Adalimumab

1.0 Title Page

AbbVie Corporation (AbbVie)

CLINICAL STUDY PROTOCOL (P12 – 678)

Amendment 2: Canadian Humira Post Marketing Observational Epidemiological Study: Assessing Effectiveness in Psoriasis (Complete - Psoriasis)

Product Name:	Adalimumab (Humira)
Type of Study:	Observational Study
Date:	August 8th, 2013
CRO(s):	Cato Research 9900 Blvd Cavendish, suite 400 Montreal, Quebec H4M 2V2 Phone (514) 856 2286 [redacted]
Sponsor:	[redacted] AbbVie Corporation, Limited. 8401 Trans-Canada Highway Montreal, Qc H4S 1Z1
Medical Writer:	[redacted]

2.0 Table of Contents

List of Tables

List of Appendices

3.0 Introduction

Psoriasis is an autoimmune illness characterized by chronic non-contagious skin manifestations[1] caused by an immunologically accelerated cell turnover[2]. The result is an abnormal accumulation of cells to the skin surface[2] causing inflammation, thickening, scaling, pruritic changes and pain that could extend to the surrounding joints[3].

There are five types of psoriasis depending on the symptoms and severity. The most common type of psoriasis (approximately 80%) is "plaque psoriasis" where raised and inflamed red lesions covered by silver-white scales develop.

The causes of psoriasis are somewhat unknown; however it is believed that genetics and the immune system are involved. It is postulated that 10% of the population has a gene that predisposes them to psoriasis; however, only 2% of the worldwide population develops the illness. The currently held belief is that a multifactorial genetic predisposition and an environmental trigger are required for the disease to manifest. Potential triggers include stress, an injury to the skin and certain medications such as lithium, antimalarials, Inderal, quinidine and indomethacin. Injury induced psoriasis is known as the Koebner phenomenon.[5] There are certain triggers that could cause specific types of psoriasis. For instance, upper respiratory infections, streptococcal throat infections, tonsillitis, beta-blockers as well as the three triggers mentioned above can cause guttate psoriasis. Appreciation of the different types of Psoriasis and related environmental triggers becomes important in studying regional variations in the epidemiology and risk factors of the disease.

On the cellular level, the causes of psoriasis begin with T-cells, which have been shown to be involved in the development of psoriasis, more specifically Th1 and Th17 cells. When the cytokine IL-12 is produced, Th1 cells differentiate which subsequently secrete TNF-α and IFN-α. These two cytokines cause vasodilatation, leukocyte migration, activation of keratinocytes and, later on, the activation of dendritic cells. The latter effect will begin a

cycle of inflammation. Th17 cells are also involved. After they are activated by IL-1, IL-6 and TGF-α, they produce IL-17 and IL-22 which also stimulate keratinocyte activation and proliferation. Clearly, the overstimulation of the keratinocytes is the main cause of the acceleration of the skin cell growth cycle mentioned earlier.[1] Understanding of the underlying disease process is essential in defining treatment targets.

Psoriasis affects approximately 125 million people worldwide, which consist of 2-3% of the total population.[6] In Canada it is estimated that more than 1 million individuals, have psoriasis. The prevalence of the disease is 0.8-1%.[7] However, these statistics vary according to race, ethnic background, region, age and gender

Psoriasis has a major impact on the patient's quality of life with approximately 60% of the patients considering the illness to greatly impact their life.[8] However, in Canada, according to a study by Lynde et al., 35% of the patients with psoriasis considered the disease to be a substantial problem in their daily life. In the same study, 54% of patients had lesions on more than 3% of their body.[9] Furthermore, psoriasis has a greater negative impact in women and younger patients.[6] Although not typically considered a severe or life threatening condition, in its severe form, affecting more than 10% of the body, life expectancy may be decreased for as much as 50% when comparing mild to severe psoriasis [6, 10]

The typical first line of treatment for early mild psoriasis is topical medications. These include creams, ointments and shampoos[11] that slow down or normalize the accelerated growth cycle of the skin cells and hence reduce the inflammation.[12] Corticosteroid ointments are generally the first line topical treatment of choice and are effective in reducing the swelling and the redness of the lesions.[13] Corticosteroids provide symptomatic relief but may not cure the disease and may even cause exacerbation with high dose or prolonged use. Topical corticosteroids are associated with possible side effects resulting in skin damage, such as skin thinning, changes in pigmentation, easy bruising, stretch marks, redness and dilated blood vessels on the surface. Furthermore, if

applied on, in or near the eye, cataracts and glaucoma may occur. [13]

There are some topical drugs that do not contain corticosteroids, like Dovonex (calcipotriene), and Vertical (calcitriol). Dovonex and Taclonex (calcipotriene and betamethasone dipropionate) have some non-severe side effects, the most common being skin irritation, stinging and burning for Dovonex and itching, rash, skin thinning and burning for Taclonex.[14] Furthermore, the patient has an increased risk of skin tumors because of the sensitivity to light. Some antipsoriatic topical drugs contain retinoids, such as Tazorac (tazarotene). These medications act less rapidly than corticosteroids, but have fewer adverse effects.[3,14] Other topical medications for psoriasis include Zithranol-RR (Anthralin), vitamin D_3 or A, coal tar and salicylic acid.[3,12] Anthralin has no long-term side effects, though it may cause skin irritation and may stain light-colored hair and unaffected skin.[14]

For moderate or severe psoriasis, affecting more than 3% of the body surface area, topical treatments are generally not effective and more aggressive therapy is required.[11] Phototherapy is an effective second line treatment for moderate psoriasis or mild disease that has not responded to topical therapy. Phototherapy consists of regularly exposing the skin to ultraviolet (UV) light which reduces inflammation by reducing T-cell proliferation.[3] Ultraviolet light treatment is classified as UVA and UVB. UVA light is the principle component of sunlight and it is used in combination with photosensitizing medications such as psoralen when it is referred to as PUVA. The disadvantages of UVA and PUVA treatments include a high risk of cancer along with immediate reactions including, nausea, headache, burning of the skin and photosensitivity. Use of topical PUVA or baths have been proven to be a safer and effective alternative. [22-23]

UVB treatment is based on another component of sunlight and it is available as broadband or narrowband therapy. Broad band UVB phototherapy uses light with a wavelength range between 290 and 350 nanometers. UVB treatment is less carcinogenic when compared to UVA and does not require co administration of medications. However, it may be less

effective. Narrowband UVB uses light in the 311-313 nanometer wavelength range. It is highly effective and does not require the use of photosensitizing medications.[22-23]

Compliance with treatment is essential for success of phototherapy. This treatment is most recommended when the patient has plaque psoriasis, guttate psoriasis or psoriasis on the palms and soles.[15] However, if employed over a long period of time, it is associated with an increase of risk of skin cancers. Recently two new phototherapy treatments have been by the FDA for mild to moderate psoriasis: the excimer and pulsed dye laser which better control the beam of light (UVB) to specifically target the affected skin area.[3, 15]

For moderate to severe psoriasis that does not respond to topical agents or phototherapy, systemic treatments are used[3]. These include traditional and biologic disease modifying agents. Methotrexate and cyclosporine are traditional systemic disease modifying agents that have been proven to be efficacious in the management of psoriasis[16]. Cyclosporine binds to dihydrofolate reductase leading to the inhibition of synthesis of DNA, RNA, thymidylates and proteins and thus reducing the skin proliferation. Adverse effects associated with methotrexate include liver damage reduced leukocytes, infections and malignancies.[17]

Cyclosporine suppresses the immune system and prevents skin cell proliferation. While efficacious in controlling the symptoms of psoriasis, cyclosporine has an increased risk for serious adverse events and prolonged use or use by patients with chronic conditions or compromised immune systems is not recommended. Among the side effects of cyclosporine the most important are decreased kidney function, headache, hypertension, elevated cholesterol, excessive hair growth, tingling or burning sensation in arms and/or legs, skin sensitivity, increased growth of gum tissues, influenza-like symptoms, upset stomach, tiredness and muscle, bone or joint pain. Also, if the drug is taken over a long period of time, the patient could develop skin cancer or kidney damage. This risk increases with a longer exposure.[18]

Biologic systemic agents and specifically anti-TNF-α inhibitors have been developed in recent years and have been proven efficacious in the management of patients. As mentioned earlier, TNF-α, a cytokine, causes the proliferation of keratinocytes through the mediation of inflammatory Th1 cells (CD4 T-cells) that bind to MHC (major histocompatility complex) class II molecules and present an antigen to the T-cells. Some of these cytokines, including TNF-α, stimulate the activation of macrophages which cause inflammation and induce vascular permeability, leukocyte migration and the formation of new vessel networks. TNF is over expressed in psoriatic plaques and TNF-induced proteins are found in psoriatic lesions but not in healthy areas. This would suggest that TNF is involved in the pathogenesis of the disease by increasing the inflammatory process and augmenting the proliferation of keratinocytes in the affected regions. It is also postulated that TNF increases cellular adhesion, activation and promotion of angiogenesis. Therefore, agents that block the activity of TNF-α have been proven to treat psoriasis and reduce inflammation.[19]

Adalimumab (Humira®) is a fully human anti-TNF-α monoclonal antibody that is an analogue to human IgG1. It attaches to TNF and prevents its binding to p55 and p75 TNF receptors on the cell surface. It is currently approved for the treatment of psoriasis, juvenile and adult rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and Crohn's disease. Currently dosing in patients with moderate to severe psoriasis involves an initial dose of 80mg subcutaneously, followed by a 40mg injection every second week beginning one week after the initial 80mg dose.

Due to their immune suppression properties, anti-TNF alpha agents including adalimumab may be associated with increased risk for serious infections including tuberculosis, candidiasis, listeriosis, pneumocystis, pneumonia, pyelonephritis, septic arthritis and septicemia. Patients may also be at risk for serious opportunistic infections. However, these events have been predominantly reported in patients with compromised immune systems. Some non-severe adverse effects are a moderately painful injection

site[20] including redness, itching, bruising, pain or swelling, stomach pain, nausea, headache and back pain.[21] Rare side effects include malignancies, reversible lupus (without renal or CNS complications) and cytopenias. Therefore all patients treated with anti-TNF alpha agents must be monitored for serious infections and particularly tuberculosis before, during and after treatment. In addition monitoring of liver function, CBC and hepatitis profile are recommended.[20]

The efficacy of adalimumab in controlling the symptoms of psoriasis has been demonstrated in several controlled clinical trials. Taken collectively the results of these studies that have been conducted on over 1600 patients with moderate to severe chronic plaque psoriasis who were candidates for systemic therapy or phototherapy have shown that adalimumab is efficacious in controlling the symptoms of psoriasis and in improving the quality of life of patients. More specifically, when compared to placebo or methotrexate, patients treated with adalimumab had a significantly higher therapeutic response rate, defined as achieving a PASI 75 and a Physician Global Assessment (PGA) value of ≤ 1 (indicating clear or minimal disease) at 16 weeks. The magnitude of effect versus placebo ranges from four-fold (79.6% versus 18.9%) to ten-fold (70.9% versus 6.5%) for PASI 75 and from 2.5 times (73.1% versus 30%) to 14.5 times (62.2% versus 4.3%) for PGA of clear or minimal. When compared to methotrexate the magnitude of effect is 2.2 times for PASI 75 (79.6% versus 35.5%) and 2.5 times for PGA of "clear or minimal" (73.1% versus 30%) [1,11-18,22-29]. In addition, in one clinical trial patients crossed over to placebo after 33 weeks of treatment with adalimumab were significantly more likely to lose therapeutic response when compared to patients that were maintained on adalimumab up to week 52. With respect to quality of life, when compared to patients treated with placebo or methotrexate those treated with adalimumab in these controlled clinical trials have had better improvement in the Dermatology Quality of Life Index (DLQI) total score as well as in the disease severity, pain and pruritus subscales. Better improvement in the Physical and Mental subscales of the Medical Outcomes Study Short Form 12 (SF-12) was also observed for the adalimumab treated patients when compared

to placebo.

In Canada, the Canadian Expert Drug Advisory Committee (CEDAC) of the Canadian Agency for Drugs and Technologies in Health has recommended adalimumab in the treatment of psoriasis under the following conditions:

i. Patient is diagnosed with severe debilitating psoriasis; and

ii. Body surface involvement of more than 10% and / or significant involvement of the face, hands, feet or genital areas; and

iii. Failure to respond to, contraindication or intolerance to methotrexate and cyclosporine; and

iv. Failure to respond to, intolerant to or unable to access phototherapy.

4.0 Rationale

Complete is a three part Canadian observational research study program aimed at assessing the real life effectiveness of adalimumab in the management of Psoriasis, Psoriatic Arthritis and Ankylosing Spondylitis. The general aim of the program will be to identify and describe common elements in these three conditions with respect to the population at risk, comorbidities, burden of illness, prognostic factors and response to treatment in the real – life setting. This will have significant implications for educating physicians and patients in the assessment and identification of signs and symptoms that would prompt further investigation and possible earlier diagnosis and treatment of these conditions. The results will also have an important impact on the advancement of our understanding of the causal pathways for these conditions that could eventually lead to improved patient management. Therefore, in addition to addressing the objectives of the individual studies, the data obtained in the program will also be used to address this

general aim.

With respect to Psoriasis, adalimumab has been approved in Canada for patients with moderate to severe Psoriasis that are candidates for systemic therapy. For patients with moderate plaque Psoriasis adalimumab should be used for after phototherapy has been ineffective or inappropriate (Canadian Product Monograph). To date real – life observational data allowing the comparison of the effectiveness of adalimumab to topical agents and traditional systemic agents in patients failing current treatment have not been reported. There is also currently a knowledge gap with respect to the practice patterns and regional variation in the approach used by Canadian physicians in the management of patients with psoriasis.

Psoriasis presents a significant burden of illness through the physical and emotional manifestations that significantly affect the patient's quality of life as well as loss of productivity and direct and indirect costs. Assessment of the impact of different approaches to the management of moderate to severe psoriasis on these patient centric outcomes is therefore of paramount importance. Given that patient reported outcomes have a cultural and regional influence, the assessment of these outcomes in specific regions is also of high relevance and importance in the assessments of regional and global benefit – risk ratios.

An important consideration of Psoriasis is the fact that approximately 30% of the patients develop psoriatic arthritis (PsA). To date, there are no known predictors of progression to PsA among patients with psoriasis. In addition, it is known that triggers of psoriasis flare - ups and disease progression have an environmental and genetic determinant. There is currently a knowledge and patient management gap with respect to the screening and detection of flare – up triggers or articular and extra articular signs and manifestations indicating progression of psoriasis or onset of PsA. There is therefore a general need for the assessment of these questions. However, given the potential genetic and environmental effect on the incidence of Psoriasis as well as it severity and progression,

these questions must be addressed at the regional level.

Finally, continuous monitoring of the safety of adalimumab is essential in order to assess whether the safety profile in a real – life setting is comparable to that expected on the basis of the data reported in controlled clinical trials and to ensure detection of any emerging signal.

The current study will address the above questions by conducting a prospective observational study of Canadian patients with moderate to severe psoriasis for whom change of current treatment is indicated. Patients will enter the cohort at the time that their treatment is changed and therefore patients treated with topical agents, traditional systemic agents and adalimumab will be eligible to be included in the study. The rationale for limiting the anti-TNF alpha agent to adalimumab is based on the prevention of within class variation with respect to clinical decision making, response to treatment and incidence of adverse events.

Follow up will be for 24 months and assessments will be as per routine clinical care and according to the judgment of the treating physician. However, follow up visits at approximately 3, 6, 12, 18 and 24 months will be recommended.

There will be a total of 660 patients with psoriasis enrolled from the clinics of 30 – 40 Canadian community dermatologists. The sample of clinicians will be a random proportional representation of the distribution of dermatologists and patients in Canada, thus allowing valid generalization to the Canadian population of psoriasis patients. In addition, enrollment of the patients in the study will be on the basis of change in current treatment due to lack of response or tolerability. The decision to change treatment must be reached prior to enrollment in and independently of the current study.

The study will assess clinical and patient reported outcomes that are relevant in the management of psoriasis and its impact on the patient's quality of life and societal burden

of illness. The design is that of a prospective observational study with its inherent biases including confounding by indication. Statistical methods including multi-variate models and propensity scores will be used to adjust between group differences with respect to prognostic baseline characteristics. Mixed effects models will be incorporated to compensate for unequal follow up and lack of precisely scheduled visits. The design and statistical analysis employed are therefore required and appropriate to produce a valid real – life assessment and comparison of the different modes for the management of psoriasis that are currently used in Canada.

5.0 Study Objectives

5.1 Primary Objective:

To compare the real – life effectiveness of adalimumab to topical and traditional systemic agents in the management moderate to severe Plaque PS.

5.2 Secondary Objectives:

i. To compare the real – life effectiveness of adalimumab to topical and traditional systemic agents in the prevention of development of articular and extra-articular manifestations in patients with moderate to severe Plaque PS.

ii. To describe the profile and regional variation in terms of demographics, disease parameters, flare – up trigger, comorbidities and concomitant medication use of Canadian patients with moderate to severe Plaque PS.

iii. To describe the current practices and regional variation among Canadian dermatologists with respect to the screening and detection of articular manifestations indicating onset of PsA in patients with moderate to severe Plaque PS.

iv. To describe the incidence of and risk factors for the development of articular and extra-articular manifestations in Canadian patients with moderate to severe Plaque PS.

v. To describe the current population based burden of illness incorporating Health Care Utilization, Health Care Costs, Quality of Life, Psychological impact Work Productivity of moderate to severe Plaque PS in Canada.

vi. To assess the impact of topical agents, traditional systemic agents and adalimumab on the Plaque PS related burden of illness incorporating Health Care Utilization, Health Care Costs, Quality of Life, Psychological impactWork Productivity in Canada.

vii. To provide an ongoing assessment of the safety and tolerability of adalimumab, systemic and topical agents used in the management of moderate to severe Plaque PS in Canada.

5.3 Study Endpoints

5.3.1 Primary Endpoint

The primary effectiveness outcome measure for the current study will be the physician global assessment (PGA) of "0" or "1" indicating clear or minimal disease according to the following classification:

Score	Category	Description
0	Clear	Plaque elevation = 0 (no elevation over normal skin) Scaling = 0 (no scale) Erythema = ± (hyper pigmentation, pigmented macules, diffuse faint pink or red coloration)
1	Minimal	Plaque elevation = ± (possible but difficult to ascertain whether there is a slight elevation above normal skin) Scaling = ± (surface dryness with some white coloration) Erythema = up to moderate (up to definite red coloration)

Score	Category	Description
2	Mild	Plaque elevation = slight (slight but definite elevation, typically edges are indistinct or sloped) Scaling = fine (fine scale partially or mostly covering lesions) Erythema = up to moderate (up to definite red coloration)
3	Moderate	Plaque elevation = moderate (moderate elevation with rough or sloped edges) Scaling = coarser (coarse scale covering most of all of the lesions) Erythema = moderate (definite red coloration)
4	Severe	Plaque elevation = marked (marked elevation typically with hard or sharp edges) Scaling = coarse (coarse, non tenacious scale predominates covering most or all of the lesions) Erythema = severe (very bright red coloration)
5	Very severe	Plaque elevation = very marked (very marked elevation typically with hard sharp edges) Scaling = very coarse (coarse, thick tenacious scale over most of all of the lesions; rough surface) Erythema = very severe (extreme red coloration; dusky to deep red coloration)

The primary outcome measure will be the percent of patients with PGA score of ≤ 1.0 at 6 months of treatment.

5.3.2 Secondary Endpoints:

The following secondary endpoints will be assessed:

i. Time to achieving PGA ≤ 1 over 24 months of follow up.

ii. Percent of patients with PGA ≤ 1 at 3, 12, 18 and 24 months

iii. Signs and symptoms suggesting onset of PsA:

   i. Change in the modified Psoriasis and Arthritis Screening Questionnaire (PASQ). This is an 11 item tool that ascertains self reported presence of joint pain and swelling. This will be assessed at 3, 6, 12, 18 and 24

months.

iv. Change in Body Surface Area (BSA) of psoriasis involvement at 6, 12, 18 and 24 months. The BSA is an indicator of disease severity and the affected area is expressed as a percentage of the total body surface area.

v. Change in Patient Global Assessment of Disease Activity based on a six point Likert Scale at 3, 6, 12, 18 and 24 months.

vi. Change in the Dermatology Quality of Life Index (DLQI) at 3, 6, 12, 18 and 24 months. The DLQI is a self administered questionnaire comprised of 10 items assessing a patient's skin and problems associated with skin disease. The 10 questions in the DLQI converge into six domains that measure symptoms and feelings, daily activities, leisure, work and / or school, personal relationships and satisfaction with treatment.

    i. Proportion of patients achieving and time to DLQI $\leq$ 1 through the 24 months of treatment.

vii. Change in Beck Depression Inventory at 6, 12 and 24 months: This will be used to assess the presence and severity of depression. It consists of 21 items converging to two scales measuring somatic and affective components of depression. The questions assess hopelessness and irritability, cognition such as guilt or feelings of being punished, as well as physical symptoms such as fatigue, weight loss and loss of interest in sex. Given the important emotional and social impact of psoriasis assessing psychological impairment is important in order to fully appreciate the impact of the disease and effect of treatment on the patient's life.

viii. Change in Medical Outcomes Study Short Form 12 (SF-12) at 6, 12 and 24 months. The SF-12 Health is a 12-item general health self administered

questionnaire consisting of 8 scales measuring Physical Function, Physical Role limitations, Vitality, General Health, Pain, Social Function, Emotional Role limitations, and Mental Health.

ix. Change in Work Limitation Questionnaire at 6, 12 and 24 months. The WLQ is a self-administered questionnaire comprised of 25 questions. It assesses the degree to which the patient's work is affected due to health problems or health-related productivity loss. The 25 questions are further divided into four scales: time management, physical demands, mental-interpersonal demands and output demands. The scoring for the WLQ ranges from 0 (none of the time) to 100 (all of the time) and represent the portion of time in the prior two weeks that those answering the questionnaire were limited in their abilities while at work. Furthermore, an algorithm is present that can convert scores obtained using the WLQ into an estimate of productivity loss. Considering the important effect of psoriasis on the patient's ability to deal with the emotional and physical demands of employment, the assessment of the impact of disease and treatment on work related productivity loss is highly relevant.

x. Health Care Utilization Questionnaire through the 24 months of treatment. This will be a descriptive self administered series of questions aimed at measuring the patient's health care utilization and economic impact of the disease. More specifically the questionnaire will ascertain the frequency of physician visits, utilization of other health care professionals, visits to clinics, emergency rooms and hospitalizations that are related to psoriasis. In addition, use of prescription and non–prescription medications for the management of psoriasis will be determined. Out of packet expenses for medications and health care will be assessed. The patient's occupation and household income range will be used as a proxy to socioeconomic status.

xi. Compliance with treatment will be assessed through the 24 months of treatment

by self report of missed topical applications, medication doses or adalimumab injections.

xii. Change in medical history and concomitant medication use through the 24 months of treatment will be recorded assessed by the treating physician as per routine care.

xiii. Use and frequency change of phototherapy for psoriasis through the 24 months of treatment will be ascertained by a targeted question in the patient assessment.

6.0 Investigational Plan

This is a Canadian Post Marketing Observational Study utilizing a prospective cohort design. Patients are entered into the study cohort at the time of change of their Psoriasis treatment for any reason and are followed for a maximum of 24 months with recommended assessments at 3, 6, 12, 18 and 24 months after baseline. Treatment of the patients and follow up will be according to the physician's judgment, regional regulations and the product monograph. Off-label use will not be permitted and these patients will not be included in the study. Dose changes including escalation will be allowed as per the physician's judgment for patients that were treated as per indication when they were enrolled in the study.

There will be 660 patients enrolled from the practices of approximately 30 – 40 dermatologists across Canada. The study sample will be randomly selected and proportional to the Canadian population and distribution of dermatologists in Canada.

The following patient cohorts will be defined:

i. Initiated treatment with a new topical agent that was not used before or already on treatment with a topical agent and not responding requiring a change of treatment

type, frequency or dose.

ii. Initiated treatment with a new systemic agent that was not used before alone or in combination with topical agents.

iii. Initiated on treatment with adalimumab alone or in combination with topical agents.

In the case that the patient is switched from one cohort to another during the course of the study, follow up will continue as per the study protocol. For these cases, the treatment will be considered as a time dependent variable in the assessment of the study outcomes. In addition, depending on the number of patients switching cohorts, separate cohorts may be defined to include those patients that change treatment during the study.

Effectiveness outcome measures will include changes in clinical outcomes and quality of life. Health economic assessments will be conducted to determine the impact of treatment on Psoriasis related burden of illness. The impact of Psoriasis and different treatments on work productivity will be assessed. The study will also identify prognostic factors for progression to Psoriatic Arthritis and treatment gaps in the detection and screening for articular and extra-articular manifestations. Regional differences within Canada with respect to the patient profile and the management of patients with Psoriasis will be described.

6.1 Selection of Study Population

Patients will be enrolled from the offices of community dermatologists across Canada treating patients with Psoriasis. The sample of physicians invited to participate in the study will be selected in a way that it is a random representative sample of the Canadian population and distribution of dermatologists.

All patients with psoriasis treated at the participating centers will be potentially eligible

to be included in the study. Those fulfilling the study inclusion and exclusion criteria will be invited to participate in the study by the site investigator or designee. Treatment will be according to the treating physician's judgment and routine care and must adhere to the product monograph and regional regulatory requirements. Use of medications for the management of psoriasis that is off–label or not in accordance with existing regulations will not be permitted. Prior to inclusion in the study all patients will be required to sign a written informed consent agreeing to allow use of their data in the study. Since this is not an interventional study and patients are treated as per routine care the purpose of the informed consent will be to allow the use of the data and contact of the patients by the study personnel as required. The study protocol, informed consent, questionnaires and participating physicians will be approved by a central or local independent ethics review board as required by regional or institutional regulations.

Changing the patient's treatment including initiation of treatment with adalimumab must be exclusively the treating physician's decision and must be reached prior to patient screening and enrollment and has to be entirely independent of the conduct of the study. The observational nature of the study dictates that all treatments used in the current study, including adalimumab, must be prescribed as per routine care and in accordance to the Canadian and provincial marketing authorization and criteria.

6.1.1 Inclusion Criteria

The following inclusion criteria will be applied:

i. Adult $\geq$ 18 years old

ii. Has provided written informed consent allowing the use of their data for the study and providing permission for contact by the study personnel.

iii. Active moderate or severe Plaque PS according to the judgment of the treating physician.

iv. The treating physician has decided to change the current treatment or add additional treatments for any reason including but not limited to inadequate response, intolerance, sub-optimal compliance or patient preference.

6.1.2 Exclusion Criteria

The following exclusion criteria will be applied:

i. Currently participating in another prospective study with similar objectives.

ii. Patient cannot or will not sign informed consent.

iii. Presence of other condition that, in the opinion of the treating physician, prohibits the patient from participating in the study or obscures the assessment of the treatment of Plaque PS.

6.2 Number of Patients to be Enrolled

A total of 660 patients will be enrolled in the current study from the practices of 30 – 40 dermatologists. A maximum of 30 patients per site will be allowed. Recruitment will be over a 24 month period. In order to provide adequate power to assess the effect of different treatment modalities, it will be recommended that 50% of the patients from each site will be initiated on treatment with adalimumab.

6.3 Investigator Selection Criteria

i. A random sample of 30-40 dermatologists will participate in the study.

   a. Physicians participating in the study must have experience in the conduct of clinical research and in particular good clinical practices (GCP) or must be willing to be trained in GCP.

6.4 Study Duration

All patients will be followed for 24 months. Given the observational nature of the study there will be no pre-defined protocol driven assessments and physician visits could take place according to the routine practice or the judgment of the treating physician. However, assessments at 3, 6, 12, 18 and 24 months after baseline will be recommended and encouraged given that this is within the acceptable practice patterns for patients undergoing treatment for moderate to severe psoriasis. In certain cases patients may be assessed more frequently than what will be recommended. Physicians will be asked to record in the Case Report Forms data from all visits occurring during the study period.

6.5 Study Conduct

The following sections describe the details regarding the execution of the study.

This is a multi-center Canadian observational study utilizing a prospective cohort design. As an observational study there will be no interventions or interference with the routine care of the patient.

All treatments will be prescribed and utilized as per the judgment of the treating physician and in accordance with the product monograph and regional requirements.

As per the product monograph: “Before initiation, during and after treatment with adalimumab patients should be evaluated for active or latent tuberculosis infection with a

tuberculin skin test. Treatment of latent tuberculosis infections should be initiated prior to therapy with adalimumab. When tuberculin skin testing is performed for latent tuberculosis infection, an induration size of 5 mm or greater should be considered positive, even if vaccinated previously with Bacille Calmette-Guérin (BCG). The possibility of undetected latent tuberculosis should be considered especially in patients who have immigrated from or traveled to countries with a high prevalence of tuberculosis or who had close contact with a person with active tuberculosis. If latent infection is diagnosed, appropriate prophylaxis in accordance with the Canadian Tuberculosis Standards and Centers for Disease Control and Prevention guidelines should be instituted. Anti-tuberculosis therapy prior to initiating HUMIRA® should also be considered in patients who have a negative test for latent tuberculosis but have risk factors for tuberculosis infection. The decision to initiate antituberculosis therapy in these patients should only be made after taking into account both the risk for latent tuberculosis infection and the risks of anti-tuberculosis therapy. If necessary, consultation should occur with a physician with expertise in the treatment of tuberculosis. Active tuberculosis has developed in patients receiving adalimumab whose screening for latent tuberculosis infection was negative, and some patients who have previously received treatment for latent or active tuberculosis have developed active tuberculosis while being treated with TNF-blocking agents. Patients receiving adalimumab should be monitored for signs and symptoms of active tuberculosis, particularly because tests for latent tuberculosis infection may be falsely negative. The risk of false negative tuberculin skin test results should be considered especially in patients who are severely ill or immunocompromised. Patients should be instructed to seek medical advice if signs/symptoms (e.g., persistent cough, wasting/weight loss, low grade fever) suggestive of a tuberculosis infection occur, and physicians should monitor for signs and symptoms of active tuberculosis, including patients who are tuberculosis skin test negative" (HUMIRA® Product Monograph).

With respect to the frequency and schedule of assessments, although there are no study specific requirements, follow up visits at 3, 6, 12, 18 and 24 months after baseline will be

recommended. Data obtained from more frequent visits or visits conducted at other time points will also be recorded in the study Case report Form. In fact, in order to avoid any bias and loss of information all information regarding the management of the patients during the 24 month follow up period of the study should be recorded in the study data collection forms. In addition to clinical data that will be ascertained by the treating physician, patient reported outcomes will also be ascertained through self administered questionnaires.

The following table describes the data that will be collected and the recommended timing of the assessments.

Table 1: Study Data Variables Collected by Visit

	Month					
Variable	0	3	6	12	18	24
Visit Number	1	2	3	4	5	6
Demographics:						
Age	X					
Gender	X					
Employment status	X					
Smoking	X					
Alcohol use	X					
Anthropometric measurements:						
Height	X					
Weight	X	X	X	X	X	X
Physical Examination	X	X1	X1	X1	X1	X1
Medical History: Previous Conditions Current Comorbidity Family History	X	X1	X1	X1	X1	X1
Psoriasis History						
Date of diagnosis	X					
Known triggers	X					
Frequency and Pattern of Flare – Ups	X					
Family History of Psoriasis	X					
Prior Treatment Details: Dose Duration Reason for discontinuation	X					
Concomitant Medications (Emphasis on Psoriasis Treatment)	X	X	X	X	X	X
Concomitant Psoriatic Arthritis	X2					
Rheumatoid Factor	X2					
C - Reactive Protein or hs-CRP	X2	X2	X2	X2	X2	X2
Erythrocyte Sedimentation Rate (ESR)	X2	X2	X2	X2	X2	X2
Clinical Laboratory Tests	X2	X2	X2	X2	X2	X2

	Month					
Variable	0	3	6	12	18	24
Visit Number	1	2	3	4	5	6
Body Surface Area (BSA)	X		X	X	X	X
Psoriasis and Arthritis Screening Questionnaire (PASQ)	X	X	X	X	X	X
Use of Phototherapy	X	X	X	X	X	X
Physician's Global Assessment of Disease Activity (6 Point Likert)	X	X	X	X	X	X
Patient's Global Assessment of Disease Activity (VAS)	X3	X3	X3	X3	X3	X3
Dermatology Life Quality Index	X3	X3	X3	X3	X3	X3
Medical Outcomes Study – Short Form 12	X3		X3	X3		X3
Health Care Utilization Questionnaire	X3		X3	X3		X3
Beck Depression Inventory	X3		X3	X3		X3
Work Limitations Questionnaire	X3		X3	X3		X3
Rheumatology Consult4	X	X	X	X	X	X
Compliance assessment		X	X	X	X	X

1. Only changes from previous visit will be recorded

2. Only if used as part of routine care. For the baseline visit, historical data up to 6 months could be used.

3. Self Administered questionnaires. These could be completed at the physician's office, at home and sent by mail.

4. Relevant sections of the Case Report Form to be completed by rheumatologists or information must be obtained from the rheumatologists.

6.5.1 Description of Activities

Screening and Baseline Assessments:

Participating physicians will be asked to assess for potential eligibility all sequential patients with Psoriasis for whom a change in treatment regimen is being considered.

Following an explanation of the study by the physician or designee, a written informed consent will be signed by the patients that agree to participate. Subsequent to obtaining written informed consent, potential eligible patients will be assessed for inclusion and exclusion criteria. Those that qualify will be entered in the study cohort. All baseline assessments will be conducted during the baseline / screening visit. The physicians or designee will be required to complete all data on the baseline visit section of the Case report Form using data ascertained by interview or examination of the patient or review of the patient's chart.

There are no laboratory examination requirements for the current study beyond those that are part of routine care. Historical data of up to six months could be used for the baseline values for laboratory tests.

Follow-Up Assessments (3, 6, 12, 18 and 24 months):

Given the observational nature of the study there no pre-determined protocol defined requirements for follow up schedules. Physicians will manage the patients in accordance with their current practice, their judgment and regional requirements in the case of reimbursement policies. However, investigators will be encouraged to follow the recommended schedule of assessments for the patients that are enrolled in the study. In addition, all information and data obtained at any visit occurring during the 24 follow up period of the study, including those that are outside of the recommended schedule, will be recorded in the study Case Report Form.

Laboratory tests are not required for the purposes of the study. However, when any tests are conducted as part of routine care or indicated by the condition of the patient, all results should be recorded in the study Case Report Form in physical changes section.

Informed Consent:

Signed written informed consent will be obtained from all patients prior to conducting any study activities including eligibility assessments. Informed consent may be obtained

from the patient or legally authorized representative.

Physical Examination and Medical History:

During the baseline assessment the results of a complete physical examination and medical history will be recorded in the study Case Report Form. For subsequent follow up assessments, only clinically important changes in the Medical History and Physical Examination will be recorded.

Prior and Concomitant Therapy:

Details of any treatment whether prescription or over the counter used for Psoriasis before and during the study will be recorded in the Case Report Form. These will include dose, frequency and duration of treatment and route.

Compliance:

Compliance with the treatment for Psoriasis will be ascertained by a self administered questionnaire and interview by the treating physician.

Self Administered Questionnaires:

Patients will be informed about the study requirements with respect to the completion of the self administered questionnaires and will be asked to complete the baseline set of questionnaires while at the physician's office. This will allow the patients to ask any questions and obtain guidance on how the questionnaires are to be completed. Patients will complete the questionnaires and mail them to the data management center, or return them to the treating physicians. During the baseline assessments, patients will be asked to indicate the methods by which they wish to be contacted by the study personnel. The options will be telephone, mail or e-mail. As part of the written informed consent patients will be asked to explicitly agree to be contacted using these methods for the purposes of the study and will be asked to provide their contact coordinates.

Patients will be identified only through the randomly generated study patient ID number.

Any identifying information will never be included on any questionnaire. If the patient chooses to mail-in or complete the questionnaire at the investigator sites, the return envelop will include only the patient ID and no other identifying data. Only the study coordinators will have access to patient information that will be use to follow up for non-responders.

Physician and Patient Recruitment and Retention:

Given the observational nature of the study one of the most important challenges will be patient retention and minimization of loss to follow up. The project manager will monitor patient follow up in the study.

Patient Discontinuation from the Study:

Patients could be withdrawn from the study at any time by the treating physician or on their own accord. Patients that participate in another trial will be withdrawn from the study. Patients that terminate treatment or switch from their current treatment will be followed for the 24 month study follow up period. Patients may change treatment at the discretion of the physician including switching from one of the defined treatment cohorts to another. Lack of therapeutic response, low compliance to treatment or the incidence of adverse events will not necessitate study withdrawal.

6.5.2 Product Supply:

In the current study patients will be treated with topical agents, traditional systemic agents and adalimumab as monotherapy or in combination. As an observational study all treatments will be accessed as per routine customary practice in the region. More specifically, AbbVieE will not supply or reimburse for any treatment used by the patients in the study. Patients will be prescribed the medications by the treating physician and will acquire these through the available insurance plan / government reimbursement or purchase with their own funds. All medications will be used in accordance to the current marketing label, the product monograph and regional requirements.

7.0 Adverse Events

The primary aim of the current PMOS is to assess real life effectiveness. Given that the primary objective is not to assess any safety parameters only spontaneously reported Serious Adverse Events (SAEs), unusual failure in efficacy and Pregnancies must be reported.

7.1 Adverse Event Definition and Serious Adverse Event Categories

An adverse event (AE) is defined as any untoward medical occurrence in a patient, which does not necessarily have a causal relationship with their treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event.

If an adverse event meets any of the following criteria, it is considered a **serious adverse event (SAE):**

Death of Subject An event that results in the death of a subject.

Life-Threatening An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.

Hospitalization An event that results in an admission to the hospital for any length of

time. This does not include an emergency room visit or admission to an outpatient facility.

Prolongation of Hospitalization An event that occurs while the study subject is hospitalized and prolongs the subject's hospital stay.

Congenital Anomaly An anomaly detected at or after birth or any anomaly those results in fetal loss.

Persistent or Significant Disability/Incapacity An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza and accidental trauma (*e.g.*, sprained ankle**).**

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (*i.e.,* death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Spontaneous Abortion Miscarriage experienced by study subject.

Elective Abortion Elective abortion performed on study subject.

7.2 Severity

The physician will use the following definitions to rate the severity for any adverse event being collected as an endpoint/data point in the study and for all serious adverse events.

Mild The adverse event is transient and easily tolerated by the subject.

Moderate The adverse event causes the subject discomfort and interrupts the subject's usual activities.

Severe The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

7.3 Relationship to Pharmaceutical Product

The physician will use the following definitions for any adverse event being collected as an endpoint/data point in the study and for all serious adverse events, to assess the relationship of the adverse event to the use of the pharmaceutical product:

Probably Related An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and another etiology is unlikely or significantly less likely.

Possibly Related An adverse event has a strong temporal relationship to the study drug and an alternative etiology is equally or less likely compared to the potential relationship to study drug.

Probably Not Related An adverse event has little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.

Not Related An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (*e.g.*, has no temporal relationship to study drug or has a much more likely alternative etiology).

If an investigator's opinion of possibly, probably not, or not related to pharmaceutical product is given, an alternate etiology must be provided by the investigator for the adverse event.

7.4 Serious Adverse Event Collection Period

Serious adverse events will be reported to AbbVie from the time the physician obtains the patient's authorization to use and disclose information (or the patient's informed consent) until 30 days or 5 half-lives following the intake of the last dose of physician-prescribed treatment.

7.5 Serious Adverse Event Reporting

For serious adverse events from patients using an AbbVie product, the physician will notify the AbbVie contact person identified below **within 24 hours of the physician becoming aware of the event**.

Medical Information

AbbVie Corporation
8401 Trans-Canada Highway
St-Laurent, Qc H4S 1Z1

The reporting physician must state that he/she is involved in the P12-678 trial and must report SAE to medical information.

7.6 Pregnancy Reporting

In the event of pregnancy, the physician will notify by telephone only the AbbVie contact identified in Section 7.5 within 24 hours of the physician becoming aware of the pregnancy.

7.7 Unusual Failure in Efficacy

Lack of efficacy is the failure of health product to produce the expected intended benefit. The Canadian Food and Drug Act and Regulations require that manufacturers report cases of unusual failure in efficacy to Health Canada for new drugs in the post-marketing setting, including in Phase IV studies.

Physicians should exercise clinical judgment to determine if the lack of efficacy is related to the drug itself, rather than one of treatment selection or disease progression since health products cannot be expected to be effective in 100% of the subjects.

The Investigator shall report all cases of unusual failure in efficacy coincident with the use of the study drug to AbbVie within 24 hours by telephone at [redacted] or by email at [redacted]. When calling this number, the Investigator will identify himself as an Investigator of the study reporting an unusual failure in efficacy to Medical Information. If there is any need to fax information, the Investigator will use the following fax number: Fax: [redacted].

8.0 Ethics and Quality

The study will be submitted for review and approval at a central ethics committee, local ethics review boards, as required for individual sites and the College of Physicians and

Surgeons of Alberta. The boards will review the study protocol, informed consent and patient questionnaires. A list of participating physicians will be provided to the review boards. No study activities will be undertaken prior to obtaining the relevant approval of the Independent Ethics Review Boards.

Prior to being enrolled in the study and the conduct of any study assessments, written informed consent will be obtained from the patient or designated legal representative. The investigator will explain the study to the patient along with the requirements for completion of the self administered questionnaires. The informed consent will provide permission for the patient's data to be used **anonymously** in the study. In addition, written authorization will be provided by the patient to authorize contact by the study personnel at specified coordinates.

Patient confidentiality will be protected at all times by using a randomly generated patient study identification number that will identify each unique patient. The name, address, telephone numbers, provincial insurance numbers, hospital record numbers or any other identifier will **NEVER** be entered in any page of the Case Report Form, questionnaire or return envelope. The link between patient contact information and the patient study identification number will be kept in a secure location and password protected computer folder that is separated from other information and is accessed only by authorized study personnel.

Prior to being included in the study all sites will be assessed for compliance with local requirements for the practice of medicine including validation of the physician's license and specialization certificates. In addition, all site personnel will be educated with respect to Good Clinical Practices (GCP) and the requirements for data reporting and in particular adverse event reporting of the study. Sites with experience in the conduct of clinical research will be preferred.

Data quality will be ensured by conducting a study audit, random sample monitoring,

logic edit checks and statistical assessments. An audit of 100% of the sites will be conducted to ensure that the patients entered in the study fulfill the inclusion and exclusion criteria.

Monitoring with source document verification when possible will be conducted on a maximum random 10% sample of the sites.

Edit checks will be programmed in the data management system by Cato Research. The edit checks identify out of range and illogical entries. Edit checks generate queries that are reviewed by the project manager who will either proceed with a level I correction or will issue a data clarification request to the site. Level I corrections are those that could be decided by the project manager or the project scientific director without requiring contact with the site. *Typical example of level I corrections is the year of the study visit date.* The criteria for level I corrections will be described in the data management plan. In addition a listing of all level I corrections will be transmitted to the study sites at regular intervals for confirmation.

Statistical methods employed to identify out of range or outlying datapoints will include frequency distributions, box plots and contingency tables. Statistical analyses to identify these issues will be conducted on a regular basis as part of the data management process. Patient records with potential errors will be flagged and queries will be generated that will be reviewed by the project manager who will determine whether a data clarification request should be transmitted to the site.

All data clarification requests will be transmitted to the sites by fax or by email depending on the preference of the site investigator. Corrections will be entered into the database depending on the response from the site. A patient record will be considered close when there are no pending data clarifications.

Data management for the current study will be conducted on Cato Research system The

data management procedures and computer systems used by Cato Research have been subjected to regular validation and verification. The data management system developed for the current study will be subjected to a study specific audit. In addition, the study will be audited by the Director of Quality Assurance for compliance with the company and study specific standard operating procedures. Compliance with GCP, 21 CRF Part 11 are assured through these processes and the Quality Assurance master Plan.

9.0 Case Report Forms

Data collection for the current study will be conducted on traditional paper Case Report Forms (CRFs) that will be faxed to the Cato Research Data Collection Center or by using an Electronic Data Capture (EDC) system. The faxed CRFs will be reviewed and after verification the data will be collected in the data base. All edit checks will be programmed in the ORACLE Clinical platform and all study databases will be in ORACLE. The EDC system will be based on a paper CRF that will be approved by the sponsor and the principle investigators.

The study CRF or EDC interface will consist of the following sections:

1. Baseline / Screening: This will be used to enter all the data collected during the baseline / screening visit as described in Table 1 section 6.5.

2. Follow-Up Visits: These will be labeled as Visit 2 – 6 with the suggested time points of 3, 6, 12, 18 and 24 months indicated. However, as mentioned earlier this is the recommended schedule of visits and the investigators will be allowed to conduct the assessments according to their routine practice and judgment. Consequently the investigators will be instructed to use the individual CRF visit sections for visits that take place on time period that is nearest to the suggested time point. The date of the visit will be clearly indicated. The information

collected on these follow up visits are described in detail in Table 1 section 6.5.

3. Additional (Non Scheduled) Follow Up Visits: Blank CRF sections will be provided for the site investigators to enter the available data from additional visits.

4. End of Study: This will be a separate section of the CRF describing the final status of the patient in the study as "completed" or withdrawn. For patients that are withdrawn from the study the reason and date will be reported.

All CRF sections will contain the anonymous random site number, patient ID and date of the visits.

At the conclusion of the study, the completed signed and dated case report forms for the enrolled patients should be provided to the study data management center by the investigator for every patient enrolled in the study. Electronic signatures will be used in the case of an EDC system. A distinct case report form should be created for each unique instance when data is to be collected. ONLY data specified in the protocol should be collected and submitted to the study data management center. The investigator or staff under his/her supervision must complete the case report forms and neither AbbVie nor any agents acting on behalf of AbbVie may complete the case report forms.

10.0 Data Analysis Plan

10.1 Overview:

The following sections provide a brief overview of the statistical methods used to address the study objectives. Detailed description of the statistical analyses, any deviation from the protocol and assumptions employed will be presented in the Statistical Analysis Plan that will be prepared prior to database close and initiation of any statistical analyses. In

addition the final sections describe particular considerations relevant to the observational nature of the current study.

10.2 General Considerations:

Descriptive statistics consisting of the mean, median, standard deviation and 95% confidence interval of the mean for continuous scale variables and frequency distributions for categorical variables will be produced for the baseline characteristics. These descriptive statistics will be produced for the study cohort as a whole and for the three treatment cohorts as described in section 6.0.

Between cohort differences with respect to the baseline parameters will be assessed with the Chi-Square statistic for categorical variables and One Way Analysis of variance (ANOVA) for continuous scale variables. Variables for which a trend for statistical significance ($P < 0.15$) or clinically important difference (more than 2 – fold) are observed will be considered as potential confounders and will be included in the multivariate analyses or propensity score development described later. Descriptive statistics will be produced for all variables and the changes from baseline when Statistical Methods to Address the Study Objectives:

Between group differences with respect to achieving the primary effectiveness outcome, specifically a PGA of "0" or "1" at 24 months will be assessed with simple logistic regression analysis and multivariate logistic regression models adjusting for potential confounders or the propensity score. A more relevant analysis will be to assess the differences between the groups with respect to the time to achieving the end point. For this analysis Kaplan Meier based time to event (survival) analysis will be used with the log-rank test to assess the statistical significance of the between group differences. Cox's proportional hazards model will also be used to adjust for potential confounders or the propensity score.

Between groups differences with respect to the changes in the BSA, PGA, DLQI, Psoriasis

Related Pruritus Assessment VAS, Plaque Psoriasis and Psoriatic Arthritis Pain VAS, BDI,9SF-12 (second version) WLQ from baseline to 24 months of treatment will be assessed with One Way ANOVA or repeated measures, mixed effects general linear model adjusting for potential confounders or the propensity score. Planned contrasts will be used to assess between group differences at the other follow up time points. Pairwise between group comparisons will be adjusted for multiplicity with the Tukey's Least Significance Test.

In order to better assess the impact of the treatment received and changes in the regimen the treatment will be handled as a time – dependent covariate in these analyses.

With respect to achieving therapeutic response end points and incidence of articular and extra-articular manifestations between group differences will be assessed with multi-variate logistic regression while Cox proportional hazard models will be used to assess between group differences with respect to the time of achieving therapeutic response and first occurrence of articular and extra–articular manifestations.

Descriptive statistics will be used to assess the between group and regional differences with respect to patient characteristics and disease parameters. Descriptive statistics will also be used to assess the practice patterns of Canadian dermatologists in the management of patients with moderate to severe PLAQUE PS. The study cohorts will be divided into Canadian regions as Quebec, Ontario, Maritimes and Western Canada.

Underdiagnosis of articular and extra articular manifestations will be assessed by the prevalence of existing articular manifestations and a survey of participating physicians with respect to their estimates of the prevalence of articular and extra- articular manifestations in the patients.

Safety will be assessed by the incidence of treatment emergent adverse events with adjusted relative risks used to compare the three treatment groups.

10.3 Sample Size Calculations

Sample size considerations are based on the primary objectives of the study, specifically the proportion of patients that achieve a PGA rating of "0" or "1" at 24 months of follow up.

The following data and assumptions were used to determine the sample size requirements for the study:

- In the Champion study after 16 weeks of treatment 73% of the patients treated with adalimumab, 30% of the patients treated with methotrexate and 11.3% of the patients treated with placebo achieved PGA values of 0 or 1 indicating clear or minimal disease.

- The Champion study was a randomized placebo controlled clinical trial that was based on a strict protocol not allowing any concomitant treatment and enrolling a very well defined patient population. In the current study we can assume that we will observe similar trends in the order of treatment effectiveness, by which adalimumab will be superior to traditional systemic agents, which will be superior to topical agents. However, due to case mix and use of concomitant medications the actual therapeutic effect and difference between groups may be more variable and lower than that observed in the CHAMPION study. We can therefore assume that due to patient profile, and in order to be conservative, that the observed proportion of patient achieving and maintaining a PGA≤ 1 at 6 months will be approximately 50%. A relative reduction of 20% (RR = 0.80) in PGA would be considered as the minimum acceptable for clinical importance. Therefore, the current study we should be powered to detect a 20% relative reduction between adalimumab and traditional systemic agents, and a similar difference between systemic and topical agents. It follows that if we assume that the proportion of patients treated with adalimumab that achieve PGA ≤1.0 at six months will be

50%, the proportion in the patients treated with traditional systemic agents will be 40% (RR=0.8) and that in patients treated with topical agents will be 32% (RR = 0.8).

- For an expected treatment group ratio of 1:1 for adalimumab: traditional systemic agents and topical agents a total of 360 (180: 180) patients will be required for 80% power and two tailed significance of 5%. Assuming a 25% attrition rate and allowing for 100 additional patients (10 per variable) in the multivariate analysis 660 (330:165:165) patients will be recruited.

11.0 Final Report and Publications

At the end of the study, a study report will be written by the study investigators who will also sign the report. This report will contain a description of the objectives of the study the methodology of the study and its results and conclusions. The completed case report forms and the study report are the confidential property of AbbVie Corporation and will not be released to unauthorized individuals in any form (publications or presentations) without expressed written approval from AbbVie Corporation. The results of this PMOS may be published by AbbVie Corporation or by any one of the participating investigators after agreement with AbbVie Corporation.

12.0 References

1. SIVAMANI, R. K., CORREA, G., ONO, Y., BOWEN, M. P., RAYCHAUDHURI, S. P., MAVERAKIS, E., Biological Therapy of Psoriasis, Indian Journal of Dermatology, California, United States, April-June 2010; 55(2): 161–170.

2. Psoriasis, http://www.nlm.nih.gov/medlineplus/psoriasis.html, MedlinePlus, consulted on July 20th, 2010.

3. X-Plain Psoriasis – Reference Summary, The Patient Education Institute, Inc., U.S. National Library of Medicine, NIH National Institutes of Health, 2008.

4. About Psoriasis – Types of psoriasis, https://www.psoriasis.org/NetCommunity/SSLPage.aspx?pid=386, National Psoriasis Foundation, consulted on July 21st, 2010.

5. About Psoriasis – Causes of psoriasis and triggers, https://www.psoriasis.org/NetCommunity/SSLPage.aspx?pid=374, National Psoriasis Foundation, consulted on July 21st, 2010.

6. About Psoriasis – Statistics, https://www.psoriasis.org/NetCommunity/SSLPage.aspx?pid=372, National Psoriasis Foundation, consulted on July 21st, 2010.

7. Psoriasis Statistics, http://www.psoriasis-aid.com/psoriasis/statistics_of_psoriasis.html, Psoriasis-Aid, consulted on July 22nd, 2010.

8. STERN, R. S., NIJSTEN, T., FELDMAN, S. R., MARGOLIS, D. J., ROLSTAD, T., Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction, Journal of Investigative Dermatology, March 2004; 9(2):136-9.

9. LYNDE, C.W., POULIN, Y., GUENTHER, L., JACKSON, C., The burden of psoriasis in Canada: insights from the pSoriasis Knowledge IN Canada (SKIN) survey, Journal of cutaneous medicine and surgery, September-October 2009;13(5):235-52.

10. GELFAND, J. M., TROXEL, A. B., LEWIS, J. D., KOHLI KURD, S., SHIN, D. B., WANG, X., MARGOLIS, D. J., STROM, B. L., The Risk of Mortality in Patients With Psoriasis - Results From a Population-Based Study, Archives of Dermatology, December 2007;143(12):1493-9.

11. Treating psoriasis – Psoriasis severity, https://www.psoriasis.org/NetCommunity/SSLPage.aspx?pid=409, National Psoriasis Foundation, consulted on July 23rd, 2010.

12. Treating psoriasis – Topicals, https://www.psoriasis.org/NetCommunity/SSLPage.aspx?pid=1546, National Psoriasis Foundation, consulted on July 23rd, 2010.

13. Treating psoriasis – Mild psoriasis: topical steroids, https://www.psoriasis.org/NetCommunity/SSLPage.aspx?pid=416, National Psoriasis Foundation, consulted on July 23rd, 2010.

14. Treating psoriasis – Mild psoriasis: non-steroidal prescription topical treatments, https://www.psoriasis.org/NetCommunity/SSLPage.aspx?pid=414, National Psoriasis Foundation, consulted on July 23rd, 2010.

15. Treating psoriasis – Phototherapy, https://www.psoriasis.org/NetCommunity/SSLPage.aspx?pid=430, National Psoriasis Foundation, consulted on July 26th, 2010.

16. Treating psoriasis- Traditional systemic medications, https://www.psoriasis.org/NetCommunity/SSLPage.aspx?pid=432, National Psoriasis Foundation, consulted on July 26th, 2010.

17. Treating psoriasis – Systemic Medications: Methotrexate, https://www.psoriasis.org/NetCommunity/SSLPage.aspx?pid=440, National Psoriasis Foundation, consulted on July 27th, 2010.

18. Treating psoriasis – Systemic Medications: Cyclosporine, https://www.psoriasis.org/NetCommunity/SSLPage.aspx?pid=435, National Psoriasis Foundation, consulted on July 27th, 2010.

19. PARNHAM, M. J., BRUINVELS, J., WEINBERG, J. M., BUCHHOLZ, R., TNF-alpha Inhibitors, Birkhäuser, Basel, Switzerland, 113 pages.

20. MENTER, A., GOTTLIEB, A., FELDMAN, S. R., VAN VOORHEES, A. S., LEONARDI, C. L., GORDON, K. B., LEBWOHL, M., KOO, J. Y. M., ELMETS, C. A., KORMAN, N. J., BEUTNER, K. R., BHUSHAN, R., Guidelines of care for the management of psoriasis and psoriatic arthritis, Journal of the American Academy of Dermatology, May 2008; 58(5):826-850.

21. Adalimumab Injection, http://www.nlm.nih.gov/medlineplus/druginfo/meds/a603010.html#side-effects, MedlinePlus, consulted on July 27th, 2010.

22. Menter A., Grifffiths E M "Current and Future management of Psoriasis": The Lancet vol 370, July 21, 2007; pages: 272-370.

23. University of Maryland Medical Center: http://www.umm.edu/patiented/articles/what_phototherapy_treatments_psoriasis_000087_9.htm

24. Saurat, J-H. Stingl, G. Dubertret, L. Papp, K. Langley, R G. Ortonne, J-P. Unnebrink, K. Kaul, M. Camez, A. CHAMPION Study Investigators: Efficacy and safety results from the randomized controlled comparative study of adalimumab vs. methotrexate vs. placebo in patients with psoriasis (CHAMPION). British Journal of Dermatology. 158(3):558-66, 2008 Mar

25. Rigopouls D., Gregoriou S., Lazaridou E., Belyayeva E., Apalla Z., makris M., katsambas A., Ioannidis D. treatment of nail psoriasis with adlaimumab; an open label unblinded study. Journal European Academy of Dermatology and Venereology 2010, 24, 530-534.

26. Menter A., Grodon K B., leonardi G., Gu Y., Goldblum O. J AM ACAD Dermatol Voulme 63, number 3, 448-456.

27. Gordon K.B., Langley R., Leonarid G., Toth D., Menter MA., kang S., Heffernan M., Miller B., Hamlin R., Lim L., Zhong J., Hoffman R., Okun M. Clinical response to adalimumab treatment in patients with moderate to severe psoriasis. Double blind randomized controlled clinical trial and open label extension study. J Am Acad Dermatol 2006;55:598-606.

28. Bongiorino MR., Pistone G., Doukaki S., Arico M. Adalimumab for treatment of moderate to severe psoriasis and psoriatic arthritis. Dermatologic Therapy Vol 21,

2008, S15-S20

29. Papoutsaki,M, Chimenti M-S. Costanzo A.,Talamonti M, Zangrilli A., Giunta A, Bianchi L, Chimenti S. Adalimumab for severe psoriasis and psoriatic arthritis: An open-label study in 30 patients previously treated with other biologics. J Am Acad Dermatol 2007;57:269-75.

Appendix A. List of Abbreviations and Definition of Terms

AE	Adverse Event
ANOVA	Analysis of Variance
BCG	Bacille Calmette-Guérin
BDI	Beck Depression Inventory
BSA	Body Surface Area
CBC	Complete blood count
CD4 T-cells	Antigenic marker on helper/inducer T cell
CEDAC	Canadian Expert Drug Advisory Committee
CNS	Central Nervous System
CRF	Case Report Form
CRP	C-reactive protein
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic acid
EDC	Electronic Data Capture
ESR	Erythrocyte Sedimentation Rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ID	Identification
IFN-α	Interferon-Alpha
IgG –IgG1	Immunoglobulin
IL	Interleukin
MedDRA	Medical Dictionary for Regulatory Activities
MHC	major histocompatility complex
NDA	non disclosure agreement
PASI	Psoriasis Area and Severity Index
PASQ	Psoriasis and Arthritis Screening Questionnaire
PGA	Physician Global Assessment
PMOS	Post marketing observational studies
PS	Psoriasis
PsA	Psoriasis Arthritis
PUVA	Psoralen-Ultraviolet A treatment
RNA	Ribonucleic acid
RR	Relative Risk
SAE	Serious Adverse Event

SF-12	Medical Outcomes Study Short Form 12
T-cells	T Lymphocyte
TFN-α	Tumor Necrosis Factor α
TGF-α	Transforming growth factor α
Th	T-Helper cell
UV	Ultraviolet
UVA	Ultraviolet A
UVB	Ultraviolet B
VAS	Visual Analog Scale
WLQ	Work Limitation Questionnaire

ABBVIE CORPORATION

Clinical Study Protocol _ (P12-678)

Canadian Humira Post Marketing Observational Epidemiological Study: Assessing Effectiveness in Psoriasis (Complete - Psoriasis)

Approved by:

[redacted]

Nov 4th, 2013
Date

5 Nov 2013
Date

26 Nov 2013.
Date

26 NOV 2013
Date