T30

A Phase 1 SAD and MAD Trial of EVX-101, a Novel Gastro-Retentive Prolonged Release 5-HTP/Low-dose Carbidopa Tablet, in Healthy Subjects Taking Escitalopram

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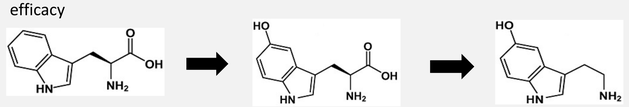
Background

- 5-hydroxytryptophan (5-HTP) is the natural rate-limiting precursor of 5-HT (aka serotonin)
- Historical evidence suggests adjunctive 5-HTP may benefit MDD patients responding inadequately to 1st-line antidepressants
- However, native 5-HTP is impractical for oral (po) use because of poor PK, i.e., rapid absorption/elimination, low bioavailability, and narrow absorption window
- EVX-101 is a novel gastro-retentive sustained-release formulation of 5-HTP (250 mg/tablet) plus low-dose carbidopa (0.3125-2.5 mg/tablet) designed to overcome the PK-related shortcomings of native 5-HTP
- Low-dose carbidopa delivered in close spatial and temporal proximity with 5-HTP to the upper intestine enhances 5-HTP bioavailability many-fold
- EVX-101 is in development as an adjunctive treatment for MDD patients responding inadequately to 1st-line antidepressants (SSRIs, SNRIs)
- Adjunctive EVX-101 is designed to elevate extracellular 5-HT (5-HT_{Ext}) beyond the 1st-line antidepressant effect, which evidence suggests will augment antidepressant efficacy



Tryptophan → 5-HTP → Serotonin (5-HT)

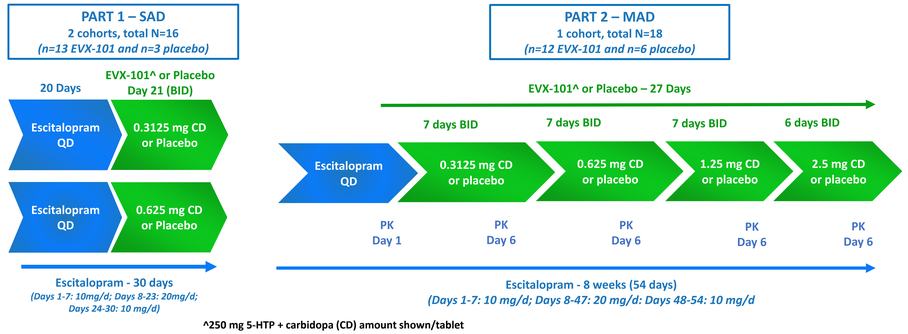
Key Objectives

1) Safety, tolerability, and PK of single-ascending doses (SAD) and multiple-ascending doses (MAD) of EVX-101 administered to healthy subjects taking escitalopram
2) Effect of adjunctive EVX-101 on serum cortisol, a pharmacodynamic biomarker of acute elevation in brain extracellular 5-HT

Methods

- Randomized, double-blind, placebo-controlled, 2-part (SAD-MAD) trial
- Healthy male & female adult subjects (SAD:18-55y, MAD: 25-55y); BMI (18-32 kg/m^2)
- Escitalopram (1st-line SSRI antidepressant) was dosed pre-randomization to 20 mg/day and continued at that dose throughout the in-patient portion of the study
- The 5-HTP total daily dose was fixed at 500 mg (250 mg BID)
- Plasma 5-HTP levels were escalated by increasing carbidopa total daily dose
- The carbidopa dose range/tablet was 0.3125 mg – 0.625 mg BID in SAD Part 1 and 0.3125 mg – 2.5 mg BID in MAD Part 2 (See Study Schema panel)
  - In SAD Part 1, separate cohorts were utilized to evaluate each dose level
  - In MAD Part 2, a single cohort was up-titrated weekly based on overall tolerability
- Study medication was given approximately 30 min after the subject had completed a moderate-fat/moderate-calorie (morning) or high fat/high-calorie (evening) meal
- Safety and tolerability were assessed via:
  - AE incidence and changes in VS, ECGs, safety labs, and physical examinations (PE)
  - Columbia-Suicide Severity Rating Scale (C-SSRS)
  - Hunter Criteria for Serotonin Toxicity
- In Part 2, steady state PK profiling occurred on Day 6 of each Dose Level
- PD profiling occurred on Day 1 at each dose level for both parts

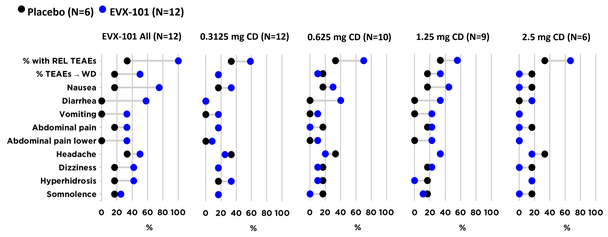
EVX101-102 Study Schema



^250 mg 5-HTP + carbidopa (CD) amount shown/tablet

Safety and Tolerability Results

Most Frequent[1] RELATED[2] Treatment-Emergent AEs (TEAEs) – Part 2 (MAD) Phase



[1]-Incidence ≥ 25% in All-Active (EVX-101) population; [2]-TEAEs where relationship to IMP is 'possibly related' or 'related'; 5-HTP Total Daily Dose at each dose level = 500 mg (250 mg BID); CD=carbidopa (mg) dose (BID)

Safety and Tolerability Summary:

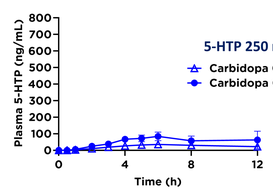
- ✓ No serotonin toxicity
- ✓ No serious or severe AEs
- ✓ No safety signals based on VS, labs, ECGs or physical exams
- ✓ IMP-related AE incidence was similar for each 5 HTP/carbidopa dose level
- ✓ GI-related AEs (primarily nausea) were most frequent
- ✓ Up-titration of carbidopa improved GI-tolerability

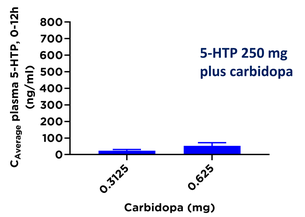
PK/PD Results

Data presented as mean ± SEM

PK

SAD

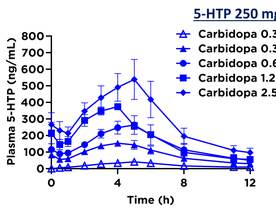


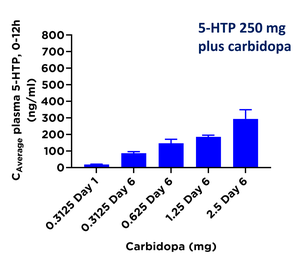


PART 1 5-HTP PK Parameters[1]	5-HTP 250 mg BID	
	Escitalopram 20 mg QD	
	Carbidopa BID	
	0.3125 mg	0.625 mg
N	7	5
$C_{Max0-12}$ (ng/ml)	47.7	122
$C_{Avg0-12}$ (ng/ml)[2]	23.4	52.8
AUC_{0-12} (ng/h/mL)	281	633
$T_{max0-12}$ (h)	5.6	6.2
T1/2 (h)	4.1	NC[3]
Dose tolerated?	Yes	No

[1]Arithmetic means shown; [2]Avg concentration in plasma during the dosing interval (AUC_{0-12}/12, NOT at steady state); [3]Not calculated

MAD





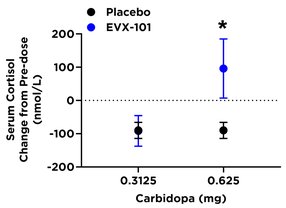
Anticipated therapeutic level ≥ ≈ 100 ng/mL

PART 2 5-HTP PK Parameters[1]	5-HTP 250 mg BID				
	Escitalopram 20 mg QD				
	Carbidopa BID				
	0.3125 mg (Day 1)	0.3125 mg (Day 6)	0.625 mg (Day 6)	1.25 mg (Day 6)	2.5 mg (Day 6)
N	12	10	9	6	6
$C_{Max0-12}$ (ng/ml)	56.5	188	321	392	606
$C_{Avg0-12}$ (ng/ml)	16.3^	86	146	188	295
AUC_{0-12} (ng/h/mL)	195	1030	1760	2250	3540
$T_{max0-12}$ (h)	3.9	3.7	4.1	3.2	4.0
T1/2 (h)	---	---	---	---	6.5
AI[2]	---	8.22	---	---	---
Dose tolerated?	Yes		Yes	Yes	Yes

[1]Arithmetic means shown; [2]Accumulation Index (AUC_{0-12} Day6/AUC_{0-12} Day1); ^Average 5-HTP plasma concentration during the dosing interval (AUC_{0-12}/12, NOT at steady state)

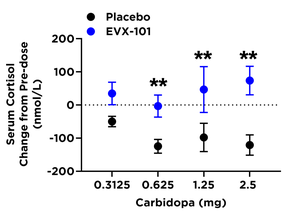
PD

SAD



T=5h

MAD



T=4h

**p<0.05, *p<0.1; post-hoc analyses

Conclusions

- Escalating does of adjunctive EVX-101 up-titrated every 7 days over four weeks appeared to be safe in healthy volunteers taking a 1st-line antidepressant
- No serotonin toxicity reported
- Mild-moderate GI-related AEs most frequent, consistent with a serotonergic mechanism
- Dose titration improved tolerability
- Tolerability is anticipated to be further improved in MDD patients taking 1st-line antidepressants for longer durations, and where EVX-101 will be individually titrated
- All 4 dose levels of EVX-101 achieved steady state plasma 5-HTP levels at or above the anticipated therapeutic level (≥ ≈ 100 ng/mL)
- Preliminary evidence of target engagement, i.e., brain 5-HT_{Ext} elevation beyond the maximal 1st-line antidepressant effect
- These results support progression of all 4 dose levels of EVX-101 into Phase 2 trials in MDD patients who are responding inadequately to 1st-line SSRI/SNRI antidepressants

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