**Speaker 2: Jaskaran Singh, USA**  
**Title:** Intranasal Esketamine in Treatment Resistant Depression - A Double-blind, Randomized, Efficacy and Dose Response Study  

**Abstract**  
**Background:** Esketamine and ketamine have been shown to produce rapid antidepressant action in patients with treatment-resistant depression (TRD). The aim of the current study was to assess the efficacy, safety and dose response of intranasal esketamine in patients with TRD.  

**Methods:** This was a 2-Panel, double-randomized, double-blind, placebo-controlled, multicenter study. Panel A was conducted in the United States and Belgium and Panel B is currently ongoing in Japan. In both panels, each subject participated in up to 4 phases: a screening phase of up to 4 weeks, a double-blind treatment phase which included two 1-week periods (Periods 1 and 2), a 9-week optional open-label treatment phase and an 8-week follow-up phase. Only Panel A double blind data are available, and will be presented at this time. The primary efficacy endpoint was the change from baseline to Day 8 in each period in the Montgomery-Asberg Depression Rating Scale (MADRS) total score combined. Safety and secondary efficacy endpoints were also assessed.  

**Results:** A total of 67 subjects with TRD were randomly assigned in a 3:1:1 ratio to one of four treatment groups: placebo (n=33), esketamine 28 mg (n=11), esketamine 56 mg (n=11), or esketamine 84 mg (n=12) in Period 1. In Period 2, 28 placebo subjects who were eligible for re-randomization at the end of Period 1 were randomly assigned to placebo (n=6), esketamine 28 mg (n=8), esketamine 56 mg (n=9), or esketamine 84 mg (n=5) in a 1:1:1:1 ratio. Subjects were eligible for re-randomization if the patient-rated 16 item Quick Inventory of Depressive Symptomatology (QIDS-SR16) total score was ≥11 at the end of Period 1. The analysis of Period 1 and Period 2, combined using the weighted combination test, showed that the mean change in MADRS total score in all three esketamine groups was statistically superior to that obtained under placebo, based on a one-sided 0.05 significance level (p=0.021, p=0.001 and p<0.001 for esketamine 28 mg, 56 mg and 84 mg respectively). The mean differences (SE) from placebo (after one week of treatment) were -4.2(2.09) for esketamine 28 mg, -6.3(2.07) for esketamine 56 mg, and -9.0(2.13) for esketamine 84 mg. The magnitude of effect size in Period 1 increases from a low Cohen’s D effect size in the 28 mg group (0.43) to a high Cohen’s D effect size for the 56 (0.92) and 84 mg (1.19) dose groups.  

The most common TEAEs during the double-blind phase (≥10% of subjects in any group) were: dizziness, dissociation, headache, dysgeusia, nasal discomfort, nausea, hypoaesthesia oral, dissociative symptoms, tunnel vision, oropharyngeal pain, throat irritation, blurred vision, hypsomnoria, feeling abnormal, insomnia, hypertension, vertigo, polyuria and sedation. No death was reported. Transient elevation in blood pressure and heart rate was also observed on dosing days. The perceptual changes and dissociative symptoms measured by the Clinician administered Dissociative Symptom Scale (CADSS), suggest onset of these symptoms occurred shortly after the start of intranasal dosing and resolved by 2 hours postdose, and with repeated dosing these symptoms reduced significantly.  

Conclusions: Intranasal esketamine administered in doses of 28, 56 and 84 mg across the study period showed statistically and clinically significant improvement of depressive symptoms in subjects with TRD, as demonstrated by the mean changes in the MADRS total score for the combined analysis of both periods.

The doses evaluated were well tolerated and adverse events were similar to what has been observed previously with IV ketamine and esketamine.

**Speaker 3: Christina Kurre Olsen, Denmark**  
**Title:** A multimodal antidepressant: Effects on cognitive dysfunction in depression  

**Abstract**  
The multimodal antidepressant vortioxetine is thought to exert its therapeutic effects through 5-HT1A receptor agonism, 5-HT1B receptor partial agonism and 5-HT3, 5-HT1D and 5-HT7 receptor antagonism in addition to inhibition of serotonin (5-HT) reuptake. This presentation will describe the approach that was taken in the vortioxetine clinical development program to assess vortioxetine’s potential to treat cognitive dysfunction (CD) in Major Depressive Disorder (MDD), and how this led to the inclusion of vortioxetine’s positive effects on aspects of CD in MDD patients in the prescription information to doctors and patients in more than 50 countries worldwide including the European Community. The presentation will review the alignment between preclinical and clinical research with a particular emphasis on cognition, and discuss the value of continued research to elucidate vortioxetine’s pharmacological potential even at an advanced stage of clinical development.  

The clinical evidence for vortioxetine’s beneficial effects on CD in MDD includes the results from 3 large, prospective, placebo-controlled studies in both elderly and adult MDD patients, two of which had CD as the primary endpoint. Vortioxetine over a dose range of 5 to 20 mg was consistently statistically significantly better than placebo in improving CD, as assessed using the Digit Symbol Substitution Test (DSST). DSST was chosen because it is an objective measure that is sensitive to change and to the integrity of multiple cognitive domains relevant for MDD. In the two studies that had an active reference included, duloxetine did not improve DSST performance versus placebo despite improvement in depressive symptoms. Moreover, in all three studies, after adjusting for the effect on depressive symptoms, most of vortioxetine’s benefit on cognitive performance was retained, indicating a mood-independent effect on the DSST. This presentation will also include evidence from additional neuropsychological tests, measures of functionality including the UCSD Performance-Based Skills Assessment (UPSA), and from patient-reported cognitive functioning.  

Vortioxetine’s distinct clinical profile is supported by its pharmacological profile. Preclinical studies of vortioxetine using clinically equivalent doses demonstrated positive effects in several animal models of CD where other antidepressants had no effect. Furthermore, vortioxetine enhanced glutamatergic output from cortical and hippocampal pyramidal cells (key integrators of cognitive processing) through attenuation of the inhibitory control of GABA interneurons. Morphologically this led to a superior effect of vortioxetine on neurogenesis, dendritic branching and maturation of dendritic spines; all measures that further substantiate the mechanistic rationale for vortioxetine’s positive effects on cognitive function. Doses corresponding to the high end of the clinical dose range increased extracellular levels of norepinephrine, dopamine, acetylcholine, and histamine in hippocampus and prefrontal cortex. These effects might also contribute to vortioxetine’s beneficial effects on cognition. Lastly, recent data from a human imaging study in remitted MDD patients suggested that vortioxetine improves neuronal efficiency during cognitive processes, which provides
Further mechanistic evidence for its beneficial effect on cognitive function.

Through continued research efforts, vortioxetine showed to be an antidepressant with a distinct clinical and pharmacological profile different from other currently available antidepressants, with a proven beneficial effect on CD in patients with MDD.

**Speaker 4: Trevor Robbins, UK**

**Title: Translational models for drug discovery in depression**

**Abstract**
Clinical depression entails cognitive deficits often across a range of domains including impairments, not only of memory but also executive functioning, such as decision-making, sustained attention (‘concentration’) and working memory, although those deficits are frequently age-dependent and correlated with discrete brain pathology. I will review evidence of heterogeneous and homologous patterns of cognitive deficit across a number of human and animal studies focusing especially on decision-making and attention, measured in a variety of ways. In addition, it is evident that depression is also associated with distinctive cognitive or affective biases evident in different settings, such as a tendency to say “no” in tests of memory recognition, to over-respond to faces expressing negative emotion, to over-react to negative feedback and also to respond more quickly to sad rather than happy words. These phenomena indicate the importance in depression of a motivational interface with respect to cognitive function and vice versa. By comparison, preclinical models of depression have frequently been criticised for their emphasis on species-typical maladaptive responses to stress (as in chronic mild stress, learned helplessness and ‘behavioural despair’), that are more predictive of the effects of drugs assumed to have anti-depressant effects than the symptoms of human depression themselves. Recently however, relevant aspects of behaviour such as affective bias and response to negative feedback have been employed successfully in rodents in a manner parallel to what is measured in human depressed patients, using for example tests of generalisation and probabilistic reversal learning. These new tests may complement the rich translational tests we already have available for assessing other aspects of cognition in humans and experimental animals and their neural correlates.

**References**
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**Speaker 2: Sophia Frangou, USA**

**Title: Neurobiology of Cognition in Bipolar Disorder**

**Abstract**
Bipolar disorder (BD) is a mood disorder characterized by recurrent episodes of depression and mania with variable inter-episode remission. Our group and others have shown that patients and their relatives show specific brain abnormalities in task-based functional magnetic resonance imaging (fMRI). BD patients and their relatives show enhanced frontolimbic activity during tasks of emotional processing while hyperconnectivity within the ventral visual stream has been observed in resilient relatives. In contrast executive tasks are most commonly associated with frontoparietal dysfunction in patients but not their relatives. While task-based fMRI provides evidence of functional abnormalities in specific cognitive networks, resting-state fMRI informs about abnormalities in intrinsic functional architecture. The aim of the current study was to examine brain functional topology in patients with BD (n=78), their unaffected siblings (n=48), and 41 healthy controls using graph theory measures. In each participant, we estimated graph theory measures of randomization (clustering coefficient, efficiency, participation, small-worldness, characteristic path length), and resilience to targeted and random attack. We found that global measures of network interconnectivity were not affected by disease expression or genetic risk for BD. In contrast, at the local level, patients showed reduced efficiency in the middle occipital gyrus (BA 18/19) and the ventral caudate nucleus, relative to both their siblings and the healthy volunteers. Reduced connectivity of the sensorimotor cortex was present both in patients with BD and their siblings. Our results strongly suggest that disease and genetic risk in BD converge to affect local network organization while global measures appear unaffected.