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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kinselby (RFD)

International non-proprietary name: Resminostat

Procedure No. EMEA/H/C/006259/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AlloSCT	Allogeneic Stem Cell Transplantation
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
AUC	Area Under the Curve
AUC _{ss}	AUC at Steady State
BSA	Body Surface Area
CD	Cluster of Differentiation
CI	Confidence Interval
CL/F	Apparent Total Clearance of Drug from Plasma After Oral Administration
C _{max}	Peak Plasma Concentration
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus Disease 2019
CR	Complete Response
CrCL	Creatinine Clearance
CT	Computer Tomography
CTCL	Cutaneous T-Cell Lymphoma
CYP	Cytochrome P450
DDI	Drug-Drug Interaction
DLT	Dose-Limiting Toxicity
DNA	Deoxyribonucleic Acid
DOR	Duration Of Response
DSC	Differential Scanning Calorimetry
ECG	Electrocardiogram
ECP	Extracorporeal Photopheresis
EORTC	European Organization for Research and Treatment of Cancer
FACT-G	Functional Assessment of Cancer-General
FDA	Food and Drug Administration
GC	Gas Chromatography
GRA	Global Response Assessment
HCC	Hepatocellular Carcinoma
HDAC	Histone Deacetylase
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
HR	Hazard Ratio
HrQoL	Health-related Quality of Life
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFN-α	Interferon Alpha
IR	Infrared

ITT	Intention-To-Treat
ITT-SS	Subgroup of Sézary Syndrome patients of the ITT Population
KF	Karl Fischer titration
LCT	Large Cell Transformation
LDPE	Low density polyethylene
MF	Mycosis Fungoides
MMRM	Mixed Models for Repeated Measures
MoA	Mechanism of action
MS	Mass Spectrometry
mSWAT	Modified Severity-Weighted Assessment Tool
NDMA	N-Nitrosodimethylamine
NK	Natural Killer
NHL	Non-Hodgkin's Lymphoma
NMBA	N-nitrosomethylbutylamine
NMR	Nuclear Magnetic Resonance
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-Free Survival
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetics
popPK	Population Pharmacokinetics
PR	Partial Response
PVC/PE/PVdC	Polyvinyl chloride/Polyethylene/Polyvinylidene chloride
QD	Once Daily (Quaque Die)
QoL	Quality of Life
QTc	Corrected QT Interval
QTcF	Corrected QT Interval by Fridericia
QTPP	Quality target product profile
RH	Relative Humidity
RR	Relative Risk
SAE	Serious Adverse Event
SD	Stable Disease
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SS	Sézary Syndrome
STAT	Signal Transducer and Activator of Transcription
t _{1/2}	Elimination Half-life
TGA	Thermo-Gravimetric Analysis
Th	T-helper
TSE	Transmissible Spongiform Encephalopathy
TSEB	Total Skin Electron Beam Therapy
TTNT	Time To Next Treatment
TTP	Time To Progression
TTSW	Time To Symptom Worsening
TTTE	Time To Development or Worsening of Skin Tumours

USA	United States of America
UV	Ultraviolet
VAS	Visual Analogue Scale
XRPD	X-Ray Powder Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant 4Sc AG submitted on 9 February 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Kinselby, through the centralised procedure and falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 December 2022.

Kinselby, was designated as an orphan medicinal product EU/3/23/2835 on 13 October 2023 in the following condition: Treatment of cutaneous T-cell lymphoma (CTCL).

The applicant applied for the following indication: treatment of patients with advanced stage mycosis fungoides (MF) and Sézary syndrome (SS) that have achieved at least stable disease with at least one prior systemic therapy or total skin electron beam therapy (TSEB).

1.2. Legal basis and dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0376/2017 on the granting of a product-specific waiver for all subsets of the paediatric population.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's request for consideration

1.5.1. New active Substance status

The applicant requested the active substance resminostat contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal

product previously authorised within the European Union.

1.6. Scientific Advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
28 January 2016	EMA/CHMP/SAWP/33911/2016	Hans Ovelgönne and Paolo Foggi
14 December 2017	EMA/CHMP/SAWP/796264/2017	Martin Mengel and Markku Pasanen
25 March 2021	EMA/SA/0000050948	Jan Sjöberg and Ole Weis Bjerrum

The scientific advice pertained to the following quality, non-clinical, and clinical aspects:

- The definition of the starting materials, the level of impurity in the drug substance and commercial scale;
- The proposed non-clinical program for marketing authorisation;
- The design of the phase 2 study 4SC-201-6-2015, in particular the proposed study population, the use and definition of PFS as primary endpoint, the proposed approach for assessing response based on the global response score for Mycosis fungoides / Sézary syndrome, the secondary endpoints and Quality of Life assessments, the proposed cardiac safety monitoring strategy, the statistical assumptions and analysis method.
- The proposed protocol change from event-triggered to time-point triggered, the planned reduction of the study population size, the introduction of simulations as statistical tool to compensate for missing patients and missing events.

Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Alexandre Moreau Co-Rapporteur: Elita Poplavska

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Lina Seibokiene

The application was received by the EMA on	09 February 2024
The procedure started on	29 February 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	21 May 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	03 June 2024

The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	27 June 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	20 December 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	03 February 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 February 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	27 February 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 March 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	09 April 2025
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	20 May 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Kinselby on	22 May 2025
The CHMP adopted a report on similarity of Kinselby with Adcetris, Poteligeo and Ledaga on (see Appendix on similarity)	22 May 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Kinselby is intended for the treatment of patients with advanced stage mycosis fungoides (MF) and Sézary syndrome (SS) that have achieved at least stable disease with at least one prior systemic therapy or total skin electron beam therapy (TSEB).

2.1.2. Epidemiology

Cutaneous T-cell lymphoma (CTCL) is a rare and heterogeneous subgroup of NHL, comprising 2% of lymphomas and approximately 83% of primary cutaneous lymphomas. The most common subtype of CTCL is MF, accounting for 62% of primary CTCL, whereas SS, an erythrodermic and leukemic CTCL variant, occurs less frequently and accounts for 3% of primary CTCL.

The incidence of CTCL has shown a 3-fold increase since the 1970s and appears to have stabilized in the last decade. In North America, the annual overall incidence of CTCL rates vary from 7.7 per million persons from 2001 to 2005 in the United States (US) [Korvgavkar et al., 2013] to 11.32 cases per million individuals per year from 1998 to 2010 in Canada [Ghazawi et al., 2017]. The overall incidence rate for CTCL in Europe was estimated to be 0.29 – 0.39 per 100,000 person-years [Dobos et al., 2020, Saunes et al., 2009].

Data from the Public Health England report in 2016 showed an overall incidence of MF of 3.7 per million persons per year in the United Kingdom (UK) [Kaufmann et al., 2020], which is comparable to the incidence data from the Netherlands (0.49 per 100,000 persons in 2019). In Finland, the prevalence of diagnosed MF rose from 2.04/100,000 to 5.38/100,000 from 1998 through 2016.

The incidence of SS in Europe is considerably lower, at about 0.075 per 100,000 persons with a prevalence of 0.36 per 100,000 [Ottervanger et al., 2021, Keto et al., 2021]. Only limited data are available from Asia, where the incidence of MF was reported to be 0.17 – 0.24 per 100,000 person-years and the prevalence was 0.39 – 0.72 per 100,000 person-years [Park et al., 2022].

2.1.3. Biologic features, aetiology and pathogenesis

An heterogeneous spectrum of genetic abnormalities have been identified in CTCL cells, mostly deletions and translocations that involve different chromosomes or chromosomal segments. One report identified dozens of driver mutations, including some that are predicted to affect chromatin; immune surveillance; RNA splicing; and signaling through MAPK, NFkB, PI3K, and T cell receptor. Gene expression profiles and microRNA profiling suggest that MF and SS may be separate entities with differing pathogenesis. Whole-exome sequencing analysis on samples from MF and SS found that, compared with normal controls, the tumour-suppressors MLL3 (KMT2C) and TP53 were the most frequently mutated genes. Point mutations and copy number gains of TNFRSF1B (which encodes tumour necrosis factor receptor 2 [TNFR2]), which is expressed in mature T cells and regulates signaling pathways related to T cell survival and proliferation, were also found with high frequency.

The neoplastic cells in MF and SS are thought to derive from skin tropic memory CD4+ T cells. Based on the studies demonstrating different T cell molecular profiles in MF and SS, it has been hypothesized that MF and SS originate from distinct memory T cell subsets. Malignant T cells from MF skin express the CCR4+/CLA+/CCR7-/L-selectin- immunophenotype of the skin resident memory T cells (TRM). In contrast, clonal malignant T cells from the blood of SS patients express the CCR4+/CCR7+/L-selectin+ phenotype of the skin-tropic central memory T cell (TCM). The expression of surface ligand CCR4 determines the T cell skin homing ability, while CCR7/L-selectin determine their ability to re-circulate between blood and lymph node.

The tumour microenvironment plays a role in the pathogenesis and progression of MF and SS. While in early stage MF, the T cell infiltrate is composed of both malignant CD4+ and reactive CD8+ T cells, with a dominant Th1 cytokine pattern; in advanced lesions and in Sezary syndrome, there is gradual increase in CD4+ T cells and a switch to a Th2-dominated microenvironment. This suggests a loss of CD8-mediated immunity and anti-tumour response with disease progression. The increased production Th2 cytokines interleukin (IL)-4, IL-5, and IL-13 is concurrent with a decrease in the expression of Th1 factors such as T cell-specific T-box transcription factor (T-bet), interferon gamma (IFN-γ), Stat4, and IL-12.

The cause of MF is unclear, but T cell receptor (TCR)/T cell activation, altered JAK-STAT signalling, RNA splicing abnormalities, and epigenetic alterations are common features.

The cause of most cases of SS remains unclear. Tumour cells in SS appear to be derived from skin-homing CD4-positive (CD4+) T cells or central memory T cells. Expression of cutaneous lymphocyte antigen (CLA) and high levels of the chemokine receptors CCR4 and CCR7 provide the T cells with the capacity to traffic bi-directionally into and out of the skin in response to the appropriate chemokines.

Impaired immunity in patients with SS has been attributed, at least partially, to the increased production of Th2 cytokines by the malignant clone; these cytokines antagonize Th1 immunity and lead to decreased production of interleukin (IL)-12 and interferon (IFN) gamma, which are critical for anti-tumour immunity. Activated T cells of patients with SS may also produce increased IL-10 and transforming growth factor (TGF)-beta, which can further impair cell-mediated immunity. In some cases, the malignant T cells can behave like regulatory T cells by manifesting FOXP3, increased CTLA4 expression, and enhanced production of IL-10 or TGF-beta, leading to suppression of normal T cell function. Increased production of IL-31 by the malignant T cells has been associated with worsening pruritus among patients with SS. Abnormalities of immune checkpoint molecules also contribute to depressed Th1 immunity and impaired cell-mediated immunity.

Defects of proapoptotic pathways have been identified, including decreased expression of Fas (CD95), which may be due to hypermethylation of the FAS promoter. Other apoptotic defects include increased expression of the apoptosis inhibitor cFLIP and tumour cell loss of TRAIL-receptor 2, leading to resistance to TRAIL.

Molecular abnormalities among individuals with SS/MF are heterogeneous. However, the pathophysiology appears to involve an intricate network of aberrant signaling through the T cell receptor, NFκB, CCR4/MAPK, and JAK/STAT pathways; aberrant tumour microenvironment, altered cell migration; and abnormal DNA damage response and chromatin structure. Upregulation of GATA3 and decreased expression of STAT4 transcription factors may account for the Th2 phenotype in many cases of SS. TP53 alterations appear to be the most common molecular abnormality in SS, but mutations and/or deletions in ZEB1, RB1, PTEN, DNMT3A, and CDKN1B and gain-of-function mutations in the JAK-STAT pathway are often found.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

MF and SS are typically diagnosed in adults with a median age of 55 – 60 years; the prevalence of these conditions is higher among men than in women (approximately 1.6:1, respectively).

For clinical staging of MF and SS, the revised tumour, node, metastasis and blood (TNMB) staging system should be used (Tables below). Apart from clinical stage, older age, large cell transformation and increased LDH values have been identified as independent unfavourable prognostic factors in MF.

MF is typically slow growing and often remains localized to the skin. In early stages of the disease (Stage I and IIA), MF is localized to the skin where it presents clinically as skin discomfort, patches and/or infiltrating plaques. In advanced stages of the disease (Stage IIB, III and IV), lymph nodes and visceral organs may become involved.

SS is defined by the presence of T4 erythroderma (ie, involvement of ≥ 80 percent body surface area) plus B2 involvement of peripheral blood (ie, ≥ 1000 Sézary cells/microL), and is staged based on the presence of nodal and/or visceral involvement, as follows:

Stage IVA1 – No significant lymph node or visceral involvement

Stage IVA2 – Lymph node involvement, but no visceral involvement

Stage IVB – Visceral involvement, with or without nodal involvement

Table 1 The clinical stages for MF and SS adapted from Olsen et al.2007

Clinical stages (5-year disease free survival [DSS] according to Olsen et al. [1]).

Stage	T	N	M	B	5-year DSS (%)
IA	1	0	0	0,1	98
IB	2	0	0	0,1	89
IIA	1,2	1,2	0	0,1	89
IIB	3	0–2	0	0,1	56
IIIA	4	0–2	0	0	54
IIIB	4	0–2	0	1	48
IVA1	1–4	0–2	0	2	41
IVA2	1–4	3	0	0–2	23
IVB	1–4	0–3	1	0–2	18

Table 2 TNMB stage for MF and SS

Table 2
TNMB staging for mycosis fungoides and Sézary syndrome [1].

<i>Skin</i>	
T1	Limited patches, papules, and/or plaques covering <10% of the skin surface. May further stratify into T1a (patch only) versus T1b (plaque +/- patch).
T2	Patches, papules, or plaques covering ≥10% of the skin surface. May further stratify into T2a (patch only) versus T2b (plaque +/- patch).
T3	One or more tumours (≥ 1-cm diameter)
T4	Confluence of erythema covering ≥80% body surface area
<i>Node</i>	
N0	No clinically abnormal peripheral lymph nodes; biopsy not required
N1	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or National Cancer Institute (NCI) LN ₀₋₂ N1a Clone negative N1b Clone positive
N2	Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN ₃ N2a Clone negative N2b Clone positive
N3	Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3–4 or NCI LN ₄ ; clone positive or negative
Nx	Clinically abnormal peripheral lymph nodes; no histologic confirmation
<i>Visceral</i>	
M0	No visceral organ involvement
M1	Visceral involvement (must have pathology confirmation and organ involved should be specified)
<i>Blood*</i>	
B0	Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sézary) cells
B0a	Clone negative
B0b	Clone positive
B1	Low blood tumour burden: >5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B2
B1a	Clone negative
B1b	Clone positive
B2	High blood tumour burden: ≥1000/μl Sézary cells with positive clone

SS is staged as T4 N2/3/x M0 B2.

* Blood staging for MF/SS is further defined as B0 = <250/ml of CD4⁺/CD26⁺ or CD4⁺/CD7⁺ cells, B1 = does not meet criteria for B0 or B2, and B2 = ≥1000/ml of CD4⁺/CD26⁺ or CD4⁺/CD7⁺ cells or other aberrant population of lymphocytes identified by flow cytometry [3,240].

Pruritus is the most common symptomatic complaint in patients with MF and may cause severe distress. Ulceration, with secondary infection of the tumours, is a common cause of morbidity [Dummer et al., 2021]. SS is a more aggressive disease and is characterized by the triad of erythroderma, generalized lymphadenopathy, and the presence of neoplastic T-cells (Sézary cells) in the skin, lymph nodes and peripheral blood [Willemze et al., 2019]. SS tends to progress more rapidly than MF and has a worse prognosis [Dummer et al., 2021]. Patients present with generalized erythroderma with exfoliation, edema and lichenification (often > 80% of body surface area). Lymphadenopathy and pruritus are common, alopecia, ectropium, mild palmoplantar keratoderma, and nail onychodystrophy may be present. Patients often shiver and complain of chills and general fatigue [Jawed et al., 2014].

Advanced-stage MF and SS are associated with a major symptom burden, including pruritus (the most prevalent and disturbing symptom), inability to sleep, cutaneous dysesthesia, pain, and disfigurement [Sampogna et al., 2009, Wright et al., 2013]. These symptoms may cause severe distress and adversely affect patients' quality of life (QoL) [Wilcox, 2014].

For patients with advanced stage disease (Stage IIB, III and IVA), the median survival has been estimated to be approximately 2 –5 years; for those with visceral involvement (Stage IVB), the median survival is less than 2 years [Agar et al., 2010]. A recent meta-analysis of stage-specific overall survival (OS), which included 6,279 patients with MF and SS, demonstrated a significant difference in the OS for Stage IB versus Stage IIB-IVB disease with a strong increase of the pooled hazard ratio (HR) from Stage IIB (HR 7.24; 95%

confidence interval (CI) = 5.91, 8.86) to Stage IVB (HR 39.21; CI = 19.73, 77.93). The pooled 5-year calculated OS rates ranged from 62.2% (best 67.9%, worst 56.0%) in Stage IIB to 23.3% (best 39.7%, worst 10%) in Stage IVB [Mourad & Gniadecki, 2020]. The same analysis showed that the development of skin tumours (Stage IIB), SS (Stage IVA1), nodal effacement (Stage IVA2), and metastatic spread (Stage IVB) had a powerful negative impact on survival [Mourad & Gniadecki, 2020].

2.1.5. Management

In addition to a correct diagnosis, appropriate staging is fundamental to choose the best therapeutic approach for each individual patient. It is of importance to keep in mind that, although appropriate treatment will be effective in most patients, therapy in MF/SS is generally palliative and should follow a step wise, stage-adapted approach giving priority to maintenance of quality of life.

Patients with early-stage disease (Stages IA, IB and IIA) are generally treated with skin-directed therapies (SDTs) such as topical steroids, psoralen photochemotherapy (psoralen + ultraviolet A light (UVA), PUVA), narrow band ultraviolet B light (UVB), localized and whole skin radiotherapy, and topical cytostatic agents such as chlormethine gel (mechlorethamine).

Systemic therapies are recommended in early-stage disease refractory to SDT and in advanced stages of MF and SS. Response rates and durations are typically short and time to next treatment may provide a useful surrogacy of real-life drug benefit.

In patients developing few infiltrated plaques of tumours (Stage IIB) low-dose local radiotherapy is recommended. Systemic treatment is indicated in patients with more infiltrated plaques and tumours; interferon- α (IFN- α) or retinoids (bexarotene) commonly combined with PUVA or other SDTs, or a combination of IFN- α and retinoids, or total skin electron beam (TSEB) therapy should be considered. For patients with SS or erythrodermic MF (i.e., leukemic forms of CTCL), European Society for Medical Oncology (ESMO) guidelines suggest extracorporeal photopheresis (ECP), either alone or in combination with other skin-directed or systemic therapies (Willemze et al 2018). Targeted therapies such as brentuximab vedotin (CD30 antibody) and mogamulizumab (CCR4 antibody) are approved for patients with relapsed or refractory CTCL, i.e., after at least one prior systemic therapy. Other agents such as the fusion toxin denileukin diftitox and the histone deacetylase (HDAC) inhibitors vorinostat and romidepsin have been approved in the US by the FDA for patients with relapsed and refractory CTCL but have not been approved for CTCL in Europe.

Treatment for SS is similar to that for advanced MF, with some distinctive exceptions, including the use of extracorporeal photopheresis (ECP) and low dose alemtuzumab, and the need for adjuvant treatment to control pruritus.

For refractory SS patients, alemtuzumab (off-label), systemic chemotherapy and allogeneic stem cell transplantation (alloSCT) are recommended. AlloSCT has been associated with treatment-free long-term remissions and holds a potential for cure in this disease in highly selected, younger patients, but is associated with considerable morbidity and non-relapse mortality. There remains therefore a need for additional treatment options.

2.2. About the product

Resminostat is an oral histone deacetylase (HDAC) inhibitor with particular activity against HDAC6. It is selective for class I, IIb and IV HDAC enzymes, with pronounced activity against HDAC6, and dose-

dependently induces acetylation of histone and non-histone proteins. HDACs are enzymes that catalyze the removal of acetyl groups from specific histone sites, in particular at promotor and enhancer regions of the DNA, which is an essential part of the regulation of cellular gene transcription. HDACs also regulate gene expression in an indirect fashion by mediating the acetylation of non-histone proteins such as DNA-binding proteins, transcription factors, signal transducers, and DNA repair and chaperone proteins. Histone modification is one of three major mechanisms of epigenetic modification which alters DNA accessibility, chromatin structure, and, subsequently, regulation of gene expression patterns, with significant relevance in a wide range of physiological and pathophysiological processes [Bondarev et al., 2021]. HDAC expression and activity are frequently increased in tumours, indicating a therapeutic potential of HDAC inhibitors in various hematological and solid malignancies [Li & Zhu 2014, Gryder et al., 2012, Ellis & Pili 2010].

The proposed indication for resminostat is treatment of patients with advanced stage mycosis fungoides (MF) and Sézary syndrome (SS) that have achieved at least stable disease with at least one prior systemic therapy or Total Skin Electron Beam therapy (TSEB).

The recommended dose of resminostat is 600 mg per day taken orally once daily. This corresponds to 3 tablets of 200 mg resminostat. Treatment is to be administered on Days 1 - 5 of a 14-day treatment cycle; the 5 days of treatment are followed by a 9-day treatment-free period. Treatment continues until disease progression or unacceptable toxicity.

2.3. Type of Application and aspects on development

This is an application for a standard MA.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablets containing 200 mg of resminostat. The product contains the salt resminostat mesilate.

Other ingredients are:

Tablet core: Lactose monohydrate, microcrystalline cellulose, povidone, crospovidone, magnesium stearate.

Film coating: Lactose monohydrate, hypromellose (E464), titanium dioxide (E171), triacetin, iron oxide (yellow) (E172).

The product was proposed to be available in blisters of PVC/PE/PVdC (thermoforming foil) and aluminium (heat sealing foil).

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of resminostat mesilate is (2E)-3-[1({4-[(dimethylamino)methyl]phenyl}sulfonyl)-1H-pyrrol-3-yl]-N-hydroxyprop-2-enamide methanesulfonate corresponding to the molecular formula $C_{17}H_{23}N_3O_7S_2$. It has a relative molecular mass of 445.51 g/mol and the following structure:

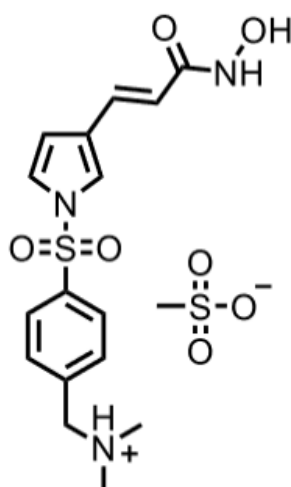


Figure 1: active substance structure

The chemical structure of resminostat was elucidated by a combination of elemental analysis, ^1H -NMR, ^{13}C -NMR, IR, MS, UV spectroscopy. The solid state properties of the active substance were measured by XRPD, TGA, DSC.

The active substance is a white-off-white to light brown powder, it exhibits pH dependent aqueous solubility, in the pH range of 1.2 - 4.5 the active substance is highly soluble while at pH 6.8 the solubility is low. It is non-hygroscopic.

Resminostat mesilate has a non-chiral molecular structure and polymorphism has not been observed.

2.4.2.2. Manufacture, characterisation and process controls

Resminostat mesilate is synthesized in five main steps using well defined starting materials with acceptable specifications. There is one optional recrystallisation step for one of the starting materials before commencing the synthetic process, which is referred to as step 0.

The description of the resminostat mesilate manufacturing process is acceptable, and the operating parameters and in-process controls are suitably presented and justified. The specifications and control methods for intermediate products, starting materials and reagents have been presented. One of the initially proposed starting materials RESI-05 was not considered acceptable and the applicant was requested to redefine the starting material to a precursor used in the synthesis, 4-BrTosCl. A major objection (MO) was

raised on this aspect; it was, thus appropriate for this material (4-BrTosCl) to be regarded as the starting material. The applicant redefined the starting material in line with the request and the MO was resolved.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. The product is intended for the treatment of a condition within the scope of the ICH S9 guideline and this is accounted for in the evaluation of potential impurities.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in LDPE bags which are placed into HDPE drums the primary packaging complies with Commission Regulation (EU) 10/2011, as amended.

2.4.2.3. Specification

The active substance specification includes tests for: appearance (visual), identity (IR, HPLC), assay (HPLC, ion-chromatography), impurities (HPLC), residual solvents (GC), water content (KF), sulfated ash (Ph. Eur.), particle size (laser light diffraction), microbiological quality (Ph. Eur.).



The active substance specification parameters and limits are in line with relevant guidelines and are acceptable. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. The impurity RESI-07 is a primary metabolite of the product and the limit is toxicologically appropriate.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data of nine commercial scale batches of the active substance from the proposed commercial manufacturing site are provided. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from six commercial batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 60 months under long term conditions (25 °C / 60% RH) and for up to six months under accelerated & intermediate conditions (40 °C / 75% RH & 30 °C / 65% RH) according to the ICH guidelines were provided.

The parameters tested are the same as for release. At long term and accelerated conditions all tested parameters were within the specifications and no trends were observed.

Photostability testing following the ICH guideline Q1B was performed on one batch. Results on stress conditions of acidic, basic, aqueous, oxidative and increased temperatures were also provide on one batch.

The photostability testing demonstrated the active substance is sensitive to light. During the forced degradation studies the active substance was relatively stable when exposed to aqueous, acidic conditions, and when exposed to elevated temperatures. Degradation was however observed upon exposure to basic and oxidative conditions.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months at the applicant's selected storage condition of 15-25°C and protected from light in the proposed container.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is a 200 mg film-coated tablet, it is yellow, approximately 5.5 × 10.2 mm, biconvex, round, with a bevelled edge.



The aim of development was to create a suitable immediate release oral dosage form for the intended oncology based indication. A quality target product profile (QTTP) was developed on this basis



Physical characteristics of the active substance which could impact the performance of the finished product are appropriately justified and controlled. The active substance demonstrates pH dependant solubility, and particle size limits for the active substance have been defined in the specification based on the development performed. No polymorphism of the active substance is reported and in addition it is non-hygroscopic.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. Functionality related characteristics are included for relevant excipients to ensure appropriate control.

The formulation for the product was developed in conjunction with the clinical programme, in early studies 100 mg and 200 mg gelatin capsules were used for administration to patients. Following this development of a tablet formulation was initiated. Initially two strengths of tablets were to be pursued, with 100 mg and 200 mg strength tablet formulations, however development of the 100 mg strength was discontinued. The development of the 200 mg strength aimed to identify a formulation with sufficient mechanical strength and stability, and a number of potential formulations were trialled. These investigations led to the final formulation which was named as formulation 4, this formulation is the same as was used in the final pivotal clinical study.

The information provided with respect to product dissolution and the selected method was initially not considered acceptable. An MO was raised which encompassed a number of dissolution related aspects, and as part of this the applicant was requested to select a dissolution limit which was in line with the performance of the batches used in the clinical studies. The applicant was also requested to outline the potential impact of the particle size of the active substance on the dissolution performance, and to provide data demonstrating that the dissolution profiles of proposed commercial batches were similar to the batches used in the clinical studies. In response to the MO the applicant demonstrated that the particle size of the active substance within the ranges that are manufactured do not impact the performance of the finished product. The

applicant also developed a new dissolution method aimed at reducing variability in early time-points which was considered acceptable and the applicant demonstrated that the dissolution performance of the clinical and commercial batches was similar. Following a further request the applicant also tightened the proposed dissolution limit proposed for use with the revised method to align with the dissolution performance of the clinical batches and the MO was resolved. Discriminatory power of the revised dissolution method was demonstrated as differences in profiles were observed with tablets of varying hardness.

The primary packaging is blisters of PVC/PE/PVdC (thermoforming foil) and aluminium (heat sealing foil). Where relevant the material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured at one manufacturing site and satisfactory information concerning GMP has been provided. The manufacturing process consists of eight main steps including dry blending, wet granulation, drying, main blending, final blending, compression, coating and packaging. The process is considered to be a standard process.



The steps that can have a significant impact on the processability of the intermediates and on the resulting properties of the finished product have been identified as critical process steps. These steps are controlled by the respective normal operating range (NOR) and proven acceptable range (PAR) and adequate in-process controls.

The manufacturing process is standard, and major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. Information on potential bulk hold times are presented and appropriately supported by stability data.

2.4.3.3. Product specification

The finished product release specifications includes appropriate tests for this kind of dosage form; description (visual), size (caliper), uniformity of mass (Ph. Eur.), disintegration (Ph. Eur.), uniformity of dosage units (Ph. Eur.), dissolution (HPLC), identification (IR, HPLC), assay (HPLC), impurities (HPLC), microbiological quality (Ph. Eur.).



The specification for the control of the finished product contains the typical tests for this type of pharmaceutical form and the limits have been adequately justified.

The limit for one specified impurity (RESI-07) exceeds the ICH Q3B qualification threshold, the proposed limit for this impurity is considered justified on the basis of toxicological data outlining that this impurity is a primary metabolite of the active substance. The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental

Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls. The information on the control of elemental impurities is satisfactory.

The product is within the scope of ICH S9 which is relevant to the assessment of potential mutagenic impurities such as nitrosamines. In the context of ICH S9 the potential limits for these impurities would be set in accordance with ICH Q3B. A risk assessment concerning the potential presence of nitrosamine impurities along with supportive testing data for the potential presence of NDMA and NMBA was provided. The risk assessment and testing data demonstrate that the relevant limits of ICH Q3B will not be exceeded. Considering the ICH S9 indication and the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results have been provided for batches manufactured across the clinical program including two commercial scale batches and two pilot scale batches produced at the proposed manufacturing site. The results confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from two commercial and one pilot scale batch of finished product stored for up to 60 months under long term conditions (25 °C / 60% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative of those proposed for marketing and were packed in the intended primary packaging.

Samples were tested for appearance, disintegration (Ph. Eur.), dissolution (HPLC), assay (HPLC), impurities (HPLC), and microbiological quality (Ph. Eur.). The analytical procedures used are stability indicating. The long term and accelerated data shows very little change over time and all results remain within the specifications.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is not sensitive to light.

Based on available stability data, the proposed shelf-life of 5 years without any special storage conditions are acceptable.

2.4.3.5. Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

In the course of the procedure two major objections concerning quality aspects were raised, these concerned the definition of one of the starting materials used for the manufacture of the active substance and the development and limit selected for the dissolution method proposed for the control of the finished product. To resolve these objections the applicant redefined the starting material as requested and developed a new dissolution method and demonstrated that the limit proposed using this method provided suitable assurance for quality control of the finished product.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there was one minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product,. This is put forward and agreed as recommendations for future quality development.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the proposed SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

1. The applicant is recommended to update the manufacturing process of one of the starting materials (4-BrTosCl). Timeline; prior to the next manufacture of an active substance batch which is expected to take place in 2026.

2.5. Non-clinical aspects

2.5.1. Introduction

Resminostat is an oral histone deacetylase (HDAC) inhibitor 6. Resminostat is selective for class I, IIb and IV HDAC enzymes, with pronounced activity against HDAC6, and dose-dependently induces acetylation of histone and non-histone proteins. The pharmacodynamic activity of resminostat has been characterised in a wide range of *in vitro* and *in vivo* studies, demonstrating both its mode of action as an inhibitor of human histone deacetylases and its anticancer activity in murine tumor models. The safety pharmacology of resminostat with respect to CNS, respiration and the cardiovascular system has been scrutinised in a large panel of assays (in agreement with ICH M3(R2)). Pharmacokinetic studies comprised: Plasma protein binding in various species, Metabolite profiling in hepatocytes from various species, metabolism in human liver microsomes and CYP enzymes, inhibition of CYP enzymes, [14C]-Pharmacokinetics, [14C]-Tissue distribution and metabolite profiling and a comprehensive *in vitro* study to assess the **drug-drug interaction** potential

of resminostat. The nonclinical toxicology program is developed in line with the ICH S9 Guideline and the corresponding Q&A document (2018).

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Resminostat inhibits class I, IIb and IV HDAC enzymes (HDAC1-11) *in vitro* with IC₅₀ in a nanomolar range. The most pronounced effect is on HDAC6 with IC₅₀ of 10 nM in biochemical assays. The resminostat metabolites M7, M10, M12 and M16 did not show significant inhibitory activity against the tested HDACs. In addition, HDAC inhibition, acetylation of α -tubulin and histone H3 were established.

The antiproliferative activity was further confirmed in the CTCL cell lines My-La CD4+ (Mycosis fungoides), HH (Mycosis fungoides) and HuT78 (Sézary syndrome), and it was comparable to vorinostat. The antiproliferative activity was observed in HH cells (EC₅₀ 0.74 μ M after 72 h). A broad spectrum of antiproliferative activity against 77 different human cancer cell lines was established, with GI₅₀ values of 0.05–5.81 μ M (mean GI₅₀: 2.03 μ M), and the selectivity towards specific tumour entities was not detected. For non-tumour cells PBMCs and human fetal lung myofibroblast line IMR90, IC₅₀ values of 8.7 and 10.9 μ M were observed, respectively.

In addition, anti-proliferative effects of resminostat mesilate and resminostat hydrochloride were also tested on panels of 22 and 26 different human cancer cell lines. Differences between those two resminostate salts were determined. Later, both substances were used in different studies *in vivo*. However, considering that in later developmental studies (including clinical studies) only resminostat mesylate was used, this issue was not pursued further.

Studies on cell cycle distribution revealed that treatment with resminostat increases cells in SubG1 phase (representing cells undergoing apoptosis) in all three cell lines HH, My-La CD4+ and HuT78, and the strongest effect is in HH cells. However, overall, resminostat induces only minor changes in cell cycle distribution. The reversibility of the cell cycle alterations was established in A549 cells.

The activity of resminostat in normal human dermal fibroblast (NHDF) and prostate endothelial cells (PrEC) during density-arrested, non-proliferating conditions was considerably lower. Under proliferating conditions, weak and non-cytotoxic growth inhibitory effects were observed for resminostat.

The provided results from study on the CTCL-associated genes STAT4 and STAT6 *in vitro* using HH and My-La CD4+ cell lines, showed a dose-dependent increase of STAT4 (Th1-type) expression and a reduced STAT6 (Th2-type) expression in both cell lines after treatment with resminostat. It suggests a reversion of Th2 to Th1 phenotype in CTCL cells by resminostat and support the involvement of other mechanisms in regulation of gene repression by resminostat.

Further studies were performed analysing resminostat's effect on T-cell and NK cell responses to cancer cells. Resminostat reduced the inducible expression of immunosuppressive enzymes IDO1 and ARG1 and the constitutive expression of IDO1. Also, resminostat increased the expression of various TAAs, MHC class I and II molecules and co-stimulatory molecules on tumour cells and upregulated the expression of activation marker and co-stimulatory molecules on pDCs and monocytes/macrophages. This supports the Applicant's suggestion that resminostat might enhance tumour immunogenicity and activate immune cells. Provided *in vitro* data also suggest that resminostat enhances cell lysis of tumour cells via NKG2D ligand interaction.

The data from cytotoxicity studies of resminostat in combination with rituximab (anti-CD20 antibody), suggest that resminostat may enhance the B-cell lymphoma's sensitivity towards rituximab-mediated cytotoxicity by NK cells. Another study, done with combination of resminostat and mogamulizumab, showed that HuT78 cells pre-treated with resminostat become more susceptible to NK cell-mediated lysis, in the presence of anti-chemokine receptor 4 (CCR4) opsonizing antibody mogamulizumab. However, considering that KINSELBY is indicated as monotherapy for the treatment of patients with advanced stage mycosis fungoides (MF) and Sézary syndrome (SS), these studies could be considered as supportive.

In vivo studies were conducted in different mouse orthotopic and subcutaneous xenograft tumour models. Resminostat hydrochloride or resminostat mesylate were administered orally (suggested clinical administration route) as suspensions of 4% Methocel or 20% PEG/4% Methocel to nude mice inoculated subcutaneously with tumour cells or PBS (different formulation). The effect of resminostat was evaluated based on treated to control (T/C) value to compare tumour volume changes before and after treatment.

The data are limited only to models of lung, colon, prostate, breast, and liver tumours. No histological or laboratory findings apart from tumour volume change are provided.

Results from different studies were inconsistent. E.g. resminostat at 120 mg in A549 xenograft model in two different studies [327-2006] and [328-2006] showed different *in vivo* effects in tumour growth. In addition, differences were observed using different resminostat salts in the same mouse model (HCl and mesylate, study [328-2006]). In most *in vivo* studies, resminostat HCl was used, while the form for authorisation is resminostat mesylate. Considering that further PK and safety studies were performed with resminostat mesylate, this issue was not pursued further.

Noteworthy, relevant data could have been obtained from *in vivo* cancer models other than CTLC (SS/MF). For example, *in vitro* data suggested that treatment with resminostat strongly increased the expression of CD56 and CD69 markers reflecting NK cell activation and demonstrated increased cytotoxicity against cancer cells as well as the possible protective role of ADCC mechanism when resminostat was used in combination with opsonizing antibodies; however, no NK-mediated effects of resminostat were assessed in the selected *in vivo* models to validate the *in vitro* effects, which is a shortcoming. It is also worth noting that the chosen rodent models (immunodeficient mice lacking either functional T/B cells or T/B/NK cells) inherently cannot validate the obtained *in vitro* data regarding the immune system-mediated mode of action (MoA) of resminostat (Th1/Th2 balance, T-cell mediated effects).

In all tumour models, repeated oral dosing of resminostat for up to 21 days was well tolerated with mild and transient body weight losses. In the A549 model, treatment with resminostat resulted in dose-related inhibition of tumour growth (15 to 120 mg/kg/dose). However, in an orthotopic xenograft model of human Hep3B2.1-7 hepatic carcinoma, only a trend in dose-dependent inhibition of tumour growth was observed; there was a large variability in the data.

In vivo, anti-tumour activity was observed in various human orthotopic and subcutaneous xenograft mouse tumour models at doses inducing mild to moderate and reversible body weight losses and changes in hematological parameters. Lethality was reported for single animals treated in some of the high-dose cohorts well exceeding anticipated human doses.

2.5.2.2. Secondary pharmacodynamic studies

To estimate resminostat target binding parameters such as affinity and selectivity, displacement assays with resminostat hydrochloride were performed using histamine H1 and H2 receptors, rat L-type Ca^{2+} -channels

(dihydropyridine site) and Na⁺-channels. Only weak inhibition of human TACE was detectable for resminostat hydrochloride with 26% inhibition at 10 µM. From these data, an IC₅₀ value of ≥ 50 µM is estimated. Since it is an inhibitor of HDAC 1 in low nanomolar concentrations (IC₅₀ value of 42.5 nM), it could be agreed that the weak inhibition of TACE with IC₅₀ ≥ 50 µM (> 100-fold above) is of low clinical relevance. At single concentrations of 10 µM resminostat hydrochloride, no significant inhibition of enzymatic activity was detected using human phosphodiesterase 3, human metalloproteinases 1 and 7 and human acetylcholine esterase, and no significant activity on ligand binding using histamine H1 and H2 receptors, rat L-type Ca²⁺-channels (dihydropyridine site) and Na⁺-channels.

2.5.2.3. Safety pharmacology programme

Safety pharmacology studies include analyses of resminostat (mesilate or hydrochloride) effects on central nervous system, respiratory and cardiovascular parameters.

No **CNS effects** were seen in sexually mature mice and rats following a single oral or intravenous dose at levels up to 30 mg/kg. Segregation and slightly decreased activity were observed both in mice and in rats up to 60 min after administration of 300 mg/kg. In both mice and rats, the dose of 30 mg/kg was considered the NOEL for behavior after oral or i.v. administration of resminostat. Following repeated dosing in mice and dogs (5-day repeat-dose studies in rats and dogs and 4-week and 3-month, repeat-dose studies in mice and dogs), CNS effects were not observed.

No treatment-related **respiratory effects** were observed in single-dose or repeated-dose toxicity studies in rats and dogs.

Noteworthy, the behavioural effects were evaluated exclusively in female rodents while the respiratory function only in males.

In vitro **hERG inhibition** was evaluated in CHO K1 cells of resminostat hydrochloride at concentrations up to 300 µM. Dose-dependent reduction of the hERG peak tail was detected: 7% (10 µM), 19% (30 µM), 33% (100 µM) and 54% (300 µM), with a calculated IC₅₀ of 245 µM. These data indicate a potential for QT prolongation. The QT prolongation properties are also evident from the *in vivo* assessment. The hERG patch clamp data indicate that the max concentration of resminostat free base on hERG at therapeutic doses (600 mg) would be 1.494 µM, which is 0.6% of the IC₅₀.

The **hemodynamic effects** of cumulative infusions of resminostat were analyzed in anesthetized guinea pigs. Effects on **cardiovascular parameters** were established after single and multiple oral administration of resminostat in conscious telemetered dogs. In both species, slight decreases in blood pressure were reported more frequently at higher doses. The slight to moderate increases in heart rate (early tachycardia) noted after treatment with resminostat were without dose-relationship, reversible and considered of minor toxicological relevance. Transient shortening of QT and QTc intervals was observed early (within 8.5 h) after treatment and transient prolongation of QT was observed late (within 13–22 h) after dosing, partially accompanied by decreased heart rates, but without correlation to plasma levels of resminostat. However, in clinical studies, there were a few clinically significant ECG findings, such as permanent atrial fibrillation or signs of a previous myocardial infarction, though no correlation between ΔQTcF and resminostat plasma concentrations was observed.

2.5.2.4. Pharmacodynamic drug interactions

The provided information on PD interactions includes the results from *in vitro* and *in vivo* combination studies of resminostat and drug substances used in FOLFIRI and FOLFOX chemotherapy regimens (5-FU, SN-38 (the active metabolite of irinotecan), and oxaliplatin, and sorafenib.

In vitro combination studies with 5-FU, SB-38 and oxaliplatin were performed in colon carcinoma cell lines, and combination indices (Cis) were calculated using Chou-Talalay method. The combinations with oxaliplatin at ED₅₀ in all three colon cancer cell lines indicate additive or antagonistic effects, while combinations with 5-FU or SN38 show synergistic activity *in vitro*.

In vivo combination studies with irinotecan or sorafenib were done in colon and liver xenograft mouse models. Resminostat at 140 mg/kg/d (p.o.), irinotecan at 50 mg/kg/week (i.p.) and their combination after 14 days of treatment inhibited HCT116 colon tumour growth significantly. The combination of resminostat and irinotecan at the same concentrations was more effective. The body weight losses were comparable between all treated groups; however, the mortalities were observed only in the combination group. The results from the study in orthotopic xenograft mouse model using Hep3B2.1-7 human liver tumour cells revealed higher effect of resminostat mesilate (15 or 40 mg/kg) and sorafenib (40 mg/kg) combination than monotherapy with either one component once daily for three weeks.

2.5.3. Pharmacokinetics

2.5.4. Toxicology

Toxicological evaluations aligned with ICH S9 (Nonclinical Evaluation for Anticancer Pharmaceutical, 2019). The non-clinical toxicity profile of oral resminostat was characterized in non-GLP and GLP-compliant single and repeat-dose toxicity studies (up to 3 months) in mice, rats and dogs. The mouse and dog were the toxicological species selected for pivotal toxicity studies based on suitable pharmacokinetic (PK) profiles and metabolism. In addition, *in vitro* and *in vivo* genotoxicity studies and an *in vitro* phototoxicity study were conducted. Genotoxicity was evaluated using the standard battery of genotoxicity studies according to ICH Guidance on genotoxicity testing and data interpretation for pharmaceuticals intended for human use [ICH S2.R1]. All pivotal repeat-dose toxicity studies and genotoxicity phototoxicity studies were conducted according to GLP. Nonclinical carcinogenicity or developmental and reproductive toxicity were not assessed as this is not required for pharmaceuticals intended for the treatment of patients with advanced cancer according to ICH S9. In addition, no studies on the embryo-fetal development have been conducted. In accordance with ICH S5 Detection of Toxicity to Reproduction for Human Pharmaceuticals (2020) [ICH S5], nonclinical developmental and reproductive toxicity (DART) studies may be waived if warranted by a thorough consideration of the targeted patient population, formulation and route of administration, relevant data on toxicity, pharmacodynamics, pharmacokinetics, and pharmacological similarity (class effects), or aspects of the general biology of the pharmaceutical target. Phototoxicity was tested using the 3T3 Neutral Red Uptake Phototoxicity Test for which an OECD guideline [Test No. 432] was available. This complies with ICH Guideline for photosafety evaluation of pharmaceuticals [ICH S10].

2.5.4.1. Single dose toxicity

Single dose toxicity of oral resminostat was evaluated in rats and dogs using gavage [393-2006, 384- 2006] or capsules [400-2006]. Single doses of 0 (vehicle control), 196, 392 or 784 mg/kg resminostat were administered orally (gavage) to rats [393-2006]. All animals (3 males and 3 females per dose) were sacrificed on Day 15. The dose of 196 mg/kg was considered the no observed adverse effect level (NOAEL), since only small and reversible hematological changes were detected at this dose level. Dogs were orally administered single doses of 78.4 or 157 mg/kg resminostat in one study [384-2006]. Only one animal per sex was observed in study 384-2006. Typically, acute toxicity studies involve multiple animals per sex (at least 3) to account for individual variability and ensure a more reliable toxicity evaluation. In another study [400-2006], dogs received single doses of 157 mg/kg resminostat orally via capsules, followed by a 2-week recovery phase.

The administration of single doses of resminostat to dogs by gavage showed dose-dependent effects, with adverse effects such as marked vomiting, slightly decreased activity, slightly softer feces observed, particularly at higher doses. Hematological changes were noted but transient, indicating reversible effects. Resminostat administered orally by capsule to beagle dogs at a single dose of 200 mg/kg also caused vomiting. Administration by capsule did not reduce the emetic effect, but the systemic exposure was lower than the plasma AUCs obtained after administration of the same dose by gavage. The 157 mg/kg dose was determined as the maximum tolerated dose (MTD), supported by AUC_{0-24h} values. Additionally, single-dose studies lacked GLP conditions, though they may be considered appropriate given support from GLP repeated-dose toxicity studies.

2.5.4.2. Repeat dose toxicity

Non-pivotal repeat-dose toxicity studies of oral resminostat were conducted in mice [13-2007, 313-2007, 1186], rats [394-2006, 22-2007] and dogs [449-2006, 21-2007] using oral gavage for administration. The majority of findings following repeated oral dosing of resminostat were observed in the hemolymphopoietic system, the gastrointestinal tract, and the male reproductive organs.

In mice [study 13-2007], resminostat doses ranged from 24 to 141 mg/kg/day, with a NOAEL of 24 mg/kg/day. This study demonstrated hematological, clinical chemistry, and histopathological changes in the hemolymphopoietic system, particularly at the highest dose (141 mg/kg). However, partial recovery was observed in hematological and histopathological changes. Study [313-2007] investigated all BYK compounds, with compound BYK 408740 (used in further pivotal repeat-dose toxicity studies) not showing the highest systemic exposure. The highest exposure was observed with BYK397957, while the lowest was with BYK406490. Non-pivotal studies in mice were not conducted under GLP conditions.

Rats were used in 2 non-pivotal repeat dose studies, with one study [22-2006] conducted under GLP conditions. In rats, resminostat doses ranged from 100 to 471 mg/kg/day. The NOAEL observed in rats was 118 mg/kg/day [394-2006] and 100 mg/kg/day [22-2007]. Mortality was observed at the dose of 471 mg/kg/day [394-2006]. Partially reversible hemolymphopoietic changes were mainly observed with resminostat doses starting from 200 mg/kg/day. Histopathological changes were found in the GI tract and reproductive system.

Dogs were used in 2 non-pivotal repeated dose studies, with one study [21-2007] conducted under GLP conditions. In dogs, resminostat doses ranged from 20 to 80 mg/kg/day. The NOAEL observed in dogs was 20 mg/kg/day, while the MTD ranged from 40 to 80 mg/kg/day in both studies. It is important to note that

ECG changes (increased QT and QTc) were observed at resminostat doses starting from 40 mg/kg/day. Mortality was observed at the dose of 80 mg/kg/day in both studies. Partially reversible changes in hematology and clinical biochemistry were observed at lower doses. Doses of 40 and 80 mg/kg showed histopathological changes mainly in the hemolymphopoietic, reproductive, and digestive systems. In non-pivotal studies, rats were found to be less exposed to resminostat following oral administration. Mouse and dog have comparable steady state AUCs based on dose per body surface area, appropriate pharmacokinetic profiles and metabolism.

Pivotal repeat dose studies were conducted using two different species (mice and dogs). All four studies were conducted under GLP conditions. According to the Guideline on repeated dose toxicity (18 March 2010 CPMP/SWP/1042/99 Rev 1 Corr*), repeated dose toxicity studies should be carried out in conformity with the provisions relating to good laboratory practice (GLP) laid down by Council Directives 87/18/EEC and 88/320/EEC. Therefore, this requirement is fully met.

In mice, resminostat doses ranged from 17.5 to 140 mg/kg/day. The NOAEL in a shorter duration (28-days) study [344-2007] was 35 mg/kg/day, while in the 3-month duration study, the NOAEL was established at 70 mg/kg/day. The MTD in study [344-2007] was indicated as 140 mg/kg/day, and mortality was observed at this dose. The studies showed dose related decreases in hematological parameters at all doses (up to ~60% decrease in leukocytes and neutrophils, up to ~36% decrease in platelets at dose of 70 mg/kg). Decreases in lymphocytes were seen at 70 mg/kg dose in 13 weeks study, but at all doses in the 28-day study. All effects were usually almost reversible during the recovery period. Hematology parameters did not recover only at the highest dose (140 mg/kg). Also, the histopathological changes in the hemolymphopoietic and reproductive systems were significant only at the highest resminostat dose. Histopathological changes in the hemolymphopoietic system at all doses included lymphoid depletion of the thymus and lymph nodes, increased severity of extramedullary hemopoiesis of the spleen.

Reproductive toxicities in male animals included decreased testicular weights, germ cell depletion and decreased spermatozoa in the testes and epididymides at a dose of 140 mg/kg/day. These changes were not completely reversible after the recovery period (germ cell depletion, spermatozoa reduction, intratubular degenerated germ cells were reported). In female mice, changes in the ovaries (follicular atrophy), were detected in all dose groups, and atrophy of the uterus and vagina, reduced (relative and absolute) weight of the ovaries were detected at 140 mg/kg/day. After the recovery period, only animals in the 140 mg/kg/day group still showed findings in the ovaries; in all other groups these changes were completely reversible within 14 days.

No findings in the reproductive organs in male and female animals and no histopathological changes in the hemolymphopoietic system are detected in the 13 weeks study in mice.

In dogs, resminostat doses varied from 10 to 40 mg/kg/day across two separate studies. When considering the toxicity objectives and severity, the effects of repeated resminostat doses at 10 and 20 mg/kg/day showed similar outcomes between the 28-Day and 3-month studies. In the 28-days study increased toxicity manifested as vomiting, decreased activity, decreased food intake and weight loss, decreased muscle tone and/or tremor were observed at the high dose 40 mg/kg/day. The doses of 10 mg and 20 mg kg/day were well tolerated. Reduced leukocytes (20-70% at the end of the treatment period), red blood cells (0 to 35% lower at the end of the treatment period), reticulocytes (65-100% on Day 15) and thrombocytes were observed at all dose levels. These changes were reversible during the recovery period. Dose-related changes in clinical chemistry parameters such as increases in total bilirubin (up to 4-fold), decreases in AST (up to 10%), decreases in ALT (up to 45%) and decreases in electrolytes (up to 15% decrease in potassium in females) were observed. In addition, lymphoid depletion in thymus at all doses, in lymph nodes at 20-40

mg/kg/day and in spleen at 40 mg/kg/day was observed. Lymphoid depletion in the thymus was still observed after the recovery period.

In all dose groups, germ cell depletion in the testes, oligospermia in the epididymides and atrophy of the prostate were observed in males and changes in the ovaries, uterus, and mammary glands in females. Changes in the male genital tract were seen even after the recovery period.

An increased incidence of duodenal crypt dilatation, with necrotic debris in the lumen, was seen in males at 10 mg/kg/day and in both sexes at the doses of 20 and 40 mg/kg/day. These changes were completely reversible.

No treatment-related changes were observed in ECG, ophthalmoscopy and in coagulation and urinary parameters.

No treatment-related deaths were observed during the 3-month study. Slight signs of systemic toxicity were observed at a dose of 5 mg resminostat/kg b.w./day, including salivation, emesis, a pale gingiva and head tremor, changes in biochemical parameters and a decreased liver weight. Histopathological examination revealed changes in the testes (spermiogenesis disorders, atrophy of the germinal epithelium), epididymides (oligo- /aspermia), prostate (atrophy), liver (increased severity of brownish pigment in Kupffer cells), uterus (inactivation of the uterine mucosa), mammary gland (inactivation) and a slight decrease in the severity of the lymphatic activation (lymphoid hyperplasia) in the lymph nodes and the intestines of males and/or females.

At the dose of 10 mg /kg b.w./day, additional changes were observed in the form of changes in haematological parameters (reduced lymphocytes (up to 40%), leukocytes (up to 60%), erythrocytes (up to 12%), increased reticulocytes (up to 97%)) and reduced testicular and/or prostate weights.

Animals in the 20 mg/kg b.w./day group showed changes in the form of a reduced body weight and pronounced changes in the testes (disturbance of the spermiogenesis (reduced number, viability and motility of spermatids)). At the end of the 12-week recovery period (limited to the high-dose group) most of the changes observed during the treatment period had completely recovered. However, the sperm analysis still showed a slight reduction in sperm count, viability and motility of spermatids in the previously high-dosed males.

In repeat-dose toxicity studies in dogs, slightly increased heart rate (HR), shortened RR- and PR-intervals and prolonged QT- and QTc-intervals with maximum increases of up to 60 ms were reported in individual animals, particularly at higher dose levels. Changes in heart rate and QT-interval are considered as relevant for human and are proposed to be included as a warning in the SmPC.

The variance in determining the NOAEL (28-Day tox: 10 mg/kg/day; 3-Month tox: > 20 mg/kg/day) can be attributed to the extended recovery period in the 3-Month study, resulting in complete restoration of all affected organ systems except for male reproductive systems, aligning with findings from the 28-Day repeat-dose study. In the 28-Day study, the intermediate dose of 20 mg/kg/day was formally recognized as the MTD. The MTD was established based on dose-limiting toxicities observed at the high dose level of 40 mg/kg/day, which was not evaluated in the 3-month study.

The design, duration, methodology, and the number of pivotal repeated-dose studies as well as the number of animals tested are sufficient to characterize the toxicological profile of resminostat. The selection of three main animal species (one non-rodent) is justified. Toxicokinetics (TK) of resminostat was evaluated in all pivotal repeated dose toxicity studies.

2.5.4.3. Genotoxicity

The genotoxic potential of resminostat was evaluated *in vitro* analyzing gene mutations in bacteria (Ames test) and chromosome aberrations in Chinese hamster V79 cells and *in vivo* using the micronucleus test in mice after oral administration.

Positive findings in either *in vitro* or *in vivo* tests: The Ames assay demonstrated a slight mutagenic potential of resminostat, particularly in strain TA100, indicating the ability to induce gene mutations. Additionally, the *in vitro* study using Chinese hamster V79 D3 cells showed that resminostat induced chromosomal aberrations, supporting its clastogenic potential. In the *in vivo* micronucleus tests in mice, the first study indicated a potential chromosome-breaking effect of resminostat, especially in female animals at certain doses, while the second study using flow cytometry suggested non-mutagenicity. The findings from the Ames assay suggest that resminostat induces gene mutations by base pair changes, while the *in vitro* study on V79 D3 cells indicates its ability to cause chromosomal aberrations. These mechanisms contribute to its genotoxic potential observed across different test systems. Although a specific threshold was not identified, the Ames assay results suggest that mutagenicity occurs at higher doses of resminostat. However, the doses of 40 and 125 mg/kg resminostat have not been applied during the first and were negative in the second mouse micronucleus test.

Resminostat is considered potentially genotoxic based on the positive findings in the Ames assay and the induction of chromosomal aberrations in V79 cells. Considering the plasma exposures in mice and humans, the risk for genotoxic effects in humans is deemed low, particularly at lower doses

2.5.4.4. Carcinogenicity

No carcinogenicity studies were conducted with resminostat as this is not required for pharmaceuticals intended to treat patients with advanced cancer (ICH S9 Nonclinical Evaluation for Anticancer Pharmaceuticals, 2010). The Scientific Advice of 25 January 2018 concluded that "CHMP does not agree that the proposed target population of 'patients with stage IIB–IVB MF/SS' as a whole falls under the scope of ICH S9, given the variable overall survival of the patient population, and that treatment options providing benefit are available. To enable assessment on the applicability of ICH S9 specifically for the second- and later-line population the Applicant needs to provide specific information for this setting."

The Applicant provided the more detailed information on the disease in different populations and disease stages. It can agree that the proposed indication 'advanced stage mycosis fungoides (MF) and Sézary syndrome (SS)' falls under the scope of ICH S9 and no carcinogenicity studies are required.

2.5.4.5. Reproductive and developmental toxicity

No fertility, early embryonic, or pre- and postnatal studies have been conducted with resminostat, as this is not required for pharmaceuticals intended for the treatment of patients with advanced cancer [ICH S9]. In addition, no studies have been conducted on embryo-fetal development because detrimental effects on embryo-fetal development have been described as a class effect of HDAC inhibitors. Therefore, it is assumed that resminostat is teratogenic. Furthermore, male and female germ cells have been identified as sites of toxicity of resminostat in repeat-dose toxicity studies.

2.5.4.6. Toxicokinetic data

The provided TK data includes information on the doses administered to mice, rats, and dogs and the resulting plasma concentrations measured in terms of AUC and $C_{\max}$ (peak plasma concentration). These parameters are essential for evaluating the pharmacokinetics and safety profile of resminostat. Based on the provided data, it appears that resminostat has been extensively studied in various animal models, with doses ranging from 5 mg/kg to 471 mg/kg in rats, 10 mg/kg to 140 mg/kg in mice, and 5 mg/kg to 80 mg/kg in dogs. The corresponding plasma concentrations (AUC and $C_{\max}$) were also measured.

The safety margin based on $F_{u,p}$ was calculated in mice [28193] and dogs [28194] over a duration of 3 months, as required by the duration of clinical use to support marketing according to the EMA/CPMP/ICH/286/1995 guidelines.

Based on the *in vitro* fraction unbound in plasma for mouse, dog and human, the obtained safety factors of 1.45 - 5.66 indicate that the unbound resminostat levels of the rodent and non-rodent species selected for toxicity assessments are above plasma exposure levels observed in human and thus considered appropriate for evaluation of adverse effects. Additionally, when comparing the *in vivo* unbound plasma fraction in humans to exposures derived from *in vitro* data in mice and dogs, safety factors indicate comparable exposures across species for $C_{\max}$, except for a slightly higher AUC_{0-24} in human males than mice.

2.5.4.7. Local Tolerance

Dedicated local tolerance studies have not been conducted using resminostat. Resminostat was developed as a solid formulation intended for oral administrations (film-coated tablet formulation) and does not have the potential to come into contact with different sites of the human body following normal clinical use or after unintentional administration. Local tolerance was assessed as part of the repeat-dose toxicity studies.

2.5.4.8. Other toxicity studies

According to ICH guidelines, general toxicology studies suffice to evaluate immunotoxic potential for most anticancer pharmaceuticals, with this aspect incorporated into repeated dose toxicity studies. Separate evaluation for metabolites identified in humans is generally unnecessary for advanced cancer patients. Impurity BYK404186 (RESI-07) is justified as a metabolite of resminostat. *In vitro* phototoxicity study of resminostat shows concentration-dependent cytotoxicity but falls within acceptable ranges according to OECD guidelines. UV spectrum analysis indicates no absorption of light within the natural sunlight range, suggesting no phototoxic potential. Therefore, resminostat does not require further photosafety evaluations.

2.5.5. Ecotoxicity/environmental risk assessment

Based on the data provided, the logarithm of the partition coefficient ($\log K_{ow}$) of resminostat mesilate fell within the acceptable range for each pH value, demonstrating favorable characteristics of the substance. Importantly, the $\log K_{ow}$ values remained significantly below the threshold level of $\log K_{ow} > 4.5$ for all tested pH values. This indicates that resminostat mesilate is unlikely to persist, bioaccumulate, or exert toxicity in the environment, as per the EU technical guidance document (TGD) referencing OSPAR.

Furthermore, the calculation of PEC_{surface water} (PEC_{sw}) using the refined F_{pen} value yielded a PEC_{sw}

below the threshold of concern (0.01 µg/L). Given that no other environmental concerns were identified, it is concluded that the medicinal product is unlikely to pose a significant risk to the environment when used as directed. Therefore, based on these findings, the environmental impact of the medicinal product is deemed negligible.

Summary of main study results

Substance (INN/Invented Name): Resminostat mesilate			
CAS-number (if available): 934004-03-2			
PBT screening		Result	Conclusion
Bioaccumulation potential- log K_{ow}	shake flask method	pH 5 = log K_{ow} (-0.85) pH 7 = log K_{ow} (0.74) pH 9 = log K_{ow} (-0.22)	Potential PBT: (N)
PBT-assessment			
Parameter	Result relevant for conclusion		Conclusion
Bioaccumulation	log K_{ow}	N.A.	not B
	BCF	N.A.	not B
Persistence	DT50 or ready biodegradability	N.A.	not P
Toxicity	NOEC or CMR	N.A.	not T
PBT-statement:	The compound is considered to be not PBT, nor vPvB		
Phase I			
Calculation	Value	Unit	Conclusion
PEC _{sw} , refined	0,00807	µg/L	≥ 0.01 threshold: (N)
Other concerns (e.g. chemical class)	N.A.		(N)

2.5.6. Discussion on non-clinical aspects

The preclinical development of resminostat mesilate was conducted according to guidelines ICH S9 for

nonclinical evaluation for anticancer pharmaceuticals and ICH M3.R2 on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals.

Overall, the **PD results** indicate that resminostat is a potent inhibitor of class I, IIb and IV HDAC enzymes (HDAC1-11) with pronounced activity against HDAC6 at nanomolar concentrations (IC₅₀ 10 nM). In a dose-dependent manner, resminostat induces acetylation of histone and non-histone proteins, which results in the transcriptional activation and/or repression of genes that mediate pleiotropic effects such as pathway modulation, cell growth arrest, differentiation, and apoptosis, including CTCL.

The mechanism of action of resminostat was established in several biochemical and cellular assays.

Specifically, in CTCL cell lines (three cell lines were used in the *in vitro* studies: My-La CD4+ (Mycosis fungoides, stage II), HH (Mycosis fungoides, stage IVa) and HuT78 (Sézary syndrome)), resminostat treatment: increased total protein and histone acetylation; showed anti-proliferative and pro-apoptotic activity comparable to the reference HDAC inhibitor vorinostat, with EC₅₀ values between 0.7 and 1.2 µM; the sensitivity of resminostat against the 3 CTCL cell lines was different with HH cells demonstrating the highest sensitivity; resulted in a dose-dependent upregulation of genes associated with the Th1 phenotype (protective) and reduced expression of genes associated with the Th2 phenotype; sustainably decrease IL 31 mRNA and protein levels in My La CD4+ cells (MF) suggesting a potential for resminostat to reduce itching (pruritus) in CTCL patients.

Antitumor effects were further increased in combination with the opsonizing antibodies mogamulizumab (anti-CCR4) approved for the treatment of CTCL (FDA) and IPH4102 (anti-KIR3DL2) in development for CTCL. Overall, the increased anti-tumoral immune responses observed upon treatment with resminostat may also contribute to the clearance of CTCL cells in patients.

Analyses of resminostat's anti-proliferative activity in a large panel of human cancer cell lines did not reveal selectivity for certain cancer cells yet demonstrated differential sensitivity of the cell lines to resminostat treatment. The observed effects of resminostat were dose-dependent and long-lasting.

Overall, the presented studies are of sufficient quality to draw the conclusions of the mechanism of action of resminostat. In most cases, the statistical significance of the obtained effect was convincingly demonstrated. None of the studies had GLP status, however, it is generally acceptable that proof-of principle in-house studies are performed in a non-GLP setting, nor the GLP status is required by relevant guidelines.

In vivo, resminostat showed a broad range of antitumor activity in various orthotopic and subcutaneous xenograft mouse tumor models. However, data on the resminostat's activity *in vivo* are limited to lung, colon, prostate, breast, and liver tumours.

Safety pharmacology studies compliant with the ICH S7A and S7B guidelines were performed in both *in vitro* and *in vivo* test systems to assess the potential cardiovascular, respiratory, and neurobehavioral effects of resminostat after single and multiple p/o and/or i/v dose administration. The only exceptions were *in vitro* hERG assay and hemodynamic effect evaluation in guinea pigs. Safety pharmacology *in vivo* studies of resminostat were performed in mouse, rat, guinea pig, and dog. Taken together, the results did not identify a significant impact on respiratory system function (in male rats at doses up to 800 mg/kg, NOEL) or central nervous system functions (in female mice and rats NOEL was set to doses (tested both, i/v and p/o) up to 30 mg/kg, while doses of 300 mg/kg resulted in decreased activity and segregation of animals of both species for up to 1 h). Noteworthy, the behavioural effects were evaluated exclusively in female rodents while the respiratory function – in males only leaving no possibility to compare these effects between both sexes of animals.

There were no safety pharmacology findings of concern following single doses, except the transient prolongation of QT, partially accompanied by decreased heart rates, but without correlation to plasma levels of resminostat. The hemodynamic effects of cumulative infusions of resminostat were analyzed in anaesthetized guinea pigs (non-GLP study). The effects on cardiovascular parameters after single and multiple oral administration of resminostat in conscious telemetered dogs (both sexes). In both species, slight decreases of blood pressure were reported more frequently at higher doses. The slight to moderate increases in heart rate (early tachycardia) were noted after treatment with resminostat – this effect was not related to the resminostat dose, it was reversible and considered of minor clinical relevance.

Transient shortening of QT and QTc intervals was observed early (within 8.5 h) after treatment and transient prolongation of QT was observed late (within 13–22 h) after dosing in dogs, partially accompanied by decreased heart rates, but without correlation to plasma levels of resminostat. However, in clinical studies, there were a few clinically significant ECG findings, such as permanent atrial fibrillation or signs of a previous myocardial infarction, though no correlation between Δ QTcF and resminostat plasma concentrations was observed. The calculated IC₅₀ in the hERG inhibition assay is 245 μ M, which indicates a potential for QT prolongation. The validation of the non-GLP hERG assay results is questionable. However, considering that dedicated safety pharmacology studies are not warranted as per ICH S9 for this indication, this issue was not pursued. Moreover, the *in vitro* observed QT prolongation is consistent with the observed *in vivo* effects. It is known that HDAC inhibitors as a class effect induce QT interval prolongation, and this was also demonstrated for resminostat.

In conclusion, none of the risks evaluated in the safety pharmacology program were identified as clinically relevant (considering the doses chosen for administration in humans), which can be agreed.

No in-depth screening for off-target effects of resminostat was performed to provide information on secondary effects via binding to a selection of extracellular receptors or ion channels. Since the obtained results from toxicology studies and clinical trials have shown that there is no indication for secondary interactions with main receptor systems, the performed study portfolio is deemed satisfactory and the choice of omitting further in-depth non-clinical secondary PD studies is appropriate.

The applicant evaluated and reported on the additive to synergistic effects of resminostat mesilate in combination with irinotecan and 5-FU in three CRC cell lines. Gene expression data provided mechanistic insights and suggested that resminostat has the potential for re-sensitization of resistant cells to treatment with 5-FU. *In vivo* combination with irinotecan was further confirmed also in a colon cancer xenograft mouse model showing the potential to almost completely inhibition of tumor growth. A similar effect was demonstrated by combining resminostat mesilate and kinase inhibitor sorafenib in orthotopic xenograft mouse model of human liver cancer. Thus, there is sufficient evidence provided to acknowledge the synergistic anticancer effect of the drug combination. The Applicant has not further discussed how the obtained data could be extrapolated to the CTCL treatment options in humans.

Since no appropriate animal models have been used for resminostat anti-CTCL efficacy testing, it is agreed that the antitumor activity of resminostat in the proposed indication CTCL was based on the obtained *in vitro* analyses only and the presented *in vivo* data can only be used for consideration. Noteworthy, the human cancer cell lines chosen for xenografting were among those that were used for the evaluation of MoA of resminostat *in vitro* and the obtained *in vivo* study results generally were in agreement with the *in vitro* data – tumour development was suppressed in a dose-dependent manner in experimental animals, although mechanistically the responsible MoA for resminostat was not further elaborated in these *in vivo* studies. For example, *in vitro* data suggested that treatment with resminostat strongly increased the expression of CD56 and CD69 markers reflecting NK cell activation and demonstrated increased cytotoxicity against cancer cells

as well as the possible protective role of ADCC mechanism when resminostat was used in combination with opsonizing antibodies; however, no NK-mediated effects of resminostat were assessed in the selected *in vivo* models to validate the *in vitro* effects, which is a shortcoming. Moreover, the chosen rodent models (immunodeficient mice lacking either functional T/B cells or T/B/NK cells) inherently cannot validate the obtained *in vitro* data regarding the immune system-mediated MoA of resminostat (Th1/Th2 balance, T-cell mediated effects).

Another issue identified was the use of exclusively female mice, omitting males in the *in vivo* studies. Considering the known differences in CTCL prevalence between males and females (more frequent in males), it would have been of even higher importance to assess sex as an independent variable in the *in vivo* studies evaluating resminostat anticancer efficacy. Another fact that adds to this issue is the identified differences in systemic exposure of the resminostat (data from the performed safety pharmacology and PK studies). Despite the fact that non-CTCL animal models were used for resminostat testing, addressing sex as an independent variable would have been of value for translating the *in vivo* results to clinics.

In addition, the presented *in vivo* studies demonstrated limited repeatability of the results and/or lack of statistical power.

Finally, the *in vitro* hERG assay resulted in QT prolongation, which is consistent with the observed *in vivo* effects. It is known that HDAC inhibitors, as a class effect, induce QT interval prolongation, and this was also demonstrated for resminostat.

A comprehensive **PK program** was conducted to evaluate the pharmacokinetics, absorption, distribution, metabolism, and excretion properties for resminostat in mouse, rat, dog and monkey. Species and strains used for pharmacokinetic evaluation were the same as for pharmacology and toxicology evaluations and identical resminostat formulations were administered.

Analytical methods. Plasma concentrations of resminostat free base were determined by HPLC-MS/MS methods that were developed and validated for mouse, rat, dog and human plasma. For monkey plasma, a qualified (unvalidated) HPLC-MS/MS method was applied, which was shown to be reliable to produce credible results. Adequate calibration ranges and synchronous internal standards were chosen for all test species allowing proper comparison of the obtained results. For toxicokinetic analyses, plasma samples of the pivotal (GLP-compliant) repeat dose toxicity studies of oral resminostat mesilate were analyzed using the validated methods only. The radiochemical purity of radiolabeled [¹⁴C]-resminostat mesilate was sufficient; methods of appropriate sensitivity were chosen for the detection of radiolabeled resminostat in biological samples.

Absorption. The presented *in vitro* data with human colorectal adenocarcinoma cell (Caco-2 cell) monolayers suggests intermediate moderate-to-high permeability of resminostat without major permeability limitation in intestinal absorption. The efflux ratio was defined as 1.45 indicating no active transport of resminostat in the Caco-2 cells. Appropriate study design was applied with all the controls necessary for the assessment.

In vivo resminostat as single dose was administered either orally (mouse, rat, dog, monkey) or intravenously (dog, monkey) only in male animals, which is a shortcoming. Resminostat after oral administration was rapidly and almost completely absorbed in mouse (92%) and dog (82%) and well absorbed in rat (up to 72%, only if high dose of 150 mg/kg was used) with time of occurrence of maximum plasma concentration (t_{max}) values in the range of 0.6 – 2.0 h. Oral bioavailability was determined in dog (67%) and monkey (89%).

Data from pivotal GLP-compliant 3-month oral repeat-dose toxicity studies showed that systemic exposure to resminostat is dose-related and linear in both males and females in mouse and dog. However, in mouse

systemic exposure was higher in female than in male animals at all dose levels. The mean plasma elimination half-life of resminostat ranged from 0.83 – 3.47 h. No accumulation of resminostat was reported. In dog, the mean plasma elimination half-life of resminostat ranged from 0.98 - 1.21 h. Accumulation factors of 1.06 – 1.24 for males and 1.28 – 1.79 for females were reported across all dose groups. No gender differences were noted in rats.

Distribution. After administration of radiolabeled resminostat to mouse and rat, radioactivity was rapidly and widely distributed to various tissues with a similar pattern of distribution. In order of declining exposure, large intestine, followed by liver, kidneys and adrenals were most exposed to radioactivity after oral administration while large intestine, followed by liver, kidneys and spleen were most exposed after intravenous administration of [14C]-resminostat.

In partially pigmented Lister Hooded rat after oral administration, [14C]-resminostat showed highest exposures in the uveal tract/retina, liver, stomach mucosa, bile ducts, skin (pigmented) and preputial gland. Exposure to drug-related radioactivity in the melanin-rich uveal tract/retina of partially pigmented rats was higher than in any other tissue, suggesting that melanin binding is prevalent. Low levels of radioactivity were detected in the brain.

No distinct retention of drug-related material was observed in any organ or tissue as assessed for up to 48 h (mouse) and 168 h (rat) post-dose.

Distribution of resminostat was assessed only in males, which is a shortcoming.

A mean plasma protein binding of 85.0% was determined for resminostat mesilate in human after single oral doses during a clinical mass balance study, with a mean fraction unbound of 15.0%. *In vitro*, plasma protein binding was observed in mouse, rat, dog, and human plasma with around 30% of unbound fraction in mouse, rat, and dog and 6.7% in human. The mean human blood/plasma-partitioning coefficient was 1.03 (10 min incubation) and 0.954 (60 min incubation).

The absence of placental and milk transfer data of resminostat is regarded dispensable given the envisaged patient population.

Metabolism. *In vitro* data from liver microsomes and hepatocytes model suggested a low proclivity of resminostat to hepatic biotransformation in the non-clinical species and human – resminostat showed low to moderate clearance. However, *in vivo* physiologically scaled plasma clearances was shown to be higher than *in vitro* in dog (2.2 L/h × kg versus 0.71 L/h × kg *in vitro*), monkey (3.5 L/h × kg versus 0.55 L/h × kg *in vitro*), and human (0.72 L/h × kg versus 0.29 L/h × kg *in vitro*). Resminostat was rapidly and extensively metabolized *in vivo*, thus it can be concluded that the used standard *in vitro* models of metabolic stability were not predictive for the *in vivo* behavior of resminostat.

Incubations with recombinant human CYP enzymes revealed CYP2C8 as the major CYP enzyme for metabolic degradation of resminostat and several metabolites formed by almost all CYP enzymes tested. Resminostat is metabolized predominantly at the hydroxamic acid group, leading to formation of various metabolites. In addition to hydroxamic acid modifications, direct glucuronidation of the parent was identified to be a metabolic pathway of resminostat in the tested species.

Overall, the *in vitro* and *in vivo* results from studies in mouse, rat, dog, monkey and human suggest several metabolic pathways for resminostat. The major metabolites observed at ≥ 5% in non-clinical *in vivo* studies in plasma, urine and/or feces included M4-gluc, M7, M11, M12, M15 and M16 and the taurine conjugates M30 and M33. In human, the major metabolites identified at ≥ 5% were M14-gluc, M15, M4-gluc, M16 and M39. All of these metabolites as well as their proposed pathway-related intermediate products were also detected

in experimental animals indicating similar or identical metabolic pathways, except for M14-gluc, the major plasma metabolite in human.

Of note, the metabolites M7, M10, M12 and M16 were tested *in vitro* for their inhibitory activity against HDACs and none of these metabolites was shown to be pharmacologically active, besides, no accumulation was observed for any of the metabolites. Thus, it can be agreed that none of the metabolic pathways could result in significant deviations from the expected pharmacological effects of resminostat.

Excretion. Appropriate methodological approaches were chosen for the evaluation of resminostat excretion *in vivo* – administration of radiolabeled resminostat mesilate was performed orally and intravenously to mouse, rat and dog. Excretion of resminostat was demonstrated via both feces and urine, with around 60% and 30% in mouse, 50% and 50% in rat, and 25% and 70% in dog determined for fecal and urinary excretion, respectively, after oral administration thus demonstrating species difference. For all routes and doses a complete or near-complete recovery of the radioactivity administered was observed within the sampling periods of 48 h (mouse), 72 h (rat), and 168 h (dog).

Pharmacokinetic drug interactions. *In vitro* data revealed that resminostat is a substrate of CYP2C8 (expected to be responsible for up to 86% of hepatic metabolism), but also of CYP1A2 and 2C19 indicating alternative metabolic pathways for resminostat (confirmed via human mass balance study). Based on the obtained results, CYPs are considered the major enzymes contributing to $\geq 25\%$ of overall elimination of resminostat. No additional phase I metabolizing enzymes have been tested, which is in line with current EMA guidelines. However, *in vivo* DDIs related to inhibition or induction of one of the metabolic pathways such as CYP2C8 activity (resminostat as victim) are expected to be unlikely due to the observed variety of metabolic pathways and the wide therapeutic range of resminostat reported during clinical trials.

According to *in vitro* data, resminostat is a substrate of the P-gp.

In vitro transporter interaction data revealed that resminostat inhibited the hepatic uptake transporters OATP1B1, OATP1B3 and OCT1. No interaction was reported for the efflux transporter BCRP. A small inhibition was noted towards the renal uptake transporters OAT1, OAT3 and OCT2. The renal transporters multidrug and toxin extrusion protein (MATE) 1 and MATE2-K have not been tested, which is agreed since these tests are not mandatory according to current EMA guidelines.

Static modeling of the obtained *in vitro* data did not indicate a risk of *in vivo* DDIs related to inhibition of P-gp (MDR1), OATP1B1, OATP1B3 and OCT1. Based on the current EMA thresholds, the risk for *in vivo* DDIs related to inhibition of the hepatic uptake transporters OATP1B1, OATP1B3 and OCT1 by resminostat cannot be fully excluded. However, inhibition kinetics indicate $> 85\%$ (OATP1B1, OATP1B3) and $> 90\%$ (OCT1) of transporter activity remaining at the expected hepatic concentrations of resminostat. Based on all other guidances (FDA, PMDA and ICH M12 draft), *in vivo* DDIs related to inhibition of hepatic uptake transporters are unlikely, which is agreed.

Taken together, the DDI potential of resminostat was assessed based on *in vitro* data of transporter and metabolizing enzyme interactions and clinical data on exposure, metabolism and safety and subject to static modeling. Dynamic data such as enzyme kinetics and rapid metabolic degradation of resminostat were taken into account to estimate the risk of *in vivo* DDIs. In conclusion, it is agreed that *in vivo* DDIs related to the tested transporter and enzyme interactions of resminostat are considered unlikely.

Justification of omission of the NC placental transfer studies is based on test article teratogenic properties and significant effects on human reproduction. Argumentation of the Applicant and related awareness measures in PI are acceptable.

The most important findings from the non-clinical studies on resminostat include dose-dependent effects observed in non-GLP single-dose studies. Single dose toxicity studies were conducted in rats and dogs administered resminostat orally by gavage or as a capsule. No mortality or significant clinical signs were observed in any animal species or dose group. Resminostat was well tolerated in both species. The target organs of toxicity were similar in rats and dogs: hemolymphopoietic system and gastrointestinal tract. Resminostat administered orally by gavage and capsules to beagle dogs caused marked vomiting. Capsule administration did not reduce the emetic effect, but the systemic exposure was lower than the plasma AUCs obtained after administration of the same dose by gavage. The dose of 200 mg/kg (157.0 mg), corresponding to an AUC of 17130 to 20966 $\mu\text{g}\cdot\text{h/L}$, can be considered as the maximum tolerated dose (MTD). Vomiting was considered the dose-limiting toxicity in this study.

Mice, rats and dogs were studied in non-pivotal repeat-dose studies, but mice and dogs were selected as the rodent and non-rodent species for pivotal repeat-dose toxicity studies and toxicokinetic evaluation. In non-pivotal studies, rats were found to be less exposed to resminostat following oral administration. Mouse and dog have comparable steady state AUCs based on dose per body surface area, appropriate pharmacokinetic profiles and metabolism.

The chronic toxicity of resminostat has been assessed in repeat-dose oral toxicity studies in mice and dogs for up to 13 weeks. Resminostat was administered by oral gavage once daily in mice and dogs.

Repeat-dose toxicity studies showed a broadly consistent profile of toxicities that were dose-dependent. Target organs for resminostat toxicity included the hemolymphopoietic system, the gastrointestinal tract and the reproductive organs. No treatment-related deaths were observed. The studies showed dose-related decreases in hematological parameters at all doses. Decreases in lymphocytes were seen at the 70 mg/kg dose in the 13-week study, but at all doses in the 28-day study. All effects were generally nearly reversible during the recovery period. At the 140 mg/kg dose, a slight decrease in red blood cells parameters (erythrocyte count, hematocrit, haemoglobin) and thrombocytes was also observed that was recovered by day 43. Histopathological changes in the hemolymphopoietic system at all doses included lymphoid depletion of the thymus and lymph nodes, increased severity of extramedullary hemopoiesis of the spleen.

Reproductive toxicities in male animals included decreased testicular weights, germ cell depletion and decreased spermatozoa in the testes and epididymides at a dose of 140 mg/kg/day. These changes were not completely reversible after the recovery period (germ cell depletion, spermatozoa reduction, intratubular degenerated germ cells were reported). In female mice, changes in the ovaries (follicular atrophy), were observed in all dose groups, and atrophy of the uterus and vagina, reduced (relative and absolute) weight of the ovaries were observed at 140 mg/kg/day. After the recovery period, only animals in the 140 mg/kg/day group still showed findings in the ovaries; in all other groups these changes were completely reversible within 14 days.

In the 28-day study the dose of 140 mg/kg/day was considered to be the MTD (maximum tolerated dose). Based on the low incidence and almost complete reversibility of hemolymphopoietic system and genital tract changes, the NOAEL was determined to be 35 mg/kg/day, with an exposure multiple of 0.26-fold the human AUC.

In the 3-month study decreases in leukocytes, platelets and neutrophils were observed at all dose levels, but a decrease in lymphocytes was observed at the high dose of 70 mg/kg/day. In the 3-month study in mice, there were no findings in the reproductive organs of male and female animals and no histopathological changes in the hemolymphopoietic system are detected. However, the effects of repeated doses of resminostat mesilate at 35 and 70 mg/kg/day were comparable between the 28-day and 3-month studies

with regards to the targets of toxicity and severity. In dogs, resminostat was tested at doses of 10, 20 and 40 mg/kg/day for 28 days (+ 2-week recovery) and at doses of 5, 10 and 20 mg/kg/day for 13 weeks (+ 4-week recovery). Treatment-associated deaths were observed in 1 female dog at dose 40 mg/kg due to toxicity in the hemolymphopoietic system.

In the 28-day study increased toxicity was observed at the high dose of 40 mg/kg/day. The doses of 10 mg and 20 mg/kg/day were well tolerated. Reduced leukocytes, red blood cells, reticulocytes and thrombocytes were observed at all dose levels. These changes were reversible during the recovery period. Lymphoid depletion was also observed in the thymus at all doses, in the lymph nodes at 20 -40 mg/kg/day and in the spleen at 40 mg/kg/day. Lymphoid depletion in thymus was noted even after the recovery period.

In all dose groups, germ cell depletion in the testes, oligospermia in the epididymides and atrophy of the prostate were observed in males and changes in the ovaries, uterus, and mammary glands in females. Changes in the male genital tract were observed even after the recovery period. The NOAEL was determined to be 10 mg/kg/day for treatment period of 4 weeks. On Day 28 C_{max} and AUC₀₋₂₄ values were 1.145 µg/mL and 1.718 µg·hr/mL, respectively with an exposure multiple of 4.57-fold human AUC. The dose of 20 mg/kg/day was considered to be the formal MTD.

Additionally, findings from genotoxicity studies indicated a slight mutagenic potential in the Ames assay and chromosomal aberrations in *in vitro* studies. However, the risk of genotoxic effects at the dose levels administered to humans is considered to be low. The Applicant did not perform the carcinogenicity studies in line with ICH S9. In line with the Scientific Advice of 25 January 2018 the Applicant has provided more detailed information on the disease in different populations and disease stages. It can be agreed that the proposed indication 'advanced stage mycosis fungoides (MF) and Sézary syndrome (SS)' falls under the scope of ICH S9 and no carcinogenicity studies are required.

No specific fertility and early embryonic development toxicity studies were conducted. Reproductive organs of mice, rats, and dogs were assessed in the repeat dose toxicity studies. Resminostat should not be used during pregnancy, which is proposed to be reflected in section 4.6 of the SPC.

No embryofetal development studies were conducted. Considering the teratogenicity as the class effect of HDAC inhibitors, this can be accepted.

No pre- and postnatal development studies were conducted. In line with ICH S9 and the intended indications, this can be accepted.

Resminostat did not demonstrate phototoxicity risk in the *in vitro* Neutral Red uptake assay. While the non-clinical study program for resminostat included a comprehensive set of studies, including single-dose, repeat-dose toxicity, and genotoxicity studies, the risk-based approach in study selection is not explicitly stated.

The Predicted Environmental Concentration in surface water (PEC_{surfacewater}) was calculated using a refined F_{pen}, which is considered acceptable given the prevalence of CTCL in Europe. Based on these assumptions, the PEC_{surfacewater} is calculated to be 0.00807 µg/L, which is below the action limit of 0.01 µg/L.

Resminostat is not classified as an endocrine active substance. A Phase II assessment is not warranted. The log of the n-octanol/water partition coefficient (log P_{ow}) of resminostat was determined to be -0.85 at pH 5, 0.74 at pH7 and -0.22 at pH 9. These values are considered to be well below the threshold level of log K_{ow} > 4.5. No further PBT assessment is required.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore resminostat is not expected to pose a risk to the environment.

Assessment of paediatric data on non-clinical aspects

Not applicable

2.5.7. Conclusion on the non-clinical aspects

Overall, the PD results indicate that resminostat is a potent inhibitor of class I, IIb and IV HDAC enzymes with pronounced activity against HDAC6 at nanomolar concentrations. There were no safety pharmacology findings of concern following single doses, except the transient prolongation of QT, partially accompanied by decreased heart rates, but without correlation to plasma levels of resminostat. The PK of resminostat has been studied in a large panel of studies elucidating ADME and DDI features of orally applied resminostat mesilate. From the toxicological point of view, non-clinical studies highlight resminostat's dose-dependent effects and potential genotoxicity. The toxicological profile of resminostat has been adequately addressed by the studies submitted.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 3: Tabular overview of clinical studies

Study Number	Phase	Population N (M/F), Age	Treatment(s) (Doses Referring to Resminostat Free Base)	Study Design	Study Objectives
4SC-sponsored Studies					
7341/EM-001 (FIM)	I	19 patients with advanced solid tumors (9 male/10 female) Median age 58 (range: 37 – 70 years)	Resminostat: 100 – 800 mg “5 + 9” regimen once daily administration	Open label, single-center, and inter-patient dose-escalating study	Dose escalation, MTD, safety, PK, PD
4SC-201-7-2020 (hAME)	I	5 healthy male subjects Median age 48.0 years (range: 37 – 55) years	Resminostat: 400 mg containing approximately 150 µCi (5.55 MBq) of [¹⁴ C]-resminostat Single dose administration	Open label, nonrandomized, single dose study	Absorption, metabolism, excretion
4SC-201-1-2009 (SHELTER)	II	57 patients with advanced HCC progressing on sorafenib (50 male/7 female) Median age 65.0 years (range: 25 – 80 years)	Combination therapy of resminostat + sorafenib (200 + 400, 400 + 400, 600 + 400 or 600 + 800 mg) “5 + 9” regimen once daily administration (resminostat)	Open label, uncontrolled, nonrandomized, two-arm parallel group study	Dose escalation + extension part of resminostat monotherapy <i>versus</i> combination therapy (resminostat + sorafenib), safety, PK, efficacy, PD
4SC-201-2-2009 (SAPHIRE)	II	37 patients with advanced Hodgkin's lymphoma (19 male/18 female) Median age 34 years (range: 19 – 71 years)	600 or 800 mg resminostat as ≥ third line therapy “5 + 9” regimen once daily administration	Open label, multicenter, single-arm study	Efficacy, safety, PK, PD

Study Number	Phase	Population N (M/F), Age	Treatment(s) (Doses Referring to Resminostat Free Base)	Study Design	Study Objectives
4SC-201-3-2010 (SHORE)	I/II	17 patients with advanced CRC (12 male/5 female) Median age 61 years (range: 41 – 73 years)	Combination therapy of 200 – 800 mg resminostat and FOLFIRI regimen “5 + 9” regimen once or twice daily administration (resminostat)	Open label, exploratory, multicenter study	Dose escalation, MTD, safety, PK, PD
4SC-201-6-2015 (RESMAIN)	II	201 patients with advanced MF or SS (123 male/78 female) Median age 64.0 years (range: 30 – 87 years)	Resminostat: 600 mg “5 + 9” regimen once daily administration	Multinational, multicenter, randomized, double-blind, placebo-controlled study	Efficacy, safety, PK, PD
Yakult Honsha-sponsored Studies					
YHI-1001-ST-01	I	12 patients with advanced solid tumors (5 male/7 female) Mean age 60.3 years (range: 33 – 70 years)	400 – 800 mg resminostat “5 + 9” regimen once daily administration	Open label, single center study	Dose escalation, MTD, efficacy, safety, PK, PD
YHI-1001-FE-07 (see Section 2.7.1.2.3)	I	12 male healthy subjects Median age 31.0 years (range: 25 – 37 years)	200 mg resminostat Single dose administration	Single-center, open label, randomized, two-period, two arm crossover study	Effect of food on resminostat PK profile

N: Number of subjects/patients; M: Male; F: Female; MTD: Maximum Tolerated Dose; PK: Pharmacokinetics; PD: Pharmacodynamics; HCC: Hepatocellular Carcinoma; CRC: Colorectal Carcinoma; FOLFIRI: Folinic acid, 5-Fluorouracil and Irinotecan regimen; MF: Mycosis Fungoides; SS: Sézary Syndrome.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Resminostat (resminostat mesilate) is an oral selective inhibitor of class I, IIb and IV histone deacetylases (HDAC) enzymes. The intended commercial pharmaceutical formulation for this drug product is an immediate-release film-coated tablets with one dose strength of 200 mg.

The proposed recommended oral dose is 600 mg (3 tablets of 200 mg resminostat) administered once daily (QD) in repeated 14-day treatment cycles, each consisting of 5 days of once daily resminostat administration followed by a 9-day resminostat-free period (the “5 + 9” schedule).

Resminostat has a molecular weight of 445.51 g/mol. The molecular formula is C₁₇H₂₃N₃O₇S₂. The compound is achiral.

In support to the clinical pharmacology program, the Applicant submitted, additionally to *in vitro* investigations (*in vitro* metabolite profiling, CYP inhibition and induction, Caco-2 permeability evaluation and protein binding ...), PK and PD data from 8 clinical studies, including one pivotal study 4SC-201-6-2015 (RESMAIN) in target patients with advanced Cutaneous T-Cell Lymphomas (CTCL).

Two population PK (Pop-PK) analyses were performed: an initial Pop-PK analysis (report 4SC-201-PoPPK-003) conducted to determine the optimal sparse sampling strategy for the phase 2 pivotal study RESMAIN in advanced MF and SS, and a final popPK analysis using a revised dataset from six clinical studies, including the pivotal Resmain study.

No specific exposure-response analysis was conducted at the time of the present submission. However, a PK/PD modeling analysis based on results from the FIM Study 7341/EM-001 (report 4SC-201-PKPD-004) and a concentration-ECG effect analyses for resminostat was performed.

Methods

Different bioanalytical methods (HPLC-MS/MS) were developed to quantify resminostat free base in human plasma with K-EDTA as anticoagulant.

Absorption

After single or multiple dose administration of resminostat in both healthy subjects (food Study YHI-1001-FE-07) and CTCL patients (pivotal Study 4SC-201-6-2015) using the intended commercial tablets, the median T_{max} was achieved at 1h (range: 0.5 to 2 h); indicating that absorption of resminostat is rapid. This is supported by similar T_{max} values observed in patients with oncologic indications and using others formulations.

Based on the Pop-PK model, at C1D5, after a multiple dose of 600 mg QD (given as 3 tablets each containing 200 mg) in patients with CTCL, the geometric mean C_{max} and AUC_{0-24h} are expected to be 5012 ng/mL and 16187 ng.h/mL, respectively.

Absolute Bioavailability

The absolute bioavailability of resminostat has not been investigated.

Based on the results from the mass balance study 4SC-201-7-2020, a readable absorption (>85%) of resminostat can be concluded as approximately 85.4% ($\pm 2.6\%$) of the administered dose was recovered in urine. In addition, most of the 11.8% ($\pm 2.3\%$) of the dose recovered in feces occurred after 24 to 36h, suggesting that this amount was absorbed and then excreted by biliary route rather than due to unabsorbed drug.

Relative Bioavailability

Different resminostat formulations and strengths were used during the pharmaceutical development. The formulation proposed for commercial use is a film coated tablet (one strength 200 mg of resminostat free base) that have been used in the target population for B/R demonstration and also in the phase 1 food effect study. This formulation showed an increased bioavailability of approximately 20 to 50% for C_{max} and AUCs compared to the initial formulations.

Influence of food

The effect of a high fat meal on the PK of resminostat was investigated in a dedicated formal Study YHI-1001-FE-07. The study included 12 healthy volunteers who received, in a crossover design, a single oral dose of 200 mg resminostat as a film-coated tablet (the intended commercial formulation) under fasting and fed states. PK results indicated that administration of a high fat meal increased slightly the geometric means of AUC_{last} and C_{max} by 9.9% and 6.3%, respectively. The median T_{max} was not affected by food and remains unchanged at around 1h under both conditions. Based on these data, resminostat can be administered regardless of food intake.

Influence of gastric modifier food

The effect of pH modulators such as antacids, PPI or H₂ receptor antagonists on the systemic exposure of resminostat was not discussed.

Distribution

Based on *in vitro* investigations (Report ADM-22-4066b), Resminostat was found to be moderately bound (93.3 $\pm$ 0.6) to human plasma proteins. *In vivo* results confirm that resminostat is moderately bound to

plasma proteins with an estimated mean fraction of unbound resminostat in plasma of 15.0% (protein binding of about 85%). Resminostat binds preferentially to human serum albumin (HSA). At 10 µM, the bound fraction was approximately 76.3% in HSA and 11.6% in alpha-1-acid glycoprotein (AGP).

The geometric mean blood-to-plasma ratio for the total radioactivity was 0.26 less than 1, indicating limit penetration of resminostat or its metabolites into red blood cells.

Based on the mass balance Study, the geometric mean V_z/F (SD) of resminostat was estimated at 162 (22.2) in healthy volunteers. In the Pop-PK analysis (2-compartment model), the mean apparent volume of distribution (V_c/F) was found to be significantly affected by age. The geometric mean apparent V_z/F was estimated at 121.6 L in target patients with advanced MF and SS. Overall, both non-compartmental analysis and Pop-PK results suggest a high tissue distribution of resminostat.

Elimination

Metabolism

In vitro data (incubation in liver microsomes and recombinant human CYP enzymes) indicated that resminostat is mainly metabolized by CYP2C8 (86.0%) and minor contributions of CYP1A2 (10.8%) and CYP2C19 (3.1%).

Resminostat underwent extensive metabolism that appears to be primarily displayed by hydrolysis, hydrogenation, glucuronidation, oxidative cleavage, demethylation and methylation, all of which contributed to the formation of several resminostat metabolites.

Following a single oral dose of [¹⁴C] resminostat, unchanged resminostat (parent drug) accounted for only approximately 10.5% of the total drug-related systemic exposure (0 to 48 hours) and a total of 35 potential metabolites were detected in plasma. The most abundant circulating component was the M14/P21 glucuronide metabolite (oxidative cleavage and glucuronidation of resminostat) representing 15.1% of the total exposure. Then, the metabolites M16, M4 (resminostat glucuronide), M15 (oxidative cleavage and reduction of resminostat) and M39 (desmethyl M16) accounting for around 7%, 7%, 8% and 7% of the total exposure, respectively. All other metabolites detected in plasma accounted for 1% to 5% of the total exposure.

In urine, the unchanged drug accounted for 6% of the total administered dose (0 to 48 hours) and up to 43 possible metabolites were detected. The most abundant metabolites were characterized as M16 (20%), M39 (13%), and M15 (10%). In feces, a total of 32 metabolites were detected and M15 was the most abundant metabolite accounting for around 4% of the dose.

Excretion

Following oral administration, resminostat is predominantly excreted by the kidneys with complete recovery (mean $\pm$ SD of 97.2% $\pm$ 0.4%) of the dose achieved in urine (85.4% $\pm$ 2.59%) and faeces (11.8% $\pm$ 2.29%).

The renal clearance of resminostat was not calculated or could not be found.

Very rapid $t_{1/2}$ elimination in healthy volunteers (1.77 h and 2.2 h in the food effect and ADME studies, respectively) and in patients with advanced solid malignancy or malignant lymphomas (mean values ranging from 1.5 h to 3.8 h) was initially found.

Based on the Pop-PK analysis (two-compartment model), the elimination of resminostat is shown to be biphasic with an initial mean (CI 95%) $t_{1/2}$ of 1.9 h (1.8–2.0 h) followed by terminal mean (95% CI) $t_{1/2}$ of

approximately 29 hours (range 24-34) in the target patients with advanced-stage of MF or SS. Following multiple dose of resminostat 600 mg QD in patients, the geometric mean apparent oral clearance (CL/F) is 47.6 L/h.

Dose proportionality and time dependencies

Following ascending single or multiple doses in patients with advanced malignancies, the systemic exposures of resminostat appear to exhibit a more than dose proportional increase across the dose range [100-800 mg]. On one hand, after single dosing, the geometric mean C_{max} and AUC_{last} were 487 ng/mL and 1230 ng.h/mL at 100 mg versus 4970 ng/mL and 21100 ng.h/mL at 800 mg, respectively; indicating an increase of AUC by more than 2-fold the increase of dose. On the other hand, mean apparent CL/F clearly decreases with increasing dose levels: CL/F was 80.9 mL/h at 100 mg versus 37.7 mL/h at 800 mg.

PK data after repeated 600 mg QD administrations following the "5 + 9" schedule did not indicate any evident trend of accumulation of the systemic exposure of resminostat (R_{acc} near to 1 for both AUC_{tau} and C_{max}) after repeated cycles. The lack of time dependency appears consistent with the elimination t_{1/2} of resminostat (around 30 hours) and particularly given the 9-day resminostat-free period within the proposed "5 + 9" dosing schema that allow theoretically a complete elimination of resminostat between cycles of 14 days.

Steady state achievement remains unclear as no PK data (C_{trough}, C_{max}, AUC_{24h}) after more than 5 days of treatment were available. Theoretically, steady state is expected by day 6 to 7 after continuous daily treatment.

Pharmacokinetics in target population

The PKs of resminostat in the target patients with advanced MF or SS, following the claimed 600 mg QD dosing according to the "5 + 9" schedule and using the to-be marketed tablets, was evaluated, as a monotherapy, in one pivotal phase 2 study 4SC-201-6-2015 (Resmain).

No non-compartmental analysis calculation was performed given the sparse PK sampling (3 samples at C_{3D1} 0.75, 2 and 4h post dose and 3 samples at C_{3D5} predose, 2 and 7h post dose). Therefore, the available data (489 samples from 91 patients) were pooled in the population PK dataset and PK parameters / exposures metrics of resminostat were estimated using the Pop-PK analysis.

Resminostat concentration-time profiles after single dosing (C_{1D1}) and repeated dosing (C_{1D5}) of 600 mg QD are plotted in **Figure 1**. In patients, model-based exposures predictions are summarised in **Table 8**. The geometric mean C_{max} was 5012.2 ng/mL, the AUC was 16187.5 ng.h/mL at day 5 post dose after repeated QD 600 mg dosing. The geometric means of CL/F and the terminal t_{1/2} were estimated at 47.6 mL/h and 29 h.

Figure 2. Mean (SD) concentration-time profiles of resminostat after SD or multiple dose

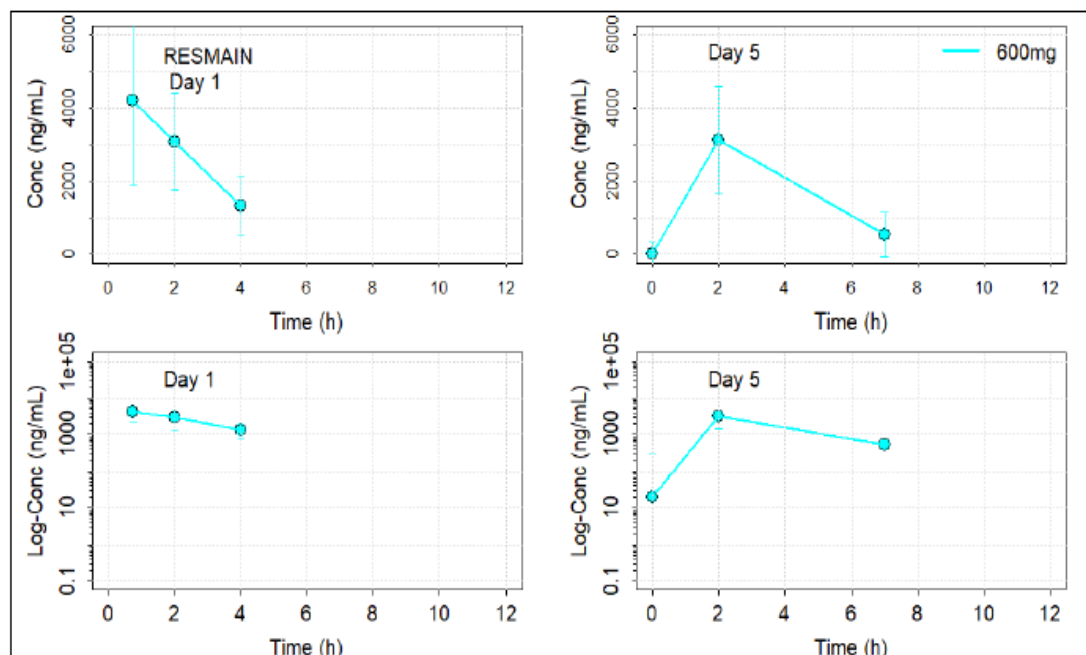


Table 4: Estimated PK parameter values at D5 post-dose for patients with Cutaneous T-cell Lymphoma (RESMAIN study) Following Repeated Oral Resminostat Administration (600 mg QD) with the commercial formulation

Parameter	Mean	Std Dev	Lower 95% CL for Mean	Upper 95% CL for Mean	Median	Q1	Q3
Tmax (hr)	1.03	1.34	0.91	1.16	0.80	0.40	1.20
Cmax (ng/mL)	5012.21	1566.68	4867.56	5156.87	4970.10	3972.40	5956.60
AUCss (ng*hr/mL)	16187.46	6305.35	15605.25	16769.66	14926.80	11761.19	19224.33
Cav (ng/mL)	674.48	262.72	650.22	698.74	621.95	490.05	801.01
Initial Half-life (hr) *	1.87	0.71	1.78	1.95	1.73	1.33	2.31
Terminal Half-life (hr)*	28.93	54.27	23.91	33.94	12.12	5.78	28.60
V/F (L)	121.57	30.83	116.58	126.56	117.81	98.73	138.44
CL/F (L/h)	47.60	20.54	44.27	50.92	43.58	32.82	58.66
Ka (h-1)**	12.63	42.19	5.80	19.46	2.95	0.99	11.76
Q1, Q3: first and third quartiles							
* Initial-half life estimated in the initial 7 hours post-dose							
*Terminal half life estimated from 7 to 24 hours post-dose							
**Estimated at 1h post-dose							

Population Pharmacokinetic analysis

A revised population pharmacokinetic analysis aiming to characterize the PK of resminostat and identify / quantify sources of variability was developed and submitted as part of the Applicant's Day 120 responses. The population PK dataset was expanded by including roll over patients from the pivotal Resmain study. From this new analysis, the predicted systemic exposure metrics for the target population were obtained.

The PPK of resminostat was based on PK data pooling 6 clinical studies including healthy volunteers (**YHI-1001-FE-07**) and patients of the target population (**RESMAIN**) which received the commercial formulation (Tablet formulation 4), and patients (**YHI-1001-ST-01**, **7341/EM-001**, **4SC-201-2-2009**, and **4SC-201-1-2009**) treated by resminostat for other indications and using initial clinical formulations (Capsules and tablet formulation 1).

Covariates of interest were baseline demographic covariates (age, body weight, gender, race/ethnicity), formulation, dose, and renal function (CrCL).

PPK was built using nonlinear mixed effects model with the SAEM algorithm for parameter estimation implemented in NONMEM (version 7.5.1, ICON Development Solutions, Ellicott City, MD). PK parameters was assumed to follow a log-normal distribution. RUV (residual unexplained variability) was explored using standard error models (additive, proportional or combined). Covariate effects were first explored graphically, then testing of the covariate effects was performed using a SCM building strategy (single addition, forward inclusion and backward elimination) with $p < 0.01$ for inclusion and $p < 0.01$ for exclusion. The PPK model was evaluated using standard diagnostic plots, visual predictive check and bootstrap.

Overall 3914 observations from 228 subjects were included. **Table 9** provide the final PK parameter estimates and Figure 2 and Figure 3 the associated GOF plots and VPC. The predicted PK parameters for the target population are summarised in **Table 8**.

Table 5: Population PK parameter estimates of the final PPK model

Parameters	PopPK model			Non-Parametric Bootstrap (500 replicates)			
	Median	RSE	Shr (%)	Median	RSE	5th percentile	95th percentile
Fixed-effect							
KAM (h-1)	1.24	10.60%		1.16	13.92%	1.05	1.25
TD (h)	0.88	13.80%		0.74	19.92%	0.64	0.83
B	1.77	10.80%		1.95	18.40%	1.70	2.17
CL/F(L/h)	20.50	25.50%		19.94	27.45%	16.04	24.00
K23(h-1)	0.02	8.30%		0.02	8.70%	0.02	0.02
k21(h-1)	0.03	16.40%		0.03	29.63%	0.02	0.03
V /F(L)	38.10	28.10%		38.92	29.96%	29.92	46.27
LAG1 (hr)	0.31	6.50%		0.33	6.15%	0.31	0.34
A (h-1)	7.29	14.80%		6.85	20.61%	5.77	7.72
TD1 (h)	44.60	15.90%		45.38	29.97%	35.26	52.75
B1	11.20	24.60%		12.35	31.68%	9.65	14.56
F2 (%)	1.27	1.30%		1.27	2.05%	1.25	1.29
D2 (hr)	0.18	19.60%		0.18	26.23%	0.15	0.22
LAG2 (hr)	0.38	5.60%		0.36	8.84%	0.34	0.38
cl_p	0.37	19.30%		0.38	20.26%	0.33	0.44
v_p	1.26	12.10%		1.24	13.23%	1.13	1.35
Residual error							
Add_err1	3.03	0.10%		2.96	19.18%	2.69	3.29
Prop_err	0.30	1.50%		0.30	3.65%	0.30	0.31
Add_err2	2.79	0.00%		3.83	42.53%	2.83	5.09
Random-effect							
KAM (h-1)	0.90	33%	46.6	0.72	26.80%	0.59	0.84
TD (h)	1.24	29.40%	51	0.98	35.44%	0.72	1.18
B	1.14	21.20%	59.4	1.09	20.42%	0.94	1.23
CL/F(L/h)	0.11	16.80%	6.15	0.10	14.71%	0.09	0.11
K23(h-1)	0.67	14.10%	25.6	0.70	26.32%	0.57	0.80
k21(h-1)	0.68	27%	68.1	1.08	26.92%	0.87	1.25
V /F(L)	0.06	22.10%	22	0.05	19.23%	0.05	0.06
LAG (hr)	0.26	28.70%	45.7	0.23	27.75%	0.18	0.27
A (h-1)	1.18	26.50%	50.4	1.59	24.23%	1.32	1.85
TD1 (h)	1.03	32.90%	58.9	2.30	31.90%	1.81	2.72
B1	0.76	55.70%	78.1	1.12	34.23%	0.86	1.32
F2 (%)	0.00	49.70%	78.6	0.00	33.33%	0.00	0.00
D2 (hr)	2.21	24.20%	45.1	2.21	29.95%	1.69	2.66
LAG2 (hr)	0.13	21.30%	59	0.13	29.85%	0.10	0.16

The final PPK model consisted of a two compartment PK model with first order elimination and:

- a time varying absorption with a lag time (double weibull function) to describe the absorption of the capsule or the tablet formulation 1, or
- a zero-order process with a lag time to describe the absorption of the commercial formulation parameterized by D2 (duration of the zero-order absorption process), ALAG2 (lag time of the zero-order absorption process) and FF1 (relative bioavailability of the commercial formulation with respect to the clinical formulations).

The fixed effects estimates for the final model were for CL/F, V/F, Kam, LAG2, D2 and F2 were 20.5 L/h, 38.1 L, 1.24 h⁻¹, 0.38 h, 0.18 h and 1.27h. IIV was considered on all the PK parameters and was moderate to low for CL/F (33%) and low for V/F (24%) and F2 (0%). For the absorption related parameters associated to the double weibull function IIV ranged from 51% (Lag) to 101% for TD1. For the parameters associated to the

zero-order absorption model with lag-time, IIV was moderate to very high with 36% for LAG2 and 148% for D2. Finally for the parameters characterizing the second compartment IIV was high ranging from 112 to 158%. Overall all main fixed effects were estimated with a good precision (RSE<20% except for some of the parameters from the double weibull function and for D2). A significant effect of body weight on both CL/F and V/F was identified.

Overall, GOF plots suggested that the model describe adequately the PK data. The VPCs showed that the model performs well in each study as the 5th, the 50th and the 95th percentiles were reasonably well predicted indicating that the population model properly described the observed data in each of the six trials included in the analysis.

Figure 3: GOF for the final PPK model

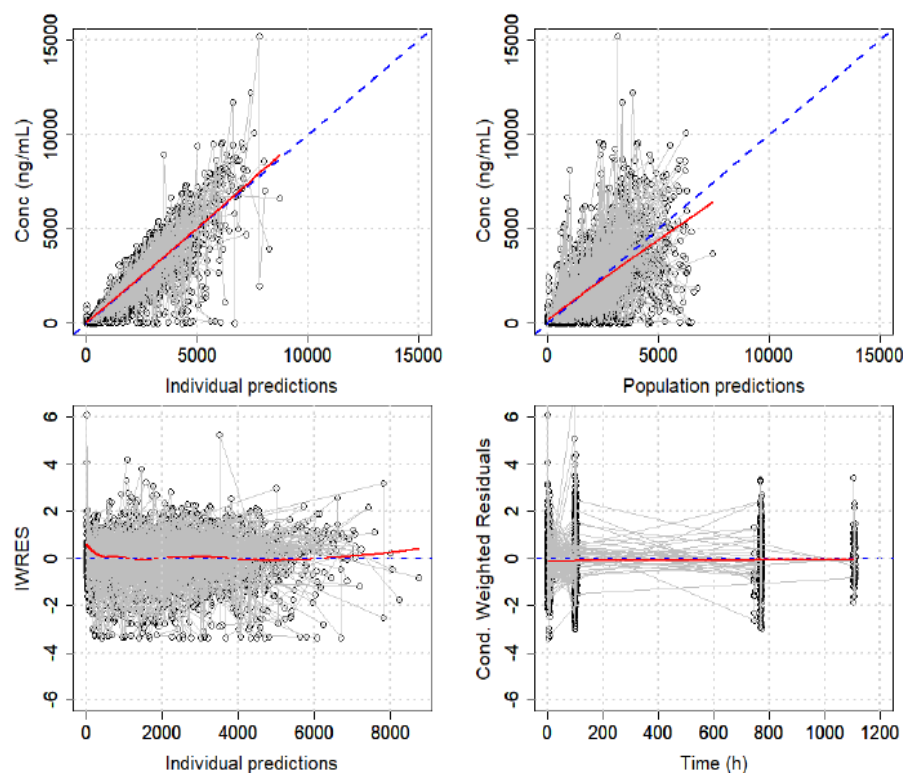
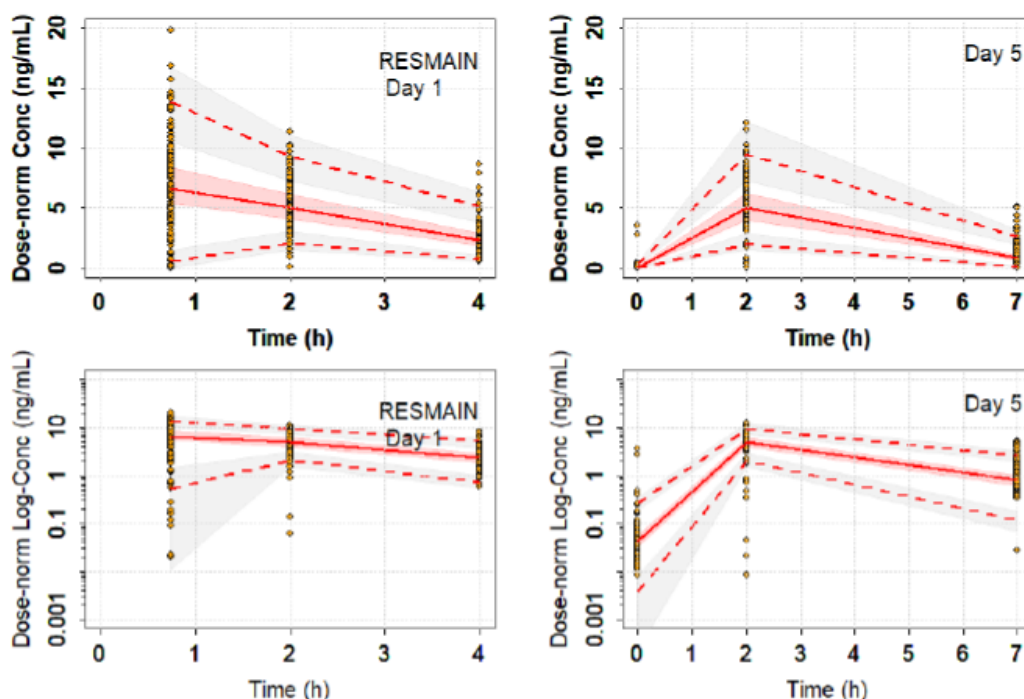


Figure 4: VPC for the RESMAIN study



Special populations

Impaired renal function

No formal dedicated PK study was performed to investigate the effect of renal impairment on resminostat PKs.

In the PK population analysis, subjects were characterized with regard to renal status using the creatinine clearance metric (CLCR as expressed mL/min) calculated by the Cockcroft-Gault formula. The Pop-PK dataset included $n=135$ (59.2%), $n=75$ (32.9%), $n=18$ (7.8%) and $n=0$ (0%) patients with normal renal function, mild, moderate and severe renal impairment, respectively. The effect of renal impairment as continuous covariate was evaluated in Pop-PK model and was not retained in the final model as a significant covariate on resminostat PKs. Therefore, it was concluded that no significant impact on the PK of resminostat is to be expected in patients with mild and moderate renal impaired function and no dose adjustment is proposed in these two subgroups of patients.

Impaired hepatic function

No formal dedicated PK study was conducted to assess the effect of hepatic impairment on resminostat PK parameters and the effect of hepatic impairment was not evaluated within the Pop-PK approach.

Gender

The effect of gender on the PKs of resminostat was investigated within the population PK analysis. Approximately 62.7% ($n=143$ of 228) male vs 37.3% female (85 of 228) of patients included in the population dataset. Data issued from the target population appear well-balanced between men and women (48 and 43 patients of 91, respectively). In the covariate analysis, no significant dependency between PK parameters of resminostat and the gender was detected and then the covariate was not retained in the final model.

Race / Ethnicity

Study YHI-1001-ST-01

A dedicated phase has been performed to evaluate the efficacy, safety and PKPD of resminostat in patients of Japanese ethnicity (n= 12) with solid tumours. 3 doses levels were tested: 400 mg, 600 and 800 mg, with resminostat administered once daily according to the "5 + 9" schedule. The study was supported by tablet formulation 1 (not the commercial tablets). The median t_{max} was achieved at around 1.3 to 1.9 h and the geometric mean of CL/F ranged between 24.9 to 51 mL/h. In the 600 mg cohort, the geometric means of C_{max} and AUC_{24h} after single dose were 6020 ng/mL and 24000 ng.h/mL, respectively

Pop-PK modelling

The effect of ethnicity on the PKs of resminostat was assessed within the Pop-PK analysis. The analysed dataset included a majority of Caucasian (94.7%, n=216 of 228) and n= 12 (5.3%) Japanese patients. The covariate analyses suggested no effect on PK parameters of resminostat based on ethnicity. Additional VPC plots at day 5 were provided and show similar observed and simulated systemic exposure on resminostat in both populations (Caucasian versus Japanese) following the same dosage regimen.

Body weight

No formal studies were conducted to investigate the effect of body weight (BW) on the PK of resminostat.

The body weight effect was investigated within the population PK analysis. Among the 228 participants included in the population PK dataset, mean BW was 73.2 kg (median = 73 kg, min = 35 kg, max = 113 kg). Out of the 91 patients with MF and SS, mean BW was 75.9 kg (median = 75 kg, min = 50 kg, max = 109.2 kg). BW was found to be a statistically significant covariate on both resminostat's CL/F and V/F and retained in the final Pop-PK model. PK simulations indicate clearly that the systemic exposure of resminostat (C_{max}, AUC) increases as patient's weight decreases and vice versa. For patients weighting between 50 to 100 kg, the geometric mean ratios (and 95%CI) of the log-transformed exposure parameters C_{max} und AUC compared to the reference BW of 74 kg were within the interval [0.8-1.25], indicating no clinically significant difference in exposures of resminostat for patients with a BW between 50-100kg. However, the mean resminostat exposure at steady state (AUC_{ss}) is expected to be increased by approximately 49.5% (26114/17459 ng.hr/mL) and by 37% (24024/17459 ng.hr/mL) for patients with low weigh of 30 and 40 kg respectively; and in contrast high BW of 110kg and 120 kg would result on a reduced AUC_{ss} in average by approximately 21.3% (13751/17459 ng.hr/mL) and 27.4% (12684/17459 ng.hr/mL), respectively after repeated daily dose of 600 mg resminostat. Overall, it was concluded that no dosing adjustment is warranted based on BW.

Age / Elderly

No formal investigations in elderly was performed.

The effect of age on the PKs of resminostat was investigated within the population PK analysis and was not found to be a statistically significant covariate. The impact of age (40, 60, and 80 years old) on the expected resminostat PK parameters (T_{max}, C_{max}, C_{min}, Coverage, AUC_{0-24h}, t_{1/2}) at day 5 using the commercial tablet formulation at the dose of 600 mg QD was assessed based on the final population PK model. The analysis indicated a minimal decrease (<10%) of the systemic exposure with the increase of age. Based on these findings, it was concluded that no dosing adjustment is warranted based on age.

Pediatric population

The safety and efficacy of resminostat in children below 18 years have not been established. No clinical / PK data are available.

Pharmacokinetic interaction

Resminostat as victim drug

To address resminostat drug-drug interaction (DDI) potential, CYPs's isoforms contribution to resminostat metabolism was tested. *In vitro* data showed that resminostat is a substrate of CYP2C8, which is expected to be responsible for up to 86% of hepatic metabolism of resminostat, but also of CYP1A2 and 2C19. Based on the obtained results, CYPs are considered the major enzymes contributing to $\geq 25\%$ of the overall elimination of resminostat. Overall, metabolism of resminostat by CYP2C8 is predicted to result in the formation of the metabolites M6, M2, and demethylated M2. Other CYP enzymes are involved in the formation of metabolites M7 and M2.

No clinical study was conducted to assess resminostat potential interactions with CYP2C8, CYP1A2, and CYP2C19 inhibitors as victim drug, or resminostat induction by other drugs.

Two studies were conducted enabling the assessment of PK interactions of resminostat with Sorafenib (Study 4SC-201-1-2009 SHELTER) in patients with hepatocellular carcinoma and the PK interaction of resminostat with FOLFIRI regimen (study 4SC-201-3-2010 SHORE) in patients with k-ras mutated advanced colorectal carcinoma, although these studies were not conducted for formal drug-drug interactions assessment.

These two studies did not show 400 mg sorafenib BID, or FOLFIRI regimen respective co-administration with 600 mg resminostat QD 5 + 9 days cycle affected resminostat PK.

Resminostat as perpetrator drug

Based on *in vitro* DDI studies, no clinically relevant interaction with CYPs, and P-gp substrates would be expected.

Pharmacokinetics using human biomaterials

N/A

2.6.2.2. Pharmacodynamics

Mechanism of action

Resminostat is a histone deacetylase (HDAC) inhibitor. HDACs catalyze the removal of acetyl groups from acetylated lysine residues in histones, resulting in the modulation of gene expression. HDACs also deacetylate non-histone proteins, such as transcription factors. These enzymes are known to play a central role in the regulation of several cellular properties linked with the development and progression of cancer. By inhibiting these enzymes, resminostat induces changes in the acetylation status of histone and non-histone proteins which results in the transcriptional activation and/or repression of genes that mediate pleiotropic effects such as pathway modulation, cell growth arrest, differentiation, and apoptosis.

Primary and Secondary pharmacology

The pharmacodynamics of resminostat were evaluated using serial blood sampling in several studies (monotherapy and combination therapy). Data has shown that resminostat dose-dependently inhibits HDAC enzyme activity. Dose levels of 400 mg or higher demonstrated between 80% and 100% enzyme activity inhibition occurring when resminostat achieved peak plasma levels. The inhibition of HDAC enzyme activity by resminostat is transient and returns to baseline activity at 24 h after administration.

Multiple dosing of resminostat increases histone H4 acetylation levels by 1.5 to 2.0-fold at 2 h post-dose

compared to baseline (pre-dose) and 2.0 to 4-fold at 2 h post-dose compared to C1D1, regardless of dose level. Median H4 acetylation was restored to baseline levels at 24 h post-dose after resminostat dosing in C1, but from C4D3 onwards some residual hyperacetylation was observed compared to C1D1.

Relationship between plasma concentration and effect and safety

An efficacy exposure-response analysis based on the clinical and the PK data collected in the target patients with SS or MF (RESMAIN study) was conducted. The efficacy endpoint was the primary variable Progression Free Survival (PFS) and the exposures metrics were the observed resminostat concentrations at C3D5 at 2h post dose (Cmax-2h) and the derived AUC. The analysis was performed by evaluating the relationship between the median PFS time and the median levels of exposure (Cmax and AUC) estimated in four groups (placebo, low, intermediate and high exposure).

The median Cmax-2h values with the associated estimated median survival time in each strata is presented in **Table 10**. The exposure-response relationship between the increase of Cmax-2h and the increase of the median survival is shown in **Figure 4**. The stratified Kaplan-Meier plot of PFS is presented in **Figure 5**.

Table 6. Median Cmax-2h values with the associated estimated median PFS time in each strata

Cmax	Median Cmax-2h (ng/mL)	Median PFS (month)
Placebo	0	4.17
<3100 ng/mL	2330	5.60
>=3100 and <4180 ng/mL	3540	12.94
>=4180 ng/mL	4730	22.04

Figure 5. Exposure/Response Relationship between Cmax-2h at C3D5 and Median PFS

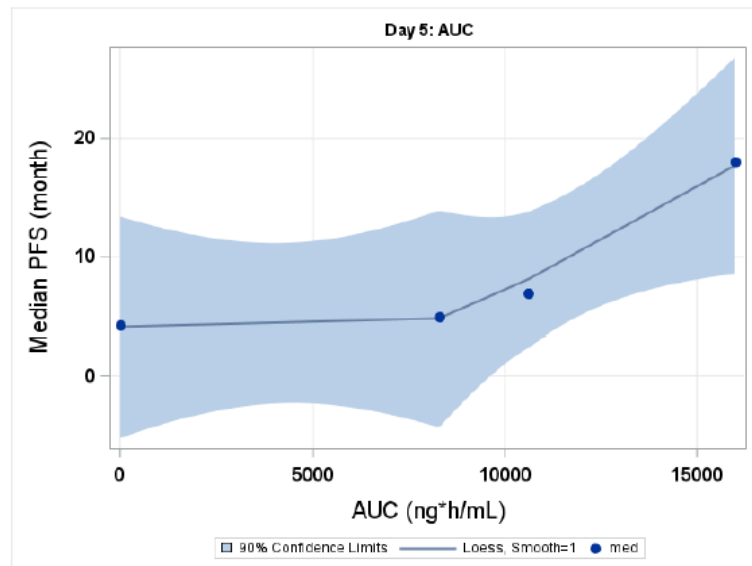
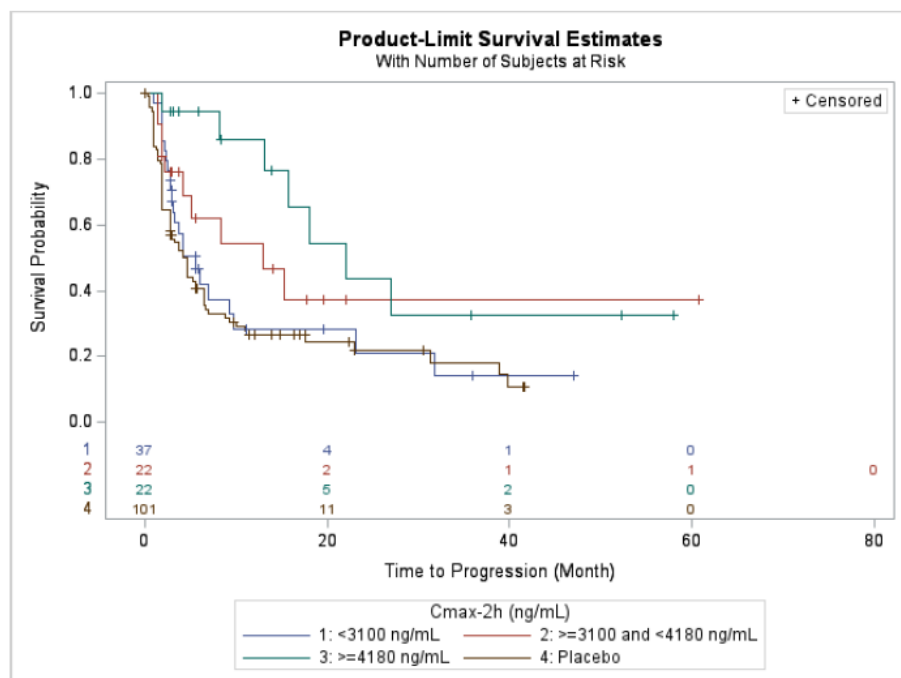


Figure 6. Kaplan-Meier Plot of PFS stratified by levels of Cmax-2h



Similar relationship between the PFS outcomes and the AUC metric was identified. Overall, these results indicate a clear correlation between the level of exposure on resminostat and the clinical benefit in terms of PFS.

An exposure/response analysis to assess potential cardiovascular toxicities was performed. Please refer to the safety clinical part.

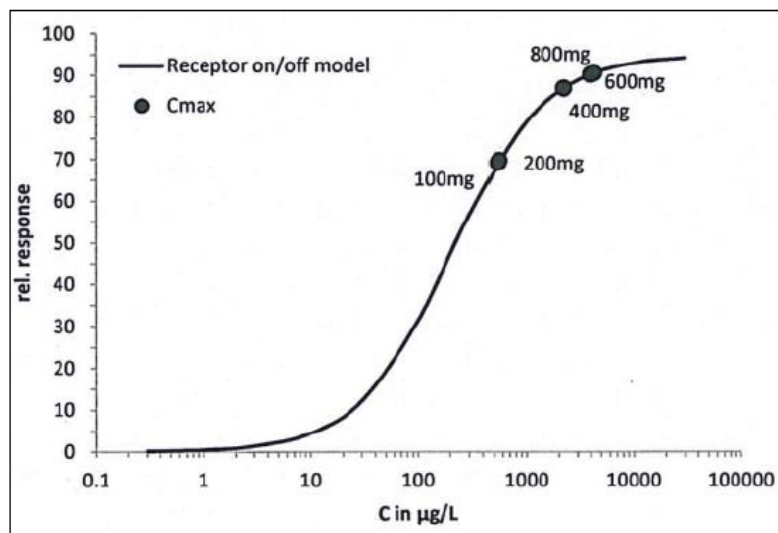
Pharmacokinetics-Pharmacodynamics (PK/PD)

A PKPD model was developed based on PK and HDAC inhibition data of resminostat acquired during the FIM 7341/EM-001 (ascending multiple resminostat doses from 100 to 800 mg) in patients with advanced malignancies.

The PK data were described using a one-compartment model with zero order input (inconsistent with the 2-compartment model identified in the final population analysis). Furthermore, the FIM study was supported by an initial capsule formulation (not the proposed commercial tablet with increased BA of around 40% for Cmax).

The HDAC inhibition, measured *ex vivo* in peripheral blood mononuclear cells (PBMC), was best described by a Receptor on/off model able to capture the shifts of PD response maxima. The derived model-based apparent KD value was 454 ± 168 nM overall consistent to measured inhibition values (570 ± 260 nM). Maximum HDAC inhibition occurred within 2h of start of dosing (not well captured by the model). Overall, model-based simulations of PD response (**Figure 4**) indicated that doses ≥ 400 mg are expected to achieve more than 50% of target engagement with the highest degree of HDAC inhibition (close to 90%) observed for the 600 and 800 mg doses. The derived t_{1/2} PD response was estimated at 6h post dose.

Figure 7. Concentration-Response curve for *in Vivo* HDAC inhibition in Human.



The curve was derived from E_{max} and k_D values obtained from PK/PD modeling. C_{max} for each dose level was obtained with a non-compartmental analysis of PK data from Study 7341/EM-001 (FIM).

Overall, the data indicate that HDAC inhibition represents a suitable marker for resminostat PD activity

2.6.3. Discussion on clinical pharmacology

Bioanalysis

Validation of analytical methods was performed before the implementation of ICH guideline M10 (January 21, 2023), therefore, differences between the bioanalytical method validation conducted were questioned. The impact on reliability of data was investigated by considering all validation parameters according to ICM M10. The main differences which could be found with regard to ICH M10 are reliability of data of specificity, matrix effect and reinjection reproducibility. The Applicant has sufficiently justified negligible effect on reliability of the data considering appropriate validation results of used bioanalytical methods.

Influence of gastric modifiers

No investigation was performed to assess the effect of pH modulators such as antacids, PPI or H₂ receptor antagonists on the systemic exposure of resminostat. However, given the provided solubility data of resminostat mesilate at the relevant pH values, potential effects on absorption of resminostat mesilate resulting from pH modulations could be considered unlikely.

Pharmacokinetic of metabolites

The Applicant clarified the elimination pathway of P21.M14-glucuronide as being the most abundant circulating metabolite (~15% of the systemic exposure) and its PD activity as well as that of its precursor. Excretion of P21.M14-gluc was shown via urine. However, the metabolite could also be subject to further glucuronidation (to form P24.M14-gluc) or deglucuronidation (to form M14-methylated) followed by excretion (urine, feces) or further metabolic transformation (to form M15). The plasma concentrations over time indicate that formation and disappearance of metabolite P21.M14-gluc was well balanced without peak concentrations. Based on the many options for metabolic pathways, accumulation of P21.M14-gluc or any of

the other identified metabolites is considered unlikely. Regarding the PD activity, neither the metabolite P21.M14-gluc nor its precursor M14-methylated (for structures, see Figure 3) have been tested for their inhibitory activity towards human HDAC enzymes. However, based on the proposed structures of these compounds, the probability of a PD activity of P21.M14-gluc and its precursor is assessed as low.

Dose proportionality

Based on the PK data of the FIM study 7341/EM-001, the Applicant concluded that resminostat exhibited linear PKs in the dose range of [100 -800 mg]. Such claim is not endorsed. First, the study used an initial capsule formulation with significantly lower biopharmaceutical performances (40 to 50% on C_{max} and AUC) compared to the commercial tablet formulation and very limited patients (n=2 to 3) were available in each dose level. Thus, no formal conclusion regarding dose proportionality could be drawn. Further, the observed systemic exposures of resminostat indicated rather a more than dose proportional increase. On one hand, after single dosing, the geometric mean C_{max} and AUC_{last} were 487 ng/mL and 1230 ng.h/mL at 100 mg versus 4970 ng/mL and 21100 ng.h/mL at 800 mg, respectively, indicating that AUC_{last} increased by more than 2-fold the increase of dose in the claimed interval [100-800 mg]. On the other hand, the mean apparent CL/F clearly decreases with increasing dose levels: CL/F was 80.9 mL/h at 100 mg versus 37.7 mL/h at 800 mg. Overall, dose proportionality remains unclear. In this context, it should be highlighted that a unique dose level (i.e 600 mg) was investigated in the target population and using the formulation of interest. The Applicant was asked to comment the issue and amend the SmPC if applicable. The Applicant shared the uncertainty regarding the conclusion of dose proportionality and consequently the reference to PK linearity of resminostat in the dose range of 100 to 800 mg was agreed to be removed from section 5.2 of the SmPC (dedicated "Linearity/non-linearity" paragraph and mentions in the absorption paragraph).

Pharmacokinetic in the target population / Population PK analysis

Overall, the methodology used to develop the PPK model for resminostat is supported. The Applicant was asked to clarify the definition and implementation of some parameters (especially on the time-varying absorption model), to generate additional predictive performances plots and to further investigate covariates effects. As part of the Applicant's Day 120 responses, a new Pop-PK analysis was performed and the provided results (final model parameters estimates, covariate analysis, GOF plots, pcVPCs) are considered acceptable.

Impaired renal function

The recommendation that no dose adjustment is needed in patients with moderate renal impairment was challenged. The Applicant provided the mean (SD) serum concentration-time profiles of resminostat at day 5 stratified by renal impairment groups, as well as a forest plot illustrating the effect of each renal impairment category on predicted model-based exposures metrics (C_{max}, C_{min}, AUC_{tau}) at day 5 in comparison to the reference group of normal renal function. As per the provided data, the geometric mean ratios and 95% CI distribution of the log-transformed exposure parameters (AUC_t, C_{max}, C_{last}) were within the interval [0.8-1.25]. Hence, the recommendation that no dose adjustment is needed in patients with moderate renal impairment is considered agreed.

In section 5.2 of the SmPC, adequate wording was proposed to reflect that no PK data are available in the severe renal impaired group. Thus, the PK of resminostat in this subgroup of patients is considered unknown and consequently no dosing recommendation can be made. Given the major role of the renal elimination in the excretion of resminostat (up to 85%) and the absence of an adequate dosing regimen, a clear statement

indicating that use of resminostat should be avoided in this patient population is to be added in sections 4.2 and 4.4 of the SmPC.

Impaired hepatic function

Resminostat has not been studied in patients with hepatic impairment. Therefore the SmPC was expected to explicitly indicate in section 4.2, 4.4 and 5.2 that no dosing recommendation could be made in this population and that resminostat should be avoided in patients with hepatic impairment. (Please also refer to the clinical safety part).

Gender

The Applicant was asked to further inform the potential effect of gender on the PKs of resminostat. The requested investigations / analyses were performed within the new Pop-PK analysis. The provided data (Pop-PK model-based simulations, pcVPCs) confirmed the higher systemic exposure on resminostat in females by approximately 30% (in terms of mean C_{max} values 5725 versus 4384 ng/mL and mean AUC_t 11257 versus 8725 ng.hr/mL) compared to male patients. However, the observed decreased resminostat's CL/F and V/F in women by 20% and 24% respectively, appears to be driven / explained by difference on body weight (BW) rather than gender. Indeed, a significant correlation between PK of resminostat and BW is identified and the distribution of weight indicate ~20% higher mean weight in males than in females (79.2 versus 65.3 kg). Overall, based on aggregated data, the Applicant's conclusion that no dose adaptation is warranted based on gender could be endorsed.

Race / ethnicity

The Pop-PK dataset included a majority of Caucasian (94.7%, n=216 of 228) while only n= 12 (5.3%) Japanese patients (Phase 1 study YHI-1001). As such, the SmPC was proposed to be adequately amended to reflect the lack of PK data in others Asian ethnicities and in Black subjects.

Body weight

The Applicant was asked to further investigate the effect of BW on the PKs of resminostat in obese (BW>100 kg) and underweighted (<50 kg) patients. The requested analyses were performed within the revised Pop-PK analysis submitted at Day 120. BW as a continuous covariate was tested and retained in the final Pop-PK model as a statistically significant covariate on both resminostat's CL/F and V/F. The analysis indicated a clear trend for increase of the systemic exposure on resminostat (C_{max}, AUC) as patient's weight decreases and vice versa. For illustration, the mean resminostat exposure at steady state (AUC_{ss}) is expected to increase by approximately 49.5% (26114/17459 ng.hr/mL) and by 37% (24024/17459 ng.hr/mL) for patients with low BW of 30 and 40 kg respectively; and in contrast high BW of 110kg and 120 kg would result on a reduced AUC_{ss} in average by 21.3% (13751/17459 ng.hr/mL) and 27.4% (12684/17459 ng.hr/mL), respectively after daily dose of 600 mg resminostat.

Even if it can be shared that a dose adjustment in underweighted patients < 50 kg is not deemed necessary (at least at start of treatment), given the wide therapeutic range of the drug product and that a deteriorated safety profile is manageable by dose reduction as planned in the dosing regimen, the opportunity of a higher dose (i.e 800 mg) in obese patients with a BW >100 kg, especially in view of the PFS results in this subgroup (hazard ratio of 1.486 in favour of placebo) suggesting a limited efficacy in obese patients, should have been further explored. This should be scrutinized based on the available clinical efficacy outcomes and considered in the overall assessment of efficacy/safety background of the 600 mg dose (Please refer to clinical efficacy part).

Elderly

A dedicated paragraph was proposed to be included in section 5.2 of the SmPC to inform the available PK data included in the analysed population PK dataset. As such, 30% (n=93/312) and 10% (n=31 /312) were in the [65-74 years] and [75-84 y] groups of age, respectively and only n=1 patient >85 years was available. Lack of PK data in patient ≥85 years is clearly acknowledged.

Pharmacokinetic interactions

Resminostat is mainly metabolised by CYP2C8 and to a lesser extent by CYP1A2 and CYP2C19. No clinical study was conducted to assess resminostat potential interactions with CYP2C8, CYP1A2, and CYP2C19 inhibitors as victim drug, or resminostat induction by other drugs. These interactions were considered unlikely by the MAH due to the observed variety of metabolic pathways and the wide therapeutic range of resminostat reported during clinical trials.

Based on *in vitro* data [study 4SC-201-DDI-001], resminostat interactions as perpetrator drug is considered unlikely.

2.6.4. Conclusions on clinical pharmacology

The PK of resminostat was investigated using the non-compartmental and nonlinear-mixed effects modelling approaches. Data from 2 phase 1 studies in healthy volunteers, 4 phase 1/ 2 studies in patients with different oncologic indications and one pivotal phase 2 study in the claimed patients with advanced CTCL (MF and SS) were used for analyses. Overall, the PK properties of resminostat (200 mg tablet) are considered sufficiently characterized.

The provided Population-PK analyses show overall acceptable descriptive performance. An efficacy E-R analysis based on the clinical and PK data collected in the target patients with MF or SS indicate a clear correlation between the level of systemic exposure on resminostat (C-2h and AUC) and the clinical benefit in terms of PFS.

The proposed mechanism is considered understood; however, the effects are complex and multifaceted. The main PD biomarkers are specified and are supported by the non-clinical development.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

Study 7341/EM-001

Open label, dose escalation trial of oral BYK408740 in patients with advanced malignancy: First-In-Man Study of a newly developed, oral HDAC inhibitor.

The 19 included patients were treated at five dose levels between 100 mg and 800 mg. Eighteen patients (18, 95%) were evaluable for the determination of MTD, and 18 were evaluable for response. Patients received 4SC-201 once a day on Days 1-5 of 14-day treatment cycles; the optional twice daily treatment regimen was not explored in this study.

The first DLT was observed in a patient treated at the highest dose level (DL IV, 800 mg); the event in question (grade 3 nausea and vomiting, with ALT elevation, hypokalemia and thrombocytopenia) was not

strictly a DLT in accordance with the protocol definition, but was considered by the investigators and sponsor as a DLT due to the effect on the patient; three additional patients were added, with no further DLT reported. Thus the formal MTD for 4SC-201 administered on Days 1-5 of a 2-week cycle was not reached in this study. There is no exposure efficacy analysis to support the choice of the recommended dose.

2.6.5.2. Main study

Title of Study

RESMAIN: 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.

Methods

Trial 4SC-201-6-2015 was a multi-center, double-blind, randomized, placebo-controlled phase II trial to evaluate the efficacy and safety of maintenance treatment with resminostat. Adult patients with advanced stage (Stage IIB - IVB) MF or SS who had achieved disease control (CR, PR or SD) with previous systemic therapy were enrolled. The last systemic therapy had to be completed 2 - 12 weeks prior to randomization. Patients were randomized in a ratio of 1:1 to treatment with oral resminostat or matching placebo including stratification for current remission status (CR/PR versus SD) and disease stage (IIB/III/IVA1 versus IVA2/IVB) prior to last systemic therapy. All patients were treated until progression of disease or unacceptable toxicity. Patients on placebo had the option to roll-over to open-label treatment with resminostat.

Study Participants

Inclusion Criteria

-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 IFN- α , bexarotene, ECP, chemotherapy) or 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

-Eastern Cooperative Oncology Group (ECOG) status score of 0 - 2

-Adequate hematological, hepatic and renal function, as demonstrated by:

a) hemoglobin ≥ 9.0 g/dL (International System [SI] of Units: 5.6 mmol/L)

b) absolute neutrophil count (ANC) $\geq 1.0 \times 10^9/L$

c) platelets $\geq 75 \times 10^9/L$

d) ALT and aspartate aminotransferase (AST) ≤ 2 times upper limit of normal

e) total bilirubin ≤ 2 mg/dL (SI units: 34.2 $\mu\text{mol/L}$) (unless known Gilbert syndrome)

f) serum creatinine ≤ 1.5 mg/dL (SI units: 132 $\mu\text{mol/L}$)

g) prothrombin time: International Normalized Ratio (INR) ≤ 2.3

-Adequate recovery from non-hematological toxicities, excluding alopecia, to $\leq$ common terminology criteria for adverse events (CTCAE) Grade 1

Exclusion Criteria

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 (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 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-tumour therapy including PUVA, chemotherapy, immunotherapy, hormonal therapy, radiation therapy, or experimental medications
8. Previous or concurrent cancer that was distinct in primary site or histology from 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 in situ, treated basal cell carcinoma, superficial bladder tumours (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 medication
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 tumoural stage MF, presenting at baseline only with tumours (thereof at least one tumour ≥ 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)

Treatments

Each patient received treatment with oral resminostat or a matching oral placebo. The treatment was administered in a double-blind fashion based on the treatment arm to which the patient had been

randomized. Treatment was administered QD in repeated cycles of 5 days on therapy followed by a treatment-free period of 9 days (i.e., D1 - D5, q2w) until PD, unacceptable toxicity or patient withdrawal.

After each EOT visit, patients who discontinued treatment due to progression were unblinded individually. Patients who had been randomized to treatment with placebo were offered to roll-over to open-label treatment with resminostat QD, D1 - D5, q2w for as long as they benefited from therapy in the opinion of the investigators, or until unacceptable toxicity or patient withdrawal.

Based on the obtained data on safety, tolerability, PK and pharmacodynamics, the dose of 600 mg QD (3 tablets of 200 mg each), D1 - D5, q2w was the recommended dose and dosing regimen for repeated treatment cycles with resminostat and thus selected for the present trial.

Missed doses should not be administered at a later time. In these cases, the doses should be skipped, and the next dose administered as scheduled.

Objectives

The primary objective of the trial was to determine the superior efficacy of resminostat as a maintenance treatment based on progression free survival (PFS) in patients with advanced stage (Stage IIB - IVB) MF or SS who had achieved disease control (CR, PR or SD) with prior systemic therapy.

Secondary objectives of the trial were to:

- Determine efficacy of resminostat as a maintenance therapy based on secondary efficacy parameters (i.e., TTP, TTNT, PFS on the next treatment following study therapy (PFS2), PFS on the subsequent treatment (PFS3), ORR, DOR, and OS),
- Determine safety and tolerability of resminostat
- Determine changes in health-related quality of life (HrQoL) based on the key secondary endpoint (time to symptom worsening (TTSW): pruritus) and additional secondary QoL parameters (VAS for itching, FACT-G and Skindex-29 questionnaires).

The Applicant did not make use of the estimand framework. Nevertheless, the following estimand attributes are implied by the statistical analysis details that are provided as part of the SAP.

Table 7: Estimands for primary objective

Population	Patients according to eligibility criteria, with advanced stage (Stage IIB - IVB) MF or SS who had achieved disease control (CR, PR or SD) with prior systemic therapy
Treatment condition<s>	Assignment to resminostat in the hypothetical scenario of no subsequent cancer therapy before progression, compared to assignment to placebo in the hypothetical scenario of no subsequent cancer therapy before progression. Treatment administered on Days 1 - 5 (600 mg p.o. QD) of a 14-day treatment cycle; 5 days of treatment followed by a 9-day treatment-free period. Treatment until PD or unacceptable toxicity.
Endpoint (variable)	Progression Free Survival (PFS) defined as the time from date of randomization to first date the criteria for PD are met according to the GRS or death by any cause in the absence of documented PD. Only assessments within randomized

	period are taken into account for derivation of PFS. The Randomized period is defined as the period from date of randomization to date blinded EOT data is collected.
Population-level summary	As population level summary, the Hazard Ratio of the two treatment groups (Resminostat/Placebo) together with the corresponding 95% CI using Cox's proportional hazards model stratified by stage of disease and remission status is calculated. Hazard Ratio (HR) from a Cox proportional hazards model stratified by randomisation stratification factors.
Intercurrent events and strategy to handle them	
Patients received non-study cancer treatment before disease progression	Hypothetical: censored in primary analysis at the date of last complete GRA before non-study cancer treatment or randomisation day (whichever comes later), thereby ignoring data after non-study cancer treatment and assuming censored at random.
Death	Composite: event, to reflect treatment failure

The primary objective is a comparison of PFS between resminostat and placebo arms, in the hypothetical scenario that no non-study cancer treatment were received before progression. The intercurrent events (ICE) of initiation of non-study cancer before disease progression is handled using a hypothetical strategy, by censoring patients at the date of last complete GRA before its occurrence. In other words, data following non-study cancer treatment are ignored and the corresponding patients are assumed to be censored at random (CAR).

Outcomes/endpoints

Primary endpoint:

Progression Free Survival (PFS) defined as the time from date of randomization to first date the criteria for PD are met according to the GRS or death by any cause in the absence of documented PD.

Secondary efficacy endpoints included:

- TTSW (pruritus; key secondary endpoint), defined as the time from date of randomization to first date the criteria for symptom (pruritus) worsening had been met.
- TTP, defined as the time from date of randomization to first date that criteria for PD (per the GRS) have been met.
- TTNT, defined as the time from date of randomization to first date that new treatment is received; for placebo patients, roll-over to open-label resminostat was considered as the next treatment
- PFS2 and PFS3, defined as the time from date of randomization to second/third objective disease progression, or death of any cause, whichever comes first (note: will only be available upon the final data analysis at the end of the clinical study)
- ORR (CR, PR), defined as the percent of patients within each treatment arm that achieve CR or PR relative to the number of patients belonging to the analysis population of interest

- DOR, defined as the time from date of CR or PR (whichever is first) until the criteria for PD per the GRS as specified in the protocol have been met.
- OS, defined as the time from the day of randomization to death from any cause.
- The analysis of HrQoL based on VAS for itching, FACT-G and Skindex-29 questionnaires, safety and the PK of resminostat and its metabolites.

Sample size

Final sample size determination from protocol version 7.0, 15 November 2021

The sample size calculation was based on the primary endpoint PFS. In order to calculate the number of required events, a PFS of 4.2 month in the control Arm (Arm B; placebo) was assumed. Based on a hazard ratio of 0.6, a median PFS of 7 months should be reached in the treatment Arm (Arm A; resminostat). An enrolment period of 24 months and 12 months FU was assumed. Based on the commonly used significance level, a two-sided $\alpha = 0.05$ for the type 1 error was allocated as the significance level for the primary endpoint. Applying a power of 80% and a drop-out rate of 33% the total patient number needed was calculated with 200 patients to get 125 PFS events. For enrolment of 100 patients per treatment arm, a total of approximately 200 patients would be enrolled. The sample size calculation was performed with Pass 14 by NCSS, LLC.

No detailed results for the key secondary endpoint TTSW are available to be used as assumptions for the sample size calculation. However, the trial was powered to detect a hazard ratio of 0.6 for TTSW and such a hazard ratio was considered as clinically relevant in this context.

Sample size determination from protocol version 6.0, 28 February 2019

The same assumptions as above were considered, with the exception of the drop-out rate which was assumed to be 30%. Accordingly, the total patient number needed was calculated to be 189 patients to get 125 PFS events. For enrolment of 95 patients per treatment arm, a total of approximately 190 patients were to be enrolled.

Sample size determination in preceding protocol versions

The same assumptions as above were considered, with the exception of the drop-out rate which was assumed to be 10%. Accordingly, the total patient number needed was calculated to be 150 patients to get 125 PFS events.

Randomisation and blinding (masking)

Eligible patients were randomized to treatment with resminostat or placebo at a ratio of 1:1 using IWRS. Randomization of patients was stratified by remission status (CR/PR versus SD, i.e., the best response achieved with the last systemic therapy) and by MF/SS disease stage immediately prior to the last systemic treatment which resulted in CR, PR or SD (stage IIB, III, IVA1 versus stage IVA2, IVB as assessed based on International Society for Cutaneous Lymphomas (ISCL)/European Organisation for Research and Treatment of Cancer (EORTC) revised staging system for MF/SS).

The trial was conducted as a double-blind trial.

Subsequently to stratification and randomization, the IWRS assigned a specific medication kit (per kit number) to each patient. The kit numbers were assigned to wallets, each containing one resminostat or

placebo blister. This procedure was followed to ensure that investigators and patients (as well as Sponsor and CRO) did not know which treatment a patient received.

Each patient was unblinded individually at the time of progression to determine subsequent treatment or FU procedures. This EOT unblinding was performed by the investigator via the IWRS.

Emergency unblinding for a patient was also performed via the IWRS by the investigator or authorized team members with immediate access to the randomization code, if it was in the best interest of the patient. Once the randomization code was broken, the patient had to be withdrawn from treatment and entered FU for survival. The investigator had to inform the Medical Monitor about an emergency unblinding in writing within 24 hours. Unblinding of an individual patient did not affect the double-blind character of the trial. Unblinding of all ongoing patients was performed once the results of the main analysis (primary data analysis) were available.

Prior to unblinding of each patient, the patient and their Investigator were questioned for the assumed treatment arm of the patient. A total of 60.0% of both patients and Investigators guessed treatment with resminostat correctly, while 17.0% each assumed treatment with placebo (missing: 23.0% each). For placebo, 70.3% of the patients and 76.2% of the Investigators guessed the correct treatment arm, with 19.8% and 13.9%, respectively, assuming treatment with resminostat (missing: 9.9% each).

Statistical methods

Analysis populations

The main analysis of trial endpoints was based on the following analysis populations:

- ITT population: all randomized patients
- PP population: patients randomized, treated with at least one dose of trial medication and with no major protocol violations at the time of data review meeting for the main analysis
- Safety population: patients treated with at least one dose of trial medication
- TTSW (pruritus) population: all randomized patients with a VAS itching score of ≤ 7 at treatment start; patients without VAS itching score at baseline were excluded
- Roll-over population: patients from treatment arm B (placebo), who opted to receive open-label resminostat treatment after unblinding and were treated with at least one dose of resminostat

Adjustment for multiplicity and interim analyses

The results for analysis of TTSW (pruritus) would only be considered confirmative, if the analysis of the primary endpoint showed a significant result ($p\text{-value} \leq 0.05$). This hierarchical approach keeps the global significance level to 0.05 two-sided and required no further adjustment.

There was no planned adjustment for multiplicity for other secondary endpoints.

No interim analysis was planned for this study. Thus, the full significance (α) level of 0.05 was used for this main analysis and all analyses within the scope of the final analysis will be considered exploratory.

Primary endpoint

PFS was defined as the time from date of randomisation to first date that criteria for PD have been met or death due to any cause in the absence of documented PD. The Global Response Score reported by the Investigator in the eCRF was used for the analysis. Global Response Scores may be based on less than four

components in case of missing values/assessments. An event of progression was considered to be present as soon as PD was observed in at least one of the four components (regardless of the other (possibly unavailable/missing) assessments). Censoring for the PFS endpoint was assigned on the dates according to the rules in the table below.

ID	Situation	Date of Progression or Censoring	Outcome
1	Baseline GRA missing/incomplete (for exceptions see 5.1.3.6)	Date of randomisation day	Censored
2	Patient received non-study cancer treatment before disease progression	Date of last complete GRA before non-study cancer treatment or randomisation day (whichever comes later)	Censored
3	No progression or death (at least 1 complete post-baseline GRA)	Date of last complete GRA	Censored
4	Death or progression directly after at least two consecutive incomplete/missing GRAs	Date of last complete GRA	Censored
5	Progression or death documented between or on scheduled visits	Date of PD or date of death (whichever comes first)	Progressed
6	No complete post-baseline GRA	Date of randomisation day	Censored

Note: the date of last global response assessment (GRA) is defined as the date of the last GRA = all four components of the GRA measured with censoring date being the last of the four components. If all 4 components were assessed before Day 43 and no later complete GRA assessment or PD exists, these assessments should be used for censoring. A component that is not involved is not considered to be missing.

A two-sided stratified log-rank test, taking strata (stage of disease, remission status) into account, was used to compare the median PFS between the two treatment arms.

Kaplan-Meier PFS curves (product-limit estimates) were presented by treatment arm including the number of patients at risk at selected time points.

The Hazard Ratio (HR) of the two treatment groups (Resminostat/Placebo) was calculated together with the corresponding 95% CI using Cox's proportional hazards model stratified by stage of disease and remission status.

Sensitivity analyses

1. A sensitivity analysis was conducted where patients who leave the study due to toxicity or start of new treatment (and no PD was observed prior to that) are not censored but considered as having PD on the date of discontinuation.
2. A sensitivity analysis was conducted where the censoring rule ID 4 was changed to:

4	Death or progression directly after one or more consecutive incomplete/missing GRAs	Date of last complete GRA	Censored
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3. A sensitivity analysis was conducted where PFS was not only considered to be present until the last Global Response Score without PD that is based on all four components but also until the last

Intermediate Response Assessment without PD that is based on the remaining two components (mSWAT and Flow Cytometry) for visits where no CT is to be conducted.

4. A sensitivity analysis was conducted where the response assessment rules for skin from protocol version 3.0 was applied. PD in skin was derived separately as increase of $\geq 25\%$ from baseline in mSWAT. The exception for patients who entered the study with a CR (mSWAT of 0) or with a very good PR to prior therapy (mSWAT below 16) and for whom any increase in mSWAT to less than 20 and without new tumours (reflecting still stage IA skin disease) should not be considered progressive disease, but SD in skin, is not applicable for this sensitivity analysis. In consequence, any increase in mSWAT is considered as PD for patients with mSWAT of 0 at baseline.
5. A sensitivity analysis recommended by the DSMB was conducted for PFS where censoring rule ID 2 was changed to:

2	Patient received non-study cancer treatment before disease progression	Date of study treatment discontinuation	Progressed
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Key secondary endpoint

The same analysis method as that described for PFS was used for analysis of TTSW (pruritus worsening).

Censoring for the TTSW (pruritus) endpoint was assigned on the date of the last on trial assessment of symptom (pruritus) worsening if criteria for symptom (pruritus) worsening had not been met.

Other secondary endpoints

The same method as that described for PFS were to be used for analysis of TTP, TTNT, PFS2, and PFS3.

TTP: The censoring rules for PFS were applied with the exception, that only disease-related deaths were considered in rule 3, 4 and 5.

TTNT: If a patient does not start a new (next) treatment after discontinuing from study drug, then TTNT was censored on the date of last contact. For placebo patients, rollover to Resminostat was considered as the next treatment.

PFS2/PFS3: A comparison is planned at the final analysis between the patients who were randomized to Resminostat and the patients who were randomized to Placebo and did not roll over to Resminostat. Patients who were randomized to Placebo and roll over to Resminostat are planned to be excluded to compare Resminostat patients with those who were never treated with Resminostat. Censoring rules for analysis are given below:

ID	Situation	Date of Progression or Censoring	Outcome
1	No progression during first or second subsequent treatment or death	End date of last subsequent CTCL therapy or radiotherapy or date of last complete GRA (whichever comes later). If therapy is ongoing, date of study discontinuation is used instead.	Censored
2	PD during first or second subsequent treatment	Date of PD	Progressed
3	Death during any randomized or subsequent treatment	Date of death	Progressed

ORR: Only Global Response Scores that are based on all four components were considered for the evaluation of the ORR. If no post-baseline Global Response Score based on all components exists, the overall response cannot be derived for the respective patient. A comparison of the ORR (CR or PR) in each of the treatment arms was made using a Cochran-Mantel-Haenszel (CMH) test taking strata used for randomisation (stage of disease, remission status) into account. The ORR (CR or PR) together with corresponding 95% CI, odds ratio and corresponding 95% Clopper-Pearson exact CI and p-value for the CMH test were presented.

DOR

For patients who achieve a PR or CR during the trial, DOR was calculated as the number of months from the date measurement criteria are first met for a PR or CR (whichever is recorded first) as determined by global response score assessment (based on four components) until the first date that PD is determined by global response score assessment. Patients with baseline remission status CR are excluded from this analysis. DOR was calculated as (date of first PD - date of PR/CR) + 1. Patients who achieve PR or CR but for whom subsequent PD is not observed during the trial are censored at the time when the patient is last known to be non-progressing. Last known to be non-progressing is the date of last global response score assessment meeting the criteria for CR or PR or SD not limited to global response score assessments based on all four components. DOR was analysed for the patients in the ITT population who had CR/PR during the randomised treatment period.

OS

The number and percentage of patients that died, together with reason for death was summarised for the ITT population. A two-sided stratified log-rank test, taking strata (stage of disease, remission status) into account, was used to compare the median OS between the two treatment arms.

For patients who are known to be still alive at the time of trial analysis or who are lost to FU, survival time was censored at the last recorded date that the patient is known to be alive (i.e. the date of last attended visit or the date of the follow-up phone call). Not only data from randomised period but also rollover and follow-up data were taken into account for derivation of overall survival.

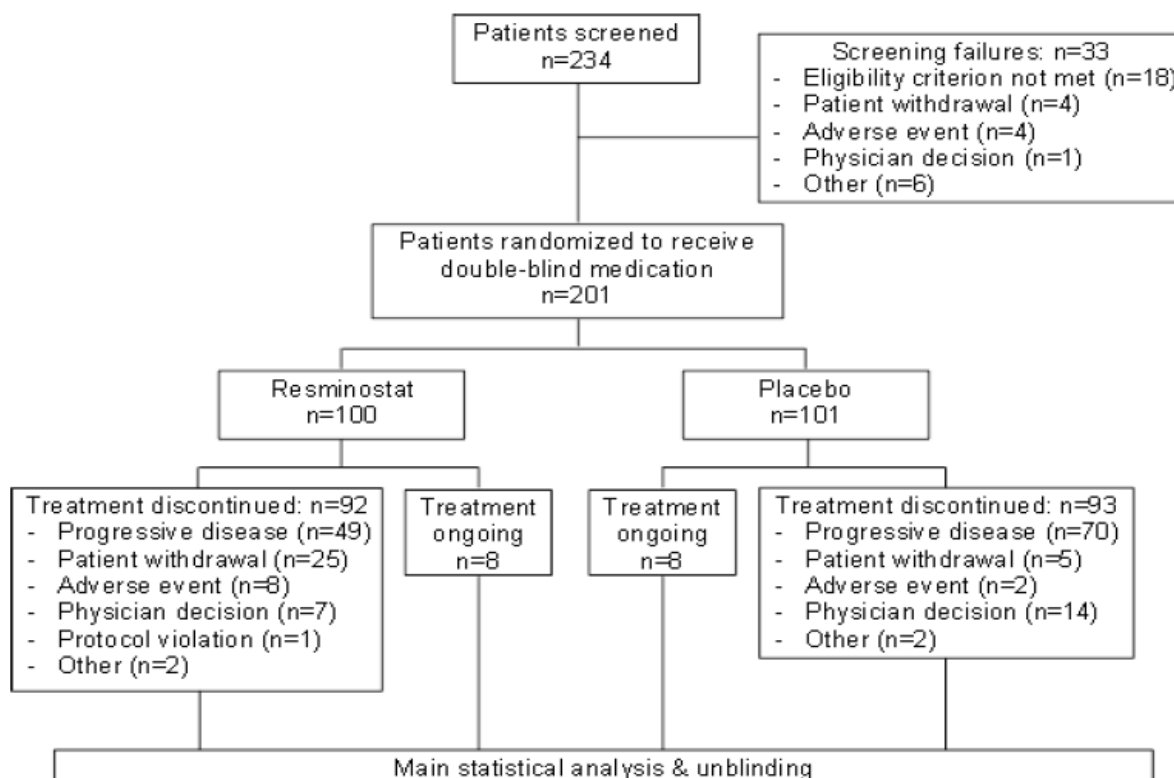
HrQoL

A linear MMRM approach was applied to analyse change from baseline over time of HrQoL data. The MMRM included treatment arm, baseline, time point (continuous), time point (continuous) by treatment interaction and time point (continuous) by baseline interaction as fixed effects.

Results

Participant flow

Figure 2 Disposition of Trial Participants (as of 10-Mar-2023)



Source: [Tables 14.1.1.1 and 14.1.1.2](#); [Listings 16.2.1.1, 16.2.1.2 and 16.2.1.4](#).

Recruitment

Patients were enrolled at 55 trial sites in 12 countries, including 11 European countries (i.e. Austria, Belgium, France, Germany, Greece, Italy, The Netherlands, Poland, Spain, Switzerland and United Kingdom (UK)) and Japan.

First patient enrolled: 14-Dec-2016

DCO primary analysis: 10-Mar-2023

Conduct of the study

Protocol Amendments

The original protocol was issued on 07-Apr-2016. There were 7 amendments to the protocol. At Japanese sites, the trial was conducted according to protocol versions 4.0 through 8.0 but required additional protocol appendices due to country-specific regulation.

Table 9 Protocol and Protocol Amendments

Protocol Version	Date	Note
1.0	07-Apr-2016	not submitted to any IEC/CA
1.1	29-Apr-2016	non-substantial changes only; submitted to all IECs/CAs (except for Greece) and approved in all countries (except Greece, Germany and UK)
2.0	26-Jul-2016	submitted and approved in UK only
3.0	24-Oct-2016	Submitted and approved in Germany only
4.0	09-Mar-2017	submitted to all IECs/CAs and approved in all countries
5.0	23-Jul-2018	submitted to all IECs/CAs and approved in all countries
5.1 ¹	03-Apr-2019	Submitted and approved in Belgium only
6.0	28-Feb-2019	submitted to all IECs/CAs and approved in all countries (except Belgium and Germany)
6.1 ²	07-May-2019	Submitted and approved in Germany only

Protocol Version	Date	Note
6.2 ³	01-Jul-2019	Submitted and approved in Belgium only
7.0	15-Nov-2021	submitted to all IECs/CAs except Germany and Belgium
7.1 ¹	19-Nov-2021	Submitted and approved in Germany only
7.2 ²	19-Nov-2021	Submitted and approved in Belgium only
8.0	21-Dec-2022	submitted to all IECs/CAs except Germany and Belgium
8.1 ¹	22-Dec-2022	submitted and approved in Germany only
8.2 ²	22-Dec-2022	submitted and approved in Belgium only
The following country-specific protocol appendices were used in Japan:		
3.0	27-Nov-2017	submitted in Japan in addition to the protocol
3.1	25-Mar-2019	submitted in Japan in addition to the protocol
3.2	23-Mar-2020	submitted in Japan in addition to the protocol
3.3	02-Oct-2020	submitted in Japan in addition to the protocol
3.4	01-Apr-2021	submitted in Japan in addition to the protocol
3.5	18-Nov-2021	submitted in Japan in addition to the protocol

CA: competent authority; IEC: independent ethics committee; UK: United Kingdom.

¹ Country-specific protocol amendment as requested by the Belgian EC.

² Country-specific trial protocol as requested by national regulatory authority: the German regulatory authority (Bundesministerium fuer Arzneimittel und Medizinprodukte, BfArM) requested changes to protocol version 6.0, leading to modified and approved version 6.1 and subsequent country-specific protocol versions 7.1 and 8.1.

³ Country-specific trial protocol as requested by local EC: the Belgian EC requested changes to protocol version 6.0, leading to modified and approved version 6.2 and subsequent country-specific protocol versions 7.2 and 8.2.

Protocol Deviations

In the resminostat arm, a total of 10 patients (10.0%) were excluded from the PP population. In 5 patients, this was due to determination of PD not fulfilling the PD criteria defined in the study protocol (and thus the blind broken). Another 5 patients were excluded for not being able to be assessed for the ECG parameter of QTc (leading to early discontinuation), missing first 2 post-baseline GRS assessments, violation of eligibility criteria, missing GRS before PD and wrong subject medication given (in 1 patient each).

In the placebo arm, a total of 17 patients (16.8%) were excluded from the PP population due to determination of PD not fulfilling the PD criteria defined in the study protocol (and thus the blind broken) in 13 patients, missing GRS before PD in 3 patients and wrong subject medication given in 1 patient.

Table 14.1.3.1 Analysis Populations based on Treatment as Randomised (ITT Population)

Analysis Population	Resminostat (N=100) n (%)	Placebo (N=101) n (%)	Total (N=201) n (%)
Patients in the ITT Population	100 (100)	101 (100)	201 (100)
Patients Randomised but not Treated	0	0	0
Patients in the PP Population	90 (90.0)	84 (83.2)	174 (86.6)
Patients Excluded from PP Population	10 (10.0)	17 (16.8)	27 (13.4)
Reasons for exclusion*			
Blind Broken	5 (50.0)	13 (76.5)	18 (66.7)
Discontinued early due to not being able to be assessed for ECG - PD for Inclusion/exclusion	1 (10.0)	0	1 (3.7)
GRS for first 2 assessments post-baseline are missing	1 (10.0)	0	1 (3.7)
Inclusion/exclusion criteria	1 (10.0)	0	1 (3.7)
Missing GRS before PD	1 (10.0)	3 (17.6)	4 (14.8)
Wrong Subject medication given	1 (10.0)	1 (5.9)	2 (7.4)
Patients in the TTSW Population	72 (72.0)	82 (81.2)	154 (76.6)
Patients Excluded from TTSW Population	28 (28.0)	19 (18.8)	47 (23.4)
Reasons for exclusion*			
No VAS Itching Score at Baseline	9 (32.1)	9 (47.4)	18 (38.3)
VAS Criteria Not Met at Baseline	19 (67.9)	10 (52.6)	29 (61.7)
Subgroups			
Mycosis Fungoides (ITT-MF)	80 (80.0)	84 (83.2)	164 (81.6)
Sézary Syndrome (ITT-SS)	20 (20.0)	17 (16.8)	37 (18.4)
Complete or Partial Response (ITT-MR)	63 (63.0)	69 (68.3)	132 (65.7)
Stable Disease (ITT-SD)	37 (37.0)	32 (31.7)	69 (34.3)
Disease stage IIB, IIIA/IIIB, or IVA1 (ITT-DS1)	84 (84.0)	82 (81.2)	166 (82.6)
Disease stage IVA2 or IVB (ITT-DS2)	16 (16.0)	19 (18.8)	35 (17.4)

Table 14.1.2.1 Major Protocol Deviations (Randomised Period) (ITT Population)

Table 14.1.2.1 Major Protocol Deviations (Randomised Period) (ITT Population)

Classification [1] Deviation Sub Type	Resminostat (N=100) n (%)	Placebo (N=101) n (%)	Total (N=201) n (%)
Number of Patients with at least one Major Deviation	80 (80.0)	75 (74.3)	155 (77.1)
Comeds			
Took Prohibited Med During Treatment	13 (13.0)	7 (6.9)	20 (10.0)
Icf Issues			
Icf Signed On Different Dates	0	1 (1.0)	1 (0.5)
Icf Signed On Wrong Date	1 (1.0)	1 (1.0)	2 (1.0)
Incorrect Icf Signed By Subject	5 (5.0)	2 (2.0)	7 (3.5)
Signed Icf Not In Site File/Lost	0	1 (1.0)	1 (0.5)
Specify In Comments	21 (21.0)	6 (5.9)	27 (13.4)
Unapproved Or Obsolete Version Signed	2 (2.0)	0	2 (1.0)
Inclusion / Exclusion			
Deviations In Incl./Excl. Criteria	10 (10.0)	7 (6.9)	17 (8.5)
Specify In Comments	2 (2.0)	1 (1.0)	3 (1.5)
Laboratory			
Labs Lost By Courier/Received Late	0	2 (2.0)	2 (1.0)
Labs Not Done	10 (10.0)	10 (9.9)	20 (10.0)
Specify In Comments	5 (5.0)	2 (2.0)	7 (3.5)
Other			
Specify In Comments	18 (18.0)	18 (17.8)	36 (17.9)
Unreported Sae	1 (1.0)	1 (1.0)	2 (1.0)
Procedures / Tests			
Performed Outside Window	25 (25.0)	22 (21.8)	47 (23.4)
Procedure Not Done	58 (58.0)	48 (47.5)	106 (52.7)
Specify In Comments	11 (11.0)	8 (7.9)	19 (9.5)
Visit Not Done	1 (1.0)	0	1 (0.5)

Table 14.1.2.1 Major Protocol Deviations (Randomised Period) (ITT Population)

Classification [1] Deviation Sub Type	Resminostat (N=100) n (%)	Placebo (N=101) n (%)	Total (N=201) n (%)
Study Drug			
Blind Broken (Potential Or Actual)	5 (5.0)	12 (11.9)	17 (8.5)
Dosing Non-Compliance	1 (1.0)	1 (1.0)	2 (1.0)
Incorrect Medication/Randomization	2 (2.0)	2 (2.0)	4 (2.0)
Specify In Comments	5 (5.0)	7 (6.9)	12 (6.0)
Visit Schedule			
Specify In Comments	3 (3.0)	0	3 (1.5)
Visit Incomplete	3 (3.0)	1 (1.0)	4 (2.0)
Visit Not Done	2 (2.0)	5 (5.0)	7 (3.5)
Visit Outside Protocol Window	9 (9.0)	9 (8.9)	18 (9.0)

Table 14.1.2.2 Minor Protocol Deviations (Randomised Period) (ITT Population)

Table 14.1.2.2 Minor Protocol Deviations (Randomised Period) (ITT Population)

Classification [1] Deviation Sub Type	Resminostat (N=100) n (%)	Placebo (N=101) n (%)	Total (N=201) n (%)
Number of Patients with at least one Minor Deviation	93 (93.0)	94 (93.1)	187 (93.0)
Concomitant medications			
Other	1 (1.0)	0	1 (0.5)
Inclusion / Exclusion Deviations In Incl./Excl. Criteria	2 (2.0)	0	2 (1.0)
Laboratory			
Labs Lost By Courier/Received Late	1 (1.0)	0	1 (0.5)
Labs Not Done	58 (58.0)	59 (58.4)	117 (58.2)
Other	33 (33.0)	26 (25.7)	59 (29.4)
Procedures / Tests			
Performed Outside Window	50 (50.0)	49 (48.5)	99 (49.3)
Procedure Not Done	47 (47.0)	38 (37.6)	85 (42.3)
Other	37 (37.0)	32 (31.7)	69 (34.3)
Study Drug			
Dosing Non-Compliance	6 (6.0)	3 (3.0)	9 (4.5)
Subject Took Incorrect Dose	1 (1.0)	0	1 (0.5)
Other	12 (12.0)	11 (10.9)	23 (11.4)
Visit Schedule			
Performed Outside Window	1 (1.0)	0	1 (0.5)
Visit Not Done	18 (18.0)	7 (6.9)	25 (12.4)
Visit Outside Protocol Window	68 (68.0)	40 (39.6)	108 (53.7)
Other	1 (1.0)	1 (1.0)	2 (1.0)
Other			
Other	9 (9.0)	1 (1.0)	10 (5.0)

[1] Includes protocol violations and protocol deviations which are available at the time of the data review meeting for the main analysis. Major and minor protocol deviations are key and non-key protocol deviations according to the protocol deviation criteria form, respectively. If a patient has more than one protocol deviation they will be counted only once in the 'at least one' summary.

Table 3. GCP inspections

Site (Full address)	Country	Date of inspection	Regulatory Agency
DE02 PD Dr. med. Chalid Assaf Helios Klinikum Krefeld Klinik für Dermatologie Lutherplatz 40 47805 Krefeld	Germany	23.-24. Jul 2018	Gesundheitsamt Landeshauptstadt Düsseldorf – Zentrales Inspektorat für klinische Prüfstellen in Nordrhein- Westfalen Will-Becker- Allee 10 40227 Düsseldorf Germany
DE09 Prof. Dr. med. Dorothee Nashan Klinikum Dortmund gGmbH Klinikzentrum Mitte, Hautklinik Beurhausstr. 40 44137 Dortmund	Germany	1.-2. Aug 2018	Gesundheitsamt Landeshauptstadt Düsseldorf – Zentrales Inspektorat für klinische Prüfstellen in Nordrhein- Westfalen Will-Becker- Allee 10 40227 Düsseldorf Germany
CH-01 Prof. Dr. med. Reinhard Dummer Universitätsspital Zürich Dermatologische Klinik Gloriastr. 31 8091 Zürich	Switzerland	17. Oct 2018	Swissmedic Swiss Agency for Therapeutic Products Hallerstr. 7 3012 Bern Switzerland

Baseline data

Table 11 Patient Baseline Characteristics (ITT Population)

Characteristic		Resminostat N=100	Placebo N=101	Total N=201
Age, years	median min, max	63.5 32 - 87	64.0 30 - 84	64.0 30 - 87
Age group, n (%)	≤ 65 > 65	56 (56.0) 44 (44.0)	55 (54.5) 46 (45.5)	111 (55.2) 90 (44.8)
Gender, n (%)	male female	53 (53.0) 47 (47.0)	70 (69.3) 31 (30.7)	123 (61.2) 78 (38.8)

Characteristic		Resminostat N=100	Placebo N=101	Total N=201
Race, n (%)	Caucasian/White	85 (85.0)	88 (87.1)	173 (86.1)
	Asian	11 (11.0)	8 (7.9)	19 (9.5)
	African/Black	0	2 (2.0)	2 (1.0)
	Multiple/Other	4 (4.0)	3 (3.0)	7 (3.5)
Region, n (%)	Europe	92 (92.0)	94 (93.1)	186 (92.5)
	Japan	8 (8.0)	7 (6.9)	15 (7.5)
Weight, kg	median	74.8	80.0	77.1
	min, max	49.1 - 109.2	48.0 - 119.7	48.0 - 119.7
BMI, kg/m ²	median	25.95	27.16	26.66
	min, max	19.1 - 40.5	15.1 - 41.9	15.1 - 41.9
ECOG performance status at baseline, n (%)	0	82 (82.0)	81 (80.2)	163 (81.1)
	1	15 (15.0)	19 (18.8)	34 (16.9)
	2	3 (3.0)	1 (1.0)	4 (2.0)
CTCL subtype, n (%)	MF	80 (80.0)	84 (83.2)	164 (81.6)
	SS	20 (20.0)	17 (16.8)	37 (18.4)
Duration of disease, years	median	4.50	5.08	5.02
	min, max	0.2 - 34.1	0.6 - 33.1	0.2 - 34.1
Disease stage at baseline, n (%) [Stratum I]	IIB	59 (59.0)	58 (57.4)	117 (58.2)
	IIIA	8 (8.0)	4 (4.0)	12 (6.0)
	IIIB	7 (7.0)	4 (4.0)	11 (5.5)
	IVA1	10 (10.0)	16 (15.8)	26 (12.9)
	IVA2	13 (13.0)	13 (12.9)	26 (12.9)
	IVB	3 (3.0)	6 (5.9)	9 (4.5)
Remission status, n (%) [Stratum II]	CR	14 (14.0)	11 (10.9)	25 (12.4)
	PR	49 (49.0)	58 (57.4)	107 (53.2)
	SD	37 (37.0) → 37.0%	32 (31.7) → 31.7%	69 (34.3)
Large cell transformation, n (%)	yes	24 (24.0)	13 (12.9)	37 (18.4)
	no	76 (76.0)	88 (87.1)	164 (81.6)
Anti-itching treatment at baseline, n (%)	yes	37 (37.0)	35 (34.7)	72 (35.8)
	no	63 (63.0)	66 (65.3)	129 (64.2)
Time from last systemic therapy, days	median	37.0	41.0	39.0
	min, max	5 - 86	10 - 87	5 - 87
Last prior systemic treatment, n (%)	bexarotene/ other retinoids	28 (28.0)	19 (18.8)	47 (23.4)
	chemotherapy	21 (21.0)	26 (25.7)	47 (23.4)
	brentuximab vedotin	10 (10.0)	20 (19.8)	30 (14.9)
	TSEB	13 (13.0)	11 (10.9)	24 (11.9)
	ECP	6 (6.0)	6 (5.9)	12 (6.0)
	other	22 (22.0)	19 (18.8)	41 (20.4)

BMI: body mass index; CR: complete response; CTCL: cutaneous T-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; ECP: extracorporeal photopheresis; MF: mycosis fungoides; N: number of patients randomized; n: number of patients affected; PR: partial response; SD: stable disease; SS: Sézary syndrome; TSEB: total skin

Disease History

Table 12 Disease History and Previous Therapies for CTCL (ITT Population)

Characteristic		Resminostat N = 100	Placebo N = 101	Total N = 201
Stage at initial diagnosis, n (%)	IA	9 (9.0)	16 (15.8)	25 (12.4)
	IB	24 (24.0)	20 (19.8)	44 (21.9)
	IIA	3 (3.0)	3 (3.0)	6 (3.0)
	IIB	34 (34.0)	34 (33.7)	68 (33.8)
	IIIA	6 (6.0)	5 (5.0)	11 (5.5)
	IIIB	3 (3.0)	1 (1.0)	4 (2.0)
	IVA1	11 (11.0)	16 (15.8)	27 (13.4)
	IVA2	8 (8.0)	3 (3.0)	11 (5.5)
	IVB	1 (1.0)	1 (1.0)	2 (1.0)
	unknown	1 (1.0)	2 (2.0)	3 (1.5)
Previous systemic therapy, n (%)		100 (100)	101 (100)	201 (100)
Number of prior systemic treatment lines	mean (SD)	4.3 (3.8)	3.9 (3.4)	4.1 (3.6)
	median	3.0	3.0	3.0
	min - max	1 - 20	1 - 21	1 - 21
Number of prior systemic treatments per patient, n (%)	1 - 4	71 (71.0)	73 (72.3)	144 (71.6)
	5 - 8	18 (18.0)	23 (22.8)	41 (20.4)
	9 - 21	11 (11.0)	5 (5.0)	16 (8.0)
Previous systemic treatments, n (%)	Alkylating agents	9 (9.0)	8 (7.9)	17 (8.5)
	Bendamustine	1 (1.0)	1 (1.0)	2 (1.0)
	Busulfan	1 (1.0)	0	1 (0.5)
	Carmustine	5 (5.0)	3 (3.0)	8 (4.0)
	Chlorambucil	5 (5.0)	2 (2.0)	7 (3.5)
	Chlorambucil/prednisone	0	1 (1.0)	1 (0.5)
	Chlormethine hydrochloride	1 (1.0)	1 (1.0)	2 (1.0)
	Ifosfamide	0	1 (1.0)	1 (0.5)
	Anti-acne preparations	1 (1.0)	0	1 (0.5)
	Isotretinoin	1 (1.0)	0	1 (0.5)
	Antimetabolites	50 (50.0)	47 (46.5)	97 (48.3)
	Cytarabine	2 (2.0)	0	2 (1.0)
	Fludarabine	1 (1.0)	0	1 (0.5)
	Gemcitabine ¹	18 (18.0)	25 (24.8)	43 (21.4)
	Methotrexate ¹	40 (40.0)	35 (34.7)	75 (37.3)
	Antipsoriatics	12 (12.0)	13 (12.9)	25 (12.4)
	Acitretin	8 (8.0)	9 (8.9)	17 (8.5)
	Etretinate	4 (4.0)	3 (3.0)	7 (3.5)
	Dimethyl fumarate	0	1 (1.0)	1 (0.5)
	Corticosteroids	4 (4.0)	3 (3.0)	7 (3.5)
	Betamethasone	1 (1.0)	0	1 (0.5)
	Methylprednisolone	1 (1.0)	0	1 (0.5)
	Prednisolone	1 (1.0)	1 (1.0)	2 (1.0)
	Prednisone	1 (1.0)	2 (2.0)	3 (1.5)

Characteristic		Resminostat N = 100	Placebo N = 101	Total N = 201
	Cytotoxic antibiotics and related substances	15 (15.0)	18 (17.8)	33 (16.4)
	Daunorubicin	1 (1.0)	0	1 (0.5)
	Doxorubicin ¹	6 (6.0)	4 (4.0)	10 (5.0)
	Idarubicin	1 (1.0)	0	1 (0.5)
	Liposomal doxorubicin hydrochloride	0	2 (2.0)	2 (1.0)
	Pegylated liposomal doxorubicin ¹	9 (9.0)	12 (11.9)	21 (10.5)
	Immunostimulants	62 (62.0)	46 (45.5)	108 (53.7)
	Interferon	62 (62.0)	46 (45.5)	108 (53.7)
	Interferon alfa-2a	0	2 (2.0)	2 (1.0)
	Immunosuppressants	4 (4.0)	0	4 (2.0)
	Azathioprine	1 (1.0)	0	1 (0.5)
	Ciclosporin	1 (1.0)	0	1 (0.5)
	Dupilumab	1 (1.0)	0	1 (0.5)
	Mycophenolate mofetil	1 (1.0)	0	1 (0.5)
	Secukinumab	1 (1.0)	0	1 (0.5)
	Tacrolimus	1 (1.0)	0	1 (0.5)
	Other antineoplastic agents	75 (75.0)	72 (71.3)	147 (73.1)
	Alemtuzumab	5 (5.0)	4 (4.0)	9 (4.5)
	Alisertib	1 (1.0)	0	1 (0.5)
	Alitretinoin	4 (4.0)	2 (2.0)	6 (3.0)
	Atezolizumab	0	1 (1.0)	1 (0.5)
	Bexarotene	68 (68.0)	56 (55.4)	124 (61.7)
	Brentuximab vedotin	17 (17.0)	24 (23.8)	41 (20.4)
	CHOP/CHOP-like ² combination chemotherapy	4 (4.0)	9 (8.9)	13 (6.5)
	Dasatinib	0	1 (1.0)	1 (0.5)
	Gemcitabine/oxaliplatin	0	1 (1.0)	1 (0.5)
	Mogamulizumab	6 (6.0)	9 (8.9)	15 (7.5)
	Monoclonal antibodies	2 (2.0)	2 (2.0)	4 (2.0)
	Panobinostat	0	1 (1.0)	1 (0.5)
	Quisinostat	1 (1.0)	0	1 (0.5)
	Romidepsin	2 (2.0)	5 (5.0)	7 (3.5)
	Talimogene laherparepvec	1 (1.0)	0	1 (0.5)
	Vorinostat	2 (2.0)	5 (5.0)	7 (3.5)
	Plant alkaloids and other natural products	2 (2.0)	3 (3.0)	5 (2.5)
	Etoposide	2 (2.0)	3 (3.0)	5 (2.5)
	Surgical and medical procedures	39 (39.0)	33 (32.7)	72 (35.8)
	TSEB	21 (21.0)	14 (13.9)	35 (17.4)
	ECP	20 (20.0)	21 (20.8)	41 (20.4)
	Investigational drug	1 (1.0)	1 (1.0)	2 (1.0)
Previous local radiotherapy, n (%)		34 (34.0)	42 (41.6)	76 (37.8)
Previous stem cell transplantation, n (%)		1 (1.0)	2 (2.0)	3 (1.5)

Prior and Concomitant Diseases

Table 13 Medical History in $\geq 5\%$ of Patients by SOC and PT (ITT Population)

System Organ Class/Preferred Term, n (%) ¹	Resminostat N = 100	Placebo N = 101	Total N = 201
Patients with any diseases	47 (47.0)	49 (48.5)	96 (47.8)
Surgical and medical procedures	20 (20.0)	27 (26.7)	47 (23.4)
Neoplasms benign, malignant and unspecified	14 (14.0)	12 (11.9)	26 (12.9)
Infections and infestations	8 (8.0)	13 (12.9)	21 (10.4)
Injury, poisoning and procedural complications	9 (9.0)	5 (5.0)	14 (7.0)
Gastrointestinal disorders	4 (4.0)	7 (6.9)	11 (5.5)
Nervous system disorders	5 (5.0)	6 (5.9)	11 (5.5)
Skin and subcutaneous tissue disorders	3 (3.0)	5 (5.0)	8 (4.0)
Vascular disorders	2 (2.0)	6 (5.9)	8 (4.0)
Musculoskeletal and connective tissue disorders	5 (5.0)	2 (2.0)	7 (3.5)
Respiratory, thoracic and mediastinal disorders	2 (2.0)	5 (5.0)	7 (3.5)

N: number of patients randomized; n: number of patients affected; PT: preferred term; SOC: system organ class.

¹ No PTs were reported in $\geq 5\%$ of patients.

Source: [Table 14.1.5.1](#).

Table 14 Concomitant Conditions in $\geq 5\%$ of Patients by SOC and PT (ITT Population)

System Organ Class/Preferred Term, n (%) ¹	Resminostat N = 100	Placebo N = 101	Total N = 201
Patients with any concomitant conditions	87 (87.0)	89 (88.1)	176 (87.6)
Vascular disorders	41 (41.0)	40 (39.6)	81 (40.3)
Hypertension	38 (38.0)	39 (38.6)	77 (38.3)
Metabolism and nutrition disorders	32 (32.0)	33 (32.7)	65 (32.3)
Dyslipidaemia	7 (7.0)	9 (8.9)	16 (8.0)
Hypercholesterolaemia	7 (7.0)	9 (8.9)	16 (8.0)
Hyperlipidaemia	7 (7.0)	6 (5.9)	13 (6.5)
Hyperuricaemia	2 (2.0)	8 (7.9)	10 (5.0)

System Organ Class/Preferred Term, n (%) ¹	Resminostat N = 100	Placebo N = 101	Total N = 201
Diabetes mellitus	5 (5.0)	4 (4.0)	9 (4.5)
Type 2 diabetes mellitus	6 (6.0)	2 (2.0)	8 (4.0)
Skin and subcutaneous tissue disorders	32 (32.0)	21 (20.8)	53 (26.4)
Pruritus	11 (11.0)	3 (3.0)	14 (7.0)
Psoriasis	5 (5.0)	4 (4.0)	9 (4.5)
Alopecia	5 (5.0)	0	5 (2.5)
Endocrine disorders	22 (22.0)	25 (24.8)	47 (23.4)
Hypothyroidism	19 (19.0)	19 (18.8)	38 (18.9)
Gastrointestinal disorders	23 (23.0)	16 (15.8)	39 (19.4)
Nervous system disorders	15 (15.0)	23 (22.8)	38 (18.9)
Neuropathy peripheral	1.0 (1.0)	6 (5.9)	7 (3.5)
Psychiatric disorders	18 (18.0)	20 (19.8)	38 (18.9)
Insomnia	7 (7.0)	11 (10.9)	18 (9.0)
Depression	8 (8.0)	5 (5.0)	13 (6.5)
Musculoskeletal and connective tissue disorders	25 (25.0)	11 (10.9)	36 (17.9)
Blood and lymphatic system disorders	14 (14.0)	21 (20.8)	35 (17.4)
Anemia	7 (7.0)	11 (10.9)	18 (9.0)
Respiratory, thoracic and mediastinal disorders	14 (14.0)	16 (15.8)	30 (14.9)
Asthma	6 (6.0)	5 (5.0)	11 (5.5)
Investigations	13 (13.0)	14 (13.9)	27 (13.4)
Eye disorders	11 (11.0)	13 (12.9)	24 (11.9)
Infections and infestations	8 (8.0)	13 (12.9)	21 (10.4)
Reproductive system and breast disorders	11 (11.0)	10 (9.9)	21 (10.4)
Benign prostatic hyperplasia	6 (6.0)	7 (6.9)	13 (6.5)
Immune system disorders	9 (9.0)	8 (7.9)	17 (8.5)
Renal and urinary disorders	7 (7.0)	10 (9.9)	17 (8.5)
General disorders and administration site conditions	10 (10.0)	5 (5.0)	15 (7.5)
Fatigue	6 (6.0)	2 (2.0)	8 (4.0)
Cardiac disorders	7 (7.0)	5 (5.0)	12 (6.0)
Injury, poisoning and procedural complications	10 (10.0)	0	10 (5.0)
Neoplasms benign, malignant and unspecified	3 (3.0)	7 (6.9)	10 (5.0)
Ear and labyrinth disorders	5 (5.0)	3 (3.0)	8 (4.0)
Surgical and medical procedures	1 (1.0)	7 (6.9)	8 (4.0)

N: number of patients randomized; n: number of patients affected; PT: preferred term; SOC: system organ class.

¹ In some SOCs, no PTs were reported in ≥ 5% of patients, therefore only numbers for SOC are presented.

Source: Table 14.1.5.2.

Prior and Concomitant Medications

Table 15 Concomitant Medications in $\geq 5\%$ of Patients by ATC Classification and Drug Name (ITT Population)

Anatomic Therapeutic Chemical Level 3 Classification/Drug Name, n (%) ¹	Resminostat N = 100	Placebo N = 101	Total N = 201
Patients with any concomitant medications	97 (97.0)	97 (96.0)	194 (96.5)
Corticosteroids, plain	51 (51.0)	46 (45.5)	97 (48.3)
Betamethasone ²	12 (12.0)	6 (5.9)	18 (9.0)
Clobetasol propionate	22 (22.0)	17 (16.8)	39 (19.4)
Mometasone furoate	16 (16.0)	14 (13.9)	30 (14.9)
Antihistamines for systemic use	45 (45.0)	43 (42.6)	88 (43.8)
Other analgesics and antipyretics	43 (43.0)	31 (30.7)	74 (36.8)
Paracetamol	27 (27.0)	23 (22.8)	50 (24.9)
Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)	43 (43.0)	30 (29.7)	73 (36.3)
Omeprazole	10 (10.0)	7 (6.9)	17 (8.5)
Pantoprazole sodium sesquihydrate	14 (14.0)	10 (9.9)	24 (11.9)
Lipid modifying agents, plain	25 (25.0)	29 (28.7)	54 (26.9)
Emollients and protectives	31 (31.0)	20 (19.8)	51 (25.4)
Antithrombotic agents	26 (26.0)	24 (23.8)	50 (24.9)
Acetylsalicylic acid	9 (9.0)	13 (12.9)	22 (10.9)
Beta-lactam antibacterials, penicillins	28 (28.0)	16 (15.8)	44 (21.9)
Antiinflammatory and antirheumatic products, non-steroids	22 (22.0)	21 (20.8)	43 (21.4)
Ibuprofen	16 (16.0)	14 (13.9)	30 (14.9)
Thyroid preparations	21 (21.0)	20 (19.8)	41 (20.4)
Levothyroxine ²	21 (21.0)	20 (19.8)	41 (20.4)
Propulsives	29 (29.0)	11 (10.9)	40 (19.9)
Metoclopramide ²	28 (28.0)	10 (9.9)	38 (18.9)
Corticosteroids for systemic use, plain	24 (24.0)	15 (14.9)	39 (19.4)
Dexamethasone	10 (10.0)	1 (1.0)	11 (5.5)

Anatomic Therapeutic Chemical Level 3 Classification/Drug Name, n (%) ¹	Resminostat N = 100	Placebo N = 101	Total N = 201
Antiemetics and antinauseants	27 (27.0)	8 (7.9)	35 (17.4)
Aprepitant	12 (12.0)	3 (3.0)	15 (7.5)
Prochlorperazine ²	11 (11.0)	5 (5.0)	16 (8.0)
Selective calcium channel blockers with mainly vascular effects	15 (15.0)	19 (18.8)	34 (16.9)
Amlodipine ²	10 (10.0)	15 (14.9)	25 (12.4)
Angiotensin II antagonists, plain	11 (11.0)	18 (17.8)	29 (14.4)
Antidepressants	17 (17.0)	11 (10.9)	28 (13.9)
Hypnotics and sedatives	17 (17.0)	11 (10.9)	28 (13.9)
ACE inhibitors, plain	13 (13.0)	13 (12.9)	26 (12.9)
Viral vaccines	14 (14.0)	12 (11.9)	26 (12.9)
Other viral vaccines ³	10 (10.0)	6 (5.9)	16 (8.0)
Opioids	16 (16.0)	9 (8.9)	25 (12.4)
Beta blocking agents	13 (13.0)	11 (10.9)	24 (11.9)
Other beta-lactam antibacterials	13 (13.0)	11 (10.9)	24 (11.9)
Antifungals for topical use	12 (12.0)	11 (10.9)	23 (11.4)
Direct acting antivirals	10 (10.0)	12 (11.9)	22 (10.9)
Other mineral supplements	13 (13.0)	8 (7.9)	21 (10.4)
Anxiolytics	11 (11.0)	8 (7.9)	19 (9.5)
Other dermatological preparations	7 (7.0)	11 (10.9)	18 (9.0)
Macrolides, lincosamides and streptogramins	11 (11.0)	5 (5.0)	16 (8.0)
Other antineoplastic agents ⁴	11 (11.0)	3 (3.0)	14 (7.0)

ATC: anatomic therapeutic chemical; N: number of patients randomized; n: number of patients affected; NOS: not otherwise specified.

¹ In some ATCs, no drugs were reported in $\geq 10\%$ of patients, therefore only numbers for ATC are presented.

² Some medications were listed twice in [Table 14.1.8.1](#): Betamethasone/Betamethasone butyrate propionate, Levothyroxine/Levothyroxine sodium, Metoclopramide/Metoclopramide hydrochloride, Prochlorperazine/Prochlorperazine maleate and Amlodipine/Amlodipine besilate. Since the pairs describe the same medication, these were verified manually in [Listing 16.2.4.6.1](#) and reported here as a single value.

³ The same vaccines (e.g., COVID-19) were sometimes reported as "viral vaccines" or "other viral vaccines", sometimes even as different categories for basic vaccination and booster in the same patient.

⁴ Anti-neoplastic agents were not allowed and not administered to patients during the randomized phase of the trial. In some patients, treatment with anti-neoplastic agents started immediately after EOT, therefore these drugs were reported as concomitant medications.

Source: [Table 14.1.8.1](#).

Numbers analysed

All randomized patients were included in the ITT population (n = 201) which was the primary population for assessment of efficacy. Selected efficacy parameters were also analyzed for the PP population (n = 174) comprising all randomized patients without protocol violations. Analysis of the key secondary endpoint TTSW pruritus was based on the TTSW population and included all patients with a VAS itching score of ≤ 7 at baseline (n = 154).

Outcomes and estimation

- Primary endpoint (PFS)

Analysis of PFS in the ITT population was based on 47 events (in 47.0% of patients) observed on resminostat and 70 events (in 69.3% of patients) on placebo. 53 and 31 patients, respectively, were censored in each treatment arm.

Table 16 Analysis of the Primary Endpoint PFS

Patient Population	Median PFS, months [95% CI]		p-Value (stratified log-rank test)	Hazard Ratio ¹ , [95% CI] (stratified Cox proportional hazards model)
	Resminostat N = 100	Placebo N = 101		
ITT	N = 100; n = 47 8.3 [4.2, 15.7]	N = 101; n = 70 4.2 [2.8, 6.4]	0.015 *	0.623 [0.424, 0.916]
PP	N = 90; n = 46 8.2 [4.2, 15.2]	N = 84; n = 67 3.7 [2.8, 4.7]	0.007 *	0.585 [0.395, 0.867]

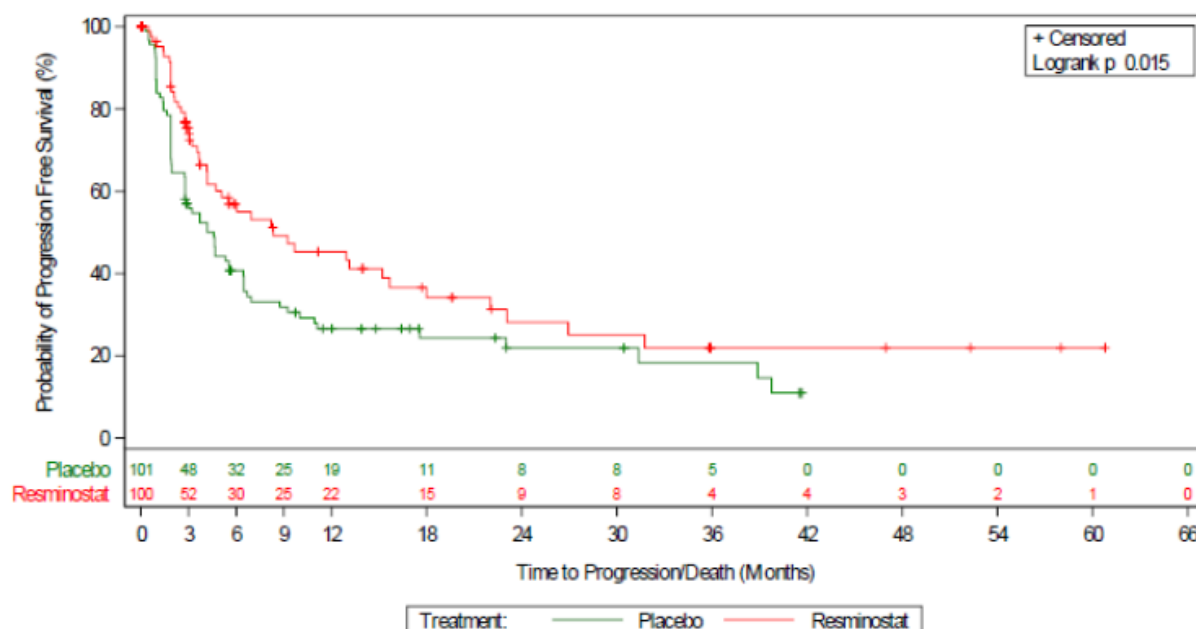
CI: confidence interval; ITT: intention-to-treat; N: number of patients; n: number of events; PFS: progression-free survival; PP: per protocol.

* Statistical significance (p-value ≤ 0.05).

¹ Assuming proportional hazards, an HR less than 1 indicates a reduction in HR in favor of resminostat.

Source: [Tables 14.2.1.1.1](#) and [14.2.1.1.2](#).

Figure 3 Kaplan-Meier Plot of Progression-Free Survival (ITT Population)



Source: [Figure 14.2.1.1.1](#).

The following sensitivity analyses were conducted for the primary endpoint:

Table 17 Sensitivity Analyses of the Primary Endpoint PFS

Patient Population	Median PFS, months [95% CI]		p-Value (stratified log-rank test)	Hazard Ratio ¹ [95% CI] (stratified Cox proportional hazards model)
	Resminostat N = 100	Placebo N = 101		
ITT, with event based on modified assessment in skin (PD: increase of mSWAT by $\geq 25\%$ from baseline; or, if baseline mSWAT=0: any increase)	N = 100; n = 52 5.6 [3.5, 11.8]	N = 101; n = 81 2.8 [1.9, 3.0]	0.001*	0.550 [0.382, 0.790]

Patient Population	Median PFS, months [95% CI]		p-Value (stratified log-rank test)	Hazard Ratio ¹ [95% CI] (stratified Cox proportional hazards model)
	Resminostat N = 100	Placebo N = 101		
ITT, with event defined as PD, death or discontinuation due to toxicity or start of new treatment	N = 100; n = 54 6.5 [4.2, 12.9]	N = 101; n = 72 4.2 [2.8, 6.4]	0.057	0.701 [0.486, 1.010]
ITT, with event defined as PD or death (censored if it occurred directly after ≥ 1 missed or incomplete GRA)	N = 100; n = 44 9.2 [4.7, 18.0]	N = 101; n = 68 4.6 [2.8, 6.4]	0.009 *	0.591 [0.398, 0.878]
ITT, with event defined as PD or death (censoring based on last complete GRA or IRA)	N = 100; n = 47 9.7 [5.6, 18.0]	N = 101; n = 68 4.6 [2.8, 6.5]	0.006 *	0.581 [0.393, 0.859]
ITT, with event defined as PD, death or start of new treatment	N = 100; n = 47 8.3 [4.2, 15.7]	N = 101; n = 70 4.2 [2.8, 6.4]	0.015 *	0.623 [0.424, 0.916]

CI: confidence interval; GRA: global response assessment; IRA: intermediate response assessment; ITT: intention-to-treat; mSWAT: modified severity-weighted assessment tool; N: number of patients; n: number of events; PD: progressive disease; PFS: progression-free survival.

* Statistical significance (p-value ≤ 0.05).

¹ Assuming proportional hazards, an HR less than 1 indicates a reduction in HR in favor of resminostat.

Source: [Tables 14.2.1.4.1, 14.2.1.4.2, 14.2.1.4.4, 14.2.1.4.5 and 14.2.1.1.5.](#)

- Secondary Efficacy Endpoints

Time to Progression

Table 18 Analysis of the Secondary Endpoint TTP

Patient Population	Median TTP, months [95% CI]		p-Value (stratified log-rank test)	Hazard Ratio ¹ [95% CI] (stratified Cox proportional hazards model)
	Resminostat N = 100	Placebo N = 101		
ITT	N = 100; n = 47 8.3 [4.2, 15.7]	N = 101; n = 70 4.2 [2.8, 6.4]	0.015 *	0.623 [0.424, 0.916]
PP	N = 90; n = 46 8.2 [4.2, 15.2]	N = 84; n = 67 3.7 [2.8, 4.7]	0.007 *	0.585 [0.395, 0.867]

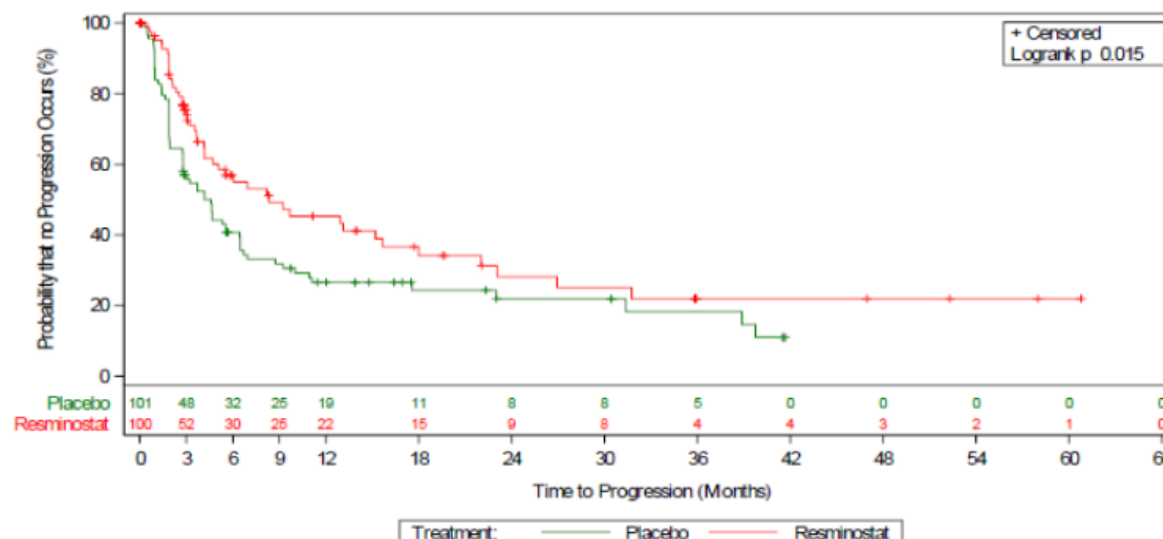
CI: confidence interval; ITT: intention-to-treat; N: number of patients; n: number of events; PP: per protocol; TTP: time to progression.

* Statistical significance (p-value ≤ 0.05).

¹ Assuming proportional hazards, an HR less than 1 indicates a reduction in HR in favor of resminostat.

Source: [Tables 14.2.2.2.1](#) and [14.2.2.2.2](#).

Figure 5 Kaplan-Meier Plot of Time to Progression (ITT Population)



Time to Next Treatment (TTNT)

Analysis of TTNT in the ITT population was based on 69 events (in 69.0% of patients) observed on resminostat and 85 events (in 84.2% of patients) on placebo. Thirty-one and 16 patients, respectively, were censored in the two treatment arms.

Table 19 Analysis of the Secondary Endpoint Median TTNT

Patient Population	Median TTNT, months [95% CI]		p-Value (stratified log-rank test)	Hazard Ratio ¹ [95% CI] (stratified Cox proportional hazards model)
	Resminostat N = 100	Placebo N = 101		
ITT	N = 100; n = 69 8.8 [7.4, 13.8]	N = 101; n = 85 4.2 [3.0, 6.0]	0.002 *	0.594 [0.428, 0.825]

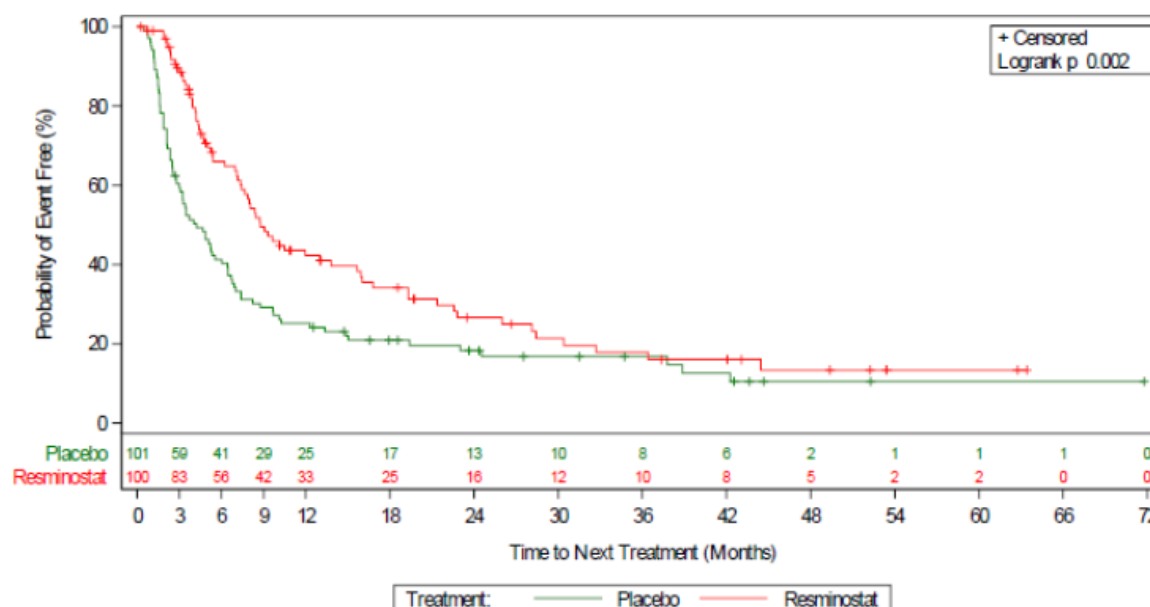
CI: confidence interval; ITT: intention-to-treat; N: number of patients; n: number of events; TTNT: time to next treatment.

* Statistical significance (p-value ≤ 0.05).

¹ Assuming proportional hazards, an HR less than 1 indicates a reduction in HR in favor of resminostat.

Source: [Table 14.2.2.3.1](#).

Figure 6 Kaplan-Meier Plot of Time to Next Treatment (ITT Population)



Source: [Figure 14.2.4.1.1](#).

Overall Response Rate

Patients with a baseline remission status of CR (n = 25) were excluded; the ORR rate was evaluated in patients with baseline remission status of PR or SD only (n = 176), with response evaluated by the GRS based on all four categories.

On resminostat (n = 86), 3 patients (3.5%) achieved CR and 12 patients (14.0%) achieved PR, leading to an ORR of 17.4% [95% CI: 10.104, 27.131]. On placebo (n = 90), none of the patients achieved CR and 9 patients (10.0%) achieved PR, leading to an ORR of 10.0% [4.676, 18.136].

Table 14.2.2.5.1 Analysis of Overall Response Rate (ORR) (Randomised Period)
(ITT Population – Patients with Baseline Remission Status PR or SD only)

	Resminostat (N=86)	Placebo (N=90)
Complete Response (CR) n (%)	3 (3.5)	0
Partial Response (PR) n (%)	12 (14.0)	9 (10.0)
Overall Response Rate (ORR) n (%)	15 (17.4)	9 (10.0)
95% CI	(10.104, 27.131)	(4.676, 18.136)
Odds Ratio [a]		
Resminostat/Placebo	2.022	
95% CI for Odds Ratio [b]	(0.764, 5.565)	
P-value	0.120	

Notes: Overall Response Rate (ORR) is defined as the percentage of subjects within each treatment group who achieved Complete Response (CR) or Partial Response (PR) during the randomised period. Therefore, patients with baseline remission status CR are excluded from this table. Only Global Response Scores that are based on all four components will be considered for the evaluation of the ORR.

The Randomised period is defined as the period from date of Randomisation to date of blinded end of treatment.

a. Odds Ratio and its related p-value from a Cochran-Mantel-Haenszel (CMH) test with stage of disease (IIB/IIIA/IIIB/IVA1 vs IVA2/IVB)

and remission status (CR/PR vs SD) as strata.
b. 95% CI based on the Clopper-Pearson method.

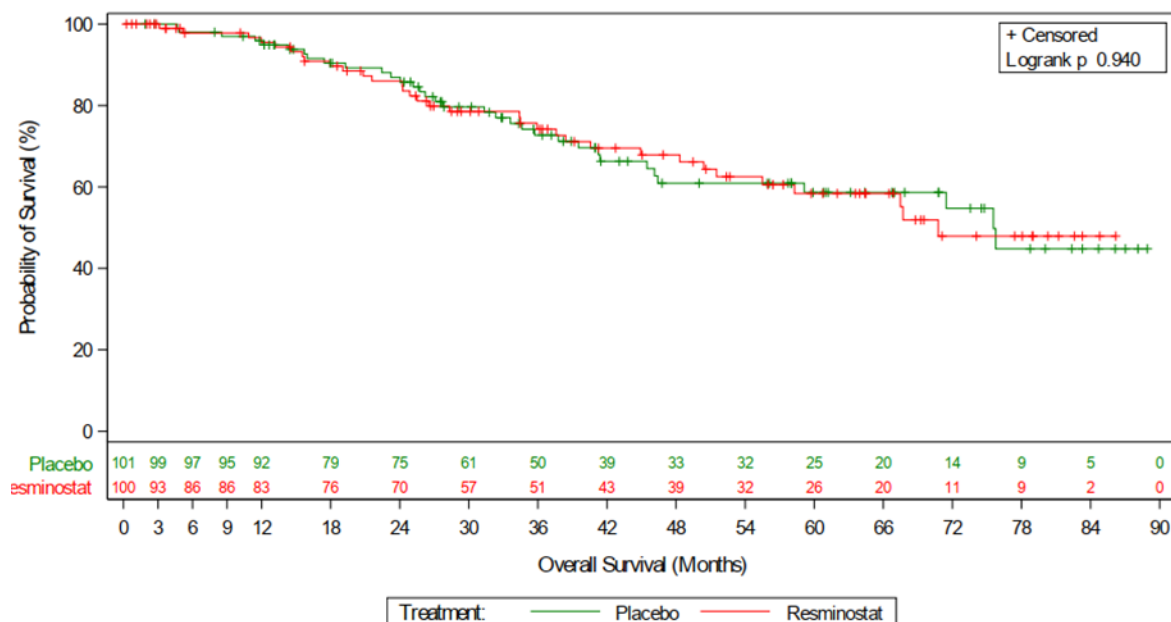
Duration of Response

The DOR was evaluated in patients with response to trial treatment (n = 24). With 19.4 months [6.5, not evaluable (NE)] on resminostat and 20.3 months [7.3, NE] on placebo, median DOR was similar in both treatment arms.

Overall Survival

The results for OS at the final analysis (data cut off: 08 August 2024) were similar to those at the main analysis and showed no significant difference between the treatment arms (p-value 0.940, HR 0.983 (0.606, 1.590)). The respective Kaplan-Meier curves are depicted in Figure 5.

Figure 8 Overall Survival (ITT Population, Final Analysis)



Analyses of PFS on 2nd (PFS2) and on 3rd line therapy (PFS3), for the ITT population were performed at the final analysis time point (data cut off: 08 August 2024). The results obtained by a stratified log-rank test and a Cox-PH model do not indicate a statistically significant difference between treatment arms for PFS2 (p-value 0.156, HR 0.758 (0.516, 1.113)) and PFS3 (p-value 0.921, HR 1.021 (0.674, 1.547)).

Figure 9 PFS on Second Line Therapy (PFS2, ITT Population, Final Analysis Results)

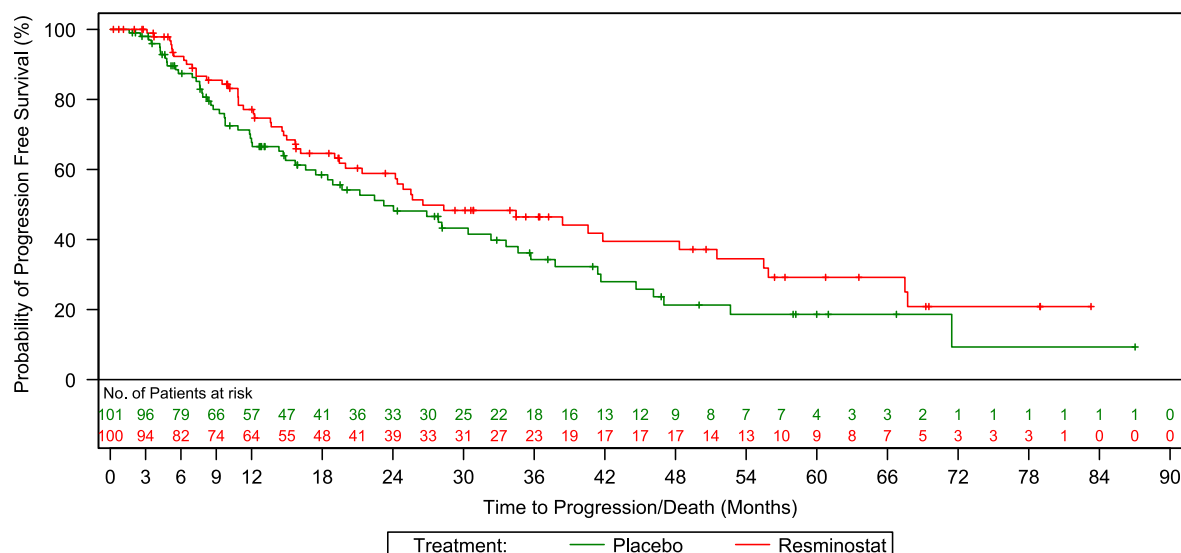
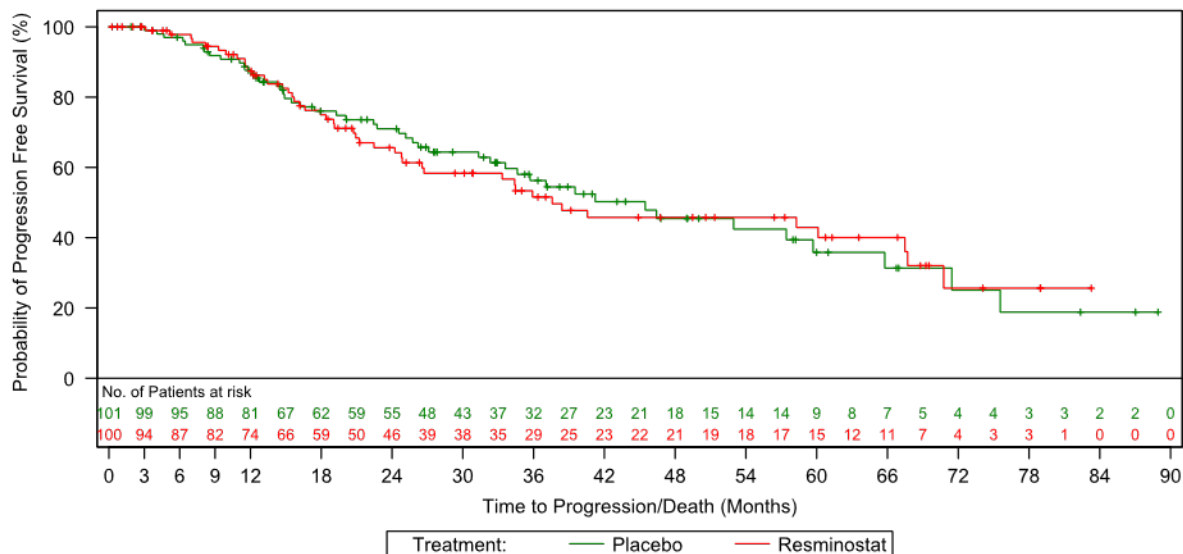


Figure 10 PFS on Third Line Therapy (PFS3, ITT population, final analysis results)



Key Secondary Endpoint: Time to Symptom Worsening (Pruritus)

Within the TTSW population (n = 154), the estimation of median TTSW was not possible due to the limited number of patients with a TTSW pruritus event within the TTSW population.

Table 22 Analysis of the Key Secondary Endpoint TTSW Pruritus

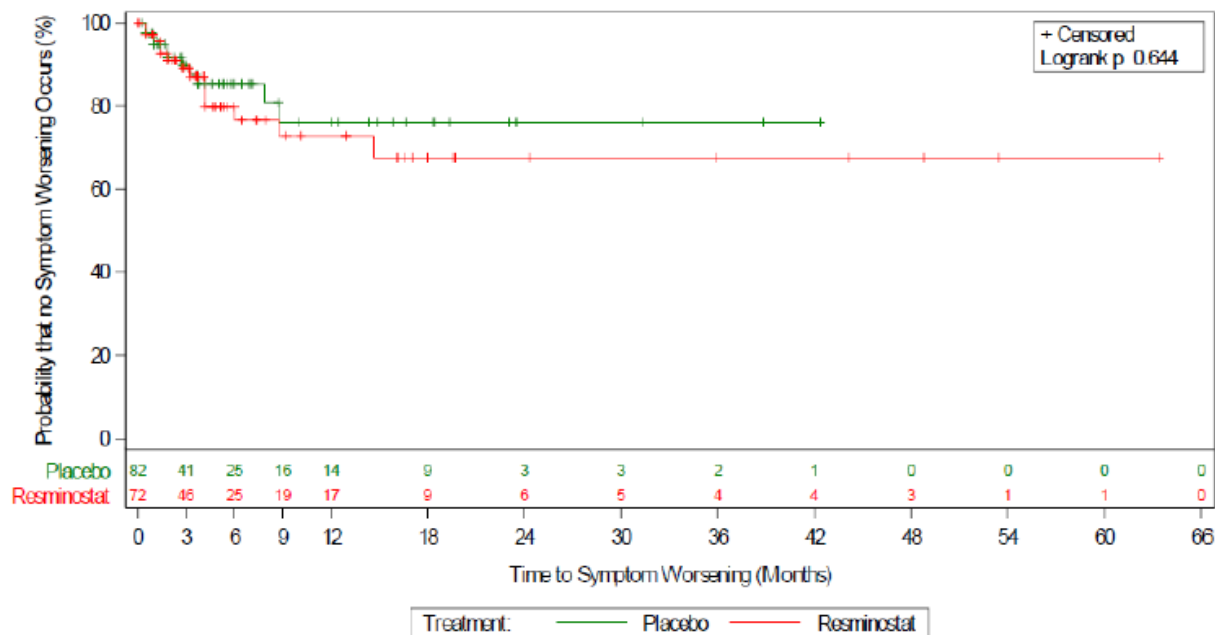
Patient Population	Median TTSW pruritus, months [95% CI]		p-Value (stratified log-rank test)	Hazard Ratio ¹ [95% CI] (stratified Cox proportional hazards model)
	Resminostat N = 100	Placebo N = 101		
TTSW	N = 72; n = 14 NE [14.7, NE]	N = 82; n = 11 NE [NE, NE]	0.644	1.215 [0.538, 2.742]

CI: confidence interval; ITT: intention-to-treat; N: number of patients; n: number of events; NE: not evaluable; TTSW: time to symptom worsening.

¹ Assuming proportional hazards, an HR less than 1 indicates a reduction in HR in favor of resminostat.

Source: [Table 14.2.2.1.1](#).

Figure 8 Kaplan-Meier Plot of Time to Symptom Worsening Pruritus (TTSW Population)



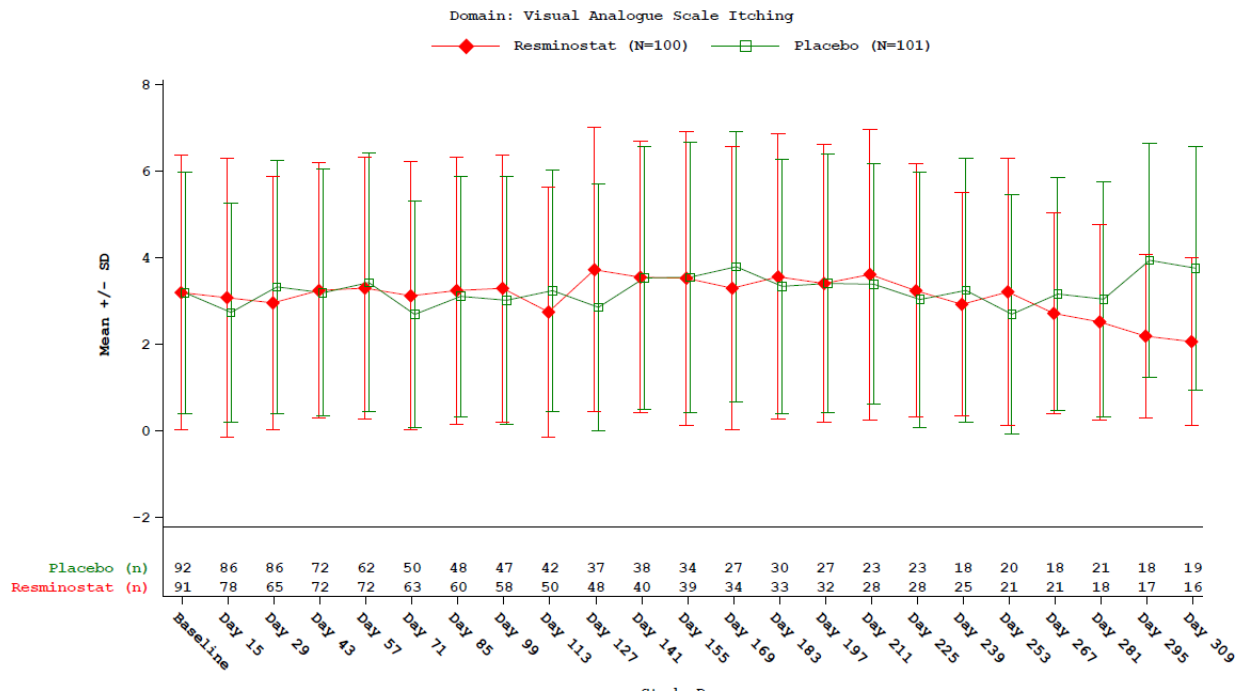
Source: Figure 14.2.2.1.

Secondary Quality of Life Endpoints

Visual Analogue Scale for Itching

The Visual Analogue Scale (VAS) of 0 -10 points for itching (higher value = worse) was collected every 14 days, i.e., at baseline and at Day 1 of each new treatment cycle. At baseline, analysis of VAS itching was based on 91 patients on resminostat and 92 patients on placebo and comprised mean scores of 3.20 points (median: 1.80; range: 0 - 10) and 3.20 points (median: 2.40; range: 0 - 10), respectively.

Figure 14.2.11.3 Mean (SD) VAS Itching Scores by Time Point (Randomised Period) (ITT Population)



Functional Assessment of Cancer - General (FACT-G) Questionnaire

The FACT-G score (total score of 0 - 108 points including the domains physical, social, emotional and functional well-being; lower value = worse) was collected every 28 days, i.e., at baseline and at Day 1 of every other treatment cycle. At baseline, analysis of FACT-G was based on 92 patients on resminostat and 93 patients on placebo.

On resminostat, FACT-G scores were assessed from baseline up to Day 1905. At baseline, a mean total score of 81.4 points (median: 84.8; range: 26 - 103) was reported. Over time, mean total scores were in the range of 65.0 - 93.0 points. A decrease (worsening) was observed predominantly in the "physical well-being" domain, from a mean of 23.3 points (median: 25.0; range: 7 - 28) at baseline to the lowest mean of 15.7 points (median: 18.0; range: 4 - 25) reported at Day 1037 (n = 7).

On placebo, FACT-G scores were assessed from baseline up to Day 1345. At baseline, a mean total score of 80.9 points (median: 82.0; range: 41 - 107) was reported. Over time, mean total scores were in the range of 79.4 - 100.7 points. In particular, the "physical wellbeing" score did not decrease as observed for resminostat, but remained stable.

Changes from baseline in FACT-G total scores were analyzed based on the ITT population using a linear MMRM. 83 patients on resminostat and 89 patients on placebo were included in the analysis.

Timepoints/visits with less than 5 observations for at least one treatment arm were not included in the analysis. The observed changes from baseline over time (i.e. Day 29 to Day 981) for resminostat versus placebo were statistically significant in favor of placebo (p = 0.041).

Table 14.3.6.2 Analysis of Change from Baseline in QOL FACT-G Total Scores (Randomised Period) (ITT Population)

	Effect size (CI) p-value for Effects	Resminostat (N=100)	Placebo (N=101)
Number of Patients Included in Model		83	89
Effects			
Treatment	-3.736 (-7.310, -0.162) 0.041*		
Timepoint	0.024 (-0.006, 0.054) 0.288		
Treatment*Timepoint	-0.016 (-0.026, -0.005) 0.003*		
Timepoint*Baseline	0.000 (-0.001, 0.000) 0.301		
Baseline	-0.169 (-0.291, -0.047) 0.007*		
Day 29			
LS Mean (SE) (95% CI)		-5.34 (1.23) (-7.77, -2.91)	-1.14 (1.20) (-3.51, 1.23)
LS Mean for Difference (Resminostat - Placebo) (SE) (95% CI); p-value		-4.20 (1.72) (-7.59, -0.80); 0.016*	
Day 57			
LS Mean (SE) (95% CI)		-5.54 (1.18) (-7.86, -3.22)	-0.90 (1.15) (-3.16, 1.36)
LS Mean for Difference (Resminostat - Placebo) (SE) (95% CI); p-value		-4.64 (1.64) (-7.88, -1.40); 0.005*	
Day 85			
LS Mean (SE) (95% CI)		-5.75 (1.13) (-7.97, -3.53)	-0.66 (1.10) (-2.83, 1.50)
LS Mean for Difference (Resminostat - Placebo) (SE) (95% CI); p-value		-5.09 (1.57) (-8.19, -1.99); 0.001*	

Abbreviations: FACT-G = Functional Assessment of Cancer Therapy-General, LS = Least-square, CI = Confidence Interval, QOL = Quality of Life, SE = Standard Error.
 Note: Analysis is based on a linear mixed model for repeated measures including treatment group (Placebo as reference treatment), timepoint (continuous), timepoint (continuous) by treatment interaction and timepoint (continuous) by baseline interaction as fixed effects, and baseline value as a covariate and timepoint (categorical) included in the repeated statement of proc mixed to accommodate the repeated measurement effects.

Table 14.3.6.2 Analysis of Change from Baseline in QOL FACT-G Total Scores (Randomised Period) (ITT Population)

	Effect size (CI) p-value for Effects	Resminostat (N=100)	Placebo (N=101)
Day 113			
LS Mean (SE) (95% CI)		-5.96 (1.09) (-8.09, -3.82)	-0.42 (1.06) (-2.52, 1.67)
LS Mean for Difference (Resminostat - Placebo) (SE) (95% CI); p-value		-5.53 (1.52) (-8.52, -2.54); <0.001*	
Day 141			
LS Mean (SE) (95% CI)		-6.16 (1.05) (-8.23, -4.09)	-0.18 (1.03) (-2.22, 1.85)
LS Mean for Difference (Resminostat - Placebo) (SE) (95% CI); p-value		-5.98 (1.47) (-8.88, -3.08); <0.001*	
Day 169			
LS Mean (SE) (95% CI)		-6.37 (1.02) (-8.39, -4.35)	0.05 (1.02) (-1.95, 2.06)
LS Mean for Difference (Resminostat - Placebo) (SE) (95% CI); p-value		-6.42 (1.44) (-9.27, -3.58); <0.001*	
Day 197			
LS Mean (SE) (95% CI)		-6.57 (1.01) (-8.56, -4.59)	0.29 (1.01) (-1.70, 2.28)
LS Mean for Difference (Resminostat - Placebo) (SE) (95% CI); p-value		-6.87 (1.43) (-9.68, -4.05); <0.001*	
Day 225			
LS Mean (SE) (95% CI)		-6.78 (1.00) (-8.76, -4.80)	0.53 (1.02) (-1.47, 2.54)
LS Mean for Difference (Resminostat - Placebo) (SE) (95% CI); p-value		-7.31 (1.43) (-10.13, -4.50); <0.001*	
Day 253			
LS Mean (SE) (95% CI)		-6.99 (1.01) (-8.97, -5.00)	0.77 (1.03) (-1.27, 2.81)
LS Mean for Difference (Resminostat - Placebo) (SE) (95% CI); p-value		-7.76 (1.44) (-10.61, -4.91); <0.001*	

Abbreviations: FACT-G = Functional Assessment of Cancer Therapy-General, LS = Least-square, CI = Confidence Interval, QOL = Quality of Life, SE = Standard Error.
 Note: Analysis is based on a linear mixed model for repeated measures including treatment group (Placebo as reference treatment), timepoint (continuous), timepoint (continuous) by treatment interaction and timepoint (continuous) by baseline interaction as fixed effects, and baseline value as a covariate and timepoint (categorical) included in the repeated statement of proc mixed to accommodate the repeated measurement effects. Timepoints/visits with less than 5 observations for at least one treatment group were not included in analysis.
 The auto-regressive co-variance matrix was used to adjust for the withinpatient error variance co-variance.

Skindex-29 Questionnaire

The Skindex-29 score (total score of 0 - 100 points including the domains symptoms, emotional and functioning scale; higher value = worse) was collected every 28 days, i.e., at baseline and at Day 1 of every other treatment cycle. At baseline, analysis of Skindex-29 was based on 92 patients on resminostat and 91 patients on placebo and comprised mean total scores of 35.46 points (median: 34.53; range: 0.7 - 100) and 33.41 points (median 30.10; range: 0 - 80.4), respectively. In both treatment arms, the number of patients with available Skindex-29 scores decreased over time. On resminostat, Skindex-29 scores were assessed from baseline up to Day 1,905, with mean total scores in the range of 15.63 - 48.24 points. On placebo,

Skindex-29 scores were assessed from baseline up to Day 1,345, with mean total scores in the range of 19.27 - 37.49 points

Changes from baseline in Skindex-29 total scores were analyzed based on the ITT population using a linear MMRM. 82 patients on resminostat and 88 patients on placebo were included in the analysis. The LS mean difference (resminostat-placebo) was 0.04 (-3.55, 3.63) at day 85.

Table 14.3.6.3 Analysis of Change from Baseline in Skindex-29 Total Scores (Randomised Period) (ITT Population)

	Effect size (CI) p-value for Effects	Resminostat (N=100)	Placebo (N=101)
Number of Patients Included in Model		82	88
Effects			
Treatment	-0.771 (-4.878, 3.336) 0.712		
Timepoint	-0.004 (-0.017, 0.008) 0.958		
Treatment*Timepoint	0.010 (-0.003, 0.022) 0.133		
Timepoint*Baseline	0.000 (0.000, 0.000) 0.962		
Baseline	-0.240 (-0.343, -0.137) <0.001*		
Day 29			
LS Mean (SE) (95% CI)		-0.41 (1.42) (-3.21, 2.40)	0.09 (1.38) (-2.63, 2.81)
LS Mean for Difference (Resminostat - Placebo) (SE) (95% CI); p-value		-0.50 (1.98) (-4.40, 3.41); 0.803	
Day 57			
LS Mean (SE) (95% CI)		-0.26 (1.36) (-2.94, 2.42)	-0.03 (1.32) (-2.63, 2.57)
LS Mean for Difference (Resminostat - Placebo) (SE) (95% CI); p-value		-0.23 (1.90) (-3.97, 3.51); 0.904	
Day 85			
LS Mean (SE) (95% CI)		-0.11 (1.31) (-2.69, 2.46)	-0.15 (1.27) (-2.65, 2.35)
LS Mean for Difference (Resminostat - Placebo) (SE) (95% CI); p-value		0.04 (1.82) (-3.55, 3.63); 0.984	

Abbreviations: LS = Least-square, CI = Confidence Interval, QOL = Quality of Life, SE = Standard Error.
Note: Analysis is based on a linear mixed model for repeated measures including treatment group (Placebo as reference treatment), timepoint (continuous) and timepoint (continuous) by treatment interaction and timepoint (continuous) by baseline interaction as fixed effects, and baseline value as a covariate and timepoint (categorical) included in the repeated statement of proc mixed to accommodate the repeated measurement effects. Timepoints/visits with less than 5 observations for at least one treatment group were not included in analysis. The auto-regressive co-variance matrix was used to adjust for the withinpatient error variance co-variance.

Table 14.3.6.3 Analysis of Change from Baseline in Skindex-29 Total Scores (Randomised Period) (ITT Population)

	Effect size (CI) p-value for Effects	Resminostat (N=100)	Placebo (N=101)
Day 113			
LS Mean (SE) (95% CI)		0.04 (1.26) (-2.45, 2.52)	-0.27 (1.23) (-2.69, 2.16)
LS Mean for Difference (Resminostat - Placebo) (SE) (95% CI); p-value		0.30 (1.76) (-3.17, 3.78); 0.864	
Day 141			
LS Mean (SE) (95% CI)		0.19 (1.23) (-2.23, 2.60)	-0.38 (1.20) (-2.76, 1.99)
LS Mean for Difference (Resminostat - Placebo) (SE) (95% CI); p-value		0.57 (1.72) (-2.82, 3.96); 0.741	
Day 169			
LS Mean (SE) (95% CI)		0.33 (1.20) (-2.04, 2.70)	-0.50 (1.19) (-2.85, 1.84)
LS Mean for Difference (Resminostat - Placebo) (SE) (95% CI); p-value		0.83 (1.69) (-2.51, 4.18); 0.623	
Day 197			
LS Mean (SE) (95% CI)		0.48 (1.19) (-1.86, 2.83)	-0.62 (1.19) (-2.96, 1.73)
LS Mean for Difference (Resminostat - Placebo) (SE) (95% CI); p-value		1.10 (1.69) (-2.23, 4.43); 0.515	
Day 225			
LS Mean (SE) (95% CI)		0.63 (1.19) (-1.71, 2.97)	-0.74 (1.20) (-3.11, 1.63)
LS Mean for Difference (Resminostat - Placebo) (SE) (95% CI); p-value		1.37 (1.70) (-1.98, 4.72); 0.422	
Day 253			
LS Mean (SE) (95% CI)		0.78 (1.20) (-1.59, 3.14)	-0.86 (1.23) (-3.28, 1.57)
LS Mean for Difference (Resminostat - Placebo) (SE) (95% CI); p-value		1.63 (1.73) (-1.77, 5.04); 0.345	

Abbreviations: LS = Least-square, CI = Confidence Interval, QOL = Quality of Life, SE = Standard Error.
Note: Analysis is based on a linear mixed model for repeated measures including treatment group (Placebo as reference treatment), timepoint (continuous) and timepoint (continuous) by treatment interaction and timepoint (continuous) by baseline interaction as fixed effects, and baseline value as a covariate and timepoint (categorical) included in the repeated statement of proc mixed to accommodate the repeated measurement effects. Timepoints/visits with less than 5 observations for at least one treatment group were not included in analysis. The auto-regressive co-variance matrix was used to adjust for the withinpatient error variance co-variance.

Exploratory Analyses

Requirement of Anti-Itching Treatment

The number of patients who did not have any anti-itching treatment at baseline but started at least once such a treatment during the randomized period was the same in both treatment arms (n = 21 each). In these patients, the use of anti-itching medication was similar in both treatment arms and comprised predominantly corticosteroids and antihistamines for systemic use.

The number of patients with at least one anti-itching treatment at baseline who at least once did not receive any anti-itching treatment for ≥ 7 consecutive days during the randomized period was similar on resminostat (n = 16) and on placebo (n = 14).

The number of patients with at least one anti-itching treatment at baseline who continued this treatment during the randomized period was similar on resminostat (n = 15) and on placebo (n = 12). Dose changes were reported for 8 patients (8.0%) on resminostat and 5 patients (5.0%) on placebo and comprised, in all patients, the addition of a new anti-itching treatment while the existing one was stable during the randomized period.

Efficacy of Blinding

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Table 14.7 Summary of Efficacy of Blinding Survey (Actual vs Assumed Treatment) (ITT Population)

Assumption of Treatment Arm	Assumed Treatment Arm	Resminostat (N=100) n (%)	Placebo (N=101) n (%)	Total (N=201) n (%)
Patients Assumption	Resminostat	60 (60.0)	20 (19.8)	80 (39.8)
	Placebo	17 (17.0)	71 (70.3)	88 (43.8)
	Missing	23 (23.0)	10 (9.9)	33 (16.4)
Investigator's Assumption	Resminostat	60 (60.0)	14 (13.9)	74 (36.8)
	Placebo	17 (17.0)	77 (76.2)	94 (46.8)
	Missing	23 (23.0)	10 (9.9)	33 (16.4)

Post-hoc Analyses

PFS from Start of Last Prior Systemic Therapy to First PD

Analysis of PFS from start of last prior systemic therapy to first occurrence of PD (= total PFS) in the ITT population was based on the same events as described for the primary endpoint of PFS.

Table 23 Post-hoc Analysis of PFS from Start of Last Prior Systemic Therapy to First PD

Patient Population	Median PFS from start of last prior therapy to PD, months [95% CI]		p-Value (stratified log-rank test)	Hazard Ratio ¹ [95% CI] (stratified Cox proportional hazards model)
	Resminostat N = 100	Placebo N = 101		
ITT	N = 100; n = 47 24.3 [15.5, 33.6]	N = 101; n = 70 14.9 [12.6, 19.2]	0.1273	0.745 [0.509, 1.090]
PP	N = 90; n = 46 21.1 [14.3, 32.2]	N = 84; n = 67 13.6 [10.3, 16.4]	0.0584	0.691 [0.469, 1.016]
ITT-PSDT	N = 81; n = 36 28.4 [15.7, 51.6]	N = 84; n = 63 14.5 [12.6, 18.0]	0.0290 *	0.626 [0.409, 0.958]

CI: confidence interval; ITT: intention-to-treat; N: number of patients; n: number of events; PD: progressive disease; PFS: progression-free survival; PP: per protocol; PSDT: prior systemic drug therapy.

* Statistical significance (p-value ≤ 0.05).

¹ Assuming proportional hazards, an HR less than 1 indicates a reduction in HR in favor of resminostat.

Source: [Post-hoc Table T1](#).

Effect of Treatment on mSWAT Scores over Time

Changes from baseline in mSWAT scores were analyzed based on the ITT population using a linear MMRM. 90 patients on resminostat and 96 patients on placebo were included in the analysis. Timepoints/visits with less than 5 observations for at least one treatment arm were not included in the analysis. The observed changes from baseline over time (i.e., Day 29 to Day 1,093) for resminostat versus placebo were statistically significant in favor of resminostat ($p = 0.0199$).

Time to Development or Worsening of Skin Tumours

The time to development or worsening of skin tumours was analyzed as TTTE based on mSWAT assessments for the ITT population as well as the subgroups ITT-TTTE1 (no skin tumour present at baseline) and ITT-TTTE2 (skin tumour present at baseline).

Table 24 Post-hoc Analysis of Time to Development or Worsening of Skin Tumors

Patient Population	Median TTTE, months [95% CI]		p-Value (stratified log-rank test)	Hazard Ratio ¹ [95% CI] (stratified Cox proportional hazards model)
	Resminostat N = 100	Placebo N = 101		
ITT	N = 100; n = 17 44.2 [23.1, NE]	N = 101; n = 42 6.5 [3.7, NE]	0.0001 *	0.333 [0.186, 0.597]
ITT-TTTE1 (patients without skin tumor present at baseline)	N = 77; n = 10 44.2 [18.0, NE]	N = 76; n = 24 NE [NE, NE]	0.0098 *	0.367 [0.167, 0.805]

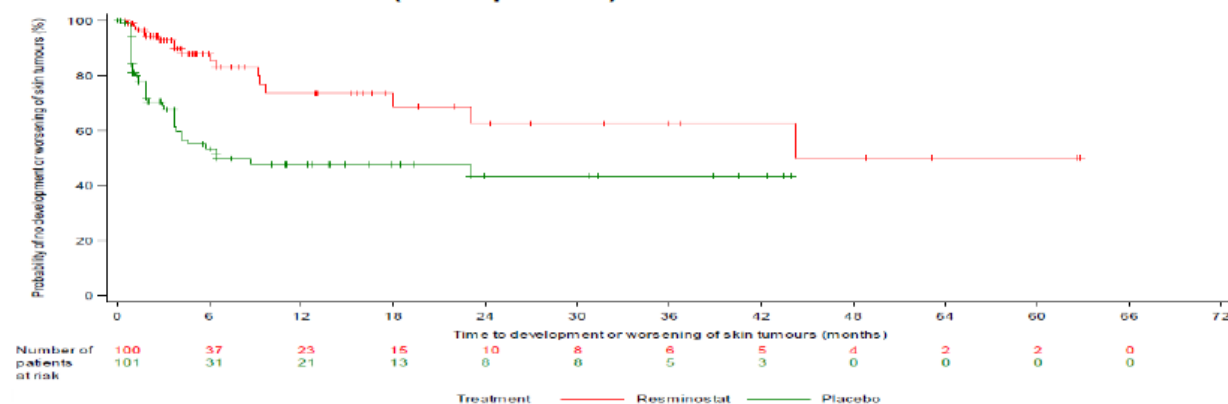
Patient Population	Median TTTE, months [95% CI]		p-Value (stratified log-rank test)	Hazard Ratio ¹ [95% CI] (stratified Cox proportional hazards model)
	Resminostat N = 100	Placebo N = 101		
ITT-TTTE2 (patients with skin tumor present at baseline)	N = 23; n = 7 NE [NE, NE]	N = 25; n = 18 1.9 [1.0, 3.8]	0.0382 *	0.392 [0.160, 0.960]

CI: confidence interval; ITT: intention-to-treat; N: number of patients; n: number of events; NE: not evaluable; TTTE: time to tumor event.

* Statistical significance (p -value ≤ 0.05).

¹ Assuming proportional hazards, an HR less than 1 indicates a reduction in HR in favor of resminostat.

Figure 9 Post-hoc Analysis: Kaplan-Meier Plot of Time to Development or Worsening of Skin Tumors (ITT Population)

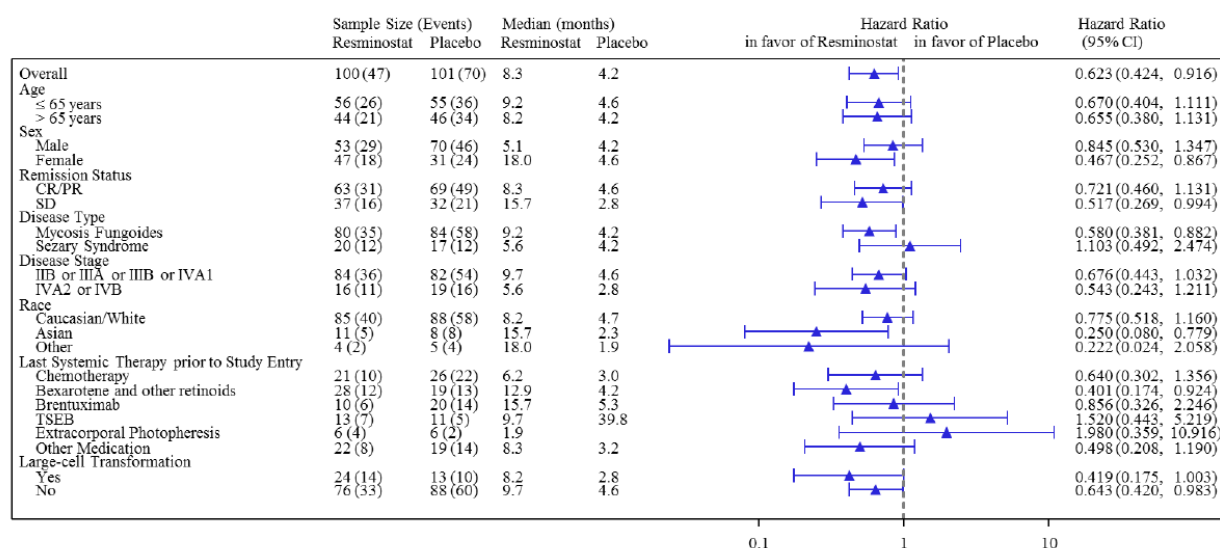


Source: Post-hoc Figure G3.

Ancillary analyses

The primary endpoint PFS was also analyzed in subgroups of the ITT population, i.e. according to the last systemic therapy prior to study entry, the disease subtypes of MF or SS, the response status to prior systemic therapy of PR/CR or SD and the disease stage.

Figure 4 Forest Plot of PFS Subgroup Analysis (based on ITT Population)



For "Overall", HR was derived using a Cox proportional hazards model with stage of disease (IIB/IIIA/IIIB/IVA1 vs IVA2/IVB) and remission status (CR/PR vs SD) as stratification factors. For all other variables, HRs were derived using an un-stratified Cox proportional hazards model.

Table 21 Subgroup Analysis of the Secondary Endpoints TTP and OS (based on ITT Population)

Parameter	Predefined Subgroup	Resminostat (N = 100)	Placebo (N = 101)	p-Value (stratified log-rank test)	Hazard Ratio ¹ [95% CI] (stratified Cox proportional hazard model)
Median TTP, months [95% CI]	Patients with MF (ITT-MF population)	N = 80; n = 35 9.2 [4.2, 18.0]	N = 84; n = 58 4.2 [2.8, 6.4]	0.022 *	0.599 [0.386, 0.929]
	Patients with SS (ITT-SS population)	N = 20; n = 12 5.6 [1.9, 23.1]	N = 17; n = 12 4.2 [1.6, 31.4]	0.835	0.858 [0.294, 2.507]
	Patients with CR or PR at baseline (ITT-XR population)	N = 63; n = 31 8.3 [4.7, 18.0]	N = 69; n = 49 4.6 [3.2, 6.7]	0.182	0.737 [0.467, 1.164]

Parameter	Predefined Subgroup	Resminostat (N = 100)	Placebo (N = 101)	p-Value (stratified log-rank test)	Hazard Ratio ¹ [95% CI] (stratified Cox proportional hazard model)
	Patients with SD at baseline (ITT-SD population)	N = 37; n = 16 15.7 [3.1, NE]	N = 32; n = 21 2.8 [1.9, 6.4]	0.016 *	0.428 [0.213, 0.863]
	Patients with Stage IIB - IVA1 at baseline (ITT-DS1 population)	N = 84; n = 36 9.7 [4.7, 22.0]	N = 82; n = 54 4.6 [2.9, 6.7]	0.081	0.682 [0.446, 1.042]
	Patients with Stage IVA2 - IVB at baseline (ITT-DS2 population)	N = 16; n = 11 5.6 [1.9, 26.9]	N = 19; n = 16 2.8 [1.9, 5.3]	0.050 *	0.417 [0.165, 1.056]
Median OS, months [95% CI]	Patients with MF (ITT-MF population)	N = 80; n = 20 67.7 [51.5, NE]	N = 84; n = 27 NE [37.8, NE]	0.320	0.741 [0.409, 1.342]
	Patients with SS (ITT-SS population)	N = 20; n = 8 38.4 [13.2, NE]	N = 17; n = 2 NE [45.5, NE]	0.009 *	10.308 [1.253, 86.025]
	Patients with CR or PR at baseline (ITT-XR population)	N = 63; n = 16 NE [50.4, NE]	N = 69; n = 18 NE [45.5, NE]	0.723	0.885 [0.449, 1.745]
	Patients with SD at baseline (ITT-SD population)	N = 37; n = 12 67.7 [28.3, 67.7]	N = 32; n = 11 41.4 [33.6, NE]	0.651	1.209 [0.530, 2.760]
	Patients with Stage IIB - IVA1 at baseline (ITT-DS1 population)	N = 84; n = 22 67.7 [50.4, NE]	N = 82; n = 23 NE [37.8, NE]	0.848	0.944 [0.525, 1.700]
	Patients with Stage IVA2 - IVB at baseline (ITT-DS2 population)	N = 16; n = 6 35.9 [20.8, NE]	N = 19; n = 6 NE [39.5, NE]	0.686	1.266 [0.403, 3.981]

CI: confidence interval; CR: complete response; ITT: intention-to-treat; MF: mycosis fungoides; N: number of patients; n: number of events; NE: not evaluable; OS: overall survival; PR: partial response; SD: stable disease; SS: Sézary syndrome; TTP: time to progression.

* Statistical significance (p-value ≤ 0.05).

¹ Assuming proportional hazards, an HR less than 1 indicates a reduction in HR in favor of resminostat.

Source: [Tables 14.2.2.10.1-3](#) and [14.2.2.11.1-3](#).

To account for the heterogeneity of the CTCL population, PFS was analyzed in additional subgroups, including demographic parameters (age, sex, race) as well as baseline disease parameters known as unfavorable prognostic factors such as histologically confirmed lymph node (N3) and/or visceral involvement (stage IVA2 and IVB) or presence of LCT. The forest plot of PFS for all subgroups is presented.

A post-hoc subgroup analysis of the primary endpoint PFS was performed based on the ITT population for each of the disease stages IIB (ITT-DSIIB), III (ITT-DSIII) and IV (ITT-DSIV) and for the disease stages III and IV (ITT-DSIII/IV) combined.

Table 25 Post-hoc Analysis of the Primary Endpoint PFS by Post-Hoc-Defined Subgroups (based on ITT Population)

Patient Population	Median PFS, months [95% CI]		p-Value (stratified log-rank test)	Hazard Ratio ¹ [95% CI] (stratified Cox proportional hazards model)
	Resminostat N = 100	Placebo N = 101		
ITT-DSIIB (patients with stage IIB disease at baseline)	N = 59; n = 26 9.2 [4.2, 15.7]	N = 58; n = 39 4.6 [2.8, 6.5]	0.0301 *	0.572 [0.347, 0.943]
ITT-DSIII (patients with stage III disease at baseline)	N = 15; n = 4 NE [NE, NE]	N = 8; n = 5 20.4 [0.5, 38.9]	0.2879	0.462 [0.109, 1.953]
ITT-DSIV (patients with stage IV disease at baseline)	N = 26; n = 17 5.6 [1.9, 22.0]	N = 35; n = 26 3.0 [1.9, 10.9]	0.3648	0.731 [0.358, 1.490]
ITT-DSIII/IV (patients with stage III or IV disease at baseline)	N = 41; n = 21 8.3 [2.1, 23.1]	N = 43; n = 31 3.0 [1.9, 10.9]	0.1283	0.626 [0.336, 1.165]

CI: confidence interval; DS: disease stage; ITT: intention-to-treat; N: number of patients; n: number of events; NE: not evaluable; PFS: progression free survival.

* Statistical significance (p-value ≤ 0.05).

¹ Assuming proportional hazards, an HR less than 1 indicates a reduction in HR in favor of resminostat.

Source: Post-hoc Table T4

Post-hoc subgroup analysis of the secondary endpoint TTNT was based on the ITT population for each of the disease stages IIB (ITT-DSIIB), III (ITT-DSIII) and IV (ITT-DSIV) and for the disease stages III and IV (ITT-DSIII/IV) combined.

Table 26 Post-hoc Analysis of TTNT by Post-hoc-Defined Subgroups (based on ITT Population)

Patient Population	Median TTNT, months [95% CI]		p-Value (stratified log-rank test)	Hazard Ratio ¹ [95% CI] (stratified Cox proportional hazards model)
	Resminostat N = 100	Placebo N = 101		
ITT-DSIIB (patients with stage IIB disease at baseline)	N = 59; n = 41 9.6 [7.4, 19.3]	N = 58; n = 50 4.5 [2.3, 5.6]	0.0016 *	0.517 [0.341, 0.783]
ITT-DSIII (patients with stage III disease at baseline)	N = 15; n = 9 9.3 [3.2, 19.3]	N = 8; n = 6 8.7 [0.7, 38.9]	0.6225	0.766 [0.264, 2.221]
ITT-DSIV (patients with stage IV disease at baseline)	N = 26; n = 19 7.4 [4.2, 16.0]	N = 35; n = 29 4.0 [2.8, 8.8]	0.1167	0.590 [0.302, 1.150]
ITT-DSIII/IV (patients with stage III or IV disease at baseline)	N = 41; n = 28 8.4 [4.7, 16.0]	N = 43; n = 35 4.0 [2.6, 10.3]	0.1334	0.659 [0.381, 1.141]

Evaluation of FACT-G Subscales and a Modified FACT-G Total Score

In addition to evaluation of changes from baseline in FACT-G total scores using an MMRM approach, the 4 subscales of the FACT-G questionnaire were analyzed separately and subject to the same MMRM model. The difference in changes from baseline was statistically significant in favor of placebo in both the functional well-being and the physical well-being subscale scores (Table 27). Furthermore, a modified FACT-G total score was determined, with the physical well-being question "I have nausea" set to "not at all" for all patients to test the impact of nausea (an AE frequently observed in patients on resminostat). The modified score was also subject to MMRM analysis. The treatment effect using the modified FACT total score was -2.9463 [95%

CI: -6.4123, 0.5197], i.e., still in favor of placebo ($p = 0.0954$), but smaller than the effect of the original FACT-G total score (-3.736 [-7.310, -0.162]) (Table 27).

Table 27 Post-hoc Analysis of Change from Baseline in QoL FACT-G Scores (ITT Population)

FACT-G Questionnaire [Score Range]	Treatment Effect [95% CI]	p-Value (Type III Test)
FACT-G total score ¹ [0 - 108]	-3.736 [-7.310, -0.162]	0.041 *
Modified FACT-G total score ² [4 - 108]	-2.9463 [-6.4123, 0.5197]	0.0954
Emotional well-being subscale [0 - 24]	0.1713 [-0.8159, 1.1584]	0.7330
Functional well-being subscale [0 - 28]	-1.1885 [-2.3164, -0.0605]	0.0390 *
Physical well-being subscale [0 - 28]	-2.9168 [-4.1872, -1.6463]	<0.0001 *
Family/Social well-being subscale [0 - 28]	-0.0818 [-1.3276, 1.1640]	0.8973

CI: confidence interval; FACT-G: functional assessment of cancer – general; ITT: intention-to-treat; QoL: quality of life.

For the purpose of the analysis, 83 resminostat and 89 placebo patients were included, respectively.

* Statistical significance (p -value ≤ 0.05).

¹ As determined during main data analysis (Table 14.3.6.2).

² Post-hoc analysis of FACT-G total score with the physical well-being question "I have nausea" set to "not at all" for all patients.

Source: Post-hoc Table T6.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 8 Summary of efficacy for trial RESMAIN

Title: 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	
Study identifier	RESMAIN
Design	multicenter, double blind, randomized, placebo controlled, cross-over

Title: 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			
Study identifier	RESMAIN		
	Duration of main phase:	Resminostat: until progressive disease, or unacceptable toxicity. Placebo arm; until progressive disease, or unacceptable toxicity, patients had the option to crossover to receive open-label resminostat	
	Duration of Run-in phase:	not applicable	
	Duration of Extension phase:	resminostat: Treatment continued indefinitely as appropriate, as outlined above. Placebo arm: Treatment continued indefinitely as appropriate, as outlined above.	
Hypothesis	Superiority		
Treatments groups	resminostat	600 mg per day on Days 1 - 5 of a 14-day treatment cycle, until progression or unacceptable toxicity, N=100	
	placebo	600 mg per day on Days 1 - 5 of a 14-day treatment cycle, until progression or unacceptable toxicity, N=101.	
Endpoints and definitions	Primary endpoint	PFS	Time from date of randomization to first date the criteria for PD are met according to the GRS or death by any cause in the absence of documented PD.
	Secondary endpoint	TTSW	Time from date of randomization to first date the criteria for symptom (pruritus) worsening had been met.
	Secondary endpoint	TTNT	Time from date of randomization to first date that new treatment is received; for placebo patients, roll-over to open-label resminostat was considered as the next treatment
Database lock	10 March 2023		

Title: 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			
Study identifier	RESMAIN		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	resminostat	placebo
	Number of subject	100	101
	PFS	8.3	4.2
	Median (months)		
	95%CI	[4.2, 15.7]	[2.8, 6.4]
	TTSW	NE	NE
	95%CI	[14.7, NE]	[NE, NE]
	TTNT	8.8	4.2
Effect estimate per comparison	Primary endpoint PFS	Comparison groups	Resminostat/placebo
		HR	0.623
		95%CI	[0.424, 0.916]
		P-value	0.015
	Secondary TTSW	Comparison groups	Resminostat/placebo
		HR	1.215
		95%CI	[0.538, 2.742]
		P-value	0.644

Title: 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			
Study identifier	RESMAIN		
	Secondary endpoint TTNT	Comparison groups	Resminostat/placebo
		HR	0.594
		95%CI	[0.428, 0.825]
		P-value	0.002
	Secondary endpoint OS	Comparison groups	
		HR	0.983
		95%CI	(0.606, 1.590)
		P-value	0.940
Notes	data cut off: 08 August 2024 for OS		

2.6.5.3. Clinical studies in special populations

	Controlled Trials (RESMAIN, YHI-BTC-06, YHI-HCC-02, YHI-LC-03)	Non-controlled trials (FIM, hAME, SAPHIRE, SHELTER, SHORE, YHI- BTC-04, YHI-FE-07, YHI- ST-01)
Renal impairment ^a patients (Subjects number /total number)	349/595	75/186
Hepatic impairment ^b patients (Subjects number /total number)	2/595	11/186
Paediatric patients <18 years (Subjects number /total number)	0/595	0/186
Age 65-74 (Subjects number /total number)	233/595	56/186
Age 75-84 (Subjects number /total number)	68/595	8/186

Age 85+ (Subjects number /total number)	3/595	0/186
Other (Subjects number /total number)	NA	NA

2.6.5.4. *In vitro* biomarker test for patient selection for efficacy

N/A

2.6.5.5. *Analysis performed across trials (pooled analyses and meta-analysis)*

No comparative analyses with results from other studies are presented as only one pivotal study has been conducted to investigate the efficacy of resminostat as maintenance monotherapy in the proposed therapeutic indication and at the proposed dose and schedule.

2.6.5.6. *Supportive study(ies)*

There was no other supportive study.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal study was a multi-centre, double-blind, randomized, placebo-controlled phase II trial to evaluate whether resminostat in maintenance setting was able to prolong PFS (primary endpoint) or delay symptom worsening of pruritus (key secondary endpoint) compared with placebo in patients with advanced stage (Stage IIB - IVB) MF or SS with ongoing clinical benefit (CR, PR) or SD after at least one prior systemic therapy or TSEB. Patients were randomized in a ratio of 1:1 to resminostat or matching placebo. Patients on placebo had the option to roll-over to open-label treatment with resminostat and continue on treatment for as long as they derived benefit in the opinion of the investigator or until unacceptable toxicity.

Enrolment was limited to patients with histologically confirmed, advanced stage ($\geq$ IIB) MF or SS which can be endorsed, since they represent the population with the highest medical need, and because only patients with advanced disease may have received prior systemic treatments. It is however important to note that although overlaps may exist, MF and SS are distinct entities with different prognosis, which may have an impact on efficacy results and their interpretation. Disease stage was assessed according to the ISCL/EORTC revised staging system for MF/SS (Olsen et al 2007). Patients were also required to present adequate cardiac function and hematological, hepatic and renal function to avoid increased safety risks on study treatment. Anticancer treatment other than resminostat was not allowed. The study included patients that had received at least one systemic treatment according to local institutional standards. The choice of not limiting the possible prior treatments was endorsed by CHMP during the SA (EMA/CHMP/SAWP/33911/2016), taking into account that, no recognized standard in the treatment of advanced MF/SS can be identified.

The placebo-controlled study design was considered adequate by CHMP during the SA (EMA/CHMP/SAWP/33911/2016) considering the absence of maintenance treatment options. However, for

patients experiencing SD or PR with their last systemic treatment, in practice many treatments could be offered as long as the patient did not experience complete response. Indeed, either the treatment was considered effective for the patient and then should have been continued given that many treatments are administered until disease progression, or it was considered insufficient or with unacceptable toxicity and then it should have been modified which is considered a change of line of therapy for greater efficiency and not a maintenance treatment. In summary, patients included in the trial actually correspond to two types of populations, one population justifying maintenance treatment, i.e. patients in complete response for whom no maintenance treatment exists and another population justifying a change in treatment line for unacceptable toxicity or other eligible reasons i.e. patients with partial response or stable disease for whom the choice of placebo as a comparator is questioned given that many treatments could be offered among the range of treatments for advanced MF and SS. However, given that placebo as comparator was accepted in the SA (EMA/CHMP/SAWP/33911/2016) and that at this stage, there is no way to address this retrospectively, this issue was not further pursued.

176 patients with PR (N = 107; 53.2%) or SD (N = 69; 34.3%) at baseline were included in the study. The majority of patients (N = 117, 66.4%) had completed their last prior therapy as planned. This was the case in particular for treatment options with cumulative or irreversible toxicity (e.g. myelosuppression, cardiotoxicity or neuropathy) that are usually given for a defined treatment period or maximum dose, like TSEB radiation therapy, chemotherapy and brentuximab vedotin. The remaining third of patients (N = 59, 33.5%) had discontinued their last prior therapy due to toxicity. To better identify the intended patient population, it was indicated in the SmPC that the treatment should be initiated 2 to 12 weeks after the last systemic therapy has been completed as planned or terminated due to unacceptable toxicity.

The randomisation was stratified by remission status and disease stage. The high heterogeneity of the study population was highlighted as a general concern during scientific advice (EMA/CHMP/SAWP/33911/2016) and other important baseline characteristics (including but not limited to CTCL subtype and prior therapies) may represent relevant prognostic and/or predictive factors.

The study was a double-blind trial. Each patient was unblinded at the time of progression to determine subsequent treatment, and all remaining patients were unblinded once the main analysis results were available. Due to the gastrointestinal side effects associated with resminostat, the efficacy of blinding was questioned during scientific advice (EMA/CHMP/SAWP/33911/2016). The applicant clarified at the time that only an average of 2.5 patients per site were expected, which might reduce observer bias. A survey was also conducted to collect the patients and investigators' assumptions regarding the assigned treatment arm, prior to unblinding. In the resminostat arm, 60.0% of both patients and investigators correctly assumed their treatment arm, while 17.0% each incorrectly assumed treatment with placebo. In the placebo arm, 70.3% of the patients and 76.2% of the investigators correctly assumed their treatment arm, with 19.8% and 13.9%, respectively, incorrectly assuming treatment with resminostat. Assumptions were missing for both investigators and patients for 23.0% of patients in the resminostat arm, and for 9.9% of patients in the placebo arm. The Applicant's view that these survey results indicate "that blinding of the trial treatments was successful" is not shared. Instead, the large proportion of patients correctly assuming their treatment in both arms (and the small proportion of patients guessing incorrectly) likely reflects an important level of functional unblinding, which may have introduced bias in several efficacy analyses (including the analysis of primary and secondary endpoints).

A composite primary endpoint was PFS per the global response score or death from any cause, whichever occurs first. This is considered an appropriate primary endpoint and GRS is endorsed by the International Society for Cutaneous Lymphomas (ISCL), the United States Cutaneous Lymphoma Consortium (USCLC) and

the European Organisation for Research and Treatment of Cancer (EORTC) (Olsen et al., 2011). GRS includes assessment of response based on four components clinically relevant to MF/SS patients: skin, lymph, viscera, and blood. However, it was highlighted during the SA (EMA/CHMP/SAWP/33911/2016) that the expected PFS advantage with resminostat may be considered somehow limited, especially taking into account that the median overall survival of the MF (IIb-IVb)/SS patient population may vary between 2 to 5 years (depending on the stage of disease at the time of diagnosis) and that disease-specific survival shows an even larger spreading (2 to >10 years, see. i.e. Horwiz et al., Journal of the National Comprehensive Cancer Network, 2008). In recommendations endorsed by ISCL, USCLC and EORTC (Olsen et al., 2011) it was stressed that due to the importance of skin response in MF/SS, both skin and global response should be reported in clinical trials to ensure that skin response which independently affects prognosis and quality of life is not lost within the global score. mSWAT was not included as a secondary endpoint in the pivotal clinical trial; a post hoc summary of the changes of mSWAT scores was provided, and patient reported outcomes including VAS itching score was evaluated, which is considered sufficient to assess skin response.

Overall survival was included as a secondary endpoint but was not included in the multiplicity adjustment strategy and was not alpha controlled. As median overall survival is approximately 5 years in patients with advanced CTCL, the applicant considered not feasible to include survival as a primary endpoint. This can be supported but still requires that no detrimental effect is observed on survival. PFS2, PFS3, and TTNT were included as secondary endpoints, which are considered particularly important for the evaluation of long-term efficacy and the actual extent of the clinical benefit of resminostat maintenance, as indicated in EMA SA (EMA/CHMP/SAWP/33911/2016), however, TTNT is also influenced by cross-over study design. Secondary endpoints of confirmed ORR, DOR, and TTP are standard in oncology and thus acceptable. HRQoL assessed using FACT-G, Skindex-29, and VAS itching score is also considered clinically important for patients with MF/SS, and thus acceptable.

The study was 80% powered only to test a hypothesis for the primary endpoint of PFS, where the key secondary endpoint (TTSW) is tested using a hierarchical approach if the null hypothesis for the primary endpoint is rejected. No adjustments for multiple tests were applied for subsequent secondary endpoint analyses, and the results for these endpoints, therefore, can only be considered as descriptive. The results for analysis of TTSW (pruritus) would only be considered confirmative, if the analysis of the primary endpoint showed a significant result ($p\text{-value} \leq 0.05$). This hierarchical approach keeps the global significance level to 0.05 two-sided and required no further adjustment.

There was no planned adjustment for multiplicity for other secondary endpoints.

In Resmain study, progressive disease was assessed according to the definition of the consensus statement of the International Society for Cutaneous Lymphomas, the US Cutaneous Lymphoma Consortium and the EORTC Cutaneous Lymphoma Task Force using the proposed global response score comprising of the assessment of tumour response in skin, lymph nodes, viscera and blood (Olsen 2011). This was endorsed during the SA (EMA/CHMP/SAWP/33911/2016) since the proposed global response score (GRS) combining responses in skin, lymph nodes, blood, and viscera is considered, a standard efficacy measure in trials involving MF/SS.

According to inclusion criteria, the diagnosis of MF/SS was confirmed histologically. Initially, biopsy of one lesion was mandatory at the start of the trial and after PD. The performance of skin biopsies was terminated in Protocol Version 8.0. Additionally, PD or relapse of the disease in the lymph nodes should have been histologically proven. The protocol amendment was implemented on December 21, 2022 and according to the

date of main analysis, all patients should have been randomised, therefore it is considered that this amendment will have minor influence on eligibility of study participants, as diagnosis should be confirmed in a skin biopsy before trial initiation. For evaluation of response in skin according to Olsen et. al. (2011) recommendations a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease, and is more important for differentiating CR vs PR, however, as there were only few patients with CR, it is considered that this amendment have minor influence on evaluation of response. If a bone marrow biopsy was performed at baseline and was determined to unequivocally be indicative of lymphomatous involvement, then to confirm a global CR, a repeat bone marrow biopsy must show no residual disease or the response should be considered PR only; however, bone marrow biopsy was not routinely performed in every participant. According to Olsen et al. (2011) bone marrow involvement in MF/SS can be considered to be an extension of blood involvement and not visceral disease, and therefore bone marrow aspirate biopsies are not considered obligatory for evaluation or response assessment. Based on this the applicant's approach is not concerning.

The use of the mSWAT instrument to assess skin response in trials with a mixed MF and SS population was endorsed by CHMP during the SA since it allows to simultaneously evaluate both erythrodermia and any present tumour. The every 4 weeks' assessment schedule was also acceptable. However, a modification of the standard assessment was introduced, to allow for PD assessment in patients entering the study with a mSWAT of 0 (CR in skin): a mSWAT of at least 20 and a $\geq 25\%$ increase in skin disease from baseline was considered PD instead of: a $\geq 25\%$ increase in skin disease from baseline. Therefore, for a patient who entered the study with a CR (mSWAT of 0) or with a very good PR to prior therapy (mSWAT below 16), any increase in mSWAT to less than 20 and without new tumours should not be considered progressive disease, but SD in skin. This is acknowledged since in this study, patients were enrolled with a very low mSWAT, and that this would mean that a very small increase (25%) in skin disease would already meet the criteria for disease progression. However, a sensitivity analysis of PFS using the current response criteria of the 2011 ISCL/USCLC/EORTC consensus statement in skin disease, without the modification related to mSWAT value at baseline was provided. The applicant presented steps that were taken to reduce inter-observer variability in assessing skin lesions. These steps were overall reassuring. It was emphasized that the mSWAT assessment should be performed by the same investigator at all-time points to eliminate inter-observer variability for a given patient.

Centralised flow cytometry identification of circulating neoplastic lymphocytes (either CD4+CD26- or CD4+CD7-) is proposed to assess response in peripheral blood. This was endorsed, by CHMP although it was advised, to rely on the absolute number of pathologic lymphocytes rather than on binary positive/negative evaluations given that results based only on immunophenotype can be sometimes misleading due to the possible presence of non-neoplastic CD4+CD26-CD7-.

The use of computed tomography (CT) for assessment of lymph nodes and visceral involvement and the proposed assessment schedule were acceptable by CHMP. CT scan were performed at baseline and repeated every 12 weeks during the study.

Complete response assessments as per GRS (mSWAT, lymph nodes, viscera, blood) were to be performed at start of treatment and then once every 84 days (± 7 days) until blinded EOT. Intermediate response assessments (IRA), i.e., mSWAT and blood only, were to be performed at the start of treatment and then once every 28 days (± 7 days) until blinded EOT. If one of two tested compartments was PD, then a GRS response of PD was assigned. However, an improvement in GRS response (CR or PR) or stable in GRS response (SD) could only be assigned with a complete GRS assessment (i.e., lymph nodes and viscera assessed by CT in addition to mSWAT and blood analysis).

HrQoL was determined using the validated questionnaires FACT-G, skindex-29 and visual analogue scale (VAS). FACT-G is a 27-item questionnaire designed to measure physical, social, emotional, and functional well-being in patients undergoing cancer therapy. Skindex-29 is a dermatology-specific questionnaire to measure the effects of skin disease on patients' QoL. The VAS is a psychometric response scale to quantify the severity of itching. Overall, the proposed HRQoL instruments are considered sufficiently validated and adequate to capture relevant changes in patient reported outcomes as reported in SA (EMA/CHMP/SAWP/33911/2016).

The primary analysis set for PFS (ITT population) includes all randomized patients. A per protocol population has also been defined for sensitivity analysis. A TTSW (pruritus) population has been used for the key secondary population, restricting the analysis to randomised patients with a VAS itching score ≤ 7 at baseline, and excluding patients without a VAS itching score at baseline. The intent to only include patients at risk of worsening can be understood, but in the absence of stratification by VAS itching score may have led to some imbalance across treatment arms. Nevertheless, given the lack of treatment effect observed for the TTSW (pruritus) key secondary endpoint, and acknowledging the sensitivity analysis in the ITT population, no related questions were raised.

The censoring rules defined for PFS are not in line with EMA guidance (EMA/CHMP/27994/2008/Rev.1). Indeed, a treatment policy strategy would have been preferred for the primary analysis, i.e. with no censoring applied prior to non-study cancer treatment nor in case of at least two consecutive incomplete / missing global response assessments (GRAs). As requested, the Applicant provided an alternative PFS analysis where censoring rules were modified with no censoring applied to non-study cancer treatment nor in case of at least two consecutive incomplete / missing GRAs. The results were consistent with the primary PFS results. However, there are limitations with this additional analysis which prevent a meaningful interpretation, in particular the inconsistency in response assessment between the blinded period and the follow-up period. It is unfortunate that GRA was not continuously collected after treatment discontinuation until at least the first PD.

Moreover, the treatment policy approach requires for the primary analysis of PFS that outcome data should be collected according to the intended schedule of assessment and the date of progression should be assigned based on the time of the first evidence of objective progression regardless of intercurrent events (violations, discontinuation of study drug or change of therapy) for all randomised patients. Patients who discontinued for any reason other than PD were considered dropouts and last available evaluation was used for endpoint evaluation. These patients were included in the survival follow-up. As the PFS data for the primary endpoint was not available after the dropout, this is not in accordance with the treatment policy approach.

The presence of functional unblinding based on the results of the blinding survey is of concern. The impact of several scenarios involving the unblinding of either the patient or the investigator were discussed by the Applicant, with a focus on the impact on treatment withdrawal. However, not only treatment withdrawal may be affected by functional unblinding, but also the actual measurements themselves (for GRS components that are investigator-assessed).

The Applicant clarified that an independent central review of mSWAT assessment is not feasible based on photographs. Indeed, it would often be impossible to differentiate between patches and plaques, or skin areas with inflammatory changes from erythrodermic skin, based on photographs only. Skin being the leading disease compartment with 82% of disease events occurring in skin, a potential central review of other components (LN and viscera) would not substantially change the reliability of the primary endpoint. The impossibility to perform a blinded central review prevents a meaningful assessment of the potential bias

introduced by functional unblinding.

The key secondary endpoint TTSW (pruritus) may also be subject to informative censoring for the same reasons. Due to the lack of demonstration of a treatment effect based on the current set of statistical analyses, the issue was not pursued for TTSW.

Based on the current OS results, very few patients were lost to follow up for survival status (1 in resminostat group, 2 in placebo), thereby indicating negligible impact of informative censoring. However, the analysis of OS is confounded by the crossover design.

The endpoint TTNT is confounded by the crossover design. Indeed, the definition of next treatment includes crossover, which can only be an option for patients in the placebo arm. The Applicant clarified that 72 (84.7%) of TTNT events in the placebo arm correspond to patients crossing over to resminostat. This confirms that TTNT is very likely biased. Indeed, crossover can only be an option for patients in the placebo arm. Whether as many patients would have initiated a subsequent therapy in the absence of crossover, and whether these subsequent therapies would have been initiated at the same time point, is speculative and unlikely.

HrQoL endpoints (VAS, FACT-G, Skindex-29) and the post-hoc analysis of changes in mSWAT score were assessed using a mixed model that assumes the linearity of measurements over time. This is a rather strong assumption, which has not been discussed. It is also noted that HrQoL and mSWAT score analyses are not adjusted for the randomisation stratification factors. .

It is noted that some emphasis is given in the study report and in the summary documents to the post-hoc analysis of PFS from start of last prior systemic therapy to first PD. However, the use of last prior systemic therapy as a starting point, instead of randomisation, is subject to immortal time bias which has not been accounted for. This has likely resulted in a distortion of the observed treatment effect.

The main changes to planned analyses were incorporated in protocol amendments 4.0, 6.0 and 7.0, which were subsequently also included in the relevant SAP versions. The sample size, in terms of number of patients to be enrolled, was increased in protocol amendments 6.0 and 7.0. The increase was from 150 to 190 patients with protocol version 6, then from 190 to 200 patients with protocol version 7, to account for larger anticipated drop-out rates, from 10% to 30%, and then from 30% to 33% respectively. It is acknowledged that the targeted number of events ($n=125$) remained the same across all protocol versions, as well as all other sample size assumptions. The main impact of these modifications is therefore the expected lower maturity. The resulting PFS analysis may also be driven by earlier events than initially expected. Another important concern related to the higher drop-out rate is the impact of informative censoring on the PFS primary analysis, as already discussed above.

A hierarchical testing procedure was followed, with the analysis of TTSW (pruritus) only being performed if the PFS primary analysis showed a significant result at the two-sided 0.05 alpha level. There was no multiplicity adjustment for other secondary endpoints, which should therefore be considered of exploratory nature.

Efficacy data and additional analyses

A total of 234 patients (including 11 patients who were re-screened and thus each counted twice) were screened for trial participation at 55 active study sites across Europe and Japan. A total of 201 patients were randomized to either resminostat (100) or placebo (101), with eligibility criterion not met being the main reason for screening failure (18/33).

As of 10 March 2023, 92 subjects (92%) in the resminostat arm had discontinued their treatment compared to 93 subjects (92%) in the placebo arm. The most commonly reported reasons for treatment discontinuation were PD, which was more common in the placebo arm (69%) than in the resminostat arm (49%); patient withdrawal which was more common in the resminostat arm (25%) than in the placebo arm (5%) and AEs, which was more common in the resminostat arm (8%) than in the placebo arm (5%). Until the DCO date (10 March 2023) for the primary analysis, 72 patients randomized to placebo rolled over to resminostat. A total of 30 patients (14.9%) have withdrawn the consent during the course of the study, 25 of these patients were treated in the resminostat group and 5 in the placebo group. The most frequent reason for this imbalance was tolerability complaints (19 patients in resminostat vs 0 in placebo) mainly related to gastrointestinal disorders like nausea (mainly grade 1 or 2), dysgeusia and fatigue.

There were 7 amendments to the protocol. The main changes were the addition of evaluation of changes in the VAS itching score, modification of the allowed window between completion of prior treatment and randomization (from 8 weeks to 12 weeks), modification of exclusion criterion #8 (history of prior cancers), to add systemic steroids as anti-itching medication to the list of prohibited medication, and to allow reescalation of the dose to 600 mg/day if the dose was reduced due to nausea, vomiting or similar gastrointestinal events.

Minor protocol deviations were reported in 187 patients (93.0%). Major protocol deviations were highly reported in the study; 80% in resminostat arm and 74% in placebo arm. Major PD were related to procedures not done, or outside time window, deviations in incl./excl. criteria, administration of prohibited medication, ICF issues, laboratory issues (samples lost or received late, not done), study drug issues (potential/actual blind broken, dosing non-compliance, incorrect medication/randomization) and visit schedule issues (incomplete, not done, outside time window).

A total of 10 patients (10.0%) and 17 patients (16.8%) in the resminostat and placebo arm respectively were excluded from the PP population. This was due to the following reasons: determination of PD not fulfilling the PD criteria, absence of assessment for the ECG parameter of QTc (leading to early discontinuation), missing first 2 post-baseline GRS assessments, violation of eligibility criteria, missing GRS before PD and wrong subject medication given.

The applicant indicated that the study 4SC-201 was conducted in accordance with local and/or national regulations, the ICH GCP guideline and the ethical principles of Declaration of Helsinki and applicable regulatory requirements, and informed consent was obtained from participants. Several GCP audits were conducted on behalf of the sponsor at the trial sites, including remote audits due to the COVID-19 pandemic, which comprised the EMA guidance on the management of clinical trials during the COVID-19 pandemic and the EMA guidance on remote GCP inspections during the COVID-19 pandemic. Three regulatory inspections were conducted at the trial sites (two in Germany and one in Switzerland). It was considered that the clinical trial was conducted in accordance with GCP and review of the provided CAPA plan has shown that the measures are sufficient and suitable to eliminate the deficiencies and avoid them in future studies. Overall, the study included a broad range of patients with advanced-stage MF or SS who received a large variety of prior systemic therapies, resembling the real world CTCL patient population. The last prior systemic therapy was bexarotene/other retinoids (23%), chemotherapy (23.4%), brentuximab vedotin (15%), TSEB (12%) and ECP (6%).

The demographic characteristics were median age of 64 years (30 to 87 years) with 45% of patients' ≥ 65 years. 61% of patients were male, 39% were female. Disease stage at baseline was IIB-IVA1 in 83% (58% stage IIB, 6% stage IIIA, 6% stage IIIB, 13% stage IVA1) and IVA2-IVB in 17% of patients (13% stage IVA2, 5% stage IVB). At baseline 12.4% of patients had CR, 53.2% of patients had PR and 34.3% of patients

had SD. Patients were slightly younger than reported in the literature and therefore might have better prognosis. Groups were similar in terms of median age, ECOG performance, CTCL subtype and anti-itching treatment at baseline. Resminostat group had lower median weight (74.8 vs 80 kg), slightly shorter duration of the disease and fewer patients with more advanced - IVA1 un IVB stages compared to placebo. In terms of remission status, more patients in resminostat group had CR and SD while placebo group had more patients with PR. More patients in resminostat group had large cell transformation (n=24; 24%) vs placebo (n=13; 12.9%) which is associated with more aggressive disease course. Although there are several discrepancies between the groups it is difficult to assess whether any of them could introduce a systematic bias in the results. There were more women in the resminostat group (n=47; 47%) compared to placebo group (n=31; 30.7%). Literature data suggest that being women is independently associated with better outcomes in the MF diagnosis ([https://www.jaad.org/article/S0190-9622\(21\)00171-7/fulltext](https://www.jaad.org/article/S0190-9622(21)00171-7/fulltext)). The applicant argues that although women are reported to have better outcomes there are still conflicting results regarding the role of gender as a prognostic factor when accounting for disease characteristics and treatment. In addition, the applicant considers that based on the pharmacological mechanism of resminostat as HDAC inhibitor possible gender-specific differences are considered unlikely. The Applicant suggests that observed changes notably lower PFS for men subgroup compared to women may be driven by increased body weight in male participants as the PK data indicate that increased body weight is associated with decreased exposure.

All patients had received previous systemic therapy with up to 21 treatment lines (mean: 4.1; median: 3.0). As expected, due to the lack of established treatment recommendations, patients had been treated with a variety of different previous therapies.

Based on subgroup analysis, it seems that patients with less than 3 prior lines of therapies retrieve better efficacy with resminostat (PFS of 26.9 months with resminostat vs 4.2 months with placebo (HR 0.464, 95% CI: 0.260, 0.829)) than patients with extensive prior line of therapies (more than 3 prior therapy) (PFS of 6.0 months vs 4.6 months with placebo (HR 0.9, 95% CI: 0.522, 1.554)). Regarding the high mPFS reported in the resminostat arm (26.9 months) of the subgroup of patients with 1, 2 or 3 prior therapy, this seems overestimated by the KM curves due to the late extensive censoring.

In total, nearly half of the patients (47.8%) had at least one prior disease. SOC's were distributed similarly between the resminostat and placebo arms for the most common SOC's (20.0% versus 26.7% for surgical and medical procedures, 14.0% versus 11.9% for neoplasms benign, malignant and unspecified, and 8.0% versus 12.9% for infections and infestations). The majority of patients (87.6%) had at least one concomitant condition.

Almost all patients (96.5%) received concomitant medications during study. However, some imbalances were reported with higher use of some classes of drug in resminostat arm, reflecting the need to manage safety risks of resminostat. This particularly concerns drugs for peptic ulcer and gastrooesophageal reflux disease (GORD), emollients and protectives, propulsives, anti-emetics and anti-nauseants to manage gastrointestinal side effects, beta-lactam and other anti-bacterials for the management of infections related to treatment and analgesics, antipyretics, and corticosteroids for systemic use mainly to manage pain and nausea or vomiting.

Patients in the resminostat arm received slightly more corticosteroids than patients in the placebo arm (51 vs. 45.5%), more antihistamines (45 vs 42.6%), more systemic corticosteroids (24 vs 14.9%). Emollients and protectives 31 (31.0%) in resminostat group vs 20 (19.8%) in placebo and opioids 16 (16.0%) in resminostat group vs 9 (8.9%) in placebo group. These discrepancies may confound study results on pruritis improvement in favour of resminostat group.

The main analysis showed a statistically significant improvement in PFS for resminostat compared with

placebo, with a median PFS of 8.3 months versus 4.2 months, respectively, and an HR of 0.623 in favor of treatment with resminostat in the overall patient population.

The stability of study results was questioned based on the sensitivity analysis where discontinuation due to toxicity or start of new treatment before PD were considered as an event. Indeed, this sensitivity analysis showed a smaller effect size and did not reach nominal statistical significance. Given the safety profile of resminostat and the imbalance observed in treatment withdrawals for toxicity, it may be reasonable to consider discontinuations due to toxicity or new treatments before PD as unfavourable outcomes – and therefore a sensible assumption to consider them as events in this alternative PFS analysis.

It was confirmed that the vast majority of the PFS censoring is non-administrative and indicates informative censoring. As suspected, it is also apparent that withdrawals due to tolerability issues or drug-related adverse events were the main non-administrative reason for PFS censoring in the resminostat treatment group. This pattern was not observed in the placebo arm. Instead, several censored measurements in the placebo arm (more than in the resminostat arm) were due to physician decisions based on increases in mSWAT not fulfilling PD criteria, and a few others due to treatment withdrawal for lack of efficacy / patient's assumption to be on placebo.

Based on these censoring patterns, the Applicant concludes that post-censoring hazards are likely increased in both treatment groups, but that this increase is probably less pronounced in the placebo arm, so that the treatment effect in PFS might actually be larger than in the primary analysis results. This is based on the Applicant's assumption that withdrawals due to tolerability are unrelated to PFS outcomes, whereas withdrawals related to increases in mSWAT not fulfilling PD criteria would be indicative of a negative outcome. This interpretation is not agreed.

Firstly, and as further discussed above, it seems reasonable to assume that treatment withdrawals due to tolerability issues are associated with more negative outcomes, because of the adverse effect itself and/or the delay it may cause to further treatment. Given the very large imbalance in withdrawals because of tolerability or drug-related side effects (n=19 with resminostat vs n=2 with placebo), this is likely to result in a more pronounced increase in post-censoring hazard in the resminostat group.

Moreover, although the larger proportion of censoring in the placebo group due to increases in mSWAT not fulfilling PD might be associated with a higher risk of post-censoring hazard to some degree, it is unclear whether such increase is truly meaningful. Indeed, some of the increases observed, although describing a trend towards disease worsening, do not seem close to reaching PD criteria. Moreover, such decision to withdraw from treatment early based on increases that do not reach the protocol criteria is likely influenced by the extent of functional unblinding.

Therefore, a post-censoring hazard higher in the resminostat arm than in the placebo arm for non-administratively censored patients is a plausible assumption. In this context, the results of the tipping point analysis are of concern. Indeed, most investigated scenarios with higher multiplicative increases in the resminostat arm than in the placebo arm result in loss of statistical significance, with smaller effect sizes than in the primary analysis. For instance, increasing the post-censoring hazard for the resminostat group by only a factor of 1.25 leads to the loss of significance in the log-rank test (p=0.06).

The robustness of the PFS analysis could not be shown in the single pivotal trial. This is due to the extent of informative censoring, the large imbalance in withdrawals due to toxicity and the potential impact of functional unblinding. The effect of resminostat on PFS may be over-estimated to the point where the effect is not statistically significant. Moreover, there is no treatment difference in OS, and the absence of treatment effect persists after adjustment for crossover (with sensitivity analyses indicating a potential detriment).

Importantly, given the large confidence limits, the OS data cannot rule out a substantial detriment on survival. There is also no clear support from other secondary endpoints. Consequently, the efficacy of resminostat was not considered established.

TTP and TTNT results were in favour of resminostat, with a median TTP of 8.3 months on resminostat and 4.2 months on placebo (HR of 0.623) and a median TTNT of 8.8 months on resminostat and 4.2 months on placebo (HR of 0.594). The statistical significance claim of these endpoints is not supported given that results are purely exploratory due to absence of multiplicity adjustment. Furthermore, patient drop-out rate was high with more premature withdrawals in the resminostat group which raises a concern of informative censoring with an imbalance between treatment arms.

Among patients with baseline remission status of PR or SD, ORR rate was 17.4% (10.104, 27.131) and 10% [4.676, 18.136] in resminostat and placebo arm, respectively with similar median DOR. These results should be interpreted with caution given their exploratory nature, and the risk of bias due to elimination of a subpopulation (patients with CR at baseline). The relevance of ORR in a maintenance therapy setting is limited, since patients were already in remission (CR or PR) or at least in SD when starting with maintenance treatment. Further, the prior therapy may have contributed to the responses observed during treatment with resminostat or placebo.

The results for OS at the final analysis (data cut off: 08 August 2024) were similar to those at the main analysis and showed no significant difference between the treatment arms (p-value 0.940, HR 0.983 (0.606, 1.590)). Two analyses were performed by the Applicant to investigate the effect of crossover on OS results: censoring at time of crossover (planned by SAP), and a RPSFTM analysis (post-hoc, one of several analyses mentioned in EMA/845963/2018 to explore the effect of crossover on OS). These analyses did not provide reassurance on the OS data. Indeed, analyses adjusting for crossover consistently showed no treatment effect on OS, and even indicated a potential detriment.

Analyses of PFS2 (p-value 0.156, HR 0.758 (0.516, 1.113)), and PFS3 (p-value 0.921, HR 1.021 (0.674, 1.547)) at the final analysis time point (data cut off: 08 August 2024) do not indicate a statistically significant difference between treatment arms and do not provide reassurance on long-term effect of treatment.

The analysis of the key secondary endpoint TTSW pruritus in the TTSW population including the sensitivity analysis in the ITT population and in a population including only patients with all scheduled assessments of symptom (pruritus) worsening do not allow to retrieve any conclusion about the potential effect of resminostat on pruritus symptoms. Within the TTSW population (n = 154), 14 TTSW pruritus events (19.4% of patients) were observed on resminostat and 11 events (13.4% of patients) on placebo. The estimation of median TTSW was not possible due to the limited number of events. Limited information on TTSW pruritus is considered as an important limitation in B/R analysis of resminostat.

In summary, no benefit of resminostat on itching based on results of changes from baseline in VAS itching could be demonstrated. The mean scores of itching based on VAS did not change over time (mean values about 2-4) in both arms and there was no clinically significant difference in the observed changes from baseline over time for resminostat versus placebo using a MMRM. In addition, there were high number of missing assessments over time.

No benefit of resminostat on FACT-G scores were reported over time, contrariwise, results were in favour of placebo. Also, the number of patients with available FACT-G scores decreased over time. Precisely worsening in the "physical well-being" domain was observed with resminostat but remained stable with placebo. Furthermore, the observed changes from baseline in FACT-G scores for resminostat versus placebo based on

the ITT population using a linear MMRM were in favor of placebo.

There was no benefit of resminostat on Skindex-29 questionnaire. The difference in the observed changes from baseline over time for resminostat versus placebo was slight and not clinically significant. The requirement of anti-itching treatment or doses change of anti-itching treatment during the study was similar in both treatment arms and comprised predominantly corticosteroids and antihistamines for systemic use, which is in line with the results of the VAS itching scale where no benefit of treatment on itching symptoms was reported.

In summary, QoL endpoints did not show improvement in the resminostat group. Some analysis suggests worsening in resminostat group compared to placebo.

A post-analysis of PFS from start of last prior systemic therapy to first occurrence of PD (= total PFS) in the ITT population based on the same events as described for the primary endpoint of PFS, showed a median total PFS of 24.3 months for resminostat compared with 14.9 months for placebo with an HR of 0.745 in favor of resminostat. However, the use of last prior systemic therapy as a starting point, instead of randomisation, is subject to immortal time bias which has not been accounted for. This has likely resulted in a distortion of the observed treatment effect.

The difference in median PFS between the treatment arms for the subgroup of SS patients was smaller (4.2 months for placebo vs 5.6 months for resminostat) than for the subgroup of MF patients (4.2 months for placebo vs 9.2 months for resminostat) mainly due to the lower mPFS reported in the resminostat arm for SS group. The Applicant acknowledges that data concerning the efficacy of resminostat in SS is limited and agrees that PFS results are neither clinically or statistically significant. OS data in this subgroup are uninterpretable given the very low number of death events. The applicant provided a detailed analysis of prognostic factors that favouring placebo to justify the reported results in this subgroup of patients. The imbalance in disease characteristics and prognostic factors could possibly explain the reported limited results in PFS. However, it cannot be excluded that these results may as well translate an absence of a clinical effect in SS a different entity of CTCL than MF with more aggressive disease course. The extent of efficacy of resminostat in SS could not be assessed and there is no retrospective solution to this issue.

The results of patients who switched to rollover treatment with open-label resminostat due to PD are difficult to interpret given that patients who crossed-over do not correspond to the target population. These are relapsed/progressive patient population and have received resminostat as a treatment alternative after PD. Whereas resminostat targets patients that have achieved at least stable disease with at least one prior systemic therapy.

Patients with TSEB as the last systemic therapy prior to trial entry had a median PFS of 9.7 months, on resminostat versus 39.8 months for placebo (HR 1.520 (0.443, 5.219)). The number of events was very small and survival curves intersect rendering interpretation of survival data in this subgroup very difficult.

The applicant presented PFS subgroup analyses and corresponding Kaplan-Meier curves for subgroups by prior remission status (CR vs. PR vs. SD) and for combined subgroups (CR vs. PR/SD) as requested. Overall, results in these subgroups are consistent with primary analysis.

Consistently with PFS subgroup analysis, the increase in median TTP on resminostat was limited in patients with SS rather inexistent given the overlapping CIs (5.6 months [1.9, 23.1] vs 4.2 months [1.6, 31.4] HR 0.858 [0.294, 2.507]) but was consistent to the primary analysis for patients with MF, subgroup of patients based on the response status to prior therapy and the disease stage.

A post-hoc subgroup analysis of PFS and TTNT was performed for each of the disease stages IIB, III and IV

and for the disease stages III and IV combined. Although limitations related to the small sample size in some subpopulations, PFS and TTNT results in all disease stage subgroups were overall consistent with the results reported in ITT population. The treatment effect using a modified FACT-G total score, with the physical well-being question "I have nausea" set to "not at all" for all patients to test the impact of nausea, was -2.9463 [95% CI: -6.4123, 0.5197], i.e., still in favor of placebo, but smaller than the effect of the original FACT-G total score (-3.736 [-7.310, -0.162]).

2.6.7. Conclusions on the clinical efficacy

The efficacy of resminostat was assessed in one single pivotal phase 2 study in patients with advanced-stage CTCL (MF or SS) that had achieved disease control or clinical response (SD, PR and CR) with previous systemic therapy or TSEB. PFS results were statistically significant (4 months of PFS gain) but it was not possible to interpret given the lack of robustness of results due to various methodological concerns, the absence of support from other secondary endpoints considered clinically relevant (QoL and pruritis improvement) and OS sensitivity analyses indicating a potential detriment. The population of the study is too heterogeneous in terms of class of response, number of prior therapies, and type of CTCL and inconsistencies in PFS results were reported in many subpopulations (particularly SS) reflecting the heterogeneity of the trial population. These uncertainties do not allow to conclude on the efficacy of resminostat.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

Table 9: Summary of Clinical Studies Contributing with Safety Data for the Current Submission

Study Number	Study Design	Patient Population N (M/F) Age	Number of Study Centers Location(s)	Study Start/ Completion Duration/ Status	Individuals Enrolled/ in Safety Assessments	Treatment, Dose, Regimen and Duration of Treatment
Pivotal Study with Resminostat Monotherapy in Patients with Advanced CTCL						

Study Number	Study Design	Patient Population N (M/F) Age	Number of Study Centers Location(s)	Study Start/ Completion Duration/ Status	Individuals Enrolled/ in Safety Assessments	Treatment, Dose, Regimen and Duration of Treatment
4SC-201-6-2015 (RESMAIN)	Phase II, multinational, multicenter, randomized, double-blind, placebo-controlled prospective study	201 patients with advanced MF or SS (123 male/ 78 female) Median age: 64.0 years (range: 30 – 87 years)	55 centers across 12 countries: 18 in Germany; 5 in France; 5 in Italy; 5 in Japan; 5 in Spain; 4 in Poland; 4 in the UK; 3 in Switzerland; 2 in Austria; 2 in Belgium; 1 in Greece; 1 in the Netherlands	14.12.2016/ June 2024 (expected) Cut-off date for main analysis 10.03.2023/ Ongoing	201 patients / 201 patients	Resminostat: 600 mg QD "5 + 9" schedule a Duration: until disease progression or unacceptable toxicities
Supportive Studies with Resminostat Monotherapy in Other Oncologic Indications						
7341/EM-001 (FIM)	Phase I, open label, single-center, and inter-patient dose-escalating study	19 patients with advanced solid tumours (9 male/ 10 female)	1 center in the UK	19.09.2007/ 25.06.2009 Approximately 21 months/ Completed	19 patients/ 19 patients	Resminostat: 100 – 800 mg QD "5 + 9" schedule a Duration: 4 treatment cycles or

Study Number	Study Design	Patient Population N (M/F) Age	Number of Study Centers Location(s)	Study Start/ Completion Duration/ Status	Individuals Enrolled/ in Safety Assessments	Treatment, Dose, Regimen and Duration of Treatment
		Median age: 58 years (range: 37 – 70 years)				more, in case of clinical benefit
4SC-201-2-2009 (SAPHIRE)	Phase II, open label, multicenter, single-arm study	37 patients with advanced Hodgkin's lymphoma (19 male/ 18 female) Median age: 34 years (range: 19 – 71 years)	Centers: 5 centers in 3 countries 2 in Poland; 2 in Romania; 1 in the Czech Republic	17.12.2009/ 01.10.2012 Approximately 33 months/ Completed	37 patients/ 37 patients	Resminostat 600 or 800 mg QD "5 + 9" schedule a Duration: treatment up to 1 year
YHI-1001-ST-01	Phase I, open label, single-center study	12 patients with advanced solid tumours (5 male/ 7 female) Median age: 62.5 years (range: 33-70 years)	1 center in Japan	08.05.2012/ 26.07.2013 Approximately 14 months/ Completed	12 patients/ 12 patients	Resminostat: 400 – 800 mg QD "5 + 9" schedule a Duration: until disease progression or unacceptable toxicity
4SC-201-1-2009 (SHELTER) (safety data presented only for resminostat)	Phase II, open label, uncontrolled, nonrandomized, two-arm parallel group study	57 patients with advanced HCC progressing on sorafenib; 19 patients	Centers: 15 centers in 2 countries 8 in Germany; 7 in Italy	20.07.2009/ 02.07.2013 Approximately 4 years/ Completed	57 patients/ 57 patients (19 treated with monotherapy)	Treatment: Dose escalation phase: Combination therapy of resminostat

Study Number	Study Design	Patient Population N (M/F) Age	Number of Study Centers Location(s)	Study Start/ Completion Duration/ Status	Individuals Enrolled/ in Safety Assessments	Treatment, Dose, Regimen and Duration of Treatment
monotherapy arm)		treated with monotherapy (16 male/ 3 female) Median age: 61.0 years (range: 35 – 80 years)				+ sorafenib (200 + 400, 400 + 400, 600 + 400 or 600 + 800 mg) Extension phase: Resminostat alone (600 mg) versus combination therapy of resminostat + sorafenib (600 + 400 mg) Regimen: Resminostat: "5 + 9" schedule a, once daily administration Sorafenib: twice daily administration every day Duration: Dose escalation phase: Until disease progression or

Study Number	Study Design	Patient Population N (M/F) Age	Number of Study Centers Location(s)	Study Start/ Completion Duration/ Status	Individuals Enrolled/ in Safety Assessments	Treatment, Dose, Regimen and Duration of Treatment
						unacceptable toxicity

Table 10: Patient exposure (cut off 10 March 2023)

	Patients enrolled	Patients exposed*	Patients exposed to the proposed dose range	Patients with long term** safety data
Blinded studies (placebo-controlled) RESMAIN and YHI 1001 BTC 06	302	222	172	TBC
Blinded studies (active -controlled)	0	0	0	0
Open studies	482	341	144	TBC
Post marketing	0	0	0	0
Compassionate use	TBC	TBC	TBC	TBC

* Received at least 1 dose of active treatment

** In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

Table 11: Duration of exposure

Duration of exposure (months)	Pivotal study 4SC-201-6-2015 N = 172 ¹	All other studies N = 391
< 1	20	99
1 to < 3	49	171
3 to < 6	46	79

Duration of exposure (months)	Pivotal study 4SC-201-6-2015 N = 172 ¹	All other studies N = 391
6 to < 9	20	28
9 to < 12	6	6
12 to < 18	15	5
18 to < 24	5	2
≥ 24	11	1

N: Number of patients in the Safety Population.

1: including 100 patients treated with resminostat during the double blind treatment phase and 72 patients treated during open label treatment after rollover from placebo; the study is ongoing (data cut-off: 10 Mar 2023)

Table 12 Duration of Treatment and Dose Intensity (Safety Population)

Characteristic		Resminostat N = 100	Placebo N = 101	Total N = 201
Total number of cycles	mean (SD)	19.3 (26.5)	16.8 (21.5)	18.0 (24.1)
	median	9.0	8.0	9.0
	min, max	1 - 136	1 - 95	1 - 136
Total number of cycles per patient, n (%)	1 - 10 cycles	55 (55.0)	58 (57.4)	113 (56.2))
	11 - 20 cycles	21 (21.0)	19 (18.8)	40 (19.9)
	> 20 cycles	24 (24.0)	24 (23.8)	48 (23.9)
Duration of treatment, days	mean (SD)	287.20 (398.86)	245.43 (323.29)	266.21 (362.56)
	median	127	110	126
	min, max	10 - 1939	14 - 1365	10 - 1939
Total cumulative dose, mg	mean (SD)	50004.0 (70158.2)	50374.3 (64578.0)	50190.0 (67243.3)
	median	27000.0	24000.0	26600.0
	min, max	600 - 407400	3000 - 285000	600 - 407400
Relative dose intensity, %	mean (SD)	87.51 (16.36)	98.10 (4.90)	92.83 (13.14)
	median	97.29	100.00	99.54
	min, max	28.0 - 103.7	71.7 - 103.7	28.0 - 103.7
Actual dose intensity, mg/week	mean (SD)	1312.64 (245.36)	1471.53 (73.50)	1392.48 (197.09)
	median	1459.41	1500.00	1493.12

	min, max	420.0 - 1555.6	1075.7 - 1555.6	420.0 - 1555.6
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N: number of patients randomized; n: number of patients affected; SD: standard deviation.

2.6.8.2. Adverse events

Table 13 Summary of Treatment-emergent AEs Reported in Study 4SC-201-6-2015 (RESMAIN) (Safety Population)

Treatment-emergent AEs	Randomized Phase		Rollover Phase
	Resminostat 600 mg N = 100	Placebo N = 101	Resminostat 600 mg N = 72
	Number of Patients [%]		
Any AE	96 (96.0)	81 (80.2)	68 (94.4)
Any AE ≥ Grade 3 Severity	38 (38.0)	15 (14.9)	27 (37.5)
Any Related AE	88 (88.0)	42 (41.6)	64 (88.9)
Any Related AE ≥ Grade 3 Severity	26 (26.0)	3 (3.0)	15 (20.8)
Any SAE	19 (19.0)	12 (11.9)	13 (18.1)
Any Related SAE	11 (11.0)	1 (1.0)	3 (4.2)
Any AE Leading to Changes in Study Treatment	51 (51.0)	12 (11.9)	39 (54.2)
Dose Reduction	32 (32.0)	2 (2.0)	22 (30.6)
Dose Delay	27 (27.0)	7 (6.9)	13 (18.1)
Interruption	21 (21.0)	7 (6.9)	10 (13.9)
Discontinuation	8 (8.0)	3 (3.0)	10 (13.9)
Any AE Leading to Death	0 (0.0)	0 (0.0)	0 (0.0)

AE: Adverse Event; N: Number of patients in the safety population; SAE: Serious Adverse Event.

For the randomized phase, a treatment-emergent AE was defined as any event that started, or any pre-existing AE that worsened in severity, on or after the date of first study treatment administration, until the day prior to the start of rollover administration for placebo patients that rolled over, or until 30 days after the last dose for all other patients. For the rollover phase, AEs were defined as treatment-emergent from the date of the first study treatment administration in the rollover period, until 30 days after the last dose. AEs that started on or after the date of first study treatment dose in the randomized phase, but before the start of the rollover phase, were assigned as treatment-emergent AEs for the treatment received in the randomized phase but were considered non-treatment-emergent for the rollover phase [4SC-201-6-2015, 16.1.9].

A related AE was defined as an AE with a relationship of definite, probable, possible, or missing.

Treatment-emergent AEs reported for $\geq 10\%$ of patients in either treatment group by PT during the randomized phase and for $\geq 10\%$ of patients during the rollover phase are presented by SOC and PT for the Safety Population in Table 18.

Table 14 Treatment-emergent AEs Reported for $\geq 10\%$ of Patients in Either Treatment Group during the Randomized Phase or in the Rollover Phase by PT, in Study 4SC-201-6-2015 (RESMAIN) (Safety Population)

SOC PT	Randomized Phase		Rollover Phase
	Resminostat 600 mg N = 100	Placebo N = 101	Resminostat 600 mg N = 72
	Number of Patients [%]		
Any treatment-emergent AE	96 (96.0)	81 (80.2)	68 (94.4)
Gastrointestinal disorders	84 (84.0)	37 (36.6)	57 (79.2)
Abdominal pain	15 (15.0)	1 (1.0)	5 (6.9)
Abdominal pain upper	16 (16.0)	5 (5.0)	6 (8.3)
Diarrhoea	50 (50.0)	17 (16.8)	24 (33.3)
Nausea	69 (69.0)	10 (9.9)	46 (63.9)
Vomiting	36 (36.0)	3 (3.0)	22 (30.6)
General disorders and administration site conditions	55 (55.0)	32 (31.7)	45 (62.5)
Asthenia	13 (13.0)	4 (4.0)	5 (6.9)
Fatigue	33 (33.0)	15 (14.9)	23 (31.9)
Pyrexia	8 (8.0)	8 (7.9)	10 (13.9)
Infections and infestations	51 (51.0)	45 (44.6)	29 (40.3)
Nasopharyngitis	14 (14.0)	17 (16.8)	5 (6.9)
Investigations	44 (44.0)	16 (15.8)	26 (36.1)
Blood creatine phosphokinase increased	10 (10.0)	2 (2.0)	5 (6.9)
Blood creatinine increased	10 (10.0)	2 (2.0)	6 (8.3)
Metabolism and nutrition disorders	26 (26.0)	15 (14.9)	23 (31.9)
Decreased appetite	21 (21.0)	2 (2.0)	15 (20.8)

SOC PT	Randomized Phase		Rollover Phase
	Resminostat 600 mg N = 100	Placebo N = 101	Resminostat 600 mg N = 72
	Number of Patients [%]		
Musculoskeletal and connective tissue disorders	40 (40.0)	24 (23.8)	27 (37.5)
Muscle spasms	21 (21.0)	5 (5.0)	14 (19.4)
Myalgia	10 (10.0)	1 (1.0)	4 (5.6)
Pain in extremity	13 (13.0)	1 (1.0)	2 (2.8)
Nervous system disorders	53 (53.0)	21 (20.8)	37 (51.4)
Dizziness	10 (10.0)	3 (3.0)	4 (5.6)
Dysgeusia	24 (24.0)	2 (2.0)	22 (30.6)
Headache	20 (20.0)	10 (9.9)	10 (13.9)
Psychiatric disorders	25 (25.0)	6 (5.9)	14 (19.4)
Insomnia	17 (17.0)	4 (4.0)	13 (18.1)
Skin and subcutaneous tissue disorders	56 (56.0)	34 (33.7)	23 (31.9)
Alopecia	11 (11.0)	2 (2.0)	2 (2.8)
Pruritus	19 (19.0)	14 (13.9)	5 (6.9)

AE: Adverse Event; PT: Preferred Term; SOC: System Organ Class; N: Number of patients in the Safety Population.

Table 15 Related AEs Reported for ≥ 10% of Patients in Either Treatment Group During the Randomized Phase or in the Rollover Phase by PT, in Study 4SC-201-6-2015 (RESMAIN) (Safety Population)

SOC PT	Randomized Phase		Rollover Phase
	Resminostat 600 mg N = 100	Placebo N = 101	Resminostat 600 mg N = 72
	Number of Patients [%]		
Any related AE	88 (88.0)	42 (41.6)	64 (88.9)
Gastrointestinal disorders	81 (81.0)	20 (19.8)	54 (75.0)
Abdominal pain	11 (11.0)	1 (1.0)	4 (5.6)
Abdominal pain upper	13 (13.0)	0 (0.0)	4 (5.6)

SOC PT	Randomized Phase		Rollover Phase
	Resminostat 600 mg N = 100	Placebo N = 101	Resminostat 600 mg N = 72
	Number of Patients [%]		
Diarrhoea	44 (44.0)	9 (8.9)	21 (29.2)
Nausea	68 (68.0)	6 (5.9)	46 (63.9)
Vomiting	32 (32.0)	1 (1.0)	21 (29.2)
General disorders and Administration site conditions	46 (46.0)	18 (17.8)	33 (45.8)
Asthenia	11 (11.0)	3 (3.0)	5 (6.9)
Fatigue	29 (29.0)	14 (13.9)	19 (26.4)
Metabolism and nutrition disorders	23 (23.0)	3 (3.0)	15 (20.8)
Decreased appetite	21 (21.0)	2 (2.0)	15 (20.8)
Musculoskeletal and connective tissue disorders	24 (24.0)	8 (7.9)	18 (25.0)
Muscle Spasms	16 (16.0)	4 (4.0)	12 (16.7)
Nervous system disorders	44 (44.0)	8 (7.9)	33 (45.8)
Dysgeusia	24 (24.0)	2 (2.0)	22 (30.6)
Headache	16 (16.0)	2 (2.0)	9 (12.5)
Psychiatric disorders	19 (19.0)	1 (1.0)	13 (18.1)
Insomnia	14 (14.0)	1 (1.0)	11 (15.3)

AE: Adverse Event; PT: Preferred Term; SOC: System Organ Class; N: Number of patients in the safety population.

For the randomized phase, a treatment-emergent AE was defined as any event that started, or any pre-existing AE that worsened in severity, on or after the date of first study treatment administration, until the day prior to the start of rollover administration for placebo patients that rolled over, or until 30 days after the last dose for all other patients. For the rollover phase, AEs were defined as treatment-emergent from date of the first study treatment administration in the rollover period, until 30 days after the last dose. AEs that started on or after the date of first study treatment dose in the randomized phase, but before the start of the rollover phase, were assigned as treatment-emergent AEs for the treatment received in the randomized phase but were considered non-treatment-emergent for the rollover phase [4SC-201-6-2015, 16.1.9].

A related AE was defined as an AE with a relationship of definite, probable, possible, or missing.

TEAEs by severity

Treatment emergent AEs of Grade 3 severity were more frequently reported in the resminostat group during the randomized phase (34% of patients) and in patients in the rollover phase (35%) than in the placebo group during the randomized phase (13% of patients); events of Grade 4 severity were reported in 4% of patients in the resminostat group (randomized phase), 3% of patients in the rollover phase, and 2% of patients in the placebo group (randomized phase). No events of Grade 5 severity were reported.

Table 16 Patients with Adverse Events of maximum CTCAE Grade 3 Observed in ≥ 3 Patients or of Grade 4 by SOC and PT (Safety Population) RESMAIN study (randomized phase)

Number of patients with AE by SOC/PT, n (%)	Resminostat (N = 100)		Placebo (N = 101)		Total (N = 201)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Any AE	34 (34.0)	4 (4.0)	13 (12.9)	2 (2.0)	47 (23.4)	6 (3.0)
Gastrointestinal disorders	11 (11.0)	0	1 (1.0)	0	12 (6.0)	0
Diarrhoea	5 (5.0)	0	0	0	5 (2.5)	0
Nausea	7 (7.0)	0	0	0	7 (3.5)	0
Infections and infestations	5 (5.0)	1 (1.0)	6 (5.9)	0	11 (5.5)	1 (0.5)
Pneumonia	2 (2.0)	0	1 (1.0)	0	3 (1.5)	0
Sepsis	0	1 (1.0)	0	0	0	1 (0.5)
Investigations	8 (8.0)	3 (3.0)	1 (1.0)	0	9 (4.5)	3 (1.5)
Blood creatine phosphokinase increased	1 (1.0)	1 (1.0)	0	0	1 (0.5)	1 (0.5)
Lymphocyte count decreased	0	1 (1.0)	1 (1.0)	0	1 (0.5)	1 (0.5)
Neutrophil count decreased	4 (4.0)	1 (1.0)	0	0	4 (2.0)	1 (0.5)
Skin and subcutaneous tissue disorders	4 (4.0)	0	4 (4.0)	0	8 (4.0)	0
Pruritus	2 (2.0)	0	3 (3.0)	0	5 (2.5)	0
Vascular disorders	6 (6.0)	0	1 (1.0)	0	7 (3.5)	0
Hypertension	5 (5.0)	0	1 (1.0)	0	6 (3.0)	0
Blood and lymphatic system disorders	6 (6.0)	0	0	1 (1.0)	6 (3.0)	1 (0.5)
Lymphopenia	1 (1.0)	0	0	1 (1.0)	1 (0.5)	1 (0.5)
Neutropenia	4 (4.0)	0	0	0	4 (2.0)	0

Respiratory, thoracic and mediastinal disorders	5 (5.0)	0	0	0	5 (2.5)	0
Pulmonary embolism	3 (3.0)	0	0	0	3 (1.5)	0
Injury, poisoning and procedural complications	1 (1.0)	0	1 (1.0)	1 (1.0)	2 (1.0)	1 (0.5)
Fall	1 (1.0)	0	0	1 (1.0)	1 (0.5)	1 (0.5)
Injury	0	0	0	1 (1.0)	0	1 (0.5)

AE: adverse event; N: number of patients randomized; n: number of patients affected; PT: preferred term; SOC: system organ class. Source: Table 14.3.1.4.1.

During the rollover phase, events of Grade 3 severity reported for more than one patient (1%) were lymphocyte count decreased (three patients, 4%), and vomiting, decreased appetite, and squamous cell carcinoma (two patients, 3%, each); Grade 4 myocardial infarction and supraventricular tachycardia were reported for one patient (1%) each.

Serious adverse events, deaths, and other significant events

AESI

None.

Serious AEs

Table 21 presents a summary of treatment-emergent SAEs reported during the randomized and rollover phases of the study by SOC, PT, and relatedness for the Safety Population.

Table 17 Treatment-emergent SAEs Reported in Study 4SC-201-6-2015 (RESMAIN) (Safety Population)

SOC PT	Randomized Phase				Rollover Phase	
	Resminostat 600 mg N = 100		Placebo N = 101		Resminostat 600 mg N = 72	
	Number of Patients [%]					
	Related	Total	Related	Total	Related	Total
Any treatment-emergent SAE	11 (11.0)	19 (19.0)	1 (1.0)	12 (11.9)	3 (4.2)	13 (18.1)
Blood and lymphatic system disorders	0 (0.0)	1 (1.0)	1 (1.0)	2 (2.0)	0 (0.0)	1 (1.4)
Lymphadenopathy	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.4)
Lymphopenia	0 (0.0)	0 (0.0)	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Cardiac disorders	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.2)

SOC PT	Randomized Phase				Rollover Phase	
	Resminostat 600 mg N = 100		Placebo N = 101		Resminostat 600 mg N = 72	
	Number of Patients [%]					
	Related	Total	Related	Total	Related	Total
Coronary artery disease	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Myocardial ischaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Supraventricular tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Ear and labyrinth disorders	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deafness bilateral	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Ectropion	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	4 (4.0)	5 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Abdominal pain upper	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anal fistula	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Colitis	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea	2 (2.0)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	0 (0.0)	4 (5.6)
Chest pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Face oedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Impaired healing	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Influenza like illness	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Peripheral swelling	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.8)
Infections and infestations	2 (2.0)	8 (8.0)	0 (0.0)	5 (5.0)	1 (1.4)	4 (5.6)
Anal abscess	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

SOC PT	Randomized Phase				Rollover Phase	
	Resminostat 600 mg N = 100		Placebo N = 101		Resminostat 600 mg N = 72	
	Number of Patients [%]					
	Related	Total	Related	Total	Related	Total
Bronchitis	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Cellulitis	1 (1.0)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Corona virus infection	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cytomegalovirus chorioretinitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Fungal oesophagitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Influenza	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.4)
Lower respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Metapneumovirus infection	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	1 (1.0)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia bacterial	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Postoperative wound infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Sepsis	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.4)
Staphylococcal bacteraemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Streptococcal bacteraemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Injury, poisoning, and procedural complications	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	0 (0.0)	0 (0.0)
Fall	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Hip fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Injury	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Investigations	1 (1.0)	1 (1.0)	0 (0.0)	1 (1.0)	2 (2.8)	2 (2.8)
Alanine aminotransferase increased	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.4)
Aspartate aminotransferase increased	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.4)

SOC PT	Randomized Phase				Rollover Phase	
	Resminostat 600 mg N = 100		Placebo N = 101		Resminostat 600 mg N = 72	
	Number of Patients [%]					
	Related	Total	Related	Total	Related	Total
Lymphocyte count decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.4)
C-reactive protein increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	2 (2.0)	2 (2.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Decreased appetite	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetes mellitus	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyponatraemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (1.0)	3 (3.0)	0 (0.0)	2 (2.0)	0 (0.0)	0 (0.0)
Arthralgia	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Arthropathy	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intervertebral disc disorder	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intervertebral disc protrusion	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Osteoarthritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Tenosynovitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.4)
Breast cancer	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Chronic myeloid leukaemia	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Squamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Nervous system disorders	1 (1.0)	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Facial paralysis	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Headache	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders	1 (1.0)	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Acute kidney injury	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

SOC PT	Randomized Phase				Rollover Phase	
	Resminostat 600 mg N = 100		Placebo N = 101		Resminostat 600 mg N = 72	
	Number of Patients [%]					
	Related	Total	Related	Total	Related	Total
IgA nephropathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	1 (1.0)	4 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bronchospasm	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoxia	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonitis	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary embolism	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary granuloma	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	1 (1.0)	1 (1.0)	0 (0.0)	1 (1.0)	1 (1.4)	2 (2.8)
Dermatitis exfoliative	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.4)
Pain of skin	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (1.4)	1 (1.4)
Pruritus	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.4)
Skin burning sensation	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Swelling face	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	2 (2.0)	2 (2.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Deep vein thrombosis	1 (1.0)	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Peripheral artery occlusion	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

SAE: Serious Adverse Event; SOC: System Organ Class; PT: Preferred Term; N: Number of patients in the Safety Population; incl.: including; IgA: Immunoglobulin A; AE: Adverse Event; MedDRA: Medical Dictionary for Regulatory Activities.

Classification of AEs was based on MedDRA version 19.1.

Table 18 Overview of Related SAEs in Patients with 600 mg Resminostat Monotherapy Treatment Across all Clinical Studies

SOC PT	RESMAIN Randomized N = 100	RESMAIN Rollover N = 72	7341/EM- 001 (FIM) N = 3	SAPHIRE N = 19	YHI- 1001- ST-01 N = 3	SHELTER N = 19
	Number of Patients [%]					
Any Related SAE	11 (11.0)	3 (4.2)	0 (0.0)	4 (21.1)	1 (33.3)	1 (5.3)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)	4 (21.1)	0 (0.0)	0 (0.0)
Anaemia	0 (0.0)	0 (0.0)	0 (0.0)	4 (21.1)	0 (0.0)	0 (0.0)
Thrombocytopenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	-	0 (0.0)
Ear and labyrinth disorders	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deafness bilateral	1 (1.0)	0 (0.0)	-	-	-	-
Gastrointestinal disorders	4 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
Abdominal pain upper	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	-	0 (0.0)
Diarrhoea	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
Infections and infestations	2 (2.0)	1 (1.4)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)
Cellulitis	1 (1.0)	0 (0.0)	-	-	-	-
Herpes zoster	0 (0.0)	0 (0.0)	-	-	1 (33.3)	-
Metapneumovirus infection	1 (1.0)	0 (0.0)	-	-	-	-
Pneumonia	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	-	0 (0.0)
Skin infection	0 (0.0)	1 (1.4)	-	-	-	0 (0.0)
Investigations	1 (1.0)	2 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Alanine aminotransferase increased	1 (1.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Aspartate aminotransferase increased	1 (1.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphocyte count decreased	0 (0.0)	1 (1.4)	-	-	0 (0.0)	-

SOC PT	RESMAIN Randomized N = 100	RESMAIN Rollover N = 72	7341/EM- 001 (FIM) N = 3	SAPHIRE N = 19	YHI- 1001- ST-01 N = 3	SHELTER N = 19
	Number of Patients [%]					
Metabolism and nutrition disorders	2 (2.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)
Decreased appetite	1 (1.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
Diabetes mellitus	1 (1.0)	0 (0.0)	-	-	-	-
Hypercalcaemia	-	-	-	1 (5.3)	-	-
Musculoskeletal and connective tissue disorders	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Arthralgia	1 (1.0)	0 (0.0)	-	0 (0.0)	-	0 (0.0)
Nervous system disorders	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	-	0 (0.0)
Renal and urinary disorders	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acute kidney injury	1 (1.0)	0 (0.0)	-	-	-	-
Respiratory, thoracic, and mediastinal disorders	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary embolism	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Skin and subcutaneous tissue disorders	1 (1.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain of skin	0 (0.0)	1 (1.4)	-	-	-	-
Swelling face	1 (1.0)	0 (0.0)	0 (0.0)	-	-	-
Vascular disorders	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deep vein thrombosis	1 (1.0)	0 (0.0)	-	-	-	0 (0.0)
Peripheral artery occlusion	1 (1.0)	0 (0.0)	-	-	-	-

SAE: Serious Adverse Event; SOC: System Organ Class; PT: Preferred Term; FIM: First-In-Man; N: Number of patients; AE: Adverse Event.

Notes: Treatment-emergent AEs are presented for all studies except Study YHI-1001-ST-01.

If the PT was not reported in any of the treatment groups in a certain study, the value is entered as '-' for that study.

Deaths

No deaths were reported during study treatment in Study 4SC 201 6 2015 (RESMAIN). There were no treatment-related deaths during Studies 7341/EM-001 (FIM) or 4SC-201-2-2009 (SAPHIRE), or in the 600 mg resminostat monotherapy group in Study 4SC-201-1-2009 (SHELTER), and no deaths occurred within 30 days of the last dose of resminostat in Study YHI-1001-ST-01. Until data cut-off in Study 4SC-201-6-2015 (RESMAIN) (10 March 2023), 28 patients in the resminostat group and 29 patients in the placebo group, including those subsequently treated with resminostat in the rollover phase, had died. In Study 7341/EM-001 (FIM), 2 patients died within 30 days of study termination. In Study 4SC 201 2 2009 (SAPHIRE), 1 death occurred during the treatment period and 24 deaths occurred during the follow-up period; all except one (unknown cause) were related to disease progression. In the 600 mg resminostat monotherapy group in Study 4SC 201 1 2009 (SHELTER), there were 17 deaths which were mostly due to disease progression/underlying disease (due to unknown cause and myocardial infarction in 1 patient each).

Laboratory findings

Table 19 Number of Patients with Abnormal Laboratory Test Results by Worst NCI CTCAE Grade (Safety Population)

Parameter	Resminostat 600 mg N = 100 Number of Patients					Placebo N = 101 Number of Patients				
	1	2	3	4	Total	1	2	3	4	Total
Hematology										
Hemoglobin	48	9	1	0	58	48	8	1	0	57
Leukocytes	30	19	2	0	51	15	3	0	1	19
Lymphocytes	24	35	8	5	72	20	23	9	3	55
Neutrophils	9	21	11	1	42	5	3	0	0	8
Platelets	53	5	0	0	58	6	0	0	0	6
Prothrombin INR	10	1	0	0	11	9	3	2	0	14
Clinical Chemistry										
ALT	31	1	1	0	33	25	2	0	0	27
Albumin	13	0	0	0	13	14	3	0	0	17
Alkaline Phosphatase	19	1	0	0	20	18	1	0	0	19
AST	31	2	1	0	34	34	1	0	0	35

Parameter	Resminostat 600 mg					Placebo				
	N = 100					N = 101				
	Number of Patients					Number of Patients				
Grade	1	2	3	4	Total	1	2	3	4	Total
Bilirubin	14	7	0	0	21	5	3	0	0	8
Calcium	28	3	0	4	35	20	2	0	1	23
CK	22	12	2	1	37	28	6	0	0	34
Creatinine	76	22	0	0	98	83	2	1	0	86
Glucose	47	27	3	2	79	66	15	4	0	85
Potassium	34	4	4	0	42	33	6	1	0	40
Sodium	26	0	1	1	28	27	0	3	0	30
Urate	25	0	0	1	26	40	0	0	5	45

NCI: National Cancer Institute; CTCAE: Common Terminology Criteria for Adverse Events; N: Number of patients in the safety population; INR: International Normalized Ratio; ALT: Alanine Aminotransferase; AST: Aspartate aminotransferase; CK: Creatine Kinase.

2.6.8.3. Serious adverse event/deaths/other significant events

Serious AEs

Table 21 presents a summary of treatment-emergent SAEs reported during the randomized and rollover phases of the study by SOC, PT, and relatedness for the Safety Population.

Table 20 Treatment-emergent SAEs Reported in Study 4SC-201-6-2015 (RESMAIN) (Safety Population)

SOC PT	Randomized Phase				Rollover Phase	
	Resminostat 600 mg N = 100		Placebo N = 101		Resminostat 600 mg N = 72	
	Number of Patients [%]					
	Related	Total	Related	Total	Related	Total
Any treatment-emergent SAE	11 (11.0)	19 (19.0)	1 (1.0)	12 (11.9)	3 (4.2)	13 (18.1)

SOC PT	Randomized Phase				Rollover Phase	
	Resminostat 600 mg N = 100		Placebo N = 101		Resminostat 600 mg N = 72	
	Number of Patients [%]					
	Related	Total	Related	Total	Related	Total
Blood and lymphatic system disorders	0 (0.0)	1 (1.0)	1 (1.0)	2 (2.0)	0 (0.0)	1 (1.4)
Lymphadenopathy	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.4)
Lymphopenia	0 (0.0)	0 (0.0)	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)
Cardiac disorders	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.2)
Coronary artery disease	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Myocardial ischaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Supraventricular tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Ear and labyrinth disorders	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deafness bilateral	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Eye disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Ectropion	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	4 (4.0)	5 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Abdominal pain upper	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anal fistula	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Colitis	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea	2 (2.0)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pancreatitis acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	0 (0.0)	4 (5.6)
Chest pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Face oedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Impaired healing	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Influenza like illness	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)

SOC PT	Randomized Phase				Rollover Phase	
	Resminostat 600 mg N = 100		Placebo N = 101		Resminostat 600 mg N = 72	
	Number of Patients [%]					
	Related	Total	Related	Total	Related	Total
Peripheral swelling	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Pyrexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.8)
Infections and infestations	2 (2.0)	8 (8.0)	0 (0.0)	5 (5.0)	1 (1.4)	4 (5.6)
Anal abscess	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bronchitis	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Cellulitis	1 (1.0)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Corona virus infection	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cytomegalovirus chorioretinitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Fungal oesophagitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Influenza	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.4)
Lower respiratory tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Metapneumovirus infection	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	1 (1.0)	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia bacterial	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Postoperative wound infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Sepsis	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.4)
Staphylococcal bacteraemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Streptococcal bacteraemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Injury, poisoning, and procedural complications	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	0 (0.0)	0 (0.0)
Fall	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Hip fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Injury	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)

SOC PT	Randomized Phase				Rollover Phase	
	Resminostat 600 mg N = 100		Placebo N = 101		Resminostat 600 mg N = 72	
	Number of Patients [%]					
	Related	Total	Related	Total	Related	Total
Investigations	1 (1.0)	1 (1.0)	0 (0.0)	1 (1.0)	2 (2.8)	2 (2.8)
Alanine aminotransferase increased	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.4)
Aspartate aminotransferase increased	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.4)
Lymphocyte count decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1 (1.4)
C-reactive protein increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	2 (2.0)	2 (2.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Decreased appetite	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetes mellitus	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyponatraemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (1.0)	3 (3.0)	0 (0.0)	2 (2.0)	0 (0.0)	0 (0.0)
Arthralgia	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Arthropathy	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intervertebral disc disorder	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Intervertebral disc protrusion	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Osteoarthritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Tenosynovitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.4)
Breast cancer	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Chronic myeloid leukaemia	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Squamous cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Nervous system disorders	1 (1.0)	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)

SOC PT	Randomized Phase				Rollover Phase	
	Resminostat 600 mg N = 100		Placebo N = 101		Resminostat 600 mg N = 72	
	Number of Patients [%]					
	Related	Total	Related	Total	Related	Total
Facial paralysis	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Headache	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal and urinary disorders	1 (1.0)	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Acute kidney injury	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
IgA nephropathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	1 (1.0)	4 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bronchospasm	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoxia	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonitis	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary embolism	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary granuloma	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	1 (1.0)	1 (1.0)	0 (0.0)	1 (1.0)	1 (1.4)	2 (2.8)
Dermatitis exfoliative	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.4)
Pain of skin	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (1.4)	1 (1.4)
Pruritus	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	1 (1.4)
Skin burning sensation	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Swelling face	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	2 (2.0)	2 (2.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Deep vein thrombosis	1 (1.0)	1 (1.0)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)
Peripheral artery occlusion	1 (1.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

SAE: Serious Adverse Event; SOC: System Organ Class; PT: Preferred Term; N: Number of patients in the Safety Population; incl.: including; IgA: Immunoglobulin A; AE: Adverse Event; MedDRA: Medical Dictionary for Regulatory Activities.

Table 21 Overview of Related SAEs in Patients with 600 mg Resminostat Monotherapy Treatment Across all Clinical Studies

SOC PT	RESMAIN Randomized N = 100	RESMAIN Rollover N = 72	7341/EM- 001 (FIM) N = 3	SAPHIRE N = 19	YHI- 1001- ST-01 N = 3	SHELTER N = 19
	Number of Patients [%]					
Any Related SAE	11 (11.0)	3 (4.2)	0 (0.0)	4 (21.1)	1 (33.3)	1 (5.3)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)	4 (21.1)	0 (0.0)	0 (0.0)
Anaemia	0 (0.0)	0 (0.0)	0 (0.0)	4 (21.1)	0 (0.0)	0 (0.0)
Thrombocytopenia	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)	-	0 (0.0)
Ear and labyrinth disorders	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deafness bilateral	1 (1.0)	0 (0.0)	-	-	-	-
Gastrointestinal disorders	4 (4.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
Abdominal pain upper	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	-	0 (0.0)
Diarrhoea	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.3)
Infections and infestations	2 (2.0)	1 (1.4)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)
Cellulitis	1 (1.0)	0 (0.0)	-	-	-	-
Herpes zoster	0 (0.0)	0 (0.0)	-	-	1 (33.3)	-
Metapneumovirus infection	1 (1.0)	0 (0.0)	-	-	-	-
Pneumonia	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	-	0 (0.0)
Skin infection	0 (0.0)	1 (1.4)	-	-	-	0 (0.0)
Investigations	1 (1.0)	2 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Alanine aminotransferase increased	1 (1.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Aspartate aminotransferase increased	1 (1.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphocyte count decreased	0 (0.0)	1 (1.4)	-	-	0 (0.0)	-

SOC PT	RESMAIN Randomized N = 100	RESMAIN Rollover N = 72	7341/EM- 001 (FIM) N = 3	SAPHIRE N = 19	YHI- 1001- ST-01 N = 3	SHELTER N = 19
	Number of Patients [%]					
Metabolism and nutrition disorders	2 (2.0)	0 (0.0)	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)
Decreased appetite	1 (1.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
Diabetes mellitus	1 (1.0)	0 (0.0)	-	-	-	-
Hypercalcaemia	-	-	-	1 (5.3)	-	-
Musculoskeletal and connective tissue disorders	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Arthralgia	1 (1.0)	0 (0.0)	-	0 (0.0)	-	0 (0.0)
Nervous system disorders	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	-	0 (0.0)
Renal and urinary disorders	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Acute kidney injury	1 (1.0)	0 (0.0)	-	-	-	-
Respiratory, thoracic, and mediastinal disorders	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary embolism	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Skin and subcutaneous tissue disorders	1 (1.0)	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pain of skin	0 (0.0)	1 (1.4)	-	-	-	-
Swelling face	1 (1.0)	0 (0.0)	0 (0.0)	-	-	-
Vascular disorders	2 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Deep vein thrombosis	1 (1.0)	0 (0.0)	-	-	-	0 (0.0)
Peripheral artery occlusion	1 (1.0)	0 (0.0)	-	-	-	-

SAE: Serious Adverse Event; SOC: System Organ Class; PT: Preferred Term; FIM: First-In-Man; N: Number of patients; AE: Adverse Event.

Notes: Treatment-emergent AEs are presented for all studies except Study YHI-1001-ST-01.

If the PT was not reported in any of the treatment groups in a certain study, the value is entered as '-' for that study.

Deaths

No deaths were reported during study treatment in Study 4SC 201 6 2015 (RESMAIN). There were no treatment-related deaths during Studies 7341/EM-001 (FIM) or 4SC-201-2-2009 (SAPHIRE), or in the 600 mg resminostat monotherapy group in Study 4SC-201-1-2009 (SHELTER), and no deaths occurred within 30 days of the last dose of resminostat in Study YHI-1001-ST-01. Until data cut-off in Study 4SC-201-6-2015 (RESMAIN) (10 March 2023), 28 patients in the resminostat group and 29 patients in the placebo group, including those subsequently treated with resminostat in the rollover phase, had died. In Study 7341/EM-001 (FIM), 2 patients died within 30 days of study termination. In Study 4SC 201 2 2009 (SAPHIRE), 1 death occurred during the treatment period and 24 deaths occurred during the follow-up period; all except one (unknown cause) were related to disease progression. In the 600 mg resminostat monotherapy group in Study 4SC 201 1 2009 (SHELTER), there were 17 deaths which were mostly due to disease progression/underlying disease (due to unknown cause and myocardial infarction in 1 patient each).

2.6.8.4. Laboratory findings

Table 22 Number of Patients with Abnormal Laboratory Test Results by Worst NCI CTCAE Grade (Safety Population)

Parameter	Resminostat 600 mg N = 100 Number of Patients					Placebo N = 101 Number of Patients				
	1	2	3	4	Total	1	2	3	4	Total
Hematology										
Hemoglobin	48	9	1	0	58	48	8	1	0	57
Leukocytes	30	19	2	0	51	15	3	0	1	19
Lymphocytes	24	35	8	5	72	20	23	9	3	55
Neutrophils	9	21	11	1	42	5	3	0	0	8
Platelets	53	5	0	0	58	6	0	0	0	6
Prothrombin INR	10	1	0	0	11	9	3	2	0	14
Clinical Chemistry										
ALT	31	1	1	0	33	25	2	0	0	27
Albumin	13	0	0	0	13	14	3	0	0	17
Alkaline Phosphatase	19	1	0	0	20	18	1	0	0	19

Parameter	Resminostat 600 mg N = 100 Number of Patients					Placebo N = 101 Number of Patients				
	1	2	3	4	Total	1	2	3	4	Total
Grade										
AST	31	2	1	0	34	34	1	0	0	35
Bilirubin	14	7	0	0	21	5	3	0	0	8
Calcium	28	3	0	4	35	20	2	0	1	23
CK	22	12	2	1	37	28	6	0	0	34
Creatinine	76	22	0	0	98	83	2	1	0	86
Glucose	47	27	3	2	79	66	15	4	0	85
Potassium	34	4	4	0	42	33	6	1	0	40
Sodium	26	0	1	1	28	27	0	3	0	30
Urate	25	0	0	1	26	40	0	0	5	45

NCI: National Cancer Institute; CTCAE: Common Terminology Criteria for Adverse Events; N: Number of patients in the safety population; INR: International Normalized Ratio; ALT: Alanine Aminotransferase; AST: Aspartate aminotransferase; CK: Creatine Kinase

2.6.8.5. In vitro biomarker test for patient selection for safety

N/A

2.6.8.6. Safety in special populations

Age

Resminostat is not indicated for use in the paediatric population due to missing data from clinical trials regarding efficacy and safety in that group. Furthermore, the overwhelming majority of paediatric patients present with early-stage disease (Stages IA, IB, IIA), and in contrast to adults, progression to more advanced stages, such as tumour stage, erythrodermic MF, and lymph node, blood or visceral involvement is extremely rare or even not reported (Ferenci 2016, Delost 2019, Kothari 2022).

45% (256/563) of the subjects who were enrolled in the clinical studies and received resminostat were older than 64 years. Therefore, there was a high percentage of elderly patients in the clinical study program. The efficacy and safety of resminostat has been established in subjects in the age range of 19 to 87 years.

The results of the PopPK covariate analysis showed that the volume of distribution of resminostat was significantly affected by age. This had minimal impact on exposure and was therefore assessed as clinically not relevant.

Hepatic and Renal Impairment

No targeted studies have been performed in patients with renal disorders. In patients with renal impairment, efficacy and safety of resminostat was not different compared to patients with normal renal function. In a population PK study data from 228 patients from 6 clinical trials were included and investigated for covariates with influence on the PK parameters of resminostat. Of these patients, 32.9% (75) had mild and 7.9% (18) had moderate renal impairment according to approximated glomerular filtration rate (GFR) assessed by using the Cockcroft Gault formula. Population PK analysis showed that renal function has no influence on the PK of resminostat.

Thus, there is currently no evidence for increased risk for patients with mild to moderate renal impairment.

No targeted studies have been performed in patients with hepatic impairment. Four studies have been performed in patients with hepatic disorders (hepatocellular carcinoma, biliary tract cancer). However, only 12 of the 227 patients (5.3%) showed a moderately impaired liver function (Child-Pugh B7 & B8). It should be noted that resminostat is metabolized by several Cytochrome P450 (CYP) enzymes, especially CYP2C8, that are not exclusively expressed in the liver but also present in other organs. Thus, in the case of hepatic impairment, a compensatory extrahepatic metabolic capacity might be present.

2.6.8.7. Immunological events

N/A

2.6.8.8. Discontinuation due to adverse events

Table 37 Patients with Adverse Events Leading to Changes or Discontinuation of Trial Treatment (Safety Population)

Number of Patients with AE, n (%) by SOC/PT	Resminostat (N = 100)	Placebo (N = 101)	Total (N = 201)
AE leading to changes in trial treatment	51 (51.0)	12 (11.9)	63 (31.3)
AE leading to dose reduction	32 (32.0)	1 (1.0)	34 (16.9)
AE leading to dose delay	27 (27.0)	7 (6.9)	34 (16.9)
AE leading to interruption	21 (21.0)	7 (6.9)	28 (13.9)
AE leading to discontinuation	8 (8.0)	3 (3.0)	11 (5.5)

AE: adverse event; N: number of patients randomized; n: number of patients affected; PT: preferred term; SOC: system organ class.

During the randomized phase, AEs leading to changes in study treatment were reported more frequently in the resminostat group than in the placebo group (51 patients (51%) versus 12 patients (12%). In the resminostat group, there were dose reductions (from 600 mg to 400 mg resminostat) in 32 patients (32%), dose delays in 27 patients (27%), and treatment interruptions in 21 patients (21%); related events led to dose reductions in 31 patients (31%), dose delays in 16 patients (16%), and treatment interruptions in 16 patients (16%). In the placebo group, there were dose reductions in 2 patients (2%), dose delays in

7 patients (7%), and treatment interruptions in 7 patients (7%); related events led to dose reductions in 1 patient (1%), dose delays in 2 patients (2%), and treatment interruptions in 2 patients (2%).

Permanent discontinuation of resminostat due to AEs was reported in eight patients (8%) during the randomized phase. Related AEs led to withdrawal of resminostat in seven patients (7%); by patient and severity these were Grade 1 nausea, vomiting, and weight decreased, Grade 3 vomiting, Grade 2 dermatitis allergic, Grade 3 myocardial ischaemia, Grade 3 pulmonary embolism, Grade 2 nausea, and Grade 2 fatigue. Events resolved in six patients and outcome was unknown for events in one patient. One event assessed as not related (dementia Alzheimer's type) led to permanent discontinuation of study treatment in a patient in the resminostat group. A possibly related event of lymphopenia of Grade 4 severity led to permanent discontinuation of study treatment in a patient in the placebo group; the event did not resolve.

In the rollover phase, 39 patients (54%) experienced AEs that led to changes in study treatment. There were dose reductions in 22 patients (31%), dose delays in 13 patients (18%), interruptions to study treatment in 10 patients (14%), and permanent discontinuation of study treatment in 10 patients (14%). Related AEs led to permanent discontinuation of study treatment in 7 patients; by patient and severity these were Grade 2 headache, paraesthesia, and flushing, Grade 1 dysgeusia, Grade 2 fatigue, Grade 2 vomiting and nausea, Grade 3 vomiting, Grade 2 nausea, and Grade 3 lymphocyte count decreased (SAE due to requirement for hospitalization); all events except for fatigue resolved.

Overall, gastrointestinal disorders were the main reason leading to changes in study treatment, including dose reductions mainly due to nausea (in 16% of the patients), diarrhea (5%), vomiting (4%), as well as due to fatigue (in 3% of the patients). Additionally, delays or interruptions were mainly due to nausea (in 5% of the patients) and vomiting (4%), as well as due to neutrophil count decreased or neutropenia (4%), and infections such as corona virus infection and influenza like illness (3% each).

2.6.8.9. Post marketing experience

N/A

2.6.9. Discussion on clinical safety

The safety profile of resminostat mainly derives from the pivotal study SC-201-6-2015 (RESMAIN). The other studies evaluating resminostat monotherapy in other malignancies were considered as supportive for safety.

It is acknowledged that safety data from the different studies were not pooled considering the different patient populations (other malignancies), treatment dosage (from 400 to 800mg QD) and regimen (monotherapy and combination) that could affect the characterization of the safety profile of resminostat in the claimed indication.

Despite the small number of patients evaluated in the pivotal phase II study 4SC-201-6-2015 (RESMAIN) in the target population (during the randomized phase resminostat was administered in 100 patients and during rollover phase resminostat was administered in 72 patients) data are available for patients who have been taking the medicinal product for an extended period of time. Considering the rarity of the CTCL, the main safety data set from the randomized and open label phase of the pivotal phase II study in patients with advanced MS or SS with supportive safety data from studies in which resminostat was assessed as monotherapy in other oncological indications could be considered as sufficient in this case. The safety data from the supportive studies are limited by the small number of patients treated at the intended dosage.

The safety assessment is based on the safety data submitted in the initial application, with a data cut-off of 10 March 2023. In the response to D150 LOQ, the applicant presented the overall summary of adverse events from the final safety analysis with the cut-off date of 8 August 2024. Overall, the frequency of TEAE, treatment-related TEAE and serious TEAE is comparable between the 2 analyses with only minor differences. A comprehensive list of all TEAE, SAE, and ADRs (resminostat vs placebo) has been presented and forms the basis for reporting in the SmPC. As of the data cut-off date of 10 March 2023, of the 172 subjects treated with resminostat in RESMAIN study, 57 patients (33.1%) had a duration of exposure of ≥ 6 months and 31 (18.0%) had a duration of exposure of ≥ 12 months. Considering the prognosis of the disease, the median OS observed in the pivotal study (i.e. 67.7 months in the resminostat group) and the intended maintenance setting of treatment that could lead to a long treatment exposure (up to 5.3 years in RESMAIN study), the amount of safety data ≥ 12 months is considered limited with regards to ICH E1 requirements. In the final analysis with the cut-off date of 8 August 2024, data is available for 180 patients treated with resminostat and 100 treated with placebo.

In the safety analysis with data cut-off of 8 August 2024 only 33 patients were followed for > 12 months. A summary of adverse events with start date within 12 months and after 12 months after treatment start is presented comparatively. The higher frequency of events with onset > 12 months (e.g. dose delay and neoplasms) supports the need for long-term safety data. Neoplasms occurred with higher frequency in resminostat treated than in placebo (10 AE occurred in the 12 months from resminostat treatment and 6 additional ones after 12 months from treatment start, while only 4 occurred in the placebo treated patients), however each event (except squamous cell carcinoma) occurred in a single subject and causality assessment is difficult. In fact, according to applicant's assessment of causality, only squamous cell carcinoma was considered related to study drug. In addition, according to literature, CTCL is associated with higher risk of secondary neoplasms.

The risk for carcinogenicity/secondary malignancy is an 'important potential risk' in the safety specification in the RMP to be further characterized in the long-term safety study. On the same note, duration of follow-up beyond 12 months after treatment start remains limited and long-term follow-up is included as 'missing information' in the safety specification of the RMP.

The duration of treatment was comparable across the 2 treatment groups, i.e. mean duration of 287 days (median (range): 127 days (10 – 1939)) and 245 days (median (range): 110 days (14 – 1365)) in resminostat and placebo groups, respectively. The median Relative dose intensity (RDI) was 97.29% in resminostat group and 100% in placebo group suggesting a favourable tolerability of treatment. A wide variation of the RDI of resminostat was however observed, i.e. from 28.0% to 103.7% (vs 71.7% to 103.7% in placebo arm). In the D120 response, the applicant clarified that by number of treatment cycles, 62.2% of patients had a relative dose intensity of 90 to $< 110\%$ and only 4.1% had a RDI of $< 50\%$ up to 20 treatment cycles. The RDI decreased with the increase number of treatment cycles, potentially indicating a less favorable tolerability of the treatment in long-term setting.

The description below refers to the cut-off date 8-Aug-2024, except for $\geq$ Grade 3 TEAE and treatment related TEAE, which refer to the data cut-off 10-March-2023.

Adverse events

At the data cut-off of 8-Aug-2024, the incidence of TEAEs was higher in the resminostat group compared to placebo in the randomized phase of RESMAIN study, (95.6% vs 82.2% respectively for TEAEs, 37.8% vs 14.9% for Grade ≥ 3 TEAEs, 23.9% versus 3% for Grade ≥ 3 related TEAEs, 18.3% vs 12.9% for SAEs and 53.3% vs 11.9% for TEAEs leading to changes in study treatment). No Grade 5 AEs were reported in both

groups. The AE rates reported in the rollover phase were consistent with the resminostat group of the randomized part. The results of AE analysis in the pivotal and supportive studies were similar. However, it should be noted that the supportive studies were very small.

Overall, the adverse events reported with resminostat were consistent with the other HDAC inhibitors. The most frequently reported TEAEs all grades by PT in patients in the resminostat group were nausea (66.7% vs 9.9% in placebo), diarrhoea (42.2% vs 16.8% in placebo), vomiting (32.8% vs 3.0% in placebo), fatigue (33.3% vs 14.9% in placebo), dysgeusia (25.6% vs 2.0% in placebo), muscle spasms (15.6% vs 5.0% in placebo), decreased appetite (20.6% vs 2.0% in placebo), and headache (17.8% vs 9.9% in placebo). PTs reported for > 20% of patients in the rollover phase were similar to the resminostat group of the randomized phase. Also TEAEs reported in the supportive studies with resminostat monotherapy were consistent with RESMAIN study.

The TEAEs reported with resminostat were mainly treatment-related, i.e. 88.0% in resminostat group vs 41.6% in placebo group in the randomized phase, and 88.9% in the rollover phase. The most frequently reported treatment-related TEAEs in the resminostat group vs placebo group in the randomized phase were nausea (68% vs 5.9% respectively), diarrhoea (44.0% vs 8.9%), vomiting (32.0% vs 1.0%), fatigue (29.0% vs 13.9%), dysgeusia (24.0% vs 2.0%), decreased appetite (21% vs 2%)

The majority of Grade ≥ 3 events observed in the resminostat group (data cut-off 10-March-2023) were gastrointestinal disorders reported in 11% of subjects in the randomized phase (0 in placebo), blood disorders including 6% of SOC Blood and lymphatic system (1% in placebo), infection and infestations (6% vs 6% in placebo) and hypertension (5% vs 1% in placebo). In the rollover phase, grade 3 TEAEs were mostly consistent with the randomized phase, i.e. 4% of lymphocyte count decreased, 3% of vomiting, decreased appetite and squamous cell carcinoma, while grade 4 TEAEs were myocardial infarction and supraventricular tachycardia (1% each).

The most represented SOC was gastrointestinal disorders in resminostat group in the randomized phase, i.e. 84.0% versus 36.6% in placebo arm (treatment-related GI disorders: 81.0% vs 19.8%). Most frequent PTs included nausea (69.0% vs 9.9%, treatment-related 68.0% vs 5.9%, and 7% vs 0 grade 3), diarrhoea (50.0% vs 16.8%, treatment-related 44.0% vs 8.9%, and 5% vs 0 grade 3) and vomiting (36.0% vs 3.0%, treatment-related 32.0% vs 1.0%, and 2% vs 0 grade 3). Gastrointestinal disorders in the placebo arm were low grade except for one grade 3 event of pancreatitis. Although no grade 4 events were reported, grade 3 events represented about 10% of the events. The severe cases of gastrointestinal disorders are reflected in the description of ADR in section 4.8 of the proposed SmPC.

Gastrointestinal toxicity is a class effect of HDAC inhibitors, and the majority of these events were assessed as treatment-related.

Gastrointestinal side effects nausea, diarrhoea, and vomiting occurred in a large number of patients and typically started within the 1st or 2nd treatment cycle, on treatment days and resolved during the off-treatment days; median duration of event was 3-5 days. Most of these events have resolved without treatment modifications (84% of vomiting, 89% of nausea, 95% of diarrhea), however few events led to dose reduction and treatment discontinuation.

About 33% of events of vomiting, 61% of nausea, and 27% of diarrhea required treatment with anti-emetics (metoclopramide, aprepitant and prochlorperazine) and loperamide.

Specific recommendations for management of gastrointestinal side effects nausea, vomiting, and diarrhoea are to be given in section 4.2 and 4.4 of the proposed SmPC.

Myelosuppression is considered a class effect of HDAC inhibitors which may lead to an increased risk for infections and bleeding events. Haematological toxicity as observed under the SOC Blood and lymphatic system disorders, were more frequently reported with resminostat (18.3%) than placebo (11.9%) in the randomized phase of RESMAIN study (treatment-related 14.0% vs 5.9%). PT under this SOC included neutropenia (5.0% in resminostat group vs 0 in placebo group), anaemia (5.6% vs 4%), thrombocytopenia (3.9% vs 1%), leukopenia (1.7% vs 0), lymphopenia (1.7% vs 2%), monocytosis (2.2% vs 0), lymphadenopathy (2.2% vs 4%)

Haematological events represented 31% of reported AE. Of these, 23% were Grade 3 and 1% Grade 4. Grades ≥ 3 events were reported for PTs of neutropenia (6% vs 0), lymphopenia (1% in both groups) and lymphadenopathy (1% vs 0). Events of grade 4 in the resminostat group were neutrophil count decreased and lymphocyte count decreased (1% each). A grade 4 lymphopenia occurred in placebo group. Although all thrombocytopenia observed were grade 1, one case of fatal tumour haemorrhage, concomitant with a thrombocytopenia has been reported in a supportive study.

It is noted that a Grade 3 lymphocyte count decreased (SAE due to requirement for hospitalization) occurring in the rollover phase led to treatment discontinuation and resolved.

93% of haematological events resolved, 83% without dose modifications, and 96% did not require treatment. 2 events of anaemia grade 2 and 1 event of neutrophil count decreased required treatment (RBC transfusion and respectively GCSF).

Neutropenia and thrombocytopenia are to be described in section 4.8. and recommendations for monitoring and dose modifications for events of thrombocytopenia and neutropenia are to be given in section 4.2 and 4.4 of the SmPC. The need for at least monthly haematological monitoring is indicated in the proposed SmPC.

Lymphopenia or lymphocyte count decreased were reported for both treatment groups in the RESMAIN study with similar frequency (5.8% of patients in the resminostat group vs 5.0% in the placebo group). Considering the myelosuppressive effect of resminostat, the Grade 3/4 lymphocyte count decreased with resminostat versus placebo (3.7% vs 2.0%), and a related Grade 3 lymphopenia SAE in the rollover phase, the term 'lymphopenia' was added to the Tabulated list of adverse reactions. In addition, infections due to neutropenia are to be described in the SmPC and included as 'important potential risk' in the RMP.

Vascular disorders were reported 2 times more in resminostat than placebo group, i.e. 18.9% vs 9.9%, respectively. Hypertension was the vascular TEAE the most reported with resminostat (7.2% in resminostat and 7.9% in placebo group) and hot flush (2.2% vs 0 in resminostat and placebo groups, respectively). One case of serious deep vein thrombosis reported in resminostat group was considered as treatment-related.

Cardiac disorders were more frequently reported in resminostat than in placebo group in the randomized phase of RESMAIN study, i.e. 10% vs 5% (treatment-related 5% vs 1%). In the rollover phase, 9.7% of subjects experienced a cardiac disorder (treatment-related 2.8%). The most reported cardiac TEAEs with resminostat was palpitations (3.9 vs 0 in placebo group and 2.8% in the randomized phase and rollover phase, respectively). Severe and serious cardiac TEAEs were reported with resminostat, i.e. one Grade 3 myocardial ischaemia in resminostat group (treatment-related), one Grade 3 myocardial ischaemia in the rollover phase (SAE), one Grade 4 myocardial infarction in the rollover phase (SAE), one Grade 4 supraventricular tachycardia in the rollover phase (SAE). Myocardial ischaemia and blood creatinine phosphokinase B increased are to be included in section 4.8 of the proposed SmPC and cardiac disease (Myocardial infarction, myocardial ischaemia, and supraventricular tachycardia) are to be included in the description of selected adverse drug reactions in the SmPC. In addition, cases of tachycardia, arrhythmia, sinus tachycardia, atrial fibrillation, ventricular extrasystole were reported in subjects treated with

resminostat 600mg in the supportive studies.

Extensive cardiac monitoring was performed during all the clinical studies. Overall, the data suggest that resminostat does not prolong QT. Changes in T wave morphology and ST segment depression, which have been reported with HDAC inhibitors, were noted, but patients did not develop severe ventricular arrhythmias. QT prolongation is considered an 'important potential risk' in the RMP. It is mentioned in the proposed SmPC that patients with uncontrolled or significant cardiac disease (e.g., unstable angina pectoris, uncontrolled hypertension, congestive heart failure (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 in the last 6 months) have not been studied and should be monitored.

AEs of special interest, serious adverse events and deaths, other significant events (data cut-off 10-Mar-2023)

Considering the mechanism of action of resminostat, the nonclinical findings and the safety profiles of other HDAC inhibitors and their potential class effects, the following were identified as AESI: myelosuppression, (including infections and bleeding events), QT prolongation and arrhythmia, thromboembolic events, second primary malignancy, hepatotoxicity (increased ALT/AST) and acute renal failure.

SAEs and treatment-related SAEs occurred at a higher rate in patients in resminostat group compared to placebo group in the randomized phase of RESMAIN study, i.e. 19% vs 11.9% and 11.0% vs 1.0%, respectively. No TEAE leading to death was reported in RESMAIN study.

In RESMAIN study, the SAEs by SOC that were more reported with resminostat than placebo were infections (8% vs 5%, incl. cellulitis 2% vs 0 and pneumonia 2% vs 0), gastrointestinal disorders (5% vs 0, incl. diarrhoea 2% vs 0) and respiratory disorders (4% vs 0). The majority of SAEs considered as related to resminostat across all studies belong to the SOC gastrointestinal disorders (4% vs 0). One treatment-related SAE of pulmonary embolism and one treatment-related SAE of deep vein thrombosis occurred in resminostat group and are supportive of a risk of thromboembolic events within resminostat and the warning included in section 4.4 of the SmPC is supported. Other SAEs of interest due to the drug class included Alanine aminotransferase increased (1 patient in the randomized part and 1 patient in the roll over part), Aspartate aminotransferase increased (1 patient) and acute kidney injury (1 patient in the randomized part).

No treatment-related deaths were reported during the randomised phase of pivotal study or any of the supportive studies. Until data cut-off in Study 4SC-201-6-2015 (RESMAIN) (10 March 2023), 28 patients in the resminostat group and 29 patients in the placebo group, including those subsequently treated with resminostat in the rollover phase, had died. In the response to D120 LOQ, the applicant provided information on the seven deaths cases due to TEAEs reported with resminostat monotherapy and in combination across all clinical studies. Only 2 cases were considered possibly or probably related to resminostat: one case of liver failure/renal failure was considered unlikely related to resminostat or sorafenib and one case of tumour haemorrhage induced shock haemorrhagic was considered probably related to resminostat.

The majority of patients in both groups of pivotal study RESMAIN had MF Stage IIB disease (59 patients in resminostat group, 58 patients in placebo group), however no significant differences in treatment related adverse events have been observed in MF Stage IIB disease versus later stage MF and SS. The frequency of SAE (33.3% vs 15.5%) and hospitalizations (30.0 vs 14.8%) was higher in Sezary Syndrome than the Mycosis Fungoides disease, notably in the SOC 'Infections and infestations' however of same order of magnitude for SmPC reporting (common).

Discontinuations (data cut-off 10-Mar-2023)

Overall the AEs leading to changes in trial treatment were more frequent in resminostat than placebo group in the randomized phase of RESMAIN study, i.e. 51.0% vs 11.9%. These included dose reductions, dose delays, treatment interruptions, and permanent discontinuation of resminostat 600 mg. GI events led to most cases of dose modification (reduction or interruption).

The serious TEAE myocardial infarction and myocardial ischaemia chest pain, lymphopenia, and pulmonary embolism (1 case each) led to treatment discontinuation. Diarrhoea (2 cases), cellulitis, ALT/AST increased, decreased appetite, diabetes mellitus, and acute kidney injury (1 case each) led to dose modifications. One event of myocardial infarction and one of blood creatinine phosphokinase increased were grade 4.

The TEAEs leading to treatment discontinuation were reported in 8.0% of subjects from resminostat group and 3.0% of subjects in placebo group in the randomized part of RESMAIN study and in 14% of patients in the rollover phase. In addition to the higher rate of treatment discontinuation due to a TEAE in resminostat group compared to placebo group, it is noticed an unusual higher rate of discontinuation due to patient withdrawal in resminostat compared to placebo (i.e. 25.0% vs 5.0%, refer to participant flow in efficacy section) that cannot exclude a safety reason, suggesting an unfavorable safety profile of resminostat. The most reported related TEAEs by SOC leading to resminostat discontinuation was gastrointestinal disorders including low grade events (Grade 1 nausea and vomiting, Grade 2 nausea and vomiting, Grade 3 vomiting).

Related AEs led to dose reductions in almost all patients who had dose reductions (31%) and to dose delays and treatment interruptions in 16% of patients, each. These included serious diarrhea, acute kidney injury, decreased appetite, diabetes mellitus, and cellulitis (dose reductions in five patients) and serious upper abdominal pain, transaminase increases, decreased appetite, and cellulitis (dose delays in three patients). Seven patients (7%) in the resminostat group experienced related AEs of Grade 1 – 3 severity that led to permanent discontinuation of treatment (vomiting and nausea (two patients each) and weight decreased, dermatitis allergic, myocardial ischaemia, pulmonary embolism (SAE), and fatigue (one patient each)).

The majority of TEAEs leading to permanent discontinuation of resminostat resolved. However, in addition to several unresolved cases, time to resolution was quite long for a few events (e.g. fatigue, myocardial necrosis marker increased, neutropenia). It appears that persistence of AE of low grade led to treatment discontinuation (consent withdrawn, physician decision), while multiple or prolonged dose modifications (reduction, delay) during the treatment course resulted possibly in disease progression.

In the rollover phase of the pivotal study (RESMAIN)], 54% of patients experienced AEs that led to changes in study treatment. There were dose reductions in 22 patients (31%), dose delays in 13 patients (18%), treatment interruptions in 10 patients (14%), and permanent discontinuation of study treatment in 10 patients (14%). Seven patients experienced related AEs of Grade 1 – 3 severity that led to permanent discontinuation of study treatment (vomiting and nausea (2 patients each)), and headache, paraesthesia, flushing, dysgeusia, fatigue, and lymphocyte count decreased (SAE) (1 patient each)).

Resminostat exposure data with cut-off 08-Aug-2024 for patients who had dose reduction, dose interruption or delay compared to the patients who did not have these dose modifications are provided. Based on data on dose intensity, total cumulative dose, it seems that in the randomised and rollover phase of this study treatment modifications did not interfere with administration of resminostat.

Special populations

In terms of age, 58 of 172 patients (33.7%) treated with resminostat had an age of ≥ 65 to 74 years and 25 of 172 patients (14.5.0%) were 75 years or older, including 1 patient older than 85 years. The highest incidence of TEAE is noted in the 65-75 years range. Patients above 65 years of age had higher incidence of

SAE, hospitalization, blood and lymphatic disorders (mainly thrombocytopenia) diarrhea, and thromboembolic events, supporting the proposed recommendation to monitor patients > 65 years closely for gastrointestinal and haematological toxicity.

No dedicated studies were performed in patients with hepatic impairment and this is proposed to be reflected in the SmPC.

Regarding renal impairment, 68 of 172 patients (39.5%) treated with resminostat had mild renal impairment and 19 of 172 patients (11.0%) had moderate renal impairment. In patients with mild renal impairment, frequency and severity of AEs were similar compared to patients with no renal impairment. In patients with moderate renal impairment, diarrhea, vomiting and thrombocytopenia were more frequently reported than in no/mild impairment patients; however the small sample size does not allow to draw any conclusion.

Based on non-clinical data, resminostat is expected to be teratogenic due to its mechanism of action. Genotoxicity of resminostat cannot be excluded based on *in vitro* and *in vivo* data. There are no data from the use of resminostat in pregnant women. Therefore, in view of the molecule's profile and, in particular, its mechanism of action, pregnancy and breastfeeding should be contraindicated during treatment. A contraception should be used during treatment and for at least six months after the last dose in women of childbearing potential and for at least three months after the last dose in sexually active men. With regard to fertility and the ability to conceive, although there are no dedicated non clinical study (ICH S9), effects on male and female fertility can be expected considering the findings on male and female reproductive organs observed without significant safety margins in repeat dose toxicity studies in both mice and dogs. These effects are not limited to high doses. In addition, studies in dogs (beagles) have shown a lack of reversibility in sperm parameters (amount and quality of ejaculate decreased).

Drug interactions

According to the Applicant, electrocardiogram QT prolongation was an important potential risk of Kinselby. Nonetheless, considering the limitations of the interpretation of the safety results regarding the QT prolongation, a conservative wording regarding the concomitant use of medicinal products known to prolong the QT interval is to be included in the SmPC.

Laboratory findings

In the randomized phase of the pivotal study RESMAIN, most changes in laboratory parameters were of Grade 0 – 2 severity.

Haematology abnormalities were more observed in resminostat group than placebo group in the randomized phase, i.e. leukocytes (51% vs 19%), lymphocytes (72% vs 55%), neutrophils (42% vs 8%), platelets (58% vs 6%), reflecting the known class effect of HDAC inhibitors of myelosuppression.

Abnormal laboratory parameters considered clinically significant in the opinion of the investigator were reported as AE under the SOCs 'Blood and lymphatic system disorders', 'Investigations', and 'Metabolism and nutrition disorders'. There were more grade 3 neutrophils decreased in resminostat arm than in placebo arm (11% vs 0). Leukocytes decreased and platelets decreased that were more frequent in resminostat arm than placebo arm were mostly grade 1 and 2.

Regarding clinical chemistry, treatment related grade 1 ALT increased, bilirubin increased, and calcium decreased occurred more frequently in resminostat arm (31%, 14%, and 28% respectively) than in placebo arm (25%, 5%, and 20%). In addition, grade 2 creatine kinase, creatinine, and glucose were higher in resminostat arm (12%, 22%, and 27% respectively) than in placebo arm (6%, 2%, and 15% respectively).

Cases of increased glucose, potassium, calcium, and sodium are described, however none are considered adverse reactions of resminostat.

Considering the prominent gastrointestinal toxicity reported with resminostat (mainly nausea, diarrhoea and vomiting), electrolyte imbalances were expected; however no clear difference between the two groups was observed. The proposed wording regarding the monitoring of fluid and electrolyte blood levels in section 4.4 is agreed at the present time.

No summary of vital signs was provided by the Applicant. Based on safety data from the RESMAIN study, it is noticed a more important change from baseline of mean and median weight in resminostat compared to placebo group, as expected considering the gastrointestinal toxicity. The PT weight decreased is to be reported as an ADR of resminostat in section 4.8 of the SmPC.

2.6.10. Conclusions on the clinical safety

The overall safety profile of resminostat is consistent with other HDAC inhibitors including a prominent gastrointestinal toxicity (mainly nausea, diarrhoea, vomiting), myelosuppression (anemia, lymphopenia, neutropenia, and thrombocytopenia) and cases of thromboembolic events including serious AEs. Frequent side-effects of resminostat (especially gastro-intestinal side-effects, cytopenias) can impact the patient's quality of life and long-term treatment compliance, which is a concern in the maintenance treatment setting. The non-negligible rates of grade ≥ 3 TEAEs, discontinuation of treatment due to TEAEs and due to patient withdrawal also raise concerns on its tolerability as long-term treatment. The frequency of neoplasms is considerably higher in the resminostat treated than in placebo treated, and although the majority of these events are not considered related to resminostat, this remains a significant uncertainty. To this end, lack of long-term (> 12 months) safety data for a larger dataset is a major limitation of this submission. The safety profile of resminostat in patients with renal or hepatic impairment was not studied.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	Thromboembolic events

Summary of safety concerns	
Important potential risks	Acute renal failure Arrhythmia Hepatotoxicity Carcinogenicity/secondary malignancy
Missing information	Long term safety

2.7.2. Pharmacovigilance plan

Table Part III.3: Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities				
RES NI PASS Study planned	The overall goal of the study is to further evaluate the frequency and severity of safety concerns of KINSELBY (resminostat).	Thromboembolic events Acute renal failure Arrhythmia Hepatotoxicity Carcinogenicity/secondary malignancy Long term safety	Start of PASS	<i>Upon PRAC approval of protocol</i>
			Start of data collection	First Informed Consent Form of PASS signed
			End of data collection	5 years from start of data collection
			Study progress reports	Annual
			Final report of study results	12 months after end of data collection

2.7.3. Risk minimisation measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities

<i>Important identified risk:</i> Thromboembolic events	Routine risk communication: • SmPC sections 4.4 and 4.8 • PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: <i>Patients and physicians should be aware of the risk of thromboembolic events, especially in patients with previous venous thromboembolism, myocardial infarction within previous 6 months, hormone replacement therapy or oral contraception (SmPC section 4.4).</i> Other routine risk minimisation measures beyond the Product Information: <i>Legal status: Medicinal product subject to restricted medical prescription</i>
<i>Important potential risk:</i> Acute Renal Failure	Routine risk communication: • SmPC section 4.2, 4.4, and 4.8. • PL section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: <i>Fluid and electrolyte blood levels (especially potassium, magnesium and calcium) should be monitored at baseline and during therapy, especially in patients experiencing severe nausea, diarrhoea or vomiting, and corrected as clinically indicated to prevent potential dehydration and electrolyte disturbances. Prophylactic anti-emetics (e.g. prochlorperazine) may be considered. Replacement of intravenous fluids and electrolytes may be used as appropriate. (SmPC sections 4.2 and 4.4, PL section 2)</i> Other routine risk minimisation measures beyond the Product Information: <i>Legal status: Medicinal product subject to restricted medical prescription</i>
<i>Important potential risk:</i> Arrhythmia	Routine risk communication: • SmPC sections 4.2, 4.4, and 4.8 • PL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: <i>Fluid and electrolyte blood levels (especially potassium, magnesium and calcium) should be monitored at baseline and during therapy, especially in patients experiencing severe nausea, diarrhoea or vomiting, and corrected as clinically indicated to prevent potential dehydration and electrolyte disturbances. Prophylactic anti-emetics (e.g. prochlorperazine) may be considered. Replacement of intravenous fluids and electrolytes may be used</i>

	as appropriate. (SmPC sections 4.2 and 4.4, PL section 2). Other routine risk minimisation measures beyond the Product Information: <i>Legal status: Medicinal product subject to restricted medical prescription</i>
Important potential risk: Hepatotoxicity	Routine risk communication: • SmPC section 4.2, 4.4, and 4.8. • PL section 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: <i>Liver function tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin should be performed prior to start of treatment and regularly during treatment as clinically indicated. Treatment of patients with impaired liver function should be avoided (SmPC sections 4.2 and 4.4, PL section 2).</i> Other routine risk minimisation measures beyond the Product Information: • <i>Legal status: Medicinal product subject to restricted medical prescription</i> • <i>Treatment should be initiated by a physician experienced in the use of anti-cancer therapies</i>
Important potential risk: Carcinogenicity/secondary malignancy	Routine risk communication: • SmPC section 4.8 and 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other routine risk minimisation measures beyond the Product Information: <i>Legal status: Medicinal product subject to restricted medical prescription</i>

No additional risk minimisation measures are considered needed.

2.7.4. Conclusion

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion, however the PSUR cycle cannot be agreed in view of the negative outcome of the MAA.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

2.9.2. Additional monitoring

N/A

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Kinselby is proposed to be indicated for treatment of patients with advanced stage mycosis fungoides (MF) and Sézary syndrome (SS) that have achieved at least stable disease with at least one prior systemic therapy or Total Skin Electron Beam therapy (TSEB).

The recommended dose of resminostat is 600 mg per day taken orally once daily. Treatment is to be administered on days 1 - 5 of a 14-day treatment cycle; the 5 days of treatment are followed by a 9-day treatment-free period. Treatment is to continue until disease progression or unacceptable toxicity.

3.1.2. Available therapies and unmet medical need

At present, there is no curative treatment available for patients with CTCL except for allogenic stem cell transplantation which is suitable to a limited number of patients.

Patients with early-stage disease (Stages IA, IB and IIA) are generally treated with skin-directed therapies (SDTs) such as topical steroids, psoralen photochemotherapy (psoralen + ultraviolet A light (UVA), PUVA), narrow band ultraviolet B light (UVB), localized and whole skin radiotherapy, and topical cytostatic agents such as chlormethine gel (mechlorethamine).

For advanced-stage MF (IIB, III and IV) and SS, systemic therapies are the treatment of choice. The most frequently used or recommended therapies include retinoids (e.g., bexarotene), interferons, HDAC inhibitors (not approved in the European Union (EU)), brentuximab vedotin, the anti-CCR4 monoclonal antibody mogamulizumab, extracorporeal photopheresis (ECP; for erythrodermic MF and SS), and chemotherapy.

Table 2 presents the treatment recommendations for MF and SS based on EORTC guidelines.

Treatment	Disease Stage						
	IA	IB	IIA	IIB	III	IV	SS
Wait & See	R	R					
Topical Steroids	R	R	R				
Chlormethine Gel	R	R	R				
Phototherapy	R	R	R				
Local RT	R	R	R				
TSEB Therapy		A	A	R	R		
Interferon		A	A	R	R	R	R
Bexarotene		A	A	R	R	R	R
Brentuximab Vedotin ^a		A	A	R	R	R	R
Methotrexate		A	A	R	R	R	R
ECP					R	R	R
Mogamulizumab				A	A	A	A
Mono CT				R	A	R	A
Poly CT				A	A	R	A
AlloSCT				A	A	A	A

Source: [Willemze et al., 2018](#)

MF: Mycosis Fungoides; SS: Sézary Syndrome; EORTC: European Organisation for Research and Treatment of Cancer; R: treatment recommended for the respective stage; RT: Radiotherapy; TSEB: Total Skin Electron Beam; A: subsequent and alternative choice; ECP: Extracorporeal Photopheresis; CT: Chemotherapy; alloSCT: allogenic Stem Cell Transplantation.

Currently available treatment approaches are very heterogenous and rarely lead to durable remissions and eventually become less effective, requiring multiple therapy changes for the patients. Treatment response rates are typical between 30-40% and response duration tend to be less than 1 year underlining the unmet medical need for improved therapies maintaining durable response and offering improved quality of life.

3.1.3. Main clinical studies

One pivotal study 4SC-201-6-2015 (RESMAIN) was submitted. RESMAIN was a phase II multicenter, double-blind, randomized, placebo-controlled study which assessed the efficacy, and safety of resminostat monotherapy versus placebo in patients with advanced-stage CTCL (MF or SS) that had achieved disease control (SD, PR and CR) with previous systemic therapy.

The primary endpoint was progression-free survival (PFS). Secondary endpoints were TTP, TTNT, PFS2, PFS3, OS, and changes in HrQoL parameters including time to symptom worsening (TTSW) in terms of pruritus as a key secondary endpoint, and other additional secondary QoL parameters assessed through VAS, Skindex-29, and FACT-G questionnaires.

3.2. Favourable effects

The main analysis showed a statistically significant improvement in PFS for resminostat compared with placebo, with a median PFS of 8.3 months on resminostat and 4.2 months on placebo, and a HR of 0.623 (95%CI: XXXX; p = 0.015). The provided sensitivity analyses showed a consistent and significant PFS

difference in favor of resminostat, except the sensitivity analysis, where discontinuation due to toxicity or the start of a new treatment before PD were considered as an event (PD), however, the PFS result was numerically in favour of resminostat.

Consistent improvements in TTP (HR 0.623; 95% CI [0.424, 0.916] median TTP: 8.3 vs 4.2 months) and TTNT (HR 0.594; median TTNT: 8.8 vs 4.2 months) were reported.

Subgroup analyses of PFS revealed HRs in favor of resminostat (particularly for patients with bexarotene and other retinoids as last systemic therapy prior to study entry, patients with MF, patients with SD and patients with stage IVA2 – IVB disease at baseline and patients with LCT) except for TSEB or ECP therapy as last prior systemic therapy. Subgroup analyses for patients with SS and male patients have shown poorer PFS improvement with treatment.

Post-hoc mSWAT MNAR analysis of the observed changes from baseline over time (i.e., Day 29 to Day 1,093) for resminostat versus placebo were nominally statistically significant in favor of resminostat (p-value: 0.0199).

In line with these findings, time to development or worsening of skin tumours (TTTE) was delayed with resminostat (44.2 months 95% CI: 23.1, NE) compared with placebo (6.5 months; 95% CI: 3.7, NE) with a HR of 0.333.

Data do not indicate a statistically significant difference between treatment arms for PFS2 (p-value 0.156, HR 0.758 (0.516, 1.113)) and there is no difference in PFS3 between treatment arms (p-value 0.921, HR 1.021 (0.674, 1.547)). However, the KM curve suggests a slight trend for a longer PFS2 in patients in the resminostat arm compared to placebo. The results for OS at the final analysis were similar to those at the main analysis and showed no significant difference between the treatment arms (p-value 0.940, HR 0.983 (0.606, 1.590)).

3.3. Uncertainties and limitations about favourable effects

The placebo as a comparator for patients with SD or PR is questioned. In clinical practice, many treatments could be offered as long as the patient did not experience complete response among the range of treatments for advanced MF and SS, notably at initial therapy or after the use of a few systemic therapies.

The population enrolled is too heterogeneous in terms of number of prior systemic therapy received (1-21 lines) without stratification.

Due to the gastrointestinal side effects associated with resminostat, the efficacy of blinding was questioned during scientific advice (EMA/CHMP/SAWP/33911/2016), and a survey was conducted to collect the patients and investigators' assumptions regarding the assigned treatment arm, prior to unblinding. The large proportion of patients correctly assuming their treatment in both arms likely reflects an important level of functional unblinding, which may have introduced bias in several efficacy analyses (including the analysis of primary and secondary endpoints).

The censoring rules defined for PFS are not in line with EMA guidance EMA/CHMP/27994/2008/Rev.1. Indeed, a treatment policy strategy would have been preferred for the primary analysis, i.e. with no censoring applied prior to non-study cancer treatment nor in case of at least two consecutive incomplete / missing GRAs. As requested, the Applicant provided an alternative PFS analysis where censoring rules were modified. However, the absence of GRS scheduled assessments after treatment discontinuation prevents any meaningful interpretation.

Functional unblinding may have introduced bias in PFS analyses, considering that the skin, nodes and viscera components of the global response score used to derive PFS were investigator-assessed. The Applicant clarified that an independent central review of mSWAT assessment is not feasible based on photographs. Indeed, it would often be impossible to differentiate between patches and plaques, or skin areas with inflammatory changes from erythrodermic skin, based on photographs only. Skin being the leading disease compartment with 82% of disease events occurring in skin, a potential central review of other components (LN and viscera) would not substantially change the reliability of the primary endpoint. The impossibility to perform a blinded central review prevents a meaningful assessment of the potential bias introduced by functional unblinding.

The stability of study results was questioned based on the sensitivity analysis where discontinuation due to toxicity or start of new treatment before PD were considered as an event. Indeed, this sensitivity analysis showed a smaller effect size and did not reach nominal statistical significance. Given the safety profile of resminostat and the imbalance observed in treatment withdrawals for toxicity, it may be reasonable to consider discontinuations due to toxicity or new treatments before PD as unfavourable outcomes – and therefore a sensible assumption to consider them as events in this alternative PFS analysis.

It was confirmed that the vast majority of the PFS censoring was non-administrative and indicates informative censoring. As suspected, it is also apparent that withdrawals due to tolerability issues or drug-related adverse events were the main non-administrative reason for PFS censoring in the resminostat treatment group. This pattern was not observed in the placebo arm. Instead, several censored measurements in the placebo arm (more than in the resminostat arm) were due to physician decisions based on increases in mSWAT not fulfilling PD criteria, and a few others due to treatment withdrawal for lack of efficacy / patient's assumption to be on placebo.

A post-censoring hazard higher in the resminostat arm than in the placebo arm for non-administratively censored patients is a plausible assumption. In this context, the results of the tipping point question the statistical robustness. Indeed, most investigated scenarios with higher multiplicative increases in the resminostat arm than in the placebo arm result in loss of statistical significance, with smaller effect sizes than in the primary analysis. For instance, increasing the post-censoring hazard for the resminostat group by only a factor of 1.25 leads to the loss of significance.

Results of TTP and TTNT are of exploratory nature given the absence of adjustment for multiplicity. The Applicant clarified that 72 (84.7%) of TTNT events in the placebo arm correspond to patients crossing over to resminostat. This confirms that TTNT is very likely biased. Indeed, crossover can only be an option for patients in the placebo arm. Whether as many patients would have initiated a subsequent therapy in the absence of crossover, and whether these subsequent therapies would have been initiated at the same time point, is speculative and unlikely.

It is noted that some emphasis is given to the post-hoc analysis of PFS from start of last prior systemic therapy to first PD. However, the use of last prior systemic therapy as a starting point, instead of randomisation, is subject to immortal time bias which has not been accounted for. This has likely resulted in a distortion of the observed treatment effect.

PFS2, PFS3 and OS are of exploratory nature due to the absence of adjustment for multiplicity. Importantly, given the large confidence limits, the OS data cannot rule out a substantial detriment on survival. PFS3 analysis showed no difference between treatment arms. Analyses were performed by the Applicant to investigate the effect of crossover on OS results. These analyses did not provide reassurance on the OS data.

In fact, analyses adjusting for crossover consistently showed no treatment effect on OS, and even indicated a potential detriment.

In both treatment arms, the key secondary endpoint TTSW pruritus was not evaluable due to the low number of events in the TTSW and ITT population. The difference in TTSW was not statistically significant between the treatment arms (HR 1.215 [0.538, 2.742]).

There was no difference in the observed changes from baseline for resminostat and placebo in the VAS itching and skindex-29 questionnaire. The observed changes from baseline over time for resminostat vs placebo in the FACT-G questionnaire were in favor of placebo (notably functional and physical well-being subscales), even when the modified FACT-G total score (without counting "nausea"), was used. In line with the results in VAS itching, the use of anti-itching medication was similar between the two treatment arms.

The difference in median PFS between the treatment arms for the subgroup of SS patients was smaller (4.2 months for placebo vs 5.6 months for resminostat) than for the subgroup of MF patients (4.2 months for placebo vs 9.2 months for resminostat) due mainly to the lower mPFS reported in the resminostat arm for SS group. The imbalance in disease characteristics and prognostic factors could possibly explain the reported limited results in PFS. However, it cannot be excluded that these results may as well translate an absence of a clinical effect in SS a different entity of CTCL than MF with more aggressive disease course. It is then difficult or even impossible to assess the extent of efficacy of resminostat in SS and there is no retrospective solution to this issue.

Patients in the resminostat arm received slightly more corticosteroids than patients in the placebo arm (51 vs. 45.5%), more antihistamines (45 vs 42.6%), and more systemic corticosteroids (24 vs 14.9%). This could reflect a lack of relevant efficacy.

3.4. Unfavourable effects

The incidence of TEAEs was higher in the resminostat group compared to placebo in the randomized phase of RESMAIN study, (95.6% vs 82.2% respectively for TEAEs, 37.8% vs 14.9% for Grade ≥ 3 TEAEs, 23.9% versus 3% for Grade ≥ 3 related TEAEs, 18.3% vs 12.9% for SAEs and 53.3% vs 11.9% for TEAEs leading to changes in study treatment). No Grade 5 AEs were reported in both groups. The AE rates reported in the rollover phase were consistent with the resminostat group of the randomized part. The results of adverse events (AE) analysis in the pivotal and supportive studies were similar. However, it should be noted that the supportive studies were very small.

The safety profile of resminostat is mainly driven by gastrointestinal toxicity. Indeed, 81.1% of patients experienced an event within the SOC gastrointestinal disorders. Most frequent PTs included nausea (66.7% vs 9.9), diarrhoea (42.2% vs 16.8) and vomiting (32.8% vs 3.0). Although no grade 4 events were reported, grade 3 events represented about 10% of the events, and 5% of the patients who experienced a SAE were related to gastro-intestinal toxicity. Gastrointestinal events were the main reason for treatment dose modification (16% of patients). Overall, the ADRs related to GI toxicities and the severe cases of gastrointestinal disorders are reflected in the description of ADR in section 4.8 of the proposed SmPC. Management of GI events is addressed in the proposed SmpC.

Haematological toxicity as observed under the SOC Blood and lymphatic system disorders were more frequently reported with resminostat (18.3%) than placebo (11.9%) in the randomized phase of RESMAIN study. PTs under this SOC were neutropenia (5.0% in resminostat vs 0 in placebo), anaemia (5.6% vs 4%), thrombocytopenia (3.9% vs 1%), leukopenia (1.7% vs 0), lymphopenia (1.7% vs 2%), monocytosis (2.2%

vs 0), lymphadenopathy (2.2% vs 4%). Additional events were reported within the SOC investigations. Grades ≥ 3 events were reported for PTs of neutropenia (4% vs 0) lymphopenia (1% in both groups) and lymphadenopathy (1% vs 0). Grade 4 events (neutropenia and lymphopenia, 1 each) were reported. Management of haematological events is described in the proposed SmPC.

Furthermore, vascular disorders were reported 2-times more in resminostat than placebo group, i.e. 18.9% vs 9.9%, respectively. Hypertension was the vascular TEAE the most reported with resminostat (7.2% in resminostat and 7.9% in placebo group) and hot flush (2.2% vs 0 in resminostat and placebo groups, respectively). One case of serious deep vein thrombosis reported in resminostat group was considered as treatment-related and included as ADR in section 4.8 of the proposed SmPC.

Finally, cardiac disorders were more frequently reported in resminostat than in placebo group in the randomized phase of RESMAIN study, i.e. 10% vs 5% (treatment-related 5% vs 1%). In the rollover phase, 9.7% of subjects experienced a cardiac disorder (treatment-related 2.8%). The most reported cardiac TEAEs with resminostat was palpitations (3.9% vs 0 in placebo group and 2.8% in the randomized phase and rollover phase, respectively). Severe and serious cardiac TEAEs were reported with resminostat, i.e. one Grade 3 myocardial ischaemia in resminostat group (treatment-related), one Grade 3 myocardial ischaemia in the rollover phase (SAE), one Grade 4 myocardial infarction in the rollover phase (SAE), one Grade 4 supraventricular tachycardia in the rollover phase (SAE). In addition, cases of tachycardia, arrhythmia, sinus tachycardia, atrial fibrillation, ventricular extrasystole were reported in subjects treated with resminostat 600mg in the supportive studies. Electrocardiogram QT prolonged is a known ADR of panobinostat (Farydak) and, conservatively, wording is included in the proposed SmPC with regards to the possibility of co-prescription of drugs susceptible to prolong the QTc in these indications and the predisposition of certain patients.

The frequency of neoplasms is considerably higher in the treatment group than in placebo (16 vs 4 cases). The majority of these events are observed in one single subject each and are not considered related to resminostat. Squamous cell carcinoma of the skin is considered treatment related.

3.5. Uncertainties and limitations about unfavourable effects

Frequent side-effects (especially gastro-intestinal side-effects, cytopenias) of resminostat can impact the patient's quality of life, treatment tolerability, and long-term treatment compliance with potential impact on the treatment efficacy

The extent of safety database does not fulfil the requirement of ICH E1 for long term safety with only 3 patients who received resminostat 600 mg for a duration > 12 months. 

An unusual higher rate of discontinuation due to patient withdrawal in resminostat compared to placebo was observed, which cannot exclude a safety reason.

A considerably higher rate of neoplasms occurred in the resminostat treated subjects compared to placebo. The majority occurred in a single subject each, and causality assessment is difficult.

3.6. Effects Table

Effects Table for resminostat for treatment of patients with advanced stage mycosis fungoides (MF) and Sézary syndrome (SS) that have achieved at least stable disease with at least one prior systemic therapy or Total Skin Electron Beam therapy (TSEB). Data cut-off: 10 March 2023

Effect	Short Description	Unit	Treatment resminostat	Control Pb	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS	Progression free survival	months	8.3	4.2	HR 0.623[0.424, 0.916] p=0.015 Functional unblinding likely leading to bias, PFS results not supported by secondary endpoints (e.g. TTSW) and detriment in OS cannot be excluded,	RESMAIN
TTSW	Time to symptom worsening pruritis		NE	NE	HR 1.215 [0.538, 2.742] P=0.65	
Unfavourable Effects * cut-off date 8 August 2024.						
Nausea	Incidence	%	66.7	9.9		
Diarrhoea	Incidence	%	42.2	16.8		
Vomiting	Incidence	%	32.8	3.0		
Fatigue	Incidence	%	33.3	14.9		
Dysgeusia	Incidence	%	25.6	2.0		
Decreased appetite	Incidence	%	20.6	2.0		
Neutropenia	Incidence	%	5.0	0	Only within SOC Blood and lymphatic system disorders, events with SOC investigations remain to be further discussed	

Abbreviations:

Notes: * Unfavorable effects updated based on the final safety analysis with cut-off date 8 August 2024.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy of resminostat was assessed in one single pivotal randomised, double-blind, placebo-controlled phase II study. Primary endpoint was met and was statistically significant, however, the observed PFS effect is modest, and its robustness is questioned due to methodological issues, i.e., the extent of informative censoring, the large imbalance in withdrawals due to toxicity and the potential impact of functional unblinding. Furthermore, the PFS finding is not supported by clinically relevant secondary endpoints, in particular TTSW and QoL, thus significantly limiting interpretation of resminostat clinical benefit particularly for SS subtype associated with poorer prognosis and for which a limited mPFS gain of 1.4 months was reported in the study. Moreover, there is no treatment difference in OS, and the absence of treatment effect persists after adjustment for crossover (with sensitivity analyses indicating a potential detriment).

Overall, due to high frequency of adverse events (38 % of $\geq$ grade 3 events, 18 % of SAE and with 53 % of patients experiencing an AE that led to modification in study treatment, of which 10% of discontinuation), the safety profile of resminostat appears burdensome with regards to the sought indication of maintenance treatment in the context of the uncertainties discussed. The main toxicities are related to gastrointestinal events and neutropenia, the proposed management of which would have been addressed in the SmPC. In addition, there is also an uncertainty on the notable higher discontinuation due to patient withdrawal and respectively higher frequency of neoplasms in resminostat arm vs placebo. In view of the uncertainties in relation to the efficacy the added burden of toxicities is of concern.

3.7.2. Balance of benefits and risks

There are important limitations and uncertainties preventing the conclusion on the clinical benefit of resminostat in patients with advanced stage MF and SS that have achieved at least SD with at least one prior systemic therapy. These are mainly related to concerns on the translation of PFS gain into clinical benefit, and the statistical/methodological robustness of results. Although the overall safety profile of resminostat is consistent with the other HDAC inhibitors, and mainly related to gastrointestinal toxicity, the non-negligible rates of grade ≥ 3 TEAEs, discontinuation of treatment due to TEAEs and to patient withdrawal, and relatively high rate of neoplasms and raise concerns on its tolerability as long-term treatment, would be a substantial burden to the patient in the absence of a clinical relevant benefit.

3.7.3. Additional considerations on the benefit-risk balance

N/A

3.8. Conclusions

The overall benefit/risk balance of Kinselby is negative.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Kinselby is not similar to Adcetris, Ledaga, and Porteligeo within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Kinselby in the treatment of patients with advanced stage mycosis fungoides (MF) and Sézary syndrome (SS) that have achieved at least stable disease with at least one prior systemic therapy or Total Skin Electron Beam therapy (TSEB), the CHMP considers by consensus that

[a] the efficacy of the above-mentioned medicinal product is not sufficiently demonstrated,

and therefore, recommends the refusal of the granting of the marketing authorisation for the above-mentioned medicinal product. The CHMP considers that:

- The robustness of the PFS analysis could not be shown in the single pivotal trial aimed at investigating the maintenance treatment of patients with advanced stage mycosis fungoides and Sézary syndrome due to methodological weaknesses. This is due to the extent of informative censoring, the increased treatment discontinuation rate in the resminostat arm for toxicity reasons, and the potential impact of functional unblinding. The assessment of PFS is complicated by the absence of consistent global response assessments after patients discontinuing from blinded study treatment.
- In addition to this, no effect on PFS2 could be demonstrated in this study of maintenance treatment. No treatment difference could be observed for overall survival (OS), with large confidence limits reflecting considerable uncertainty. No clear improvement was seen in patient reported outcomes. In this context, the substantial adverse event burden of treatment is noted.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and post-authorisation measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Furthermore, following review of the available data in the context of the applicant's claim of new active substance status, the CHMP position at the time of this report is reflected in Appendix 2. However, in light of the negative recommendation, the CHMP is of the opinion that it is not appropriate to conclude on the new active substance status at this time.