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Pilot Scale Human Clinical Trials with a Scientifically Validated Probiotic Formulation - Kibow Biotics® With CKD Stage III and IV Patients (Mid-term and partial data analysis from Canada)

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1. INTRODUCTION

Probiotics are increasingly utilized clinically. As their safety and health benefits are established, it is reasonable to anticipate that probiotic bacteria will be incorporated into a growing number of clinical regimens.

Following exploratory testing of orally administered probiotic bacteria in rats and minipigs with surgically induced chronic kidney disease (CKD), a trial is now in progress to determine whether daily treatment with gastrointestinal (GI) probiotic bacteria will delay the onset of and/or improve established signs and symptoms of human CKD.

Hypothesis:
To assess the potential benefit in devising a gut-based probiotic formulation (Kibow Biotics®) as therapy in CKD:
•The bowel can serve as a complement to the kidneys' excretory function
•A specifically formulated probiotic product comprised of defined and tested microbial strains may afford renoprotection in what has been called "enteric dialysis"®

2. PRIOR STUDIES

- Performed extensive *in vitro* R&D investigations in Kibow's laboratories for bacterial strain screening.
- Simulated Human Intestinal Microbial Ecosystem (SHIME, Ghent University, Belgium) utilized in a computer-controlled *in vitro* system. Bacterial strains studied were *Streptococcus thermophilus* (KB27), *Lactobacillus acidophilus* (KB31) and *Bifidobacterium longum* (KB35).
- Oral administration of these bacterial formulations, tested in the 5/6th nephrectomized rat model (at Thomas Jefferson University, Phila., PA) and minipig model (at Indiana University, Indianapolis, IN), decreased both blood urea nitrogen (BUN) and serum creatinine (Scr) levels.
- Two independent veterinarians investigated the effect of Kibow Biotics® on clinically manifested renal failure in uremic cats and dogs of both genders and varying body weights. Based on positive results, this formulation, marketed and distributed as Azodyl™, is currently licensed for veterinary applications to Vetoquinol SA worldwide (A European publicly traded veterinary business with its corporate headquarters in Paris, France)

3. GOALS

- Confirm the alleviation of uremic syndrome hypothesis
- Determine the outcome of probiotics treatment
- Confirm U.S. FDA's Generally Recognized As Safe (GRAS) status

4. INCLUSION CRITERIA

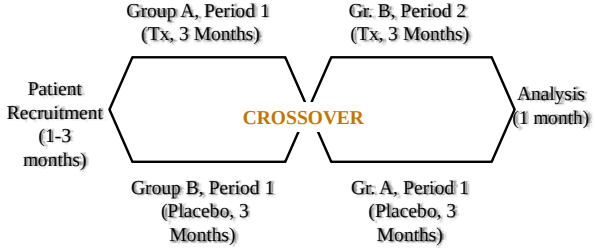
- CKD patients Stage III and IV
- 18 to 75 years old, able and willing to give an informed consent
- Baseline serum creatinine >2.5 mg/dL

5. TREATMENT REGIMEN AND STUDY DESIGN

Treatment Regimen
- 1st treatment period – 3 months
- Crossover after 3 months
- 2nd treatment period – 3 months
- Data analysis – 1 month

As soon as recruitment period began, the participants (n=14) were randomized and treated on a rolling basis according to the date of enrollment

Study Design
Multi-site, randomized, double blind, placebo controlled crossover study in an outpatient setting. Each patient will act as their own placebo control. Minimum enrollment at each site is 30 patients (present data is on patients (n=14) who completed the study at the Canadian site).



6. CLINICAL PARAMETERS

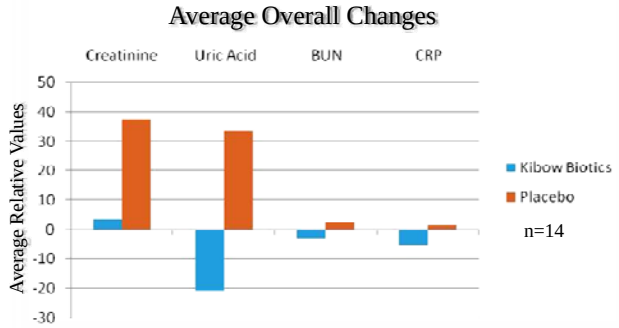
Control and treated preliminary cohorts were monitored and compared by following parameters known to vary and correlate with progressive CKD:

PRIMARY: Body weight or body mass index (BMI), blood pressure (BP), complete blood count (CBC).

SECONDARY: Blood chemistry determinations (including blood urea nitrogen (BUN), serum creatinine, phosphorus, uric acid) and a standardized metabolic profile in CKD. Additionally, alanine aminotransferase (ALT), C-reactive protein (CRP), serum ammonia, random urine collection for measurement of creatinine and urinary protein concentrations and fecal microbial content will be assayed.

TERTIARY: Quality of life (QOL) will be assessed on a scale of 1 to 5.

7. RESULTS



8. CONCLUSION

From these preliminary data, we infer that oral ingestion of a probiotic regimen as formulated for these CKD patients appear safe and may proffer benefit by augmenting gut microflora. Similar studies are in progress in Argentina, Canada, Mexico, Nigeria and USA. Clinical trials towards potential clinical applications for a gut-based uremia therapy is strongly warranted including additional dosage escalation studies.