USTEKINUMAB: A REVIEW OF THE EFFECTIVENESS OF TARGETING INTERLEUKIN-12/23P40 IN PSORIASIS AND OTHER IMMUNE-MEDIATED DISEASES

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USTEKINUMAB: A REVIEW OF THE EFFECTIVENESS OF TARGETING INTERLEUKIN-12/23P40 IN PSORIASIS AND OTHER IMMUNE-MEDIATED DISEASES

By Nicholas Patrick Swendrowski

We recommend acceptance of this thesis in partial fulfillment of the candidate's requirements for the degree of Master of Clinical Microbiology.

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ABSTRACT


Interleukin-12 (IL-12) and interleukin-23(IL-23) are cytokines that have been shown to have a role in the development of several autoimmune diseases including psoriasis, multiple sclerosis, Crohn’s disease, and sarcoidosis. IL-12 and IL-23 are heterodimers composed of a p40 subunit and a p35 (IL-12) or p19 (IL-23) subunit. These cytokines activate the T-helper-1 and T-helper-17 pathways. Ustekinumab is a fully human monoclonal antibody that was designed to bind to the p40 subunit found on both IL-12 and IL-23, blocking their effects. Ustekinumab received FDA approval for psoriasis on September 25, 2008 and is being studied as a possible therapy for multiple sclerosis and Crohn’s disease. This review examine the safety and efficacy of ustekinumab for psoriasis, multiple sclerosis, and Crohn’s disease, compare the efficacy and cost of ustekinumab and etanercept as top line psoriasis treatments, and provide future perspectives for its continued study in these and other immune mediated disorders, such as sarcoidosis and psoriatic arthritis.
ACKNOWLEDGEMENTS

I would like to thank my mother and father for their support throughout this journey.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>SECTION</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TABLE OF CONTENTS</td>
<td>v</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>vii</td>
</tr>
<tr>
<td>INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>Ustekinumab: an anti-IL-12/23p40 Therapeutic mAb for Psoriasis</td>
<td>2</td>
</tr>
<tr>
<td>Figure 1. Ustekinumab and its Target. Adapted from “Therapeutic targeting of the IL-12/23 pathways: generation and characterization of ustekinumab,” by J. Benson, C. Sachs, G. Treacy, H. Zhou, C. Pendley, C. Broedmerkel, C., ... M. Mascelli, 2011, <em>Nature Biotechnology</em>, 29, p. 616. Copyright 2011 by Nature America Incorporated. Adapted with permission.</td>
<td>3</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>3</td>
</tr>
<tr>
<td>Environmental and Genetic Risk Factors for Psoriasis</td>
<td>4</td>
</tr>
<tr>
<td>Roles of Cytokines and Immune System Cells in Psoriasis</td>
<td>5</td>
</tr>
<tr>
<td>Multiple Sclerosis and its Disease Mechanism Relationship with Psoriasis</td>
<td>7</td>
</tr>
<tr>
<td>Crohn’s Disease and its Disease Mechanism Relationship with Psoriasis</td>
<td>10</td>
</tr>
<tr>
<td>CLINICAL TRIALS OF USTEKINUMAB FOR TREATMENT OF PSORIASIS</td>
<td>12</td>
</tr>
<tr>
<td>Phase-I Trials</td>
<td>12</td>
</tr>
<tr>
<td>Phase-II Trial</td>
<td>14</td>
</tr>
<tr>
<td>Phase-III Trial, PHOENIX 1</td>
<td>15</td>
</tr>
<tr>
<td>Phase-III Trial, PHOENIX 2</td>
<td>20</td>
</tr>
<tr>
<td>Comparator Trial, ACCEPT</td>
<td>25</td>
</tr>
</tbody>
</table>

v
CLINICAL TRIALS OF USTEKINUMAB FOR MULTIPLE SCLEROSIS .............. 30
CLINICAL TRIALS OF USTEKINUMAB FOR CROHN’S DISEASE ............... 34
SUMMARY AND PERSPECTIVES ................................................................ 40
REFERENCES ......................................................................................... 43
## LIST OF TABLES

<table>
<thead>
<tr>
<th>TABLE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Twelve-week Psoriasis Area and Severity Index (PASI)</td>
<td>15</td>
</tr>
<tr>
<td>2. Phase 3 study results with ustekinumab in the treatment</td>
<td>19</td>
</tr>
<tr>
<td>3. Phase 3 study results with ustekinumab</td>
<td>24</td>
</tr>
<tr>
<td>4. Ustekinumab vs etanercept in the treatment</td>
<td>27</td>
</tr>
</tbody>
</table>
INTRODUCTION

IL-12 and IL-23 are heterodimers composed of the same p40 subunit with a disulfide link to either a p19 subunit (IL-23) or a p35 subunit (IL-12) (Benson et al., 2011; Chien et al., 2009; Weber & Keam, 2009). IL-12 is responsible for inducing a T\textsubscript{H}1 response in psoriasis, multiple sclerosis, and Crohn’s disease. Elevated levels of activated T-cells were found in these three autoimmune diseases and contribute to their pathophysiology.

Produced mainly by phagocytic cells and dendritic cells, IL-12 activates natural killer cells and CD8+ T cells and promotes differentiation of CD4+ T cells into the T\textsubscript{H}1 cells that produce the proinflammatory cytokines IFN-\gamma and TNF-\alpha (MS, CD, and psoriasis) and IL-2 (CD only) (Bellizzi et al., 2010; Benson et al., 2011; Weber & Keam, 2009; Yeilding et al., 2011).

IL-23 induces the development of T\textsubscript{H}17 cells that produce other proinflammatory cytokines, such as IL-17A, IL-17F, and IL-22, in psoriasis, MS and CD (Bellizzi et al., 2010; Benson et al., 2011; Weber & Keam, 2009). IL-17A, IL-17F, and IL-22 are responsible for promoting the activation and migration of neutrophils in all three autoimmune diseases (Bellizzi et al., 2010; Benson et al., 2011; Chien, Elder, & Ellis, 2009; Weber & Keam, 2009; Yeilding et al., 2011). Through expanded understanding of the IL-12 and IL-23 pathways, it was evident that a targeted treatment could block IL-12-
and IL-23-mediated T_{H1} and T_{H17} cell production of IFN-γ, TNF-α, IL-17, and IL-22 (Benson et al., 2011; Reich, Yasothon, & Kirkpatrick, 2009).

**Ustekinumab: an anti-IL-12/23p40 Therapeutic mAb for Psoriasis**

Ustekinumab (proprietary commercial name Stelara; Janssen Biotech, Inc., Philadelphia, PA) is a fully human IgG1κ monoclonal antibody that binds with high specificity and affinity to the p40 subunit of IL-12 and IL-23 and thus prevents these cytokines from binding to the IL-12Rβ1 receptor on the surface of immune cells (see Figure 1) (Cada, Levien, & Baker, 2010; Reich et al., 2009; Weber & Keam, 2009).

Traditional treatments for psoriasis, such as topical corticosteroids, have proved generally effective in treating mild cases of plaque psoriasis, but moderate to severe cases require systemic treatments with traditional immunosuppressive drugs (cyclosporine, methotrexate) or phototherapy (psoralen, a medication that increases UV absorbance, plus UVA radiation (PUVA)), which are limited by safety issues and cause major health concerns (Reich et al., 2009). These concerns increased the demand for novel biologic therapies that target a specific component of the immune system, such as Etanercept (Enbrel; Amgen/Wyeth), which blocks the activity of the inflammatory cytokine TNF-α (Reich et al., 2009). Biologics, such as Etanercept or Ustekinumab, markedly improved the treatment for moderate to severe psoriasis and have ignited the investigation into further forms of treatment for those who do not respond to the existing treatments or for whom these therapies are unsuitable (Reich et al., 2009). Enhanced understanding of psoriasis led to the development of Ustekinumab which received US Food and Drug Administration (FDA) approval for plaque psoriasis on September 25, 2009 (Cada et al., 2010). Since this time, further understanding of the genetics and immunopathologies of
MS and CD combined with the improved knowledge of the IL-12 and IL-23 pathways have led to clinical trials to determine the safety and efficacy of Ustekinumab use for these disorders.


**Psoriasis**

Psoriasis is a chronic, recurring inflammatory skin disease that affects 1-3% of the world’s population and roughly 2% of the population in the United States. Psoriasis is characterized by a thickening of the epidermis due to excessive keratinocyte cell proliferation (Yeilding et al., 2011). It is associated with significant morbidity and decreased health-related quality of life (Keating & Croxtall, 2008; Weber & Keam, 2009). Symptoms begin to present between the ages of 15 and 35 with the most common form being plaque psoriasis, which afflicts 80-90% of psoriasis patients. Plaque psoriasis manifests itself as raised, well-isolated, erythematous and painful plaques with silvery, white scales. The plaques are most commonly found on the elbows, knees, and lower
back as well as in cosmetically sensitive regions such as the scalp, face, hands, and feet (Yeilding et al., 2011). Psoriasis is also associated with multiple comorbidities that include psoriatic arthritis, hypertension, cardiovascular disease, obesity, diabetes, metabolic syndrome, and Crohn’s Disease (Yeilding et al., 2011). In addition to the physical burdens the disease causes, there are also social and psychological burdens. Psoriasis can interfere with everyday activities and affect relationships. People with psoriasis have higher rates of anxiety, depression, and suicidal tendencies compared to the general public. Furthermore, people afflicted with psoriasis have lower levels of employment, job retention and income (Yeilding et al., 2011).

**Environmental and Genetic Risk Factors for Psoriasis**

Psoriasis manifests as a result of two major components: a polygenic inheritance that includes 36 chromosomal susceptibility loci, and the other, a strong immunological component (Tsoi et al., 2012). In addition to genetic variations, an environmental trigger, such as sunburn, medication, dry skin, obesity, smoking, hormones, stress or infections, is usually necessary for the manifestation of psoriasis symptoms. The chromosomal loci have been identified by multiple genetic linkage studies and only the Psoriasis Susceptibility 1 location (PSORS1), which resides within the Major Histocompatibility Complex (MHC,) has been widely confirmed (Chien et al., 2009). The HLA-Cw6 allele has been identified as the major susceptibility allele at PSORS1 for this condition. There are additional genetic loci, that encode subunits of IL-12 and IL-23, that have been identified via genetic association versus controls, rather than by genetic linkage in families. The particular alleles of IL-12 and IL-23 associated with psoriasis are IL12B, IL23A, and IL23R (Chien et al., 2009; Weber & Keam, 2009).
Roles of Cytokines and Immune System Cells in Psoriasis

Interleukin-12 and IL-23 both contain a p40 subunit that is encoded by the *IL12B* gene implicated in psoriasis (Chien et al., 2009). IL-12 is composed of the p40 subunit in complex with a p35 subunit, which is encoded by *IL12A* (Chien et al., 2009; Weber & Keam, 2009). IL-23 is composed of the same p40 subunit in association with a p19 subunit, which is encoded by *IL23A* (Chien et al., 2009; Weber & Keam, 2009). The receptors for IL-12 and IL-23 also share a common p40 binding subunit, *IL12Rβ1*. The receptor specificity for each cytokine is therefore conferred by the receptor associated subunits. IL12Rβ2 is the receptor for the IL-12 p35 subunit (Chien et al., 2009; Elliott et al., 2009; Weber & Keam, 2009). IL23R is the receptor for the IL-23 p19 subunit (Chien et al., 2009; Elliott et al., 2009; Weber & Keam, 2009). IL-23 appears to be the more significant cytokine in psoriasis because p40 and p19 are substantially over expressed in psoriatic lesions, while p35 is not (Chien et al., 2009). In addition, the genes that encode the p40 subunit and the receptor for the p19 subunit, *IL12B* and *IL23R* respectively, have been identified through genetic association (Chien et al., 2009; Weber & Keam, 2009). Further, the genes that encode the p35 subunit and the receptor for the p35 subunit, *IL12A* and *IL12Rβ1* respectively, have not been identified (Chien et al., 2009; Weber & Keam, 2009).

With genetic susceptibility and a trigger, the immunological component will then ensue. The immunological involvement in psoriasis includes T-lymphocyte and macrophage activation and the release of various cytokines (Weber & Keam, 2009). IL-12, secreted by dendritic cells, B-cells, and macrophages, promotes differentiation of CD4+ T cells into T helper-1 (T_h1) cells that release the pro-inflammatory cytokines
interferon (IFN)-γ and tumor necrosis factor (TNF)-α (Weber & Keam, 2009). IL-12 also induces cutaneous lymphocyte antigen (CLA), which causes T-cell homing to the skin and activates CD8+ T cells and natural killer cells (CD16+/CD56+) (Weber & Keam, 2009). IL-23, also secreted by dendritic cells and macrophages, is believed to play a role in promoting a T helper-17 (Th17) response which causes expression of IL-17 (Elliott et al., 2009). Th helper-17 cells can produce IL-17A, IL-17F, IL-22, IL-26, IFN-γ, CCL20, and TNF-α which activate keratinocytes (see Figure 2) (Elliott et al., 2009; Weber & Keam, 2009). In turn these activated keratinocytes induce the production of antimicrobial peptides (β-defensins), proinflammatory cytokines (TNF-α, IL-1β, and IL-6), chemokines (CXCL8-CXCL11 and CCL-20) that attract more neutrophils and macrophages, and S100 proteins (act as cytokines in inflammation) that all feed back into the disease cycle and produce the clinical features (Bellizzi et al., 2010; Benson et al., 2011; Chien et al., 2009; Weber & Keam, 2009; Yeilding et al., 2011). With all of these mechanisms working in conjunction the immune system mistakenly organizes an attack against normal skin epithelial cells. IL-23 and IL-17 are implicated in several autoimmune disorders, including multiple sclerosis and Crohn’s disease, and Th17 cells are believed to mediate tissue damage in these disorders (Elliott et al., 2009; Weber & Keam, 2009).

Multiple Sclerosis and its Disease Mechanism Relationship with Psoriasis

Multiple sclerosis (MS) is a chronic, progressive inflammatory disease of the central nervous system that affects roughly 2.5 million people worldwide and over 400,000 people in the United States (Jelinek & Hassed, 2009; Mäurer & Rieckmann, 2000). The most common form of multiple sclerosis is relapsing-remitting multiple sclerosis (RRMS) which is characterized by periods of neurological dysfunction (relapse) followed by periods of healing (remission) and affects approximately 85% of patients at onset and is present in 55% of patients at any given time (Mäurer & Rieckmann, 2000;
Terrie, 2011). MS is characterized by periods of unpredictable neurological dysfunction due to attacks on myelinated axons in the central nervous system (Mäurer & Rieckmann, 2000; Segal et al., 2008; Terrie, 2011). The demyelination of axons results in nerve conduction being interrupted or lost resulting in pain and loss of function (MacLean, 2010). Following the periods of demyelination, oligodendrocytes attempt to repair the damage via remyelination (MacLean, 2010). If the oligodendrocytes or the axon itself sustains damage then the function of the axon is compromised, the damage is permanent, and the disease will progress (MacLean, 2010). The most common symptoms of numbness in the limbs, muscle weakness, paralysis, and/or impaired vision become more apparent with each subsequent relapse because the healing becomes less complete. Furthermore, people afflicted with MS may experience loss of bladder and bowel control, slurred speech, swallowing disorders, tremors, depression, and cognitive and memory difficulties (Terrie, 2011). The resulting visual, sensorimotor, autonomic and cognitive disabilities have a profound impact on daily life (Segal et al., 2008).

Despite many years of research, little is definitively known about what triggers this autoimmune disease, but it is believed to be a multifactorial disease that includes genetic, geographic, and other environmental components with possible infectious disease involvement (Jelinek & Hassed, 2009; MacLean, 2010; Terrie, 2011). It has been shown that MS is much more common in northern latitudes and much less common in regions closer to the equator. The genetic and environmental factors are widely accepted as root causes although the timing and extent are not fully known (MacLean, 2010). Environmental factors, including vitamin D insufficiency, low sunlight exposure, and viruses, are being examined more closely as triggers for MS (MacLean, 2010).
Fifty-seven genes have been linked to the development of MS and among them are *IL12A* (p35 subunit of IL-12) and *IL12B* (p40 subunit of IL-12 and IL-23) (Sawcer et al., 2011). IL-12/23p40 and IL-23p19 have been detected in human MS lesions and IL-12 has been found in the CNS of patients with MS as well (Elliott et al., 2009). In lesions, these cytokines are primarily produced by activated myeloid cells (dendritic cells, macrophages, and microglia) and bind to receptors chiefly found on lymphocytes (T cells and natural killer cells) (Segal et al., 2008). Circulating mononuclear cells from MS patients expressed increased concentrations of IL-12 and IL-23 (Segal et al., 2008). IL-12 and IL-23 have been strongly implicated in the development of MS and experimental autoimmune encephalitis (EAE), a mouse model that is similar to human MS (Elliott et al., 2009; Segal et al., 2008). IL-12 can intensify EAE, whereas treatment with an anti-IL-12p40 antibody has been shown to delay the onset or prevent relapse in both murine models and primates (Elliott et al., 2009). Furthermore, systemic injection of recombinant IL-12 or intracerebral injection of an IL-23 encoding adenoviral vector causes clinical relapses of EAE (Segal et al., 2008). Mice genetically deficient in IL-23p19 or IL-12/23p40 showed complete resistance to the induction of EAE (Elliott et al., 2009; Segal et al., 2008). Ustekinumab (an anti-IL-12/23p40 antibody) delayed white matter demyelination, prevented T2 lesion accumulation (indicators of myelin damage and long term disease progression), and suppressed inflammation in existing brain lesions in marmosets with established EAE (Segal et al., 2008). Multiple sclerosis and psoriasis share the common disease mechanism of elevated IL-12 and IL-23 and thus make MS a prime candidate for research with Ustekinumab.
Crohn’s Disease and its Disease Mechanism Relationship with Psoriasis

Crohn’s disease (CD) is a chronic inflammatory bowel disease that affects 1-16/100,000 people worldwide and over 400,000 people in the United States alone (Bellizzi et al., 2010; Parray et al., 2011). CD is found most commonly in developed countries and is characterized by abnormal inflammation of the intestinal walls, particularly in the lower part of the small intestine (ileum) and portions of the large intestine (colon) that cause the inflamed tissues to become thick, swollen, and even develop open sores, or ulcers (National Institute of Health, 2012). CD most commonly manifests between the ages of 15 and 25 with symptoms of persistent diarrhea or intestinal blockage, abdominal pain, loss of appetite, weight loss, and constant fatigue (National Institute of Health, 2012; Parray et al., 2011). The chronic bleeding from ulcers can, over time, lead to anemia and other medical problems affecting the joints, eyes, and skin (National Institute of Health, 2012). Due to the chronic nature of this disease, most patients experience frequent hospitalizations, eventual surgery, and increased health care costs.

A number of factors contribute to the development and severity of CD, including genetics, environmental exposures, and intestinal flora. CD seems to occur when the intestinal immune system is activated by an antigen in genetically susceptible people (Bellizzi et al., 2010). This results in over activation of the enteric immune and inflammatory pathways leading to the clinical manifestations (Bellizzi et al., 2010). Four genes have been identified that are associated with the development of CD, and among them is \( IL23R \) (encodes receptor for IL-23 p19 subunit) (National Institute of Health, 2012). IL-12 and IL-23 have been implicated in both murine models of CD as well as the
human disease. In murine models, anti-IL-12 antibodies given at early or late points in disease improved clinical symptoms (Neurath, Fuss, Kelsall, Stüber, & Strober, 1995). In other animal models, selective inhibition of IL-23, but not IL-12, prevents mucosal inflammation (Bellizzi et al., 2010). IL-12 and IL-23 have also been found in elevated concentrations in inflamed human CD mucosa (Bellizzi et al., 2010).

It is clear that genetics alone cannot explain the development of CD. Agents that break the mucosal barrier, such as nonsteroidal anti-inflammatory drugs, antibiotics, smoking, and viral and bacterial infections, are common triggers for CD (Bellizzi et al., 2010). Microbial agents, such as *Mycobacterium paratuberculosis*, *Listeria monocytogenes*, and measles virus, appear to be involved in the development of CD. Decreased numbers of anaerobic bacteria and *Lactobacillus spp.* in the gastrointestinal tract are associated with CD, but a consistent, established link has not been shown (Bellizzi et al., 2010). With so few controlled studies and a vast array of gut flora to investigate, all that is known for certain is that there is a complex system of genetic, microbial, and environmental factors that leads to sustained over activation of the immune system and results in chronic inflammation and tissue damage (Bellizzi et al., 2010).
CLINICAL TRIALS OF USTEKINUMAB FOR TREATMENT OF PSORIASIS

A total of five clinical trials have been published to determine the safety and efficacy of Ustekinumab for the treatment of moderate-to-severe psoriasis along with one head-to-head comparative analysis study to compare the efficacy of Ustekinumab to that of Etanercept. The clinical efficacy was assessed primarily based on the Psoriasis Area and Severity Index (PASI) and Physician Global Assessment (PGA) (Lebwohl et al., 2009). The PASI rates the severity of psoriatic lesions in four specified body regions based on the degree of lesional erythema, scaling, and induration with a score given for each category between 0 and 4 (4 being worst). Then the extent of involvement within each region is scored on a scale of 0 to 6. This means that each region of the body has a potential for 18 points with the total scores ranging from 0 to 72 and the lower scores indicating less severe psoriasis (Lebwohl et al., 2009). The PGA grades the hardening, scaling, and erythema of lesions as cleared (0) to severe (5) (Lebwohl et al., 2009).

PASI, which is less commonly used in the clinical setting than PGA, does however capture the degree of body surface area affected with psoriasis (Lebwohl et al., 2009).

Phase-I Trials

The proof-of-concept for the use of Ustekinumab for moderate-to-severe psoriasis was established in two phase I studies (Cada et al., 2010; Chien et al., 2009; Elliott et al., 2009). In a non-randomized, open-label, dose-escalation, phase I study, 18 patients with moderate-to-severe psoriasis were enrolled and divided into four groups that received a
one-time intravenous administration of either 0.1, 0.3, 1, or 5 mg/kg Ustekinumab (Chien et al., 2009). Overall, >50% PASI improvement was seen in 83% of patients during the 16 week follow up period, and 67% of patients even achieved a PASI-75 (75% reduction in PASI score from baseline) (Chien et al., 2009). In a group analysis through week 8, 25%, 25%, 25%, and 50% of patients attained a PASI-75 in the 0.1, 0.3, 1, and 5 mg/kg dosages, respectively and through week 12 the values were 50%, 50%, 60%, and 100%, respectively (Chien et al., 2009).

A separate, randomized, double-blind, placebo-controlled, dose-escalation, phase I study, 21 patients with moderate-to-severe psoriasis were enrolled and divided into groups to receive ustekinumab 0.27, 0.675, 1.35, or 2.7 mg/kg or placebo as a single subcutaneous dose (Cada et al., 2010). Thirteen of 17 patients receiving ustekinumab achieved PASI 75 from baseline compared to none who received placebo (Cada et al., 2010). At least a PASI 75 was achieved at one or more time points in three of five subjects treated with 0.27 mg/kg, all four treated with 0.675 mg/kg, two of four treated with 1.35 mg/kg, and all four treated with 2.7 mg/kg. Improvement was apparent within two weeks of administration with maximum PASI response observed between weeks 8 and 16 after administration (Cada et al., 2010). The patients treated with 2.7 mg/kg maintained clinical response (PASI 67- PASI 89) from weeks 12 through 24 (the end of the trial) (Cada et al., 2010). No adverse events were reported during the trial and these studies indicated a significant and dose-dependent improvement in psoriasis signs and symptoms, warranting further investigation.
Phase-II Trial

A double-blind, placebo-controlled, phase II trial enrolling 320 patients with moderate-to-severe plaque psoriasis and a PASI of at least 12 was conducted with patients receiving placebo or ustekinumab as a single 45 mg dose, a single 90 mg dose, weekly 45 mg doses for four weeks, or weekly 90 mg doses for four weeks subcutaneously over a 52-week period (Cada et al., 2010; Chien et al., 2009; Elliott et al., 2009). Patients assigned to ustekinumab therapy who did not respond by week 16 were given one additional dose and patients assigned to placebo were given one single 90 mg dose of ustekinumab at week 20 (Cada et al., 2010; Chien et al., 2009; Elliott et al., 2009). The primary endpoint, PASI 75 at week 12, was seen in 52% and 59% of patients receiving single doses of 45 mg and 90 mg ustekinumab, respectively, and 67% and 81% of those who received four weekly 45 mg and 90 mg doses, respectively, compared to 1.6% of patients who received placebo ($P < 0.001$ for each comparison) (Cada et al., 2010; Chien et al., 2009; Elliott et al., 2009). With the respective doses (single 45 mg dose, single 90 mg dose, weekly 45 mg doses, and weekly 90 mg doses), a PASI 90 was achieved in 23%, 30%, 44%, and 52% of patients and a PASI 100 score was achieved in 5%, 16%, 16%, and 20% (see Table 1) (Cada et al., 2010; Chien et al., 2009). A PGA score of clear (0) was achieved in 6% and 17% of subjects treated with the single doses and in 16% and 23% treated with the weekly doses (Cada et al., 2010). Also, a greater improvement in the Dermatology Quality Life Index (DLQI) score was achieved in each of the ustekinumab groups compared to placebo ($P < 0.001$) with a score of zero, indicating psoriasis had no effect on quality of life, being achieved in 20%, 30%, 42%, and 41% of the respective ustekinumab groups (Cada et al., 2010). Additional studies
were then conducted to confirm the efficacy and safety of ustekinumab in a larger patient population, for a longer period of time.

Table 1. Twelve-week Psoriasis Area and Severity Index (PASI) response rates with Ustekinumab. Adapted from “Ustekinumab,” by D.J. Cada, T.L. Levien, and D.E. Baker, 2010, Hospital Pharmacy, 45, p. 322. Copyright 2010 by Thomas Land Publishers Incorporated. Adapted with permission.

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<th>Patients with PASI 75</th>
<th>Patients with PASI 90</th>
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<td>Placebo</td>
<td>64</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
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<tr>
<td>Ustekinumab 45 mg single dose</td>
<td>64</td>
<td>33 (52%)</td>
<td>15 (23%)</td>
</tr>
<tr>
<td>Ustekinumab 90 mg single dose</td>
<td>64</td>
<td>38 (58%)</td>
<td>19 (30%)</td>
</tr>
<tr>
<td>Ustekinumab 45 mg weekly x 4 wk</td>
<td>64</td>
<td>43 (67%)</td>
<td>28 (44%)</td>
</tr>
<tr>
<td>Ustekinumab 90 mg weekly x 4 wk</td>
<td>64</td>
<td>52 (81%)</td>
<td>33 (52%)</td>
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*Note: PASI = Psoriasis Area and Severity Index*

**Phase-III Trial, PHOENIX 1**

Two phase III trials were conducted to determine the efficacy of 45 mg and 90 mg ustekinumab dosing regimens for the treatment of moderate-to-severe psoriasis. The first, PHOENIX 1, enrolled 766 patients into a three phase, randomized, double-blind, placebo-controlled, multicenter study. In the first phase (weeks 0 to 12), patients were randomized to receive subcutaneous ustekinumab 45 mg (n=255) or 90 mg (n=256) or placebo (n=255) at weeks 0 and 4 (Weber & Keam, 2009). In the second phase (weeks 12 to 40), ustekinumab was administered every 12 weeks in the ustekinumab 45 mg and 90 mg dosing groups, while patients who initially received placebo were randomized to receive ustekinumab 45 mg or 90 mg at weeks 12 and 16, then every 12 weeks until the end of the phase (Cada et al., 2010; Elliott et al., 2009; Keating & Croxtall, 2008; Weber & Keam, 2009). During the third phase (weeks 40 to 76), patients who received
ustekinumab that achieved a long-term response (PASI 75) at weeks 28 and 40 were re-randomized to continue ustekinumab treatment or receive placebo until week 76 (Cada et al., 2010; Elliott et al., 2009; Keating & Croxtall, 2008; Weber & Keam, 2009). Patients who did not achieve long-term response were not re-randomized, and treatment was withdrawn or adjusted so that ustekinumab was administered every 8 weeks (Weber & Keam, 2009). Ustekinumab was reintroduced to the patients that were re-randomized to placebo and dropped below PASI 50 (Weber & Keam, 2009). The primary endpoint was the proportion of patients achieving PASI 75 at week 12, and major secondary endpoints were the proportion of patients achieving PGA of 0 (cleared) or 1 (cleared or minimal) at 12 weeks, the change from baseline in patient-assessed DLQI (score range of 0 to 30), and the time to loss of PASI 75 response in the randomized withdrawal phase (Cada et al., 2010; Weber & Keam, 2009).

The primary endpoint was achieved by more patients in both ustekinumab groups and ustekinumab was more effective compared to placebo as assessed by PASI response, PGA, and change in DLQI score (Cada et al., 2010). By week 12, PASI 75 was achieved by 67.1% and 66.4% of patients receiving ustekinumab 45 mg and 90 mg, respectively, compared to only 3.1% of those receiving placebo (P<0.0001) (Cada et al., 2010; Keating & Croxtall, 2008). By week 28, 65.9% and 84.9% of patients that were moved from placebo to ustekinumab 45 mg or 90 mg at week 12 achieved PASI 75 (Cada et al., 2010). Maximum efficacy was observed at about week 24 and generally maintained to week 40 (when re-randomization occurred) where long-term response was achieved by 150 patients in the 45 mg group and 172 patients in the 90 mg group (Chien et al., 2009). Those who were re-randomized to ustekinumab maintenance therapy (treatment every 12
weeks) maintained PASI improvement through week 76 whereas those who had
treatment withdrawn showed a decline from week 44 with a median time to loss of PASI
75 of 15 weeks (Cada et al., 2010; Keating & Croxtall, 2008). There was no evidence of
rebound psoriasis (psoriasis returning worse than before and spreading when a treatment
is stopped) due to withdrawal of ustekinumab and the decline in PASI 75 rate was
reversible by reinitiating therapy (Keating & Croxtall, 2008). Of the 195 patients who
had ustekinumab therapy restored, 85.6% achieved PASI 75 within 12 weeks (Cada et al.,
2010). When results of this study were assessed by body weight, PASI 75 response rates
in patients weighing 100 kg or less were statistically equal in the 45 mg group and the 90
mg group (74% and 65%), but were higher in the 90 mg dosage group (68%) than the 45
mg group (54%) in patients weighing more than 100 kg (Cada et al., 2010). The results
of the other secondary endpoints favored ustekinumab over placebo and further indicate
its efficacy. Significantly more 45 mg or 90 mg ustekinumab recipients had a PGA score
of cleared compared to placebo recipients (18.4% and 17.6% vs. 0.4% all p<0.0001) at
week 12 (Keating & Croxtall, 2008). Further, 60.4% of patients receiving ustekinumab
45 mg and 61.7% of ustekinumab 90 mg recipients had a PGA score of cleared or
minimal compared to 3.9% of those that received placebo (Cada et al., 2010; Keating &
Croxtall, 2008). Significant improvements in mean DLQI were observed as early as week
2 in both ustekinumab groups, and by week 12, 53.1% of patients receiving ustekinumab
45 mg and 52.4% receiving ustekinumab 90 mg achieved a DLQI score of 0 or 1 (no
negative effect on patient’s life) compared to 6% receiving placebo (P<0.001) (Cada et
al., 2010; Lebwohl et al., 2009). The mean DLQI score changes of -8 and -8.7 for the 45
mg dose and 90 mg dose, respectively, indicate a clinically meaningful improvement (≥ 5 points) (P<0.001) (see Table 2) (Cada et al., 2010; Lebwohl et al., 2009).

<table>
<thead>
<tr>
<th>Week 12</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Usteakinumab</td>
<td>Placebo</td>
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<th>83.5%</th>
<th>85.9%</th>
<th>10.2%</th>
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<tr>
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<td>66.4%</td>
<td>3.1%</td>
<td>71.2%</td>
<td>78.6%</td>
<td>65.9%</td>
<td>84.9%</td>
<td></td>
</tr>
<tr>
<td>PASI 90</td>
<td>41.6%</td>
<td>36.7%</td>
<td>2.0%</td>
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<tr>
<td>Mean PASI improvement</td>
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<td>77.2%</td>
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<th>0.4%</th>
<th>26.4%</th>
<th>35.4%</th>
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</thead>
<tbody>
<tr>
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<td>61.7%</td>
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<td>58.8%</td>
<td>66.3%</td>
<td>61.0%</td>
<td>73.1%</td>
<td></td>
</tr>
<tr>
<td>Marked or severe</td>
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<td>5.5%</td>
<td>41.2%</td>
<td>6.0%</td>
<td>2.1%</td>
<td>0.8%</td>
<td>1.7%</td>
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<table>
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<tr>
<th>DLQI</th>
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<th>-8</th>
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<th>-9.6</th>
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<th>-9.6</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>DLQI score of 0 or 1</td>
<td>53.1%</td>
<td>52.4%</td>
<td>6.0%</td>
<td>58.6%</td>
<td>69.0%</td>
<td>60.2%</td>
<td>76.3%</td>
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</tbody>
</table>

*Note: PASI = Psoriasis Area and Severity Index; PGA = Physician Global Assessment. DLQI = Dermatology Life Quality Index*
Phase-III Trial, PHOENIX 2

Due to the success of PHOENIX 1, ustekinumab was then assessed in a nearly identical phase III, three part, randomized, double-blind, placebo-controlled, multicenter study, PHOENIX 2, involving 1,230 patients with moderate-to-severe psoriasis with a PASI score of at least 12. In the first phase (weeks 0 to 12), patients were randomized to receive subcutaneous ustekinumab 45 mg (n=409) or 90 mg (n=411) or placebo (n=410) at weeks 0 and 4 (Elliott et al., 2009; Weber & Keam, 2009). In the second phase (weeks 12 to 28), ustekinumab was administered every 12 weeks in the ustekinumab 45 mg and 90 mg dosing groups, while patients who initially received placebo were randomized to receive ustekinumab 45 mg or 90 mg at weeks 12 and 16, then every 12 weeks until the end of the phase (Elliott et al., 2009; Weber & Keam, 2009). In the third phase (weeks 28 to 52) and unlike the PHOENIX 1 trial, partial responders who achieved a PASI 50 from baseline, but not PASI 75, were re-randomized to receive standard (every 12 weeks) or more frequent (every 8 weeks) ustekinumab maintenance therapy (Elliott et al., 2009; Weber & Keam, 2009). Those patients that failed to achieve PASI 50 at week 28 were withdrawn from the trial while those achieving PASI 75 continued on ustekinumab maintenance therapy (every 12 weeks) until the end of the phase (Weber & Keam, 2009). Again, the primary endpoint was the proportion of patients achieving PASI 75 at 12 weeks, and major secondary endpoints were the proportion of patients achieving a PGA score of 0 or 1 at 12 weeks, the change from baseline in patient-assessed DLQI score, and the number of PASI 75 responses between weeks 40 and 52 in partial responders during the dosage intensification phase (Weber & Keam, 2009).
The primary endpoint was achieved by more patients in both ustekinumab groups and was more effective than placebo as assessed by PASI response, PGA, and change in DLQI score (Cada et al., 2010). By week 12, PASI 75 was achieved by 66.7% and 75.7% of patients receiving ustekinumab 45 mg and 90 mg, respectively compared to only 3.7% of those receiving placebo (P<0.0001) (Cada et al., 2010; Chien et al., 2009; Keating & Croxtall, 2008; Krulig & Gordon, 2010; Reich et al., 2009). By week 28, 69.9% and 78.9% of patients that were moved from placebo to ustekinumab 45 mg or 90 mg at week 12 achieved PASI 75 (Cada et al., 2010). Maximum efficacy (PASI 75 in 74.9% and 83.5% for 45 mg and 90 mg groups, respectively) was observed at week 20 for both dosing regimens (Krulig & Gordon, 2010). At week 28, 22.7% of patients in the 45 mg dosage group and 15.8% of patients in the 90 mg dosage group were identified as partial responders and re-randomized for dose intensification (Cada et al., 2010; Krulig & Gordon, 2010). Partial responders tended to have higher body weight, more marked or severe disease, higher incidence of psoriatic arthritis, and a higher likelihood of preceding failure with at least one systemic treatment compared with patients who responded by week 28 (Cada et al., 2010; Krulig & Gordon, 2010). Partial responders also had lower serum drug levels at week 28 compared to responders and they were also more likely to have antibodies against ustekinumab (Cada et al., 2010; Krulig & Gordon, 2010). Dose intensification, in partial responders, from 45 mg every 12 weeks to 45 mg every 8 weeks did not show increased efficacy, however; dose intensification from 90 mg every 12 weeks to 90 mg every 8 weeks did increase the response rate (68.8% PASI 75 response with re-randomization to every 8 weeks vs. 33.3% PASI 75 response with re-randomization to dosing every 12 weeks) (Cada et al., 2010; Krulig & Gordon, 2010).
This shows that while treatment with ustekinumab every 12 weeks is beneficial for most patients with moderate-to-severe psoriasis, increasing the dosage to once every 8 weeks may be helpful in partial responders (Chien et al., 2009). Patients who achieved a PASI 75 score by week 28 sustained their clinical improvement through the end of the study (Krulig & Gordon, 2010). When results of this study were assessed by body weight, PASI 75 response rates in patients weighing 100 kg (220 lbs) or less were statistically equal in the 45 mg group and the 90 mg group (73% and 78%), but were higher in the 90 mg dosage group (71%) than the 45 mg group (49%) in patients weighing more than 100 kg (Cada et al., 2010).

The results of the other secondary endpoints favored ustekinumab over placebo and again indicated its efficacy. Significantly more 45 mg or 90 mg ustekinumab had a PGA score of cleared compared to placebo recipients (22.7% and 28% vs. 0%, all P<0.0001) at week 12 (Cada et al., 2010). Furthermore, 68.0% of patients receiving ustekinumab 45 mg and 73.5% of patients receiving ustekinumab 90 mg had a PGA score of cleared or minimal compared to only 4.9% of those receiving placebo (Cada et al., 2010; Krulig & Gordon, 2010). As in the PHOENIX 1 trial, significant improvements in mean DLQI were observed. By week 12, 55.3% of patients receiving ustekinumab 45 mg and 56.4% receiving ustekinumab 90 mg achieved a DLQI score of 0 or 1 compared to 3.2% receiving placebo, and these numbers rose to 63.4% and 64.3% by week 28 for the 45 mg and 90 mg dosing groups, respectively (Cada et al., 2010; Yeilding et al., 2011). Patients that initially received placebo and crossed over to ustekinumab at week 12, subsequently achieved marked improvements in DLQI (Yeilding et al., 2011). The mean change in DLQI scores at week 12 were -9.3, -10, and -0.5 for the ustekinumab 45
mg and 90 mg groups and placebo group, respectively (Cada et al., 2010). By week 28, those values had risen to -9.5 and -10.3 for the ustekinumab 45 and 90 mg groups, and the patients that were switched to ustekinumab at week 12 achieved a mean change in DLQI of -9.2 and -8.9 from baseline, further evidence of its efficacy (see Table 3) (Cada et al., 2010).

In addition to the secondary endpoints, the PHOENIX 2 trial also sought to analyze the role that ustekinumab played in depression and anxiety symptoms in psoriasis patients. Based on the analyses of the Hospital Anxiety and Depression Scale (HADS), roughly one-third of the patients entering the PHOENIX 2 trial reported mild-to-severe symptoms of anxiety and one-quarter of patients reported mild-to-severe symptoms of depression (Yeilding et al., 2011). By week 12, the overall proportions of ustekinumab-treated patients exhibiting symptoms decreased by 34% for anxiety and 55% for depression compared to the proportions of placebo treated patients with anxiety and depression that showed an increase of 1% in anxiety and 10% in depression (Yeilding et al., 2011). The PHOENIX 1 and PHOENIX 2 trials indicate that ustekinumab made significant and meaningful improvements in both the physical and psychosocial aspects of life in patients with moderate-to-severe psoriasis.

<table>
<thead>
<tr>
<th></th>
<th>Week 12</th>
<th></th>
<th>Week 28</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ustekinumab</td>
<td></td>
<td>Ustekinumab</td>
<td></td>
<td>Ustekinumab</td>
<td>Placebo to ustekinumab</td>
</tr>
<tr>
<td></td>
<td>45 mg (n = 409)</td>
<td>90 mg (n = 411)</td>
<td>45 mg (n = 397)</td>
<td>90 mg (n = 400)</td>
<td>45 mg (n = 193)</td>
<td>90 mg (n = 194)</td>
</tr>
<tr>
<td>PASI 50</td>
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<td>92.9%</td>
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<td>93.3%</td>
</tr>
<tr>
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<td>66.7%</td>
<td>75.7%</td>
<td>3.7%</td>
<td>69.5%</td>
<td>78.5%</td>
<td>69.9%</td>
</tr>
<tr>
<td>PASI 90</td>
<td>42.3%</td>
<td>50.9%</td>
<td>0.7%</td>
<td>44.8%</td>
<td>54.3%</td>
<td>42.5%</td>
</tr>
<tr>
<td>PASI 100</td>
<td>18.1%</td>
<td>18.2%</td>
<td>0.0%</td>
<td>18.6%</td>
<td>29.5%</td>
<td>15.5%</td>
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<tr>
<td>Mean PASI improvement</td>
<td>77.0%</td>
<td>82.1%</td>
<td>4.9%</td>
<td>79.8%</td>
<td>84.8%</td>
<td>79.7%</td>
</tr>
<tr>
<td>PGA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>22.2%</td>
<td>34.3%</td>
<td>23.8%</td>
</tr>
<tr>
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<td>4.9%</td>
<td>61.2%</td>
<td>70.0%</td>
<td>64.8%</td>
</tr>
<tr>
<td>Marked or severe</td>
<td>3.7%</td>
<td>2.4%</td>
<td>36.1%</td>
<td>2.0%</td>
<td>2.0%</td>
<td>1.6%</td>
</tr>
<tr>
<td>DLQI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean change in DLQI score</td>
<td>-9.3</td>
<td>-10</td>
<td>-0.5</td>
<td>-9.5</td>
<td>-10.3</td>
<td>-9.2</td>
</tr>
<tr>
<td>DLQI score of 0 or 1</td>
<td>55.3%</td>
<td>56.4%</td>
<td>3.2%</td>
<td>63.4%</td>
<td>64.3%</td>
<td>46.6%</td>
</tr>
</tbody>
</table>

Note: PASI = Psoriasis Area and Severity Index; PGA = Physician Global Assessment. DLQI = Dermatology Life Quality Index
Comparator Trial, ACCEPT

The PHOENIX trials indicated the effectiveness of ustekinumab in the treatment of moderate-to-severe psoriasis compared to placebo, with the clinical benefits being maintained for at least a year in most patients and extending beyond these measures to include a patient’s quality of life. However, these data do not represent the real-world environment where new treatments are typically compared to the standard of care. The data from the Active Comparator (CNTO 1275/Enbrel) Psoriasis Trial provides a useful basis to analyze the effectiveness and long term economic impact using head-to-head trial data to compare ustekinumab and etanercept (proprietary commercial name Enbrel, Pfizer Inc., New York, NY) in patients that had an inadequate response to, were intolerant to, or have contraindications to at least one conventional systemic therapy or phototherapy, such as PUVA (psoralen plus ultraviolet A rays) (Pan et al., 2011).

Etanercept is a receptor protein, TNF-α inhibitor that is the most commonly used and recommended biologic agent for the moderate-to-severe psoriasis population and was thus selected as the comparator for the ACCEPT trial. The double blind, multicenter ACCEPT trial randomized 903 patients to receive either subcutaneous ustekinumab 45 mg (n=209) or 90 mg (n=347) at weeks 0 and 4, or subcutaneous etanercept 50 mg twice weekly for twelve weeks (n=347) with assessments made through 12 weeks (Cada et al., 2010; Weber & Keam, 2009). The primary endpoint was the proportion of patients that achieved PASI 75 at 12 weeks (Cada et al., 2010; Pan et al., 2011; Weber & Keam, 2009). Pan et al., 2011 then used the data from the ACCEPT trial for the purpose of a cost-utility analysis of etanercept versus ustekinumab 45 mg because the 45 mg dose is
the principally recommended dosage in Canada (Pan et al., 2011). Comparisons were also
generated based on PGA and the safety of each treatment.

The primary endpoint was achieved by more patients in both ustekinumab groups
and was more effective than etanercept as assessed by PGA (Cada et al., 2010; Keating &
Croxtall, 2008; Pan et al., 2011; Weber & Keam, 2009). By week 12, PASI 75 was
achieved by 67.5% and 73.8% of patients receiving ustekinumab 45 mg and 90 mg,
respectively, compared to 56.8% treated with etanercept (P=0.012 for ustekinumab 45 mg
vs. etanercept; P<0.001 for ustekinumab 90 mg vs. etanercept) (Cada et al., 2010;
Keating & Croxtall, 2008; Pan et al., 2011; Weber & Keam, 2009). Additionally, at week
12, more ustekinumab 45 or 90 mg recipients than etanercept recipients had a PGA score
of 0 or 1 (65.1% and 70.6% vs. 49%) and achieved a PASI 90 or greater from baseline
(36.4% and 44.7% vs. 23.1%) (Cada et al., 2010; Keating & Croxtall, 2008; Pan et al.,
2011; Weber & Keam, 2009). In addition to exceeding the effectiveness of etanercept,
patients receiving ustekinumab 45 mg or 90 mg had fewer infections requiring treatment
(8.6% and 8.9% vs. 9.8%) and fewer injection site reactions (2.9% 45 mg ustekinumab
vs. 22.2% etanercept) (see Table 4) (Cada et al., 2010; Pan et al., 2011). Although the
financial comparison is made using the Canadian dollar, the analysis itself is still relevant
in the United States because it offers an approach to highlight the financial aspect of the
treatment options. The monitoring tests and physician visits for etanercept and
ustekinumab during the initial trial period of the model were the same as well as in the
post-trial maintenance period (Pan et al., 2011). The 45 mg unit price of ustekinumab
was $4200 and the 50 mg unit price for an etanercept prefilled syringe was $381.97
(manufacturer price list) and the drug costs were calculated for the initial trial and
maintenance periods (Pan et al., 2011). Over the life of the trial, a patient receiving ustekinumab 45 mg (dosed at weeks 0 and 4), compared to a patient receiving etanercept (dosed twice weekly from week 0 to week 12), would save over $1000 and during the maintenance period a patient receiving ustekinumab 45 mg (dosed at weeks 16 and 28), compared to a patient receiving etanercept (dosed weekly from week 12 to week 28), would save over $2000. This indicates that due to lower cost and better outcomes, that treatment with ustekinumab is a more cost effective and superior treatment option than etanercept for moderate-to-severe psoriasis.


<table>
<thead>
<tr>
<th></th>
<th>Ustekinumab 45 mg</th>
<th>Ustekinumab 90 mg</th>
<th>Etanercept</th>
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<tr>
<td>PASI 75</td>
<td>67.5%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>73.8%&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>PASI 90</td>
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</tr>
<tr>
<td>PGA: cleared or minimal</td>
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<td>70.6%&lt;sup&gt;b&lt;/sup&gt;</td>
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</tr>
<tr>
<td>Patients with at least 1 infection</td>
<td>28.2%</td>
<td>26.8%</td>
<td>26.8%</td>
</tr>
<tr>
<td>Patients with at least 1 infection requiring treatment</td>
<td>8.6%</td>
<td>8.9%</td>
<td>9.8%</td>
</tr>
</tbody>
</table>

<sup>Note:</sup> PASI = Psoriasis Area and Severity Index; PGA = Physician Global Assessment.
<sup>a</sup>P = 0.0012 vs etanercept. <sup>b</sup>P < 0.001 vs etanercept.

Subcutaneous ustekinumab 45 mg or 90 mg was generally well tolerated and most adverse events that did occur were mild. The most frequent treatment-related adverse events that occurred more commonly in ustekinumab treated patients than in placebo were headache, arthralgia, nasopharyngitis, and upper respiratory tract infections (Keating & Croxtall, 2008; Weber & Keam, 2009). In the PHOENIX trials there were no
significant differences between ustekinumab and placebo in the incidence of infection (22-31% vs. 20% and 27%) and the injections were well tolerated with approximately only 1% having a reaction (Keating & Croxtall, 2008; Weber & Keam, 2009; Yeilding et al., 2011). In the ACCEPT trial, the most common adverse events with ustekinumab or etanercept reported by ≥5% of patients at week 12 were headache (13% vs. 11%), nasopharyngitis (10% vs. 8%), upper respiratory tract infections (6% vs. 6%), back pain (5% vs. 2%), and pruritis (5% vs. 4%) (Keating & Croxtall, 2008; Weber & Keam, 2009). Approximately 10% of patients in each group had an infection requiring treatment, and malignancies were diagnosed in <1% of ustekinumab recipients (three cutaneous and one systemic malignancy) and no etanercept patients (Keating & Croxtall, 2008; Weber & Keam, 2009). The immunogenicity rates were low, with roughly 5% of patients developing anti-ustekinumab antibodies by the end of both PHOENIX trials (Keating & Croxtall, 2008; Weber & Keam, 2009; Yeilding et al., 2011).

Ustekinumab is now FDA approved for use in adult patients with moderate-to-severe plaque psoriasis. The recommended dosage for patients weighing 100 kg (220 lbs) or less is 45 mg initially and 4 weeks later, followed by 45 mg every 12 weeks (Cada et al., 2010; Weber & Keam, 2009). For patients weighing over 100 kg (220 lbs), the recommended dosage is 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks (Cada et al., 2010; Weber & Keam, 2009). After the initial dosing schedule, ustekinumab has a favorable dosing regimen in comparison to other biologics treatments like etanercept that is dosed subcutaneously weekly, adalimumab (anti-TNF-α) which is dosed subcutaneously every other week, infliximab (anti-TNF-α) which is dosed intravenously every 8 weeks, or alefacept (fusion protein that interferes with lymphocyte
activation) which is dosed intramuscularly weekly for 12 weeks with a 12-week break between courses (Cada et al., 2010).
CLINICAL TRIALS OF USTEKINUMAB FOR MULTIPLE SCLEROSIS

There have been two clinical trials to determine the safety and efficacy of ustekinumab for the treatment of relapsing-remitting multiple sclerosis (MS); a small phase I trial (n=20) that was discontinued with no data published; and a larger phase II trial. The clinical efficacy was assessed based on the cumulative number of gadolinium-enhancing (Gd-enhancing) T1-weighted lesions on serial cranial magnetic resonance imaging (MRI), the total number of MS relapses, and the change in Kurtzke’s expanded disability status scale (EDSS) score (Elliott et al., 2009; Segal et al., 2008). Gadolinium is a chemical compound given during MRI scans that highlights areas of inflammation to show active lesions which represent a breakdown of the blood-brain barrier. It is estimated that gadolinium will enhance lesions for six weeks or less and allow the doctor to tell which lesions are active and which are inactive. This allows the doctor to identify recent disease activity and determine if a relapse is occurring (Stachowiak, 2007). Kurtzke’s EDSS score is scaled from 0 (healthy) to 10 (death) and based on eight functional systems measured by a trained independent neurologist (Segal et al., 2008).

A randomized, double-blind, placebo-controlled, multicenter, phase II trial enrolling 249 patients with a Kurtzke’s EDSS score between 0 and 6.5 and at least two relapses of MS in the previous 2 years or one relapse in the previous 6 months was conducted. Following an induction phase where all patients received subcutaneous injections of placebo or ustekinumab weekly from baseline to week 3, patients then
received their corresponding treatment of placebo (n=49) or ustekinumab 27 mg (n=50), 90 mg (n=50), or 180 mg (n=50) every 4 weeks, or ustekinumab 90 mg (n=50) every 8 weeks (Elliott et al., 2009; Segal et al., 2008). From weeks 7 to 19, all groups received corresponding injections every 4 weeks except the ustekinumab 90 mg every 8 weeks group who received placebo on weeks 7 and 15 (Segal et al., 2008). The primary endpoint was the cumulative number of new Gd-enhancing T1-weighted lesions from baseline to week 23 on a serial cranial MRI (Segal et al., 2008). Major secondary endpoints were the total number of MS relapses and the change in EDSS score from baseline to week 23 (Segal et al., 2008).

The primary endpoint was not achieved by more patients receiving ustekinumab than placebo as there were no significant or clinically meaningful differences in the cumulative number of Gd-enhancing T1-weighted lesions on serial MRI (Elliott et al., 2009). By week 23, 61.2% of patients receiving placebo were found to have new Gd-enhancing T1-weighted lesions compared to 58.0%, 64.0%, and 62.0% of patients receiving ustekinumab 27 mg, 90 mg, and 180 mg every 4 weeks, respectively, and 72.0% of patients that received ustekinumab 90 mg every 8 weeks (Segal et al., 2008).

The results of the major secondary endpoints were also not in favor of treatment with ustekinumab. By week 23, 18.4% of patients receiving placebo had one or more clinical relapses compared to 20.0%, 24.0%, and 18.0% of patients receiving ustekinumab 27 mg, 90 mg, and 180 mg every 4 weeks, respectively, and 26.0% of patients receiving ustekinumab 90 mg every 8 weeks (Segal et al., 2008). Furthermore, no median change in Kurtzke’s EDSS score was observed from baseline to week 23 in any group (Segal et al., 2008). Due to the lack of efficacy, the long-term safety follow up
was terminated at week 37 as adverse events occurred in 85% of ustekinumab patients compared to 77.6% of placebo patients (Elliott et al., 2009; Segal et al., 2008). The most frequent adverse events that occurred more commonly in ustekinumab recipients than placebo recipients were injection-site reactions (22.5% vs. 8.2%), headache (14.0% vs. 4.1%), and fatigue (13.0% vs. 2.0%) (Elliott et al., 2009; Segal et al., 2008). Overall, ustekinumab was generally well-tolerated and despite its lack of efficacy did not appear to worsen MS conditions.

The lack of therapeutic benefit of ustekinumab for treating MS is surprising in light of strong preclinical animal and human model rationale for the use of an anti-IL-12/23p40 antibody as treatment. There are multiple hypotheses that exist to explain the lack of effectiveness of ustekinumab for treating MS. The first is that T₇₁ and Tᵥ₁₇ pathways are not crucial in the pathogenesis of MS disease thus indicating that the IL-12/23 pathway may not be the major T cell driver of the disease (Elliott et al., 2009; Segal et al., 2008). Although IL-12p40 cytokines and myelin-specific CD4+ T cells are essential for the manifestations of conventional experimental autoimmune encephalitis (EAE) this may not be the case for MS, which calls into question the true validity of EAE as a model, especially with recent findings that implicate B cell involvement in MS (Segal et al., 2008). A second hypothesis is that the timing of administration of the drug was too late in the progression of MS to be effective (Elliott et al., 2009; Segal et al., 2008). MRI studies have shown that most MS lesions accumulate in the absence of clinical signs or episodes, which means, that patients who were not showing clinical disease prior to the trial and presented with new lesions as the trial progressed, were actually having the lesions develop much earlier (Segal et al., 2008). With this
information and prior animal studies, ustekinumab may be better suited as a preventive treatment for those who have a genetic or familial history of MS (Segal et al., 2008). The final and most plausible hypothesis is that ustekinumab, with a molecular weight of 150 kDa (kilodaltons) did not cross the blood-brain barrier and could therefore not reach its site of action (Elliott et al., 2009; Segal et al., 2008). IL-12p40 mRNA has been found in active MS lesions indicating its role in disease and studies have shown that the breakdown of the blood-brain barrier occurs after the demyelinating lesion begins to form which indicates that inflammatory events are initiated in the central nervous system by resident cells or hematopoietic cells behind the blood-brain barrier (Segal et al., 2008). Although active MS lesions are associated with increases in cerebrovascular permeability, if IL-12 and IL-23 production are needed in such early steps of disease and lesion formation, then circulating anti-IL-12/23 antibodies may not cross the blood-brain barrier in enough time to take effect (Segal et al., 2008).
CLINICAL TRIALS OF USTEKINUMAB FOR CROHN’S DISEASE

There have been two clinical trials to determine the safety and efficacy of ustekinumab for the treatment of Crohn’s Disease (CD), an early phase IIa trial to examine the clinical effects of ustekinumab in patients with moderate-to-severe CD and a phase IIb trial that assessed the effects of ustekinumab in adults with moderate-to-severe CD who were unresponsive to anti-tumor necrosis factor (TNF) treatment. The clinical efficacy for both trials was based on the Crohn’s Disease Activity Index (CDAI) in which scores are based on 8 factors, including the number of liquid or soft stools each day for seven days, presence of complications, abdominal pain each day for seven days, and presence of an abdominal mass, with totals ranging from 0 to 600 with higher scores indicating worse disease and a 50-point change indicating the minimal clinically significant difference (Elliott et al., 2009; Sandborn et al., 2012; Toedter et al., 2009). In addition, both trials analyzed serum levels of C-reactive protein (CRP) (Sandborn et al., 2012; Toedter et al., 2009). CRP is an acute-phase serum protein produced by the liver in response to inflammatory cytokines. Elevated levels of CRP reflect inflammatory processes, and correlate with CD activity and gastrointestinal inflammation (Toedter et al., 2009).

A randomized, double-blind, placebo-controlled, multicenter, phase IIa trial was conducted by enrolling 104 patients with moderate-to-severe CD and a CDAI score of \( \geq 220 \) and \( \leq 450 \) into a primary group with a subgroup of 49 infliximab-experienced
patients being identified within the primary group (Elliott et al., 2009; Toedter et al., 2009). Patients were randomized to receive subcutaneous (SC) placebo, SC ustekinumab, intravenous (IV) placebo, or IV ustekinumab (Elliott et al., 2009; Toedter et al., 2009). The ustekinumab SC group received 90 mg ustekinumab at weeks 0, 1, 2, and 3 followed by placebo at weeks 8, 9, 10, and 11 while the IV group received 4.5 mg/kg ustekinumab at week 0 followed by placebo at week 8 (Elliott et al., 2009; Toedter et al., 2009). The placebo SC group received placebo at weeks 0, 1, 2, and 3 followed by SC ustekinumab 90 mg at weeks 8, 9, 10, and 11 while the IV group received placebo at week 0 followed by IV ustekinumab 4.5 mg/kg at week 8 (Elliott et al., 2009; Toedter et al., 2009). A small, secondary population of 27 primary or secondary nonresponders to the anti-TNF agent, infliximab, were randomized to receive open-label SC ustekinumab at weeks 0, 1, 2, and 3 or IV ustekinumab 4.5 mg/kg at week 0 (Elliott et al., 2009). The primary end point was clinical response at week 8 which was defined as a reduction of ≥25% and ≥70 points from the baseline CDAI score at week 8 (Elliott et al., 2009; Toedter et al., 2009).

The primary endpoint was not achieved; the clinical response rates were not significantly different between the combined SC and IV ustekinumab groups and the combined SC or IV placebo groups even though there was a greater proportion of ustekinumab-treated patients that achieved clinical response than placebo-treated patients (49.0% vs. 39.6%, respectively; P=0.34) (Toedter et al., 2009). There was however, a statistically significant difference in clinical response rates between the ustekinumab and placebo groups in a subgroup of infliximab-experienced patients from the primary group (59.0% vs. 26.0%, respectively; P=0.022) (Elliott et al., 2009; Toedter et al., 2009). In
addition, at week 8, the mean change of CRP concentration in the primary population was -0.3mg/l in the placebo group compared to -3.1 mg/l in the ustekinumab group, and, in the infliximab-experienced subgroup, those that received placebo had a mean increase of 2.0 mg/l in CRP concentration compared to those that received ustekinumab experienced a 2.6 mg/l mean decrease in CRP concentration (Toedter et al., 2009). Again, the change in baseline in CRP concentration was not statistically significant in the primary group (P=0.074), but was statistically significant in the infliximab-experienced subgroup (P=0.004) (Toedter et al., 2009). At week 8, following treatment with SC or IV ustekinumab, clinical response rates in the secondary population were 42.9% and 53.8%, respectively, and they also experienced mean decreases in CRP concentration, with both sets of results being consistent with the primary group (Elliott et al., 2009).

Ustekinumab was generally well-tolerated in patients with CD with similar frequency of adverse events being recorded in patients who received ustekinumab (71.2%) and placebo (78.8%) (Elliott et al., 2009). The most commonly reported adverse events were gastrointestinal disorders which were found in 32.7% of patients that received ustekinumab versus 48.1% that received placebo (Elliott et al., 2009). It was noted that treatment effects were greatest in patients who had previously been treated with an anti-TNF agent and although the design of this study does not allow clear conclusions about efficacy, this study did demonstrate that ustekinumab may induce clinical response in patients with moderate-to-severe CD, thus warranting further investigation in a larger study (Elliott et al., 2009).

A randomized, double-blind, placebo-controlled, multicenter phase IIb trial enrolling 526 patients who were at least 18 years old, had at least a 3-month history of
CD with a CDAI score of 220 to 450, and were primary nonresponders (did not respond to infliximab), secondary nonresponders (lose response or become intolerant to infliximab over time), or had negative side effects after receiving an anti-TNF agent was conducted with patients receiving IV placebo (n=132) or IV ustekinumab 1 mg/kg (n=131), 3 mg/kg (n=132), or 6 mg/kg (n=131) at week 0 for the induction phase (weeks 0 to 8) (Sandborn et al., 2012). During the maintenance phase (weeks 8 to 36), patients who had a response to ustekinumab at 6 weeks underwent a second randomization to receive SC ustekinumab 90 mg or placebo at weeks 8 and 16 with efficacy assessed at week 22 (Sandborn et al., 2012). Patients who had a response to placebo at 6 weeks would receive SC placebo at weeks 8 and 16 while those who initially received placebo and did not have a response would receive SC ustekinumab 270 mg at week 8 and SC ustekinumab 90 mg at week 16 (Sandborn et al., 2012). The primary end point was a clinical response at week 6 which was defined as a ≥100 point decrease from the baseline CDAI score with patients who had a baseline CDAI score of 248 points or less being considered to have a clinical response if the CDAI score was less than 150 (Sandborn et al., 2012). Major secondary endpoints were clinical remission at week 6, defined as a CDAI score of <150 points, clinical response at week 4, and clinical remission at week 22 among patients with a response to ustekinumab at week 6 (Sandborn et al., 2012).

The primary endpoint was achieved by significantly more patients receiving ustekinumab 6 mg/kg than among those receiving placebo (39.7% vs. 23.5%, P=0.0005) (Sandborn et al., 2012). Due to the pre-specified analysis plan, the non-significant finding for the dose of ustekinumab 3 mg/kg (34.1%, P=0.06) prevents the assertion of significance for the 1 mg/kg dose (36.6%, P=0.02) (Sandborn et al., 2012).
Among the major secondary endpoints, the rates of clinical response at week 4 and the rates of clinical remission at week 6 were not significantly different between patients in the ustekinumab groups and those in the placebo group (Sandborn et al., 2012). There was however a greater proportion of patients receiving ustekinumab 6 mg/kg that achieved a 70-point decrease in CDAI score than those receiving placebo (Sandborn et al., 2012). Furthermore, the mean reductions in CDAI score were significantly greater among patients receiving ustekinumab 6 mg/kg compared to placebo recipients (Sandborn et al., 2012). Among patients with a response to ustekinumab at week 6, 41.7% of patients receiving ustekinumab 90 mg during the maintenance phase achieved clinical remission at week 22 compared to 27.4% of patients receiving placebo (P=0.03) (Sandborn et al., 2012). In addition, the proportion of patients who had a clinical response at week 22 was significantly greater in the ustekinumab group than in the placebo group (69.4% vs. 42.5%, P<0.001), and the proportion of patients with a sustained clinical response (clinical response at weeks 8, 12, 16, 20, 22, 28, and 36) was also significantly greater in the ustekinumab group than in the placebo group (55.6% vs. 32.9%, P=0.005) (Sandborn et al., 2012). At week 22, 78.6% of patients who were in clinical remission at week 6 and received ustekinumab during the maintenance phase were able to maintain their state of remission compared to 53.3% of those that were switched to placebo (P=0.06) (Sandborn et al., 2012).

Ustekinumab was generally well tolerated and most adverse events that did occur were mild. The most frequent treatment-related adverse events that occurred during the induction phase and were more common in ustekinumab treated patients than in placebo were headache (7.6% vs. 6.1), arthralgia (5.6% vs. 3.8%), and nasopharyngitis (5.6% vs.
4.5%) (Sandborn et al., 2012). During the maintenance phase, only arthralgia was seen more commonly in ustekinumab treated patients than in placebo (5.5% vs. 4.1) (Sandborn et al., 2012). Infusion reactions, rates of adverse events, and rates of serious adverse events were similar across all groups but the results are limited due to the small sample size and limited duration of the maintenance phase (Sandborn et al., 2012).

Patients with moderate-to-severe CD that are unresponsive to anti-TNF agents were more likely to have a clinical response to ustekinumab than placebo but were not more likely to achieve clinical remission (Sandborn et al., 2012). Patients who did have a response to ustekinumab during the induction phase were more likely to maintain the response and even achieve remission when the treatment was continued during the maintenance phase (Sandborn et al., 2012). By achieving the primary endpoint in significantly more patients receiving ustekinumab 6 mg/kg than placebo but being unable to identify significant differences in the induction of remission, raises questions about the efficacy of ustekinumab for the treatment of CD, warranting further investigation.
SUMMARY AND PERSPECTIVES

With the global market for psoriasis therapies being valued at $3.5 billion and low satisfaction with current treatments, there was an opportunity for pharmaceutical companies to develop a safer, more highly effective psoriasis treatment option (Reich et al., 2009). Ustekinumab was designed for psoriasis by understanding the roles of IL-12 and IL-23 in the development of disease and is one of the first therapeutic mAbs approved for human use that was developed by using the key principals of modern drug development, and incorporating molecular, pharmacological, and rational drug design (Yeilding et al., 2011). Ustekinumab was found to be safe and effective in early phase trials and moved into the later stages of development. In three late stage trials, it continued to prove effective at treating moderate-to-severe psoriasis and even exceeded the safety and efficacy of the top line treatment option, etanercept, in a head-to-head trial. The benefits extended beyond the attenuation of disease, as was proven by significant improvements in the physical and psychosocial aspects associated with psoriasis, including anxiety and depression (Yeilding et al., 2011). However, clinical trials are always very controlled, with a cohort of stable patients, and co-morbidities, concomitant medications, and specific manifestations, such as erythrodermic and pustular psoriasis, generally included in the exclusion criteria (Vitiello, Grant, & Kerdel, 2011). Furthermore, knowledge concerning its long-term use beyond 76 weeks is lacking. Further studies need to address such questions as: Is this drug safe when used over an
extended period of many years? Can ustekinumab be used in conjunction with other systemic therapies? Is this drug effective at treating other forms of psoriasis (Vitiello et al., 2011)? Despite these questions, ustekinumab has proven its worth as a superior treatment option, with less frequent dosing, and a better safety profile than other currently available biologic agents. With further clinical development, it may set the standard for future treatment compliance and satisfaction.

Ustekinumab was originally developed as a treatment for psoriasis but other animal, clinical, and translational studies indicated its potential as a treatment for other autoimmune disorders such as MS and CD among others. Although ustekinumab was effective at treating EAE in animal models, those positive results did not extend into human trials for the treatment of MS. The exact reason why ustekinumab treatment failed remains unknown, but the studies did offer several key hypotheses which are currently being explored. On the other hand, early-stage clinical trials for the treatment of CD had enough success to warrant further investigation as it decreased signs and symptoms and even induced clinical response. Questions regarding its consistency and true efficacy do however still remain. Multiple, ongoing phase III trials will aim to answer these questions in relation to CD. There are also multiple phase III trials to establish the benefit-risk profile of ustekinumab in psoriatic arthritis (Yeilding et al., 2011). There are currently phase II trials set to evaluate the efficacy of ustekinumab in sarcoidosis, primary biliary cirrhosis, hidradenitis suppurativa, ankylosing spondylitis, and uveitis. Furthermore, there are current, ongoing, phase IV studies to establish the long-term safety of ustekinumab in psoriasis along with phase III trials to study the efficacy of ustekinumab in other forms of psoriasis, such as pustular psoriasis. Due to its
early success in the treatment of psoriasis and an array of current trials, ustekinumab presents a viable, promising, future treatment option for a variety of autoimmune disorders.
REFERENCES


