SER150: Low dose anti-thromboxane reduces urinary albumin in patients with Diabetic Kidney Disease

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ABSTRACT

SER150 is a novel, small molecule with a dual mode of action, i.e. a thromboxane synthase inhibitor and a thromboxane A_2 receptor antagonist. Inhibition of thrombocyte agglutination have previously been seen at repeated dosing with 120 – 1200 mg, BID in clinical trials causing increased bleeding time with no add-on effect to aspirin.

Oral administration of SER150 (28 days with 15 or 30 mg, BID) in Type 2 Diabetic Patients (T2D) with diabetic nephropathy showed to be safe and well tolerated.

Urinary albumin to creatinine ratio (ACR) declined statistically significantly within groups from baseline by 29.9% and 20.2% for the 15mg and 30mg groups, respectively.

All patients with macro-albuminuria (ACR >300mg/g) experienced a decrease in ACR and almost half of patients shifted to micro-albuminuria. 24% of the patients with micro-albuminuria shifted to normo-albuminuria (<30 mg/g).

At high dosages SER150 inhibits thrombocytes agglutination while at lower dosages SER150 statistically significant decreases ACR in T2D patients with diabetic nephropathy. These findings suggest two distinct sites of action with different dose-efficacy relations of SER150.

In conclusion, SER150 is safe and showed fast onset of action in decreasing ACR in T2D patients with diabetic nephropathy. In the first clinical study in T2D patients with diabetic nephropathy, SER150 showed to be safe and well tolerated. In addition, SER150 was significantly efficacious on lowering the ACR.

The next clinical study will examine the effect of SER150 on ACR and other surrogate markers after long-term dosing.

OBJECTIVES

The primary endpoint was to investigate the safety and tolerability of 15 and 30 mg/kg, po, BID of SER150, a novel dual-action thromboxane A_2 receptor antagonist and thromboxane synthase inhibitor in patients with type 2 diabetes and diabetic nephropathy.

Further, the secondary endpoint was a change from baseline values of the urine albumin to creatinine ratio (ACR) between placebo and the 2 active treatment groups administered SER150 for 28 consecutive days. In addition, to measure changes in the ACR within each active treatment group, i.e. base line values versus effect after 28 days administration.

METHODS

The study was a double-blind, placebo-controlled, multi-center, 28 days study in T2D patients diagnosed with diabetic nephropathy (i.e. ACR >30 mg/g creatinine).

In total 72 patients were randomized to receive either SER150 or placebo twice daily 28 days in a 2:1 active to placebo treatment. Two cohorts were dosed sequentially with either 15mg or 30 mg SER150 BID followed with 1 month follow-up.

In total, 49 T2D patients with HbA1c of 7,08 mmol/mol, blood pressure of 133/74 mmHg were treated orally with either 15 mg or 30 mg BID of SER150. The SER150 treatment was an add-on therapy to the patients regular medication.

ACR was measured before and at end of treatment. Various safety parameters were measured including bleeding time.

Base line characteristics of patients randomized for treatment with either SER150 (15 mg/kg or 30 mg/kg, sc, BID) or placebo.

Baseline characteristic of participants

	SER150 15 mg BID N=24	SER150 30 mg BID N=25	Placebo N=23
Age (mean (range)	67 (33-78)	64 (40-77)	67 (52-81)
Sex (Male/Female)	18/7	19/5	18/5
BMI	33	31	36
$HbA1_c$ (±SD)	7,01 (±0,84)	7,15 (±0,86)	7,04 (±1,1)
eGFR	70 (±22)	74 (±18)	63 (±19)
Systolic blood pressure	133 (±8,9)	130 (±9,3)	132 (±9,8)
Diastolic blood pressure	77 (±8,8)	74 (±9,3)	76 (±9,3)
Beta-receptor antagonist	10	13	12
ACE or ARB	20	16	22
Thiazides	7	7	6
ASA	3	10	9

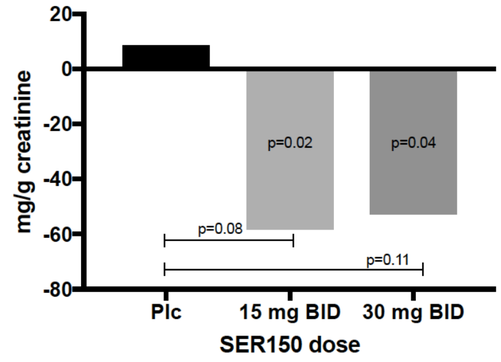
RESULTS

SER150 was safe and caused no tolerability issues. SER150 did not cause any prolongation of the bleeding time. Baseline values were all comparable between treatment groups and were unaffected during treatment and after treatment.

SER150 administration significantly shifted T2D patients ACR to a lower level. After the 4-weeks treatment, almost half (45%) of patients with macro-albuminuria were diagnosed as having micro-albuminuria.

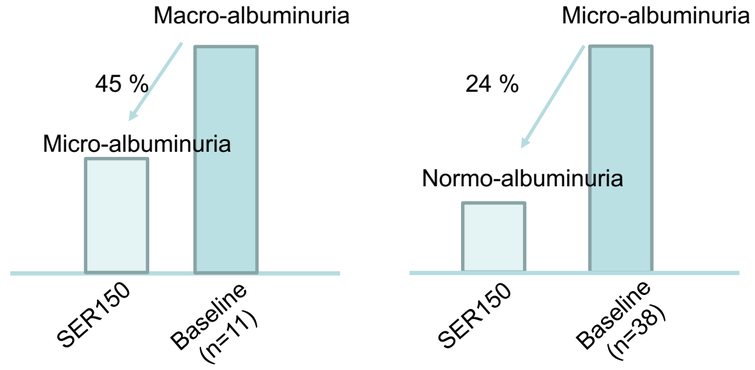
RESULTS (cont')

After 4-weeks treatment SER150 statistically significant decreased ACR within treatment groups (p<0,02 and p<0,04, n=23-25.



The SER150-induced ACR decrease was not statistically significant when each treatment group was compared to the placebo group (p=0,08 and p=0,11).

Irrespectively of active dose, 24% of the patients with micro-albuminuria reached the level of normo-albuminuria after only 28 days of SER150 treatment.



CONCLUSIONS

SER150, a novel thromboxane inhibitor, showed in a short-term clinical study (28 days) to be safe and well tolerated in T2D patients with diabetic nephropathy. Prolongation of bleeding time was not observed.

SER150 significantly decreased the ACR within both treatment groups (15 and 30 mg/kg, po BID) and shifted almost half of the macro- to micro albuminuria and one quarter of micro- to normo-albuminuria.

Presumably, SER150 has two different sites of action (e.g. lowering ACR and increasing bleeding time) with a differentiated dose-efficacy profile.

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