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4SC AG: Cancer compound resminostat meets primary endpoint in Phase II trial in advanced liver cancer ahead of schedule

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4SC's cancer compound resminostat meets primary endpoint in Phase II trial in advanced liver cancer (HCC) ahead of schedule

- Clinical Phase II data to be presented at ASCO Gastrointestinal Cancer Symposium
- Primary study endpoint met ahead of schedule both in mono and combination therapy, based on advanced data set analysis
- Resminostat/sorafenib combination therapy halts further disease progression in two thirds of patients (PFSR 66.6%) and achieves median progression-free survival (PFS) of 4.6 months
- First successful clinical evaluation of resminostat's epigenetic mode of action (resensitisation) in HCC therapy
- Company plans pivotal study programme; Conference call and webcast scheduled

Planegg-Martinsried, Germany, 19 January 2012 - 4SC AG (Frankfurt, Prime Standard: VSC), a discovery and development company of targeted small molecule drugs for autoimmune diseases and cancer, today published encouraging efficacy data from the clinical Phase II SHELTER study with the cancer drug resminostat as a second-line therapy for patients with advanced liver cancer (hepatocellular carcinoma, HCC) who had exhibited radiologically proven tumour progression under first-line therapy with sorafenib (Nexavar$^{(R)}$) prior to study entry. This open-label, two-arm, international study investigated the safety and efficacy of resminostat both as a monotherapy and in combination with sorafenib for this difficult to treat patient group, for which no approved treatment option is currently available. According to the data now presented, which is based on an advanced data set, the primary study endpoint of halting the further progression of this particularly aggressive cancer in at least 20% of the patients treated and for at least 12 weeks has been achieved ahead of schedule in both therapy arms.

The trial's lead investigator, Prof. Dr. Michael Bitzer of Tübingen University Hospital, will present the data on 20 January 2012 at 11:45 a.m. PST (8:45 p.m. CET) as part of the 2012 ASCO Gastrointestinal Cancer Symposium in San Francisco, CA in a poster, which is available as of now at www.4sc.de/product-pipeline/publications-posters/resminostat.

The presentation will highlight that resminostat in combination with sorafenib was able to prevent further progression of the disease for at least 12 weeks in two-thirds of the currently 15 evaluable patients and considerably longer - well over a year - in individual cases. Accordingly, the progression-free survival rate (PFSR) after 12 weeks is currently 66.6% for the combination therapy group and 33.3% for the monotherapy group of currently 9 evaluable patients. Furthermore, median progression-free survival (PFS), which is defined as the period of time for which the progression of the disease can be halted, is presently 4.6 months (140 days) for the combination therapy group and 1.4 months (42 days) for the monotherapy group.

In general, resminostat has proven to be safe and well-tolerated. The most frequent side-effects observed were of a gastrointestinal nature (diarrhoea, nausea). In the combination arm, in the majority of cases the side effects were attributed to the treatment with sorafenib. The majority of serious adverse events (SAEs) were attributed to the patient's underlying disease; a consistent profile of SAEs which were causally related to the study medication was not observed.

Ulrich Dauer, Chief Executive Officer of 4SC AG, said: 'The now presented data of our SHELTER study validate impressively the growing applicability of the new epigenetic mechanism of action offered by our lead anti-cancer compound resminostat. Tumour cell resensitisation, which is mediated by resminostat through the inhibition of HDAC enzymes, is highly relevant for clinical practice, since the supplementary administration of resminostat can permit the continued and effective treatment of patients with a cancer drug to which patient response is no longer adequate. In particular for patients suffering from advanced liver cancer and who urgently need new treatment options it would be a tremendous success to reduce the risk of disease progression. It is therefore very promising that in our study for two-thirds of patients with advanced HCC, who no longer responded to sorafenib - the only compound previously approved for this condition - the supplementary administration of resminostat prevented the further disease progression for at least 12 weeks and for much longer in individual cases. Resminostat also showed promising activity as a monotherapy. In order to confirm these encouraging and, as we are convinced, clinically highly relevant data, we are now planning to conduct a pivotal clinical study programme relevant for registration in this indication and we will therefore intensify our talks on this topic with the regulatory agencies and potential partners.'

The data presented now were analysed before database closure and are based on the analysis of the primary study endpoint 'progression-free survival at 12 weeks' conducted by the local trial centres. Currently, five patients who have not been evaluated after 12 weeks yet are undergoing study treatment, while another five patients continue treatment optionally after experiencing a clinical benefit through the halt of disease progression for at least 12 weeks of study participation. Patients withdrawing from the trial for other reasons than disease progression are qualified as 'drop outs' and therefore replaced. The final results of the SHELTER study, as determined following database closure and encompassing all patients enrolled as well as a final, centralised radiological report are expected to be presented at an international scientific conference in the course of 2012. Details of the efficacy data now presented based on the identification of the primary study endpoint 'progression-free survival at 12 weeks':

Treatment regime	**Combination therapy** Resminostat (600 mg) Sorafenib (400 mg)	**Monotherapy** Resminostat (600 mg)
Patients enrolled ('intention-to-treat', ITT)	**26**	**12**
of which drop-outs*	7	2
Currently evaluable patients after 12 weeks (EP)*	**15**	**9**
of which exhibiting stable disease (SD) i.e. showing 'progression-free survival' (PFS)	10	3
Of which exhibiting progressive disease (PD)	5	6
Progression-free survival rate after 12 weeks PFSR (=PFS/EP)	**10/15 = 66.6%**	**3/9 = 33.3%**

*Patients who withdrew from the study before their tumour status was determined radiologically after 12 weeks - and for whom an evaluation of tumour progression or stabilisation was therefore not possible - have not been included in the evaluable patient population (EP). Of the nine patients listed as drop-outs most left the study for personal reasons (i.e. withdrawal of consent), all of them without an observed tumour progression. Early withdrawal because of side effects was a rare occurrence and only partly attributable to the study medication.

Increasing clinical relevance of epigenetically induced tumour cell resensitisation

Resminostat, 4SC's lead oncology compound, is an oral pan-histone-deacetylase (HDAC) inhibitor with an innovative epigenetic mechanism of action that enables this compound to be deployed as a novel, targeted tumour therapy for a broad spectrum of oncological indications, both as a monotherapy and in combination with other cancer drugs. By causing structural changes to DNA, resminostat triggers a differentiation in tumour cells, can induce programmed cell death in cancer cells (apoptosis) and is able to halt tumour growth. Additionally, resminostat induces what is known as tumour cell 'resensitisation' to the treatment with other drugs. This resensitisation process can suppress or reverse drug tolerance mechanisms that tumour cells often develop against other cancer drugs and are catalysed by HDAC enzymes. Accordingly, supplementary treatment with an HDAC inhibitor such as resminostat can thus restore - or significantly improve - the efficacy of an initial cancer therapy. This mechanism of action, i.e. tolerance breakdown via resensitisation through HDAC inhibition, has previously been described in research[1]. The phase II SHELTER trial is the first clinical study where this mechanism has been investigated for the especially difficult to treat gastrointestinal indication of advanced liver cancer (HCC) and documented for the application of resminostat in combination with sorafenib, a tyrosine-kinase inhibitor (TKI).

The principle of tumour cell resensitisation is highly relevant for clinical practice, since the supplementary administration of resminostat permits the continued treatment of patients with a cancer drug to which patient response is no longer adequate. This can delay or avoid a change to different cancer drugs - a procedure that is time-consuming and potentially incriminating for the patient.

[1] See Sharma *et al*., A chromatin-mediated reversible drug-tolerant state in cancer cell subpopulations, Cell 2010;141(1):69-80.

Ends

Conference Call and Webcast

4SC will host a conference call and webcast on 19 January 2012 at 3pm CET (9am EST) to inform about the data of the SHELTER study. Access to the presentation slides can be obtained at: http://4sc190112-live.cyber-presentation.de. Participants can access the conference (conference ID: 4507526) under the following telephone numbers:

0800 10 12 072 (Germany)
0800 358 0886 (UK)
+1-877-941-1469 (USA)
+49 6103 485 3001 (other countries)

Details of the Presentation:

Presentation No / Abstract No: C26 / 262
Title: Investigation of the HDAC inhibitor resminostat in patients with sorafenib-resistant hepatocellular carcinoma (HCC): Clinical data from the phase I/II SHELTER study
Session date, time and location: Friday, 20 January 2012, 11.45 am Californian time (PST), General Poster Session B: Cancers of the Pancreas, Small Bowel, and Hepatobiliary Tract, Moscone West Building, 2012 Gastrointestinal Cancer Symposium, San Francisco, California
Presenters: M. Bitzer, M. Horger, T. Ganten, J. Siveke, M.A. Woerns, M.M. Dollinger, V. Zagonel, U. Cillo, G. Gerken, M.E. Scheulen, H. Wege, E. Giannini, V. Montesarchio, F. Trevisani, A. Mais, R. Jankowsky, B. Hauns, B. Hentsch, U.M. Lauer

About the SHELTER Trial Design

The two-arm, proof-of-concept, international Phase II SHELTER study evaluates resminostat as a second-line treatment alone or in combination with sorafenib (Nexavar$^{(R)}$), the current standard of care in advanced HCC, to see if it can prolong progression free survival (PFS) in patients who prior to study entry developed progressive disease under first-line treatment with sorafenib. In the

first study arm, according to the study protocol, at least 12 evaluable patients are being treated with the recommended dose of the combination therapy (600 mg resminostat (OD) and 400 mg sorafenib (BID)) which was determined through an initial dose-escalation part of the study. In the second study arm, at least 12 evaluable patients discontinue sorafenib treatment prior to inclusion and then receive resminostat as monotherapy, administered orally, once daily, over five consecutive days, followed by a nine day treatment-free period (5+9 dosing schedule). In the combination arm, resminostat is administered in the same 5+9 dosing schedule, while sorafenib is administered daily throughout the cycle. In both study arms, this 14-day-cycle is repeated until there is evidence of progressive disease or until the patient leaves the study for other reasons. The first two radiological tumour stagings are performed after 6 and 12 weeks; after that, tumour stagings are performed every eight weeks. Patients who experience a clinical benefit, e.g. a stabilization of their progressive disease or tumour regression, may continue the study treatment. It is the study objective to halt the further progression of this particularly aggressive cancer disease in at least 20% of the patients treated and for at least 12 weeks in both therapy arms. The primary endpoint of the study is to determine the progression free survival rate (PFSR) after 12 weeks of treatment. Secondary endpoints include the analysis of time-to-progression (TTP), progression free survival time (PFS), overall survival (OS), drug safety and tolerability, pharmacokinetics and the investigation of biomarkers.

About Liver Cancer (Hepatocellular Carcinoma, HCC)

Hepatocellular carcinoma (HCC) is the most frequent form of liver cancer. Liver cancer is the fifth most common cancer worldwide and, with approximately 700,000 deaths annually, the third most deadly. The incidence of HCC is particularly high in Pacific-Asia and Southern Europe. The aetiology of the disease varies between different areas. In Asia, hepatitis B virus (HBV) infection is the major risk factor for HCC, whereas in the Western world, hepatitis C virus (HCV) infection and alcohol abuse are the most frequent cause for liver cirrhosis, and subsequently, HCC. Even though over the past 10 years advancements in diagnosis and treatment of HCC have lead to certain improvements in the prognosis for HCC patients, the treatment options for patients with advanced HCC are still very poor. With sorafenib (Nexavar$^{(R)}$), there is currently only one compound approved for this condition. With a 5-year survival rate of less than 10%, advanced HCC has one of the lowest overall survival rates of all cancer diseases worldwide. Thus, particularly for these patients with advanced HCC, there is still a high unmet medical need for novel, systemic therapy options, especially for patients refractory or intolerant to sorafenib.

About Resminostat

Resminostat (4SC-201) is an oral pan-histone-deacetylase (HDAC) inhibitor. HDAC inhibitors modify the DNA structure of tumour cells to cause their differentiation and programmed cell death (apoptosis) and are therefore considered to offer a mechanism of action that has the particular potential to halt tumour progression and induce tumour regression. Additionally, resminostat also induces what is known as tumour cell 'resensitisation'. This process can suppress or reverse tolerance mechanisms that tumour cells often develop against other cancer drugs. Accordingly, supplementary treatment with resminostat can thus restore - or significantly improve - the efficacy of an initial cancer therapy. Resminostat is currently being investigated in the Phase II SHELTER study as a second-line treatment for advanced hepatocellular carcinoma (HCC) and in the Phase I/II SHORE study as a second-line treatment in colorectal cancer (CRC) in KRAS-mutant patients. Initial results of the SHORE study are expected in 2012. Moreover resminostat is under evaluation in patients with advanced Hodgkin's Lymphoma. In a first Phase II trial (SAPHIRE) in this indication resminostat as a monotherapy has demonstrated, with an overall response rate of 35.3% and a clinical benefit in 55.9% of the patients, substantial anti-tumour activity in a heavily pre-treated patient population together with very good safety and tolerability.

About 4SC AG

4SC (ISIN DE0005753818) discovers and develops targeted small-molecule drugs for the treatment of diseases with a high unmet medical need in various autoimmune and cancer indications. These drugs are intended to provide patients with innovative treatment options that are more tolerable and efficacious than existing therapies, and provide a better quality of life. The company's balanced pipeline comprises promising products that are in various stages of clinical development. 4SC's aim is to generate future growth and enhance its enterprise value by entering into partnerships with leading pharmaceutical companies. Founded in 1997, 4SC currently has 94 employees and has been listed on the Prime Standard of the Frankfurt Stock Exchange since December 2005.

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