Advance reports

Included in this report are highlights of recent trials on Parkinson's disease, heart failure and metabolic syndrome.

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New trial on acute heart failure launched

The first-ever acute heart failure (AHF) Phase III trial to be specifically designed to assess the effect of early treatment on cardiovascular mortality has been initiated.

TRUE-AHF (TRial of Ularitide's Efficacy and safety in patients with Acute Heart Failure) aims to show that early treatment with intravenous (IV) ularitide may reduce AHF symptoms in the short-term and cardiovascular mortality in the long-term. Health authorities have agreed with the designation of cardiovascular mortality as a primary efficacy endpoint, and patient enrolment is already underway in the US and Europe.

Heart failure is a significant public healthcare concern, with an overall population prevalence of approximately one to three per cent, rising to approximately 10% in the very elderly. AHF is one of the most common reasons for unscheduled hospitalisation of people over the age of 65 years. AHF patients are at a markedly increased risk of rehospitalisation within three months of their first episode and experience mortality rates five-times greater than that of patients following a heart attack.

TRUE-AHF is designed to build on the growing body of evidence that suggests patients suffering from AHF should be treated as early as possible. Heart failure experts, cardiologists and emergency physicians are working hand-in-hand to ensure an early enrolment of patients into the trial (within the first hours after presentation to the hospital). The trial is evaluating the following endpoints:

- A composite score that assesses the symptoms and clinical course of patients during the 48-hour infusion of ularitide.
- Cardiovascular mortality following randomisation for the entire duration of the trial.

Approximately 190 centres across the US, Europe, Canada and Latin America will be involved in the TRUE-AHF trial, and approximately 2,152 patients with AHF will be randomised to receive placebo or ularitide for 48 hours in addition to standard care.

Elmar Schnee, CEO Chairman at Cardiorentis Ltd said: "We have been in close discussions with the health authorities to achieve the most robust study design for TRUE-AHF. We wanted the study design to reflect our belief that ularitide could provide symptom improvement and a reduction in cardiovascular mortality, which are both crucial measures for new therapies being investigated for the treatment of AHF. Following promising results in previous clinical trials SIRIUS I and II, we are confident ularitide will provide clinicians with a much needed addition to their AHF treatment armamentarium. We are also encouraged that such a highly regarded group of cardiologists and emergency physicians are working in partnership with us on the clinical programme".

Deep brain stimulation in PD provides superior benefits according to new study

Results from a clinical study published recently in *The New England Journal of Medicine* show that use of Medtronic deep brain stimulation (DBS) therapy provides superior benefits for patients with early motor complications from Parkinson's disease when compared with best medical treatment only.

The first large, multicenter, randomised controlled trial to evaluate Parkinson's patients with early motor complications showed patients treated with DBS therapy and best medical treatment reported a mean improvement of

26% in their disease-related quality of life at two years, compared with no improvements in patients treated with best medical therapy alone. The clinical trial included 251 people with Parkinson's disease at 17 centers in Germany and France and followed them over the course of two years.

Additional key findings at two years include 53% improvement in motor skills (in an off-medication condition) in patients treated with DBS therapy, compared to no change in those receiving best medical therapy only. There was also a 30% improvement in various activities of daily life, including speech, handwriting, dressing and walking, in participants with DBS therapy while in the worst condition ("off time"), compared to a 12% decline in those receiving best medical therapy only ($p<0.001$).

Other results include a 61% improvement in levodopa-induced complications, including dyskinesias and motor fluctuations, in participants receiving DBS therapy at two years, compared to a 13% worsening in those only receiving best medical therapy and a 39% reduction in daily levodopa equivalent dosage in the DBS therapy group, versus a 21% increase in dosage in participants receiving best medical therapy alone.

Günther Deuschl, Professor of Neurology at Christian-Albrechts-University in Kiel, and lead investigator of the EARLYSTIM study for Germany said: "These results signal a shift in the way patients with Parkinson's disease can be treated, and prove that deep brain stimulation therapy can improve patients' quality of life even in the earlier stages of Parkinson's disease, when fluctuations and dyskinesia just start and clinicians traditionally rely solely on drugs".

New data on Bimuno for metabolic syndrome

Positive results of a clinical study of Bimuno® for metabolic syndrome have recently been published in the *The Journal of Nutrition.*

Bimuno is a unique trans-galactooligosaccharide prebiotic, and a recent study looked at whether it could alter bacteria in the human gastrointestinal tract to help prevent and manage metabolic syndrome.

The double-blind, randomised, placebo-controlled, crossover study has been conducted on behalf of Clasado by a research team led by Dr. Jelena Vulevic, School of Food Biosciences, University of Reading. The trial tested the effect of consuming the trans-galactooligosaccharide mixture Bimuno (a prebiotic used by human gastrointestinal microbes), altering which bacteria reside in the gastrointestinal tract, and its effects on metabolic syndrome. This is the first time such effects using a non-digestible oligosaccharide have been reported.

The Bimuno research is part of an on-going programme by Clasado in collaboration with the University of Reading's Food Microbial Sciences Unit and other globally recognised research institutes. Metabolic syndrome refers to the group of health conditions that includes high blood sugar, hypertension and central adiposity. These tend to occur together and increase the likelihood of developing cardiovascular disease, type 2 diabetes, and some forms of cancers.

The study demonstrated that Bimuno positively affected the gut microbiota by increasing the number of positive bifidobacteria, whilst reducing more negative bacteria. Positive effects were seen as early as six weeks. There was also a positive effect on immune responses by increasing faecal sIgA (marker of mucosal immunity), and decreasing calprotectin and CRP (markers of inflammation). Additionally insulin, total cholesterol, triglycerides and TC/HDL ratio (markers of metabolic syndrome) was reduced.

It was concluded by the team that the addition of Bimuno to the diet of individuals who are at risk of developing, or already have, metabolic syndrome could contribute to enhancing their gastrointestinal health, immune function and reduce some of the risk factors.

While efforts to improve the diet and increase exercise in at risk individuals should continue to be the primary advice, these findings may have implications for those that either cannot, or will not, change their dietary habits or lifestyle significantly.

"Poor diet and inactive lifestyles in the western world continue to increase the prevalence of metabolic syndrome, already affecting 25% of those in the US and UK, and resulting in cardiovascular disease, type 2 diabetes, and cancers," said Geoff Collins, Head of Consumer Marketing, Clasado. "It is critical to understand how modifying the gut microbiota and immune system can affect this. We are delighted that Clasado's Bimuno might be able to contribute to combating metabolic syndrome".