



SDR-CTR-SYN-06

Trial code	HP7020-02
Title of trial	An exploratory Phase I randomized, single-site, double-blind, active-controlled, parallel-group, single-administration, dose-escalation trial to investigate the safety and tolerability of neosaxitoxin alone and in combination with bupivacaine (with and without epinephrine), in perineural administrations for brachial plexus blockade in healthy subjects
Development phase	Phase I
EudraCT number	2016-003958-33
Universal Trial Number	U1111-1189-1950
Investigational medicinal products	Neosaxitoxin alone and in combination with BUPI (with and without EPI)
Indication	Not applicable
Principal investigator	██████████, MD, MSc, Research Physician C-EDS-NL
Trial site	The Netherlands (1 site)
Trial sponsor	Grünenthal GmbH, 52099 Aachen, Germany
Sponsor's signatory	Dr ██████████, Senior Clinical Pharmacologist Contact number: + 49 (0) 241-569-0
Trial period	First subject in: 30 Jan 2018 Last subject out: 21 Sep 2018
Early trial termination date	21 Sep 2018

Objectives

Primary Objective

- To evaluate the systemic and local safety and tolerability of ascending doses of NeoSTX alone and in combination with fixed doses of BUPI (with and without EPI), following brachial plexus blockade in healthy male subjects.

Secondary Objectives

- To evaluate the pharmacodynamics (PD) of ascending doses of NeoSTX, alone and in combination with fixed doses of BUPI (with and without EPI), following brachial plexus blockade.
- To characterize the pharmacokinetics (PK) of NeoSTX and BUPI after brachial plexus blockade with NeoSTX alone or different drug combinations: NeoSTX + EPI, NeoSTX + BUPI, or NeoSTX + BUPI + EPI.

SDR-CTR-SYN-06**Investigational medicinal products**

- Neosaxitoxin solution for injection (concentrate 20 µg/mL; dose: 1.25 µg to 60 µg).
Batch number: P07117, Expiration date: 31 Oct 2019
- Bupivacaine hydrochloride solution for injection (concentrate 0.5% w/v; dose: 0.05-0.4% w/v [10-80 mg], 0.5% w/v [100 mg]).
Batch number: T13622, Expiration date: 31 Jul 2019
- Epinephrine solution for injection (concentrate 1:10 000; dose: 1:200 000 [100 µg]).
Batch number: 6501729, Expiration date: 28 Feb 2019
- Bupivacaine and EPI solution for injection (concentrate 0.5% w/v, 1:10 000; dose: 0.5% w/v BUPI [100 mg] plus EPI 1:200 000 [100 µg]).
Batch number: 17072042, Expiration date: 31 Jan 2019

Trial treatments

Depending on the part of the trial, NeoSTX, BUPI, EPI, and sterile saline were combined. All treatments were administered as a single perineural injection in a fixed final volume of 20 mL.

Part A

- Test treatment (T1): Ascending doses of NeoSTX combined with BUPI (0.2% w/v [40 mg]) and EPI 1:200 000 (100 µg). The starting dose of NeoSTX was 1.25 µg, and the maximal dose of NeoSTX was 25 µg.
- Reference treatment (C1): BUPI (0.2% w/v [40 mg], low dose) combined with EPI 1:200 000 (100 µg).
- Reference treatment (C2): BUPI (0.5% w/v [100 mg], high dose) combined with EPI 1:200 000 (100 µg).

Part B

- Test treatment (T2): Ascending doses of NeoSTX (5 µg and 10 µg) combined with BUPI (0.4% w/v [80 mg]).
- Reference treatment (C3): BUPI (0.4% w/v [80 mg], low dose).
- Reference treatment (C4): BUPI (0.5% w/v [100 mg], high dose).

Non-IMP

- Sodium chloride solution for injection (concentrate: each 1 mL of solution contains 0.9% w/v of sodium chloride).
Batch number: 736505, Expiration date: 30 Sep 2020

Trial population

Male subjects aged 18 years to 55 years, with body mass index (BMI) between 20.0 kg/m² and 30.0 kg/m², inclusive, be in good health as determined by their prior/concomitant diseases, physical, and laboratory examinations, including virus serology test, and not show any clinically significant deviations from reference ranges as determined by 12-lead electrocardiogram (ECG), vital signs

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(systolic/diastolic blood pressure, pulse rate, and respiratory rate), oxygen saturation, body temperature (tympanic), and safety laboratory parameters (hematology, clinical chemistry, clotting, and urinalysis).

Summary of the trial procedures and assessments

The trial was performed in different parts to investigate different dose steps of NeoSTX in combination with fixed doses of BUPI (with and without EPI), as described below. Each subject received IMP once through perineural administrations for brachial plexus blockade during the whole trial.

Part A: It was planned to dose 8 cohorts of 5 subjects each, resulting in 40 allocated subjects. Out of 5 subjects in each cohort, 3 subjects received the test treatment of NeoSTX + BUPI + EPI (T1) and 1 subject each received the reference treatments BUPI at low (C1) or high (C2) dose with EPI. It was also planned to include 2 additional cohorts (resulting in a total of 50 subjects), if requested by the benefit-risk team (BRT). Finally, 32 subjects completed Part A before the early termination of trial; 5 subjects each in cohorts A01 to A06 and 2 subjects in cohort A07 (1 subject received T1 [25 µg] and 1 subject received C1). It is to be noted that the dose NeoSTX 25 µg was used twice across the cohorts (cohort A06 and cohort A07). Further details are available under “Trial Performance”.

Part B: A maximum of 8 cohorts were planned to be dosed in Part B, resulting in a maximum of 40 allocated subjects (8 cohorts of 5 subjects each). Out of 5 subjects in each cohort, 3 subjects received NeoSTX + BUPI (T2) and 1 subject each received reference treatments BUPI at low (C3) or high dose (C4). Finally, 10 subjects completed Part B before early termination; 5 subjects each in cohorts B01 and B02. Two NeoSTX doses (5 µg and 10 µg) were administered in 2 cohorts in Part B. Bupivacaine 80 mg was selected by the BRT and administered as a low BUPI dose for T2 and C3 treatment groups.

Part C: It was planned that 6 subjects would have received NeoSTX alone (T3) and NeoSTX + EPI (T4) and, depending on the number of subjects dosed in Part A and Part B, up to 6 subjects would have received NeoSTX + BUPI (T2) and NeoSTX + BUPI + EPI (T1). Part C of the trial was not initiated due to early termination of the trial.

There was an Enrollment Visit between 30 days and 4 days before the IMP administration, a Confinement Phase with single IMP administration in the Treatment Phase, and a Final Examination in an ambulatory setting between 8 days and 14 days after the IMP administration (i.e., Day 9 to Day 15). Subjects were confined to the trial site on the evening of Day -2. During the Confinement Assessment (Day -2 to Day -1), eligibility of the subjects was assessed according to the schedule of events. The allocation to treatment decision was taken before IMP administration on Day 1. The IMP was administered on Day 1 of the Treatment Phase as a perineural injection for brachial plexus blockade. Safety, PK and PD assessments were performed at the specified time points. Recovery was assessed by sensory and motor function testing. Subjects were not discharged from the trial site as long as there was incomplete recovery of the sensory or motor block components to ensure that subjects did not hurt themselves, e.g., on a hot plate at home. If recovery of sensory and motor block components was complete/near-complete, subjects were discharged in the afternoon of Day 3 (56 hours post-dose) at the earliest.

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If there was still a residual sensory or motor block component on Day 7, that was regarded as an adverse event (AE) and subjects stayed in-house until complete/near-complete recovery was confirmed by PD assessments.

Trial performance

There were 3 protocol amendments.

The sponsor decided to stop further dosing of healthy subjects with the IMP NeoSTX alone and with the combinations, based on the review of the efficacy data obtained from exposure of 4 healthy subjects to NeoSTX 25 µg (in combination with BUPI + EPI) in Part A. It was concluded that further efficacy was less likely to be achieved (with an acceptable benefit/risk ratio) through escalating the dose. The decision was not related to any clinical or non-clinical safety concern.

Summary of the statistical methods

Statistical analyses

Both Part A and Part B of the trial were double-blind. The investigators and staff at the site and the subjects were blinded to the treatment assignment. The dose level of NeoSTX at each cohort was not blinded. In this exploratory trial, Grünenthal staff were not blinded.

After each cohort, a BRT evaluated the relevant safety, PK, and PD data. The final analysis of the trial was performed after all subjects completed the trial and the database was locked.

All analyses in this trial were of an exploratory nature. No statistical testing of inference was planned in this trial.

Sample size rationale

No formal sample size calculation was done for this trial because the number of enrolled subjects was dependent on the number of cohorts used and, on the decisions made after the data reviews.

The goal of dose escalation in Part A and Part B was to identify a safe dose range for future trials in a clinical setting with patients. The full characterization of the safety profile of each dose was not intended in the dose escalation. Therefore, small cohorts of 3 subjects receiving test treatment were sufficient to guide the dose escalation and to recommend a new dose for the next cohort.

Subject populations

The analysis sets specified below are defined separately for each trial part.

Enrolled Set:	All subjects who signed the informed consent form.
Allocated Set:	All subjects who were allocated to treatment.
Safety Set (SAF):	All subjects with at least 1 IMP administration.
Pharmacokinetic Set 1 (PK Set 1):	All subjects with at least 1 evaluable PK parameter of NeoSTX.
Pharmacokinetic Set 2 (PK Set 2):	All subjects with at least 1 evaluable PK parameter of BUPI.
Pharmacodynamic Set (PD Set):	All allocated and treated subjects with baseline and at least 1 post-baseline value for at least 1 of the PD outcome parameters, i.e.,

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for sensory and motor function testing.

Statistical methods and analysis

Each trial part was analyzed separately. In the dose escalation Part A and Part B, a model-based Bayesian dose-escalation method was used to analyze the emerging data after each cohort and to recommend a dose for the next cohort. The method used the 2-parameter logistic model for the probability of a dose limiting event (DLE) and the analysis was done within the SAF. Dose limiting events were defined based on set thresholds for perioral tingling or numbness, negative inspiratory force (NIF), vital capacity (VC), oxygen saturation, contralateral grip strength, dizziness on a 5-point Likert scale, and clinically relevant nausea or vomiting (using the Postoperative Nausea and Vomiting [PONV] intensity scale).

Analysis of pharmacokinetic data

The analysis of PK data was performed in the PK Set 1 for NeoSTX and in the PK Set 2 for BUPI.

Plasma samples were analyzed to determine concentrations of NeoSTX and BUPI using validated bioanalytical assays under the supervision of the Department of Pharmacokinetics at the sponsor.

Descriptive statistics and graphs of NeoSTX and BUPI plasma concentrations at the respective time points were created by dose. In addition, descriptive statistics of derived NeoSTX and BUPI PK parameters were created by dose.

Analysis of pharmacodynamic data

The analysis of efficacy data was performed in the PD Set. Selected parameters from quantitative sensory testing (QST) panel as well as motor block duration and intensity of motor function testing (grip strength ipsilateral and modified Bromage scale) were analyzed by treatment and dose using descriptive statistics. Time to partial recovery and time to near-complete recovery were analyzed descriptively by treatment and dose using time-to-event methods.

Analysis of safety data

The analysis of safety data was performed in the SAF. All safety and tolerability data (AEs, vital signs, oxygen saturation, body temperature [tympanic], local tolerability, safety laboratory values, and safety ECGs) were descriptively summarized.

In addition, the following trial-specific safety data were analyzed:

- Diaphragm ultrasound: ipsilateral and contralateral phrenic ultrasonography outcome (complete paresis/partial paresis/no paresis).
- Respiratory function: NIF and VC (the volume of air in a maximum voluntary breath).
- Prodromal symptoms for systemic toxicity: PONV, intensity scale, dizziness (rated by the subject on a 1-5 Likert scale), numbness and tingling (rated by the subject on a 0-10 scale), and contralateral grip strength.

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Summary of results

Subject disposition

A total of 242 subjects were enrolled, and 42 of these subjects were allocated to IMP; 32 in Part A and 10 in Part B of the trial. None of the subjects discontinued during the course of the trial. All 42 subjects completed the trial.

Demographics

For the SAF (N = 42), the mean (standard deviation [SD]) age was 30.10 (9.71) years, mean height was 1.82 (0.08) m, mean weight was 80.60 (8.99) kg, and mean BMI was 24.49 (2.53) kg/m². Demographic data were similar in all treatment groups in both Part A and Part B, and across the population sets.

Pharmacokinetics

Neosaxitoxin

Neosaxitoxin was systemically absorbed after perineural administration and quantified in all groups who received NeoSTX in both Part A and Part B. Except for 2 subjects in cohort A01 (NeoSTX 1.25 µg) of Part A, NeoSTX was quantifiable in all subject samples analyzed. In Part A, in cohorts dosed with more than 5 µg of NeoSTX, NeoSTX was measured in plasma for up to 56 hours. In the NeoSTX 1.25 µg and 2.5 µg cohorts, the NeoSTX plasma concentrations were in the low pg/mL range and only quantifiable up to 10 hours. In both Part A and Part B, plasma concentrations of NeoSTX increased with increasing doses.

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Comparison of PK parameters of NeoSTX – PK Set 1

Parameter	NeoSTX dose [ug]	T1 n, Mean	T2 n, Mean
C _{max} (pg/mL)	1.25	1, 7.33	
	2.5	3, 9.99	
	5	3, 18.7	3, 36.5
	10	3, 41.1	3, 89
	20	3, 83.9	
	25	4, 118	
AUC _{0-t} (h·pg/mL)	1.25	1, 22.2	
	2.5	3, 46.6	
	5	3, 321	3, 250
	10	3, 781	3, 858
	20	3, 1480	
	25	4, 1902	
AUC (h·pg/mL)	1.25	0, n.c	
	2.5	1, 80.4	
	5	2, 974	0, n.c
	10	2, 1085	3, 1362
	20	3, 2302	
	25	4, 2874	
t _{max} (h) [1]	1.25	1, 0.75	
	2.5	3, 2.03	
	5	3, 2.00	3, 0.50
	10	3, 1.00	3, 0.17
	20	3, 0.78	
	25	4, 0.88	

Treatments in Part A: T1 (NeoSTX/BUPI 40 mg/EPI 100 µg); Treatments in Part B: T2 (NeoSTX/BUPI 80 mg). [1] For t_{max} the medians are displayed instead of the geometric means. AUC = area under the concentration-time curve from zero up to infinity with extrapolation of the terminal phase; AUC_{0-t} = area under the concentration-time curve from zero up to the last concentration ≥LLOQ (C_{last}); BUPI = bupivacaine; C_{max} = maximum observed concentration after administration; EPI = epinephrine; PK = pharmacokinetics; n = number of evaluable samples (or valid observations); n.c = not calculated; NeoSTX = neosaxitoxin; t_{max} = time to attain C_{max}.

In Part B of the trial, where NeoSTX + BUPI were administered without EPI, the median time to attain maximum observed concentration after administration (C_{max}; [t_{max}]) of NeoSTX ranged from 0.17 hours to 0.50 hours. Administration of NeoSTX + BUPI + EPI in Part A resulted in a delayed median t_{max}, ranging from 0.75 hours to 2.03 hours. Comparing NeoSTX 5 µg and 10 µg cohorts in Parts A and B, a 1.96-fold to 2.16-fold lower geometric mean C_{max} was observed in combination

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with BUPI + EPI in Part A and the median t_{\max} occurred 4.00 times to 5.88 times later. Observed area under the concentration-time curve from zero up to the last concentration \geq lower limit of quantification (LLOQ, C_{last}) (AUC_{0-t}) for NeoSTX was similar when NeoSTX + BUPI were administered with or without EPI.

The C_{\max} and AUC_{0-t} increased with dose. The increase in C_{\max} was dose proportional when evaluated using a power model. Overall, a 20-fold increase in dose resulted in a 16-fold increase in C_{\max} .

Analysis of dose proportionality of AUC_{0-t} and C_{\max} of NeoSTX – ANCOVA – PK Set 1

Part	PK Parameter	Regression Parameter	Estimate	Standard Error	90% CI
A	AUC_{0-t}	Intercept	2.856	0.219	(2.471, 3.240)
		Slope	1.517	0.093	(1.354, 1.680)
	C_{\max}	Intercept	1.419	0.192	(1.083, 1.755)
		Slope	1.014	0.081	(0.872, 1.156)
B	AUC_{0-t}	Intercept	2.652	0.653	(1.260, 4.045)
		Slope	1.782	0.329	(1.081, 2.483)
	C_{\max}	Intercept	1.533	0.596	(0.262, 2.804)
		Slope	1.283	0.300	(0.644, 1.923)

Analysis of Covariance of the logarithm of the PK parameter as a dependent variable and the logarithm of the NeoSTX dose as covariate. Dose proportionality is concluded, if the 90% CI of the slope includes the value 1.

ANCOVA = analysis of covariance; AUC_{0-t} = area under the concentration-time curve from zero up to the last concentration \geq LLOQ (C_{last}); CI = confidence interval; C_{\max} = maximum observed concentration after administration; PK = pharmacokinetics; NeoSTX = neosaxitoxin.

Ignoring doses levels below NeoSTX 5 μg , the half-life ($t_{1/2}$) estimates for NeoSTX in Part A and Part B ranged from 29.6 hours to 74.3 hours independently of dose level.

Bupivacaine

Bupivacaine was quantified in plasma samples obtained from all treatment groups. No difference in t_{\max} was observed for the different BUPI treatment groups. Overall, the median t_{\max} was observed between 0.50 hours to 0.77 hours after administration. Mean BUPI area under the concentration-time curve from zero up to infinity with extrapolation of the terminal phase (AUC) and C_{\max} increased proportionally with doses between C1 and C2 treatment groups in Part A. There was no relevant difference observed in BUPI exposure (AUC) when comparing C3 and C4 treatment group in Part B.

Comparing the dose normalized C_{\max} of C1 (BUPI + EPI) with C3 (BUPI) in Parts A and B, a 2.5-fold lower geometric mean C_{\max} was observed when dosing BUPI + EPI. Comparing the dose normalized C_{\max} of T1 (NeoSTX + BUPI + EPI) with T2 (NeoSTX + BUPI) in Parts A and B, a 2.1-fold lower geometric mean C_{\max} was observed for the NeoSTX + BUPI combination with EPI. This is consistent with the vasoconstrictive effect of EPI. Epinephrine lowered the geometric mean C_{\max} of BUPI in all treatment groups with a factor of 2.1 to 2.5 but without any obvious change in

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t_{\max} . The C_{\max} value in C4 (BUPI 100 mg alone) was observed to be below C_{\max} in C3 (BUPI 80 mg alone) and excluded from evaluation of influence by EPI.

Observed mean PK parameters for BUPI were similar for the T1 and C1 treatment groups in Part A. Observed mean PK parameters for BUPI were also similar for the T2 and C3 treatment groups in Part B. Therefore, NeoSTX did not change the PK of BUPI. In addition, no change was observed in the C_{\max} of BUPI when increasing the dose of NeoSTX, further supporting that NeoSTX does not influence the PK of BUPI. The $t_{1/2}$ estimates for BUPI ranged from 2.93 hours to 11.3 hours independently of dose level and treatment combination.

Pharmacodynamics

The onset of sensory and motor block was reached within the first hour both for NeoSTX + BUPI + EPI (Part A) and NeoSTX + BUPI (Part B) combinations at all tested doses.

Neosaxitoxin + BUPI + EPI (Part A) and NeoSTX + BUPI (Part B) combinations showed a reliable and prolonged duration of sensory and motor block, as assessed by QST panel, ipsilateral muscle grip test, and modified Bromage scale. In Part A, NeoSTX + BUPI + EPI produced nearly a 3-fold (for NeoSTX 2.5 µg, 5 µg, 10 µg, and 25 µg) prolongation of time (~24 hours) to near-complete recovery of mechanical detection threshold (MDT), and nearly a 2-fold (for NeoSTX 5 µg, 10 µg, and 25 µg) prolongation of time (~24 hours) to near-complete recovery of cold detection threshold (CDT) compared to the comparator BUPI (C1, C2). In addition, NeoSTX + BUPI + EPI produced a 2-fold (for NeoSTX 5 µg, 10 µg, and 20 µg [~24 hours]) to 3-fold (for NeoSTX 25 µg [~33.13 hours]) prolongation of time to near-complete recovery of ipsilateral muscle grip strength compared to the comparator BUPI (C1, C2).

The PD results observed in Part B were similar to those in Part A. However, since only 2 doses of NeoSTX in combination with BUPI 80 mg were investigated in Part B due to the early termination of the trial, and owing to the small sample size in the comparator arms (n =2 for C3 and C4), only limited conclusions can be drawn from the observed data.

For both NeoSTX + BUPI + EPI (Part A) and NeoSTX + BUPI (Part B) combinations, no differentiation in the duration of sensory and motor block could be detected over the dose ranges tested.

Prolonged sensory block duration compared to C1/C2 for nerve blockade could be observed with NeoSTX 10 µg and 25 µg (in combination with BUPI + EPI) in Part A. It should be noted that the results of NeoSTX 20 µg (cohort A05) are unreliable because of technical issues with the PD assessments in this cohort.

Safety and tolerability results

There were no deaths, serious adverse events (SAEs), AE leading to discontinuation from trial or treatment emergent adverse events (TEAEs) leading to premature termination of dose escalation. Overall, based on formal criteria, 2 DLEs occurred in Part A and 1 DLE in Part B of the trial. All of these events were regarded as not indicating true systemic effects of the IMP by the sponsor's BRT during dose-escalation decision meetings.

The most commonly reported TEAEs (at least 2 subjects [6.3%]) in Part A were Horner's syndrome, a well-known effect of the interscalene block (ISB) procedure with a local anesthetic (LA) (7 subjects [21.9%]), application site erythema (5 subjects [15.6%]), application site swelling

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(5 subjects [15.6%]), puncture site erythema (5 subjects [15.6%]), puncture site swelling (3 subjects [9.4%]), nausea (3 subjects [9.4%]) application site pain (2 subjects [6.3%]), musculoskeletal pain (2 subjects [6.3%]), musculoskeletal stiffness (2 subjects [6.3%]), dizziness (2 subjects [6.3%]), and presyncope (2 subjects [6.3%]).

The most commonly reported TEAEs (at least 2 subjects [20%]) in Part B were Horner's syndrome (6 subjects [60%]), hypoesthesia oral (2 subjects [20%]), application site erythema (2 subjects [20%]), application site swelling (2 subjects [20%]), injection site swelling (2 subjects [20%]), and headache (2 subjects [20%]).

All subjects had an ipsilateral (block-sided) transient diaphragm paresis, which is well expected for the procedure of an ISB with LA volumes as used in this trial. Changes in forced ventilation (NIF and VC) as well as oxygen saturation were consistent with expectations towards a block-sided diaphragm paresis, but did not indicate systemic neuromuscular blocking effects.

There were no major changes in the hematological, clinical chemistry, clotting, and urinalysis laboratory values from Baseline to different Visits across different cohorts in Part A and Part B. No clinically relevant hematological, clinical chemistry, clotting, and urinalysis abnormalities in both Part A and Part B of the trial were observed in any subject. There were no major changes in values of blood pressure and pulse rate from Baseline across different Visits in all groups of Parts A and B. There were no relevant trends identified in Heart Rate, PR interval, QRS duration, QT interval by Fredericia (QTcF) interval, QTc interval values from Baseline across different Visits in all groups of Parts A and B. No QTc or QTcF interval >450 ms was observed in any subject throughout the trial.

There was an apparent trend of frequency and intensity of prodromal symptoms, tingling and numbness, in the highest NeoSTX dose of 25 µg (in combination with BUPI + EPI) in Part A.

Conclusions

With the analgesic efficacy obtained for nerve blockade with NeoSTX 10 µg and 25 µg (in combination with BUPI + EPI), it was concluded to have a meaningful dose range to serve as a starting point for subsequent trials of the analgesic properties of NeoSTX in combination with BUPI + EPI in patients in need of procedural analgesia to be provided in connection with elective surgery.

Safety

- NeoSTX doses up to 25 µg (in combination with BUPI + EPI) in Part A and up to 10 µg (in combination with BUPI) in Part B were safe and generally well tolerated.
- No SAEs or deaths were reported during the trial.
- The 3 DLEs observed were considered not to indicate true systemic IMP related effects.
- Observed changes to oxygen saturation as well as forced respiration were in line with expectations towards a block-sided (ipsilateral) diaphragm paresis, which is a well-known effect of ISB.
- There was no indication of relevant systemic neuromuscular blocking effects of NeoSTX in the dose range tested.

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Pharmacokinetics

- Neosaxitoxin has a very long plasma half-life for up to 74 hours.
- The BUPI plasma half-life was significantly shorter, ranging from 2.93 hours to 11.3 hours.
- Neosaxitoxin exposure increases with dose, C_{\max} increases in a dose-proportional manner.
- Mean BUPI AUC and C_{\max} increased proportionally with doses between C1 (BUPI 40 mg) and C2 (BUPI 100 mg) treatment groups in Part A.
- In presence of EPI, an approximate 2-fold lower mean C_{\max} and 4-fold to 6-fold prolonged median t_{\max} was observed in Part A compared with Part B for NeoSTX 5 μg and 10 μg dose. Ignoring C4, EPI lowered the geometric mean C_{\max} of BUPI in all treatment groups with a factor of 2.1 to 2.5 but without any obvious change in t_{\max} .

Pharmacodynamics

- The onset of sensory and motor block was reached within the first hour.
- A dose-dependent prolongation in the duration of sensory and motor block was observed in NeoSTX (T1 and T2) compared to BUPI (C1-C4).
- Sensory blocks up to 30 hours in some QST parameters were observed at NeoSTX 25 μg (in combination with BUPI + EPI) in Part A.
- Observed time to recovery at the therapeutic dose of BUPI (C2 high dose 100 mg) in Part A was in line with block durations of BUPI in clinical practice.
- No differentiation in duration of sensory and motor block was found.