iX Biopharma Ltd

KET010 Multiple Dose Efficacy Study Results

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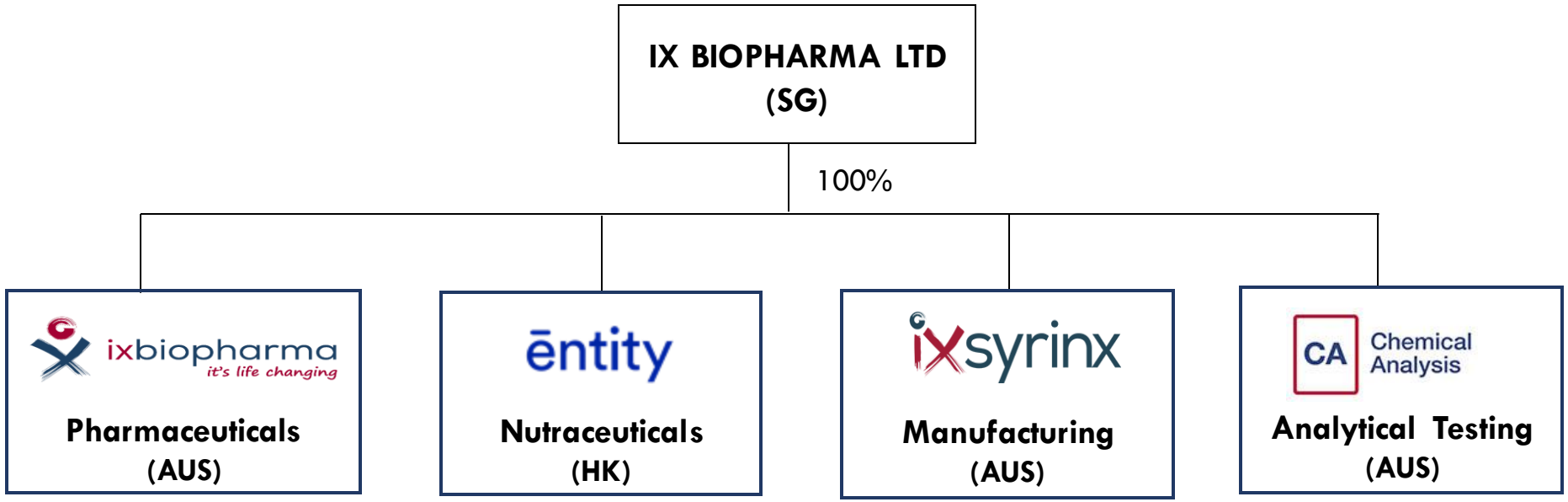
AGENDA

1. Company Overview
2. WaferiX™ Technology
3. A Painful Problem
4. Wafermine™ Development

1. COMPANY OVERVIEW

Company Profile

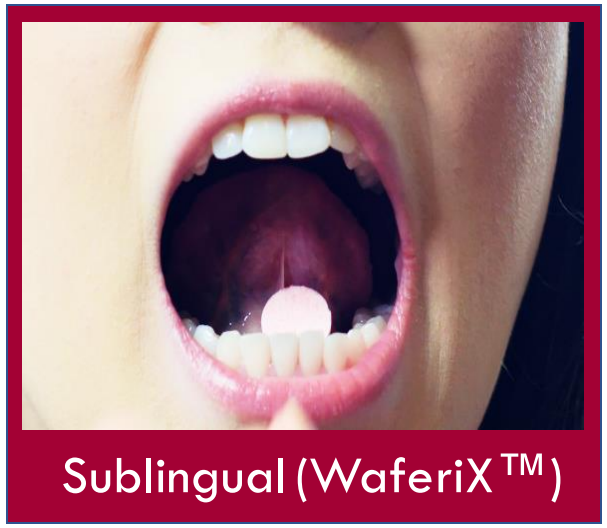
- Formed in Singapore in 2008
- Listed on SGX Catalist in July 2015
- Group has ~80 employees



2. WAFERIX™ TECHNOLOGY

WaferiX™ - iX's Drug Delivery Technology

- WaferiX™ is a novel, patented, non-invasive and fast-dissolving sublingual wafer that delivers active compounds safely via the oral mucous membrane located under the tongue



Sublingual (WaferiX™)

- ✓ Disintegrates within 1 minute
- ✓ Rapid absorption; faster therapeutic action and predictable effect
- ✓ Increased bioavailability of actives
- ✓ Convenient and easy to use

Manufacturing Process: Freeze-Dry

1. **Highly Porous Microstructure**
   - ✓ Homogeneous dispersal of active ingredient(s)
   - ✓ Enables rapid water penetration and disintegration

2. **Amorphous**
   - ✓ Non-crystalline matrix allows for rapid release of active for immediate sublingual absorption

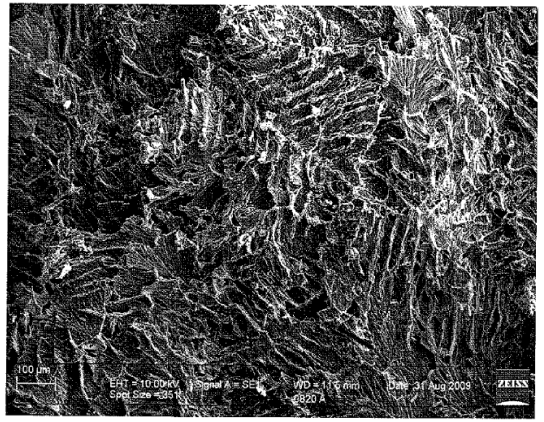


Fig 1. Scanning electron micrograph of the surface of the wafer

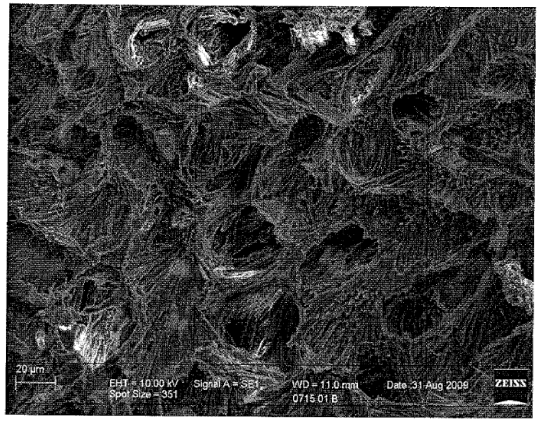


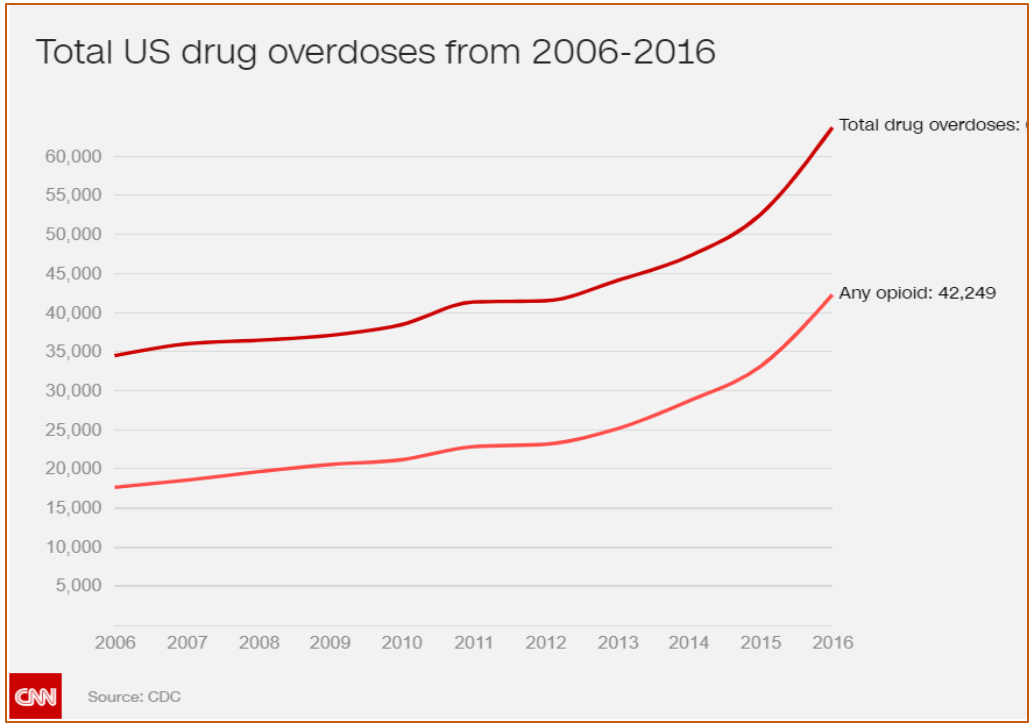
Fig 2. Scanning electron micrograph of the cross section of the matrix (WaferiX™)

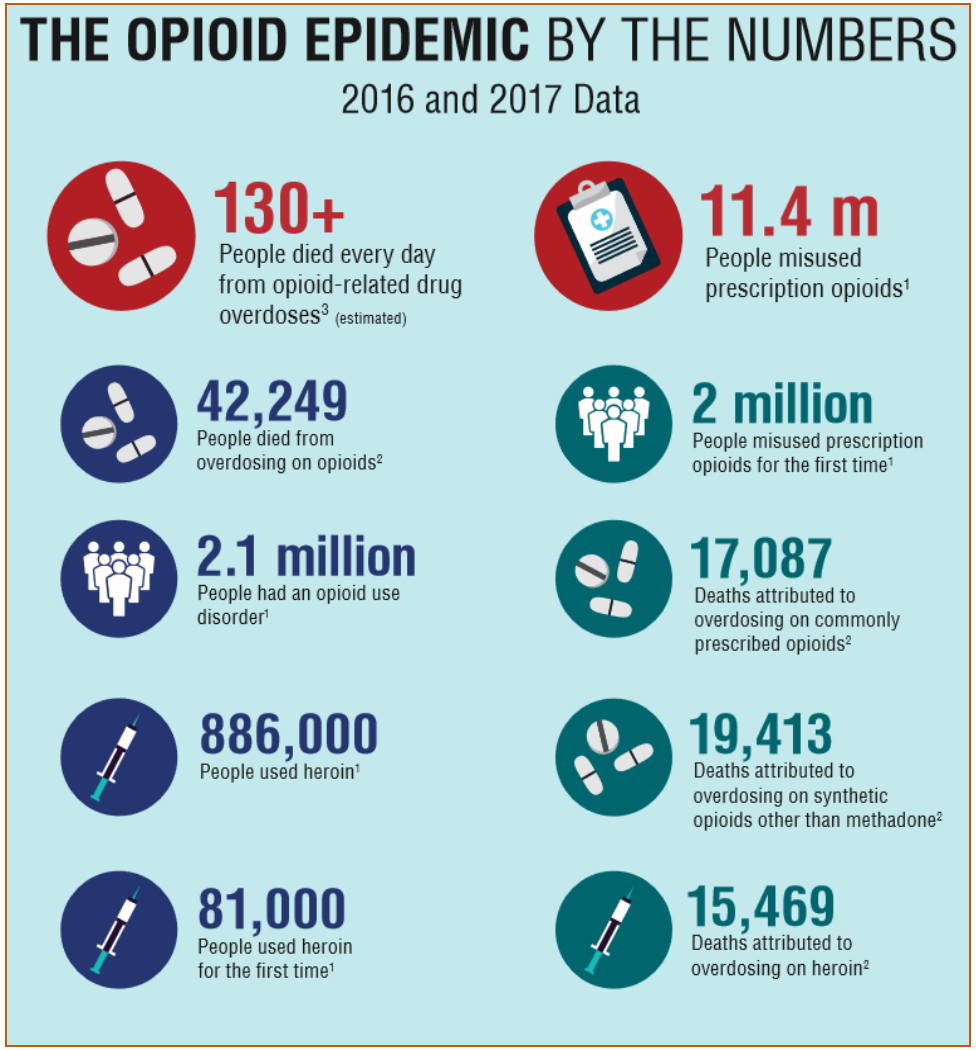
3. A PAINFUL PROBLEM

US Opioid Addiction Problem

USA in 2016:

- 42,249 deaths in the US from drug overdose
- **27,885 or 66% were caused by opioid addiction**
- Overdose from synthetic opioids have skyrocketed at an average of 88% per year since 2013





Sources: http://www.nytimes.com/2016/05/21/health/opioid-prescriptions-drop-for-first-time-in-two-decades.html?_r=0, http://static.latimes.com/oxycontin-part1/, http://www.nytimes.com/2016/03/16/health/cdc-opioid-guidelines.html, http://www.economist.com/news/international/21699363-americans-are-increasingly-addicted-opioids-meanwhile-people-poor-countries-die, American Pain Society Conference May 2016, International Narcotics Control Board (INCB statistics) http://www.asam.org/docs/default-source/advocacy/opioid-addiction-disease-facts-figures.pdf

Wafermine™ - A Non-Opioid Solution

Solution 1: IV Ketamine (NMDA antagonist)	Solution 2: WaferiX™ Technology
✓ Reduces development of acute tolerance/opioid-induced hyperalgesia ✓ Reduces postoperative pain in opioid-tolerant patients ✓ Perioperative ketamine reduces opioid consumption, time to first analgesic request and PONV compared to placebo ✓ Reduces the incidence of chronic postsurgical pain ✓ Ketamine with morphine improves analgesia and reduces sedation and PONV compared to morphine alone in postoperative patients ✓ Effective therapy for acute and chronic neuropathic pain	✓ Patented sublingual wafer technology by iX Biopharma ✓ Provides an effective non-parenteral route of administration for ketamine ✓ Fast dissolving wafer, rapid onset of action and ease of use ✓ Will broaden access to sub-anaesthetic dose ketamine for the treatment of pain and other conditions (e.g. treatment-resistant depression) ✓ Increases bioavailability and reduced variability of absorption of ketamine over oral administration

Ref: Acute Pain Management: Scientific Evidence. Australian and New Zealand College of Anaesthetists 2015

Wafermine™
(World's first sublingual ketamine wafer product)

4. WAFERMINE™ DEVELOPMENT

Wafermine™ - Sublingual Ketamine Wafer

Wafermine™: World's first sublingual ketamine wafer

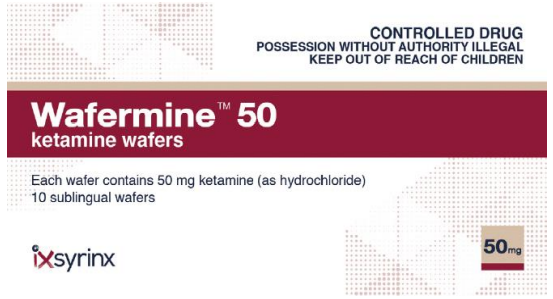
- Racemic ketamine wafer (25mg, 50mg)
- Non-opioid analgesic, non-competitive NMDA antagonist
- Target indications: Moderate to Severe Pain, Neuropathic pain

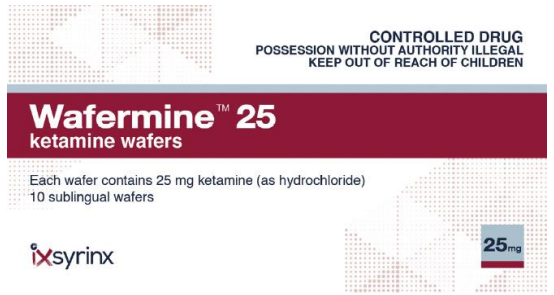
Regulatory & Development Strategy

- Developed under IND (US FDA); 505b(2) pathway
- Acute, moderate to severe pain
- Phase 2b completed 2H2018

Manufacturing

- iX Syrinx Pty Ltd- GMP licensed facility in Melbourne, Australia
- Supplied to Australian hospitals under special access scheme
  Over 100,000 wafers sold



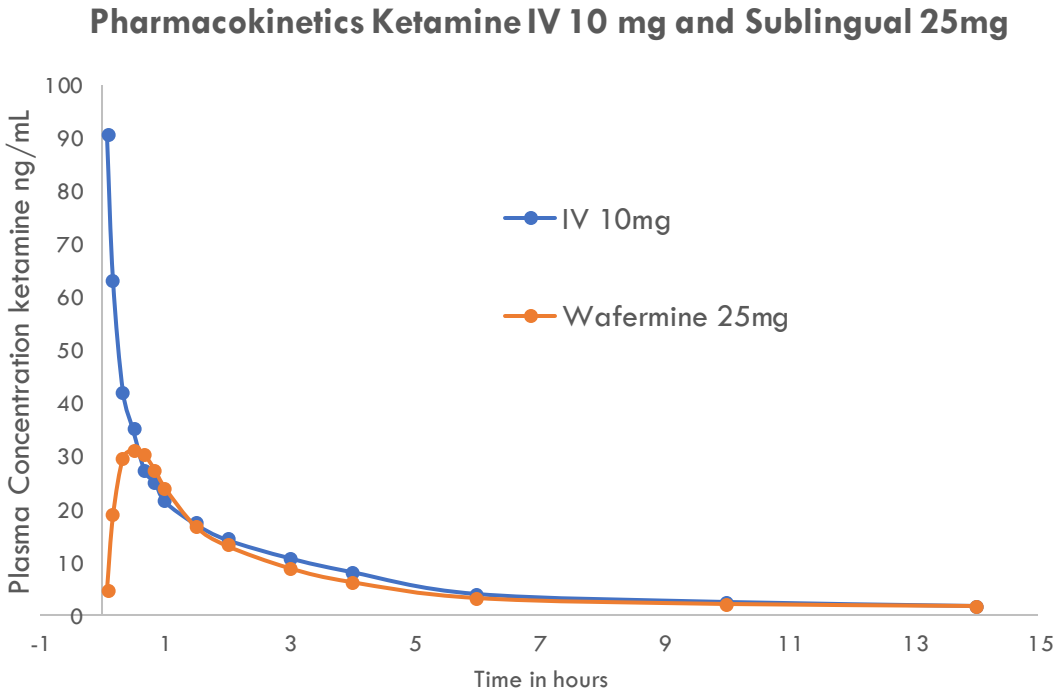


Wafermine™ - Improved Pharmacokinetics

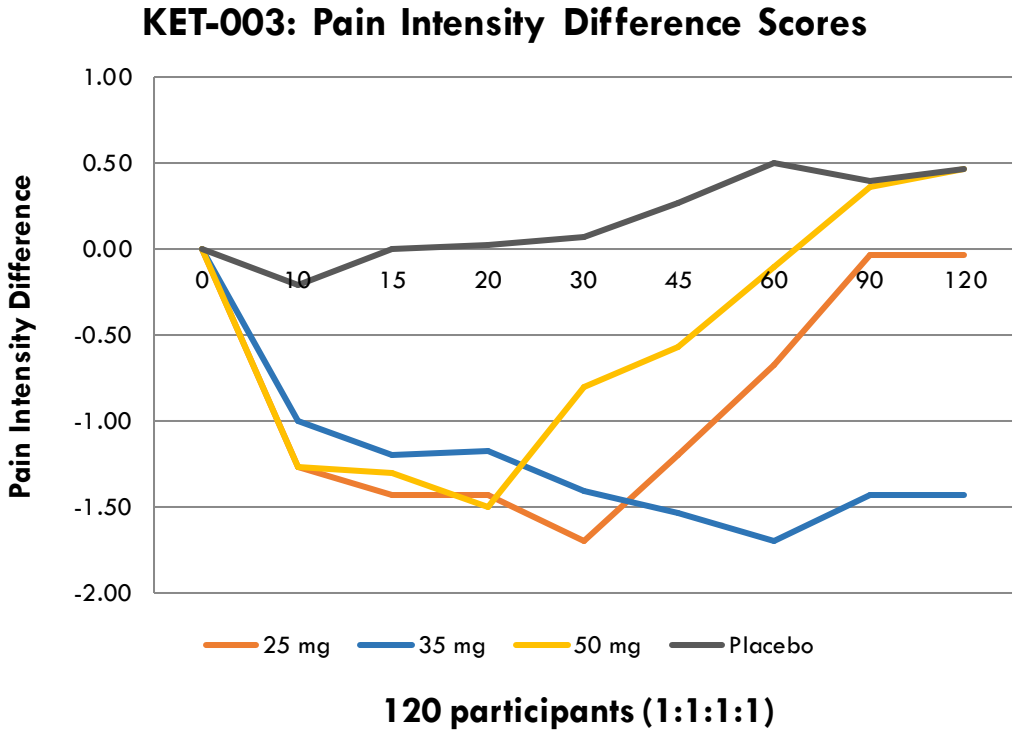
- ✓ Increased bioavailability over oral dosing (~30% vs ~15%)
- ✓ Rapid absorption- detectable ketamine in blood within 3 minutes
- ✓ Less variable absorption over oral dosing
- ✓ Avoids excessively high peak plasma concentrations compared to IV bolus dosing

Absolute Bioavailability Study

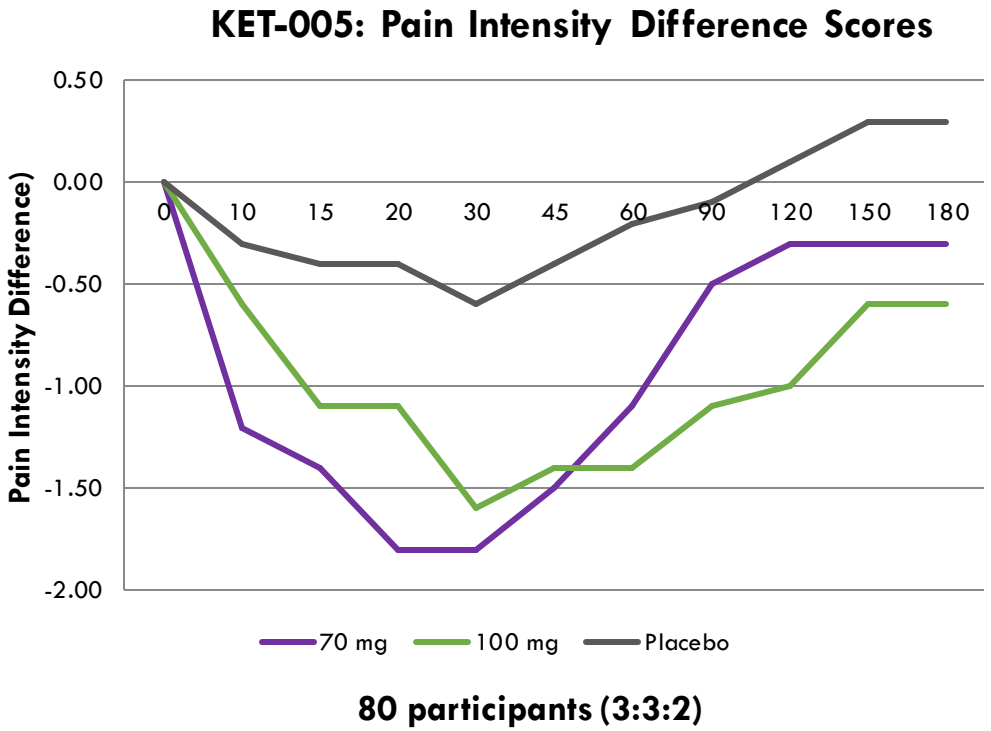
Drug	Description	Dose	Bio, F (%)	Tmax (h)	$T_{1/2}$ (h)
Wafermine	SL wafer	25mg	29	0.50	2.0



Phase 2, Single-dose, Dose-ranging Studies in Molar teeth extraction



120 participants (1:1:1:1)



80 participants (3:3:2)

- ✓ Rapid onset of analgesic action (within 10 minutes)
- ✓ Peak analgesia at 20-30 minutes
- ✓ Duration of action: ~90-120 minutes following single dose
- ✓ Safe and well tolerated - only one discontinuation across both studies.
- ✓ Dose linearity (PK) established

KET010: Multiple-dose Efficacy Study

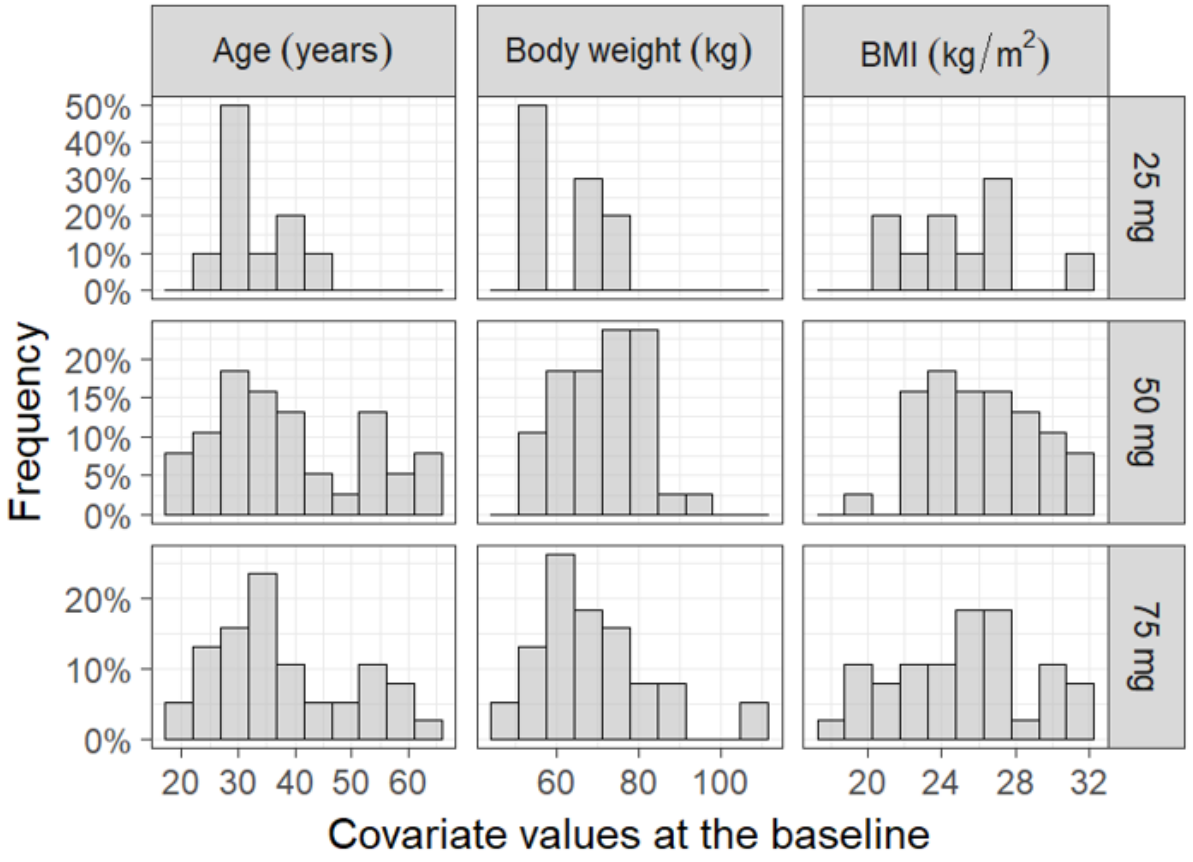
A Phase II, multiple-dose study of the efficacy and safety of Wafermine™ (Sublingual Ketamine) in participants experiencing acute post-operative bunionectomy or abdominoplasty pain

Study Overview:

- Single clinical trial site in USA. Randomised, double-blind, placebo controlled trial. 125 subjects enrolled.
- **Primary efficacy measure:** SPID12. Multiple doses administered over 12 hours.
- **Two pain models evaluated:** soft-tissue **(abdominoplasty n=40)**, bony tissue **(bunionectomy n=85)**
- Bunionectomy subjects were recruited in two parts (Bunionectomy I, n=25 and then Bunionectomy II, n=60 following a protocol amendment)
- Bunionectomy cohort: Wafermine 50mg vs Wafermine 75mg vs Placebo (1:1:1)
- Abdominoplasty cohort: Wafermine 25mg vs Wafermine 50mg vs Wafermine 75mg vs Placebo (1:1:1:1)

KET010: Demographics

- 125 subjects enrolled
- Median (range) **age** of participants:
  38yo (18 , 66)
- Subject **gender** breakdown:
  1. Female – 107 (86%)
  2. Male – 18 (14%)



KET010 Efficacy: SPID- All Bunionectomy

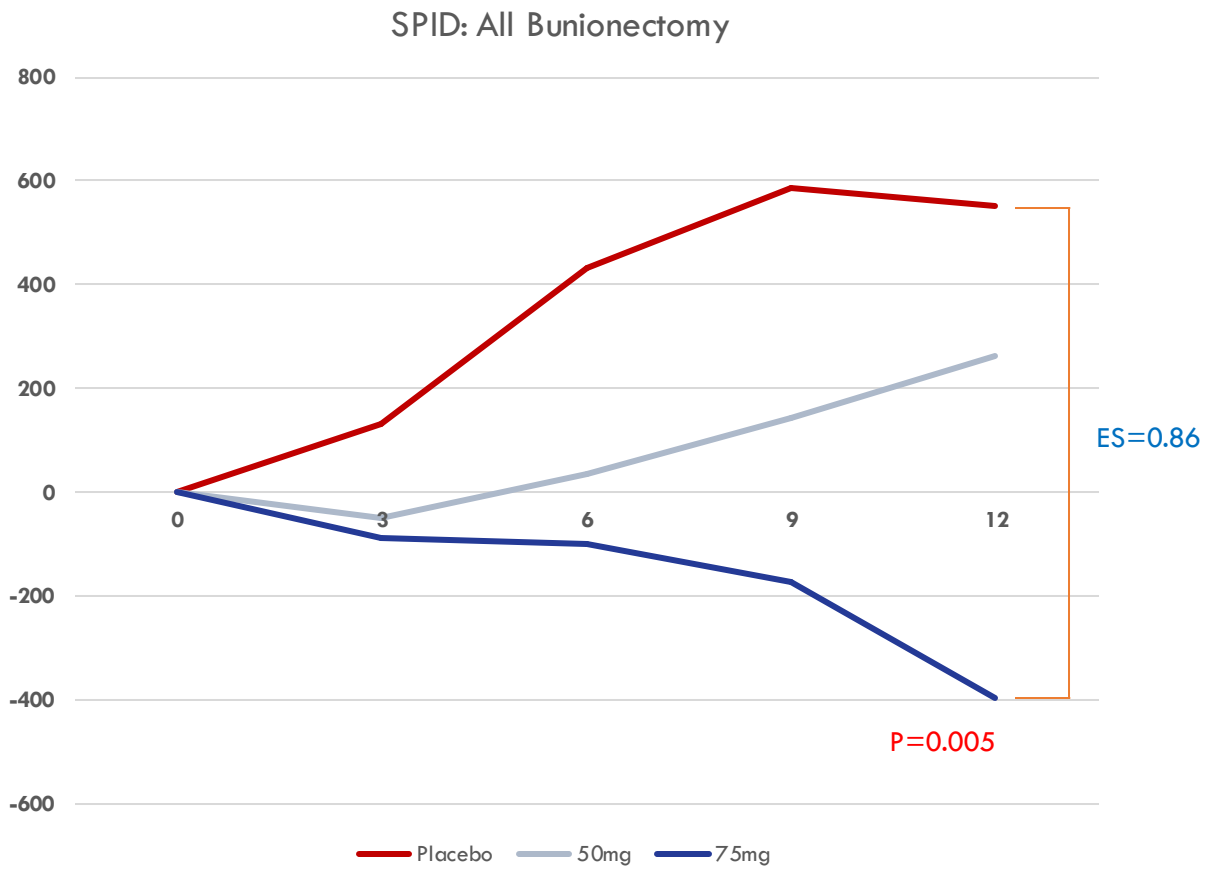
All Bunionectomy (n=85)

- **3 treatment arms:**
  placebo (n=29), 50mg (n=28), 75mg (n=28)

- **50mg group:**
  - ✓ Effect size 0.26 (low efficacy)
  - ✓ P Value 0.53

- **75mg group:**
  - ✓ Effect size 0.86 (strong efficacy)
  - ✓ P value 0.005

Effect size (ES): measure of magnitude of effect
~0.2 = low
~0.5 = moderate
~0.8 = strong



KET010 Efficacy: SPID- Bunionectomy I

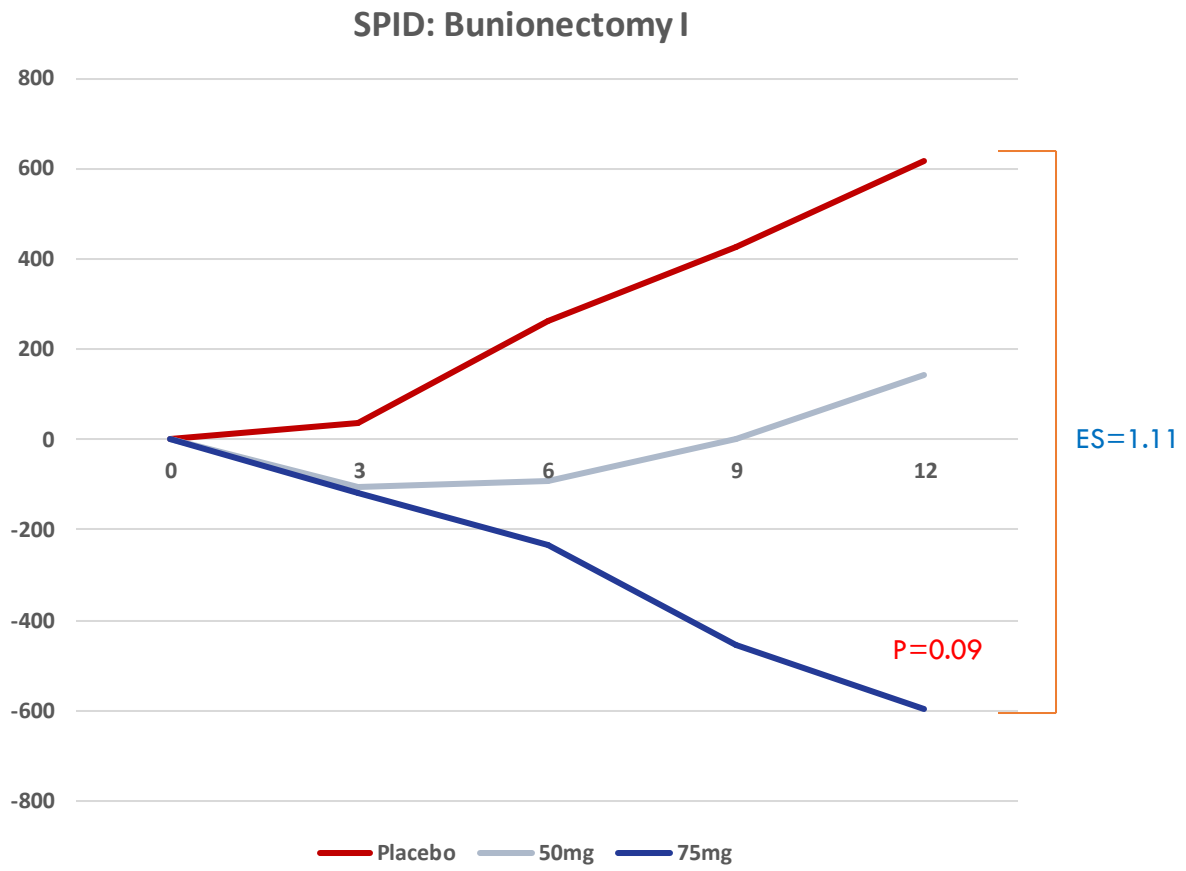
Bunionectomy I (n=25)

- **3 treatment arms:**
  placebo (n=9), 50mg (n=8), 75mg (n=8)

- **50mg group:**
  - ✓ Effect size 0.48 (moderate efficacy)
  - ✓ P value 0.63

- **75mg group:**
  - ✓ Effect size 1.11 (very strong efficacy)
  - ✓ P value 0.09

Effect size (ES): measure of magnitude of effect
~0.2 = low
~0.5 = moderate
~0.8 = strong



KET010 Efficacy: SPID- Bunionectomy II

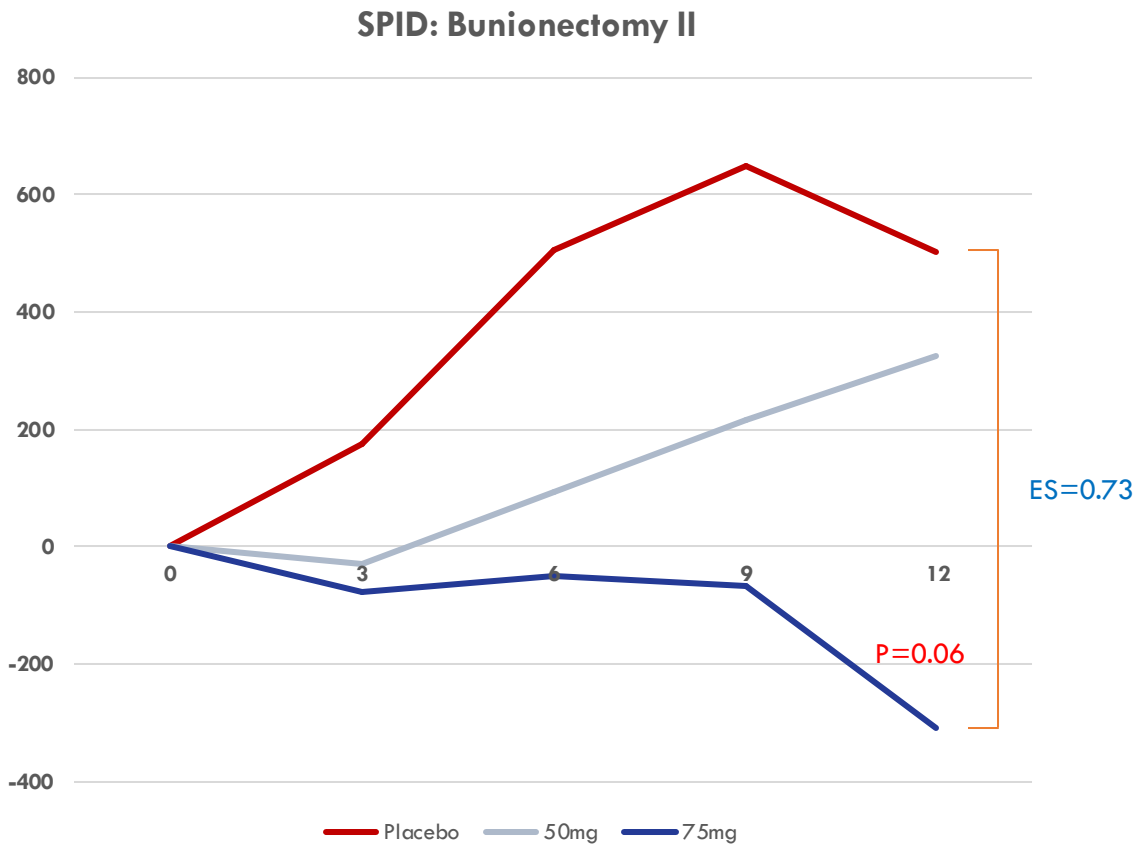
Bunionectomy Cohort (n=60)

- **3 treatment arms:**
  placebo (n=20), 50mg (n=20), 75mg (n=20)

- **50mg group:**
  - ✓ Effect size 0.17 (low efficacy)
  - ✓ P value 0.84

- **75mg group:**
  - ✓ Effect size 0.73 (strong efficacy)
  - ✓ P value =0.06
  - ✓ Sample size calculation ~ 50 subjects per arm at 90% power

Effect size (ES): measure of magnitude of effect
~0.2 = low
~0.5 = moderate
~0.8 = strong

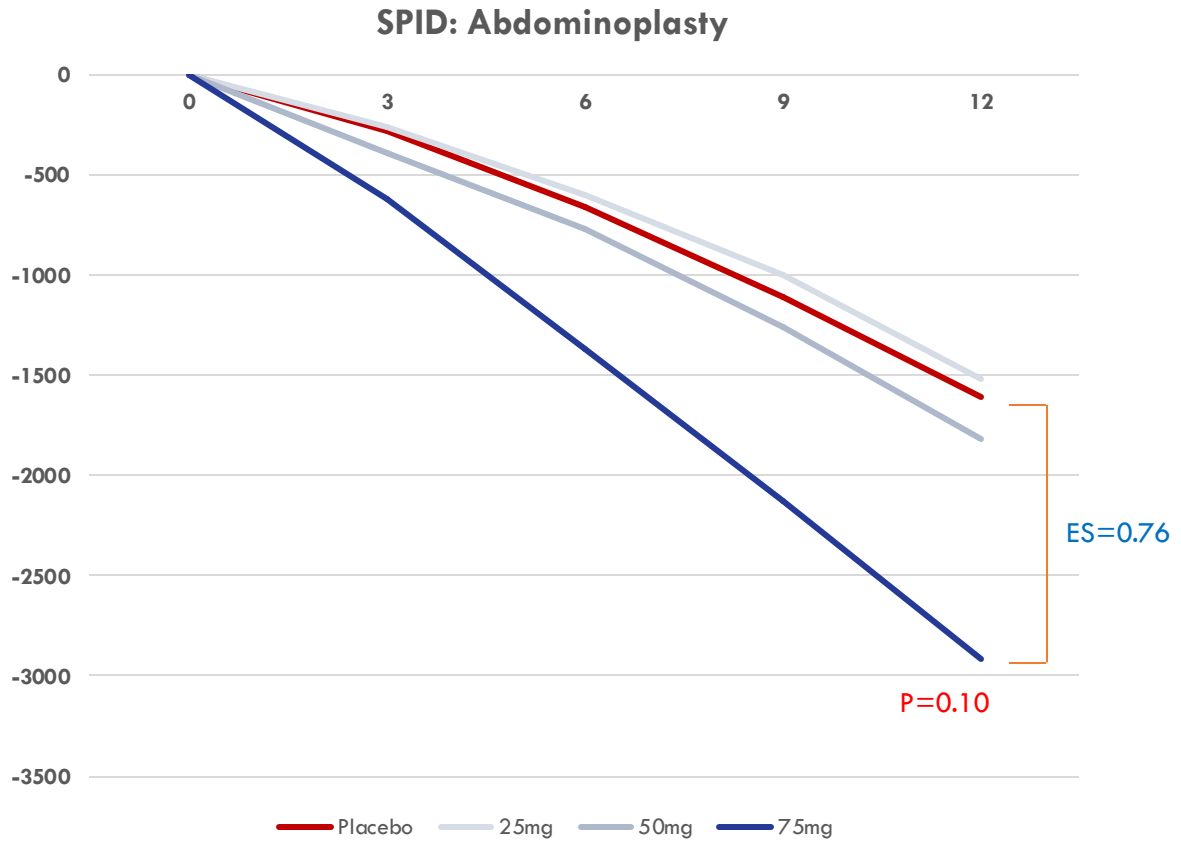


KET010 Efficacy: SPID- Abdominoplasty

Abdominoplasty Cohort (n=40)

- **4 treatment arms:**
  placebo (n=10), 25mg (10), 50mg (n=10), 75mg (n=10)
- **25mg & 50mg group**: no significant difference from placebo
- **75mg group**:
  - ✓ Effect size 0.76 (strong efficacy)
  - ✓ P Value 0.10
  - ✓ Sample size calculation ~ 40 subjects per arm at 90% power

Effect size (ES): measure of magnitude of effect
~0.2 = low
~0.5 = moderate
~0.8 = strong



KET010 Efficacy: SPID- All Subjects

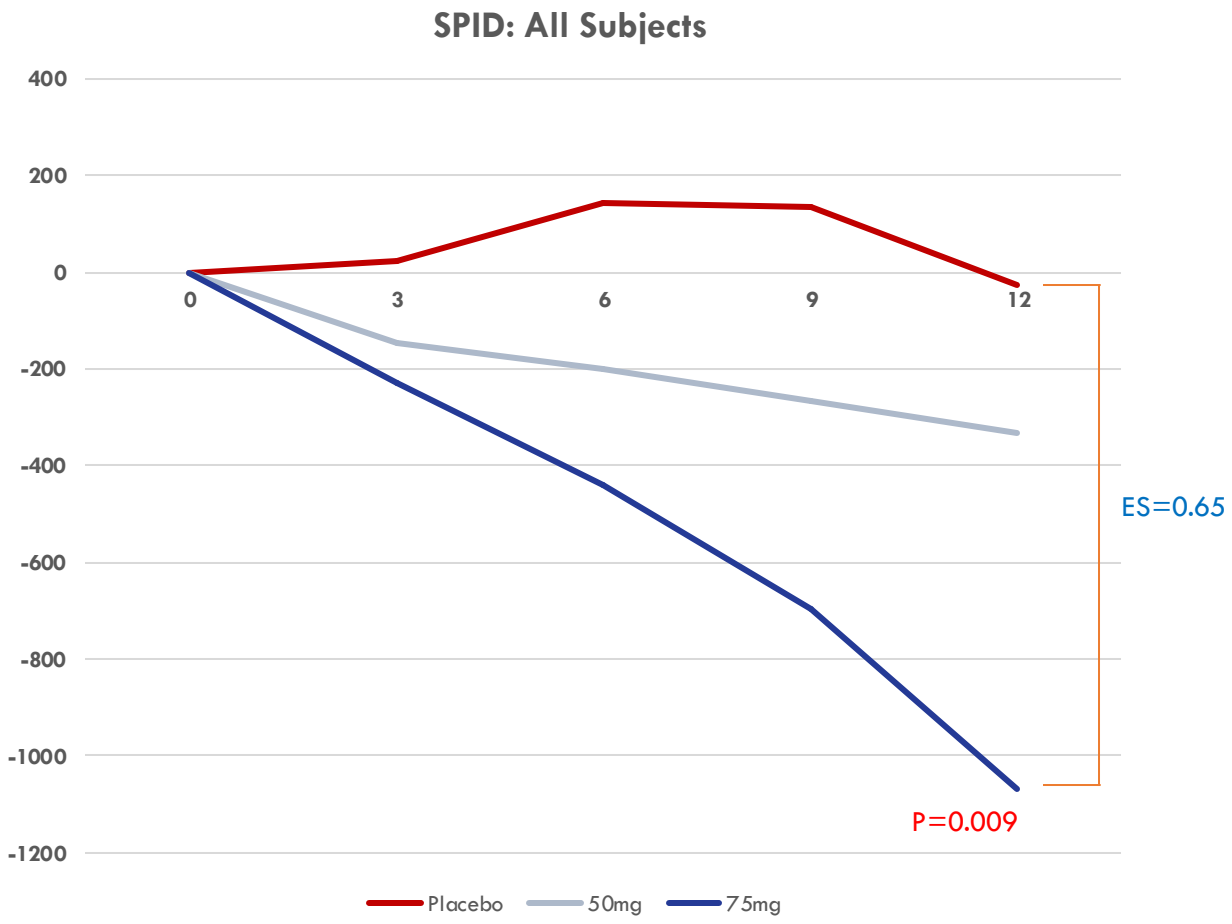
All Subjects (n=125)

- **4 treatment arms:**
  Placebo (n=39), 25mg (n=10), 50mg (n=38), 75mg (n=38)

- **50mg group:**
  - ✓ Effect size 0.13 (low efficacy)
  - ✓ P value 0.71

- **75mg group:**
  - ✓ Effect size 0.65 (moderately strong efficacy)
  - ✓ P value 0.009

Effect size (ES): measure of magnitude of effect
~0.2 = low
~0.5 = moderate
~0.8 = strong



KET010 Efficacy: Rescue Medication Usage

- Subjects in the Wafermine treatment arms were **less likely to need rescue medication** and also **used a lower number of rescue doses** than placebo

- Subjects in the **75mg groups used the lowest amount of rescue** overall (OR 0.16, p= 0.001) with **increased time to first rescue than placebo** (741 mins vs 141 mins, p=0.004)

Proportion of Subjects (N=125) Requiring Rescue

0-12hours	Placebo N =39	25mg N = 10	50mg N = 38	75mg N =38
Subjects requiring rescue medication	85%	70%	74%	47%
Odds Ratio		0.39	0.51	0.16
p-value		**0.264**	**0.251**	**0.001**

Time to First Rescue (N=125)

	Placebo N = 39	25 mg N = 10	50 mg N = 38	75 mg N = 38
Median Time (min)	141	505	257	741
Subjects requiring rescue medication	92%	90%	87%	74%
Log-rank p-value		**0.065**	**0.348**	**0.004**

KET010 Efficacy: Patient Global Assessment

All Bunionectomy (n=85)

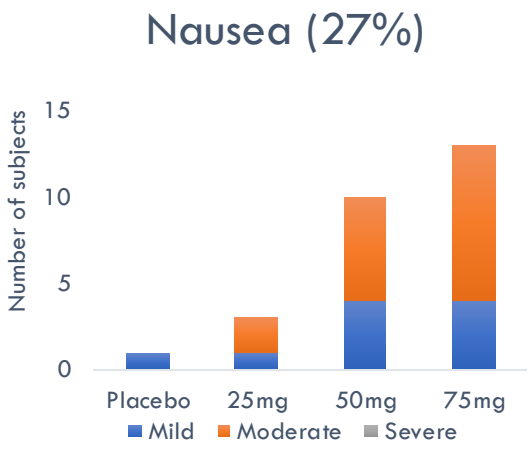
	Placebo N = 29 n (%)	50mg N = 28 n (%)	75mg N = 28 n (%)
PGA Score			
Excellent	3 (10%)	3 (11%)	3 (11%)
Good	4 (14%)	6 (21%)	6 (21%)
Fair	5 (17%)	10 (36%)	15 (54%)
Poor	17 (59%)	5 (18%)	3 (11%)
Logistic Regression			
Odds Ratio		3.83	4.17
95% C.I.		(1.36, 10.82)	(1.51, 11.48)
p-value		**0.011**	**0.006**

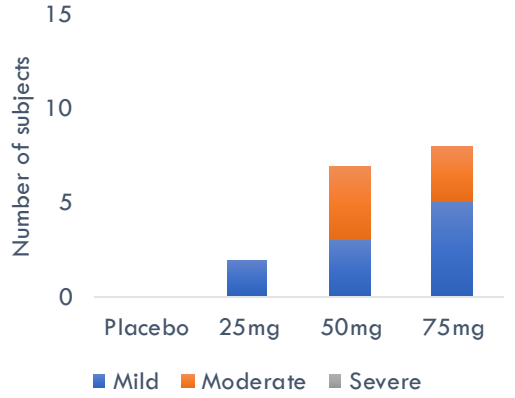
Abdominoplasty (n=40)

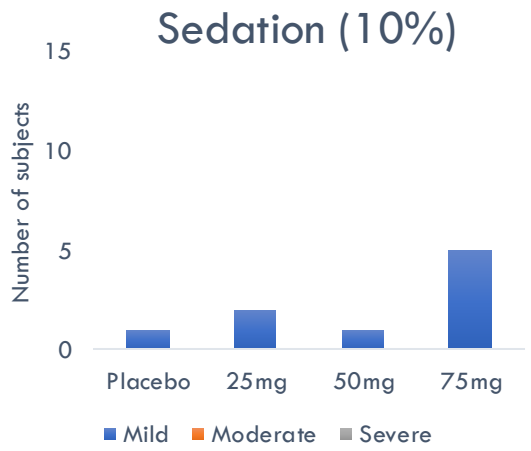
	Placebo N = 10 n (%)	25mg N = 10 n (%)	50mg N = 10 n (%)	75mg N =10 n (%)
PGA Score				
Excellent	0	3 (30%)	3 (30%)	3 (30%)
Good	4 (40%)	3 (30%)	3 (30%)	7 (70%)
Fair	4 (40%)	3 (30%)	2 (20%)	0
Poor	2 (20%)	0	1 (10%)	0
Logistic Regression				
Odds Ratio		5.64	5.06	10.88
95% C.I.		(0.93, 33.20)	(0.87, 29.47)	(1.79, 66.01)
p-value		**0.056**	**0.071**	**0.009**

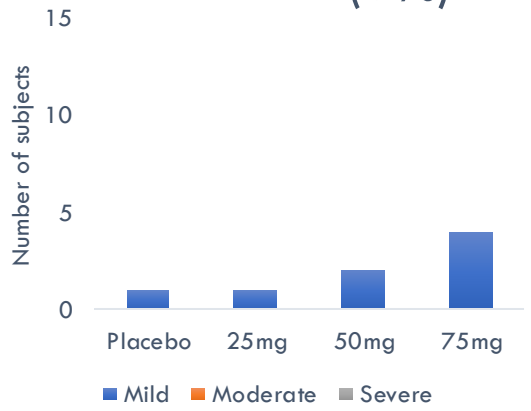
KET010 Safety: Adverse Events

- AEs observed were **consistent with the known side-effects of ketamine**
- 62% **of related AEs (n=102) were of mild severity,** 36% (n=60) were moderate severity and **only 1% (n=2) were severe**
- >70% of all related AEs had a **duration of 2 hours or less**
- Most **AEs were self-limiting** without intervention; only subjects with nausea or emesis were treated with anti-emetics
- All AEs were **resolved** at the completion of the study
- 5 subjects **discontinued** due to a AE; (50mg: dysphoria n=1, hypertension n=1, light-headedness n=1; 75mg: hypertension n=1, sedation n=1)
- There were **no Serious Adverse Events** (SAEs)



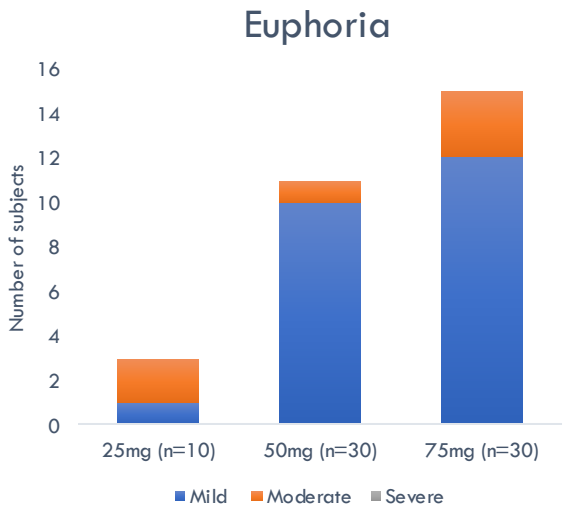


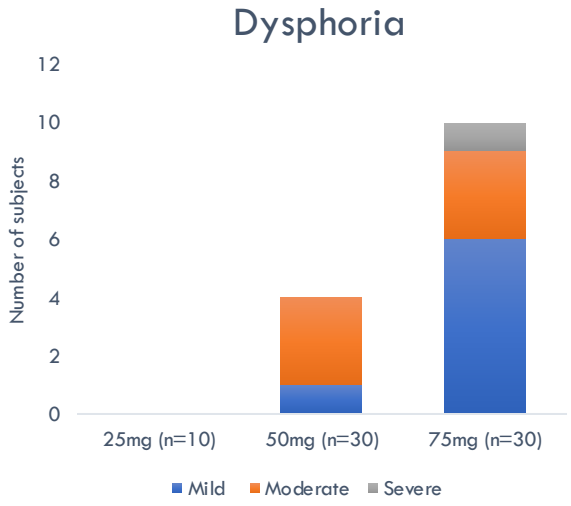




KET010 Safety: Psychotomimetic Adverse Events

- **Euphoria and Dysphoria** were the only psychotomimetic AEs observed
- Incidence of both AEs increased with increasing dose
- Most psychotomimetic AEs were of:
  - **mild severity**
  - **short duration** (mostly 1-3 hours)
  - and all **resolved spontaneously** without intervention
- Only **1 subject discontinued** the study due to a psychotomimetic AE (i.e. dysphoria in 50mg group)



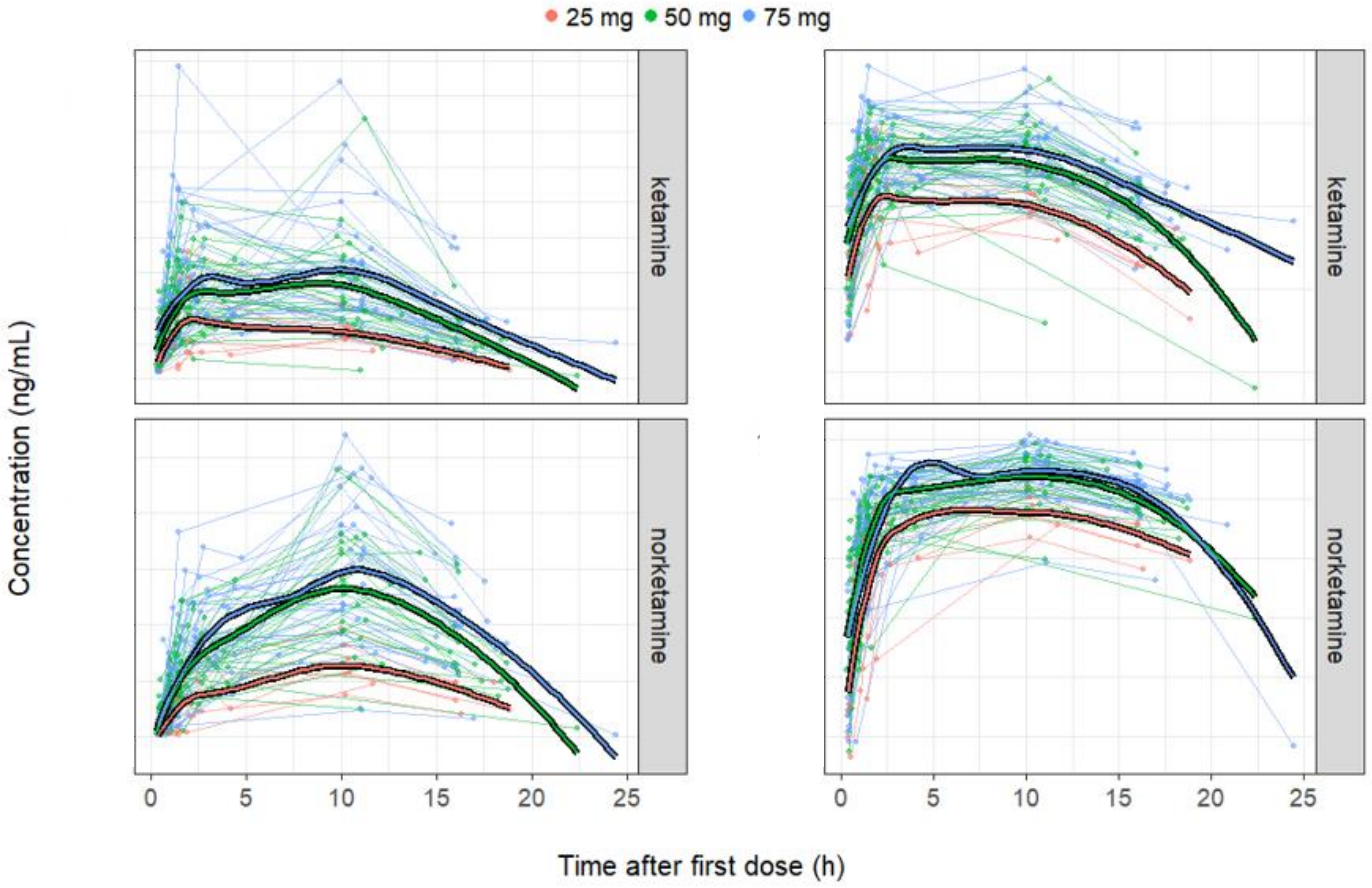


Local Tolerability & Other Safety Assessments

- **Sublingual assessment-** no inflammation and normal mucosa observed throughout the study for all subjects
- **Oral symptom questionnaire-** very well tolerated, mild transient bitter taste in mouth reported at early timepoints by a minority of subjects
- **Vital Signs-**
  - BP: 5 subjects had mild hypertension on study which spontaneously resolved. Most had pre-existing hypertension
  - Modified Wilsons Sedation Score: <10% assessed as 'drowsy' at various earlier timepoints (Wafermine > placebo subjects); 1 subject in 75mg group had severe sedation. All spontaneously resolved
  - O_2 sats/ Respiratory rate/ Temperature- no clinically significant changes
- **Laboratory bloods/ Physical Examination/ ECGs:** no clinically significant changes

KET010: Pharmacokinetic Analysis

- Dose linearity estimated following single dose model-predicted kinetics
- Higher exposure in the higher dose groups
- Higher number of doses administered in 50mg group compared to 75mg group
- Higher exposure in bunionectomy than abdominoplasty due to higher number of dose administered



Observed <u>trough</u> plasma ketamine and norketamine levels throughout 12 hour dosing period and beyond (normal/log scale)

KET010: Conclusions

- **Strong analgesic efficacy** observed with ***75mg group*** in both pain models
- **Dose response observed,** limited efficacy observed with both the 25mg and 50mg groups
- Wafermine was safe and adequately tolerated. Most **adverse events were mild,** of **short duration** and **self-limiting**
- ***75mg dose*** identified as dose to move forward with into Phase 3 analgesic clinical trials

Thank You

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