A phase I study of an injectable lidocaine paste for spermatic cord block in men with chronic scrotal content pain

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ABSTRACT

Introduction: Patients with chronic scrotal content pain (CSCP) lack effective, non-invasive treatment options. We aimed to determine the local and systemic safety, tolerability, pharmacokinetics (PK), and efficacy of a long-lasting local anesthetic in patients with CSCP.
Methods: This was a prospective, single-center, open-label, single-arm, phase 1 dose-escalating trial completed between October 2019 and March 2021. Twelve patients ≥19 years old with unilateral scrotal pain lasting ≥3 months reporting an average maximum pain score over seven days of ≥4 on a 0–10 numerical rating scale (NRS) were included. Patients underwent a test spermatic cord block and those reporting a decrease of ≥2 points were included. The investigational drug, ST-01 (sustained-release lidocaine polymer solution), is a long-acting injection of lidocaine around the spermatic cord. Subjects were provided a NRS dairy and recorded their NRS score until day 28. The Chronic Epididymitis Symptom Index (CESI) was

KEY MESSAGES

- Chronic scrotal pain currently has few effective medical treatments.
- This was a prospective, single-center, open-label, single-arm, phase 1 dose-escalating trial of a long-lasting injectable lidocaine paste.
- There were no serious adverse events reported.
- This study provides evidence that the novel ST-01 treatment is safe and well-tolerated.

completed on days 0, 7, 14, and 28. All patients underwent an examination and assessment for adverse events (AE) on days 0, 1, 7, 14, and 28. Exploratory statistical hypothesis testing was planned for this study due to its investigative nature.
Results: There were no serious adverse events (SAEs) reported. All subjects reported at least one treatment-emergent adverse event (TEAE); 83% of related AEs were injection-site reactions consisting of swelling and bruising. NRS was reduced across all cohorts between baseline and end of study.
Conclusions: This study provides evidence that the novel ST-01 treatment is safe and well-tolerated.

INTRODUCTION

Chronic scrotal content pain (CSCP) is a common entity afflicting men of all ages and has been reported to peak in the mid to late thirties.[1,2] The etiology for CSCP is varied and can be divided into scrotal and extra scrotal causes. Extra scrotal causes involve irritation of the ilioinguinal, genitofemoral or pudendal nerves. Causes within the scrotum include infection, scrotal surgery, post vasectomy pain or anatomic abnormalities.[2]

Effective treatment options for CSCP are limited and data consists primarily of non-randomized, small studies. Conservative therapies include rest, ice, scrotal supports, pain education and counselling. There is no standardized protocol for treatment, but the mainstay of medical therapy involves nonsteroidal anti-inflammatory drugs (NSAIDs) with tricyclic antidepressants or gabapentin as alternatives.[3,4] Non-invasive options include pelvic floor physiotherapy, acupuncture or transcutaneous electrical nerve stimulation (TENS).[5]

Many patients with CSCP are left with untreated pain, seeking consultation with multiple physicians and have poor behavioural, sexual and emotional outcomes.[6,7] Thus, there remains an unmet need for effective non-invasive therapeutics.

Spermatic cord block with local anesthetics provides pain relief in a subset of subjects with CSCP. Reported response rates range from 40-75%.[8–10] Unfortunately, relief after spermatic cord block is short-lived due to the rapid elimination of lidocaine (terminal half-life = 1.5-2 hours) from the body. To achieve adequate pain relief, repeated injections would be necessary. Despite its positive effect on pain control, this limitation has prevented lidocaine from being used regularly to treat CSCP.

This Phase I trial was the first study of a novel long-acting formulation of lidocaine in human subjects and was designed to evaluate the local and systemic safety, tolerability, pharmacokinetics (PK) and efficacy in a target population of patients with CSCP.

METHODS

This was a prospective, single center, open label, single arm, phase I dose-escalating trial (NCT04026945). After obtaining institutional ethics board approval 12 patients were recruited between October 2019 and March 2021.

Inclusion criteria

Male patients ≥ 19 years old with unilateral scrotal pain lasting ≥ 3 months who reported an average daily maximum pain score over 7 days of ≥ 4 on a 0-10 numerical rating scale (NRS) were recruited. Patients were then given a test spermatic cord block with 1% lidocaine (Lidocaine Hydrochloride Injection, USP, 1%, 10 mg/mL), and only those reporting a temporary decrease of ≥ two points on the NRS scale within an hour of injection were included. This was done to ensure a beneficial response to lidocaine. Patients subsequently underwent baseline blood levels (sodium, potassium, creatinine, white cells, red cells, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW)) that had to be within +/- 10% of normal reference ranges. Assessment of liver function was done (bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), albumin, prothrombin time and international normalized ratio (INR) with no value greater than 50% above the upper limit of normal being allowed.

Exclusion criteria

Subjects with a negative response to test spermatic cord block, defined as absence of a temporary decrease ≥ two points on the NRS within an hour of injection, other pain generator site with NRS ≥ 4, history of allergic reaction to lidocaine or any component of the long acting formulation, any contraindication to local anesthesia with lidocaine, active infection involving the urinary tract or scrotum, inability to give consent, inability to follow up according to the protocol, or negative response to previous spermatic cord block were excluded from the study.

Intervention

The investigational drug product, ST-01 (sustained-release lidocaine polymer solution for injection), is a long-acting injection of lidocaine into/around the spermatic cord, that is being developed for the treatment of CSCP. This is the first in-human study of ST-01. ST-01 contains two inactive ingredients, polyethylene glycol (PEG) 300 and poly (lactic-co-glycolic acid) (PLGA) which serve to modulate the slow release of lidocaine following an initial burst release.[11,12]

Primary outcome

Assess the safety and tolerability of ST-01 spermatic cord injections among patients with CSCP.

Secondary outcomes
Evaluate a range of doses of ST-01 for safety, reduction in pain, and effect on quality of life scores (compared to baseline) over 28 ± 2 days post injection.

Study design
The study had 3 planned dose-escalating cohorts: Cohort I: 2 mL of 140 mg/mL ST-01 (280 mg lidocaine); Cohort II: 3 mL of 140 mg/mL ST-01 (420 mg lidocaine); Cohort III: 4 mL of 140 mg/mL ST-01 (560 mg lidocaine).

Cohort I had a planned enrollment of 3 subjects who were treated with 2 mL of 140 mg/mL ST-01. Serum lidocaine levels were monitored up to 7 days post injection. If serum lidocaine levels remained < 5µg/mL at 1 hour, 1 and 7 days post injection and no dose limiting toxicity (DLT) were observed, the study was permitted to enroll 3 new subjects into Cohort II (3 mL of 140 mg/mL ST-01). Similarly, if these criteria were met for Cohort II the study was permitted to enroll 3 new subjects into Cohort III (4 mL of 140 mg/mL ST-01). A DLT was defined as the occurrence of more than a mild adverse event (AE) that is probably or definitely related to the study agent. This procedure continued until either a DLT occurs or all three dose levels were evaluated. The maximum tolerated dose (MTD) was defined as one dose level below the dose level associated with DLT or the dose level in Cohort III if no DLT occurred in any cohort. Once the MTD level has been reached, three more subjects were allowed to enrol at that dose to collect additional safety data.

Based upon assigned cohort dose treatment consisted of a single injection of ST-01 into/around the spermatic cord on Day 0 of the study. Prior to injection of ST-01, investigators were allowed to inject 0.5 mL of 1% lidocaine to numb the area. ST-01 was then injected into/around the spermatic cord using an 18-gauge needle. The injection site was gently massaged to disperse the product evenly. An ultrasound was performed on day 1 to document location of ST-01 inoculate.

Outcome assessment
Efficacy was assessed through three patient-reported outcome measures. Subjects evaluated pain using the validated NRS, where “0” equalled “No Pain” and “10” equalled “Worst Pain Imaginable”. Subjects completed the NRS during their in-clinic visits on Day 0 (prior to ST-01 administration), Day 1 and Day 7. Subjects were also provided a NRS dairy and recorded their NRS score three times a day on Days 0 – 14, and once daily on Days 15-27.

The Chronic Epididymitis Symptom Index (CESI) and the International Index of Erectile Function (IIEF-5) questionnaires were completed by patients on days 0, 7, 14, and 28 to assess disease specific symptoms/quality of life and sexual function respectively.[13,14]

All patients underwent a physical examination and assessment for adverse events (AE) by a physician on days 0, 1, 7, 14, and 28.

A summary of protocol scheduled events can be found in **Appendix 1**.

Statistical analysis

Exploratory statistical hypothesis testing was planned for this study due to its investigative nature. All planned summaries of the study variables employed descriptive statistics as appropriate for categorical or numerical data.

As this was a phase 1 feasibility study, no formal statistical methodology was used to determine sample size for each cohort or the study. An N=3 was used for each dose cohort, with a further N=3 subjects enrolled to Cohort 2 (MTD), following completion of cohort 3 follow-up. For missing data, last observation was carried forward

RESULTS

During the study period 20 subjects were screened, with 12 subjects ultimately being enrolled into the study protocol. Baseline patient characteristics can be found in Table 1.

Efficacy of intervention

NRS scores were collected by subjects through NRS dairies. Subjects were asked to report the maximum pain they felt. On day 1 to 14, they were asked to report in the morning, midday and in the evening. From day 15 to the end of the study (day 28 ± 2) they were asked to complete this only once per day. Three (3) subjects completed a pain diary for only 26 days; day 27 and day 28 observations were missing and the last observation was carried forward.

Subject-reported NRS (mean, median) was reduced across all cohorts studied between baseline and end of study (Figure 1). The individual pain intensity differences from baseline (PID) are displayed in Figure 2 by cohort. The majority of subjects showed good response to treatment with ST-01 over 14 days with PID values below the zero-difference line. Furthermore, the time-weighted summed pain intensity differences over 14 days ($SPID_{0\text{-}14\ d}$) are displayed in Figure 3. Negative $SPID_{0\text{-}14\ d}$ values represent a decrease of pain compared to baseline and an overall benefit for subjects treated with ST-01. Based on activity and tolerability observed, and considerations of adequate volume of inoculate to distribute across the cord, patients in Cohort II (420 mg lidocaine) were chosen to enroll an additional three patients. This group reported a baseline mean (median) NRS score of 5.3 (5), compared to an end of study score of 3.3 (3.5). Subject-reported NRS scores over the study period for all cohorts are supplied in Table 2.

Assessment of CESI score showed similar trends in reduced scores with cohort II reporting a baseline mean (median) score of 19.8 (19) and an end of study value of 16.8 (17.5).

Given that CSCP is known to negatively affect sexual function the IIEF-5 questionnaire was used to assess sexual function changes. Cohort II reported a baseline IIEF-5 mean (median) score of 18.8 (21), and an end of study value of 17.8 (20.5).

Pharmacokinetic and pharmacodynamic profile of medication

Serum lidocaine concentrations were measured in all subjects at 1 hour, 1 day and 7 days following administration of ST-01. In all cohorts, serum concentrations of lidocaine were 0 at the

7 day assessment point (Figure 4). Prior to that in each cohort, serum concentrations were similar at day 1 indicating only local release of the medication.

Ultrasound assessment of depot injection

Ultrasound detected the ST-01 depot in all subjects on Day 1 following administration. Residual paste at the injection site at the end of study (day 28± 2) was detected by ultrasound in 75% of subjects. Two of 3 subjects (67%) in Cohort I (2 mL injection volume) and 1 of 6 (17%) subjects in Cohort II (3 mL injection volume) had complete dissolution of the depot at the end of study, while all subjects in Cohort III (4 mL injection volume) showed residual paste at the injection site.

Assessment of adverse events

There were no serious adverse events (SAEs) reported throughout the study. All subjects reported at least one treatment-emergent adverse event (TEAE). No treated subject withdrew from the study. A total of 40 AEs were reported, 34 were considered related to study treatment (19 mild, 10 moderate, 5 severe), 6 were unrelated to study treatment. 83% of related AE's were injection site reactions consisting of swelling and bruising at injection site. Of the 34 related AEs, 19 were resolved within 28 days, 15 were ongoing, 7 required treatment (**Table 3**). Treatment included antibiotics in 3 patients for presumed epididymitis, and oral pain medication (acetaminophen, ibuprofen, tramadol) for injection site, pelvic or scrotal pain in 4 patients. When assessing between cohorts, Cohort III had slightly higher rates of TAEAs, leading to selection of Cohort II for further enrollment.

Long-term followup and patient experience

At 7 to 16 months after cohort completion, 3 patients from each cohort (9 total) were asked about their experience with ST-01 and if they would undergo another treatment with ST-01. Two patients had either undergone a spermatic cord denervation, or were scheduled for one. Of the remaining 7 patients, all responded that they would consider another round of treatment with the study medication.

DISCUSSION

The primary objective of this first-in-human study with ST-01 was to assess the feasibility of spermatic cord injection with ST-01 in subjects with CSCP, and to evaluate a range of doses for safety and reduction in pain scores (compared to baseline) at times out to 28 ± 2 days post injection.

The study demonstrated that injection with 2, 3, or 4 mL of ST-01 was feasible. Ultrasound confirmed deposition of polymer paste inside the cord indicating local retention of this novel injection formulation. The low levels of plasma lidocaine across all cohorts following ST-01 injection supports the low risk of toxicity from systemic lidocaine.

Chronic pain remains a poorly understood condition. Although several theories exist as to its etiology, it is generally accepted that some level of abnormal sensitization occurs within nociceptors leading to inappropriate activation to non-painful stimuli.[15] Looking beyond CSCP, chronic pain affects a large proportion of our society with studies in developed nations finding a rate between 35-50%.[16] Our limited understanding of the pathophysiology of this disease is matched by the limited number of treatment options for patients. This lack of treatment options is particularly obvious in CSCP where we have limited data surrounding the various interventions. Treatment recommendations are based on reports of non-randomized trials or extrapolation from the chronic pain literature.[17] Although studies are limited in size and design, medications aimed at neuropathic mechanisms appear to have some of the best results with ~70% of patients reporting a 50% improvement in pain in two small studies.[4,18] Surgical options provide a slightly improved outcome profile with up to 70% of patients experiencing relief at the 20 month follow-up after a microsurgical denervation of the spermatic cord.[8] However, surgical procedures bring with them short and long-term complications such as hydrocele, testicular atrophy, wound infections and scrotal hematomas.[8] This makes the development of new non-invasive medical treatment options imperative.

The study outcomes indicate that in addition to being safe and feasible to inject ST-01, patients had a sustained reduction of pain. A reduction in pain intensity of 2 or more points on the NRS was observed in 9 of 12 (75%) subjects. Clinically significant pain changes are difficult to quantify, with a wide range reported in the literature. However, a systematic review of 37 studies suggested that an improvement of as little as 13% could be significant for patients.[19] Thus, should the reduction in pain intensity of 2 or more points on the NRS hold true in future randomized trials, we can expect ST-01 to provide meaningful relief. Modest improvement in QOL, as measured by CESI/IIEF-5, was also observed over the study period. In a study assessing Botox injections for CSCP, a similar reduction of about 3 points was noted on assessment via CESI.[20]

There were no SAE's reported in the study. All subjects reported at least one TEAE during the study. Most TEAE's were mild or moderate and related to bruising/swelling at the injection site, many were confounded by pre-existing chronic pain in the region of the injection site, and most resolved within the timeframe of study. Since this was the first use in human subjects, any patients with induration post injection were treated for potential infection to ensure an infection was not missed. However, it was not possible to confirm if these symptoms and signs truly reflected infections.

Following completion of the study patients who had not undergone further definitive therapy (microsurgical spermatic cord denervation) were asked if they would consider undergoing another injection with 7 of 7 respondents indicating they would. As physician experience with the injection technique grows, along with determination of optimal syringe and needle size it is anticipated that the number of TEAEs will diminish.

Limitations

This was a Phase I dose-escalation feasibility trial and thus was not powered or designed to reliably detect changes in pain levels, although these initial results are encouraging.

Future directions

Based on the encouraging results of this Phase I trial a Phase II trial is currently in development with expected patient enrolment in 2023.

CONCLUSIONS

ST-01 was safely and feasibly injected within the spermatic cord. Most AEs were mild or moderate and related to bruising, swelling or induration at the injection site. Reduction in pain intensity was observed in 9 of 12 (75%) subjects. On balance, the trial demonstrates a positive benefit/risk to the procedure in men suffering chronic scrotal pain as 7 out of 7 of the subjects not undergoing more definitive therapy responded that they would consider another round of treatment, and supports further clinical studies to evaluate serial treatment dosing of ST-01 for the treatment of chronic scrotal pain and other neuropraxic conditions amenable to local nerve blockade.

REFERENCES

1. Wesselmann U, Burnett AL and Heinberg LJ: The urogenital and rectal pain syndromes. *Pain* 1997; 73: 269–294.
2. Granitsiotis P and Kirk D: Chronic testicular pain: an overview. *Eur. Urol* 2004; 45: 430–436.
3. Levine LA and Hoeh MP: Evaluation and management of chronic scrotal content pain. C*urr. Urol. Rep*. 2015; 16: 36.
4. Sinclair AM, Miller B and Lee LK: Chronic orchialgia: consider gabapentin or nortriptyline before considering surgery. *Int. J. Urol. Off. J. Jpn. Uro. Assoc.* 2007; 14: 622–625.
5. Moubasher A, Waqar M, Raison N, et al: A Review of the Management of Chronic Scrotal *Pain. Cureus* 2020; 12: e11979.
6. Heidenreich A, Olbert P and Engelmann UH: Management of chronic testalgia by microsurgical testicular denervation. *Eur. Urol* 2002; 41: 392–397.
7. Fall M, Baranowski AP, Elneil S, et al: EAU guidelines on chronic pelvic pain. *Eur. Urol* 2010; 57: 35–48.
8. Strom KH and Levine LA: Microsurgical denervation of the spermatic cord for chronic orchialgia: long-term results from a single center. *J. Urol* 2008; 180: 949–953.
9. Oomen RJA, Witjens AC, van Wijck AJM, et al: Prospective double-blind preoperative pain clinic screening before microsurgical denervation of the spermatic cord in patients with testicular pain syndrome. *Pain* 2014; 155: 1720–1726.
10. Marconi M, Palma C, Troncoso P, et al: Microsurgical Spermatic Cord Denervation as a Treatment for Chronic Scrotal Content Pain: A Multicenter Open Label Trial. *J. Urol* 2015; 194: 1323–1327.
11. Kesch C, Schmitt V, Bidnur S, et al: A polymeric paste-drug formulation for intratumoral treatment of prostate cancer. *Prostate Cancer Prostatic Dis* 2020; 23: 324–332.
12. Schmitt V, Kesch C, Jackson JK, et al: Design and Characterization of Injectable Poly(Lactic-Co-Glycolic Acid) Pastes for Sustained and Local Drug Release. *Pharm. Res* 2020; 37: 36.
13. Nickel JC: Chronic Epididymitis: A Practical Approach to Understanding and Managing a Difficult Urologic Enigma. *Rev. Urol* 2003; 5: 209–215.
14. Rosen RC, Riley A, Wagner G, et al: The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. *Urology* 1997; 49: 822–830.
15. Woolf CJ and Doubell TP: The pathophysiology of chronic pain--increased sensitivity to low threshold A beta-fibre inputs. *Curr. Opin. Neurobiol* 1994; 4: 525–534.
16. Fayaz A, Croft P, Langford RM, et al: Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. *BMJ Open* 2016; 6: e010364.
17. Wu C and Jarvi K: Chronic Scrotal Pain. Curr. *Urol. Rep* 2018; 19: 59.
18. Agarwal MM and Elsi Sy M: Gabapentenoids in pain management in urological chronic pelvic pain syndrome: Gabapentin or pregabalin? *Neurourol. Urodyn* 2017; 36: 2028–2033.

19. Olsen MF, Bjerre E, Hansen MD, et al: Pain relief that matters to patients: systematic review of empirical studies assessing the minimum clinically important difference in acute pain. *BMC Med* 2017; 15: 35.
20. Khambati A, Lau S, Gordon A, et al: OnabotulinumtoxinA (Botox) nerve blocks provide durable pain relief for men with chronic scrotal pain: a pilot open-label trial. *J. Sex. Med* 2014; 11: 3072–3077.

Competing interests: *Drs. Gleave and Boniface are shareholders of Sustained Therapeutics Inc. Drs. Schmitt and Kesch are part of the inventor team of the technology around ST-01. The remaining authors of this study have no competing interests to declare.*

FIGURES AND TABLES

Figure 1. Subject-reported maximum numeric rating scale (NRS) pain scores at baseline, day 1, day 7, day 14, and day 28. Bars are cohort means and dots are individual subject scores.

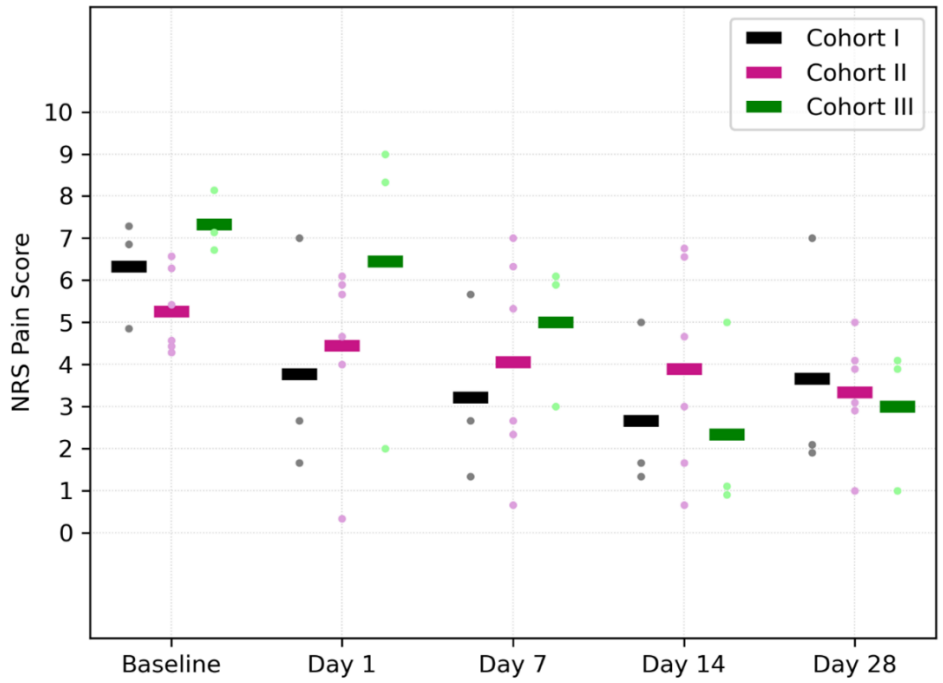

Figure 2. Pain intensity differences (PID) for cohorts I–III calculated by subtracting each subject's baseline from their reported numeric rating scale (NRS) value over time.

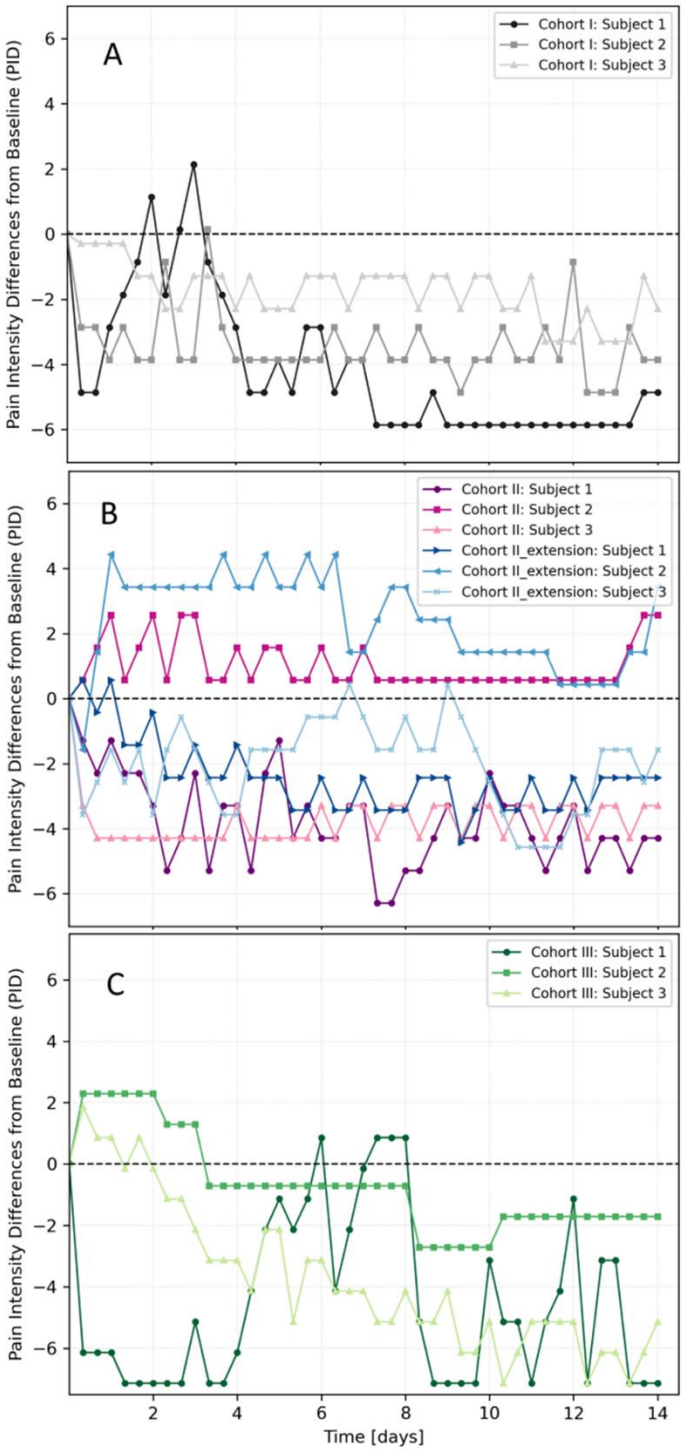

Figure 3. Time-weighted summed pain intensity differences for each subject over 14 days (SPID0-14d).

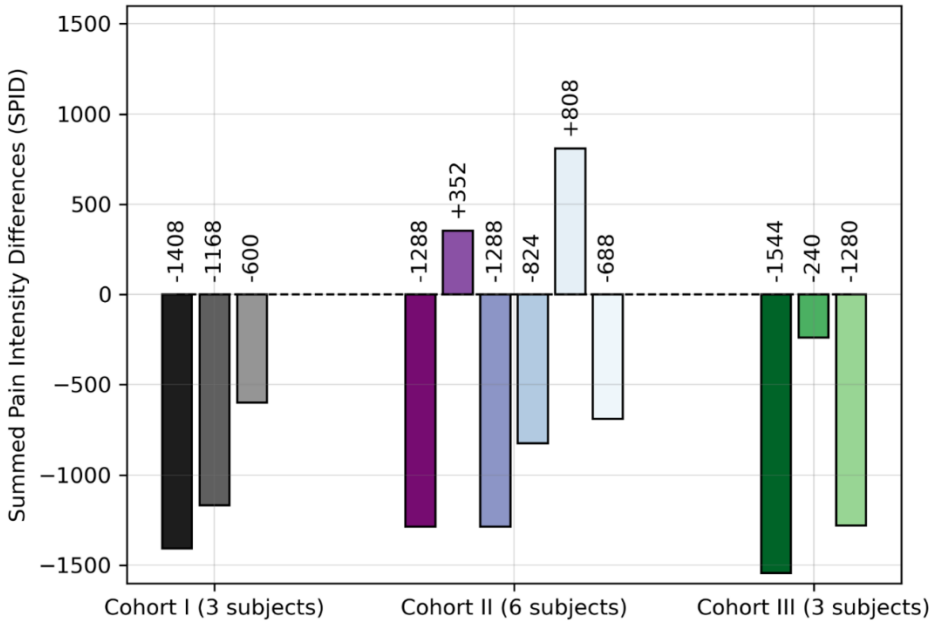

Figure 4. Mean lidocaine serum concentrations (µg/mL) after administration of ST-01 by cohort.

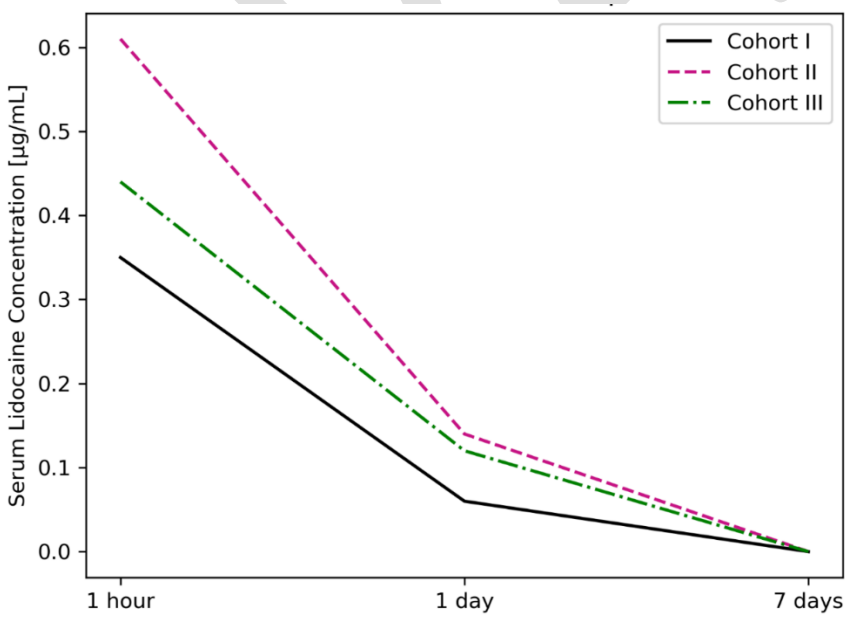

Table 1. Subject demographics and baseline scrotal pain characteristics				
Characteristic	**Cohort I**	**Cohort II**	**Cohort III**	**Total**
	n=3	**n=6**	**n=3**	**n=12**
Demographics				
Age (years)				
Mean	61.3	55.8	51.6	56
Min, max	52,68	41,75	43,55	41,75
Ethnicity				
Caucasian	3	6	2	11
Hispanic	0	0	1	1
Mean height (cm)	171	180	182	178
Mean weight (kg)	78.9	88.2	90.1	86.3
Baseline SP characteristics				
Site of pain				
Left side	2	2	2	6
Right side	1	4	1	6
Duration of pain, n				
<1 yr	0	0	0	0
1–5 yrs	1	2	2	5
>5–10 yrs	2	0	1	3
>10 yrs	0	4	0	4
Baseline NRS* score				
0–3 (no to minor pain)	3	4	3	10
4–6 (moderate pain)	0	2	0	2
7-10 (severe pain)	0	0	0	0
Patient-reported baseline NRS score				
4–6 (moderate pain)	1	3	0	4
7–10 (severe pain)	2	3	3	8
Baseline CESI scores				
Mean (range) to be adjusted by -1	22 (21–23)	18.8 (15–24)	18.3 (10–23)	19.7 (10–24)
Baseline IIEF-5 score				
22–25 (no ED)	0	2	2	4
17–21 (mild ED)	1	3	0	4
12–16 (mild to moderate ED)	1	1	0	2
8–11 (moderate ED)	0	0	1	1
5–7 (severe ED)	1	0	0	1

*After test lidocaine injection. CESI: Chronic Epididymitis Symptom Index; IIEF-5: International Index of Erectile Function; NRS: numeric rating scale.

Table 2. Subject-reported NRS scores by cohort			
Visit Parameter	**Cohort I (n=3)**	**Cohort II (n=6)**	**Cohort III (n=3)**
Baseline (day 0)			
Mean	6.3	5.3	7.3
Median	6.5	5	8
Min, max	4, 8	1, 9	5, 10
Day 1			
Mean	3.8	4.4	6.4
Median	2	5	8
Min, max	1,7	0,9	2,9
Day 7			
Mean	3.2	4.1	5
Median	3	4	6
Min, max	1, 6	0, 9	3, 8
Day 14			
Mean	2.7	3.9	2.3
Median	2	4	1
Min, Max	1, 6	0, 8	0, 5
End of study (day 28±2)			
Mean	3.7	3.3	3
Median	2	3.5	4
Min, max	2, 7	1, 5	1, 4

NRS: numeric rating scale.

Table 3. Summary of TEAEs by system organ class and preferred terms		
System organ class Preferred term	**Total (N=12)**	
	Events, n	**Subjects, n (%)**
Any event	40	12 (100%)
Injury, poisoning, and procedural complications		
Injection site reaction[1]	21	10 (83%)
Injection site bruising	6	6 (50%)
Procedural complications: Epididymitis	3	3 (25%)
Reproductive system and breast disorders		
Pain (scrotal, testicular, penile, pelvic)	6	5 (42%)
Skin and subcutaneous tissue disorders		
Hyperhidrosis	1	1 (8%)
General disorders and administration site conditions		
Chills	1	1 (8%)
Gastrointestinal disorders		
Diarrhea	1	1 (8%)
Musculoskeletal and connective tissue disorders		
Myalgia	1	1 (8%)

[1]Reported terms that were grouped as injection site reaction were: swelling, edema, induration, thickening, tenderness, erythema, redness, itching, injection site pain. TEAE: treatment-emergent adverse event.