VLS-01 Buccal Film: A Novel Formulation of a Serotonergic Psychedelic under Development for the Treatment of Treatment-Resistant Depression (TRD)

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Background

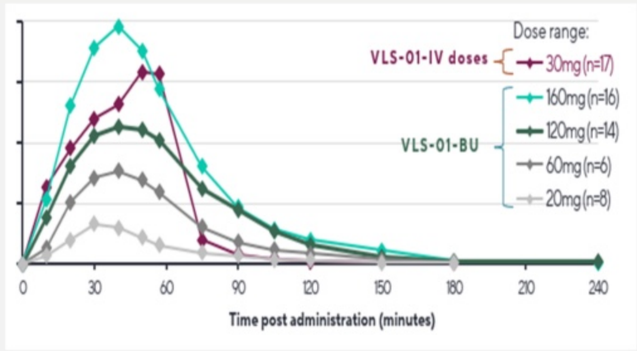
- Major depressive disorder is a serious and life-threatening psychiatric illness, associated with high rates of individual and society-level morbidity, which follows a chronic course.
- It affects an estimated 280 million adults and adolescents globally (World Health Organization [WHO, 2023]) with 10-30% of patients meeting criteria for Treatment-Resistant Depression (TRD).
- There is growing evidence that serotonergic psychedelic drugs, such as N,N-dimethyltryptamine (DMT), produce fast acting antidepressant effects. The antidepressant activity of these compounds is most likely produced by agonism at 5-HT receptors, especially the 5 $HT2_A$ receptor (Dos Santos et al, 2021).
- VLS-01-BU (buccal film containing DMT) is a serotonergic psychedelic compound which partially to fully agonizes 5-hydroxytryptamine receptor subtypes, including 5 $HT_{1/2/6/7}$ receptors.

Methods

- An initial Ph1a study in healthy adults (VLS-01-101) characterized safety, tolerability, PK, and defined the approximate exposure required to elicit perceptual changes following a single intravenous dose of VLS-01 or buccal transmucosal administration of VLS-01-BU.
- In the VLS-01-101 study VLS-01 was generally well-tolerated when administered as a single dose via intravenous (IV) or buccal routes (BU). The PK data suggested that higher doses of the buccal formulation are required to elicit similar effects to the IV formulation(data not shown). The findings from this study supported the continued clinical development of VLS-01 for the treatment of individuals with TRD.
- Building on the VLS-01-101 data, a non-randomized, open-label repeat-dose Ph1b study in healthy adults (VLS-01-102) assessed the exposure, within-participant PK variability, safety and tolerability of a modified buccal transmucosal film and an intravenous infusion (Figure 1).
- A within-participant, repeated dose design was selected for the VLS-01-102 study (Figure 1) allowing for assessment of within-participant variability in PK/PD and evaluation of the PK equivalence of IV and buccal transmucosal delivery of VLS-01 (Figures 2 and 3). The study was designed to test the highest dose of VLS-01-BU first to confirm selection of the active doses for the proposed Phase 2 clinical study.
- The VLS-01-102 study enrolled 17 healthy volunteers that were split into two cohorts (n = 8 were enrolled in cohort 1; n = 9 were enrolled in cohort 2).
- In both cohorts, participants received 1 dose of VLS-01-IV infusion (30mg over 57min) and 3 additional doses of buccal VLS-01-BU (20-160 mg) (Figure 1).
- A 28-day washout period was required before proceeding to the next dose.
- Self-reported perceptual changes were measured using the Subjective-Intensity-Rating-Scale (SIRS) using a score of 1-10 (range 0 = "No effect/the effects have completely worn off" to 10 = "Greatest intensity imaginable") (Figure 3).

Results

Figure 2: VLS-01-102 Plasma Concentrations over Time – Treatment Periods 1 & 2 (Pharmacokinetic Population)



- Observed increases in exposure to VLS-01 with dose were close to dose proportional, as the dose-normalized exposure parameters were all similar across 20 mg to 160 mg VLS-01-BU
- Bioavailability (%F) of VLS-01-BU was calculated to be ~33% relative to IV, and this was broadly consistent across the dose range.

Table 1:: VLS-01-102 Summary of Plasma Pharmacokinetic Parameters – Treatment Periods 1 & 2 for VLS-01-IV 30mg and VLS-01-BU 120mg (Pharmacokinetic Population)

VLS-01	VLS-01-IV 30mg 0.53mg/min (n=17)		VLS-01-BU 120mg (n=14)	
Parameter	n	Value[a]	n	Value[a]
C_{max} (ng/mL)	16	37.7 (16.2)	14	36.5 (17.6)
T_{max} (hr)	16	0.83 (0.33,0.98)	14	0.67 (0.33,1.5)
AUC_{last} (ng*hr/mL)	16	27.8 (10.8)	14	33.5 (15.6)
$T_{1/2}$ (hr)	16	0.33 (0.10)	14	0.32 (0.06)

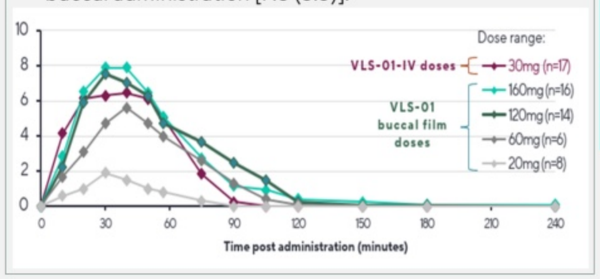
- The mean (SD) PK exposure parameters for VLS-01 following IV infusion were C_{max} [37.7 (16.2) ng/mL], AUC_{last} [27.8 (10.8) ng*hr/mL)] and $T_{1/2}$ [0.32 (0.10) hours]. These were most closely matched by the 120 mg buccal dose, which were 36.5 (17.6), 33.5 (15.6), and 0.32 (0.06) for C_{max}, AUC_{last} and $T_{1/2}$, respectively.
- The major metabolite was indole-3-acetic acid (IAA).

a. Pharmacokinetic values are reported as mean (SD) for C_{max}, AUC_{last}, and $T_{1/2}$ and median (min, max) for T_{max}

Abbreviations: IV = Intravenous; Cmax = maximum observed plasma concentration; Tmax = time to maximum concentration (Cmax); AUClast = area under the drug concentration-time curve, from time 0 (time of dosing or start of the infusion) to the last measurable concentration

Figure 3:: VLS-01-102 Subjective Intensity Rating Scale (SIRS) scores (0 to 10) Post Administration for Treatment Periods 1 & 2

- Dose-dependent effects, with robust subjective effects were seen at the VLS-01-BU 120 mg and 160 mg doses.
- Perceptual effects generally fully resolved within 90-120 mins.
- Mean (SD) post-dose SIRS scores peaked after 40 min for intravenous [6.5 (3.2)] and after 30 min for the 120 mg buccal administration [7.5 (3.5)].



Conclusion

- VLS-01-BU was generally well-tolerated and subjective effects were transient and resolved in approximately 2 hours.
- The 120 mg dose of VLS-01-BU generated sufficient exposure at the 120mg dose to proceed with efficacy testing.
- A Ph2, double-blind, randomized, placebo-controlled trial in TRD testing VLS-01-BU 120mg is currently enrolling.

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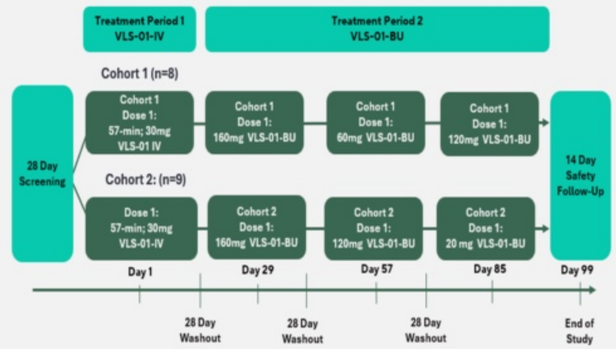
Study Design

Figure 1: VLS-01-102 Study Design



Primary Endpoint:

Plasma and urine PK characteristics

Key Secondary Endpoints:

Safety and tolerability

Subjective acute PD drug effects

Safety Summary

Table 2: VLS-01-102 Treatment Emergent Adverse Events[a] (> 10%)

No. of participants with drug-related TEAE (>10%):	VLS-01-IV 30mg (N=17)	VLS-01-BU 160mg (N=16)	VLS-01-BU 120mg (N=14)	VLS-01-BU 60mg (N=7)	VLS-01-BU 20mg (N=8)	Total (N=62)
Headache	1 (6%)	4 (25%)	4 (29%)		1 (13%)	10 (16%)
Dissociation	1 (6%)	5 (31%)	3 (21%)			9 (15%)
Euphoric mood	1 (6%)	3 (19%)	4 (29%)		1 (13%)	9 (15%)
Nausea		5 (31%)	1 (7%)	1 (14%)		7 (11%)
Emotional distress	1 (6%)	3 (19%)				4 (6%)
Feeling drunk			3 (21%)		2 (25%)	5 (8%)
Feeling hot	2 (12%					2 (3%)
Anxiety	2 (12%)					2 (3%)
Dizziness		1 (6%)		1 (14%)		2 (3%)
Vomiting		2 (13%)				2 (3%)
Myocardial ischemia[1]					1 (13%)	1 (2%)
Abdominal pain				1 (14%)		1 (2%)
Oral Discomfort		2 (13%)				2 (3%)
At least one severe TEAE						0
At least one serious TEAE						0
At least one TEAE leading to discontinuation	1 (6%)					1 (2%)

1. T-wave inversion unrelated to study drug, as assessed by the investigator, was upgraded to myocardial ischemia, mild, probably related by the Sponsor, following feedback from the FDA.
a. Treatment Emergent Adverse Events (TEAEs) are defined as adverse events that occurred following the first administration of study medication

- In the VLS-01-102 study the most common TEAEs were headache, dissociation, euphoric mood and nausea (Table 2); adverse events were transient with most resolving on the day of dosing. None were considered clinically significant. Blood pressure and heart rate increases were transient and mostly resolved within 90 min without intervention.
- Results from the Columbia-Suicide Severity Rating Scale (C-SSRS) showed participants experienced no increase in suicidal thoughts, intentions or behaviors.
- Overall impressions from healthy volunteers in the 120mg group was that VLS-01 was well-tolerated and psychologically meaningful with reports of increased self-reflection.
- In 91 subjects across the VLS-01-101 and VLS-01-102 studies no severe or serious treatment-emergent AEs were observed. The most common TEAEs were headache, dissociation, nausea; all mild to moderate in severity.

References: Dos Santos RG, Hallak JEC, Baker G, Dursun S. Hallucinogenic/psychedelic 5HT2A receptor agonists as rapid antidepressant therapeutics: Evidence and mechanisms of action. 2021;35(4):453-458; World Health Organization (WHO). Depression Facts Sheet. Retrieved from https://www.who.int/news-room/fact-sheets/detail/depression.