Supplementary Table 1. Key Inclusion and Exclusion Criteria

Inclusion Criteria

• Was male or female 18 years of age or older
• Female subjects were eligible only if all of the following applied:
  ○ Was not pregnant (female subjects of child-bearing potential had to have a negative serum pregnancy test at screening and negative urine pregnancy test before surgery)
  ○ Was not lactating
  ○ Was not planning to become pregnant while participating in the study
  ○ Was surgically sterile; or was at least 2 years postmenopausal; or had a monogamous partner who was surgically sterile; or was practicing double-barrier contraception; or was practicing abstinence (had to agree to use double-barrier contraception in the event of sexual activity); or was using an insertable, injectable, transdermal, or combination oral contraceptive approved by the FDA for greater than 1 month prior to screening visits and committed to the use of an acceptable form of birth control for the duration of the study and for 30 days from completion of the study
• Male subjects had to be surgically sterile (biologically or surgically) or had to commit to the use of a reliable method of birth control for the duration of the study until at least 1 week after the administration of study medication
• Was scheduled to undergo a primary unilateral first metatarsal bunionectomy repair, without collateral procedures, under regional anesthesia
• Did not have a contralateral bunionectomy in the nonstudy foot in the past 3 months
• Had the ability and was willing to comply with the study procedures
• Was able to understand study procedures and give informed consent for the conduct for all study procedures, using an institutional review board (IRB)-approved consent form

Exclusion Criteria

- Was unwilling to sign informed consent or not willing or able to complete all study procedures
- Had a contraindication or was allergic to any medication to be used during the trial period
- Had clinically significant cardiac abnormalities that in the opinion of the investigator would pose a health risk to the subject
- Had an American Society of Anesthesiologists (ASA) Physical Status classification system category ≥4
- Had aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3× upper limit of normal (ULN) and/or creatinine >2× ULN
- Had another pre-existing painful condition that could confound pain assessments, in the opinion of the investigator
- Had another surgery planned within 30 days of the procedure
- Had a known or suspected history of alcohol or drug abuse or a positive drug screen
- Was currently taking analgesics for a chronically painful condition, had taken long-acting opioids within 3 days of surgery, or had taken any opioids within 24 hours of scheduled surgery for this study
- Had documented sleep apnea or was on home continuous positive airway pressure (CPAP)
- Was receiving oxygen therapy at the time of screening
- Had participated in a clinical trial within 30 days of planned surgery

Supplementary Table 2. Demographics of subjects in synergy analysis from the phase 2 bunionectomy study

Baseline Characteristic	**HTX-011 120 mg/3.6 mg n = 74**	**HTX-002 120 mg n = 30**	**HTX-009 3.6 mg n = 30**	**Saline placebo n = 103**
Mean age, years (SD)	49.7 (12.7)	49.3 (12.9)	49.9 (13.4)	50.4 (13.4)
Female, n (%)	61 (82.4%)	26 (86.7%)	27 (90.0)	90 (87.4%)
Mean BMI, kg/m^2 (SD)	31.10 (6.0)	30.10 (7.3)	29.2 (6.1)	30.26 (6.7)
Race, n (%)				
White	51 (68.9)	20 (66.7)	17 (56.7)	62 (60.2)
Black or African American	21 (28.4)	8 (26.7)	10 (33.3)	36 (35.0)
Asian	2 (2.7)	1 (3.3)	2 (6.7)	2 (1.9)
American Indian/Alaska Native	0	0	1 (3.3)	1 (1.0)
Other	0	1 (3.3)	0	2 (1.9)
Ethnicity, n (%)				
Hispanic or Latino, n (%)	26 (35.1)	13 (43.3)	10 (33.3)	28 (27.2)

BMI, body mass index; SD, standard deviation.

Supplementary Figure 1. Incision and administration of treatment in postoperative pain pig model