Janssen Research & Development

Final Clinical Study Report Synopsis: 50-Week Study
Protocol: C0168T67; Phase 3b

CNTO312 (Infliximab)

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Synopsis (C0168T67 SONIC)

Name of Sponsor/Company: Centocor Ortho Biotech, Inc	**Associated with Module 5.3 of the Dossier**	
Name of Finished Product: REMICADE® (infliximab)		
Name of Active Ingredient: REMICADE® (infliximab)		

Protocol: C0168T67	**EudraCT No.:** 2004-002815-10

Title of the study: Multicenter, Randomized, Double-Blind, Active Controlled Trial Comparing REMICADE® (infliximab) and REMICADE plus Azathioprine to Azathioprine in the Treatment of Patients with Crohn's Disease Naive to Both Immunomodulators and Biologic Therapy (Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease or SONIC)

Principal/Coordinating Investigator:
[redacted], MD
[redacted], MD.

Study Centers: 125 sites were initiated to participate in the SONIC study , of which 92 sites randomized at least one patient (219 patients [40 sites] in the USA; 38 patients [10 sites] in Germany; 39 patients [7 sites] in France; 46 patients [5 sites] in Belgium; 22 patients [5 sites] in the United Kingdom; 32 patients [5 sites] in Israel; 23 patients [3 sites] in Canada; 17 patients [3 sites] in Denmark; nine patients [3 sites] in Greece; six patients [3 sites] in Spain; 25 patients [2 sites] in Austria, three patients [2 sites] in Sweden; two patients [2 sites] in Portugal and 26 patients [1 site] in The Netherlands; and one patient [1 site] in Norway)

Publication (reference): Not applicable

Studied Period: 23 March 2005/11 November 2008	**Phase of Development:** IIIb

Objectives:
The primary objective of the Main Study (Week 30) was to compare the efficacy of infliximab (IFX) + placebo (PBO) over-encapsulated tablets and IFX combined with azathioprine (AZA) with that of AZA + PBO infusions in the treatment of patients with moderate-to-severe Crohn's disease.

The secondary objectives of the Main Study were:
1. To assess the effect of IFX and/or AZA on complete mucosal healing in patients with Crohn's disease.
2. To assess the corticosteroid-sparing abilities of therapy with IFX and/or AZA in patients with moderate-to-severe Crohn's disease.

The primary objective of the Study Extension (Week 50) was to evaluate the long-term efficacy and safety of IFX and/or AZA through Week 54.

Methodology: This was a randomized, multicenter, double-blind, active-controlled study of AZA alone (Group I), IFX alone (Group II) and IFX plus AZA (Group III) in patients with moderate-to-severe Crohn's disease who were naïve to treatment with biologic agents and immunomodulators.
Patients completing the SONIC study were allowed to enter a country-specific (EU and Israel only), prospective, multicenter, Open-label Extension to evaluate the long-term safety and efficacy of scheduled IFX maintenance therapy (5 mg/kg every 8 weeks). The results of the Open-label Extension will be reported in a separate report.

Number of Patients (Planned and Analyzed): Planned: approximately 500 patients. Analyzed in Main Study: 508 patients were randomized and analyzed for efficacy; 503 were analyzed for safety. Analyzed in the Study Extension: 280 patients for efficacy and safety.

Diagnosis and Main Criteria for Inclusion: Crohn's disease for at least the previous 6 weeks, with colitis, ileitis, or ileocolitis confirmed by radiography or endoscopy, and were either corticosteroid-dependent OR being considered for the second (or more) course of oral systemic corticosteroids

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(prednisone or equivalent), OR 5-ASA (5-aminosalicylic acid) failures, OR budesonide failures. All patients were naïve to immunomodulators and biologic therapies.

Test Product, Dose and Mode of Administration, Batch Number: Group I (AZA + PBO): Placebo infusions (equivalent in volume to a 5 mg/kg infusion) administered at Weeks 0, 2, 6, 14, and 22, and one or more over-encapsulated AZA tablets (50 mg) daily with total daily doses closest to, but not exceeding, 2.5 mg/kg/day through Week 30.
Group II (IFX + PBO): Infliximab infusions of 5 mg/kg at Weeks 0, 2, 6, 14, and 22, and one or more PBO over-encapsulated tablets daily (the number of tablets equivalent to the number of tablets needed for the dose closest to, but not exceeding, 2.5 mg/kg/day AZA) through Week 30.
Group III (IFX + AZA): Infliximab infusions of 5 mg/kg administered at Weeks 0, 2, 6, 14, and 22, and one or more over-encapsulated AZA tablets daily (dose closest to, but not exceeding, 2.5 mg/kg/day) through Week 30.
Patients enrolled in the Study Extension received the same blinded study medication and dose to which they were randomized. Daily oral study medication was continued, and Study Extension infusions were continued every 8 weeks beginning at Week 30 and continuing through Week 50. Four lots of active IFX and five lots of active AZA were used in this study.

Duration of Treatment: 50 weeks blinded therapy.

Reference Therapy, Dose and Mode of Administration, Batch Number: Infliximab PBO infusion was administered by intravenous injection. Patients randomized to AZA + PBO were to receive IFX PBO infusions (equivalent in volume to a 5 mg/kg infusion) administered at Weeks 0, 2, 6, 14, and 22. For those patients who enrolled in the Study Extension, IFX PBO infusions were administered every 8 weeks through Week 50.
Azathioprine PBO over-encapsulated tables were administered daily orally at a dose close to, but not exceeding, 2.5 mg/kg/day through Week 30. Those patients who enrolled in the Study Extension were administered AZA PBO over-encapsulated tablets daily through Week 50.
Four lots of IFX PBO and four lots of AZA PBO were used in this study.

Criteria for Evaluation: All patients were included in the primary efficacy and selected secondary analyses. Patients were analyzed according to the randomized treatment group. Safety evaluations were based on patients who received at least one dose of study medication; patients were analyzed according to the actual treatment received. Pharmacokinetic (PK)/pharmacodynamic analyses were based on patients who had one or more PK samples obtained after their first study medication administration; patients were analyzed according to the actual treatment received.

Efficacy: The primary efficacy endpoint was the proportion of patients with corticosteroid-free clinical remission, based on the Crohn's Disease Activity Index (CDAI), assessed in all randomized patients at Week 26, and compared among the three treatment groups. Secondary efficacy endpoints included corticosteroid-free clinical remission at Week 50, clinical remission, clinical response, corticosteroid-free clinical response, mucosal healing, CDAI component analysis, corticosteroid endpoints, quality of life, and C-reactive protein (CRP).

Pharmacokinetics/Pharmacodynamics/Antibodies to Infliximab: Blood samples for serum IFX analyses and antibody to IFX assessment were collected prior to infusions administered during the Main Study at Weeks 0 (Baseline) and 30 (Main Study: Final Visit), and prior to infusion at Week 46 (Study Extension: Standard Infusion Visit).

Safety: Safety was assessed by the incidence and type of adverse events (AEs) and changes in routine laboratory parameters (hematology and chemistry).

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Quality of Life and Pharmacoeconomics: Assessments included disease-specific quality of life survey, Inflammatory Bowel Disease Questionnaire (IBDQ), direct costs related to treatment of Crohn's disease, and indirect costs related to impact of disease on work productivity of patient and caregiver as assessed by the Productivity Visual Analog Scale.

Statistical Methods: Baseline demographic and disease characteristics were compared with the use of the chi-square or Fisher's exact test for categorical variables and with analysis of variance on the van der Waerden normal scores for continuous variables. A two-sided Cochran-Mantel-Haenszel chi-square test, stratified by Crohn's disease duration and corticosteroid dose at Baseline, was used to compare remission, response, and mucosal healing. Changes in IBDQ scores were compared using analysis of variance on the van der Waerden normal scores, adjusting for duration of Crohn's disease and corticosteroid dose at Baseline. Descriptive statistics summarize systemic steroid use.

For subgroup analyses the odds ratios were calculated based on logistic regression.

Efficacy analyses used intention-to-treat methodology that included all randomized patients analyzed according to randomized treatment groups, except for mucosal healing, which was analyzed according to prespecified per protocol methods. After Week 30, prespecified analyses were based on data only for patients who entered the Study Extension.

All patients receiving at least one dose of study medication (oral or infusion) were analyzed for safety according to the treatment actually received. Safety comparisons used the Fisher's exact test. Infliximab concentrations were compared using analysis of variance on the van der Waerden normal scores adjusting for duration of Crohn's disease and corticosteroid dose at Baseline.

SUMMARY – CONCLUSIONS

Study Population Results: A total of 508 patients were randomized: 170 in the AZA + PBO group, 169 in the IFX + PBO group, and 169 in the IFX + AZA group. Of the 508 randomized patients, 318 completed the Main Study: 86 (50.6%) in the AZA + PBO group, 111 (65.7%) in the IFX + PBO group, and 121 (71.6%) in the IFX + AZA group. A total of 190 (37.4%) patients discontinued from the study: 84 (49.4%) in the AZA + PBO group, 58 (34.3%) in the IFX + PBO group, and 48 (28.4%) in the IFX + AZA group. The principal reason for discontinuation was occurrence of AEs, occurring in 38 (22.4%) patients in the AZA + PBO group, compared with 20 (11.8%) in the IFX + PBO group and 28 (16.6%) in the IFX + AZA group.

Among the 318 patients who completed the Main Study, 280 (88.1%) entered the Study Extension: 75 (26.8%) in the AZA + PBO group, 97 (34.6%) in the IFX + PBO group, and 108 (38.6%) in the IFX + AZA group. A total of 38 (13.6%) patients discontinued from the Study Extension: eight (10.7%) in the AZA + PBO group, 12 (12.4%) in the IFX + PBO group, and 18 (16.7%) in the IFX + AZA group. One-half of the patients who discontinued from the Study Extension, ie, 19/38, did so because of AEs, including three (4.0%) patients in the AZA + PBO group, nine (9.3%) patients in the IFX + PBO group, and seven (6.5%) patients in the IFX + AZA group.

Pharmacokinetic/Pharmacodynamic/Antibody Results: In the Main Study, median trough serum IFX concentrations at Week 30 for patients receiving IFX + PBO and IFX + AZA were 1.55 and 3.54 µg/mL, respectively ($p<0.001$). During the Study Extension, median trough serum IFX concentrations for patients receiving IFX + PBO and IFX + AZA were 0.99 and 3.77 µg/mL, respectively ($p<0.001$).

In the Main Study, antibodies to IFX were detected at Week 30 in one (0.8%) patient in the IFX + AZA group, compared with 15 (14.2%) patients in the IFX + PBO group. Patients with inconclusive IFX antibody status at Week 30 included 113 (94.2%) patients in the IFX + AZA group and 72 (67.9%) patients in the IFX + PBO group. In the Study Extension, antibodies to IFX were detected at Week 46 in three (2.8%) patients in the IFX + AZA group, compared with 11 (11.8%) patients in the IFX + PBO group.

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Patients with inconclusive IFX antibody status at Week 46 included 81 (76.4%) patients in the IFX + AZA group and 55 (59.1%) patients in the IFX + PBO group. When compared with patients who had positive or negative findings for antibodies to IFX, the patients with inconclusive antibody status had the highest trough serum IFX concentrations and had detectable IFX concentrations through Week 46.
In the Main Study, the proportion of patients in corticosteroid-free remission at Week 26 was greater in patients who had inconclusive results for antibodies to IFX at Week 30 (71.9%) than in patients who had negative (56.2%) or positive (58.8%) findings. In the Study Extension, a similar pattern was observed..

Efficacy Results: The SONIC primary endpoint, ie, the proportion of patients in corticosteroid-free clinical remission at Week 26, was met. In these analyses, clinical remission was defined as an absolute CDAI score of <150 points, corticosteroid-free clinical remission was defined as clinical remission in patients who had not received prednisone at any dose or budesonide more than 6 mg/day for at least the previous 3 weeks.
For the primary endpoint, the primary comparisons were between the IFX + AZA and AZA + PBO treatment groups and between the IFX + PBO and AZA + PBO treatment groups. In addition, the IFX + AZA and IFX + PBO treatment groups were also compared.
The proportions of patients in corticosteroid-free clinical remission at Week 26 for each treatment group were:

- 56.8% (96/169 patients) of patients receiving IFX + AZA ($p<0.001$ compared with AZA + PBO; $p=0.022$ compared with IFX + PBO).
- 44.4% (75/169 patients) of patients receiving IFX + PBO ($p=0.006$ compared with AZA + PBO).
- 30.0% (51/170 patients) of patients receiving AZA + PBO.

Furthermore, as early as Week 6, and consistently at each visit through Week 26, the proportion of patients in corticosteroid-free clinical remission was higher in both the primary comparison (IFX + AZA compared with AZA + PBO) and in the sequential co-primary analysis (IFX + PBO compared with AZA + PBO). The difference between the IFX + AZA and IFX + PBO groups was not statistically significant.
At Week 50, similar trends for the achievement of corticosteroid-free clinical remission were observed. The proportions of patients in corticosteroid-free clinical remission at Week 50 were:

- 72.2% (78/108 patients) of patients receiving the IFX +AZA ($p=0.010$ compared with AZA + PBO, $p=0.065$ compared to IFX + PBO),
- 60.8% (59/97 patients) of patients receiving the IFX + PBO ($p=0.324$ compared with AZA + PBO),
- 54.7% (41/75 patients) of patients receiving AZA + PBO.

When all patients who underwent randomization (N=508) were included with the assumption that patients who did not enter the Study Extension did not achieve corticosteroid-free clinical remission at Week 50, the proportions of patients in corticosteroid-free clinical remission were:

- 46.2% (78/169 patients) of patients receiving the IFX +AZA ($p<0.001$ compared with AZA + PBO, $p=0.035$ compared to IFX + PBO),
- 34.9% (59/169 patients) of patients receiving the IFX + PBO ($p=0.028$ compared with AZA + PBO),
- 24.1% (41/170 patients) of patients receiving AZA + PBO.

Similarly, when all patients who underwent randomization (N=508) were included with the Week 26 corticosteroid-free clinical remission status carried forward through Week 50 for those who did not enter Study Extension, significantly higher proportions of patients receiving IFX + AZA or IFX + PBO achieved corticosteroid-free clinical remission compared with the patients receiving AZA + PBO.
The following four sensitivity analyses were conducted for the primary endpoint:

- The LOCF method was used to impute any missing data that were not missing due to patient discontinuation;

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- Exclusion of patients who had at least one major protocol deviation or had the Week 26 visit outside the visit window of ± 7 days (PPP);
- PPP analysis employing LOCF;
- Stratification by study site location (North America, Europe, and Israel).

The results of the four sensitivity analyses were consistent with those of the primary endpoint analysis. Subgroup analyses were conducted to examine the consistency of efficacy in the proportion of patients in corticosteroid-free clinical remission at Week 26 across a series of demographic and baseline disease characteristics and concomitant medications. In general, similar results were observed across baseline characteristics and Crohn's disease characteristics subgroups. These included: history of prior Crohn's disease-related surgery, baseline corticosteroid use, duration of Crohn's disease, gender, age, race, weight, smoking status, study site location (North America or Europe/Israel), baseline 5-ASA use, and baseline corticosteroid-free status. In the analysis of baseline CRP, it was observed that patients with a CRP ≥0.8 mg/dL at Baseline were more likely to achieve corticosteroid-free remission with IFX treatment when compared with patients with a CRP <0.8 mg/dL at Baseline.

Mucosal healing, defined by the absence of mucosal ulceration at the Week 26 endoscopy in patients who had evidence of ulceration present at the baseline endoscopy, was a major secondary efficacy endpoint. Ninety-four percent of patients (478/508 patients) underwent baseline endoscopy; of these, 309 patients had evaluable endoscopies with evidence of ulceration at the baseline endoscopy and were included in the mucosal healing analysis. In this analysis, patients who did not have an endoscopy performed at Week 26 or whose Week 26 endoscopy was not readable (ie, presence of lesions was undetermined) were assumed to have lesions at Week 26. The proportions of patients with mucosal healing at Week 26 were as follows:

- 43.9% (47/107 patients) of patients receiving IFX + AZA ($p<0.001$ compared with AZA + PBO, $p=0.055$ compared with IFX + PBO),
- 30.1% (28/93 patients) of patients receiving IFX + PBO ($p=0.023$ compared with AZA + PBO,
- 16.5% (18/109 patients) of patients receiving AZA + PBO.

As detailed below, analysis results of additional secondary efficacy endpoints were supportive of results obtained for the primary and major secondary efficacy endpoints. In general, patients receiving IFX + AZA or IFX + PBO were more likely to respond to treatment when compared with AZA + PBO therapy. In addition, for several of these additional secondary endpoints, more patients treated with IFX + AZA than IFX + PBO responded to treatment.

- The proportion of patients in clinical remission (CDAI <150) at Week 26 was statistically significantly greater in the IFX + AZA group (60.4%) than the AZA + PBO group (31.8%), as well as in the IFX + PBO group (47.9%) compared with the AZA + PBO group.
- The proportion of patients with a clinical response (≥100-point or ≥70-point decrease from Baseline in CDAI) at Week 26 was statistically significantly greater in the IFX + AZA treatment group (62.1% and 66.9%, respectively) than the AZA + PBO treatment group (37.6% and 41.8%, respectively), as well as in the IFX + PBO group (54.4% and 56.2%, respectively) compared with the AZA + PBO group.
- The proportion of patients in corticosteroid-free clinical response (≥100-point or ≥70-point decrease from Baseline in CDAI) at Week 26 was statistically significantly greater in the IFX + AZA treatment group (58.6% and 62.7%, respectively) than the AZA + PBO group (34.1% and 38.2%, respectively), as well as in the IFX + PBO group (50.9% and 52.7%, respectively) compared with the AZA + PBO group.
- Improvement in QoL, as assessed with the IBDQ, was significantly greater (higher scores) in the IFX + AZA and IFX + PBO groups compared with the AZA + PBO group. The mean change from Baseline at Week 26 in IBDQ total scores was: 45.2 points for the IFX + AZA group; 39.9 points for the IFX + PBO group; and 31.4 points for the AZA + PBO group. The mean

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change from Baseline in IBDQ total scores at Week 50 for all randomized patients showed a similar trend, ie, 56.4 points for the IFX + AZA group, 51.6 points for the IFX + PBO group, and 43.0 points for the AZA + PBO group.

Among IFX-treated patients, the proportions of patients achieving corticosteroid-free clinical remission increased as trough serum IFX concentrations increased, but were still substantial at lower concentrations. With regard to antibody-to-IFX status, corticosteroid-free clinical remission was achieved by larger proportions of patients who had inconclusive test results for antibodies to IFX than in patients who had negative or positive findings for antibodies to IFX; response rates were similar for these subgroups. Regardless, substantial proportions of patients achieved corticosteroid-free clinical remission in each of the IFX antibody subgroups.

Safety Results through Week 50: Infliximab, either as monotherapy or in combination with AZA, was well tolerated, with a safety profile consistent with the IFX prescribing information. In addition, there was no difference in treatment-related safety findings between the IFX + AZA, IFX + PBO, or AZA + PBO groups. The major safety findings were as follows:

- Overall, the proportion of all treated patients experiencing one or more TEAE through Week 50 was similar across the treatment groups: 89.4% in the AZA + PBO group, 89.0% in the IFX + PBO group, and 89.9% in the IFX + AZA group. The most common TEAEs were gastrointestinal disorders for all treatment groups.
- Through Week 50, the proportion of patients experiencing one or more serious TEAE was highest in the AZA + PBO group (26.7%) compared with the IFX + PBO group (23.9%) and the IFX + AZA group (15.1%). For all treatment groups, the most common serious TEAEs were gastrointestinal disorders (12.7%). The most common reasonably related serious TEAEs were acute pancreatitis, which occurred only in the AZA + PBO group (four patients, 2.5%) and pancreatitis, which occurred primarily in the AZA + PBO group (four patients, 2.5%) compared with the IFX + PBO group (zero patients, 0.0%) and the IFX + AZA group (one patient, 0.6%).
- Serious treatment-emergent infections were relatively uncommon and generally distributed evenly across the three treatment groups: nine (5.6%) patients in the AZA +PBO, eight (4.9%) patients in the IFX + PBO, and seven (3.9%) patients IFX + AZA groups.
- One case of tuberculosis occurred in a patient in the IFX + AZA group. This patient recovered with appropriate therapy. No other opportunistic infections were reported during the study.
- One death occurred following colectomy in a patient treated with AZA + PBO. No other deaths occurred in the study.
- Two patients in the AZA + PBO group were diagnosed with malignancies. No other malignancies occurred in the study.
- The proportion of patients with one or more infusion reactions was highest in the IFX + PBO group, (27 patients, 16.6%), followed by the AZA + PBO (9 patients, 5.6%), and IFX + AZA (9 patients, 5.0%) groups. Across all treatment groups, the most common infusion reactions were: infusion-related reaction in five (1.0%) patients, pyrexia in four (0.8%) patients, dizziness in four (0.8%) patients, paresthesia in four (0.8%) patients, headache in three (0.6%) patients, nausea in three (0.6%) patients, flushing in three (0.6%) patients, and hypersensitivity in three patients (0.6%). There was a single event of serious infusion reaction (anaphylactoid reaction) in a patient in the IFX + PBO group that resulted in discontinuation of study medication.
- There were no notable differences among the three treatment groups in median change from Baseline through Week 50 in any hematology or blood chemistry parameters.

Conclusions: Patients with moderate-to-severe Crohn's disease treated with IFX alone or IFX in combination with AZA (when initiated together) are more likely to achieve corticosteroid-free clinical

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remission and complete mucosal healing than those receiving AZA alone. Patients with moderate-to-severe Crohn's disease treated with IFX in combination with AZA (when initiated together) are more likely to achieve corticosteroid-free clinical remission than those receiving IFX alone. Adverse events were similar in all treatment groups. Serious adverse events and discontinuations due to AEs were slightly more common in the AZA + PBO group.

Date of Report: 3 May 2010