Evidence-based Practice Center Systematic Review Protocol

Project Title: Biologic and Nonbiologic Systemic Agents and Phototherapy for Treatment of Chronic Plaque Psoriasis

I. Background and Objectives for the Systematic Review

Psoriasis is a common, chronic, autoimmune inflammatory skin disease affecting 2 to 3 percent of the worldwide population. The disease typically presents as thickened, erythematous, scaly plaques that are often pruritic. The onset of psoriasis predominantly occurs early in adulthood (between the ages of 15 and 25 years) but may affect individuals at any age.[1] The course of psoriasis is marked by chronic and acute phases with a wide variety in relapse and remission rates.[2] Additionally, psoriasis is often associated with other comorbidities such as an inflammatory arthritis known as psoriatic arthritis, obesity, inflammatory bowel disease, diabetes, and cardiovascular disease.[2] Psoriasis has been associated with markedly elevated direct medical costs, work limitations, and productivity loss. Total health care costs of psoriasis are estimated at $11.25 billion annually.[3] This economic burden, along with the clinically relevant reductions in quality of life experienced by many patients with psoriasis, underscores the need for prompt, effective, and sustained disease management.[4,5]

Among several clinical psoriasis phenotypes, chronic plaque psoriasis is the most frequent, accounting for all but 10 percent of cases.[4-6] Chronic plaque psoriasis, also known as psoriasis vulgaris, often appears as well-demarcated, erythematous plaques covered with silvery white scales that vary in size up to several centimeters. Psoriatic skin lesions typically appear symmetrically on the scalp, trunk, and limbs (particularly on the knees and elbows) but may also affect the genitals, nails, palms, and soles of the feet.[4,5] Different parameters determine disease severity such as the degree of body surface area (BSA) involved, activity of the lesions, the location of lesions in sensitive areas, duration of disease, treatment failures, and the impact on quality of life.[2,7]

Psoriasis is a multifactorial disease with genetic and environmental factors that contribute to the dysregulation of cellular inflammation. The presence of psoriatic plaques may be triggered or exacerbated by environmental conditions, including infection, physical or psychological stress, cold weather, and medications.[4] The formation of psoriatic plaques involves the interplay of dendritic cells, T cells, antigen-presenting cells, cytokines, keratinocytes, and blood vessels. The presence of activated T cells within psoriatic plaques and the response to T cell-directed therapy suggest an immunologic nature of the disease.[8,9] Various cytokines, like tumor necrosis factor (TNF)-alpha and interleukin 23 (IL-23), are also present in psoriatic lesions.[10] Both cytokines and activated T cells promote the dysregulated growth of keratinocytes, leading to plaques of erythematous, scaly skin.

While disease localized to nonsensitive areas of skin may be managed effectively with topical agents (emollients, analogs of vitamins A and D, and corticosteroids), patients with more widespread disease often require systemic treatment due to the extent of BSA involvement, as well as the adverse impact on quality of life and activities of daily living.[4,5] Therapeutic options for more widespread disease include systemic treatment with biologic agents, nonbiologic agents, and phototherapy. Nonbiologic systemic therapies may be effective but can be associated with significant short-term and long-term toxicities (hepatotoxicty, nephrotoxicity, hypertension,

dyslipidemia, malignancy, and teratogenicity).[11,12] Phototherapy, although considered to be one of the safer therapeutic options, requires strict compliance, and the long-term toxicity associated with it includes photocarcinogenesis.[13] Unfortunately, some patients have disease that is resistant to the above-mentioned therapies or becomes refractory to treatment. As a result, patients often report high levels of dissatisfaction with such approaches to psoriasis treatment.[4,5,11]

Biologic therapies for psoriasis use genetically engineered drugs that target specific steps involving T cells and cytokines (e.g., TNF-alpha and IL-23), which are important in the pathogenesis of psoriasis.[4,5] Currently, three biologic TNF-alpha inhibitors (infliximab, etanercept, and adalimumab), one T cell-targeting agent (alefacept), and one anti-IL 12/23 agent (ustekinumab) have approval from the U.S. Food and Drug Administration (FDA) for psoriasis treatment. Another T cell-targeting agent, efalizumab (Raptiva®), was withdrawn from the U.S. market due to its potential risk of causing progressive multifocal leukoencephalopathy. Other biologic agents with similar mechanisms of action have FDA marketing approval, albeit not for the treatment of chronic plaque psoriasis (e.g., certolizumab pegol, golimumab, abatacept). While biologic treatments may represent a treatment option with fewer adverse effects, there are concerns about their higher costs versus nonbiologic systemic therapies. The estimated annual per-patient cost of biologic treatment ranges from $18,000 to $42,000 (based on the average wholesale price).[14] This cost is in comparison to methotrexate, the most commonly prescribed nonbiologic systemic treatment for psoriasis worldwide, which costs approximately $1,200 per year.[14]

The American Academy of Dermatology has published guidelines for the treatment of psoriasis.[4,11,13] As stated above, topical agents, or even targeted phototherapy, are effective therapies for limited disease. When treating patients for more extensive disease, there are no clear guidelines established for selecting 1st-line therapy, albeit the presence of concomitant psoriatic arthritis is an important determinant of treatment choice (often a TNF-alpha inhibitor with or without methotrexate).[4] For patients with widespread disease, guidelines suggest therapy with either biologic or nonbiologic systemic agents or phototherapy with ultraviolet B (UVB) or with psoralen plus ultraviolet A (PUVA) therapy.[4] There are few direct comparative trials either within or between biologic and nonbiologic classes directly comparing effectiveness.[15-17] Recently, a trial that compared two biologic agents concluded a difference in efficacy, suggesting heterogeneity within the class and indicating drug comparisons may be preferred over class comparisons.[15] Currently, guidelines suggest that clinicians balance individual patient characteristics with the reported adverse events and previously used treatment modalities when making therapeutic decisions.

In 2008, Schmitt and colleagues published a meta-analysis analyzing the efficacy and tolerability of biologic and nonbiologic systemic agents for moderate-to-severe plaque psoriasis.[18] This study examined all randomized controlled trials published before January 2008 that enrolled greater than 50 patients with moderate-to-severe plaque psoriasis. Based on the results of their meta-analysis, the authors concluded that the efficacy of systemic agents approved for moderate-to-severe psoriasis likely differs considerably between biologic and nonbiologic agents, as well as within the two classes. One of the main research gaps identified in this meta-analysis was the lack of comparative effectiveness and safety data for biologic versus nonbiologic systemic treatments for moderate-to-severe plaque psoriasis. Since the completion of this systematic review, the first head-to-head trial comparing a biologic to a nonbiologic systemic treatment has been published.[17] Additionally, comparative data from nonrandomized

studies likely exist, although not sought or evaluated by Schmitt and colleagues.[18] Moreover, the efficacy of phototherapy was not addressed in this meta-analysis.

To date, no comparative effectiveness review comparing the effectiveness and safety of FDA-approved biologic systemic to nonbiologic systemic treatment options or phototherapy for chronic plaque psoriasis has been completed.

II. The Key Questions

Proposed Key Questions (KQs) were posted for public comments and were modified with consideration of the comments received. Since controversy surrounds the classification of psoriasis as mild or moderate-to-severe, moderate-to-severe disease was not included as an explicit inclusion criterion in the systematic search of the literature or in the comparative effectiveness review. As suggested in the public comments, we will consider when evaluating efficacy data whether patients were naïve to biologics, were treated previously with biologics, or were allowed drug holidays. Although a suggestion was made to evaluate combination therapy and to compare harms in patients without psoriasis or untreated controls with psoriasis, such an evaluation falls outside the scope of our review. We have now specified the measures that will be used for health-related quality of life in KQ 1. The Psoriasis Area and Severity Index (PASI) score will be considered not only as a binary outcome but as a continuous outcome as suggested. Although we had proposed the Psoriasis Scalp Severity Index (PSSI) and the Nail Psoriasis Severity Index (NAPSI) scores as outcomes, patient-reported improvement in scalp pruritus and scalp pain were suggested as additional outcomes in KQ 1; scalp pruritus and scalp pain are not as commonly reported in the literature and are less likely to add extra value over the body-wide assessments. We have not listed specific malignancies (hepatosplenic T-cell lymphoma and other lymphomas) and infections (tuberculosis and histoplasmosis) in KQ 2 as suggested to be more comprehensive. Weight and impact of neutralizing antibodies have been added as characteristics that will be evaluated in KQ 3. We did not move major adverse cardiovascular events (MACE) from final health outcomes to harms, because this is an outcome of the disease process rather than of therapeutic interventions. Subgroup analyses based on duration of followup were discussed with the Technical Expert Panelists (TEP).

The acronyms used the questions below are defined within the text and the list under Definitions of Terms.

Question 1

In patients with chronic plaque psoriasis, what is the comparative effectiveness of systemic biologic agents and systemic nonbiologic agents (between-class comparisons) or phototherapy when evaluating intermediate (plaque BSA measurement, PASI score, Patient's Assessment of Global Improvement, PGA, and individual symptom improvement) and final health outcomes (mortality, HRQoL [e.g., DLQI, HAQ-DI, EQ-5D] and other patient-reported outcomes, MACE, diabetes, and psychological comorbidities [e.g., depression, suicide])?

Question 2

In patients with chronic plaque psoriasis, what is the comparative safety of systemic biologic agents and systemic nonbiologic agents (between-class comparisons) or phototherapy (hepatotoxicity [e.g., AST, ALT], nephrotoxicity [e.g., SCr, GFR], hematologic toxicity [e.g.,

TCP, anemia, neutropenia], hypertension, alteration in metabolic parameters [e.g., glucose, lipids, weight, BMI, thyroid function], injection site reaction, malignancy, infection, and study withdrawal)?

Key Question 3

In patients with chronic plaque psoriasis treated with systemic biologic therapy, systemic nonbiologic therapy, or phototherapy, which patient or disease characteristics (e.g., age, gender, race, weight, smoking status, psoriasis severity, presence or absence of concomitant psoriatic arthritis, disease duration, baseline disease severity, affected BSA, disease location, number and type of previous treatments, failure of previous treatments and presence of neutralizing antibodies) affect intermediate and final outcomes?

Details regarding the specific therapies considered in each class of interventions and comparators can be found in Tables 1-5. There are no specific requirements in terms of followup period that will be evaluated in these key questions. The setting will include inpatient, outpatient and home therapy.

Table 1. FDA-approved biologic systemic and targeted therapies for plaque psoriasis

Drug Name*	Brand Name (dosage form)	Marketed By (Manufacturer)	Target of Therapy	FDA Indications
Adalimumab	Humira® (injectable)	Abbott Laboratories	TNF-α	Treatment of adults with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy when other therapies are medically less appropriate; reducing signs and symptoms, inhibition of structural damage of active arthritis and improving physical function in patients with psoriatic arthritis; reducing signs and symptoms, including major clinical response, inhibiting progression of structural disease and improving physical function in active moderate-to-severe rheumatoid arthritis; reducing signs and symptoms in active ankylosing spondylitis; reducing signs and symptoms, inducing and maintaining clinical remission, in adult and pediatric patients with active moderate-to-severe active Crohn's disease in patients with inadequate response to conventional therapy, including intolerance and refractory response to infliximab; reducing signs and symptoms of moderate-to-severe active polyarticular juvenile idiopathic arthritis in patients 4 years of age and older
Alefacept	Amevive® (injectable)	Astellas Pharma US, Inc.	CD2 antigen on T-lymphocytes and natural killer cells	Treatment of chronic moderate-to-severe plaque psoriasis in patients who are candidates for systemic therapy or phototherapy
Etanercept	Enbrel® (injectable)	Amgen, Inc. and Wyeth Pharmaceuticals Inc.	TNF-α and TNF-β	Treatment of adults with chronic moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy; reducing signs and symptoms, inhibition of structural damage of active arthritis and improving physical function in patients with psoriatic arthritis; reducing signs and symptoms of active ankylosing spondylitis; reducing signs and symptoms of active moderate-to-severe active polyarticular juvenile idiopathic arthritis; reducing signs and symptoms, including major clinical response, inhibiting progression of structural disease, and improving physical function in active moderate-to-severe rheumatoid arthritis
Infliximab	Remicade® (injectable)	Centocor Ortho Biotech Inc.	TNF-α	Treatment of severe chronic plaque psoriasis in adults who are candidates for systemic therapy, and other systemic therapies are medically less appropriate; reducing signs and symptoms, including major clinical response, inhibiting progression of structural disease and improving physical function in psoriatic arthritis; (in combination with methotrexate) reducing signs and symptoms, including major clinical response, inhibiting progression of structural disease and improving physical function in moderate to severe active rheumatoid arthritis; reducing signs and symptoms, inducing and maintaining clinical remission in adult and pediatric patients with moderate to severe active Crohn's disease in patients with inadequate response to conventional therapy; reducing number of draining

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				enterocutaneous, rectovaginal fistulas, maintaining fistula closure in patients with fistulizing Crohn's disease; reducing signs and symptoms in active ankylosing spondylitis; reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing and eliminating corticosteroid use in patients with moderate to severe active ulcerative colitis who have had inadequate response to conventional therapy
Ustekinumab	Stelara® (injectable)	Centocor Ortho Biotech (Cilag Ag)	IL-12 and IL-23	Treatment for moderate to severe plaque psoriasis in patients (18 years and older) who are candidates for phototherapy or systemic therapy

*Drug name is the generic formulation, if available.

Abbreviations: FDA = U.S. Food and Drug Administration; IL = interleukin; TNF = tumor necrosis factor

Table 2. FDA-approved biologic systemic agents used off-label for the treatment of psoriasis

Drug Name*	Brand Name (dosage form)	Marketed By (Manufacturer)	Target of Therapy	FDA Indications	Status in United States/ Plaque psoriasis development stage†
Abatacept (BMS188667, CTLA41g)	Orencia® (injectable)	Bristol-Myers Squibb Company	CD80 and CD86 on T- lymphocytes	Treatment of active moderate-to-severe rheumatoid arthritis in adults; treatment of active moderate-to-severe polyarticular juvenile idiopathic arthritis in pediatric patients 6 years of age and older	Currently available; Phase I (2): complete; Phase II: complete
Certolizumab pegol (CDP870)	Cimzia® (injectable)	UCB Inc.	TNF-α	Treatment for reducing signs and symptoms of Crohn's disease and maintaining clinical response in adult patients with active moderate-to-severe disease with an inadequate response to conventional therapy	Currently available; Phase II (2): complete (2006, 2007)
Daclizumab	Zenapax® (injectable)	Genentech, Inc. (Hoffmann-La Roche)	IL-2	Prophylaxis of acute organ rejection in patients receiving renal transplants	Currently available; Phase I/II (2): complete (2008)
Erlotinib	Tarceva® (oral tablet)	Genentech USA, Inc. (Schwarz Pharma Manufacturing; OSI Pharmaceuticals Inc.)	Tyrosine kinase associated with EGFR	Treatment of locally advanced or metastatic non–small cell lung cancer after failure of at least one prior chemotherapy regimen; first-line treatment of patients with locally advanced, unresectable, or metastatic pancreatic cancer, given in combination with gemcitabine	Currently available; Phase II: not yet open
Golimumab	Simponi® (injectable)	Centocor Ortho Biotech Inc.	TNF-α	Treatment of active moderate-to-severe rheumatoid arthritis in adults, given in combination with methotrexate; treatment of active psoriatic arthritis in adults; treatment of active ankylosing spondylitis in adults	Currently available; Open-label study in recruitment phase
Rituximab	Rituxan® (injectable)	Genentech, Inc. (Hoffmann-La Roche)	CD20 antigen on B-lymphocytes	Treatment of relapsed or refractory, low-grade or follicular, CD20-positive B-cell NHL as a single agent, or if previously untreated, with CVP chemotherapy; treatment of nonprogressing follicular CD20-positive B-cell NHL, as a single agent after CVP chemotherapy; treatment of previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other	Currently available; Currently not being developed for this indication

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Published Online: September 27, 2011

	anthracycline-based chemotherapy; treatment of CD20-positive CLL in combination with fludarabine and cyclophosphamide; treatment of active moderate-to-severe rheumatoid arthritis in combination with methotrexate in patients with inadequate response to other TNF antagonists

***** Drug name is the generic formulation and/or the developmental name as determined by the manufacturing company.
† Plaque psoriasis development stage is described by: Phase (number of studies): status (if applicable and available, year of completion or termination).

Abbreviations: CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy; CLL = chronic lymphocytic leukemia; CVP = cyclophosphamide, vincristine, and prednisolone chemotherapy; EGFR = epidermal growth factor receptor; NHL = non-Hodgkin's lymphoma; TNF = tumor necrosis factor

Table 3. FDA-approved nonbiologic systemic therapy for plaque psoriasis

Drug Name*	Brand Name (dosage form)	Marketed By (Manufacturer)	FDA Indications
Acitretin	Soriatane® (capsule)	Stiefel Laboratories Inc., a GlaxoSmithKline company	Treatment of severe psoriasis
Cyclosporine, modified†	Gengraf® (capsule, oral solution)	Abbott Laboratories	Treatment of adult, nonimmunocompromised patients with severe recalcitrant plaque psoriasis who have failed to respond to at least one systemic therapy or in patients for whom other systemic therapies are contraindicated or cannot be tolerated; prophylaxis of organ rejection in kidney, liver, and heart allogeneic transplants; treatment of severe active rheumatoid arthritis where disease has not adequately responded to methotrexate
	Neoral® (capsule, oral solution)	Novartis Pharmaceuticals Corp.	
Methotrexate†	Methotrexate LPF® (injectable)	Hospira, Inc.	Symptomatic control of severe, recalcitrant, disabling psoriasis that is not adequately responsive to other forms of therapy; treatment of gestational choriocarcinoma, chorioadenoma destruens, and hydatidiform mole; prophylaxis and treatment of meningeal leukemia; used alone or in combination therapy in the treatment of breast cancer, epidermoid carcinomas of the head and neck, advanced mycosis fungoides, lung cancer, and advanced-stage non-Hodgkin's lymphomas; as combination therapy in prolongation of remission in nonmetastatic osteosarcoma; management of selected adults with severe, active rheumatoid arthritis, or children with active polyarticular juvenile rheumatoid arthritis who have had an insufficient therapeutic response to, or are intolerant of, an adequate trial of first-line therapy including full-dose nonsteroidal anti-inflammatory agents; trophoblastic neoplasms; acute lymphoblastic leukemia; meningeal leukemia; cutaneous T-cell lymphoma
	Trexall® (tablet)	Teva Pharmaceuticals USA (Barr Pharmaceuticals)	
Prednisone§	Generic formulations only (tablet, oral solution, intra-lesional)	‡	Approved for use in endocrine and rheumatic disorders; collagen diseases; dermatologic diseases including pemphigus, bullous dermatitis herpetiformis, severe erythema multiforme (Stevens-Johnson syndrome), exfoliative dermatitis, mycosis fungoides, severe psoriasis, and severe seborrheic dermatitis; allergic states; ophthalmic diseases; respiratory disease; hematologic disorders; neoplastic disease; edematous states; gastrointestinal disease

* Drug name is the generic formulation, if available, or the developmental name as determined by the manufacturing company.
† Generic formulations commercially available.
‡ Various manufacturers supply this medication to the marketplace.
§ Although systemic steroids are generally contraindicated in patients with psoriasis, therapeutic use of topical or intralesional injections may be indicated.

Abbreviations: FDA = U.S. Food and Drug Administration

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Published Online: September 27, 2011

Table 4. FDA-approved nonbiologic systemic agents used off-label in the treatment of plaque psoriasis

Drug Name*	Brand Name (dosage form)	Marketed By (Manufacturer)	FDA Indications	Status in United States/Plaque psoriasis development stage†
Azathioprine‡	Imuran® (oral tablet, injectable)	Prometheus Laboratories Inc.	Adjunct for the prevention of rejection in renal homotransplantation; management of active rheumatoid arthritis to reduce signs and symptoms	Oral tablet is currently available; injectable D/C in U.S. markets; not currently being developed for this indication
Cyclophos-phamide‡	Cytoxan® (injectable)	Baxter Healthcare	Treatment of malignancies including malignant lymphomas, Hodgkin's disease, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma, multiple myeloma, various leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of the ovary, retinoblastoma, carcinoma of the breast, and biopsy-proven "minimal change" nephritic syndrome in children	Currently available; not currently being developed for this indication
Doxercalciferol	Hectoral® (oral capsule, injectable)	Genzyme Corporation (Catalent Pharma Solutions)	Treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis; treatment of secondary hyperparathyroidism in patients with stage 3 or 4 chronic kidney disease	Currently available; Phase II: complete (2009)
Hydroxyurea‡	Hydrea® (oral capsule)	Bristol-Myers Squibb Company	Indicated for use in melanoma, resistant chronic myelocytic leukemia, and recurrent, metastatic or inoperable carcinoma of the ovary; used concomitantly with radiation therapy in the local control of primary squamous cell (epidermoid) carcinomas of the head and neck, excluding the lip	Currently available; not currently being developed for this indication
Isotretinoin	Accutane® (oral capsule)	Hoffmann-La Roche	Treatment of severe recalcitrant nodular acne	Approved in 1982; no longer marketed/ manufactured in the United States since June 2009; not currently being developed for this indication
Leflunomide‡	Arava® (oral tablet)	Sanofi-aventis U.S.	Treatment of active rheumatoid arthritis in adults	Currently available; not currently being developed for this indication
Mycophenolate mofetil‡	CellCept® (oral capsule, tablet, suspension	Genentech, Inc. (Hoffmann-La Roche)	Prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac, or hepatic transplants	Currently available; not currently being developed for this indication

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Published Online: September 27, 2011

	and injectable)			
Omega-3-acid ethyl ester	Lovaza® (oral capsule)	GlaxoSmithKline (Catalent Pharma Solutions; Accucaps Industries, Ltd.; Banner Pharmaceuticals Inc.	An adjunct therapy to diet in the reduction of triglyceride levels in adults with severe (≥ 500 mg/dL) hypertriglyceridemia	Currently available; not currently being developed for this indication
Penicillin G benzathine‡	Bicillin L-A® (injectable)	King Pharmaceuticals, Inc.	Treatment of infections due to penicillin-G–sensitive microorganisms that are susceptible to the low and very prolonged serum levels common to a particular dosage form	Currently available; Phase II: recruiting
Sulfasalazine‡	Azulfidine® (oral tablet and suspension)	Pfizer Inc.	Treatment of mild-to-moderate ulcerative colitis, and as adjunctive therapy in severe ulcerative colitis; for prolongation of remission period between acute attacks of ulcerative colitis	Currently available; not currently being developed for this indication
Tacrolimus‡	Prograf® (oral capsule and injectable)	Astellas Pharma US, Inc.	Prophylaxis of organ rejection in patients receiving allogeneic renal, cardiac, or hepatic transplants	Currently available; topical dosage form: Phase II/III (1/3): complete (2008/2007)
Thioguanine	Tabloid® (oral tablet)	GlaxoSmithKline	Remission induction and remission consolidation treatment of acute nonlymphocytic leukemias	Currently available; not currently being developed for this indication

* Drug name is the generic formulation and/or the developmental name as determined by the manufacturing company.
† Plaque psoriasis development stage is described by: Phase (number of studies): status (if applicable and available, year of completion or termination).
‡Generic formulations commercially available.

Abbreviations: D/C = discontinued

Table 5. FDA-approved phototherapy for use in plaque psoriasis

Modality	Description of Therapy	Example Models (Manufacturer)*	FDA Indication†
BB-UVB	Exposure to UVB radiation ranging from 254 to 313 nm	‡	UVB phototherapy for psoriasis, vitiligo, atopic dermatitis, and leukoderma
NB-UVB	Exposure to UVB radiation ranging from 311 to 313 nm	• DuaLight system (TheraLight™, Inc.) • 3-series Phototherapy Cabinet (Daavlin Company) • MultiClear XL (Curelight Ltd.)	UVB phototherapy for psoriasis, vitiligo, atopic dermatitis, and leukoderma
PUVA	Methoxsalen (8-MOP®) administered orally or topically 75–120 minutes prior to exposure to UVA radiation, followed by exposure to UVA radiation ranging from 320–400 nm	• 8-MOP® (ICN Pharmaceuticals, Inc.) • DuaLight system (TheraLight™, Inc.) • 3-series Phototherapy Cabinet (Daavlin Company)	8-MOP®: For the symptomatic control of severe, recalcitrant, disabling psoriasis not adequately responsive to other forms of therapy and when the diagnosis has been supported by biopsy; to be administered in conjunction with long-wave ultraviolet radiation
Excimer Laser	Targeted exposure of skin lesions to a 308-nm monochromatic excimer laser	• Fencer 308 (Kera Harvest, Inc.) • Pharos EX-308 (Ra™ Medical Systems, Inc.) • XTRAC® (PhotoMedex, Inc.)	UVB phototherapy for psoriasis, vitiligo, atopic dermatitis, and leukoderma

*Listed devices are intended to represent examples of currently available products. The list is not intended to be comprehensive.
† FDA indication as listed on the 510K preapproval documentation.
‡ FDA-approved devices for BB-UVB were not located on the FDA's Web site.

Abbreviations: 8-MOP = methoxypsoralen; BB-UVB = broadband ultraviolet B light; FDA = U.S. Food and Drug Administration; MED = minimal erythema dose; NB-UVB = narrowband ultraviolet B light; PUVA = psoralen plus ultraviolet A light

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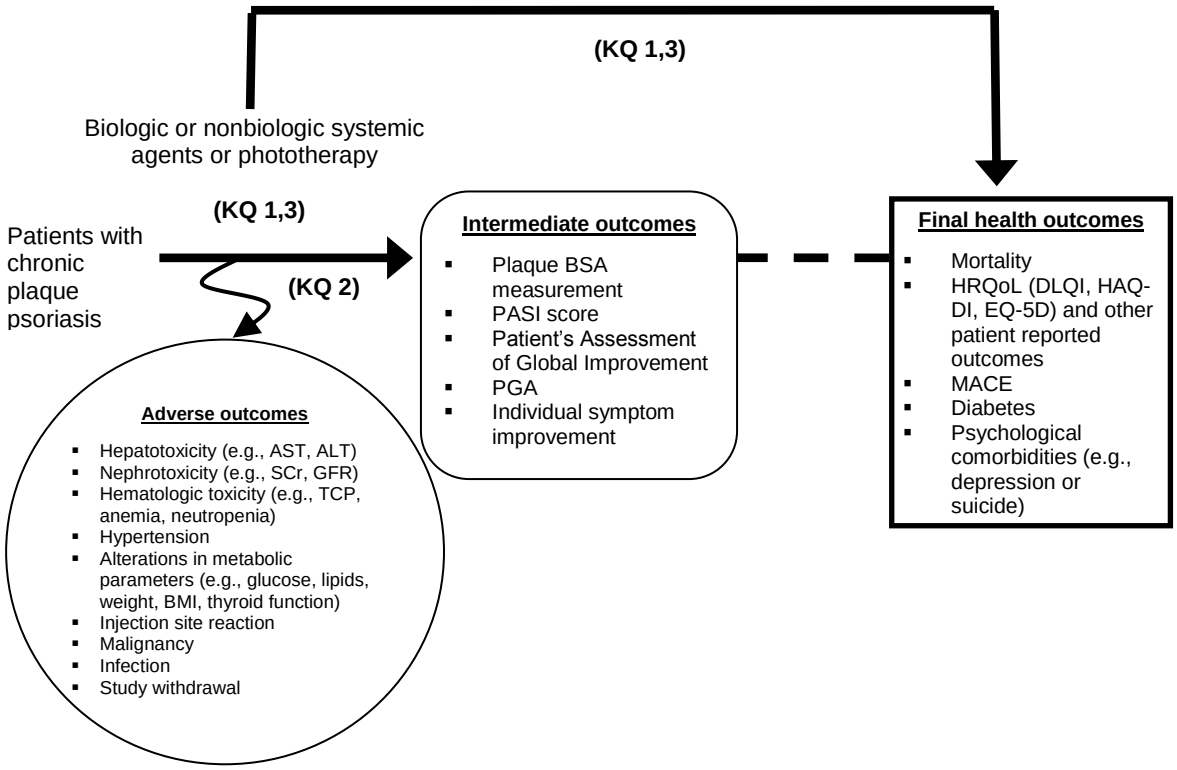
Published Online: September 27, 2011

III. Analytic Framework



Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; BSA = body surface area; DLQI = Dermatology Life Quality Index; EQ-5D = EuroQol; GFR = glomerular filtration rate; HAQ-DI = Health Assessment Questionnaire Disability Index; HRQoL = health-related quality of life; KQ = key question; MACE = major adverse cardiovascular events; PASI = Psoriasis Area and Severity Index; PGA = physician's global assessment; SCr = serum creatinine; TCP = thrombocytopenia

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

Two independent investigators will assess studies for inclusion in a parallel manner based on a priori defined criteria. Randomized trials and observational studies, including case-controlled and cohort studies that compare biologic systemic agents to either nonbiologic systemic agents or phototherapy will be included. Studies published before 1975 will be excluded as they were determined to be irrelevant in describing the currently available therapeutic interventions included in our review. Systematic reviews with or without meta-analysis will be included for manual reference searching as well as comparison of results with this review. The population evaluated in the study must be adult patients (≥18 years) with chronic plaque psoriasis, or the study must evaluate and report data on a subgroup of adult patients with chronic plaque psoriasis. Only studies that evaluate interventions and comparators with a current indication approved by the U.S. Food and Drug Administration (FDA) will be included in this review (Tables 1–5).

Studies in which patients are randomized to receive multiple therapies or are allowed to use concurrent therapies will be included only if the common interventions are similar across groups compared and the final comparison is of a single biologic systemic agent with a single nonbiologic systemic agent or phototherapy. Studies with only a comparison to placebo or untreated controls will not be included. Studies must report at least one of the prespecified outcomes (intermediate, final, or harm) to be included. Grey literature in the form of meeting abstracts, published protocols from C**linical**T**rials.gov**, and FDA regulatory documents will be included. Specifically for KQ 3, data that describe the association between the prespecified subgroups and outcomes—either through subgroup analysis in randomized trials or through control of confounding in observational studies (e.g., matching or multivariate analysis)—will be included.

B. Searching for the Evidence

A systematic literature search using the strategy detailed in Appendix A will be conducted in MEDLINE® and the Cochrane Central Register of Controlled Trials. Language restrictions will not be applied. A manual search of references from included clinical trials and systematic reviews will be conducted. A grey literature search for meeting abstracts will be conducted in Web of Science, limiting search results to meeting proceedings. For agents with an FDA-approved indication for the treatment of psoriasis, a search for completed trials with posted results will be conducted on C**linical**T**rials.gov** and a search of FDA regulatory documents will be conducted. Data from these two sources will be used to supplement published manuscripts when the trials can be matched. The Scientific Resource Center of the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program will contact the manufacturers of identified interventions and comparators for scientific information packets. The same inclusion/exclusion criteria previously described will be applied to packets that are received. The literature search will be updated concurrently with the peer review process, and the same inclusion and exclusion criteria will be applied as described previously. Relevant literature will be incorporated into the review.

C. Data Abstraction and Data Management

Two reviewers will use a standardized data extraction tool to independently extract data; disagreements will be resolved through discussion. The following data will be collected from each unique study: author identification, year of publication, funding source, study design characteristics and methodological quality criteria, study population (inclusion and exclusion criteria, geographic location, intervention, length of study, and duration of patient followup), patient baseline characteristics (including whether the patient is naïve to biologic therapy or not), intervention and comparator regimen in detail (name, strength, dose, frequency, route of administration, duration of therapy, if a drug holiday was allowed, and details regarding the regimen), use of concurrent standard medical therapies, data needed to assess intermediate and final health outcomes and harms, outcome definition, and data reported for subgroups of interest defined in KQ 3. Authors will be contacted for clarification or to provide additional data when necessary.

D. Assessment of Methodological Quality of Individual Studies

Assessment of the quality of included studies will be conducted using recommendations from the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter *Methods Guide*).[19] Using a standardized tool, two reviewers will independently assess the quality of each included study and will resolve disagreements through discussions. Randomized trials will be evaluated separately from observational studies, and each study will receive a quality rating of good, fair, or poor (Table 6). We will assess each randomized trial for the following criteria: methods for randomization, allocation concealment, similarity of groups at baseline, blinding of subjects and providers, differential loss to followup, overall loss to followup, use of intention to treat, blinding of event adjudicators, methods to ascertain outcomes, and reporting of prespecified outcomes. Observational studies will be evaluated for the following criteria: selection of comparison group, control for confounding, baseline differences, method to ascertain exposure, methods to ascertain outcomes, blinding of event adjudicators, differential loss to followup, overall loss to followup, and reporting of prespecified outcomes.

Table 6. Overall quality rating definitions

Grade	Definition
Good	Confidence that the study results are valid. Study reporting is adequate to judge that no major or minor sources of bias are likely to influence results. The study meets the majority of prespecified criteria.
Fair	Some confidence that the study results are valid. The study is susceptible to some bias and the problems are not sufficient to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems.
Poor	Low confidence that the study results are valid. The study has significant flaws that imply biases of various types that may invalidate the results. The biases may arise from serious errors in conduct, analysis or reporting, large amounts of missing information, or discrepancies in reporting.

E. Data Synthesis

KQs 1 and 2 explore the efficacy and safety of three classes of therapy for the treatment of chronic plaque psoriasis. Since differences in efficacy or safety may exist between agents within a given class (e.g., two biologic agents), individual biologic systemic agents will be compared to individual nonbiologic systemic agents or phototherapies for the base case analysis. The maximal reported duration of followup will be analyzed for the base case. We will conduct meta-analyses when two or more randomized trials adequate for pooling are available for any outcome. Observational studies will not be pooled with randomized trials and will only be considered qualitatively. For dichotomous outcomes, weighted averages will be reported as a relative measure (relative risk, odds ratio, or Peto's odds ratio) with associated 95 percent confidence intervals; a fixed or random effects model will be used as appropriate.[20] When pooling continuous end points, a weighted mean difference will be calculated using a DerSimonian and Laird random effects model.[21] In cases where mean change scores from

baseline for each group are not reported, we will calculate the difference between the mean baseline and mean followup scores for each group. Standard deviations of the change scores will be calculated using the method proposed by Follman and colleagues.[22]

In the event that there are more than one comparison being made in a trial sharing a common comparator, each comparison will be considered as a separate trial; if pooled in the same analysis, the control group will be divided equally between the comparisons.[20] The number needed to treat (NNT) or number needed to harm (NNH) will be calculated for statistically significant results of the base case analyses for KQs 1 and 2. The pooled effect estimate will be used with the range of control event rates from the trials included in the pooled analysis to obtain a range for the NNT and NNH.

Statistical heterogeneity will be addressed using the I^2 statistic (which assesses the degree of inconsistency not due to chance across studies and ranges from 0–100 percent with the higher percentage representing a higher likelihood of the existence of heterogeneity). While categorization of values for I^2 may not be appropriate in all situations, I^2 values of less than 50 percent and greater than 50 percent have been regarded, respectively, as representative of lower and higher levels of statistical heterogeneity. Egger's weighted regression statistics will be used to assess for the presence of publication bias and will be calculated for pooled analyses with 10 or more trials included, since the power to detect publication bias with fewer studies is too low to distinguish chance from true publication bias.[20] Statistical analyses will be performed using StatsDirect statistical software, version 2.7.8 (StatsDirect Ltd., Cheshire, England). A *p*-value of <0.05 will be considered statistically significant for all analyses.

Subgroup and sensitivity analyses will be conducted to assess the effect of heterogeneity (both clinical and methodological) on the conclusions of our meta-analysis. For KQs 1 and 2, we will evaluate the results based on gender, ethnicity, and patient age. As the base case analysis will be the maximal duration at which studies report the given outcome, we will conduct subgroup analyses, when possible, of studies with similar duration of followup. We will conduct sensitivity analysis limiting the analysis to only trials rated as good quality. We will also conduct subgroup analyses based on the patient population evaluated, including patients who are naïve to biologic therapy and patients allowed to have drug holidays.

KQ 3 explores the relationship between patient or disease characteristics and intermediate or final outcomes. Randomized trials that meet inclusion criteria will be reviewed for subgroup analyses of the prespecified patient and disease characteristics. In addition, nonrandomized studies that describe the association of prespecified patient or disease characteristics with outcomes and use a method to control for confounding (e.g., matching, multivariate regression) will be reported qualitatively.

F. Grading the Evidence for Each Key Question

Two reviewers will independently evaluate the strength of evidence for each comparison and outcome deemed most important, and disagreements will be resolved through discussion. Rating of the strength of evidence will be conducted using recommendations from AHRQ.[23] This system uses four required domains: risk of bias, consistency, directness, and precision. Additional optional domains will be used if determined appropriate given the identified literature.

Risk of bias is the degree to which the included studies, for a given outcome or comparison, have a high likelihood of adequate protection against bias. Risk of bias will be ranked as high,

medium, or low using the quality assessments of the individual trials included for the given outcome and comparison. Consistency refers to the degree of similarity in the direction of the effect sizes from included studies within an evidence base. We will assess whether or not the effect sizes are on the same side of unity, whether the range of effect sizes is narrow, and the degree of statistical heterogeneity and will rate the outcome as either consistent or inconsistent. When only one study is available, consistency cannot be judged and will be rated as not applicable. Directness refers to whether the evidence links the compared interventions directly with health outcomes and compares two or more interventions in head-to-head trials. Indirectness implies that more than one body of evidence is required to link interventions to the most important health outcomes. We will rate the outcome as either direct or indirect. Precision refers to the degree of certainty surrounding the effect estimate with respect to a given outcome. For example, when a meta-analysis is performed, we will evaluate the confidence interval around the summary effect size. A precise estimate is an estimate that would allow a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions (e.g., both clinically important superiority and inferiority), a circumstance that will preclude a conclusion. We will rate the outcome as either precise or imprecise. The overall grade for strength of evidence for each comparison and outcome evaluated will be rated and classified as high, moderate, low, or insufficient (Table 7). The four required domains will be considered equally when grading the strength of evidence.

Table 7. Strength of evidence rating

Grade	Definition
High	There is high confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

G. Assessing Applicability

Two reviewers will independently review the applicability of the individual studies and disagreements will be resolved through discussion. Rating of the applicability of evidence will be conducted using recommendations from AHRQ.[24] Seven domains will be evaluated in assessing individual study applicability: enrolled population, enrollment eligibility criteria, assessment of final health outcomes, adequate study duration with clinically relevant treatment modalities, assessment of adverse events, sample size, and use of intention-to-treat analysis. Data required to evaluate these domains will be extracted into evidence tables. Studies that meet five or more criteria will be classified as effectiveness studies. These data will also be reviewed to determine the overall applicability of data per outcome, describing the population and conditions to which the evidence is most applicable.

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VI. Definition of Terms

ALT = alanine aminotransferase
AST = aspartate aminotransferase
BMI = body mass index

BSA = body surface area
GFR = glomerular filtration rate
HRQoL = health-related quality of life
MACE = major adverse cardiovascular events
PASI = Psoriasis Area and Severity Index
PGA = physician's global assessment
PUVA= psoralen plus ultraviolet A (UVA) therapy
SCr = serum creatinine
TCP = thrombocytopenia

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and

conflicted opinions are common and perceived as health scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

Appendix A. Literature Search Strategy

1. psoriasis.mp. or Psoriasis/
2. Psoriasis/ or plaque psoriasis.mp.
3. 1 or 2
4. methotrexate.mp. or Methotrexate/
5. cyclosporin.mp. or Cyclosporine/
6. cyclosporine.mp. or Cyclosporine/
7. ciclosporin.mp. or Cyclosporine/
8. calcineurin inhibitor.mp.
9. acitretin.mp. or Acitretin/
10. retinoids.mp. or Retinoids/
11. antimalarials.mp. or Antimalarials/
12. hydroxyurea.mp. or Hydroxyurea/
13. isotretinoin.mp. or Isotretinoin/
14. sulfasalazine.mp. or Sulfasalazine/
15. 6-thioguanine.mp. or Thioguanine/
16. azathioprine.mp. or Azathioprine/
17. cyclophosphamide.mp. or Cyclophosphamide/
18. mycophenolate mofetil.mp.
19. nsaid.mp. or Anti-Inflammatory Agents, Non-Steroidal/
20. antihistamine.mp. or Histamine Antagonists/
21. leflunomide.mp.
22. tacrolimus.mp. or Tacrolimus/
23. fish oil.mp. or Fish Oils/
24. ergocalciferols.mp. or Ergocalciferols/
25. bicillin l-a.mp. or Penicillin G Benzathine/
26. prednisone.mp, or Prednisone/
27. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
28. etanercept.mp.
29. infliximab.mp.
30. adalimumab.mp.
31. alefacept.mp.
32. ustekinumab.mp.
33. cnto 1275.mp.
34. biologics.mp.
35. biologic agents.mp.
36. monoclonal antibody.mp. or Antibodies, Monoclonal/
37. t-cell modulator.mp.
38. tumor necrosis factor inhibitor.mp.
39. briakinumab.mp.
40. ABT 874.mp.
41. voclosporin.mp.
42. ISA-247.mp.
43. CP 690,550.mp.

44. certolizumab.mp.
45. cdp870.mp.
46. daclizumab.mp.
47. erlotinib.mp
48. abatacept.mp.
49. rituximab.mp.
50. golimumab.mp.
51. 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50
52. psoralen.mp. or Ficusin/
53. PUVA Therapy/ or puva.mp.
54. phototherapy.mp. or Phototherapy/
55. uvb.mp.
56. uva.mp.
57. laser therapy.mp. or Laser Therapy/
58. excimer laser.mp. or Lasers, Excimer/
59. goeckerman.mp.
60. ingram.mp.
61. 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60
62. 28 and 51
63. 3 and 62
64. 51 and 61
65. 3 and 64
66. 63 or 65
67. limit 66 to “review”
68. 66 not 67