SipNose - Topiramate: A Novel Breakthrough Approach to Binge Eating Management

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Research Article

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Abstract

**Background**: Binge eating disorder (BED) is the most common eating disorder in the United-States. Chronic, orally administered topiramate has shown BED treatment efficacy, but with two major limitations: frequent and severe side effects and slow time to action. SipNose is a novel-non-invasive-intranasal (IN) direct nose-to-brain (DNTB) drug delivery platform that delivers drugs to the central nervous system (CNS) consistently and fast. Herein, we study SipNose-topiramate combination product, as an acute "as needed" (PRN) solution for BED management.

**Methods**: First, we evaluate the innovative SipNose-topiramate's pharmacokinetics (PK) and safety. The second part aimed to demonstrate SipNose-topiramate's PRN-treatment efficacy in reducing the number of binge-eating episodes in 12-BED patients (2-weeks of baseline monitoring [BL], 8-weeks of treatment [TX], 2-weeks of follow up [FU]).

In this part 251 treatments were used by the 12 BED patients participated in the study.

**Results**: The PK profile showed peak plasma levels at 90 minutes post-administration, and a t1/2 > 24hr, and demonstrated consistent topiramate delivery with no AE. In the second part, mean weekly binge events (WBE) and binge event days per week (DPW) showed a significant reduction from baseline to treatment period that was maintained in follow up period. Efficacy was corroborated by improved patient illness severity scales. There were no adverse events during all administered treatments. Patients were exposed to less drug when compared with accepted oral dosing.

**Conclusions**: This study introduces the novel SipNose-topiramate drug-device combination as a safe, effective, and controlled method for BED management. Its findings represent a breakthrough approach to BED management both as an intranasal and "as needed" therapy for reducing binge eating episodes with a large-scale reduction in patient drug exposure and thus side effects and with improved patient quality of life. Further studies are needed with larger patient populations to establish SipNose-topiramate as a mainstream treatment for BED.

**Trial registration**: Registration number and date of registration of the clinical studies reported in this article are as follows: 0157-18-HMO, August 15th 2018 and 6814-20-SMC, December 2nd 2020.

**Summery**

Binge eating disorder (BED) is a common eating disorder. Chronic, oral topiramate treatment has shown efficacy in clinical studies and off-label use, with frequent and severe side effects. SipNose is a novel, rapid and consistent direct nose-to-brain drug delivery platform. This study evaluates a SipNose-topiramate combination product, as an innovative acute "as needed" (PRN) BED treatment solution.

SipNose-topiramate's pharmacokinetics (PK) and safety demonstrated consistent and dose-dependent topiramate delivery with no adverse events.

The evaluation of SipNose-topiramate's PRN-treatment efficacy in reducing the number of eating binges in 12 BED patients was studied (2-weeks baseline monitoring, 8-weeks treatment, 2-weeks follow-up). Patients were instructed to self-administer the drug when they feel an urge to binge. 251 treatments were used with lower doses when compared with chronic oral dosing, with no adverse events and minimal side effects. Mean weekly binge events and binge event days-per-week showed significant reduction from baseline to treatment periods, that was maintained during follow-up. Improved illness severity scales corroborated the improved efficacy.

In conclusion, this study introduces SipNose-topiramate as a novel, breakthrough intranasal, "as needed" BED treatment that is safe, effective, and reduces drug exposure and side effects. Additional studies are needed to validate SipNose-topiramate as a BED treatment.

**Background**

Binge eating disorder (BED) is defined under DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) as "recurrent uncontrolled and distressing episodes of binge eating".¹ "An episode of binge eating, is characterized by eating, in a discrete period of
time, an amount of food larger than most people would eat in a similar period, under similar circumstances, and with a sense of lack of control over eating during the episode.\textsuperscript{14} Most binge episodes develop following an overwhelming urge to binge. The lifetime prevalence of BED in the general population of the United States is conservatively estimated to be 3\%, making it the most common eating disorder in the US, more common than anorexia nervosa and bulimia nervosa combined\textsuperscript{2−4}.

Current treatment options for BED include both psychotherapy and pharmacotherapy. To date, only one drug has been approved for this indication by the FDA, Lisdexamfetamine (Vyvanse\textsuperscript{®}) by Takeda Pharmaceutical Company Limited, is the only FDA approved medication for treating BED.\textsuperscript{17} Despite its reported efficacy, patients are exposed to variety of unwanted side effects including the major risk of abuse that may lead to dependence. In a recent study, Dasotraline, a dopamine and norepinephrine reuptake inhibitor (DNRI) demonstrated benefit in reducing binge behavior.\textsuperscript{16} However, its development program was discontinued, due to regulatory hurdles.

Topiramate, an anti-seizure medication (ASM), has demonstrated clinical efficacy in treating BED.\textsuperscript{2,18} Its use has been limited primarily due to negative neurological and cognitive side effects.\textsuperscript{2,18} Thus, there remains a great medical need for better tolerated BED treatments.

Several lines of evidence support topiramate as a potential candidate for effective BED treatment if its side effects could be minimized. Firstly, three randomized control trials have demonstrated topiramate’s treatment efficacy in individuals with BED.\textsuperscript{5,18,19} Secondly, topiramate has shown efficacy in reducing binge-eating behavior in individuals with bulimia nervosa.\textsuperscript{20} Lastly, topiramate is widely used off-label for weight loss\textsuperscript{21,22} (including in BED patients with obesity) and has been approved by the FDA for long-term weight loss treatment when used in combination with phentermine, in the commercial drug Qsymia.\textsuperscript{23} In all the above examples, oral administration was used as a chronic treatment.

Currently, marketed dosage forms of topiramate are based on chronic daily consumption of oral capsules/tablets. Oral delivery of therapeutics, although acceptable and effective, usually has two major limitations. Firstly, achieving therapeutic topiramate concentrations in the brain requires relatively high systemic levels, and in turn, high systemic dosing. Unfortunately, the chronic use of orally administered topiramate is associated with frequent and severe side effects, including paresthesia, speech disorders, fatigue, dizziness, somnolence, nervousness, psychomotor slowing, abnormal vision and fever.\textsuperscript{24} These dose dependent and reversible adverse events/side effects occur in more than 10 percent of patients, and preclude many patients from its continued use.\textsuperscript{24} Furthermore, the necessary high systemic doses increase side effect frequency and severity. Secondly, oral administration results in slow drug delivery to the brain and delayed time to affect. To date, there is no practical market-ready product that can offer an alternative drug delivery method to overcome those limitations.\textsuperscript{25}

Intranasal (IN) delivery is a drug delivery route utilized in various therapeutic areas including CNS therapies.\textsuperscript{26,27} All currently commercially available intra-nasal drug-delivery devices deliver aerosol for systemic distribution via nasal mucosa absorption into the blood. Although nasal delivery has its advantages, such as avoiding the hepatic first-pass effect, like the oral route, the drug needs to reach high systemic levels in order to cross the blood-brain-barrier and achieve steady therapeutic brain tissue concentrations. As such, they maintain comparable limitations to the oral route. SipNose is a novel non-invasive direct nose-to-brain (DNTB) drug delivery platform that delivers drugs to the central nervous system (CNS)\textsuperscript{41} (see Fig. 1). In a recent study, Kobo-Greenhut, et al. highlight the qualitative clinical advantages of an intranasal method for direct drug-to-brain delivery, such as the SipNose non-invasive DNTB delivery platform.\textsuperscript{41}

Herein, we present a novel drug-device combination product of topiramate drug delivery via the SipNose non-invasive DNTB platform, as a new approach for treating BED patients. This drug-device combination product aims to provide an effective acute treatment on an "as needed" (PRN) basis, for stopping binge urge deterioration to binge and offers a potential solution for the limitations presented by chronic systemic delivery approaches.

The study is designed in two parts. The first aims to evaluate the SipNose-topiramate combination product’s safety and pharmacokinetics (PK). The second part aims to demonstrate its efficacy as a PRN treatment for reducing binge eating episodes in BED patients. The physiologic rationale underlying this drug-device combination takes advantage of SipNose's ability to rapidly deliver the topiramate from the upper nasal cavity directly to the brain. These two properties of rapid and direct brain delivery are anticipated to provide acute treatment to reduce/stop a binge from developing at its very early stages. Furthermore, ostensibly, PRN
direct nose to brain treatment should diminish adverse event frequency and severity reduces the required topiramate dose, and eliminates chronic steady state drug exposure, thereby diminishing adverse events. Overall, SipNose-topiramate product is studied vis-à-vis its ability to offer a new route for topiramate administration along with a novel "as needed" intra-nasal topiramate treatment protocol for BED patients.

**Method**

**Study design**

Both study parts were designed to be a single center, open label study, established by trained study staff.

**Part I**

*Setting* - Part I took place in the Hadassah Medical Center, Jerusalem, Israel, during the period September 2018- March 2019.

*Participants* - Part I participants included 8 healthy volunteers in total. Each subject participated in 3 study cohorts. Inclusion and exclusion criteria can be seen in the supplementary data.

*Design* – Part I studied the drug’s safety profile. Drug safety was evaluated based on routine laboratory evaluations (i.e., biochemistry, complete blood count, coagulation studies, blood pH and urine analysis), adverse events and side effects. Adverse events were defined as unexpected medical reactions. PK evaluation was derived from plasma topiramate concentrations in samples obtained prior to and 10, 30, 60, 90, 120, 180, 360, 540 minutes and 24 hours following topiramate administration.

Participants in Part I were studied in three separate time periods as 3 study cohorts. The time interval between successive cohorts was at least 7 days.

- Cohort #1: Participants were administered 30 mg IN topiramate, 15 mg in each nostril.
- Cohort #2: Participants were administered 60 mg IN topiramate, 30 mg in each nostril.
- Cohort #3: Participants were administered repeated doses. The size of each dose, total number of doses per day and time interval between consecutive doses was set by the Safety Monitoring Committee based on the safety and pharmacokinetic data obtained from Cohorts 1 and 2 (or PK data from Cohort 2 only).

The repeated doses were as follows:

Dose 1: 30 mg in each nostril (cumulative dose 60 mg)

Dose 2: 30 mg in each nostril 60 minutes following dose 1 (cumulative dose 120 mg)

Dose 3: 30 mg in each nostril 300 minutes following dose 2 (cumulative dose 180 mg)

**Variables**

- Adverse events and side effects were evaluated based on safety monitoring, physical examination, blood biochemistry, CBC, coagulation test and blood pH, Urine analysis, pregnancy declaration/test; ECG.
- Pharmacokinetics were evaluated, including dose response relationship between cohorts #1 and #2; and cumulative dose response in cohort #3.

**Part II**

*Setting* - Part II was performed via the Department of Eating Disorders at Sheba Medical Center, Tel HaShomer, Israel, between December 2020 - November 2021. This was a 12-week study in which BED patients self-administered the treatment at home on an "as needed" basis.

*Participants* - The study contained 12 BED patients who had met DSM-5 moderate-severe BED criteria for 6 months, at minimum, prior to the study. Inclusion and exclusion criteria can be seen in the supplementary data. Fourteen patients were enrolled in the study, 12
of whom participated fully. Two patients left the study for personal reasons, unrelated to study participation. The Eating Disorder Examination (EDE) questionnaire\(^{38}\) was used to validate the BED diagnosis in all participants.

**Design** – Enrolled BED patients participated in three study phases.

**Study phases:**

- **Baseline Phase:** This phase lasted 2 weeks, during which data was collected about each patient's baseline binge eating behavior characteristics. Patients were requested to maintain diaries and report on each binge-urge and/or binge they experienced. The research team collected baseline data and evaluated the patients' suitability for study enrollment according to entrance criteria. Visit content can be seen in the supplementary data.

- **Treatment Phase:** This Phase lasted 8-weeks, during which patients self-treated with the SipNose-Topiramate product. Patients were instructed to take an intranasal topiramate dose, whenever they felt an urge to binge or during early binge stages if the binge occurred without sensing a preceding urge, or if they did not self-treat during the urge period. Patients self-administered a 60mg topiramate dose and waited 10 minutes. If after 10 minutes the first dose was self-assessed as ineffective, patients self-administered either another single 60mg dose (total dose 120 mg) or two 60mg doses (total dose 180 mg). Patients were requested to maintain daily diaries of their urges and binges; which urges/binges were treated, doses administered, and whether the treatment was helpful. The treatment phase included follow up visits and an end-of-treatment visit. Visit content can be seen in the supplementary data.

- **Follow-up Phase:** This phase lasted 2-weeks, was treatment-free and involved data collection via patient follow-up visits regarding binge eating behavior; urges and binges. Data was also collected in search of late-onset and negative treatment withdrawal effects. Visit content can be seen in the supplementary data.

All phases involved face-to-face and remote (due to COVID-19 limitations) psychiatric therapy visits.

At study commencement and conclusion, every patient in Part II underwent a psychological and physical physician examination and laboratory testing.

During the three study phases, patients filled daily electronic diaries, and participated in weekly meetings, in which control reports were filled by a clinical dietitian.

**Variables**

The following variables were evaluated in Part II.

- Number of binge and urge events, as well as the number of days in which binge events and urge events occurred. Binge events were selected as the primary variable reflecting BED severity. Control variables included the weekly number of urge events, as well as the number of days in which an urge event occurred. Treatment effect was assessed based on the change in these variables before (baseline phase), during (treatment phase) and after (follow-up phase) treatment.

- **Patient Severity of Illness and Post-treatment Condition Scoring:** Patient baseline severity of illness and post-treatment condition were evaluated through a number of clinical scales\(^{39,40}\).

  - The Clinical Global Impression – Severity (CGI-S) is a 7-point scale that is used by the clinician to describe patient severity of illness. It is a general scale used for a variety of psychiatric conditions and is not specific to BED. The scale ranges from 1 = normal, 2 = borderline ill, 3 = mildly ill, 4 = moderately ill, 5 = markedly ill, 6 = severely ill and 7 = among the most extremely ill patients.

  - The Yale-Brown Obsessive Compulsive Scale Modified for the Assessment of Binge Eating (YBOCS-BE)\(^{35}\) is a clinician-rated BED specific scale that measures the degree of obsessive and compulsive binge eating behaviors. Total scores range from 0 to 40. A score of 0–7 is sub-clinical, 8–15 is mild, 16–23 is moderate, 24–31 is severe and 32–40 is extreme.

  High YBOCS-BE total and subscale scores represent greater severity of illness

- Adverse events and side effects.
The following were obtained for safety monitoring: physical examination (including an ear, nose and throat (ENT) exam); vital signs (blood pressure, pulse rate, and temperature); blood laboratory tests (biochemistry and CBC), and urine toxicology (cannabinoids screen, benzodiazepine screen, amphetamine screen, methadone metabolite).

**Statistical analysis**

Statistical analysis of data obtained from the diaries, was established using SAS Version 9.4. Changes in variables, including the number and proportion of binges and urges in each study phase, were assessed by the Wilcoxon Rank Sum statistic. For CGIS and YBOCS scales, the Wilcoxon Rank Sum statistic was used to test the change from baseline for each subject, for every week of the study. Statistical significance was determined if a p-value was less than 0.05.

**Results**

**Part I:**

**Pk Evaluation (See Fig.)**

A linear dose response relationship was demonstrated between cohorts #1 (30 mg) and #2 (60 mg), with a factor of two between cohorts. By 90 minutes post-administration, cohorts #1 and #2 achieved an average topiramate plasma concentration of 0.16 µg/ml and 0.3 µg/ml, respectively. These plasma levels were maintained up to 540 minutes after administration. In cohort #3 concentration levels demonstrated a cumulative dose response relationship with an additive increase in concentrations, and achieved a peak average level of 2 µg/ml.

By 24 hours plasma levels showed a decline in all three cohorts, though remained near peak levels.

**Adverse Events And Side Effects**

There were no adverse events during all 38 administrations in Part 1. There were no significant changes in clinical laboratory tests following SipNose-topiramate administration. General physical and nasal mucosa examinations were normal in all subjects in all cohorts.

One side effect was reported in cohort #1: sore throat (12.5%), which is known topiramate related side effects and do not necessarily result from the combination product.

Two side effects were reported in cohort #2: headache (12.5%) and runny nose (12.5%).

Eleven side effects were reported in cohort #3, in which the highest dose, 180mg was given: dizziness (9.09%), heaviness (4.54%), mood changes (4.54%), tiredness (4.54%), headache (4.54%), flu-like symptoms (4.54%), impaired ability to concentrate (4.54%), blurred vision (4.54%), diarrhea (4.54%), lack of appetite (4.54%).

**Part II:**

Number of individual binge or urge events, as well as the number of days in which binge or urge events occurred were collected from patient diaries. Table 1: Tally of Binges and Urges to Binge presents the Number of binges, binge urges, mean number of binges per week, mean number of binge event days per week, mean number of binge urges per week and mean number of binge urge days per week. During the three phases there were a total of 135 binges and 71 urges in the two-week baseline phase, 199 binges and 295 urges in the 8-week treatment phase, and 64 binges and 27 urges in the two-week follow-up phase.

Participant reported that 66% of urges (196) were treated (some after beginning to binge) of which 81.1% (159) were treated with 60 mg, 16.3% (32) with 120 mg, and 2.6% (5) with 180 mg.

In 86% of treated urges (169 of 196), patients reported that treatment was helpful during the treatment phase.

**Binges Table 1: Tally of Binges and Urges to Binge**
Table 1: Tally of Binges and Urges to Binge

Link: Binges

Link: Urges

Number of binges, binge urges and mean number of binges per week, mean number of binge event days per week, mean number of binge urges per week and mean number of binge urge days per week, respectively

<table>
<thead>
<tr>
<th></th>
<th>Total # binges</th>
<th>Total # urges</th>
<th>Number of Binges Per Week</th>
<th>Difference from Baseline in # Binges Per Week</th>
<th>Number of Binge Days Per Week</th>
<th>Difference from Baseline in # Binge Days Per Week</th>
<th>Number of Binge Urges Per Week</th>
<th>Difference from Baseline in # Binge Urges Per Week</th>
<th>Number of Binge Urge Days Per Week</th>
<th>Difference from Baseline in # Binge Urge Days Per Week</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Phase</strong></td>
<td>135</td>
<td>71</td>
<td>4.9 (± 2.26)</td>
<td>-2.3 (p-value 0.0005 – 0.0034)</td>
<td>4.1 (±1.49)</td>
<td>-2.8 (p-value 0.0005 – 0.0005)</td>
<td>2.56 (±1.66)</td>
<td>-0.4 (p-value 0.00176 – 0.00001)</td>
<td>2.12 (±1.33)</td>
<td>-0.2 (p-value 0.000420 – 0.006377)</td>
</tr>
<tr>
<td><strong>Treatment Phase</strong></td>
<td>199</td>
<td>295</td>
<td>1.58 (±2.23)</td>
<td>to -3.4</td>
<td>1.32 (±2.03)</td>
<td>to -2.0</td>
<td>2.20 (±2.62)</td>
<td>to 2.11</td>
<td>3.25 (±2.01)</td>
<td>to 1.13</td>
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<tr>
<td><strong>Follow-up Phase</strong></td>
<td>64</td>
<td>27</td>
<td>2.67 (±3.09)</td>
<td>-2.3 (±2.35)</td>
<td>2.24 (±2.20)</td>
<td>-1.8 (±1.90)</td>
<td>1.15 (±1.41)</td>
<td>-1.4 (±1.41)</td>
<td>2.24 (±2.20)</td>
<td>-1.1 (±1.09)</td>
</tr>
</tbody>
</table>

Mean weekly number of binge events: Composite means are presented in Table 1. The mean number of binges per week during the baseline period was 4.9 (± 2.26). During the 8-week treatment period the number of binges per week decreased and ranged from 1.58 (± 2.23) to 2.67 (± 3.63). The mean number of binges during the two-week follow-up period was 2.67 (± 3.09).

Statistically significant differences from baseline period to treatment period were found at each treatment week, with the decrease in mean number of binges ranging from −2.3 (± 1.89) to -3.4 (± 1.70) per week (p-values ranging from 0.0005 to 0.0034).

The overall mean number of binges per week for the treatment phase also differed significantly from baseline (p = 0.0005).

The mean number of binges per week in the follow-up phase was not statistically significantly different from treatment phase mean (p = 0.2881) but did differ significantly from the baseline phase (p = 0.0210).

Mean number of binge event days per week: The mean number of binge event days per week during the baseline phase was 4.08 (± 1.49). The mean number of binge event days per week during the treatment phase decreased and ranged from 1.38 to 2.08. The mean number of binge event days during the follow-up phase was 2.24 (± 2.20).

Statistically significant differences from baseline to treatment period were found at each week, with decrease in binges ranging from −2 to -2.8 (p-values ranging from 0.0005 to 0.0049). Follow-up mean number of binge event days was not statistically significant different from treatment period (p = 0.2246).

Urges Table 1: Tally of Binges and Urges to Binge

Link: Binges
Mean weekly number of urges: The mean number of urges per week during the baseline phase was 2.56 (± 1.66). Mean number of urges per week during the treatment phase ranged from 4.67 (± 3.37) to 2.20 (± 2.62). The difference between baseline and treatment phases was statistically insignificant (p = 0.8501).

The mean number of urges per week during the follow-up phase was 1.15 (± 1.41).

The mean number of urges per week during the follow-up phase differed significantly from the treatment (p = 0.0029) and from the baseline phases (p = 0.0034).

Mean number of urge event days per week: The mean number of urge event days per week during the baseline phase was 2.12 (± 1.33). The mean number of urge event days per week during the treatment phase ranged from 1.67(± 1.72) to 3.25(± 2.01). The mean number of urge event days per week during the follow-up phase was 0.98 (± 1.23)

When compared with the baseline phase, only the first week of follow-up demonstrated a statistically significant difference in number of urge event days per week (p = 0.0420).

When compared with the baseline phase, the overall follow-up period demonstrated no statistically significant difference in number of urge event days per week (p = 0.9697).

Like the mean number of urges per week, the follow-up phase had a statistically significant decrease in mean number of urge event days per week when compared with the treatment phase (p = 0.0059) but an insignificant change when compared with baseline phase (p = 0.9697).

Changes in variables between phases are presented visually in Fig. 2.

Changes over time of mean number of binges and urges per week are presented visually in Fig. 3.

Changes over time of mean number of binge and urge event days per week are presented visually in Fig. 4.

**Patient Severity Of Illness And Post-treatment Condition Scoring:**

Significances of Patient Severity of Illness and Post-treatment Condition Scoring, between weeks of treatment can be seen in Table 3.
### Table 2
Changes in variables between phases. **Statistically significant values (p < 0.05) appear in bold.**

<table>
<thead>
<tr>
<th></th>
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<td>2.20 (± 2.62)</td>
<td>-0.4 to 4.67 (± 3.37) (p-value 0.0176–1)</td>
<td>1.67 (± 1.72)</td>
<td>-0.2 to 3.25 (± 2.01) (p-value 0.0420–0.6377)</td>
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<td></td>
<td>295</td>
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<td></td>
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### Table 3
Significances of Patient Severity of Illness and Post-treatment Condition Scoring, between weeks of treatment. **(Statistically significant changes (p < 0.05) appear in bold).**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline vs. treatment periods</th>
<th>Follow-up vs. treatment periods</th>
<th>Follow-up vs. baseline periods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of Binges per Week</td>
<td>p = 0.0005</td>
<td>p = 0.2881</td>
<td>p = 0.0212</td>
</tr>
<tr>
<td>Mean number of binges event days per week</td>
<td>p = 0.0005</td>
<td>p = 0.2246</td>
<td>p = 0.0098</td>
</tr>
<tr>
<td>Mean number of Urges per Week</td>
<td>p = 0.8501</td>
<td>p = 0.0029</td>
<td>p = 0.0034.</td>
</tr>
<tr>
<td>Mean number of Urge event days per week</td>
<td>P = 0.9697</td>
<td>p = 0.0059</td>
<td>p = 0.9697</td>
</tr>
</tbody>
</table>

CGI-S: There was a statistically significant decrease during all 8 weeks of the treatment phase when compared with the baseline phase (p = 0.002- p = 0.0156).

YBOCS-BE: There was a statistically significant decrease during all 8 weeks of the treatment phase when compared with the baseline phase (p = 0.002- p = 0.0161).

Adverse events and side effects.

There were no adverse events reported during all 251 treatments in the treatment phase.

Safety monitoring revealed no deviation from baseline for all parameters: physical examination (including an ear, nose and throat (ENT) exam); vital signs (blood pressure, pulse rate, and temperature); blood laboratory tests (biochemistry and CBC), and urine toxicology (cannabinoids screen, benzodiazepine screen, amphetamine screen, methadone metabolite).

The following side effects were reported during the 8 weeks of treatment: headache (5.17%), sneezing (4.38%), tiredness (1.59%), and nausea (3.98%). Affected patients did not consider these as serious, no medical treatment was needed, and no alteration of treatment was needed as a result.

Patients reported a lingering bitter taste in the naso/oropharynx after administering treatment doses.
Discussion

This study presents a novel "as needed" approach to binge eating management by combining topiramate's potential as binge eating disorder pharmacotherapy with intranasal direct nose to brain drug delivery. A number of CNS pharmacotherapies with good BBB penetration were recently approved for intranasal administration via intranasal delivery products that deliver drugs to the systemic circulation. For example, an IN/S-ketamine (Spravato®) combination product was recently approved for the treatment of major depression.\textsuperscript{28} Also, IN midazolam (NAYZILAM® by UCB\textsuperscript{30}) was approved in patients with epilepsy 12 years of age and older, for acute treatment of intermittent, stereotypic episodes of frequent seizure activity that are distinct from a patient's usual seizure pattern. In addition, another drug substance in a dry-powder form, ONZETRA® Xsail® (sumatriptan nasal powder), was approved several years ago for acute treatment of migraine headaches with or without aura\textsuperscript{31}.

We selected the SipNose product due to its unique approach to intranasal drug delivery. The SipNose product differs from existing methods since it takes advantage of the nasal cavity's physio-anatomy that allows efficient drug absorption and delivery directly to the brain.\textsuperscript{41} Existing, commercially available intra-nasal drug-delivery devices deliver aerosol mainly to the lower and mid turbinate of the nasal cavity and only minor amounts to the upper turbinate of the nasal cavity, thus allowing systemic delivery via the rich blood capillaries' mucosa in the middle-turbinate area in the nasal cavity. In contrast, SipNose technology changes the ratios and delivers higher percentages of the aerosol to the upper turbinate, thus allowing limited systemic circulation delivery and pronounced direct delivery from the olfactory epithelium to the brain. SipNose's innovative approach enables broad, consistent drug delivery to the upper area of the nasal cavity, which improves active drug ingredient brain when compared with extant commercial nasal delivery devices. The platform offers an alternative to traditional nasal inhalers, as well as to tablets and injections, mainly in the field of central nervous system (CNS) pharmacotherapy.

In the study's first part, topiramate's pharmacokinetic profile for SipNose intranasal delivery demonstrated a linear dose response relationship between cohorts 1 and 2 and a cumulative increase in drug plasma concentrations in cohort 3. The linear dose response is consistent with oral dosing linear dose response. The additive concentration increases in cohort 3 is consistent with known data regarding the drug's long $t_{1/2}$. These results demonstrate SipNose's ability to deliver topiramate dry formulation in a consistent and controlled fashion. It also demonstrates the nasal mucosa's ability to provide consistent and controlled topiramate absorption when applied with the SipNose device, even when administered as consecutive doses. The SipNose-topiramate's efficacy in reducing binge numbers in Part II demonstrate its ability to rapidly reach and effect the CNS, long before it reaches peak levels (around 90 minutes). To that end, the direct nose-to-brain delivery offers a pharmaco-distribution and kinetic profile that is the reverse of, and better than, systemic dosing. Systemic dosing requires drug delivery to plasma at levels sufficiently elevated to allow for crossing the BBB. In contrast, DNTB delivery allows for rapid near-direct CNS drug delivery with subsequent plasma distribution. As such, any rapid rise in plasma levels demonstrated by DNTB delivery likely underestimates the rapid rate of rise of CNS tissue topiramate levels. Additionally, lower DNTB plasma levels may allow for an improved systemic side effect profile. Further study is needed to determine these assumptions. Such study should include a larger patient cohort, longer treatment period and a comparison group treated chronically with oral topiramate.

In terms of drug safety, the lack of adverse events suggests that SipNose-topiramate nasal delivery is safe for clinical use in doses ranging from 30 mg and up to 180 mg per day. This is further supported by the lack of adverse events experienced by patients in the study's second part.

It is important to highlight that most side effects were reported in cohort #3, in which a high dose of topiramate was taken (180 mg). In the second part, this constituted less than 3% of self-administered doses. A number of these side effects (headache, sneezing, tiredness and nausea) were also reported by patients in the study's second part, though it is unknown whether these were associated with higher doses. Furthermore, all reported side effects were low in frequency in both study parts, did not pose a health hazard to study participants, and did not require treatment. All are also known topiramate related side effects and do not seem to result from the combination product. The only effect that appears to be related to the combination product is the bitter taste reported by patients in Part II. In retrospect, study medical staff viewed the lingering bitter taste as a potentially advantageous. Firstly, it provides sensory confirmation of medication delivery, similar to the sensation of a pill entering the stomach. Secondly, it may prevent over/unnecessary dosing and addiction.
The SipNose–topiramate direct nose-to-brain delivery and PRN therapy reduces the topiramate dose and total drug exposure. The required daily dose of oral topiramate in chronic BED treatment is ~180mg or more (≥1,260 mg/week). In contrast, we estimate that study patients were exposed to an average of 114-193mg/week (1.58–2.67 binge events/week, 81% treated with 60mg, 16% with 120mg and 2.5% with 180mg). Furthermore, drug exposure does not occur daily, only as needed (1.38–2.08 binge event days/week). This amounts to a 6.5-11-fold reduction in drug exposure then with the chronic use of the oral formulation of the drug.

The low side effect frequency highlights the advantage of using the SipNose-topiramate product, in which more than 97% of individual effective doses were relatively low (60 or 120 mg), as was the cumulative dose per week. The intermittent "as needed" dosing allowed for an average greater time lapse and drug clearance between treatment days, thereby reducing chronic steady state drug exposure. The reduced number of urges in the follow-up phase suggest that a longer treatment phase could have resulted in even further drug exposure reduction through a gradual reduction in urges and urges requiring treatment. Further research with a longer treatment period to confirm this.

This study's second part demonstrated SipNose-topiramate's clinical efficacy as an "as needed" treatment for urges to binge in BED patients. To our knowledge, this is the first study that utilizes topiramate for PRN binge treatment rather than preventative chronic therapy. Study results demonstrated that this method was well received by patients and was assessed by patients as effective in helping them control their urges and prevent binge progression. This is supported by the reduction in number of binges and binge event days per week in the treatment phase, as well as by the reduction in CGI-S and YBOCS-BE disease severity scales. The significant reduction in both scores during all treatment weeks when compared to baseline period, is consistent with the reduction in number of binges during the treatment phase. The lack of urge reduction during the treatment phase is consistent with author anticipation of topiramate acting as a short-acting acute treatment in reducing urge severity and/or allowing the patient better cognitive control in overcoming urges to binge.

Interestingly, the number of binge events remained reduced in the follow-up phase. We hypothesize that the reduction in binges after the end of the drug treatment is a long-term behavioral effect induced by self-treatment. We suggest that during the treatment phase, patients had to engage in a mindful cognitive pause of self-assessment to assess urge severity and decide whether it required treatment. This may have positively influenced obsessive thinking. This reflective behavior pattern may have remained and improved patients' self-control and self-esteem. It may also explain the reduction in number of urges during the follow-up phase. The new behavior pattern may have allowed patients the ability to redefine their urge severity. During the follow up phase, may have downgraded their urge severity such that they completely dismissed or disregarded urges of lower intensity which they would have previously considered significant. Further research is needed with longer treatment and follow-up phases, including follow-up YBOCS-BE monitoring to assess this phenomenon.

The study has several limitations. Firstly, both parts included a small number of volunteers and patients, respectively. Secondly, the study group in Part II was not compared to a control rather to their own measurements during the baseline period, prior to commencing therapy. Larger, randomized-control groups with longer treatment and follow-up phases may yield more accurate and robust results. Thirdly, the 8-week treatment and 2-week follow-up phases in Part 2 may be too brief to conclusively determine long term treatment efficacy. Lastly, the CGI-S and YBOCS-BE were not evaluated during the follow-up phase. Extending their evaluation in the follow-up phase can lend broader and deeper understanding of BED's cognitive and behavioral components in this new "as needed" treatment method.

Our study introduces several novelties to the world of BED. We introduce the first successful acute, as-needed, direct nose-to-brain intranasal therapy for a psychiatric illness, with reduced drug exposure to eliminate side effects. Specifically, in this study, the SipNose-topiramate direct nose-to-brain drug delivery combination provided safe, effective as-needed treatment for patients suffering from binge-eating disorder and succeeded in reducing disease severity. Additionally, BED is currently defined solely based on the number and frequency of binge events without accounting for urges as a treatment requisite. The introduction of as-needed pharmaco-therapy highlights the importance of considering urges to binge and their subjective intensity as a foundation for treatment. This also opens a broader treatment consideration for the SipNose-topiramate combination. BED is a disease with obsessive and compulsive components that overlap with obsessive-compulsive disorder (OCD). Further research is needed to assess the SipNose-topiramate combination as an as-needed therapy for other forms of OCD related compulsive behaviors.

In conclusion, we present a two-part study that introduces the use of the SipNose-topiramate device-drug combination as a safe and effective "as-needed" acute therapy for binge eating disorder. Study results reveal a new therapy method for reducing binge eating.
episodes in BED patients, that is well received by patients, has a predictable PK and drug safety profile, shows strong treatment efficacy, and improves patient's health and quality of life. Despite its limitations, this preliminary study demonstrates SipNose device's therapeutic potential and the SipNose-topiramate combination product. Further research is needed to validate these results and further elucidate the treatments' long-term efficacy and influence on BED's obsessive behavioral component. Additionally, it is conceivable that this form of as-needed pharmaco-therapy may be applicable and effective in treating OCD and related disorders.

**Declarations**

- Ethical Approval and Consent to participate: Phase I: MOH-0157-18; Phase II: SMO-6814-20. Consent to participate form is available.
- Consent for publication: All authors approved the publication.
- Availability of supporting data: NA
- Competing interests: NA
- Funding: SipNose Ltd, Israel provided study funding.
- Authors' contributions: AKG & IS – Analyzed the data and wrote the manuscript; AZ, LH, IS, AK, YC, DS, DE, EG - Designed and implement the study; HF – Wrote and reviewed the manuscript; AD, LI, AZ – Reviewed the manuscript; All authors approved the final manuscript version being submitted for publication.
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**References**

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Figures

Figure 1

SipNose device
Figure 2

Cohorts 1, 2 and 3 – Average topiramate plasma concentrations vs. time
Figure 3

Mean number of binges per week

Statistically significant decrease Baseline vs. Treatment phase
p=0.0005

Follow-up vs. Treatment phase
No statistically significant difference p=0.2881

Note: Totals are adjusted according to the number of days in week that are recorded.
If <=3 days are recorded then days are included in previous week.
Figure 4

Mean number of events days (binge and urge events)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryData.docx