2. SUMMARY

Title

A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the CNS Effects of Single and Multiple Doses of CST-101, CST-103, and CST-109 in Healthy Subjects and Patients with Parkinson's Disease

Short Title

CST-101, CST-103, and CST-109 in Healthy Subjects and Patients with Parkinson's Disease

Principal investigator & Trial Site

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Background & Rationale

Parkinson's disease is a common, progressive and debilitating neurodegenerative disorder classically characterized by motor symptoms, including tremor, muscle rigidity, bradykinesia, and posture balance disorders (Kalia 2015). However, an increasing amount of clinical and epidemiological data suggests that nonmotor symptoms, including cognitive dysfunction, neuropsychiatric symptoms, autonomic dysfunction, sleep disorder, and sensory dysfunction, contribute to the entire course of Parkinson's disease. Recent evidence suggests that neurodegeneration in the locus coeruleus (LC) may occur very early in Parkinson's disease (Vermeiren 2017). This loss of noradrenaline may play an essential role in the occurrence of a wide range of prevalent non-motor symptoms and can further complicate the lives of Parkinson's disease patients (Nahimi 2018). Consequently, LC neuronal loss and the accompanying noradrenergic deficiency constitute an important pharmacological target for the treatment of Parkinson's disease.

Several epidemiology papers have been published suggesting that treatment with β-AR agonists is protective against Parkinson's disease (Aaseth 2018, Clark and Vissel 2018, Gronich 2018, Magistrelli 2019, Mittal 2017, Searles 2018). Additional data also suggested that the effect of beta-adrenoceptor (β-AR) agonists may generalize to other neurodegenerative disorders such as mild cognitive impairment and AD (Chalermpalanupap 2013, Coutellier 2014).

Based on the published effects of β-AR agonists on measures of cognition and /or neurodegeneration in rodents and humans, this study undertook an assessment of the effects of salbutamol (CST-101), clenbuterol (CST-103), and pindolol (CST-109) on measures of central nervous system (CNS) function that are relevant to neurodegenerative disorders.

Objective(s)

Primary Objective

The primary objectives of this study were:

Part A

1. To characterize the effects of single doses of beta-adrenoceptor (β-AR) agonists CST-101, CST-103, and β-AR partial agonist CST-109 on the functional domains of the central nervous system (CNS), as measured by NeuroCart (a standardized and comprehensive battery of tests to evaluate drug effects).

Parts B and C

2. To characterize the effects of multiple doses of one β-AR agonist selected from Part A (CST-101, CST-103, or CST-109) on the functional domains of the CNS, as measured by NeuroCart.

Secondary Objectives
The secondary objectives of this study were the following:

Part A
1. To assess the safety and tolerability of single doses of CST-101, CST-103, and CST-109
2. To evaluate the effects on heart rate (HR) and blood pressure (BP) after single doses of CST-101, CST-103, and CST-109

Parts B and C
1. To assess the safety and tolerability of multiple doses of the selected β-AR agonist (CST-101, CST-103, or CST-109)

Design

This was a randomized, double-blind, placebo-controlled study to evaluate the CNS effects of β-AR agonists CST-101, CST-103, and CST-109 in healthy subjects and patients with Parkinson's disease. This 3-part study (Parts A, B, and C) was conducted at a single center in the Netherlands. Part A examined the CNS effects in healthy subjects after single doses (4-way crossover treatment) of CST-101, CST-103, CST-109, and placebo.

Part B had a randomized multiple-dose, double-blind, placebo-controlled, 2-treatment, 2-way crossover design and was performed in healthy volunteers to evaluate the CNS effects after multiple doses of CST-103.

Part C had a randomized, multiple dose, investigator-blinded, placebo-controlled, parallel-group design and was performed in patients with Parkinson's disease to evaluate the CNS effects after multiple doses of CST-103.

Investigational drug

CST-101 (salbutamol) 32 mg , CST-103 (clenbuterol) 160 µg, and CST-109 (pindolol) initially 20 mg and changed to 60 mg in Part A. CST-103 was selected as study drug in Part B and C.

In Parts B and C, one of the β-AR agonists (CST-101, CST-103, or CST-109) was selected based on the emerging safety and pharmacodynamic data from Part A, as well as any available safety and neuroimaging data from two other CuraSen studies (CST101/CST107-CLIN-001 and CST103/CST107/CST109-CLIN-002). For Parts B and C, CST-103 was chosen with a dose of 80 µg. In Parts B and C the dose of CST-103 was up titrated as follows:

- 20µg (1 tablet) on day 1
- 40µg (2 tablets) on day 2
- 80µg (4 tablets) on day 3 -7

Participation and demographics

A total of 47 subjects were enrolled in this trial. Nineteen subjects were included in Part A. Sixteen subjects were included in Part B. Twelve Parkinson's disease patients were included in Part C. The mean age of the heathy volunteers in Part A was 49.2 (SD 4.7) years and in Part B , this was 51.6 (SD 6.7) years. The mean age of the Parkinson's disease patients was 63.4 (6.6) years. In Part A, 30% of the participants were female. In Part B, this was 43.8% and in Part C, this was 16.7%.

Pharmacokinetic results

All drugs showed plasma concentration curves generally consistent with previously reported PK and showed moderate inter-subject variability.

CST-101

Drug absorption varied between individuals with the time of maximum concentration (T_{max}) ranging from 1.01 to 2.15 hours for R-salbutamol and 1.00 to 2.02 hours for S-salbutamol. The mean half-life for R-salbutamol was 7.28 hours and for S-salbutamol, this was 5.89 hours. The AUC_{24h} of R-salbutamol was 34.1 h*ng/mL and for S-salbutamol, this was 603 h*ng/mL, with an almost twentyfold difference in exposure between the enantiomers.

CST-109

Drug absorption varied between individuals with the time of maximum concentration (T_{max}) ranging from 1 to 2.02 hours for R-pindolol and from 1.00 to 3.02 hours for S-pindolol. The mean half-life for R-pindolol was 4.31 hours and for S-pindolol, this was 4.38 hours. The exposure of R-pindolol was 892 h*ng/mL and for S- pindolol, this was 820 h*ng/mL.

CST-103

Drug absorption varied between individuals with the time of maximum concentration (T_{max}) ranging from 1.00 to 23.58 hours across all parts of the study for both enantiomers. In Part A, T_{max} for R-clenbuterol ranged from 1 to 8.07 hours and for S-clenbuterol from 2.02 to 8.07 hours. After 7 days of once daily dosing of CST-103 in Part B (escalating from 20 µg on Day 1, 40 µg on Day 2 up to 80 µg from Day 3 through Day 7), T_{max} for R-clenbuterol ranged from 1 to 4.02 hours and for S-clenbuterol, it ranged from 1 to 23.58 hours on day 1. In Part C, T_{max} on day 1 after the same dosing regimen ranged from 2 to 4.05 hours for R-clenbuterol and for S-clenbuterol, this ranged from 2.02 to 4.05 hours.

For CST-103, the mean half-life could not be calculated, as there was not sufficient information during the terminal phase due to the long $T_{1/2}$ of CST-103. After 7 days of once daily dosing of CST-103 (escalating from 20 µg on Day 1, 40 µg on Day 2 up to 80 µg from Day 3 through Day 7) in Part B, the observed mean AUC_{tau} was 5.46 h*ng/mL for R-clenbuterol. For S-clenbuterol, this was 4.79 h*ng/mL. In Part C, the observed mean AUC_{tau} after the same dosing regimen was 6.85 h*ng/mLfor R-clenbuterol. For S-clenbuterol, this was 5.65 h*ng/mL.

Efficacy/pharmacodynamics

CST-101

CST-101 increased the performance during the VVLT immediate word recall of correct numbers during trial 1. It had no other effects on NeuroCart CNS tests or on EEG. This lack of CNS effects might result from a hypothesized low blood brain barrier penetration.

CST-109

CST-109 decreased smooth pursuit performance, delayed word recall of correct neutral words test and decreased the pupil/iris ratio. CST-109 significantly influenced EEG ; it significantly increased theta-power both fronto-centrally and parieto-occipitally, while it decreased alpha-, beta- and gamma-power in the same regions.

CST-103

CST-103 led to several significant changes in CNS functioning. In healthy volunteers CST-103 led to small improvements in episodic memory function, however memory function was not improved in Parkinson's disease patients. Similarly, in Part B, CST-103 increased saccadic peak velocity in healthy volunteers, but had no effect in Parkinson's patients. Interestingly CST-103 increased adaptive tracking performance in healthy volunteers in Part A, but not in Part B and it decreased adaptive tracking performance in Parkinson's disease patients. CST-103 led to a significant increase in gamma power parieto-occipitally with eyes open in Part A. In Part B, CST-103 increased EEG delta power in the occipital regions both in the eyes open and eyes closed condition. In Part C, CST-103 did not significantly influence EEG frequency bands.

CST-103 increased heart rate in supine position in both healthy volunteers and Parkinson's disease patients. Furthermore CST-103 increased systolic blood pressure at Day 4 and 7, but did not affect blood pressure in Parkinson's disease patients.

Safety and Tolerability

CST-101, CST-103 and CST-109 were well tolerated in both the healthy volunteers and Parkinson's disease patients and were found to be safe in the dose range investigated in this study. There were no serious adverse events, deaths or other significant adverse events. A total of 219 AEs were reported in Part A, all of which were reported as mild and resolved spontaneously. For CST-103, 70 AEs were registered, of which 58 were assessed as related to study drug. All AEs were registered as mild. The AEs were predominantly nervous system disorders (88.2%), cardiac disorders (41.2%), general disorders (41.2%), musculoskeletal and connective tissue disorders (29.4%) and gastro-intestinal disorders (23.5%). For CST-109 20 mg, 13 AEs were registered, of which 1 was assessed as related to study drug. All AEs were registered as mild. The AEs were predominantly gastro-intestinal disorders (60.0%), general disorders (60.0%) and nervous system disorders (60.0%). For CST-109 60 mg, 52 AEs were registered, of which 51 were assessed as related to study drug. All AEs were registered as mild. The AEs were predominantly nervous system disorders (66.7%), cardiac disorders (66.7%), gastro-intestinal disorders (66.7%) and general disorders (64.7%). For CST-101, 74 AEs were registered, of which 71 were assessed as related to study drug. All AEs were registered as mild. The AEs were predominantly cardiac disorders (70.6%), nervous system disorders (66.7%), general disorders (50.0%) and gastro-intestinal disorders (35.3%).

In Part B, a total of 150 AEs were reported, of which 2 were reported as moderate and all others as mild and all AEs resolved spontaneously. For CST-103, 110 AEs were registered, of which 96 were assessed as related to study drug. All but one AE was registered as mild. One AE of musculoskeletal pain was assessed as moderate in intensity. The reported AEs were predominantly nervous system disorders (93.3%), cardiac disorders (66.7%), general disorders (46.7%) musculoskeletal and connective tissue disorders (46.7%) and gastro-intestinal disorders (33.3%).

In Part C, 27 AEs were reported of which 1 was reported as moderate and all others as mild. All AEs resolved spontaneously. For CST-103, 25 AEs were registered, of which 23 were assessed as related to study drug. All but one AE was registered as mild. One AE was registered as moderate and was musculoskeletal pain. The AEs were predominantly nervous system disorders (100%), general disorders (46.7%) musculoskeletal and connective tissue disorders (37.5%), cardiac disorders (25.0%) and gastro-intestinal disorders (25.0%).

Five subjects withdrew due to adverse events. In Part A, 3 subjects withdrew. One subject withdrew after administration of CST-109 20 mg after reporting complaints such as syncope, somnolence, nausea and cold sweat. One subject withdrew after administration of CST-103 after reporting complaints such as dizziness, nausea, headache and paraesthesia. One subject withdrew after administration of CST-101 after reporting complaints such as palpitations, somnolence and vomiting. In Part B, one subject withdrew after administration of CST-103 after reporting complaints of tremor and headache. One subject was withdrawn by the principal investigator after administration of CST-103 after T-wave inversion seen on ECG.

Adherence and exposure

In Part A, nineteen subjects were randomized to a sequence of four different treatments. Each treatment sequence consisted of 3 active and 1 placebo condition. Five (5) subjects dropped out prematurely due to adverse events. These subjects were replaced and in total fourteen subjects completed 4 treatment occasions. Seventeen subjects received CST-101, sixteen subjects received CST-103, five subjects received CST-109 20 mg, seventeen subjects received CST-109 60 mg and sixteen subjects received placebo.

In Part B, subjects were randomized in a 2-way crossover fashion to receive CST-103 and placebo. Sixteen patients were treated. An up-titration scheme was used; subjects received 20 µg on Day 1, 40 µg on Day 2 and 80 µg on Day 3 to Day 7. The total duration of exposure to CST-103 was 7 days per subject. One subject did not receive all doses and only completed half of the placebo occasion before dropping out due to ECG abnormalities.

In Part C, patients with Parkinson's disease were randomized to either CST-103 or placebo in a parallel fashion. Twelve patients were included; eight were randomized to CST-103, and four to the placebo group. Patients received 20 µg on Day 1, 40 µg on Day 2 and 80 µg on Day 3 to Day 7. All subjects received all doses of CST-103 or placebo.

Summary – conclusions

CST-101 was safe when administered at a single dose of 32 mg to healthy volunteers. No clear improvement or decline in CNS functioning could be observed using the NeuroCart CNS test battery.

CST-109 was safe when administered at a single dose of 20 or 60 mg to healthy volunteers. CST-109 led to a decline in performance on some of the Neurocart CNS tests, while not clearly improving any CNS functions. Furthermore, CST-109 did have an effect on EEG in healthy volunteers.

CST-103 was safe when administered at a single dose of 160 µg to healthy volunteers, and when administered using an up-titration scheme in healthy volunteers and Parkinson's disease patients (20 µg on Day 1, 40 µg on Day 2 and 80 µg on Day 3 to Day 7). CST-103 increased saccadic peak velocity, improved memory function as assessed using the VVLT (immediate recall trial 1, delayed recall of neutral words and delayed recall of correct positive words) and led to an increase in pupil/iris ratio in healthy volunteers. In Parkinson's disease patients, CST-103 did not improve any of the CNS tests, but led to a decrease in performance on the adaptive tracking and one of the N-back test paradigms (percentage of correct responses for zero-back). A larger study with long term treatment is needed to determine the effects of treatment with CST-103 on the progression of Parkinson's disease.