KET010: Top-line Results

Protocol Title

A Phase 2, Multiple-Dose Study of The Efficacy and Safety of Wafermine (Sublingual Ketamine) in Participants Experiencing Acute Post-Operative Bunionectomy or Abdominoplasty Pain

Aim

The principal study objective was to investigate the efficacy and safety of Wafermine when administered in multiple doses to participants experiencing moderate to severe acute, post-operative pain following either soft tissue (abdominoplasty) or bony (bunionectomy) surgery.

Methods

The study was a randomised, double-blind, placebo-controlled study in a total of 125 female and male participants aged between 18 and 75 years. 25 participants were initially enrolled into a bunionectomy cohort prior to a protocol amendment. Following the amendment, 100 participants, comprising 40 participants in an abdominoplasty cohort and 60 participants in a bunionectomy cohort, were enrolled into the study. The study was conducted under United States Food and Drug Administration (FDA) IND #121098 at Lotus Clinical Research, a premier analgesic research clinical trial facility located in Pasadena, California.

Prior to the protocol amendment, 25 participants underwent bunionectomy and were randomised to one of three treatment arms (placebo, Wafermine 50mg or Wafermine 75mg) in a 1:1:1 ratio. An interim analysis was conducted once these participants had completed the study. The data on the first 25 participants showed strong efficacy of Wafermine but also a high discontinuation rate predominantly due to inadequate rescue medication mostly in the placebo group. A protocol amendment was made to reduce the discontinuation rate, reduce the bunionectomy cohort size (given the strong efficacy signal observed) and introduce an abdominoplasty cohort to concurrently evaluate the efficacy of Wafermine in an established soft-tissue surgery model.

Participants in the abdominoplasty cohort (n=40) were randomised to one of four treatment arms (placebo, Wafermine 25mg, Wafermine 50mg or Wafermine 75mg). Meanwhile, participants in the bunionectomy cohort (n=60) were randomised to one of three treatment arms (placebo, Wafermine 50mg or Wafermine 75mg). Participants received multiple doses of either Wafermine or placebo over the following 12-hour period. All participants were assessed for pain scores, adverse events and underwent medical evaluation. Blood samples were also collected for the measurement of ketamine and norketamine levels.

Results

Efficacy

The primary efficacy measure for the study was the summed pain intensity difference over 12 hours (SPID12). The pain intensity difference (PID) is defined as the participant-reported pain score at any given hour minus the baseline participant-reported pain score. Therefore, a negative SPID indicates less pain, and a larger negative SPID indicates larger benefit.

Abdominoplasty

The Least Square Means (LS Mean) for SPID12 for placebo, Wafermine 25mg, Wafermine 50mg and Wafermine 75mg were -1609, -1516, -1819 and -2916, respectively [see Figure 1]. The Wafermine 75mg (high dose) group showed the strongest effect and separation from placebo. The standardised effect size, a comparable measure of the magnitude of a drug's effectiveness, for Wafermine 75mg, was 0.76, confirming the strong and clinically meaningful pain suppressing effect of Wafermine in this group [P value=0.10]. Based on this reported effect size, an estimated cohort size of approximately 40 participants per arm would be required to achieve a P value <0.05 with 90% statistical power.

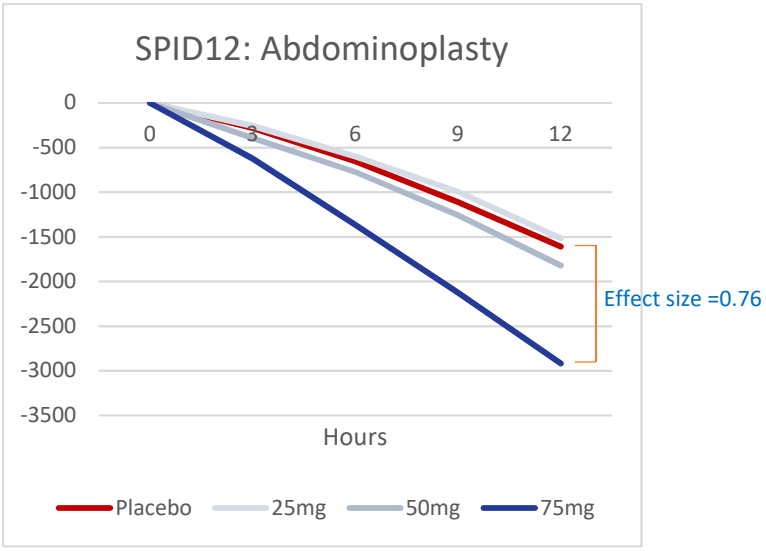

Figure 1: SPID chart (abdominoplasty cohort, n=40)

A dose response was observed, with the Wafermine 75mg group outperforming the Wafermine 50mg group, which in turn outperformed the Wafermine 25mg group. The effect size for the Wafermine 50mg group was minimal, and the Wafermine 25mg group resulted in pain scores no better than placebo.

A lower proportion of participants required rescue medication in the Wafermine 75mg group (10%) compared to placebo (40%). This is consistent with the strong analgesic effect observed in the Wafermine 75mg group.

Bunionectomy

The Least Square Means (LS Means) for SPID12 for placebo, Wafermine 50mg and Wafermine 75mg were 503, 325 and -310, respectively [see Figure 2]. Similar to the abdominoplasty cohort, the Wafermine 75mg group showed the strongest effect and separation from placebo. The standardised effect size for the Wafermine 75mg group was 0.73, confirming the strong and clinically meaningful pain suppressing effect of Wafermine in this group [P value=0.06]. Based on this reported effect size, an estimated cohort size of approximately 50 participants per arm would be required to achieve a P value <0.05 with 90% statistical power. Additionally, the Wafermine 75mg group also showed separation from placebo at SPID3 [p=0.07], SPID6 [p=0.03] and SPID9 [p=0.03].

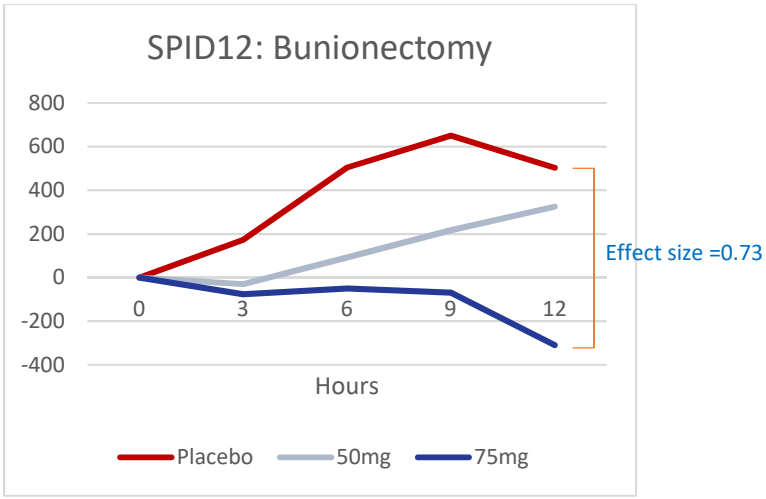

Figure 2: SPID chart (bunionectomy cohort, n=60)

A dose response was observed, with the Wafermine 75mg group outperforming the Wafermine 50mg group. The standardised effect size for the Wafermine 50mg group was 0.17, indicating low efficacy [p=0.83].

The Wafermine 75mg group had the lowest proportion of participants requiring rescue at 65% followed by Wafermine 50mg at 75%. All participants (100%) in the placebo required rescue medication. This again is consistent with the strong analgesic effect observed with the Wafermine 75mg group.

The initial 25 participants who underwent bunionectomy prior to the protocol amendment were also analysed separately. As observed with the subsequent cohorts in the revised protocol, the Wafermine 75mg group (n=8) showed strongest efficacy and separation from placebo (n=9). The standardised effect size for Wafermine 75mg was 1.11 [p value =0.09], indicating a large treatment effect. The Wafermine 50mg group (n=8) had a standardised effect size of 0.48, indicating moderate efficacy [p=0.63]. The Wafermine 75mg group also had the lowest proportion of participants requiring rescue at 50% followed by Wafermine 50mg at 88%. All participants (100%) in the placebo required rescue medication. This again is consistent with the strong analgesic effect observed with the Wafermine 75mg group.

Safety and Tolerability

Of the 100 randomised participants post protocol amendment, 89 completed all study procedures including the follow up phone visit. 11 participants discontinued from the study (3 participants in abdominoplasty cohort and 8 in the bunionectomy cohort). These included 5 participants who discontinued due to an adverse event, 4 due to lack of efficacy, 1 due to a participant decision and 1 participant was lost to follow up.

Adverse events (AEs) considered related to study drug were expected and consistent with the known side-effects of ketamine. The most common adverse events were nausea, vomiting, sedation, headache, euphoria and dysphoria. The majority of AEs were considered only of mild severity (>60%) with only 1% considered severe. Most AEs were self-limiting and of short duration (>70% less than 2 hours). All AEs were resolved at the completion of the study. There were no serious adverse events (SAEs). Euphoria and dysphoria were the only psychotomimetic symptoms observed. Most psychotomimetic AEs were of mild severity and short duration with all resolving spontaneously without intervention. Only 1 participant discontinued the study due to a psychotomimetic AE; moderate

dysphoria in a participant in the Wafermine 50mg bunionectomy group which spontaneously resolved within 50 minutes.

Of the 25 participants who were randomised prior to the protocol amendment, 12 completed all study procedures with 13 discontinuations. Of these, 8 participants discontinued due to lack of efficacy contributed to by inadequate rescue medication mostly in the placebo group whilst 5 participants discontinued due to an adverse event. All related adverse events were known potential side-effects of ketamine with the majority also being of mild severity and short duration with spontaneous resolution.

Conclusion

The Wafermine 75mg group demonstrated strong analgesic efficacy as demonstrated by the SPID12 measure in participants with moderate to severe, acute post-operative pain following both abdominoplasty (effect size 0.76, n=10, p=0.09) and bunionectomy (effect size 0.73, n=20, p=0.06) surgery. The proportion of participants requiring rescue medication was also lowest in the Wafermine 75mg group compared to placebo supporting the robust analgesic effect. Multiple administrations of Wafermine were well tolerated by participants with adverse events being anticipated and mostly of mild severity, short duration and were self-limiting.