Statistical Analysis Plan

Study Title: Canadian Humira Post Marketing Observational Epidemiological Study: Assessing Effectiveness in Psoriasis

(COMPLETE - PS)

AbbVie Corporation

Prepared by JSS Medical Research

Version 3.0

July 23rd, 2015

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STUDY NUMBER:	P12-678
INVESTIGATIONAL DRUG:	Adalimumab (Humira)
TYPE OF STUDY:	Post-Marketing Observational Study (PMOS)
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1 Introduction

The purpose of this statistical analysis plan (SAP) is to provide a detailed description of the statistical analyses that will be performed according to the study protocol.

The SAP presents a summary of the study protocol and describes the populations that will be analyzed. Relevant subject characteristics and the efficacy and safety parameters to be evaluated are described along with the specific statistical methods assessing the endpoints and safety data. Statistical outputs are presented in the form of mock tables.

2 Protocol Summary

2.1 Background

Psoriasis (PS) 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].

PS affects approximately 125 million people worldwide, which consist of 2-3% of the total population.[4] In Canada it is estimated that more than 1 million individuals, have PS. The prevalence of the disease is 0.8-1%.[5] However, these statistics vary according to race, ethnic background, region, age and gender.

PS 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.[6] However, in Canada, according to a study by Lynde et al., 35% of the patients with PS 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.[7] Furthermore, PS has a greater negative impact in women and younger patients.[4] 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 PS. [4, 8]

The typical first line of treatment for early mild PS is topical medications. These include creams, ointments and shampoos[9] that slow down or normalize the accelerated growth cycle of the skin cells and hence reduce the inflammation.[10] Corticosteroid ointments are generally the first line topical treatment of choice and are effective in reducing the swelling and the redness of the lesions.[11] 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. [11]

For moderate or severe PS, affecting more than 3% of the body surface area, topical treatments are generally not effective and more aggressive therapy is required.[9] Phototherapy, alone or in combination with photosensitizing medications such as psoralen, is an effective second line treatment for moderate PS or mild disease that has not responded to topical therapy. 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 has been proven to be a safer and effective alternative. [19-20]

For moderate to severe PS 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 PS [14].

Biologic systemic agents and specifically anti-TNF-α inhibitors have been developed in recent years and have been proven efficacious in the management of PS patients.

Among these, 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 PS, juvenile and adult rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis and Crohn's disease. Currently dosing in patients with moderate to severe PS 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[17] including redness, itching, bruising, pain or swelling, stomach pain, nausea, headache and back pain.[18] 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.[17]

The efficacy of adalimumab in controlling the symptoms of PS 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 PS who were candidates for systemic therapy or phototherapy have shown that adalimumab is efficacious in controlling the symptoms of PS 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, 9-16, 19-26]. 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 36 (MOS SF-36) 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 PS under the following conditions:

i. Patient is diagnosed with severe debilitating PS, 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.

2.2 Study Rationale

Post marketing observational studies (PMOS) have evolved into an integral and essential phase of the drug development life cycle with implications that have comparable weight to that of the Phase II and III registrational studies. While Phase II – III controlled clinical trials provide evidence of efficacy under ideal conditions, the PMOS is the only source of information that allows the assessment of real – life effectiveness. In addition, ongoing surveillance for safety signals under routine clinical practice allowing the detection of rare

but potentially serious adverse events could only be accomplished by the accumulation of data from several PMOS capturing data from large populations and over sufficient periods of treatment. Evidence regarding real life effectiveness and safety are required to establish the population based benefit – risk ratio of marketed treatments. Furthermore, valid and reliable data on real – life effectiveness and safety in combination with data on treatment acquisition costs, health care utilization, direct and indirect health care costs that are essential for a comprehensive health economic evaluation and assessment of treatment impact on burden of illness can only be acquired in properly conducted PMOS.

One of the most important considerations of a PMOS is regional specificity. This is due to regional variations in the patient profile, cultural influences, practice patterns and local reimbursement policies affecting access to care. Consequently, PMOS must be designed and conducted taking into consideration regional needs and treatment gaps while global-wide studies are less relevant. It follows, that at the minimum, country specific PMOS will be required to conduct regional evaluations of marketed treatments. However, the aggregation of evidence from several regions or countries could be employed to provide global assessments of effectiveness and benefit –risk ratios.

Highly selected patient populations, controlled treatment conditions that are dictated by the study protocol and structured standardized follow up for adverse events and therapeutic response make inference of the efficacy results from controlled trials to real-life effectiveness problematic. Consequently well designed and executed observational studies are required to provide evidence of the benefits of therapeutic agents under routine, real-life conditions.

Complete is a three part Canadian observational research program aimed at assessing the real life effectiveness of adalimumab in the management of PS, Psoriatic Arthritis (PsA) and

Ankylosing Spondylitis (AS). The general aim of the program is 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 in 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 PS, adalimumab has been approved in Canada for patients with moderate to severe PS that are candidates for systemic therapy. For patients with moderate plaque PS adalimumab should be used 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 PS.

PS 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 PS 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 PS is the fact that approximately 30% of the patients develop PsA. To date, there are no known predictors of progression to PsA among patients with PS. In addition, it is known that triggers of PS 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 PS 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 PS 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 safety signal.

The current study will assess clinical and patient reported outcomes that are relevant in the management of PS and the impact of PS on the patient's quality of life and societal burden of illness using a prospective cohort observational design.

2.3 Study Objectives

2.3.1 Primary

The primary objective of the current study will be to compare the real-life effectiveness of adalimumab to topical and traditional systemic agents in the management moderate to severe Plaque PS.

2.3.2 Secondary

1. 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.

2. 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.

3. 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.

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

4. To describe the current population based burden of illness incorporation Health Care Utilization, Health Care Costs, Quality of life, Psychological Impairment, Work Productivity of moderate to severe Plaque PS.

    i. 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 Impairment, Work Productivity in Canada.

5. 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.

2.4 Study Design

This is a Canadian Post Marketing Observational Study (PMOS) utilizing a prospective cohort design. Patients are entered into the study cohort at the time of change of their PS 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:

1. 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.

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

3. 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 PS related burden of illness. The impact of PS and the different treatment approaches on work productivity will be assessed. The study will also identify prognostic factors for progression to PsA 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 PS will be described.

2.5 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 PS. 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.

2.6 Study Procedures

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	X[1]	X[1]	X[1]	X[1]	X[1]
Medical History: • Previous Conditions • Current Comorbidity • Family History	X	X[1]	X[1]	X[1]	X[1]	X[1]
Psoriasis History:						
• Date of diagnosis	X					
• Known triggers	X					
• Frequency and Pattern of Flare – Ups	X					
• Family History of Psoriasis	X					
• Prior Treatment Details: o Dose o Duration o Reason for discontinuation	X					
Concomitant Medications (Emphasis on Psoriasis Treatment)	X	X	X	X	X	X
Concomitant Psoriatic Arthritis	X[2]					
Rheumatoid Factor	X[2]					
C - Reactive Protein or hs-CRP	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Erythrocyte Sedimentation Rate (ESR)	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Clinical Laboratory Tests	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
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)	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Dermatology Life Quality Index	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Medical Outcomes Study – Short Form 12	X[3]		X[3]	X[3]		X[3]
Health Care Utilization Questionnaire	X[3]		X[3]	X[3]		X[3]

	Month					
Variable	**0**	**3**	**6**	**12**	**18**	**24**
Beck Depression Inventory	X[3]		X[3]	X[3]		X[3]
Work Limitations Questionnaire	X[3]		X[3]	X[3]		X[3]
Rheumatology Consult[4]	X	X	X	X	X	X
Health Economic Questionnaire	X[3]			X[3]		X[3]
Compliance assessment		X	X	X	X	X

1: Only changes from baseline 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, by mail and on-line (web based) methods.

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

2.7 Sample Size

Assuming a 25% attrition rate and allowing for 100 additional patients (10 per variable) in the multivariate analysis, for a treatment group ratio of 2:1:1 for adalimumab, traditional systemic agents and topical agents a total of 660 (330:165:165) patients will be required for 80% power and two tailed 5% significance. In addition, this sample size will be sufficient to detect a 20% (Relative Risk = 0.80) relative reduction in PGA between adalimumab and traditional systemic agents, and a similar difference between systemic and topical agents.

2.8 Patient Selection

Patients will be enrolled from the offices of community rheumatologists across Canada treating patients with PS. 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 PS 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 PS 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.

2.8.1 Inclusion Criteria

The following inclusion criteria will be applied:

1. Adult >18 years old
2. Has provided written informed consent allowing the use of their data for the study and providing permission for contact by the study personnel.
3. Active moderate or severe Plaque PS according to the judgment of the treating physician.
4. The treating physician has decided to change the current treatment or add additional treatments for any reasons including but not limited to inadequate response, intolerance, sub-optimal compliance or patient preference.

2.8.2 Exclusion Criteria

The following exclusion criteria will be applied:

1. Currently participating in another prospective study with similar objectives.
2. Patient cannot or will not sign informed consent.
3. 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.

2.9 Treatment

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, ABBOTT 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.

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.

2.10 Outcome Measures

The following sections describe the outcome measures used to address the study objectives.

2.10.1 Efficacy Measures

2.10.1.1 Primary Endpoints

The primary effectiveness outcome measure of 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)
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.

2.10.1.2 Secondary Endpoints

The following secondary endpoints will be assessed:

i. Time to achieving PGA ≤ 1.0 over 24 months of follow up.

ii. Percent of patients with PGA ≤ 1.0 at 3, 12, 18 and 24 months.

iii. Signs and symptoms suggesting onset of PsA:

- 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 PS 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.

- Proportion of patients achieving and time to DLQI ≤ 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 Outcome 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 Working Limitations Questionnaire (WLQ) 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 PS 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 and Health Economics 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 related to PS. In addition, use of prescription and non-prescription medications for the management of PS 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 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. Change in use and frequency of phototherapy for PS though the 24 months of treatment will be ascertained by a targeted question in the patient assessment.

2.10.2 Safety Measures

Safety and tolerability will be assessed with the incidence of treatment-emergent adverse events. Incidence of treatment emergent serious adverse events will be recorded by the treating physician through the 24 months of treatment. Severity of the adverse event and causal relation to the treatment will be assessed by the treating physician. All adverse events will be coded as per the MedDRA dictionary of terms.

i. All serious adverse events will be recorded and reported as per regional regulatory guidelines and requirements.

3 Statistical Methods

3.1 Statistical Handling Policy

3.1.1 Analysis Conventions

This section details general guidelines to be used for the statistical analyses. Deviations from these general policies may be given in the specific detailed sections of this statistical analysis plan. When this situation occurs, the rules set forth in the specific section take precedence over the general conventions. The following policies will be applied to all data presentations and analyses:

- Two-tailed tests will be performed for all analyses that use statistical testing with a significance level of $\alpha = 0.05$.
- All p-values will be rounded to 3 decimal places. All p-values that round to 0.000 will be presented as '<0.001' and p-values that round to 1.000 will be presented as '>0.999'. Any p-value ≤0.05 will be considered statistically significant.
- Summary statistics will consist of the number and percentage of responses in each category for discrete variables, and the mean, median, standard deviation (SD), minimum, maximum, and 95% confidence interval for continuous variables.

- All mean and median values will be formatted to one decimal place. Standard deviation values will be formatted to two decimal places.

- All percentages will be rounded to one decimal place. Where appropriate, the number and percentage of responses will be presented in the form XX (XX.X %), where the percentage is in the parentheses.

- All listings will be sorted for presentation in order of treatment group, site number, subject number, and date of procedure or event.

- When necessary for analysis purposes, partial dates will be completed (i.e., turned into complete dates) using the most conservative approach. Where appropriate, all analysis and summary tables will have the population sample size for each treatment group in the column heading.

- All analyses and summary tables will have the population sample size for each treatment group in the column heading.

- Tables will include footnotes describing the analyses involved, and listings of covariates included in the analyses, where relevant.

- In order to maintain vertical alignment, all tables and listings will be incorporated into MS Word and an 8 point Courier New font will be used. For practical reasons, the point size may be reduced to (but not less than) 7 point for tables/listings that contain too much information to fit into a single page.

- Version 9.2 (or later) of SAS® will be the statistical software package used to produce all summaries, listings, statistical analyses, and graphs.

- Version 12.1 (or higher) of MedDRA will be used for adverse event and pre-treatment conditions coding.

- Version 2009 (or later) of the World Health Organization (WHO) Drug Classifications will be used for the coding of medications.

3.2 Bias by Indication

One of the most important challenges in conducting between treatment comparisons in observational or naturally occurring experiment studies is confounding by indication. This occurs because the patients are allocated to different treatment groups not randomly but on the basis of the treating physician's judgment. This may result in an imbalance of the prognostic profile between the treatment groups and therefore confounding in the assessment of differences with respect to the study outcome measures. Multi-variable models that include potential confounders as covariates or propensity scores developed with potential confounders are valid solutions for the statistical adjustment of between group baseline differences and minimization of bias. The development of the propensity score will be based on categorical or multinomial logistic regression and binary logistic regression for the assessment of the profile differences between patients treated with adalimumab, topical agents and traditional systemic agents. Stratification of the analyses into homogeneous subgroups is another solution. All of these solutions will be explored in the current study. Unfortunately determination of the appropriate approach is data driven and cannot be determined a-priori.

3.3 Unequal Time Periods for Assessments

Another problem with observational naturally occurring experiments is that patient assessments are not dictated by a strict protocol but as per the real – life setting they are based on routine clinical practice, the judgment of the physician and the availability of the patient. These create a problem with unequal duration of treatment and follow up and when assessments at defined time intervals are required. The mixed effects repeated measures

models that will be used in the current study resolve this issue. With these models the least square mean will be used to estimate the value of the variable at specific time points.

3.4 Missing Data

One more, although less unique, problem with observational studies is missing data. This is particularly problematic with self-administered questionnaires where capture of the missing data is not possible. The mixed effects models described earlier compensate for missing data points in individual visits. For clinical data all efforts will be made to retrieve any missing data point. For missing responses on questionnaire items the coding for the majority of the tools used in the current study provide imputation solutions for missing responses. Furthermore, in the current study in order to assess the likelihood of bias, the pattern of missing data will be evaluated to determine whether the data follow a missing at random pattern or whether there is a systematic non-random distribution of missing data.

3.5 Analysis Populations

All safety analyses will be based on the Safety population that will comprise all patients who signed the inform consent and received at least one dose of study medication. The remaining analyses, including the baseline profile of the patients and treatment effectiveness, will be based on the Intent-to-Treat (ITT) population that will comprise all patients who signed informed consent, meet the inclusion / exclusion criteria, and received at least one dose of study medication.

3.6 Patient Disposition and Discontinuation

The number of patients who are enrolled and who have completed each visit will be reported, including all post-enrolment discontinuations, for the total cohort and by treatment group.

In addition to an overall summary of early discontinuations and the associated reasons, the time to discontinuation since the baseline visit will be evaluated using life table methods. The following data will be presented:

1. The number and percentage of subjects who completed or discontinued prematurely from the study overall and for each scheduled visit.
2. The number and percentage of subjects who discontinued for each reason.
3. Time to event methods will be used to estimate survival/discontinuation. Mean and median time to discontinuation (with 95% CI) will be tabulated.

3.7 Treatment Exposure and Dosing

Treatment exposure will be calculated in terms of number of months exposed to topical agents, traditional systemic agents and adalimumab using the following formula:

$$\text{Exposure (months)} = \frac{(\text{Last Date of Dosing} - \text{First Date of Dosing} + 1)}{30.4}$$

In this formula, the value 30.4 corresponds to the average number of days within a month over the course of a year. The last date of dosing might not be known and so the visit date will be used.

The following information will be presented for the total study population: sample size, mean, median, SD, minimum, maximum, and 95% confidence interval.

3.8 Subject Demographics and Baseline Characteristics

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 2.4, and by Canadian regions.

Between-group differences with respect to baseline characteristics will be assessed for statistical significance with One Way Analysis of Variance (ANOVA) for continuous variables if normally distributed or the Kruskal Wallis test if not normally distributed, and the Chi-Square statistic or the Fisher's exact test for categorical variables. Variables for which a trend for statistical significance ($P<0.15$) or clinically important difference (more than 2–fold) is observed will be considered as potential confounders and will be included as covariates in the multivariable analyses or propensity score development described in the following sections.

3.8.1 Demographics and Baseline Characteristics

Descriptive statistics will be presented for all patient demographic data and baseline characteristics including age, sex, race, height, employment status, tobacco use, and alcohol use. The summary will include:

- The number and percentage of subjects within each category.
- The sample size, mean, median, SD, minimum, and maximum values for each continuous variable. Age will be calculated as follows: Age = Largest Integer ≤ [(Baseline Visit Date – Date of Birth + 1)/365.25]. The midpoint of the year of birth will be considered as the date of birth for each patient.

3.8.2 Medical History and Prior PS Treatments

The number and percentage of subjects reporting family history of PS, types of known PS triggers, prior frequency and pattern of flare-ups, concomitant PsA and who have positive

rheumatoid factor will be summarized. In addition, the number and percentage of patients with other relevant medical history will be summarized by body system.

All previous and current PS medications recorded on the CRF will be coded and summarized according to the generic drug names using the WHO Drug Classifications. Each summary will give the number and percentage of patients who took medications that were coded to each generic drug name, as well as the number and percentage of patients that took any medication at all.

3.9 Patient Follow-Up Characteristics

Descriptive statistics comprising the sample size, mean, median, SD and 95% confidence intervals of the mean for continuous variables, and number and percentage of subjects for categorical variables will be used to describe all follow-up patient characteristics including: weight, C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), rheumatology consult, clinically important changes in physical examination, patient compliance with treatment, changes in psoriasis medications/treatments, including phototherapy, Psoriasis and Arthritis Screening Questionnaire (PASQ) score, Body Surface Area (BSA), Patient Global Assessment of Disease Activity (VAS), Dermatology Quality of Life Index (DLQI), Beck's Depression Inventory (BDI) score , Medical Outcomes Study Short Form 36 (SF-36) score, Working Limitations Questionnaire (WLQ) score, and Health Care Utilization Questionnaire.

3.10 Analysis of the Primary Objective

For the primary objective, between-group differences with respect to achieving a PGA of "0" or "1" at six months will be assessed with simple logistic regression analysis and multivariate logistic regression models adjusting for potential confounders or the propensity score. In addition, a Generalized Estimating Equation (GEE) model will be used to compare

the three patient groups in terms of achieving a PGA of "0" or "1" over 24 months of treatment. 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.

3.11 Analysis of the Secondary Objectives

Between groups differences with respect to the changes in the BSA, PGA, DLQI, PASQ, BDI, SF-36 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. Descriptive statistics will be used to assess the between-group differences in healthcare resource utilization and healthcare costs associated with PS. With respect to achieving therapeutic response end points and incidence of articular and extra-articular manifestations between group differences will be assessed with multivariate 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 regional differences with respect to baseline 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 cohort will be divided into Canadian regions as Quebec, Ontario, Maritimes and Western Canada.

3.12 Analysis Schedule

Analyses will be performed as per the Communication Plan, after 335 and all patients have completed the study.

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5 List of Tables