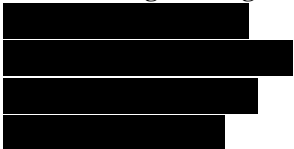


2.0 Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
Name of Study Drug: Humira	Volume:	
Name of Active Ingredient: Adalimumab	Page:	
Title of Study: Rapidity of onset of response to adalimumab in luminal Crohn's disease. RAPIDA study		
Coordinating Investigators: 		
Coordinator Study Sites: Hospital Gregorio Marañón Hospital Clínico Universitario de Santiago Hospital Universitario Vall d'Hebrón Hospital Universitario Mutua de Terrassa		
Publications: Marín-Jiménez I, Casellas F, Esteve M, et al. Rapidity of onset of response to adalimumab (ADA) in luminal Crohn's disease (CD). Data from RAPIDA trial. Poster presented at: 12 th Congress of the European Crohn's and Colitis Organisation; 2017 Feb 15-18; Barcelona, Spain. Casellas F, Barreiro-de Acosta M, Esteve M, et al. Early improvement in quality of life in patients with luminal Crohn's disease treated with adalimumab. Data from RAPIDA trial. Poster presented at: 12th Congress of the European Crohn's and Colitis Organisation; 2017 Feb 15-18; Barcelona, Spain.		
Studied Period (Years): First Subject First Visit: 27 May 2014 Last Subject Last Visit: 23 January 2017	Phase of Development: Phase IV	

Objectives:

Primary objective:

To evaluate the rapidity of onset of clinical response to adalimumab therapy in patients with luminal Crohn's disease.

Secondary objectives:

To evaluate the improvement of health-related quality of life and fatigue to adalimumab therapy in patients with Crohn's disease.

To evaluate the improvement in analytic and fecal markers of inflammation in patients with Crohn's disease treated with adalimumab in the short term.

To evaluate the correlation of a rapid response at Day 4 and Week 1 with remission at Week 12

Methodology:

An open label, one arm, prospective, multicenter study. Phase IV clinical trial.

Number of Subjects (Planned and Analyzed):

98 planned; 86 finally analyzed

Diagnosis and Main Criteria for Inclusion:

Main inclusion criteria:

1. Active Crohn's disease with documented clinical symptoms and endoscopic/radiologic findings.
2. Crohn's disease diagnosed within, at least, the previous 4 months.
3. Patients with active luminal (Harvey-Bradshaw Index \geq 8) moderate-to-severe Crohn's disease.
4. Adult patient 18-75 year-old.
5. No response to a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant.
6. Concomitant treatments for Crohn's disease will be allowed at stable dose.
7. Patient must understand and voluntarily sign an informed consent form prior to the conduct of any study related assessment/procedures.
8. If receiving any of the following treatments, their dose should be stable during the periods indicated:
 - Aminosalicylates for, at least, the last 4 weeks
 - Probiotics for, at least, the last 4 weeks
 - Analgesics for, at least, the last 4 weeks
 - Antidiarrheals for, at least, the last 4 weeks
 - CD-related antibiotics for, at least, the last 4 weeks
 - Azathioprine, 6-mercaptopurine or methotrexate for, at least, the last 12 weeks
9. If receiving any of the following treatments, their dose should not have been increase in the past two weeks (the dose reduction is permitted):
 - Oral budesonide (maximum dose of 9 mg/day)
 - Oral prednisone or equivalent (maximum dose of 40 mg/day)
10. Able to adhere to the study visit schedule and other protocol requirements.
11. Male subjects (including those who have had a vasectomy) must agree to use barrier contraception (latex condoms) when engaging in activity in which conception is possible while on study medication and for at least 28 days after taking the last dose of study medication.
12. Females of Childbearing Potential* (FCBP) must have a negative urine pregnancy test at Screening and Baseline and must be willing to use one medically approved form of birth control when engaging in activity in which conception is possible while on study medication and for at least 28 days after taking the last dose of study medication.

*A female of childbearing potential is a sexually mature female who 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral ovariectomy (the surgical removal of both ovaries) or 2) has not been postmenopausal for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months).

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Adalimumab was supplied as a sterile, preservative-free solution for injection, contained in 1 mL pre-filled syringes containing adalimumab 40 mg/0.8 mL.

The subjects received an induction dose of 160 mg at Week 0, followed by 80 mg at Week 2. After induction treatment, from Week 4 until Week 10 (included), the dose was 40 mg every two weeks via subcutaneous injection. Intensification to 40 mg weekly was allowed per investigator discretion.

Mode of Administration was subcutaneous, self-administered.

All adalimumab supplies were labeled with all information required by regulatory authorities.

Duration of Treatment: 10 weeks.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Not applicable.

Criteria for Evaluation

Efficacy:

Primary endpoints:

Proportion of patients with clinical response at Day 4. Clinical response was defined as a decrease of at least 3 points in the Harvey-Bradshaw Index, at Day 4.

Secondary endpoints:

- Proportion of patients with clinical response at Week 1. Clinical response was defined as a decrease of at least 3 points in the Harvey-Bradshaw Index, at Week 1.
- Proportion of patients with clinical remission at Weeks 2 and 4 (Harvey-Bradshaw Index < 5).
- Change in Quality of Life, assessed with the EQ-5D and IBDQ 36 questionnaires from baseline to Week 12.
- Change in Fatigue, assessed through the Fatigue Impact Scale for Daily Use (D-FIS), from baseline to Week 12.
- Change in analytic markers of inflammation from baseline to Week 12: hemogram, erythrocytes sedimentation rate (ESR), C-reactive protein (CRP), fecal calprotectin and coagulation (including fibrinogen).
- Correlation between a clinical response at Day 4 and Week 1 with remission at Week 12.

Pharmacokinetic:

Not applicable

Safety:

All adverse events (serious and non-serious) reported in the safety population throughout the study, until 70 days after last treatment dose, are described. Serious Adverse Events was the primary safety variable.

Note: Although laboratory data and vital signs were not safety endpoints, they were assessed throughout the study in order to ensure the safety of the patients.

Statistical Methods

Efficacy:

The efficacy analysis was performed in an intent-to-treat (ITT) and a per protocol (PP) populations. The ITT population was defined as those patients who had received at least one dose of treatment, and was the primary population for efficacy analysis.

The PP population was defined as those patients from the ITT population who showed no major protocol deviations.

Since this clinical trial had only one treatment arm, statistics were mainly descriptive. Quantitative variables were provided using sample size, mean, standard deviation, two sided 95% confidence interval, median, interquartile range, minimum and maximum.

Qualitative variables were summarized in a table that included absolute and relative frequencies in the whole population. Two-sided 95% confidence intervals were provided.

Statistical analysis was performed to evaluate the correlation between a clinical response at Day 4 and Week 1 with remission at Week 12.

Pharmacokinetic:

Not applicable.

Safety:

Safety analysis was performed on a safety population including all patients who have received at least one dose of study treatment (adalimumab).

Summary/Conclusions

Efficacy Results:

Clinical response at Day 4 was achieved by 53 (61.63%) patients (95% CI: 50.51-71.92) in the ITT population and 38 (69.09%) patients (95% CI: 55.19-80.86) in the PP population. Mean change of HBI score from baseline to Day 4 was -3.75 ± 3.31 ($p < 0.0001$) for ITT population, and -4.00 ± 3.32 for PP population ($p < 0.0001$). Median change of HBI from baseline to Day 4 was -4.00 (range: $-16.00, 6.00$) for both ITT ($p < 0.0001$) and PP population ($p < 0.0001$).

Clinical response at Week 1 was achieved by 65 (75.58%) patients (95% CI: 65.13-84.20) in the ITT population and 46 (83.64%) patients (95% CI: 71.20-92.23) in the PP population. Mean change of HBI score from baseline to Week 1 was -4.52 ± 3.39 ($p < 0.0001$) for ITT population, and -4.95 ± 3.52 for PP population ($p < 0.0001$). Median change of HBI from baseline to Week 1 was -4.50 (range: $-12.00, 8.00$) for ITT population ($p < 0.0001$), and -5.00 (range: $-12.00, 8.00$) for PP population ($p < 0.0001$).

Clinical remission was achieved by 47 (54.65%) patients (95% CI: 43.55-65.42) at Week 2, and 54 (62.79%) patients (95% CI: 51.70-72.98) at Week 4, in the ITT population. In the PP population, the number of patients that achieved clinical remission were 33 (60.00%) (95% CI: 45.91-72.98) and 39 (70.91%) (95% CI: 57.10-82.37) at Week 2 and Week 4, respectively.

When change in quality of life was assessed, For ITT population, mean EQ-5D-3L Index Score changed from 0.62 ± 0.22 , at baseline, to 0.76 ± 0.23 , at Week 12/early termination visit (mean change 0.14 ± 0.25 ; $p < 0.0001$), and mean EQ-5D-3L VAS changed from 55.36 ± 18.52 , at baseline, to 71.00 ± 22.42 , at Week 12/early termination visit (mean change 15.37 ± 21.36 ; $p < 0.0001$). For PP population, mean EQ-5D-3L Index Score changed from 0.63 ± 0.22 , at baseline, to 0.80 ± 0.22 , at Week 12/early termination visit (mean change 0.16 ± 0.23 ; $p < 0.0001$), and mean EQ-5D-3L VAS changed from 55.22 ± 18.39 , at baseline, to 74.38 ± 21.78 , at Week 12/early termination visit (mean change 18.48 ± 22.32 ; $p < 0.0001$).

IBDQ-36 overall score also showed a statistically significant improvement from baseline to Week 12/early termination visit in both, ITT and PP study populations. For ITT population, mean IBDQ-36 overall score changed from 145.1 ± 35.83 , at baseline, to 191.5 ± 46.20 , at Week 12/early termination visit (mean change 44.72 ± 37.98 ; $p < 0.0001$). For PP population, mean IBDQ-36 overall score changed from 145.5 ± 38.13 , at baseline, to 195.89 ± 45.76 , at Week 12/early termination visit (mean change 46.65 ± 34.88 ; $p < 0.0001$).

In the ITT population, the percentage of patients above the normality cutoff of 209 in IBDQ-36 increased significantly from 3.49% at baseline to 36.03% at Week 12/early termination visit ($p < 0.0001$). In the PP population, the percentage of patients above the normality cutoff of 209 in IBDQ-36 also showed a statistically significant increase from 5.45% at baseline to 43.64% at Week 12/early termination visit ($p < 0.0001$).

Patients' fatigue, assessed using the Fatigue Impact Scale for Daily Use (D-FIS), showed a significant improvement throughout the study. Thus, D-FIS mean overall score changed from 14.45 ± 8.53 , at baseline, to 9.63 ± 9.84 , at Week 12/early termination visit (mean change -4.69 ± 8.44 ; $p = 0.0003$) in the ITT population, and from 14.06 ± 8.72 , at baseline, to 8.20 ± 8.90 , at Week 12/early termination visit (mean change -5.53 ± 8.73 ; $p < 0.0001$) in the PP population.

When markers of inflammation were analyzed in the ITT population, at Week 12, a statistically significant increase was seen in hemoglobin, hematocrit, and lymphocytes; and a statistically significant decrease was seen in leukocytes, neutrophils, platelets, ESR, fibrinogen, C-reactive protein and fecal calprotectin. Of notice, fibrinogen was reduced from 374.5 ± 68.17 mg/dL at baseline to 330.4 ± 64.63 mg/dL at Week 12/early termination visit, mean change -43.6 ± 65.7 ($p < 0.0001$); C-reactive protein was reduced from 11.06 ± 16.19 U/L at baseline to 3.86 ± 8.00 U/L at Week 12/early termination visit, mean change -7.61 ± 16.4 ($p < 0.0001$); and fecal calprotectin was reduced from $1,550.4 \pm 2,798.4$ mg/kg at baseline to 612.2 ± 815.3 mg/kg at Week 12/early termination visit, mean change $-1,043.8 \pm 2,895.3$ ($p < 0.0001$).

In the PP population, at Week 12/early termination visit, a statistically significant increase was seen in hemoglobin, hematocrit, lymphocytes, and INR; and a statistically significant decrease was seen in leukocytes, neutrophils, platelets, ESR, fibrinogen, C-reactive protein and fecal calprotectin. Fibrinogen was reduced from 382.0 ± 67.00 mg/dL at baseline to 338.4 ± 62.75 mg/dL at Week 12/early termination visit, mean change -42.8 ± 55.6 ($p < 0.0001$); C-reactive protein was reduced from 12.53 ± 16.74 U/L at baseline to 3.76 ± 7.61 U/L at Week 12/early termination visit, mean change -8.96 ± 15.6 ($p < 0.0001$); and fecal calprotectin was reduced from $1,661.7 \pm 3,330.8$ mg/kg at baseline to 594.2 ± 679.1 mg/kg at Week 12/early termination visit, mean change $-1,306.8 \pm -3,244.7$ ($p < 0.0001$).

An association between clinical response at the beginning of the treatment (Day 4 or Week 1) and clinical remission upon completion (Week 12/early termination visit) was found in both ITT ($p = 0.0105$) and PP population ($p = 0.0076$).

Pharmacokinetic Results:

Not applicable.

Safety Results:

A total of 87 adverse events (AEs) were reported throughout the study; of them, 73 (83.90%) were considered of mild intensity, 13 (14.94%) moderate and 1 (1.16%) was considered severe. Only 3 (3.45%) out of the 87 AE were considered serious adverse events. Thirty-six (41.86%) patients experienced at least one AE, 11 (12.79%) patients experienced at least one AE related to adalimumab, 2 (2.33%) patients experienced at least one serious AE (none of them related to adalimumab), and only 1 (1.16%) patient experienced at least one severe AE. One (1.16%) patient experienced at least one AE that was considered severe and serious. Four (4.65%) patients experienced at least one AE that led to the study discontinuation, of them, only one (1.16%) was related to adalimumab.

The most frequent adverse events were those encompassed in the System Organ Class (SOC) "Infections and infestations." Thus, 17 (19.77%) patients reported 24 adverse events included in this SOC; of them, only 5 (5.81%) patients reported 6 adverse events related to the study drug.

Thirteen (15.12%) patients reported 23 adverse events included in "Gastrointestinal disorders" SOC; none of them were related to the study drug. Seven (8.13%) patients reported 11 adverse events included in "Skin and subcutaneous tissue disorders" SOC; of them, 5 (5.81%) patients reported 8 adverse events related to the study drug. Seven (8.13%) patients reported 8 adverse events included in "Musculoskeletal and connective tissue disorders" SOC; of them only 1 (1.16%) patient reported 1 adverse event related to the study drug. Seven (8.13%) patients reported 7 adverse events included in "General disorders and administration site conditions" SOC; none of them were related to the study drug.

Only statistically significant changes over time were seen with AST, albumin, total bilirubin and alkaline phosphatase. AST increased from 19.12 ± 8.86 at baseline to 22.24 ± 15.11 at Week 12/early termination visit (mean change 3.15 ± 12.34 ; $p = 0.0045$); albumin increased from 40.73 ± 3.57 at baseline to 41.48 ± 3.27 at Week 12/early termination visit (mean change 0.81 ± 3.21 ; $p = 0.0275$); total bilirubin increased from 0.53 ± 0.29 at baseline to 0.65 ± 0.45 at Week 12 (mean change 0.11 ± 0.30 ; $p = 0.0009$). Alkaline phosphatase decreased from 76.52 ± 24.53 at baseline to 73.03 ± 38.67 at Week 12/early termination visit (mean change -3.44 ± 33.49 ; $p = 0.0004$).

Only one case of hypertriglyceridemia and one case of hypertransaminasemia have been reported as adverse events during the study. Both cases were of mild intensity.

Conclusions:

Adalimumab, administered subcutaneously at a dose of 160 mg at Week 0, followed by 80 mg at Week 2, and 40 mg every other week (or 40 mg weekly per investigator discretion) from Week 4 to Week 10, in patients with luminal Crohn's disease, led to a rapid clinical response. Almost 62% of the patients in ITT population, and 69.1% of the patients in PP population achieved clinical response at Day 4. These percentages increased at Week 1 up to 75.6% and 83.6% in ITT and PP population, respectively. The median time to achieve clinical response was estimated at 2.5 days in ITT population and 1 day in PP population.

Treatment with adalimumab also leads to a rapid clinical remission in a high percentage of patients. Thus, 54.6% and 62.8% of the patients in the ITT population achieved clinical remission at Week 2 and Week 4, respectively; and 60.0% and 70.9% of the patients in the PP population achieved clinical remission at Week 2 and Week 4, respectively.

An association was seen between the clinical response at the beginning of the study (Day 4 or Week 1) and the clinical remission upon completion in both, ITT and PP population. A clinical remission at Week 12 can be expected in almost 60% of the patients with Crohn's disease that achieved clinical response within the first week after treatment initiation.

Adalimumab improves the quality of life and the fatigue of patients with luminal Crohn's disease. Significant improvements were observed on the EQ-5D-3L, IBDQ-36, and D-FIS questionnaires upon study completion.

Treatment with adalimumab also leads to a rapid and significant decrease of C-reactive protein and fecal calprotectin levels, and erythrocyte sedimentation rate.

The safety profile of adalimumab in this study is in accordance with the information that can be found in the SmPC of the drug.