1 SYNOPSIS

Study title:	An Open, Randomised, Rehabilitation-Controlled Study to Assess Safety, Tolerability, and Efficacy of Heparin Activated Recombinant Human Fibroblast Growth Factor 1 on a Biodegradable Device in Subjects with Traumatic Spinal Cord Injury
Investigational product:	SC0806: Heparin Activated Recombinant Human Fibroblast Growth Factor 1 (rhFGF1) on a Biodegradable Device Made from α-Calcium Sulphate Hemihydrate (SCI-device)
Indication:	Complete Traumatic Spinal Cord Injury (TSCI)
Design:	An open, randomised, rehabilitation-controlled study in subjects with complete TSCI, where treatment consisted of a surgical implantation of a biodegradable device with nerve implants and Heparin-activated rhFGF1.
Protocol ID:	SC0806-A101, Version 11, 26 June 2019
Investigators and study centres:	**Treatment Centre:** Karolinska University Hospital (KS), Stockholm, Sweden **Coordinating Principal Investigator (CPI):** Professor Mikael Svensson, MD, PhD **Rehabilitation Centre:** Rehab Station Stockholm, Solna, Sweden **Principal Investigator (PI):** Björn Hedman, MD, Specialist Neurology **Rehabilitation Centre**: Haapsalu Neurological Rehabilitation Centre, Haapsalu, Estonia **Principal Investigator (PI):** Malle Pakkanen, MD
Publication (reference):	N/A
Study period:	First subject in Q2 2015 to Last subject out Q3 2020
Phase of development:	Phase I/II
Primary objectives:	1. To assess the safety and tolerability of one implantation of SC0806 in subjects with complete Traumatic Spinal Cord Injury (TSCI). 2. To evaluate the efficacy of one implantation of SC0806 on Electrophysiology motor-evoked potential (MEP) in subjects with complete Traumatic Spinal Cord Injury from baseline to 18 months.
Secondary objectives:	1. To evaluate plasma concentration of FGF1 in subjects with complete TSCI following implantation of SC0806. 2. To evaluate the neurological classification after one implantation of SC0806 on neurological impairment in subjects with complete TSCI from baseline to Final Visit.

3. To evaluate efficacy of one implantation of SC0806 on motor function in subjects with complete TSCI from baseline to Final Visit.
4. To evaluate the effect of specific walking training: change from baseline to Final Visit.
5. To evaluate functional improvements of one implantation of SC0806 in subjects with complete TSCI from baseline to Final Visit.
6. To evaluate pain scores after one implantation of SC0806 in subjects with complete TSCI from baseline to Final Visit.
7. To evaluate urinary function after one implantation of SC0806 in subjects with complete TSCI from baseline to Final Visit.
8. To evaluate the efficacy of one implantation of SC0806 on Quality of Life (QoL) in subjects with complete TSCI from baseline to Final Visit.
9. To evaluate the immunogenicity (production of serum anti-FGF1 antibody) of SC0806 following single implantation in subjects with complete TSCI.
10. To evaluate the efficacy of one implantation of SC0806 on Electrophysiology (MEP) in subjects with complete TSCI from baseline to Final Visit.

Exploratory objectives:

1. To evaluate the efficacy of one implantation of SC0806 on Electrophysiology sensory-evoked potential (SEP), electromyography (EMG) (denervation activity, voluntary motor unit activity, spontaneous (spastic) motor unit activity, and characterisation of single motor unit potentials)) in subjects with complete TSCI from baseline to Final Visit.
2. To describe the lower urinary function.
3. To describe the bowel function.
4. To evaluate the efficacy of one implantation of SCI0806 on functional activity in the brain as assessed by functional MRI (fMRI).
5. Evaluation of biomarkers in blood, CSF, and spinal cord tissue.

Methodology:

This was a multi-centre (rehabilitation centres), single dose study in up to 4 sequences (A, B, C and D) in subjects with complete TSCI. The sequences were to be done sequentially, with an interim analysis after each sequence which was to be assessed by the Data Monitoring Committee (DMC) in order to decide whether the study should continue.

Sequence A: 6 subjects were to be randomised to a surgical procedure where SC0806 was implanted at the spinal cord in combination with specific walking training, and 3 subjects randomised to specific walking training only. For safety reasons, the first 3 subjects were to be treated with at least 1 month in between.

Sequence B: 6 subjects were to be randomised to SC0806 and specific walking training, and 3 subjects randomised to specific walking training only.

Sequence C: an additional 9 subjects were to be randomised (6 to surgical treatment and 3 to specific walking training only).

Sequence D: control subjects from sequence A, B and C were to be given the opportunity to receive treatment with SC0806 after completion of their 18-month rehabilitation period, provided effect had been shown any subject receiving SC0806.

The study initially included a pre-treatment phase, consisting of the screening/baseline and pre-surgery periods, surgery and an 18-month rehabilitation phase. The study was then amended to include an additional, optional 12-month training period extension and an optional 1-year follow-up visit. The initial study duration was approximately 19 months (excluding the screening period and optional extension and follow-up visits) including specific walking training 3 times/week. For subjects randomised to specific walking training only, the study period was 18 months.

Number of subjects (planned and analysed):

Up to 45 subjects with complete TSCI as classified by the American Spinal Injury Association Impairments Scale (AIS A) were planned to be included in the study. However, the recruitment time showed to be extensively longer than planned, due to a high screening failure for subjects meeting inclusion/exclusion criteria. Therefore, only 10 subjects were included in the study at the time of the interim analysis (#4), evaluating safety and efficacy at 18 months in the patients in sequence A, of which 1 subject withdrew. The Sponsor decided to stop recruitment in the study in November 2019, after DMC assessment of interim analysis #4 showing no effect in the treated subjects. The safety of the treatment was, however, assessed as acceptable. The last subject in the study was offered to complete the 12-month extension phase, which explains the last subject visit date of 25 September 2020. Due to lack of efficacy, no subjects in the control group were offered surgery with SC0806 treatment.

Eligibility Committee

All screened subjects were reviewed by an Eligibility Committee according to the Inclusion/Exclusion Criteria. The final decision regarding inclusion of a subject was made by the Study Medical Board, which was blinded to the subjects' identity prior to randomisation. The members of the Eligibility Committee were one neurosurgeon, one neurologist and the Sponsor's Chief Medical Officer (CMO).

Data Monitoring Committee (DMC)

Interim evaluations of safety, tolerability and efficacy were evaluated by an independent DMC, consisting of one neurosurgeon, one neurologist and one statistician. Based on the evaluation data, the DMC could recommend to the Study Medical Board to stop the study. If the study was stopped due to safety, all subjects who received the SC0806 implantation were followed for safety for at least 12 months. The activities and responsibility of the DMC were specified in a DMC charter.

Study Medical Board

Based on the review of the Eligibility Committee, the final decision regarding whether a subject was to be included into the study was made by the Study Medical Board. The Study Medical Board consisted of the CPI, one PI and the Sponsor's CMO. Based on the recommendations of the DMC, the Study Medical Board could stop the study at any time if judged necessary.

Main criteria for inclusion and exclusion:

Inclusion criteria

1. Traumatic Spinal Cord Injury
2. Male or female subjects aged between 18 and 65 years.
3. Body Mass Index (BMI) ≤35, body weight ≤125 kg and height ≤ 195 cm at Screening.
4. Complete spinal cord injury (ASIA Impairment Scale level A, no voluntary bladder function, negative motor and sensory evoked potentials).
5. A single spinal cord lesion injury at the neurologic level between T2-T11.
6. A Baseline MRI that indicates a pathology consistent with a traumatic SCI.
7. Minimum of 4 months and maximum 10 years post injury with no evidence of neurological improvement prior to implantation surgery unless there is a complete anatomical cut-off of the spinal cord as judged from the MRI assessment.
8. Females must not be lactating or pregnant at Screening or pre-surgery (as documented by negative pregnancy tests).
9. All females that are postmenopausal (amenorrhoeic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilised surgically (i.e., bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing).
10. Females of childbearing potential must not have had unprotected sexual intercourse within 30 days before study entry and must agree to use a highly effective method of contraception (e.g., total abstinence, an intrauterine device, a contraceptive implant, an oral contraceptive, or have a vasectomised partner with confirmed azoospermia) throughout the entire study period. If currently abstinent, the subject must agree to use an effective method as described above if she becomes sexually active during the study period. Females who are using hormonal contraceptives must have been on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and must continue to use the same contraceptive during the study.
11. Written informed consent obtained prior to any study specific procedures.
12. Eligible for surgery and specific walking training as judged by the investigator.

Exclusion criteria

1. Other life-threatening injury.
2. Serious co-existing medical condition or mental disorder.
3. Results from neurophysiological examination preoperatively are inconsistent with a spinal cord injury of one thoracic segment or less.
4. Current or prior (within the past 8 weeks or within 5 half-lives of use of such a medication prior to screening) participation in any other investigational medication or device trial.
5. Known hypersensitivity to FGF1 or heparin.
6. Subjects unable to tolerate or undergo MRI scanning, including subjects with claustrophobia unless sedation can be used, cardiac pacemaker/defibrillator, ferromagnetic metal implants e.g., in skull, cardiac devices, other than those approved as safe for use in MR scanners.
7. Ongoing drug or alcohol abuse or dependence.
8. Positive serology for Hepatitis B or C, or Human Immunodeficiency Virus (HIV) at Screening.
9. Positive test for Methicillin-resistant Staphylococcus Aureus (MRSA) at screening.
10. Any disease, concomitant injury, condition or treatment that interferes with the specific walking training, the performance or interpretation of the neurological examination.
11. Has a condition or has received medical treatment that, in the judgment of the investigator, precludes successful participation in the study.
12. Previous radiation treatment (e.g. cancer treatment) in the region of the spinal cord injury.

Investigational product, dose and mode of administration, batch number(s):

Heparin Activated Recombinant Human Fibroblast Growth Factor 1 (FGF1) in SC0806 was provided at a concentration of 50 µg/ml and supplied as 0.6 ml in a 2 ml vial and diluted to 0.5 µg/ml in a total volume of 30 ml. The diluent was provided separately. The device was soaked in diluted FGF1 for 1 h before implantation.
Device LOT:164713, 164683, 164682, 164728, 164713, 164690, 165666. FGF1 batch number: BS-107654, DE-170066. Diluent batch number: BS-107656, DE-170065.

Reference therapy:

No comparator product was used. Subjects randomised to the control group participated in the same specific walking training program as subjects randomised to the investigational drug but without any surgical implantation.

Duration of treatment:

Pre-treatment phase: up to 100 days per subject
Treatment (surgical) phase: Up to 21±7 days
Rehabilitation phase: Approximately 18 months
Excluding the pre-treatment phase, a total of up to approximately 19 months per subject randomised to treatment, and approximately

up to 18 months for subjects randomised to specific walking training only.

Criteria for evaluation:

Efficacy: The primary efficacy variable was assessed as the proportion of subjects with an improvement in MEP, from baseline to 18 months.

Safety: Safety was assessed by monitoring and recording all adverse events (AEs), adverse device effects (ADEs), observed device deficiencies (DDs), serious adverse events (SAEs) and serious adverse device effects (SADEs); regular monitoring of haematology, blood chemistry, and urine values; regular measurement of vital signs and electrocardiograms (ECGs); and the performance of physical examinations.

Immunogenicity was assessed by measuring the presence of anti-FGF1 antibodies at various time points post-dose.

MRI assessment was performed pre-dose (Day -100 to Day -1) and Day 540 (±30 days) post-dose and as clinically necessary. If a subject prematurely discontinued from the study, an MRI was to also be performed at the Early Termination Visit if the previous MRI was obtained more than 30 days prior to the termination.

CT of the device area was performed at Day 2, Day 14 (±7), Day 60 (±7 days) and Day 540 (±30 days) in order to detect any new pathological changes induced by the treatment, e.g., haemorrhages, SCI-device migration and calcification. The scans were also to confirm the resorption of the SCI-device.

Plasma exposure: The treatment with SC0806 does not result in any systemic exposure and therefore no formal pharmacokinetic (PK) parameters were reported for FGF1 in plasma. Blood samples to detect the presence of FGF1 were drawn at various time points post-dose.

Statistical methods:

All statistical analyses, including tables, figures, and listings, were performed using SAS®, Version 9.3 or higher. The statistical analysis was described in detail in the Statistical Analysis Plan (SAP) including a Data Display Plan (DDP), which was finalised and approved before database lock.

The primary efficacy variable was the proportion of subjects with an improvement, from baseline to 18 months in MEP score. Due to the small number of subjects enrolled, statistical hypothesis testing was not performed. All data collected were presented with summary statistics and subject data listings, including at least the number of subjects, mean, standard deviation, median, minimum, and maximum for continuous data and frequency and percentage for categorical data. Tables with summary statistics were divided by treatment group and visit where applicable. The Full Set Analysis population was used for both the efficacy and safety endpoints.

Efficacy results

The primary efficacy variable was the proportion of subjects with an improvement in MEP score, as recorded from the muscles of the arms and legs following transcranial electrical stimulation of the brain, in subjects with complete TSCI from baseline to 18 months.

- The study did not meet the primary efficacy endpoint. The primary outcome demonstrated no motor function below the injured area in any subject. The signal (MEP) was negative from baseline to Final Visit.
- Efficacy was also assessed with AIS concerning total score, functional improvement, the effect on specific walking training and other specified rating scales (GCP, SCI-QoL, I-QoL and ICIQ-SF), as well as urinary and bowel function. The results did not show convincing efficacy, other than some trends in temporary improvements in some subjects treated with SC0806.
- Based on the results, the Sponsor decided to stop the recruitment and terminate the study.

Safety results:

The treatment with SC086, including the surgical method, showed an acceptable safety profile in the study.

- All subjects had complete anatomical cut-off of the spinal cord and a single lesion was detected at level T2-T11 as assessed by MRI. No significant pathological changes, associated with the device, were detected on post-baseline Visits.
- During the study, there were a total of 101 AEs/ADEs in 10 subjects. Two AEs, pregnancy followed by a miscarriage in 1 subject led to study withdrawal.
- The most common possibly related AE was abnormal PK(INR). Other common AEs were headache and pyrexia. The events of headache and pyrexia, including elevated body temperature, were all reported in subjects exposed to SC0806, 5-7 days post-surgery but without any relation to infectious agents.
- There were 10 SAEs/SADEs in 5 subjects reported during the study and 1 SAE reported during the screening phase, prior to randomization. Of the 10 reported SAEs/SADEs during the study period, 6 were reported in the surgical group and 4 in the control group. One event of subdural hygroma and 1 event of suspected meningitis, reported in the surgical group, were assessed as possibly related to SC0806.
- No deaths nor any unexpected SAEs/SADEs were reported.
- No clinically relevant patterns of abnormalities related to SC0806 were identified from physical examination, vital signs, laboratory values or ECG.
- CT of the device area showed that the device was marginally and temporarily dislocated in 1 subject, but no migration was observed. The device was not fully absorbed at the last screening in 5 subjects, and some minor calcifications were detected in 3 subjects.

Conclusion:

Subjects with complete traumatic SCI were treated with a Heparin-activated rhFGF1-loaded SCI device, in combination with specific walking training aiming to achieve restored motor function as the primary objective.

None of the subjects showed an effect on motor function as measured by electrical impulses passing through the injured area after treatment, which is considered a prerequisite to restore motor function. This means that the study did not meet the primary efficacy endpoint regarding a change in MEP score. In addition, the results did not show convincing efficacy on secondary endpoints regarding AIS impairment grades, sensory or functional improvement, pain, QoL, or urinary and bowel function, other than some trends. Based on these results the Sponsor decided to stop the inclusion of subjects.

With regard to safety, the surgical implantation of SC0806 was successful and was generally well tolerated. There were no major indications that rhFGF1 or other constituents from the device had any serious adverse effects on any vital signs or clinical pathology parameters. Most of the adverse events observed in this study could be attributed to the surgical intervention itself.