The effect of extract Sceletium tortuosum (Zembrin®), targeting Phosphodiesterase subtype-4 (PDE-4), on cognitive function: a proof-of-concept randomized double-blind, single site, placebo-controlled cross-over study in healthy adults (Abstract)

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Background: There is increasing evidence from genetic and pharmacological studies that PDE-4 (Phosphodiesterase subtype-4) plays a crucial role in regulating memory and affective processes mediated through the PDE-4 cascade involving phosphorylated cAMP response element binding protein (pCREB) signaling. Based on published in-vitro studies we have characterized extract Sceletium tortuosum (Zembrin®), containing the PDE4 inhibitor mesembrenone and related alkaloids, as a putative PDE-4 modulator.

Objective :The primary objective was to evaluate the efficacy of extract Sceletium tortuosum (Zembrin®) in enhancing cognition as determined using the CNS VitalSigns® battery of tests, and the co-primary objective was to evaluate the safety and tolerability of the extract as measured with a Treatment Emergent Adverse Events check list. A secondary objective was to evaluate any affect changes using the Hamilton Rating Scale for Depression (HAM-D).

Design and Method: randomized double-blind placebo-controlled cross-over, single centre. We recruited normal subjects (total n =21) with no psychiatric or serious medical disorders to the study. Participants were randomized to receive either a capsule containing 25 mg of extract Sceletium tortuosum (Zembrin®), or an identical looking placebo, once daily for 3 weeks. Following a three week washout period with no active or placebo administration, the subjects were switched over to the respective placebo or active groups for a further 3 weeks. We administered the CNS VitalSign® battery of neuropsychological tests, and the HAM-D at baseline, week 3, week 6, and week 9. Side effects were monitored with Treatment-Emergent-Adverse-Events scale.

Results: 21 subjects (mean age: 54.6 years+/- 6.0 yrs ; male/female ratio: 9/12) recruited from a single site entered the study and 20 completed the study. The dropout rate of 4.8 % (1/21). Daily oral dosing of 25mg of extract Sceletium tortuosum (Zembrin®) in a normal cognitively intact cohort selectively and significantly improved two cognitive function domains: cognitive set flexibility ($p < 0.032$) executive function ($p < 0.022$). No carry-over effect of the extract to the placebo phase was observed. No changes occurred with pulse, blood pressure and weight. Extract Sceletium tortuosum (Zembrin®) was well tolerated with no nausea or vomiting, and only infrequent mild side effects.

Conclusion: The significant selective effects of extract Sceletium tortuosum (Zembrin®) in improving cognitive flexibility and executive function

provides supporting evidence for PDE-4 inhibition as a mechanism of action of the extract, and suggests that the extract itself, or active compounds within the extract may have therapeutic potential in cognitive aging. As a PDE4 inhibitor with cognitive enhancing activities and highly favourable safety and tolerability, extract Sceletium tortuosum (Zembrin®) warrants a randomised controlled study in neurodegenerative disorders.

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