Clinigen notes results from the MIROCALS trial investigating low dose Proleukin® (aldesleukin) in patients with amyotrophic lateral sclerosis

Clinigen Limited (‘Clinigen’), the global pharmaceutical services company, is pleased to note the announcement of top-line results from MIROCALS (Modifying Immune Response & Outcomes in Amyotrophic Lateral Sclerosis) a phase 2b randomised placebo-controlled trial investigating the efficacy and safety of low dose interleukin-2 (ld IL-2) for controlling neuro-inflammation in newly-diagnosed patients with amyotrophic lateral sclerosis (ALS).

The MIROCALS trial, conducted in 220 patients from 17 clinics across the UK and France, in collaboration with eight leading research groups in the UK, France, Italy and Sweden, investigated whether low dose IL-2 can modify aspects of neuro-inflammation, which is believed to play a central role in ALS disease progression.

Dr. Gilbert Bensimon presented the top-line results at the International Symposium on ALS / Motor Neuron Diseases. The unadjusted analysis of the primary endpoint showed a 19% reduction in risk of death in IL2 treated patients compared with placebo, which was not statistically significant. However, analysis adjusting for a pre-specified primary core biomarker, cerebrospinal fluid phosphorylated neurofilament heavy chain (CSF-pNFH), demonstrated a statistically significant decrease (73%) in the risk of death for the IL2 group over the 21-month trial period.

Interaction by CSF-pNFH levels was found to be selective. The interaction on survival was not present in patients with high CSF-pNFH (21% of study participants), which corresponded with aggressive, fast progressing disease. However, patients with low to moderate CSF-pNFH levels (79% of study participants), correlating with less aggressive disease progression, demonstrated a significant decrease in the risk of death (43%) for the IL2 group.

Similarly, a slowing of decline in ALSFRS-R (ALS Functional Rating Scale – Revised, a key metric in functional capability in patients with ALS) was found in the IL2 group of patients with low CSF-pNFH levels (c. 70% of study participants).

The treatment was well tolerated, with adverse events recorded as mostly mild to moderate, occurring across both active treatment and placebo arms.

David Bryant, Chief Executive Officer of Clinigen, said: “The MIROCALS Phase II clinical trial data presented is positive news for patients with ALS, for which there is currently no effective treatment, and we look forward to understanding what further research is planned.”

Clinigen confirms that Proleukin, interleukin-2 (aldesleukin), supplied for the MIROCALS trial, is currently licensed for metastatic renal cell carcinoma and melanoma in the US and metastatic renal cell carcinoma in certain other countries.

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Contact details

Clinigen Limited
Michelle Shearly, Director of Communications
+44 (0)7957 984570
michelle.shearly@clinigengroup.com

Consilium Strategic Communications
Mary-Jane Elliott / Matthew Cole / Jessica Hodgson
Tel: +44 (0) 20 3709 5700
Clinigen@consilium-comms.com

Notes to Editors

About Clinigen

Clinigen is a global, specialist pharmaceutical services company focused on providing ethical access to medicines. Its mission is to deliver the right medicine to the right patient at the right time. The Group operates from sites in North America, Europe, Africa and the Asia Pacific. Clinigen has more than 1,000 employees across five continents in 15 countries, with supply and distribution hubs and operational centres of excellence in key long-term growth regions. The Group works with 32 of the top 50 pharmaceutical companies providing access across more than 120 countries.

Clinigen acquired the global rights to Proleukin outside the United States in 2018 and the US rights in 2019.

For more information on Clinigen, please visit http://www.clinigengroup.com

About Proleukin

Proleukin (Aldesleukin) is a recombinant interleukin-2 (IL-2), a cytokine whose role in the immune system has been extensively studied. At conventional doses it is used in the treatment of kidney cancer that has spread to another part of the body (metastatic kidney cancer). It is also currently being studied as part of adoptive cellular therapy. At significantly lower doses than those used in oncology aldesleukin has demonstrated immunomodulatory effects in certain auto-immune and inflammatory disease states by boosting the levels of a particular subset of white blood cells called T-regulatory lymphocytes (Tregs).

The Following Information is Intended for the U.S. Audience Only.

Proleukin® (aldesleukin) is indicated for the treatment of adults with metastatic renal cell carcinoma (mRCC) and metastatic melanoma (mM).

Summary of Important Safety Information for Proleukin® (aldesleukin) for injection, for intravenous infusion.

<table>
<thead>
<tr>
<th>WARNINGS</th>
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<tbody>
<tr>
<td>Therapy with Proleukin® (aldesleukin) should be restricted to patients with normal cardiac and pulmonary functions as defined by thallium stress testing and formal pulmonary function testing. Extreme caution should be used in patients with a normal thallium stress test and a normal pulmonary function test who have a history of cardiac or pulmonary disease.</td>
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<tr>
<td>Proleukin should be administered in a hospital setting under the supervision of a qualified physician experienced in the use of anticancer agents. An intensive care facility and specialists skilled in cardiopulmonary or intensive care medicine must be available.</td>
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Proleukin administration has been associated with capillary leak syndrome (CLS) which is characterized by a loss of vascular tone and extravasation of plasma proteins and fluid into the extravascular space. CLS results in hypotension and reduced organ perfusion which may be severe and can result in death. CLS may be associated with cardiac arrhythmias (supraventricular and ventricular), angina, myocardial infarction, respiratory insufficiency requiring intubation, gastrointestinal bleeding or infarction, renal insufficiency, edema, and mental status changes.

Proleukin treatment is associated with impaired neutrophil function (reduced chemotaxis) and with an increased risk of disseminated infection, including sepsis and bacterial endocarditis. Consequently, preexisting bacterial infections should be adequately treated prior to initiation of Proleukin therapy. Patients with indwelling central lines are particularly at risk for infection with gram positive microorganisms. Antibiotic prophylaxis with oxacillin, nafcillin, ciprofloxacin, or vancomycin has been associated with a reduced incidence of staphylococcal infections.

Proleukin administration should be withheld in patients developing moderate to severe lethargy or somnolence; continued administration may result in coma.

**INDICATIONS AND USAGE**

Proleukin® (aldesleukin) is indicated for the treatment of adults with metastatic renal cell carcinoma (metastatic RCC).

Proleukin is indicated for the treatment of adults with metastatic melanoma.

Careful patient selection is mandatory prior to the administration of Proleukin.

Evaluation of clinical studies to date reveals that patients with more favorable ECOG performance status (ECOG PS 0) at treatment initiation respond better to Proleukin, with a higher response rate and lower toxicity. Therefore, selection of patients for treatment should include assessment of performance status.

Experience in patients with ECOG PS > 1 is extremely limited.

**CONTRAINDICATIONS**

Proleukin® (aldesleukin) is contraindicated in patients with a known history of hypersensitivity to interleukin-2 or any component of the Proleukin formulation.

Proleukin is contraindicated in patients with an abnormal thallium stress test or abnormal pulmonary function tests and those with organ allografts. Retreatment with Proleukin is contraindicated in patients who have experienced the following drug-related toxicities while receiving an earlier course of therapy: sustained ventricular tachycardia (≥ 5 beats), cardiac arrhythmias not controlled or unresponsive to management, chest pain with ECG changes, consistent with angina or myocardial infarction, cardiac tamponade, intubation for > 72 hours, renal failure requiring dialysis > 72 hours, coma or toxic psychosis lasting > 48 hours, repetitive or difficult to control seizures, bowel ischemia/perforation, GI bleeding requiring surgery.

**WARNINGS**

Because of the severe adverse events which generally accompany Proleukin therapy at the recommended dosages, a thorough clinical evaluation should be performed to identify patients with significant heart, lung, kidney, liver or central nervous system impairment in whom Proleukin is not indicated for use. Patients with
normal heart, lung, liver and central nervous system function may experience serious, life-threatening or fatal adverse events.

Should adverse events, requiring dose modification occur, dosage should be withheld rather than reduced.

Proleukin has been associated with exacerbation of preexisting autoimmune disease and inflammatory disorders. In some cases, the onset of new autoimmune diseases, such as vitiligo, may occur. Symptomatic hyperglycemia and/or diabetes mellitus have been reported during Proleukin therapy.

All patients should have thorough evaluation and treatment of CNS metastases and have a negative scan prior to receiving Proleukin therapy. New neurologic signs, symptoms, and anatomic lesions following Proleukin therapy have been reported in patients without evidence of CNS metastases. Neurologic signs and symptoms associated with Proleukin therapy usually improve after discontinuation of Proleukin therapy; however, there are reports of permanent neurologic defects. In patients with known seizure disorders, extreme caution should be exercised as Proleukin may cause seizures.

PRECAUTIONS

Patients should have normal cardiac, pulmonary, hepatic, and CNS function at the start of therapy. Capillary leak syndrome (CLS) begins immediately after Proleukin® (aldesleukin) treatment starts and is marked by increased capillary permeability to protein and fluids and reduced vascular tone.

Proleukin® (aldesleukin) treatment should be withheld for failure to maintain organ perfusion as demonstrated by altered mental status, reduced urine output, a fall in the systolic blood pressure below 90 mm Hg or onset of cardiac arrhythmias.

Recovery from CLS begins soon after cessation of Proleukin therapy. Usually, within a few hours, the blood pressure rises, organ perfusion is restored and reabsorption of extravasated fluid and protein begins.

Kidney and liver function are impaired during Proleukin treatment. Use of concomitant nephrotoxic or hepatotoxic medications may further increase toxicity to the kidney or liver.

Mental status changes including irritability, confusion, or depression which occur while receiving Proleukin may be due to bacteremia or early bacterial sepsis, hypoperfusion, occult CNS malignancy, or direct Proleukin-induced CNS toxicity. Patients should be evaluated for these and other causes of mental status changes. Alterations in mental status due solely to Proleukin therapy may progress for several days before recovery begins. Rarely, patients have sustained permanent neurologic deficits.

Proleukin enhancement of cellular immune function may increase the risk of allograft rejection in transplant patients.

Serious manifestations of eosinophilia involving eosinophilic infiltration of cardiac and pulmonary tissues can occur following Proleukin.

ADVERSE REACTIONS

The rate of drug-related deaths in the 255 metastatic RCC patients who received single-agent Proleukin® (aldesleukin) was 4% (11/255); the rate of drug-related deaths in the 270 metastatic melanoma patients who received single-agent Proleukin was 2% (6/270).
Adverse events are frequent, often serious, and sometimes fatal. The following adverse events (Grades 1-4) were seen in ≥ 30% of 525 patients (255 with metastatic kidney cancer and 270 with metastatic melanoma) treated with Proleukin: low blood pressure (71%), diarrhea (67%), low urine output (63%), chills (52%), vomiting (50%), shortness of breath (43%), rash (42%), increased bilirubin in blood (40%), decreased clotting of blood (37%), nausea (35%), confusion (34%), and decreased kidney function (33%).

Please see the full Prescribing Information, including Boxed Warning, for Proleukin® (aldesleukin) for injection, for intravenous infusion.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

The content contained in this website is not intended to be a substitute for professional medical advice related to any topic discussed. Patients are urged to consult with their treating physicians or other professionals. Never disregard professional, medical, or legal advice or delay seeking such advice because of something you have read on this website.