*Prepared by Branson Fok, Chloe Ip & Candice Leung*

## Intravenous Ketamine Demonstrated Non-Inferiority to Electroconvulsive Therapy in Patients with Non-psychotic Treatment-Resistant Major Depression

**Date: June 22, 2023**

Patients with major depression who fail to respond adequately in 2 or more antidepressant trials are regarded as treatment-resistant or refractory. Electroconvulsive therapy (ECT) is generally considered an effective option for this group of patients. Intranasal esketamine was approved by the U.S. Food & Drug Administration (FDA) in 2019 while intravenous (IV) ketamine is still being investigated by clinicians for its efficacy and safety in treating treatment-resistant major depression.

In this prospective, open-label, randomized trial conducted in the United States, a total of 365 patients with treatment-resistant major depression without any psychotic features participated in the study. Eligible participants were randomly assigned to receive a 3-week treatment of either IV ketamine (at a dose of 0.5 mg/kg of body weight) twice weekly (n=195) or right unilateral ECT thrice weekly (n=170), followed by a 6-month follow-up period. The primary endpoint was the drop in patient-rated Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR-16) score by at least 50% at the end-of-treatment visit compared with their first visit as baseline. The predetermined non-inferiority margin was set at -10 percentage points between the two study groups.

Treatment responses were recorded in 55.4% of patients receiving IV ketamine and 41.2% of patients undergoing ECT, which indicated a difference of 14.2 percentage points (95% confidence interval [CI], 3.9 to 4.2; P<0.001 for non-interiority) in terms of changes in their QIDS-SR-16 scores. Fewer patient-reported memory dysfunction were documented in the IV ketamine group (mean between-group difference = 9.0 points; 95% confidence interval [CI], 5.1 to 13.0) based on the Squire Memory Complaint Questionnaire (SMCQ). Higher incidence of dissociative symptoms was observed in the IV ketamine group while more patients receiving ECT reported musculoskeletal adverse effects.

The clinical study demonstrated the non-inferiority of IV ketamine to ECT in managing non-psychotic treatment-resistant major depression when subanesthetic ketamine was given in a primarily outpatient setting.

Source: www.nejm.org

## Fruquintinub Improves Overall Survival for Refractory Metastatic Colorectal Cancer Patients

**Date: July 1, 2023**

About 50% of colorectal cancer patients develop distant metastases with an overall 5-year survival rate of 15%. Current treatment options available for metastatic colorectal cancer patients include chemotherapy and targeted therapies, in which trifluridine-tipiracil and regorafenib are oral agents that have shown promising effect on median overall survival. However, these agents are often found to induce treatment-related toxicities, necessitating subsequent dose reductions. Fruquintinib is an oral tyrosine kinase inhibitor that is highly selective in vascular endothelial growth factor 1, 2, and 3. This newly developed drug agent targets at the key regulators of angiogenesis during the development of metastases.

The multicenter, randomized, double-blind and placebo-controlled phase 3 FRESCO-2 study had recruited 691 patients from 14 countries to assess the efficacy and safety of fruquintinib in refractory metastatic colorectal cancer patients. Eligible participants were randomly assigned in 2:1 ratio to receive either fruquintinib 5 mg capsule (n=461) or matched placebo (n=230) once daily on day 1-21 in 28-day cycles alongside best supportive care until disease progression, death, unacceptable toxicities or study termination. The primary endpoint was overall survival from the day of randomization to death from any cause, while progression-free survival was a key secondary endpoint of this clinical trial.

An absolute difference of 2.6 months in median overall survival were observed between the fruquintinib (7.4 months; 95% confidence interval [CI], 6.7-8.2) and placebo (4.8 months; 95% confidence interval [CI], 4.0-5.8) group (hazard ratio=0.66; 95% confidence interval [CI], 0.55-0.80; P<0.0001). The fruquintinib group also had a longer median progression-free survival compared to the placebo group (absolute difference=1.9 months; hazard ratio=0.32; 95% confidence interval [CI], 0.27-0.39; P<0.0001). However, a higher percentage of participants in the fruquintinib group (63%) reported grade 3 or worse adverse events, including but not limited to hypertension and asthenia, against the placebo group (50%).

In conclusion, the study unveiled the potential of fruquintinib as a new treatment option to prolong overall survival of refractory metastatic colorectal cancer patients.

Source: www.thelancet.com

## Dupilumab Reduces Moderate-to-Severe Exacerbations in COPD Patients with Type 2 Inflammation

**Date: July 20, 2023**

Chronic Obstructive Pulmonary Disease (COPD) refers to the long-term lung inflammation that causes airflow restriction. Approximately 20-40% of the disease population possess type 2 inflammation, which is characterized by elevated blood eosinophil counts. Current studies have also shown that COPD patients with type 2 inflammation have higher risk of exacerbations. Dupilumab is a fully humanized monoclonal antibody which blocks the receptor components of interleukin-4 and interleukin-13, which are responsible for type 2 inflammatory reactions.

In this multicenter, double-blind, randomized and placebo-controlled phase 3 study, 939 COPD patients (with an absolute blood eosinophil count ≥ 300 per microliter) who have been using standard triple inhaler (inhaled glucocorticoid + long-acting muscarinic antagonist + long-acting $\beta_2$-agonist) therapy were randomized to receive either subcutaneous dupilumab 300 mg (n=468) or matched placebo (n=471) once every 2 weeks as add-on therapy for 52 weeks across 24 countries. Upon completion of the trial period, participants were enrolled in a 12-week follow-up period to assess drug safety. The major primary endpoint was the annualized rate of moderate-or-severe exacerbations during the study period.

The dupilumab group attained an annualized rate of moderate-or-severe exacerbations of 0.78 (95% confidence interval [CI], 0.64-0.93), meanwhile the rate was 1.10 (95% confidence interval [CI], 0.93-1.30) for the placebo group (rate ratio=0.70; 95% confidence interval [CI], 0.58-0.86; P<0.001). Functional improvements in terms of prebronchodilator forced expiratory volume in 1 second (FEV1) were also more significant in the dupilumab group (least-squares mean difference=83 ml; 95% confidence interval [CI], 42-125; P<0.001). The safety profile for both study groups was similar, with comparable rates of adverse events.

As has been demonstrated by the study, the use of dupilumab lowered the annualized rate of moderate-or-severe exacerbations in COPD patients presenting type 2 inflammation. Patients who underwent dupilumab as add-on therapy also showed greater improvements in lung function and quality of life.

Source: www.nejm.org

## FDA Approves Zurzuvae (Zuranolone) as The First Oral Treatment for Postpartum Depression

**Date: August 4, 2023**

Zurzuvae (zuranolone) has been approved by the U.S. Food and Drug Administration (FDA) on August 4th, 2023, as the first oral medication specifically indicated for the treatment of postpartum depression (PPD) in adults. Previously, the only available treatment for PPD was Zulresso (brexanolone), which was administered as an intravenous injection.

PPD is a type of major depressive episode that commonly occurs after childbirth but can also present in later stages of pregnancy. It shares similar symptoms with other forms of depression, including feelings of sadness, loss of interest in previously enjoyed activities, cognitive impairment, feelings of inadequacy, or even suicidal ideation.

The efficacy of Zurzuvae in treating PPD in adults has been demonstrated in two randomized, double-blind, placebo-controlled, multicenter studies. These studies enrolled women with PPD who met the criteria for a major depressive episode according to the Diagnostic and Statistical Manual of Mental Disorders and symptoms which began in the third trimester or within four weeks of delivery. In the first study, patients received 50mg of Zurzuvae or placebo once daily in the evening for 14 days. In the second study, patients received an equivalent of 40mg of Zurzuvae or placebo, also for 14 days. Both studies monitored patients for at least four weeks after the 14-day treatment period. The primary endpoint was the change in depressive symptoms assessed by the total score on the 17-item Hamilton depression rating scale (HAMD-17) on day 15. In both studies, patients in the Zurzuvae groups demonstrated significantly greater improvements in their depressive symptoms compared to those in the placebo groups. The positive effects of treatment were maintained at day 42, which was four weeks after the last dose of Zurzuvae.

Zurzuvae carries a boxed warning to alert individuals about the potential impact on their ability to drive or perform other potentially hazardous activities. Patients should refrain from driving or operating heavy machinery for at least 12 hours after taking Zurzuvae. The most common side effects include drowsiness, dizziness, diarrhea, fatigue, nasopharyngitis, and urinary tract infection. Use of Zurzuvae may also increase the risk of suicidal thoughts and behavior.

The recommended daily dose of Zurzuvae is 50mg, to be taken once daily for a duration of 14 days. It is recommended to take the medication in the evening with a fatty meal.

Source: www.fda.gov