2.0 Synopsis

Abbott Laboratories	**Individual Study Table Referring to Part of Dossier:** N/A	**(For National Authority Use Only)**
Name of Study Drug: Adalimumab	**Volume:** N/A	
Name of Active Ingredient: Adalimumab	**Page:** N/A	

Title of Study:

A Multicentre, Open-Label, Treatment Protocol of the Human Anti-TNF Monoclonal Antibody Adalimumab in Canadian Subjects with Moderate to Severe Crohn's Disease (ACCESS)

Principal Investigator:

[redacted] MD, FRCPC redacted information 14Nov2014

Study Sites:

Multicenter with a total of 42 sites enrolling subjects in Canada

Publications:

None

Studied Period (Years):	**Phase of Development:** 3
First Subject First Visit: 17 Jan 2007	
Last Subject Last Visit: 10 Jan 2008	

Objectives:

The primary objective of this study was to make adalimumab available to subjects suffering from moderately to severely active Crohn's disease (CD) who were eligible to receive biologic therapy or who had failed to respond to, lost response to, or were intolerant to infliximab, and to expand the safety database and profile of adalimumab for the treatment of CD in Canada. The secondary objective was to assess changes in Patient Reported Outcome (PRO) measures from Baseline.

Methodology:

This was a Phase 3, multicenter, open-label, Early Access Study with an induction regimen of adalimumab 160 mg subcutaneous (SC) at Baseline and 80 mg SC at Week 2, followed by maintenance dosing of 40 mg every other week (eow) starting at Week 4 in subjects with moderately to severely active CD who were eligible to receive biologic therapy or who had failed to respond to, lost response to, or were intolerant to infliximab. Failure of prior therapy was determined by the Investigator. Subjects were to have an 8-week wash-out period prior to Baseline from the last dose of infliximab.

If during the study the subject experienced a flare or was a nonresponder (as determined by the Investigator) while receiving adalimumab 40 mg eow, the subject was allowed to dose escalate to adalimumab 40 mg weekly (ew) at or after Week 8. If the subject experienced a flare or was a non-responder (both determined by the Investigator) while the subject was receiving adalimumab ew, the subject could have been discontinued from the study.

Methodology (Continued):

Subjects were to be seen at the site at Screening; Baseline; Weeks 4, 8, 12, and 24; and then approximately every 12 weeks until study termination. Subjects were to remain in the study for a minimum of 24 weeks, or until adalimumab became commercially available for the treatment of CD in Canada. Study enrollment was stopped shortly after Humira® was approved in Canada for CD on 05 July 2007. Patients were provided with drug until they achieved insurance coverage or if lacking, coverage was to have been provided with compassionate drug supply indefinitely.

Number of Subjects (Planned and Analyzed):

Planned: 350 subjects

Analyzed: 304 subjects were enrolled and analyzed for both efficacy and safety

Diagnosis and Main Criteria for Inclusion:

Eligible subjects were to be males and females aged ≥ 18 years with a clinical diagnosis of moderate to severe CD for > 16 weeks prior to Screening. Diagnosis of CD was to be by radiologic or endoscopic evaluation and severity of CD was to be determined by the Investigator. Subjects were to be eligible for biologic therapy (those with a Crohn's Disease Activity Score (CDAI) score > 220 OR a Harvery-Bradshaw Index (HBI) score ≥ 7). Subjects were to be refractory to optimal conventional therapies such as, 5-aminosalicylic acid, glucocorticoids, and immunosuppressive therapies (azathioprine, 6-MP, and methotrexate). Subjects who failed prior infliximab therapy (as determined by the Investigator) were eligible to enter the study after a minimum wash-out period of 8 weeks (prior to Baseline) since last dose. Subjects who previously used infliximab and never clinically responded ("primary nonresponders") were also allowed as well as subjects who previously responded but who developed intolerance or lost efficacy to infliximab ("infliximab failure"). Subjects were not to have had persistent chronic or active non-CD related infections requiring treatment with intravenous antibiotics, antivirals, or antifungals within 30 days prior to Baseline or oral antibiotics, antivirals, or antifungals within 14 days prior to Baseline. Subjects were not to have history of malignancy other than a successfully treated non-metastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in-situ of the cervix. Subjects were not to have history of listeria, human immunodeficiency virus, an immunodeficiency syndrome, central nervous system demyelinating disease, chronic viral hepatitis, or untreated tuberculosis (TB). Subjects with any prior exposure to Tysabri® (natalizumab) were not permitted in the study.

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

Adalimumab 40 mg/0.8 mL SC

Lot Numbers: [redacted] redacted information 14Nov2014

Duration of Treatment:

Subjects were to remain in the study for a minimum of 24 weeks, or until adalimumab became commercially available for the treatment of CD in Canada. This study was stopped shortly after Humira® was approved in Canada for CD on 05 July 2007.

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

N/A

Criteria for Evaluation

Efficacy:

Efficacy was assessed by the following:

HBI –Used to assess CD activity on the previous day. A decrease indicates improvement and an absolute decrease of 3 points is considered clinically significant. Remission by HBI was defined as HBI ≤ 4 and response by HBI was defined as a decrease in HBI ≥ 3 points.

Short Quality of Life Inflammatory Bowel Disease Questionnaire (SIBDQ) – Used to assess health-related quality of life in patients with inflammatory bowel disease during the previous 2 weeks. The score ranges from 10 to 70 and could be subdivided into domains of Systemic System (domain score range: 2 to 14), Social Function (range: 2 to 14), Bowel Function (range: 3 to 21), and Emotional Symptoms (range: 3 to 21). Increases in SIBDQ scores indicate improved overall QoL, with larger increases indicating greater improvement. Of note, 9 point change in the SIBDQ correlated with a 100-point change in CDAI.

Health Care Resource Utilization (HCRU) – To assess health resources (visits to a health care professional, emergency room visits, and hospitalizations) used for CD.

Work Productivity and Activity Impairment (WPAI) – To assess impairment in work productivity and daily activity due to CD in the past 7 days. Four scores were generated from WPAI: percent time work missed (absenteeism), percent impairment while working (presenteeism), overall work impairment, and percent activity impairment score. A WPAI score of 0% = no impairment and a score of 100% = total loss of work productivity or activity. An absolute change in WPAI score of 7% was considered the minimal clinically meaningful change

Subjects completed these questionnaires at Baseline, Weeks 4, 8, 12, and at approximately every 12 weeks thereafter, or until study termination.

Fistula counts were performed during the physical examination.

Safety:

Safety was assessed through the evaluation of adverse events (AEs), laboratory parameters, physical examination results, and vital signs measurements.

Statistical Methods

Efficacy and safety were analyzed using the full analysis set, or intent-to-treat population, which consisted of all subjects who received at least one SC injection of adalimumab. In addition, summaries were provided for selected parameters for the following two subsets: 1) Subjects who were on adalimumab 40 mg SC from Week 4 to end of study (non-dose escalators); and 2) Subjects who were initially on adalimumab 40 mg SC eow and then dose escalated to adalimumab 40 mg SC ew (dose escalators). A per-protocol set was used to explore the impact of major protocol deviations on the results of this study. Subjects were identified according to prior infliximab history and results are presented by the following groups in addition to an Any Adalimumab group (all full analysis set subjects):

- Primary nonresponders are subjects who never responded to, or who failed to respond to previous infliximab therapy.
- Initial responders are subjects who demonstrated an initial response to infliximab and lost response later or who are intolerant to infliximab.

- Naïve subjects are subjects who were never exposed to infliximab.

Efficacy data were analyzed as observed (no data imputation was used) at Baseline (Week 0), Week 4, Week 8, Week 12, every 12 weeks thereafter until study end, and at Last Assessment Value (LAV) using descriptive statistics. LAV is the last non-missing measurement. These data came from the subject's Final visit, or the Early Termination (ET) visit or the visit just prior to study discontinuation or dose escalation / switch. These LAVs were determined for all subjects: (1) the LAV during the subject's entire participation in the study; (2) the LAV while receiving adalimumab 40 mg eow and prior to any dose-switching / escalation (LAV[EOW]); and (3) LAV after dose escalation while subject was receiving adalimumab 40 mg weekly dose (LAV[EW]).

No formal inferential analysis was performed for this open-label study; however, *P*-values from the tests of no change from Baseline (demographic and baseline data) and 95% confidence intervals (efficacy) were provided.

Adverse event frequencies were summarized by n (%). Laboratory and vital signs assessment data were presented descriptively.

Summary/Conclusions

Efficacy Results:

The study population consisted of subjects who were eligible to receive biologic therapy or had failed to respond to, lost response to, or were intolerant to infliximab. Most subjects had CD of the ileum or colon with a mean duration of CD of 11.8 years (range: 0.3 to 45.3 years). There were more females (54.5%) than males in the study, the majority of subjects (81.8%) were White, and mean age was 37.0 ± 12.05.

Results demonstrated that treatment with adalimumab resulted in improvement in CD activity, quality of life, work productivity, and draining fistula count irrespective of prior infliximab use.

All subjects treated with adalimumab (All Adalimumab group) demonstrated clinically and statistically significant improvements in HBI (mean decrease of 3 points).

	All Adalimumab N = 304		
Visit Week	**n**	**Mean ±SD**	**95% CI**
HBI			
Week 4	301	-4.39 ± 4.852	-4.94, -3.84
Week 8	292	-4.53 ± 5.175	-5.12, -3.93
Week 12	286	-5.32 ± 5.008	-5.90, -4.74
Week 24	270	-6.36 ± 5.031	-6.96, -5.75
LAV	303	-5.92 ± 5.162	-6.50, -5.34

The proportion of subjects in remission, as defined by HBI ≤ 4, increased upon study drug treatment with 2% of subjects in remission at Baseline compared to 43.8% of subjects at Week 24 (*P* = <0.001). HBI response, as defined as a decrease in HBI ≥ 3, increased from 64.1% at Week 4 to 73% at Week 24.

	Primary Nonresponders N = 22	Initial Responders N = 138	Naïve N = 144	All Adalimumab N = 304	*P*-value
			n (%)		
Remission					
Baseline	1 (4.5)	4 (2.9)	1 (0.7)	6 (2.0)	
Week 4	1 (4.5)	36 (26.1)	44 (30.6)	81 (26.6)	< 0.001
Week 24	4 (18.2)	53 (38.4)	76 (52.8)	133 (43.8)	< 0.001
Response					
Week 4	7 (31.8)	88 (63.8)	100 (69.4)	195 (64.1)	
Week 24	15 (68.2)	89 (64.5)	118 (81.9)	222 (73.0)	--

All subjects treated with adalimumab (All Adalimumab group) demonstrated clinically and statistically significant improvements in SIBDQ (minimal clinical important difference [MCID] = 9 points) at all time points. The average improvement in SIBDQ was well above the clinical meaningful change of 9 points. At Week 24, the improvement in SIBDQ for each adalimumab group was greater than the clinical meaningful change of 9 points. Mean change from Baseline in SIBDQ domain scores showed a positive improvement from Baseline for systemic system, social function, bowel function, and emotional symptoms at all time points.

	All Adalimumab N = 304		
Visit Week	**n**	**Mean ± SD**	**95% CI**
SBDIQ			
Week 4	301	10.16 ± 10.692	8.95, 11.38
Week 8	291	11.85 ± 11.591	10.51, 13.19
Week 12	284	13.14 ± 11.783	11.76, 14.52
Week 24	269	15.06 ± 12.209	13.59, 16.52
LAV	301	13.74 ± 12.629	12.30, 15.17

Statistically and clinically significant mean decreases from Baseline (MCID = 7 points) were observed in absenteeism, presenteeism, work impairment, and work activity at all visits for the All Adalimumab group. During the study, 64% to 70% of subjects were employed. At Week 24, employment rate increased from 64% to 71%, an absolute 7% increase.

	All Adalimumab N = 304		
Visit Week	**n**	**Mean ± SD**	**95% CI**
WPAI - Absenteeism			
Week 4	159	-5.99 ± 24.592	-9.84, -2.14
Week 8	155	-7.55 ± 27.543	-11.92, -3.18
Week 12	153	-8.74 ± 33.477	-14.09, -3.39
Week 24	149	-8.54 ± 27.260	-12.95, -4.13
LAV	159	-6.46 ± 29.167	-11.03, -1.89
WPAI - Presenteeism			
Week 4	171	-20.58 ± 26.115	-24.53, -16.64
Week 8	165	-19.94 ± 27.151	-24.11, -15.77
Week 12	159	-25.79 ± 30.113	-30.50, -21.07
Week 24	154	-28.96 ± 28.472	-33.49, -24.43
LAV	166	-26.69 ± 30.058	-31.29, -22.08
WPAI - Overall work impairment			
Week 4	159	-22.08 ± 28.454	-26.54, -17.63
Week 8	153	-22.36 ± 29.337	-27.04, -17.67
Week 12	153	-29.93 ± 33.669	-35.31, -24.56
Week 24	149	-31.23 ± 30.403	-36.15, -26.31
LAV	159	-28.49 ± 32.286	-33.54, -23.43
WPAI - Activity impairment			
Week 4	295	-23.59 ± 26.928	-26.68, -20.51
Week 8	288	-24.79 ± 28.431	-28.09, -21.49
Week 12	280	-30.36 ± 28.697	-33.73, -26.98
Week 24	265	-34.00 ± 29.552	-37.57, -30.43
LAV	295	-30.98 ± 30.484	-34.48, -27.49
HCRU was consistent with results observed in other adalimumab clinical programs.			

	All Adalimumab N = 304	
Overall	**n**	**Mean Change ± SD**
# of Unscheduled Visits to Physician	303	1.13 ± 2.794
# of Visits to ER	303	0.17 ± 0.522
# of Hospital Admissions	303	0.10 ± 0.346
# of Days of Hospitalization	303	0.60 ± 2.790

Approximately 57% of the subjects in all three groups (All Adalimumab group) had a 50% improvement in fistula count while 37% had fistula healing reported at Week 12.

Approximately, 51% of the subjects in all three groups (All Adalimumab group) had 50% improvement in fistula count at Week 24 while 44% had fistula healing at Week 24.

At LAV, 43% of the subjects had a 50% improvement in fistula count and 43% had fistula healing (All Adalimumab group).

Safety Results:

Adalimumab was found to be generally safe and well-tolerated. A total of 79.6 % of subjects experienced at least one treatment-emergent AE during the study. Most subjects had AEs that were not related or probably not related as per the Investigator and the majority had AEs that were moderate in severity. The most frequently reported AEs included CD (16.1%) followed by abdominal pain (7.6%), and injection site reaction (7.6%). One death occurred during the study (lung adenocarcinoma metastatic; not related per the Investigator). A total of 14.5% of subjects reported a serious adverse event (SAE). Six subjects reported SAEs that were possibly or probably related to study drug treatment (abdominal abscess [2], CD, dyshidrosis, fistula, abdominal pain, anxiety, dyspnoea). Premature discontinuation from study drug was low (10.9%) as were allergic reactions (2 subjects), malignancy (1 subject; lung adenocarcinoma [death]), and hepatic events (5 subjects). No lymphoma or NMSC was reported. A total of 18.8% of subjects experienced injection site reactions. A total of 29.6% of subjects experienced infections. Serious infections were experienced by 8 subjects (abdominal abscess [5], pneumonia legionella, perianal abscess, rectal abscess, appendicitis) and 4 subjects experienced an opportunistic infection (oral candidiasis). TB was not reported. There were no reports of lupus-like syndrome, demyelinating disorders, or congestive heart failure. Laboratory assessments and vital signs were clinically unremarkable. No new safety signals were observed.

Conclusions:

Results demonstrated that treatment with adalimumab results in improvement in CD activity, quality of life, work productivity, and draining fistula count irrespective of prior infliximab use. Adalimumab was found to be generally safe and well-tolerated.