2. SYNOPSIS

Company name: ACRAF S.p.A.	**TABULAR FORMAT** REFERRING TO	(For National Authority Use Only)
Name of the finished product: Not applicable	Volume:	
Name of the active substance: Bindarit	Page:	

Title of the study: The effects of the association bindarit + irbesartan versus irbesartan alone on albuminuria of patients with Diabetic Nephropathy. Placebo-controlled study.

[redacted]

Study centre(s): Multicentre, international study

Publication (reference): not applicable

Study period (years): 2007-2008 | **Clinical Phase:** II

Objectives: the primary objective was to to evaluate the anti-albuminuric effect of bindarit 1200 mg/daily (600 mg bid) in type 2 diabetic patients with diabetic nephropathy and hypertension.
The secondary objectives were:
i) to compare the MCP-1/CCL2 urinary levels between treatment groups;
ii) to compare the rate of remission (from micro- to normo- and from macro- to microalbuminurua) in the two treatment groups;
iii) to correlate the MCP-1/CCL2 urinary levels and UAE within treatment groups;
iv) to detect any relationship between degree of UAE reduction and serum lipids profile within treatment groups;
v) to evaluate the comparative safety and tolerability of bindarit in association with irbesartan.

Methodology: double-blind, multicentre, randomized, stratified, placebo-controlled, parallel groups trial in patients with DN undergoing irbesartan therapy. Ten visits were scheduled: V-4, V-3, V-2 ,V-1 (screening period, weeks -4, -3, -2, -1), V0 (baseline, week 0), V1, V2, V3 (intermediate visits, weeks 2, 4, 8 after bindarit or placebo treatment) V4 (final/ETV visit, week 12 after bindarit or placebo treatment), V5 (follow-up visit, week 16 after bindarit or placebo treatment).

Number of subjects (total and per treatment): 90 patients were randomized (45 bindarit and 45 placebo) and 89 (45 bindarit and 44 placebo) treated with the investigational drug.

Diagnosis and inclusion criteria: type 2 diabetes with nephropathy. The inclusion criteria were:
i) male and female patients with no limitation of race, aged 30 to 70 years;
ii) Type 2 diabetes defined as: > 30 years of age at diagnosis; insulin not required within 6 months from initial diagnosis; no history of diabetic ketoacidosis; currently treated with diet, oral hypoglycemics or insulin;
iii) microalbuminuria defined as urinary albumin excretion, 20 to 200 µg/min in at least 2 of 3 overnight urine samples or macroalbuminuria defined as urinary albumin excretion, > 200 µg/min in at least 2 of 3 overnight urine samples, confirmed in the baseline collection; should baseline albuminuria data not to be available, the patient may have been conditionally treated;
iv) glycosylated haemoglobin (Hb A_{1c}) <12% at Screening;

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v) serum creatinine ≤ 3 mg/dL at Screening;
vi) normotensive patients or hypertensive patients on stable antihypertensive therapy over the last 3 months and without specific contraindications to angiotensin antagonist therapy;
vii) female patients of childbearing potential required to have a negative pregnancy test and use an approved birth control method;
viii) patients legally able to give written informed consent to the trial (signed and dated by the patient).

Test product, dose, mode of administration: Bindarit 600 mg (2 tablets of bindarit 300 mg) bid + irbesartan 300 mg (2 tablets of irbesartan 150 mg) once a day.

Batches no of bindarit tablets. 00079IP04, 00079IP05, 00079IP06, 00079IP08

Reference therapy, dose, mode of administration: placebo (2 tablets) bid + irbesartan 300 mg (2 tablets of irbesartan 150 mg) once a day.

Batches no of placebo tablets: Placebo batches no 0007IP07.

Duration of treatment: 12 weeks

Assessment criteria:

Primary endpoint: UAE rate, measured in three consecutive overnight samples. The patient UAE levels were assessed at each visit and compared to the baseline value. Comparisons between treatment groups and subgroups were also performed.
Secondary endpoints: the comparative measurement of MCP-1/CCL2 urinary levels, the comparison in the remission rate (from micro- to normo- and from macro- to microalbuminurua) in the two treatment groups, the correlation between UAE reduction and serum lipids profile" (overall), and monitoring the safety and tolerability of bindarit in association with irbesartan compared with irbesartan plus placebo.
Efficacy variables: Albuminuria was assessed by measurements of the UAE rates in the 3 consecutive overnight urine specimens; the urinary MCP-1/CCL2 was evaluated in overnight urine specimens; serum lipids (Total cholesterol, Cholesterol-HDL, Triglycerides, Apo A and Apo B) were evaluated at Screening – 4 , at Baseline, Visit 2, 3, 4 and Follow-up.
Criteria of safety and tolerability: Safety was assessed by monitoring the frequency of adverse events in each treatment group. In addition, changes from baseline in physical examination, vital signs, laboratory analyses and ECG were assessed.

Statistical methods:
All efficacy evaluations were made on a modified ITT population which was defined as all randomised subjects who received at least one dose of the experimental drugs, had complete baseline UAE (primary parameter) and UAE (primary parameter) at week 12/visit 4. In addition, UAE analyses were also performed in a subgroup of macroalbuminuric patients with albuminuria < 2000 µg/min. In this analysis, all patients with albuminuria in the nephrotic range (albuminuria > 2000 µg/min) were excluded.

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For each visit, the log-transformed median UAE of three consecutive overnight samples was calculated. Changes from baseline were investigated with an analysis of variance (ANOVA) or covariance (ANCOVA) at each visit including treatment and centers as factors and baseline as covariate, as appropriate. Due to the exploratory nature of the study, within-groups comparisons were also assessed by performing paired t-test at each time-point to examine changes from baseline .
With regards to the rate of remission, patients were classified as "unchanged" if no modifications at week 12 from the baseline stratification were observed, "improved" if only improvements at week 12 from the baseline stratification were observed (from macro to micro or from micro to normo) and "worsened" if only worsements at week 12 from the baseline stratification were observed (from micro to macro). A Cochran-Mantel-Haenszel test was applied.
Treatment comparison on the log-transformed median MCP-1/CCL2 was analyzed by an analysis of covariance (ANCOVA) using a model for center differences with baseline as covariate.
Correlation and linear regression were applied on MCP-1/CCL2 and UAE and on serum lipids (total cholesterol, cholesterol-HDL, triglycerides, Apo A and Apo B) and UAE.
Safety and tolerability were to be assessed in the treated population. The extent of exposure beyween groups was examined by a t-test. Fisher's exact test was used for comparison between treatment groups as regards the percentage of patients with AEs. At each visit, an analysis of covariance or an analysis of variance on the difference from baseline was applied for laboratory tests, the vital signs (systolic blood pressure, diastolic blood pressure, pulse rate), body weight. Laboratory parameters which showed statistical significant difference between groups in the analysis of covariance or in the analysis of variance, were categorized using Cohen's d effect sizes.

SUMMARY – CONCLUSION

Efficacy results: The efficacy analysis investigated the reduction of the UAE and MCP-1/CCL2 over time in the two treatment arms.
In the overall study population there was a significant difference in the change in UAE (log transformed data) between treatment groups at week 2. In the bindarit arm, a significant reduction in log-transformed UAE relative to baseline, was observed at week 2, 4, and 8. These differences failed to be significant after controlling for the effect of baseline UAE.
In patients with microalbuminuria no significant effect on the UAE was observed within both treatments groups. In contrast, in patients with macroalbuminuria, a significant reduction in log-transformed UAE relative to baseline was shown within bindarit group at week 4, 8 and 12. This effect was increased when macroalbuminuric patients with UAE > 2000 µg/min were excluded. These differences failed to be significant after controlling for the effect of baseline UAE.
No statistically significant differences in the MCP-1/CCL2 median percent change over time were observed in the overall study population and in any of the study strata.
Correlations between MCP-1/CCL2 and raw median UAE scores were marginal in bindarit (r^2=0.0722) and and placebo group (r^2=0.0206). Even weaker correlations were observed between serum lipids (total cholesterol, cholesterol-HDL, triglycerides, Apo A, Apo B) and UAE in both treatments arms.

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SUMMARY – CONCLUSION

Safety results:

All patients who received at least one dose of investigational product were included in the safety analysis and there were no differences in mean days of exposure between treatment groups.

Qualitative analysis of AEs and SAEs did not reveal major differences between treatment groups in the total number and, for the AEs only, in the distribution of events across systems. The safety review of vital signs, physical findings and urinalysis did not show a clinical effect of bindarit on any of the parameters.

Patients treated with bindarit had a medium-to-large reduction in total and direct bilirubin concentration, a medium-to-large increase in levels of total cholesterol, tryglicerids and Apo B, a medium increase in γ-GT, LDH and CPK, and a medium decrease in ALT.

Patients treated with bindarit had medium to large changes in potassium, and small changes in sodium and calcium levels. The medium increase in the eosinophils and alpha-1 and alpha-2 globulin percentages and in BUN concentration in patients treated with bindarit appears to be of limited or no clinical significance.

Conclusion:

Overall safety results suggest that bindarit is well tolerated in this group of patients. The analysis of AEs was not suggestive of any major risks. Lipid metabolism (as indexed by cholesterol and Apo B-100), potassium and LDH deserve to be carefully monitored in further studies. Reduced levels of total and direct bilirubin are unlikely to be of clinical significance.

Overall efficacy results suggest that bindarit might be able to reduce albuminuria relative to placebo at least in the macroalbuminuric subgroup of patients. Whitin the bindarit group, the reduction of albuminuria relative to baseline was shown in patient with macroalbuminuria but not in patients with microalbuminuria.For macroalbuminuric patients the effect was more eviden when patients with UAE >2000 µg/min were excluded. These differences failed to be significant after controlling for the effect of baseline UAE.

Bindarit did not reduce urinary levels of MCP-1/CCL2 relative to placebo in any of the study strata. Short of a new and hitherto unknown mechanism of action, one might speculate that tissue levels of MCP-1/CCL2 are not reflected by urinary levels within the time frame of this study. The mechanism of action should be further elucidated

Patients with macroalbuminuria but without heavy albuminuria should be good candidates for adequately powered further studies aimed at investigating the long term persistency of the effects of bindarit. If confirmed these data may have major clinical relevance since this is a high risk population in urgent need for novel treatments to limit progression to end stage renal kidney disease and the excess cardiovascular mortality associated with chronic kidney disease.

Date of the Clinical Report: August 2011

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