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: A pilot study to evaluate the efficacy and safety of different bindarit dosages in preventing stent restenosis.

[redacted]

Study centre(s): Multicentre, international study

Publication (reference): not applicable

Study period (years): 2009-2011	**Clinical Phase:** II

Objectives: The main study objective was to assess the efficacy and safety of different bindarit dosages compared to placebo in preventing restenosis, in patients submitted to coronary stenting and using the Multi-link Vision® BMS, by Abbott.
The primary endpoint was the in-segment late loss (in-stent and 5 mm proximally and distally to the stent) evaluated at angiography performed at 6 months from the index procedure.
Secondary endpoints were:

- the assessment of the safety profile of the two bindarit dosages compared to placebo
- the occurrence of Mayor Cardiac Events (MACE) at 9 months (acute myocardial infarctions, death, target lesions revascularization), target vessel revascularization, binary angiographic restenosis, in-stent late loss
- the imaging parameters at 6 months from the index procedure evaluated with OCT as an optional procedure on a subgroup of patients, namely:
  - The neointimal proliferation on the surface of the struts
  - The frequency of stent malapposition
- the investigation of bindarit mechanism of action through the assessment of inflammatory biomarkers

Methodology: double-blind, double dummy, multicenter, stratified, randomized, dose-finding, placebo-controlled, parallel groups study in patients candidate to Percutaneous Transluminal Coronary Angioplasty (PTCA). Nine visits were scheduled: Screening visit (-10/0 day before the PTCA), V1, V2, V3, V3bis, V4, V4bis (1, 30, 60, 120, 150 days after the stent placement), V5 (final/ETV visit, 180 days after the stent placement), V6 (follow-up visit, 270 days after the stent placement).

Number of subjects (total and per treatment): 149 patients were randomized (48 bindarit 600 mg, 50 bindarit 1200 mg and 51 placebo) and 148 (48 bindarit 600 mg, 49 bindarit 1200 mg and 51 placebo) treated with the investigational drug.

2. SYNOPSIS (cont'd)

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:	

Diagnosis and inclusion criteria: Patients candidate to PTCA. The inclusion criteria were:

a) Male and female patients with no limitation of race, > 18 years of age (or minimum age as required by local regulations). Female patients of childbearing potential, required to have a negative pregnancy test and use a birth control method. Oral contraceptive were not allowed.
b) Diagnosis of angina pectoris as defined by Canadian Cardiovascular Society Classification (CCS I,II, III, IV) OR unstable angina pectoris (Braunwald Classification B&C, I-II-III), or patients with documented silent ischemia.
c) Maximum of two de novo lesions (>70% stenosis) per patients, to be treated with no other planned procedure within six months from the index intervention.
d) Each lesion should have been required a single stent not longer than 28 mm and with a diameter of 2.5 mm or larger. In case additional stents were needed, the operator was allowed to implant them in order to treat a suboptimal result such as residual edge stenosis or dissection. Additional stents should have been implanted with minimal overlap. Multiple stenting should have not been allowed as intention to treat strategy due to the specific inclusion criteria which had been set.
e) Patients eligible for the placement of the Vision (Abbott) bare metal stent.
f) The patient willing and able to cooperate with the protocol procedures, particularly attending the scheduled visits.
g) Patients legally able to give written informed consent to the trial.

A written informed consent to the trial signed and dated by the patient was available.

Test product, dose, mode of administration: Bindarit 300 mg (1 tablet of bindarit 300 mg + 1 placebo tablet) bid; bindarit 600 mg (2 tablets of bindarit 300 mg) bid;

Batches no. of bindarit tablets were 00079IP08, 00079IP11

Reference therapy, dose, mode of administration: placebo (2 tablets).

Batches no. of placebo tablets were 00264IP01, 00264IP02, 00264IP03

Duration of treatment: 6 months

Assessment criteria:
Primary endpoint: in-segment late loss (in-stent and 5 mm proximally and distally to the stent) measured by QCA at 6 months from the index procedure.
Secondary endpoints: the occurrence of Major Adverse Cardiac Events (MACE) at 9 months, target vessel revascularization, binary angiographic restenosis, in-stent late loss; the assessment of the safety profile of the two bindarit dosages compared to placebo; the imaging parameters (neointimal proliferation on the surface of the struts and the frequeny of stent malapposition) at 6 months from the index procedure evaluated with OCT on a subgroups of patients; the assessment of inflammatory biomarkers

2. SYNOPSIS (cont'd)

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:	

Assessment criteria:

Efficacy variables: Efficacy was assessed by QCA measurements: late loss and binary angiographic restenosis were evaluated at 6 months from the index procedure. Clinical endpoints were evaluated by the assessment of angina and/or MACE occurrence. Inflammatory biomarkers plasma levels and the imaging parameters evaluated by OCT were assessd.

Criteria of safety and tolerability: Safety was assessed by monitoring the frequency of adverse events in each treatment group. Bleeding status was evaluated globally as the documentation of any change in frequency or severity or occurrence of new bleeding from the previous visit. In addition, changes from baseline in physical examination, vital signs, laboratory analyses and ECG were assessed.

Statistical methods: All analyses, except those for angiographic data, were based on the safety population, which consisted of all patients who received at least one dose of experimental drug. All efficacy evaluations were based on two study populations: intention-To-Treat (ITT) and Per Protocol population (PP).The ITT was defined as all randomised subjects who received at least one dose of the experimental drug, had complete QCA assessment procedures (QCA POST and QCA FU).The PP population was redefined as all randomised patients who met elegibility criteria, had adequate compliance (80%) to the study treatment, received aspirin + clopidogrel as dual antiplatelet therapy and were required to have QCA POST and QCA FU, the latter under strict temporal criteria. Patients with a poor compliance but randomized in the placebo arm were included in the PP population.The Sponsor choice for a modified PP, including also patients who did not complete all assessment procedure, is reasonable given the exploratory nature of the study.

In addition, also patients with an initial stenosis just equal to 70%, but satisfying the other entry criteria and with adeguate compliance to the study procedure/experimental treatment were included in the PP. All randomized lesions were included in the descriptive analyses for the primary and secondary endpoints carried out as planned in the protocol. Each lesion was considered indipendently.

In addition, hypothesis tests were also carried out. These additional analyses were exploratory, therefore no claims are intended. No adjustment for multiplicity was planned. An alpha equal to 0.05 was used in the significance tests (Two-sides). Analysis of variance or Mantel-Haenszel Chi-square test were applied for some demographic and baseline characteristics.

To avoid inter-lesion clustering of restenosis in patients with multilesion coronary stenting, a single lesion (single-lesion analysis) was randomly selected by PROC PLAN of SAS software for analysis of late loss.The single randomly selected lesions were included in an analysis of variance to detect differences across treatment in informative QCA variables (lesion length, MLD, RVD, % of stenosis) recorded pre-procedure and post procedure at Day 0.In-segment and in-stent late loss for single lesions were evaluated with an analysis of covariance including treatment and centers as factors and pre-procedure RVD, pre-procedure lesion length and post-procedure MLD as covariates with pairwise t-test for multiple comparisons. Restenosis and the number of patients with MACE were analysed by Cochran-Mantel-Haenszel test.

2. SYNOPSIS (cont'd)

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:	

Statistical methods: MCP-1/CCL2 levels were analysed using Kruskal-Wallis test on the differences at each day with respect to Day 0, with Wilcoxon rank-sum test for pairwise comparisons. A correlation analysis was performed. Bindarit plasma levels (BND600 and BND1200 taken together and separately) at Day 180 from the index procedure were correlated with the in-segment late loss in the PP population considering a randomly selected single lesion. MCP-1/CCL2 levels at Day 1 were correlated with the in-segment late loss/RVD pre-procedure*100 in the PP population considering a randomly selected single lesion.
Laboratory parameters for BND1200 and BND600 were categorized using Cohen's d effect sizes, with respect to the PLB. The percentage of AEs in each SOC, was analysed by Fisher's exact test comparing BND1200 and BND600 vs PLB. At each visit, an analysis of covariance or an analysis of variance on the difference from the screening was applied for vital signs (systolic blood pressure, diastolic blood pressure, pulse rate) with pairwise t-test for multiple comparisons.

SUMMARY – CONCLUSION

Efficacy results: On the whole, preliminary positive conclusions regarding the efficacy of bindarit in preventing stent restenosis can be drawn from the present trial, even if confirmatory studies in a wider population are needed.
Demographic and other baseline characteristics did not show major differences between treatment groups. In particular, previous medical history and QCA parameters were in general comparable, even though lesions of Type C were less frequent in BND600 patients compared to the other treatment groups,. Compliance was excellent across treatment groups.
Patients treated with bindarit showed a clinically meaningful reduction in late loss relative to patients treated with placebo, both in-segment (0.26 mm) and in-stent (0.40 mm). This advantage was maintained even when the late loss result was normalized by acute gain (loss index). These analyses of primary and secondary endpoints included up to two lesions per patient. The results of single lesion analysis, in which each patient contributed a single randomly chosen lesion and which included adjustment for covariates, confirmed the efficacy signals observed. Additional statistical hypothesis testing for the PP population, showed a significant reduction of late loss in the BND600 group relative to placebo.MACEs and binary angiographic restenosis were comparable across treatment groups, probably owing to the relative insensitivity of these measures given the size of the trial.
It is not possible in the present report to draw firm conclusions on OCT data, since few patients in a very small sample accounted for a majority of uncovered struts visualized by OCT.
Inflammatory markers were uninformative. MCP-3/CCL7 levels were undetectable in 458/472 samples. On the other hand it was possible to reliably measure MCP-1/CCL2 in the majority of samples, but the results are not amenable to simple interpretation and call for futher investigations. Overall MCP-1/CCL2 plasma concentrations do not allow to reliably differentiate between treated and untreated patients, even at group level.
Overall patients treated with BND1200 showed no advantage in efficacy relative to patients treated with BND600, and this result was corroborated by the absence of a linear relationship between individual drug plasma concentrations and late loss

2. SYNOPSIS (cont'd)

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:	

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. Nevertheless the BND1200 group showed a marginally less favourable safety profile compared to the arms of the study. One fatal event in the BND1200 group underwent significant scrutiny but could not be reliably linked to the study medication. The safety review of vital signs, physical findings and urinalysis did not show a clinical effect of bindarit on any of the parameters. For this reason they are not further discussed in detail. A detailed quantitative analysis has been performed with clinical commentary of the laboratory parameters which showed a medium or large effect in the size of the difference of variations at each visit relative to the baseline between the treatment arm and the placebo arm. Patients treated with bindarit had a reduced total and direct bilirubin concentration in plasma. The effect size is medium to large and is sustained in time, but does not appear to be of clinical significance.

Isolated medium sized effects on liver function tests were seen in patients in the bindarit 1200 mg group. LDH, which is not liver-specific, was found to be elevated with a medium effect at visits 2,3, 4bis and 5 in the bindarit 600 mg group, and reduced at visit 1 in the bindarit 1200 mg group. The lack of a clear trend makes this finding of uncertain clinical significance.

With regards to other intracellular enzymes, CK-MB levels were shown to be generally reduced with a medium effect in patients treated with bindarit; an increase with a large effect size was noted in a single visit in the bindarit 600 mg group. There was large variability of this parameter, and no trend could be clearly identified for this effect, which makes this finding of uncertain clinical significance.

Patients treated with bindarit had an increased hs-CRP concentration in plasma at visits 2, 3bis, 4bis and 5 in the bindarit 600 mg group. This finding was replicated in the bindarit 1200 mg group only at visit 4bis. The effect size is medium to large but appears small in absolute terms and driven by a decrease vs baseline in the placebo group; its clinical significance is doubtful.

Patients treated with bindarit had a medium increase in creatinine at visit 2, 3 and 3bis and in haematocrit at visit 3bis, 4 and 4 bis. These findings were not replicated in the bindarit 1200 group.

Isolated increases in hemoglobin, lymphocytes and isolated reductions of monocytes, basophilis, eosinophilis, cholesterol-HDL, total cholesterol, triglycerides, ALT, AST and glucose cannot be considered of clinical significance in isolation and in the absence of a sustained effect.

Finally, only small to no-effect on serum potassium levels and other electrolytes were detected in bindarit treated patients.

2. SYNOPSIS (cont'd)

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:	

Conclusion: In stent stenosis is the main limitation of bare metal stents. The most important mechanism of restenosis after stent implantation is late loss due to neointimal hyperplasia through modulation of smooth muscle cell growth and migration. Overexpression of MCP-1/CCL2 is thought to play a key role in this mechanism. Bindarit has shown to be able to down-regulate MCP-1/CCL2 overexpression in cellular and animal models, and, critically, has been shown able to inhibit neointimal hyperplasia in rodent and porcine models of stent restenosis.

The results of this trial show that bindarit can reduce neointimal hyperplasia, measured as late loss at 6 months, in patients with occlusive coronaropathy undergoing implantation of a bare metal stent. The late loss reduction achieved in the BND600 arm relative to placebo in the per protocol population ranges from 0.26 mm in-segment and 0.4 mm in-stent. These results are consistent across populations (per-protocol and intention-to-treat) and type of measurement (in-segment and in-stent); they can be considered clinically significant, at the lower end of the late loss reduction achieved by drug-eluting-stents (Moreno 2007).

The hypothesized mechanism of action for the observed pharmacological effect in humans remains speculative at this stage. No relationship between systemic drug concentration and late loss was observed. It should be noted, however, that in the present study the systemic inflammatory biomarkers were found to be relatively insensitive to clinical and procedural events; in particular the expected rise of MCP-1/CCL2 after surgery was not observed.

Bindarit is generally well tolerated in patients undergoing stent implantation. The analysis of AEs and of laboratory parameters was not suggestive of any major risks. In this study BND1200 had a less favourable risk profile relative to BND 600. Taking into account the similar efficacy profiles between the two dosages, available data suggest a superior risk/benefit profile for BND600 in this indication and with this dosing regimen.

Patients with occlusive coronaropathy undergoing implantation of a bare metal stent are good candidates for adequately powered further studies aimed at confirming the safety and angiographic results of this study and investigating the clinical and long terms effects of bindarit treatment.

Date of the Clinical Report: February 2012