Report on preliminary results from study KET-009

Study Purpose
A multi-dose, placebo-controlled study of Wafermine™, alone and in combination with opioids in participants undergoing bunionectomy to evaluate the safety, tolerability and efficacy of three different dosing regimens of Wafermine™.

Study Population
The study included male and female participants aged 18 years or older undergoing bunionectomy.

Study Design and Conduct
The study was conducted at a single centre in the United States which has expertise in undertaking bunionectomy studies. A total of 72 participants were enrolled.

All participants were assessed for adverse events, pain scores and blood samples were taken for measurement of ketamine levels.

A summary of the dosing allocation was as follows:

Study Medication Wafer Doses	Study Medication Capsule Doses	
	Placebo q4H	Oxycodone 5 mg q4H
Placebo Wafer q2H[1]	A (n=6)	B (n=6)
Wafermine™ 35 mg q2H	C (n=12)	D (n=12)
Wafermine™35 mg q4H[2]	E (n=12)	F (n=12)
Wafermine™ 70 mg q4H	G (n=12)	None

[1] Dosing every two hours. [2] Dosing every four hours.

The maximum dose administered was 315 mg over a 14-hour period.

Safety Results
We are delighted to report that there was no serious adverse event. No participant was withdrawn by the investigator because of an adverse event, and no participant chose to withdraw because of an adverse event.

The most frequent adverse events reported were nausea, vomiting and dizziness which are common in post-operative populations. It was noted that these adverse events occurred with similar frequency in all treatment groups.

The frequency of the typical ketamine-related psychotomimetic adverse events was very low and the events were of mild severity.

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Efficacy Results
The study involved 72 participants (6 participants for the placebo group; 6 participants for the oxycodone group and 12 participants for each of 5 Wafermine™ groups) randomised to seven treatment groups.

Given the design of the study with the low number of participants included in each of the treatment groups, it was not unexpected that there was no statistically significant difference observed between the groups. However, it was observed that the Wafermine™ 70mg dose every four hours produced a lower pain score.

As commonly seen in a post-operative setting, high prevalence of dry mouth is observed and this is expected to have an impact on the disintegration of a drug delivered sublingually. As a result, the analysis of the blood levels showed that they were lower and more variable than those from the KET-001 study conducted in healthy volunteers.

The pooled results combining the three ketamine alone treatment groups showed a statistically significant correlation between increasing ketamine blood levels and a reduction in pain scores.

Conclusion
Wafermine™, given over a 14-hour period was safe and well-tolerated. There was evidence of pain reduction in those participants who absorbed the drug well. The pre-dose oral wetting procedure is being reviewed to improve the disintegration of the wafer to maximise sublingual absorption.

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Background
KET-001: a pharmacokinetic (PK) study to evaluate the bioavailability and clinical tolerability of a novel sublingual wafer formulation of ketamine in eight healthy volunteers.

KET-003 (USA FDA IND #121098): a single dose placebo-controlled dose ranging study (25mg, 35mg, 50mg) to assess the analgesic efficacy, tolerability, safety and pharmacokinetic/ pharmacodynamic properties of a sublingual wafer formulation of ketamine following third molar extraction.

KET-005 (USA FDA IND #121098): a single dose placebo-controlled dose ranging study (70mg, 100mg) to assess the analgesic efficacy, tolerability, safety and pharmacokinetic/ pharmacodynamic properties of a sublingual wafer formulation of ketamine following third molar extraction.

KET-009 (USA FDA IND #121098): a multi-dose placebo-controlled study of Wafermine™, alone and in combination with opioids in participants undergoing bunionectomy to evaluate the safety, tolerability and efficacy of three different dosing regimens of Wafermine™.