subgroups of patients without and with skin tumor/ulceration at baseline</li> <li>- Additional subgroup analysis for PFS and TTNT based on ITT population: patients with disease stages IIB, III, IV and III or IV</li> <li>- Evaluation of FACT-G subscale scores and a modified FACT-G total score (with physical well-being question "I have nausea" set to "not at all" for all patients) for changes from baseline</li> </ul>		
<p><b>Statistical methods:</b></p> <p>Sample size calculation was based on the primary endpoint with an assumed PFS of 4.2 months on placebo. To achieve a hazard ratio (HR) of 0.6, median PFS on resminostat had to be <math>\geq 7</math> months. Further parameters included an enrolment period of 24 months, a follow-up (FU) period of 12 months, a two-sided <math>\alpha</math> of 0.05 for the type 1 error (significance level for the primary endpoint), a power of 80% and a patient dropout rate of 33%. Using the PASS 14 software (NCSS, LLC), the sample size was determined to be 200 patients (100 patients per treatment arm) to observe a total of 125 PFS events.</p> <p>Analysis of endpoints was based on different patient populations:</p> <ul style="list-style-type: none"> <li>- ITT population: all randomized patients</li> <li>- PP population: randomized, treated with at least one dose of trial medication and no major protocol violations</li> <li>- Safety population: treated with at least one dose of trial medication</li> <li>- TTSW (pruritus) population: VAS itching score <math>\leq 7</math> at treatment start</li> <li>- Roll-over population: patients from treatment arm B (placebo), who opted to receive resminostat treatment after unblinding due to PD and were treated with at least one dose of resminostat</li> <li>- PK analysis population: treated with at least one dose of trial medication on the day of PK sampling and at least one measurement of plasma concentration available.</li> </ul> <p>Based on the ITT population, exploratory subgroup analysis was performed for the following subgroups: histologically confirmed MF (ITT-MF), histologically confirmed SS (ITT-SS), remission status of CR or PR (ITT-XR), remission status of SD (ITT-SD), disease stage of IIB, IIIA/IIIB or IVA1 prior to last systemic treatment (ITT-DS1), and disease stage of IVA2 or IVB prior to last systemic treatment (ITT-DS2).</p> <p>Time-to-event data were reported for each treatment arm as:</p> <ul style="list-style-type: none"> <li>- Number of events and censored values including reason for censoring</li> <li>- Time in months (75%, median, 25%)</li> <li>- Event rate estimates (3-, 6-, 9- and 12-month rates; further rates of 18, 24 months, etc. as long as <math>\geq 1</math> patient still in FU)</li> <li>- Kaplan-Meier plots.</li> </ul> <p>For comparison of treatment arms, the following statistical analyses were applied:</p> <ul style="list-style-type: none"> <li>- Two-sided log-rank test stratified by disease stage and remission status (p-value)</li> <li>- Cox proportional hazards model stratified by disease stage and remission status (HR)</li> <li>- Unstratified Cox proportional hazards model</li> <li>- Cochran-Mantel-Haenszel (CMH) test stratified by disease stage and remission status (odds ratio and its related p-value)</li> </ul> <p>Parameters were reported with two-sided 95% CI or 95% Clopper-Pearson exact CI (CMH test).</p> <p>A linear mixed model for repeated measures (MMRM) approach was applied to analyze change from baseline over time of HrQoL data. The MMRM included treatment arm, time point (continuous), time point (continuous) by treatment interaction, and time point (continuous) by baseline interaction as fixed effects, baseline value as covariate and time point (categorical) as repeated measures effect.</p> <p>Figures were presented as Kaplan-Meier plot, HR forest plot, assumption of proportional hazards plot, or plot over time (using mean <math>\pm</math> standard deviation (SD), mean + min/max or % change per study day).</p> <p>To assess the robustness of the obtained results, various sensitivity analyses were applied for the primary and selected secondary endpoints.</p> <p>The primary statistical analysis (main analysis) was performed 10 months after randomization of the last patient and comprised the primary and all secondary endpoints except PFS on subsequent treatments (PFS2 and PFS3).</p> <p>The secondary statistical analysis (final analysis) was performed 12 months after the last blinded EOT visit and comprised analysis of randomized patient data collected after the cut-off date for the main</p>		

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analysis (including PFS2 and PFS3) and roll-over patient data.		
<p><b>SUMMARY – Efficacy, Quality of Life and Pharmacokinetic Results:</b></p> <p>201 patients were randomized and included in the ITT population (resminostat: 100; placebo: 101). The PP population comprised 174 patients (resminostat: 90; placebo: 84) and the TTSW population comprised 154 patients (resminostat: 72; placebo: 82). The roll-over population comprised 58 patients randomized to placebo who roll-over to open-label treatment with resminostat due to progression. Baseline demographics and disease characteristics were well balanced between the two treatment arms except for gender, large cell transformation (LCT), and bexarotene/other retinoids or brentuximab vedotin as last prior systemic therapies. Data suggest a broad range of advanced-stage MF and SS patients with a large variety of previous systemic therapies.</p> <p><b>Efficacy</b></p> <p>A statistically significant improvement in the primary endpoint PFS (ITT population) was observed for resminostat compared with placebo (<math>p = 0.015</math>), with a median PFS of 8.3 months on resminostat and 4.2 months on placebo, and an HR of 0.623 [95% CI: 0.424, 0.916] in favor of treatment with resminostat. The sensitivity analysis of PFS at the secondary analysis time point confirmed these numbers (<math>p = 0.018</math>; HR = 0.629).</p> <p>PFS was also analyzed in several subgroups using important baseline characteristics. Remarkable median PFS on resminostat was observed in patients with brentuximab vedotin or bexarotene and other retinoids as last prior systemic therapy (15.7 and 12.9 months, respectively), as well as in female patients (18.0 months), Asian patients and patients with SD at baseline (15.7 months each). The PFS improvement on resminostat compared with placebo was statistically significant in disease type MF, bexarotene and other retinoids as last prior systemic therapy, and SD at baseline.</p> <p>Secondary efficacy parameters further substantiated the observed efficacy. Resminostat in comparison with placebo significantly improved TTP (HR: 0.629) and TTNT (HR: 0.609). The ORR for maintenance therapy was higher on resminostat (17.4%; CR: 3 patients; PR: 12 patients) than on placebo (10.0%; PR: 10 patients). The median DOR was similar in both treatment arms. Analysis of PFS on the next (PFS2) and subsequent treatments (PFS3) did not reveal statistically significant differences between the treatment groups; a detrimental effect of resminostat on subsequent therapies is unlikely. Median OS was 70.8 months on resminostat and 75.6 months for placebo (HR: 0.982). The difference in OS was not statistically significant between the treatment arms.</p> <p>Efficacy was also assessed in the roll-over population. In patients with PD, a median PFS of 5.6 months was reported for open-label treatment with resminostat. Based on GRS, an ORR of 15.5% was achieved on resminostat (CR: 3 patients; PR: 6 patients). Based on mSWAT, an improvement in skin response of <math>\geq 50\%</math> was observed in 16 patients (27.6%; CR: 5 patients; PR: 11 patients).</p> <p>Additional post-hoc analyses concerning the double-blind period included PFS from start of last prior systemic therapy to first occurrence of PD (= total PFS), changes from baseline in mSWAT scores, time to development or worsening of skin tumors (TTTE) and PFS in the different disease stages. In comparison to placebo, all of these endpoints were in favor of treatment with resminostat, with statistically significant results for patients with prior systemic drug therapy, effects of resminostat on skin lesions (changes from baseline in mSWAT; TTTE), and patients with Stage IIB disease at baseline.</p> <p><b>Quality of Life</b></p> <p>In both treatment arms, the key secondary endpoint TTSW pruritus was not evaluable due to the low number of events in the TTSW population. Changes from baseline in Skindex-29 questionnaire and VAS itching did not show a significant difference between resminostat and placebo in the randomized period. In line with the results in VAS itching, the use of anti-itching medication was similar between the two treatment arms. Changes from baseline in FACT-G total score over time were statistically significant in favor of placebo. The negative effect on resminostat was due to decreases in both the functional and physical well-being subscales. Of note, resminostat caused gastrointestinal disorders in several patients which may have prevented better scores of resminostat in the physical well-being parameters of the FACT-G questionnaire.</p> <p>Patient-reported VAS itching was also assessed in the roll-over population. On open-label resminostat, the mean VAS itching scores decreased over time and stayed below the baseline score for more than a year, supporting the efficacy of resminostat in patients with MF and SS.</p> <p><b>Pharmacokinetics</b></p> <p>A total of 1,307 plasma samples obtained during randomized and roll-over periods were analyzed for resminostat plasma concentrations, with 786 samples of 145 patients (88 randomized to resminostat</p>		



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<p>and 57 patients of the roll-over phase) used for population PK modeling together with PK data available from 5 other clinical trials with resminostat. Based on the established population PK model, resminostat steady state PK parameters in the CTCL patient population of the present trial could be estimated. Selected resminostat plasma samples were also screened for resminostat metabolites. The most abundant analytes (&gt; 5%) detected in the pooled plasma samples collected at different time points on C3D1 and C3D5 were resminostat parent and the metabolites M4, M7, M10, M12 and M16.</p>		
<p><b>SUMMARY - Safety Results:</b></p> <p>All randomized patients were treated with at least one dose of trial medication and included in the safety population (N = 201; resminostat: 100; placebo: 101). In addition, a subgroup of the safety population, i.e. all patients treated with resminostat (N = 180; comprising patients randomized to resminostat, as well as patients randomized to placebo who rolled-over to open-label resminostat), were analyzed for the entire treatment duration (i.e. randomized period and roll-over period).</p> <p><b>Exposure</b></p> <p>During randomized phase, resminostat was administered for a mean of 19.8 cycles (median: 9.0 cycles; range: 1 - 142 cycles), with 45% of patients receiving therapy for &gt; 10 cycles. The mean duration of treatment was 294 days (median: 127 days) and the mean relative dose intensity 87.50% (median: 97.29%). Similar numbers were obtained on placebo with a mean of 17.4 cycles (median: 8.0 cycles; range: 1 - 102 cycles), 42.6% of patients receiving therapy for &gt; 10 cycles, a mean duration of treatment of 254 days (median: 110 days) and a mean relative dose intensity of 98.14% (median: 100%). The slightly decreased dose intensity of resminostat compared with placebo was due to a higher number of dose reductions, interruptions and omissions reported on resminostat. These dose modifications, however, did not interfere with long-term administration of resminostat.</p> <p>In the roll-over population, resminostat was administered for a mean of 15.0 cycles (median: 7.0 cycles; range: 1 - 121 cycles), with 39.7% of patients receiving therapy for &gt; 10 cycles. The mean duration of treatment was 216 days (median: 102 days) and the mean relative dose intensity 88.49% (median: 95.92%).</p> <p><b>Safety</b></p> <p>AEs were frequently observed during the randomized period, with the majority of AEs being of mild to moderate intensity in both treatment arms. Both the number of reported AEs and the number of patients with AEs were higher for patients on resminostat than on placebo in all categories. In particular, the number of patients with AEs and serious adverse events (SAEs) considered related to trial treatment was higher on resminostat (88.0% and 11.0%) than on placebo (41.6% and 1.0%, respectively). Furthermore, AEs leading to changes in trial treatment were observed in 51 patients (51.0%) on resminostat compared with 12 patients (11.9%) on placebo. AEs leading to discontinuation of trial medication were reported in 8 patients on resminostat (8.0%) and 3 patients on placebo (3.0%). The frequency of AEs reported for patients treated with open-label resminostat during the roll-over period was similar to patients treated with blinded resminostat during the randomized period. On resminostat (N = 180), the most frequent AEs reported were nausea (66.7%), diarrhoea (42.2%), fatigue (33.3%) and vomiting (32.8%). On placebo, the most frequent AEs were diarrhoea (16.8%), nasopharyngitis (16.8%), fatigue (14.9%), and pruritus (13.9%).</p> <p><u>AEs by relationship to trial medication</u></p> <p>On resminostat (N = 180), AEs considered related to trial treatment included predominantly nausea (66%), diarrhoea (37%) and vomiting (30%) followed by fatigue (29%), dysgeusia (26%) and decreased appetite (21%). The majority of related AEs were of maximum CTCAE Grade 1 - 2 intensity. Related AEs of Grade 3 were observed in 23% and of Grade 4 only in 1% of patients on resminostat. These related Grade 4 AEs comprised lymphocyte count decreased and neutrophil count decreased in 1 patient each. On placebo, AEs considered related to trial treatment included predominantly fatigue, diarrhoea and nausea.</p> <p><u>Serious AEs</u></p> <p>There was no AE leading to death in any of the patients.</p> <p>On resminostat (N = 180), SAEs were reported in 33 patients (18.3%), with cellulitis as the most frequent SAE reported in 3 patients. SAEs considered related to trial medication were observed in 14 patients (7.8%), with diarrhoea, ALT increased and AST increased in 2 patients each.</p> <p>On placebo, SAEs were reported in 12 patients (11.9%) and included predominantly infections in 5 patients (5.0%).</p> <p><u>Clinical laboratory evaluation</u></p> <p>During the randomized period, a higher number of patients with changes in laboratory parameters were</p>		

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<p>observed on resminostat than on placebo for Grade 1 - 2 leukocytes, Grade 2 lymphocytes, Grade 2 - 4 neutrophils, Grade 1 - 2 platelets, Grade 1 - 2 bilirubin, and Grade 2 creatinine. All other parameters were in the same range in the two treatment arms. Despite the observed AEs on resminostat affecting predominantly the gastrointestinal tract, these side effects did not result in obvious differences in electrolyte imbalances compared with placebo.</p> <p>In all patients treated with resminostat (randomized and roll-over period), clinically significant abnormal laboratory parameters of Grade 3 considered related to treatment comprised neutrophil count decreased/neutropenia in 6 patients, lymphocyte count decreased/lymphopenia in 3 patients AST/ALT increased in 3 patients, white blood cell count decreased in 2 patients, and blood LDH increased in 1 patient. Related clinically significant abnormal laboratory parameters of Grade 4 comprised lymphocyte count decreased and neutrophil count decreased in 1 patient each.</p> <p>On placebo, all clinically significant abnormal laboratory parameters considered related to treatment were of Grade 1 and 2, except for Grade 4 lymphopenia in 1 patient.</p> <p><b>Vital signs and ECGs</b></p> <p>There were no obvious differences in vital signs between the treatment arms.</p> <p>According to ECG data assessment at the trial sites, no significant differences in QRS interval, QT interval and QTc interval were detected between the treatment arms. Resminostat did not seem to prolong the QTc interval. These findings were confirmed by central review of ECG data. Administration of resminostat did not lead to any significant alterations of the ECG parameters heart rate, QT, QTcF, interval and QRS. Furthermore, QTcF interval values above 450 ms were rare and similar for resminostat and placebo and not exceeding 480 ms..</p>		
<p><b>CONCLUSIONS:</b></p> <p>The present Phase II trial was conducted to evaluate efficacy and safety of resminostat for maintenance treatment of patients with advanced stage MF (Stage IIB-IVB) or SS who had achieved disease control (CR, PR or SD) with prior systemic therapy or TSEB. In this prospective, multi-center trial, patients were randomized to blinded treatment with resminostat or placebo at a ratio of 1:1, stratified for disease stage (stage IIB/III/IVA1 versus stage IVA2/IVB) and remission status (CR/PR versus SD). Patients were treated with trial medication until disease progression or unacceptable toxicity. Patients progressing on blinded trial treatment were unblinded and those on placebo were offered to roll-over to treatment with open-label resminostat. In total, 201 patients were enrolled including 100 patients randomized to resminostat and 101 patients to placebo. To exclude bias due to differences in disease characteristics, stratification by disease stage (stage IIB/III/IVA1 versus stage IVA2/IVB) and remission status (CR/PR versus SD) was applied not only for randomization, but also in statistical analyses comparing the two treatment arms.</p> <p>Data analysis (ITT population) showed a statistically significant improvement of the primary endpoint PFS for resminostat compared with placebo, with a median PFS of 8.3 months on resminostat and 4.2 months on placebo, and a PFS HR of 0.623 in favor of treatment with resminostat in the overall patient population. All sensitivity analyses performed for PFS indicate significance and/or HRs in favor of resminostat. Subgroup analysis of PFS using important patient baseline demographic and disease characteristics showed HRs in favor of resminostat for almost all defined subgroups, with significant increases in PFS on resminostat observed in patients with bexarotene and other retinoids as last prior systemic therapy, disease type MF, and remission status of SD at baseline.</p> <p>The results of the primary endpoint were supported by consistent and significant secondary efficacy results of treatment with resminostat and placebo, including TTP (median: 8.3 vs 4.2 months) and TTNT (median: 9.1 vs 4.2 months, respectively). Furthermore, in patients with remission status of PR or SD at baseline (N = 176), responses were observed in 15/86 patients (17.4%; CR: 3 patients; PR: 12 patients) on resminostat and in 9/90 patients (10.0%; CR: 0 patients; PR: 9 patients) on placebo. Of note, the meaning of ORR in maintenance therapy (patients already in remission or SD) differs from ORR in patients with PD and should thus be considered as a measure of further improvement in disease control under maintenance therapy.</p> <p>With an HR of 0.982, data did not suggest a difference in OS between the two treatment arms. Analyses of PFS on the next treatment following trial therapy (PFS2) and on subsequent treatments (PFS3) did not reveal significant differences between the treatment arms. Despite some limitations of these analyses due to the study design, a detrimental effect of resminostat on the efficacy of subsequent therapies is considered unlikely.</p> <p>The efficacy of resminostat is supported by data from the roll-over population, including 58 patients randomized to placebo who rolled-over due to confirmed PD. In these patients, a median PFS of</p>		

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<p>5.6 months was reported for open-label treatment with resminostat. Based on GRS, an ORR of 15.5% was achieved on resminostat (CR: 3 patients; PR: 6 patients). Based on mSWAT, an improvement in skin response of <math>\geq 50\%</math> was observed in 16 patients (27.6%; CR: 5 patients; PR: 11 patients). These observations were accompanied by a decrease of patient-reported VAS itching scores over time. In the roll-over population, resminostat was administered for a mean number of 19.8 cycles (median: 9.0; range: 1 - 142 cycles), with 45% of patients receiving therapy for <math>&gt; 10</math> cycles. The mean duration of treatment was 294 days (median: 127 days; range: 10 – 2,023 days) and the mean relative dose intensity 87.50% (median: 97.29%; range: 28.0 - 103.7%) indicating tolerability and suitability for long-term administration.</p> <p>The trial confirmed the known safety profile of resminostat, with gastrointestinal disorders such as nausea (66%), diarrhoea (37%) and vomiting (30%) as the most frequent treatment-related AEs reported in all patients treated with resminostat (N = 180), followed by fatigue (28%), dysgeusia (26%) and decreased appetite (21%). These side effects were mainly reported on the treatment days and improved or resolved during the 9-day treatment-free interval. Of note, patients could not be treated with effective anti-emetics since their use was severely restricted due to their known risk for QTc prolongation and Torsade de Pointes. However, the gastrointestinal side effects did not lead to major electrolyte disturbances. Most AEs were of mild to moderate intensity (i.e. CTCAE Grade <math>\leq 2</math>), with related AEs of Grade 3 observed in 24% and of Grade 4 only in 2% of patients on resminostat. These Grade 4 AEs comprised lymphocyte count decreased and neutrophil count decreased in 1 patient each. No patient died due to a treatment-related AE.</p> <p>SAEs considered related to resminostat were observed in 14 patients (7.8%), including mainly gastrointestinal disorders and infections,. ECG effects such as prolongation of the QTc interval known for other histone deacetylase (HDAC) inhibitors could not be detected for resminostat.</p> <p>HrQoL was assessed using patient-reported outcome measures of itching (VAS), effects of skin disease (Skindex-29 questionnaire) and effects of cancer therapy (FACT-G questionnaire). It has to be noted that the patients had a very broad range of baseline scores at study entry, i.e., from "not affected at all" to "severely impaired". Based on the applied scales and questionnaires, resminostat was similar to placebo in the VAS itching and Skindex-29 questionnaire scores. When comparing the effects of treatment with resminostat and of no treatment (placebo) on HrQoL using the FACT-G questionnaire, a significant difference in changes from baseline in favor of placebo was observed. The difference in FACT-G total scores was mainly influenced by reduced scores of resminostat in the "physical" and "functional well-being" domains of the questionnaire. Likely, the frequently reported gastrointestinal side-effects in patients on resminostat may have prevented better scores in these parameters.</p> <p>CTCL is a debilitating and life-threatening condition. The disease is responsive to current treatment modalities but responses are not durable and the disease is generally resistant to cure. Patients with advanced disease stages are confronted with lack of curative therapies, lack of long-term disease control, poor prognosis and high symptom burden leading to loss in quality of life (QoL). In particular, there are no standardized strategies or evidence-based treatment options for maintenance therapy in patients with CTCL who have achieved disease control (<a href="#">Stadler &amp; Scarisbrick 2020</a>).</p> <p>Overall, resminostat significantly prolonged PFS compared with placebo and demonstrated clinically meaningful benefit in a broad population of advanced stage MF/SS patients. Despite the risk of gastrointestinal side-effects, resminostat was considered safe and tolerable, and proved suitable for maintenance treatment. Use of effective anti-emetic medication which was severely restricted in the present trial is expected to control the observed gastrointestinal side-effects and to decrease the effects of resminostat on the patients' QoL assessed by FACT-G. As an oral formulation, resminostat is suitable for self-administration by the patients.</p> <p>In conclusion, the RESMAIN trial is the first to prove the benefit of a maintenance treatment strategy in advanced CTCL. The obtained clinical data on efficacy and safety of resminostat in CTCL demonstrate a significant benefit for patients with advanced stage MF and SS who have achieved disease control under systemic therapy or TSEB radiation.</p>		
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