The study listed may include approved and non-approved uses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Before prescribing any product mentioned in this Register, healthcare professionals should consult prescribing information for the product approved in their country.

Study No.: 113222 (SRT-501-012)

Title: A Phase II, Open Label, Clinical Study to Assess the Safety and Activity of SRT501 Alone or in Combination with bortezomib in Patients with Multiple Myeloma

Rationale: The study was designed to gather exposure and tolerability data, as well as to evaluate any potential efficacious effects of SRT501 with or without bortezomib, as assessed by disease response criteria.

Phase: 2

Study Period: 30 Mar 2009 through 04 Nov 2010

Study Design: Open label

Centres: 4 in UK and 1 in Denmark

Indication: Multiple Myeloma

Treatment: SRT501 (40149, 40184) alone or in combination with bortezomib

Objectives:

The primary objectives were:

1. To determine the safety and tolerability of SRT501 (5.0 g), with or without concurrent bortezomib administration, when administered once daily in 21 day cycles, in male and female subjects with Multiple Myeloma.
2. To define objective response (overall response rate [ORR], complete response [CR], partial response [PR], minor response [MR], stable disease [SD]) and time to progression (TTP) of SRT501 in male and female subjects with Multiple Myeloma.
3. To define objective response (ORR, CR, PR, MR, SD) and TTP of SRT501 and bortezomib administered concurrently in male and female subjects with Multiple Myeloma.

Primary Outcome/Efficacy Variables:

Efficacy:

Overall response was calculated for each subject based on modified Blade/EBMT criteria. Response was defined as either a CR, PR, MR or SD after every two cycles of therapy.

Safety:

The assessment of safety was based mainly on the frequency of adverse events (AEs), particularly adverse events leading to discontinuation of treatment and on the number of clinically significant laboratory abnormalities. Extra visits were permitted for safety follow-up.

Secondary Outcome/Efficacy Variable(s): Not Applicable

Statistical Methods:

Primary and secondary analyses included calculating the proportion of subjects having different levels of response. In addition to the ORR, the proportion of subjects displaying CR, PR, MR, SD and PD as best response and last observed response were tabulated. TTP and OS were estimated using Kaplan-Meier methodology. ORR was evaluated using criteria focusing on serum monoclonal paraprotein levels, serum and plasma light-chain levels, urine electrophoresis and immunofixation, plasmacytomas (if present and applicable) and lytic bone lesions (if present and applicable).

All study subjects (N=24) were initially treated with SRT501 monotherapy and were included in the safety and ITT analysis set. Nine of these 24 subjects crossed-over to the SRT501 + bortezomib treatment arm and data for these subjects were summarized separately.

The modified ITT (mITT) population was defined as the subjects who completed the first two (2) cycles of SRT501 monotherapy.

Study Population: Males and females, 18 years of age or older, with a confirmed diagnosis of Multiple Myeloma. All subjects of reproductive potential agreed, prior to study entry, to use adequate contraception (hormonal or barrier method of birth control; abstinence) for the duration of the study and for at least 12 weeks after the last dose of SRT501 or bortezomib. Females of child bearing potential must have had a negative pregnancy test prior to study start.

	SRT501 Monotherapy	SRT501 + Bortezomib
Number of Subjects:		
Planned, N = 30		
Entered, N	24	9
Completed, n (%)	0	0
Total Number Subjects Withdrawn, n (%)	24 (100)	9 (100)
Withdrawn due to Adverse Events, n (%)	16 (67)	5 (56)
Withdrawn due to Lack of Efficacy, n (%)	0	0
Withdrawn for other reasons, n (%)	8 (33)	4 (44)
Demographics	**SRT501 Monotherapy**	**SRT501 + Bortezomib**
N (ITT)	24 (100)	9 (100)
Females: Males	12:12	6:3
Mean Age, years (SD)	66.4 (7.83)	66.6 (7.78)
Caucasian, n (%) Afro-Caribbean, n (%)"	21 (88) 3 (13)	8 (89) 1 (11)
Primary Efficacy Results: Overall Response Rate mITT population	**SRT501 Monotherapy N=4**	**SRT501 + Bortezomib N=9**
Complete response, n (%)	0	0
Partial response, n (%)	0	2 (22.2)
Minimal response, n (%)	0	1 (11.1)
Stable disease, n (%)	3 (75.0)	4 (44.4)
Progressive disease, n (%)	1 (25.0)	2 (22.2)
Relapse from CR	0	0
Adverse events (AEs) were recorded throughout the study. On-Therapy AEs are defined as any AE occurring during the study from the start of dosing through 30 days after the last dose of SRT501 or bortezomib, any event that is considered drug-related regardless of the start date of the event, or any event that is present prior to study drug administration but worsens in intensity or is subsequently considered drug-related by the Investigator.		
Most Frequent Adverse Events – On-Therapy Adverse events occurring in more than one subject in any treatment group	**SRT501 Monotherapy N=24**	**SRT501 + Bortezomib N=9**
Subjects with any AE(s), n (%)	24 (100)	9 (100)
Nausea	17 (70.8)	5 (55.6)
Diarrhea	15 (62.5)	4 (44.4)
Vomiting	10 (41.7)	3 (33.3)
Anemia	9 (37.5)	1 (11.1)
Fatigue	8 (33.3)	4 (44.4)
Headache	8 (33.3)	2 (22.2)
Anorexia	7 (29.2)	0
Pain in Extremity	7 (29.2)	3 (33.3)
Back Pain	6 (25.0)	0
Rash	6 (25.0)	3 (33.3)
Neutropenia	5 (20.8)	2 (22.2)
Constipation	5 (20.8)	2 (22.2)
Pyrexia	5 (20.8)	1 (11.1)
Dizziness	5 (20.8)	0
Renal Failure, Acute	5 (20.8)	0
Cough	5 (20.8)	1 (11.1)
Disease progression	4 (16.7)	0
Arthralgia	4 (16.7)	3 (33.3)
Abdominal distention	3 (12.5)	1 (11.1)
Dyspepsia	3 (12.5)	2 (22.2)
Oral pain	3 (12.5)	1 (11.1)

Edema peripheral	3 (12.5)	0
Pneumonia	3 (12.5)	2 (22.2)
Hypokalemia	3 (12.5)	2 (22.2)
Dyspnea	3 (12.5)	0
Epistaxis	3 (12.5)	0
Pharyngolaryngeal pain	3 (12.5)	3 (33.3)
Hypertension	3 (12.5)	0
Thrombocytopenia	2 (8.3)	0
Tachycardia	2 (8.3)	0
Abdominal pain	2 (8.3)	0
Hypoasthesia oral	2 (8.3)	0
Nasopharyngitis	2 (8.3)	1 (11.1)
Rhinitis	2 (8.3)	1 (11.1)
Blood creatinine increased	2 (8.3)	0
Joint swelling	2 (8.3)	0
Muscular weakness	2 (8.3)	0
Musculoskeletal chest pain	2 (8.3)	1 (11.1)
Musculoskeletal pain	2 (8.3)	1 (11.1)
Neck pain	2 (8.3)	0
Lethargy	2 (8.3)	0
Anxiety	2 (8.3)	0
Confusional state	2 (8.3)	1 (11.1)
Depression	2 (8.3)	2 (22.2)
Renal Failure	2 (8.3)	0
Productive cough	2 (8.3)	0
Rhinorrhea	2 (8.3)	0
Pruitus	2 (8.3)	2 (22.2)
Serious Adverse Events - On-Therapy		
	SRT501 Monotherapy N=24	**SRT501 + Bortezomib N=9**
Subjects with non-fatal SAEs, n (%)	10 (41.7)	3 (33.3)
	n(%)[related]	**n(%)[related]**
Renal failure acute	3 (12.5) [2]	0
Renal failure	1 (4.2) [1]	0
Disease progression	1(4.2) [0]	0
Pyrexia	2 (8.3) [0]	0
Pneumonia	2 (8.3) [0]	2 (22.2) [0]
Anemia	1 (4.2) [0]	0
Sinus bradycardia	1 (4.2) [1]	0
Nausea	1 (4.2) [1]	0
Vomiting	1 (4.2) [1]	0
Neutropenic sepsis	1 (4.2) [0]	0
Urinary tract infection	1 (4.2) [0]	0
Viral infection	1 (4.2) [0]	0
Renal impairment	1 (4.2) [0]	0
Dehydration	1 (4.2) [0]	0
Sepsis	0	1 (11.1) [0]
Hospitalization	0	1 (11.1) [0]
Subjects with fatal SAEs, n (%)	2 (8.3)	0
	n(%)[related]	**n(%)[related]**
Disease progression	1 (4.2) [0]	0
Renal failure	1 (4.2) [1]	0
Conclusion: The best overall response in the mITT population while on the SRT501 monotherapy portion of the study was: stable disease (75%) and progressive disease (25%). In the combination portion of the study (SRT501 +		

bortezomib), the best overall response in the mITT population was: partial response (22.2%), minimal response (11.1%), stable disease (44.4%), and progressive disease (22.2%).

All 24 subjects participating in the study experienced at least one treatment emergent adverse event (TEAE) in both arms of the study. The most common TEAEs by preferred term were nausea, diarrhea, and vomiting. Two deaths occurred during the study in subjects receiving SRT501 monotherapy. One subject experienced life-threatening, possibly-related renal failure that resulted in death. The other subject had disease progression and died. Serious adverse events occurred in 12 subjects (50%) in the SRT501 monotherapy treatment group and in 3 subjects (33%) in the SRT501 + bortezomib treatment group. Five subjects had serious adverse events of acute renal failure/renal failure; all subjects were in the SRT501 monotherapy treatment group; these were of concern and led to early discontinuation of the study.