ABT-874, a fully human monoclonal anti-IL-12/IL-23 antibody for the potential treatment of autoimmune diseases
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ABT-874, a fully human mAb that blocks the binding of IL-12 and IL-23 to their shared IL-12 receptor β1, is currently being developed by Abbott Laboratories for the potential treatment of Crohn’s disease and psoriasis. The compound is currently in phase III clinical trials for psoriasis and phase II trials for Crohn’s disease. ABT-87 was previously being developed for the potential treatment of multiple sclerosis; however, by May 2007, development for this indication was discontinued.

Introduction
IL-12 is a 70 kDa heterodimeric cytokine (p70), comprising a 35-kDa light chain (known as p35 or IL-12α) and a 40-kDa heavy chain (known as p40 or IL-12β) linked by a disulfide bridge. IL-12 was first discovered in 1989 [865725]. p35 is homologous with other single-chain cytokines, whereas p40 is homologous with the extracellular domain of members of the hematopoietic cytokine receptor family [768923]. Production of p35 is rate-limiting and tightly regulated, and requires co-expression of p40 for secretion of biologically active IL-12 [699110]. IL-12 is predominantly produced by dendritic cells (DCs) and phagocytes (monocytes/macrophages and neutrophils) in response to microbial stimulation. It has a critical role in promoting the differentiation of naive CD4+ T-cells into mature T-helper (Th)1 effector cells, and stimulating natural killer (NK)-cells and T-cells to produce IFNγ via the IL-12 receptor, which is composed of two subunits, IL-12Rβ1 and IL-12Rβ2 [768923]. IL-12 overproduction has been correlated with enhanced proinflammatory activities and tissue damage typical of organ-specific autoimmunity in some animal models [263937], [865729], [888303]. Similarly, increased expression of IL-12 has been detected in patients with rheumatoid arthritis (RA) [865726], Crohn’s disease (CD) [865728], psoriasis [865729] and multiple sclerosis (MS) [865731], compared with non-inflammatory controls. Therefore, IL-12 has been proposed to play a major role in the etiology of these autoimmune and inflammatory diseases.

IL-23, a heterodimeric cytokine composed of a p19 subunit and the p40 subunit of IL-12, was discovered in 2000 [865732]. p19 has an overall sequence identity of approximately 40% with the p35 subunit of IL-12. Similarly to IL-12, the formation of biologically active IL-23 requires the synthesis of both p19 and p40 subunits within the same cell [699110]. IL-23 is also expressed predominantly by activated DCs and phagocytic cells [693823]. It binds to a receptor (IL-12R) that is formed by IL-12Rβ1 and a unique receptor subunit, IL-23R. IL-23 affects memory T-cell and inflammatory macrophage function, and stimulates a unique lineage of Th cells (named Th-17) to produce IL-17, a critical regulator in the establishment and perpetuation of autoimmune inflammatory response [693823]. Some studies have suggested that IL-23 rather than IL-12 is the most influential cytokine in several mouse models of autoimmune inflammation [865734], [865735]. Overproduction of IL-23 has been detected in patients with CD [865736], psoriasis [865737], RA [865738] and MS [865739], and is associated with the overproduction of proinflammatory cytokines, such as IL-6, TNFα and IL-17 [693823]. The IL-23R gene on chromosome 1p31 has been reported to be significantly associated with CD; polymorphisms in the gene confer different susceptibilities...
CD, psoriasis, RA and MS are typical T-cell-mediated autoimmune diseases, characterized by an excessive CD4+ Th1 response, resulting in enhanced production of IL-1, IL-6 and TNFα [888304]. Conventional therapy for these diseases often consists of corticosteroids or immunosuppressive drugs, although there is a subset of patients who are unresponsive to these therapies. In addition, the side effects of such drugs (eg, infections) remain a concern [888315]. TNFα inhibitors (eg, etanercept, infliximab and adalimumab) [888304] and IL-6 inhibitors (eg, tocilizumab) [479030] have proven to be effective and have been approved for the treatment of these conditions; however, they are associated with a variety of opportunistic infections, such as tuberculosis [479030], [659381], and not all patients respond well to the therapies, possibly because of underlying genetic differences [888324]. Seeking new treatments, such as the blockade of IL-12 and IL-23, may offer alternative or even better approaches for the treatment of these diseases.

Therapeutic approaches targeting p40 (eg, anti-IL-12/IL-23 p40 antibodies) can prevent the binding of IL-12 and IL-23 to IL-12Rβ1 and thus abrogate their proinflammatory effects [753334]. ABT-874, a fully human mAb against the p40 subunit of IL-12 and IL-23, is currently under development by Abbott Laboratories, under license from Cambridge Antibody Technology Group plc, for the potential treatment of autoimmune diseases, including CD and psoriasis [331466], [525630].

**Synthesis and SAR**

Antibodies to human IL-12 (including p70 and p40) were isolated by screening three separate single-chain variable fragment (scFv) phage display libraries; these were prepared using variable light (V\_\lambda) and variable heavy (V\_\kappa) cDNAs derived from human tonsil cells, peripheral blood lymphocytes and bone-marrow derived lymphocytes. Screening of human V\_\lambda and V\_\kappa cDNA libraries identified a series of anti-IL-12 antibodies. One of these (referred to as Joe 9 or Joe 9 wild-type) had relatively low affinity and a dissociation rate constant (K\_d) of approximately 0.1 sec\(^{-1}\), and was selected for further development. The affinity of Joe 9 was improved by constructing mutants of the heavy and light chain complementarity-determining regions (CDRs), which produced a panel of V\_\lambda and V\_\kappa regions that were assolated and further mutated, yielding panels of anti-human IL-12 antibodies, some of which had increased affinity [889923].

One of these antibodies, referred to as Y61, demonstrated a significant improvement in binding affinity (K\_d of approximately 2 × 10\(^{-4}\) s\(^{-1}\)). The affinity of Y61 was further optimized by individually mutating specific amino-acid residues within the heavy and light chain CDRs that occupied a preferred selective mutagenesis position, contact position and/or a hypermutation position. A Gly to Tyr substitution at position 50 of the light chain CDR2 and a Gly to Tyr substitution at position 94 of the light chain CDR3 resulted in a preferred recombinant neutralizing IgG1 antibody, named J-695 [889923] and later ABT-874 [578232].

**Preclinical development**

The in vitro binding of ABT-874 (presumed to be binding to recombinant human IL-12, as few details are given) was characterized by an association rate constant (K\_a) of 5 × 10\(^{4}\) M\(^{-1}\) s\(^{-1}\), a K\_d of 5.1 × 10\(^{-4}\) sec\(^{-1}\) and a K\_d of 100 pM. The slow K\_d value reportedly resulted in a half-life of the antibody/protein complex of approximately 300 min. ABT-874 was also reported to bind to the p40 subunit of IL-12, and to bind human IL-12 and IL-23 with comparable affinities (no values provided) [594620].

The functional activities of ABT-874 were measured in vitro [594620], [889923]. ABT-874 inhibited the binding of radiolabeled IL-12 to the IL-12Rβ2 on phytohemagglutinin (PHA)-activated lymphoblasts with an IC\_50 value of approximately 11 pM, and inhibited IL-12-stimulated PHA-activated lymphoblast proliferation with an IC\_50 value of approximately 10 pM. ABT-874 also suppressed human IFN\_γ production from IL-12-stimulated, PHA-activated lymphoblasts with an IC\_50 value of approximately 5 pM. In neutralization assays with IL-12 from different species, ABT-874 blocked the function of human, rhesus monkey, cynomolgus monkey and baboon IL-12 (IC\_50 values = 5, 10, 10 and 15 pM, respectively); it was approximately 70-fold less active against canine IL-12 than human IL-12 and did not react with mouse or rat IL-12 [594620]. The binding of ABT-874 to immobilized human IL-12 was blocked by human IL-12 p70 and p40, but not by any other cytokines, such as IL-2, IL-4 and IFN\_γ [889923].

In early in vivo studies, the effects of ABT-874 and the related, but unoptimized, mAb Y61 on IL-12-induced responses were examined in cynomolgus monkey [594620], [889923]. Y61 (1 or 10 mg/kg) significantly reversed IL-12-induced hematological changes (which included decreases in white blood cells, platelets, lymphocyte count and monocyte count) and increased plasma levels of neopterin, a marker of monocyte activation, in response to IFN\_γ [889923]. ABT-874 (0.05, 0.2 or 1.0 mg/kg, either sc or iv) prevented leukopenia and thrombocytopenia associated with human IL-12 administration, and dose-dependently suppressed neopterin production with an ED\_50 value of < 0.05 mg/kg [889923]. Approximately 90% inhibition of IL-12-induced neopterin was achieved by a serum ABT-874 concentration of 1 µg/ml. The two routes of administration were reportedly equally effective [594620].

In a mouse model, ABT-874 (16 ng/kg to 50 µg/kg ip, on days 0, 2 and 4) dose-dependently inhibited IFN\_γ production induced by injection of a chimeric IL-12 protein (composed of murine p35 and human p40 subunits; 5 µg ip, on days 1 to 4) with an ED\_50 value of approximately 1 µg/kg [594620].

Surrogate antibodies homologous to ABT-874 were tested in rodent models because ABT-874 lacks affinity to rodent IL-12. C17.15, a rat anti-mouse-IL-12 antibody, which is highly similar to ABT-874 based on the biomolecular interaction assay, receptor binding assay and PHA blast assay, was
tested in murine models of autoimmune diseases [889923]. In mice with collagen-induced arthritis, C17.15 (10 mg/kg ip, on alternate days from day 1 to 12) significantly delayed the onset and inhibited the severity of arthritis compared with controls. In a mouse model of experimental trinitrobenzene sulfonic acid-induced colitis, single doses of C17.15 (0.1, 0.25, 0.5 or 0.75 mg iv) decreased IFNγ secretion from CD4+ T-cells and IL-12 production from macrophages, significantly increased body weight and reversed histological indicators of colitis [889923]. In a mouse model of experimental autoimmune encephalomyelitis, two surrogate anti-IL-12 p40 antibodies (10F6 and C17.8) significantly reduced disease severity [594620].

Toxicity
In cynomolgus monkeys, ABT-874 was given safely at doses of 0.05, 0.2 or 1.0 mg/kg. In independent toxicity studies, doses of up to 100 mg/kg were reportedly safe in monkeys [889923].

Metabolism and pharmacokinetics
Few details have been published on the pharmacokinetic parameters of ABT-874. In a phase I clinical trial, healthy volunteers (n = 64) were administered ABT-874 at doses ranging from 0.1 to 5.0 mg/kg (sc or iv). Both the Cmax and AUC values increased linearly with increasing doses and the terminal phase half-life was approximately 9 days. A dose of 1 mg/kg was required to maintain a serum antibody concentration of 1 µg/ml [594620], [557257].

Clinical development
Phase I
In a double-blind, crossover, phase I clinical trial, healthy male volunteers (n = 64) were administered ascending doses of ABT-874 (0.1 to 5.0 mg/kg) or placebo. ABT-874 did not increase complement fragment C3a at 15 min post-dosing. C-reactive protein and fibrinogen levels were only increased in individuals in whom symptoms of concurrent infections were observed [889923].

Phase II
CD
A randomized, double-blind, multicenter, placebo-controlled, phase II clinical trial was conducted in patients (n = 79) with moderately active CD, which was defined as a score of 220 to 450 on the CD activity index (CDAI). Patients received seven weekly injections of ABT-874 (1 or 3 mg/kg sc), with either a 4-week interval between the first and second injection (cohort 1) or with no interruption (cohort 2), or placebo. Patients could continue to receive certain medications, such as antibiotics, mesalamine, sulfasalazine and prednisone (≤ 20 mg/day), but could not receive methotrexate, ciclosporin or anti-TNF therapies [578232].

In cohort 1, remission (defined as a CDAI score of ≤ 150) was achieved in 0, 19 and 12% of patients receiving placebo, 1 or 3 mg/kg ABT-874, respectively, at 4 weeks after the first injection. Remission was achieved in 38, 31 and 44% of the respective groups at the time of final injection (9 weeks) and remission was achieved in 13, 19 and 50% of patients at the end of the 18-week follow-up. The clinical response (defined as a reduction in the CDAI score of at least 100 points) rates for this cohort were also higher in the ABT-874-treated groups, but there was no statistical significance in the differences in either response or remission rates between the treatment and placebo groups [578232].

In cohort 2, a clinical response was achieved in 25, 27 and 75% of patients receiving placebo, 1 or 3 mg/kg ABT-874 at the time of final injection (7 weeks), respectively, and was achieved in 25, 20 and 69% of patients in the respective groups at the end of the 18-week follow up. A remission was achieved in 0, 8 and 38% of patients in the respective groups at the time of final injection (7 weeks), and was achieved in 0, 13 and 38%, respectively, at the end of the 18-week follow up. The response rate in the 3-mg/kg group at the end of 7 weeks of treatment were significantly higher than those in the placebo group (75 versus 25%, respectively, p = 0.03). There were no statistically significant differences in remission rates and other response rates between groups, possibly because of the small sample size [578232].

The difference in treatment effects between cohort 1 and cohort 2 may be related to the speed with which maximal serum levels of ABT-874 were attained or sustained [578232].

In a subgroup study (n = 8), treatment with ABT-874 decreased IL-12 (p = 0.03), IFNγ (p = 0.05), TNFα (p < 0.01), IL-6 (p = 0.06), IL-23 (p < 0.03) and IL-17 (p < 0.03) production by mononuclear cells of the colonic lamina propria in seven patients who achieved a clinical response (one patient who did not have a clinical response had an increase in IFNγ secretion and no change in TNFα secretion) [578232], [865736]. ABT-874 also inhibited mucosal histological abnormalities with the mean modified d’Haens score (maximal possible score being 13) decreasing from 6.9 before treatment to 3.6 at the end of treatment (p = 0.06). The histological improvement was characterized by decreased numbers of neutrophils, lymphocytes and plasma cells, and reduced epithelial damage, with the reappearance of goblet cells [578232].

A multicenter, randomized, double-blind, parallel, dose-ranging, phase IIb clinical trial was ongoing at the time of publication. The study aimed to compare the efficacy, safety and pharmacokinetics of intravenous infusions of ABT-874 (200, 400 or 700 mg iv, every 4 weeks) with placebo in patients with moderate to severe CD. The planned enrollment was 420 patients and study completion was estimated to be in December 2010 [883697].

Psoriasis
A double-blind, placebo-controlled, multicenter, randomized, phase II clinical trial was designed to evaluate the efficacy of ABT-874 in the treatment of patients with moderate to severe plaque psoriasis [824563], [883346]. Adult patients (n = 180) with psoriasis affecting ≥ 10% body surface area, and a psoriasis area and severity index (PASI) score of ≥ 12 were randomized into six groups (n = 30) to receive subcutaneous injections of: (i) ABT-874 (100 mg) every other
The rate of infection ranged from 23 to 43% (n = 64), the most commonly observed adverse events were headache and common cold/bronchitis, neither of which was categorized as severe. ABT-874 was well tolerated, with no individuals withdrawing as a result of adverse events [889923].

A double-blind trial in patients with moderate CD (n = 79) indicated that ABT-874 (1 or 3 mg/kg sc) was well tolerated. The most frequently reported adverse event was a local injection site reaction, which was significantly more common in the ABT-874 groups (77 to 88%) than in the placebo group (25%). The majority of these reactions were mild and responded to symptomatic therapy. The incidence of other adverse events, such as nausea, vomiting, urinary tract infection, cough, headache, fever and fatigue, was not significantly different among the groups. There were no serious infections. In this trial, clinically significant laboratory abnormalities were observed in 27% of patients in all ABT-874-treated groups and in 31% of patients in the placebo group. The most frequent abnormalities were hyperuricemia (17% in the ABT-874 groups and 13% in the placebo group), hypoglycemia (3% in the ABT-874 groups), hyperamylasemia (3% in the ABT-874 groups) and hyperphosphatemia (3% in the ABT-874 groups). None of these abnormalities required withdrawal from the study. Antidrug antibodies were detected in three patients who received ABT-874 (1 mg/kg) and one was considered drug-unrelated [578232].

The safety of ABT-874 in the treatment of psoriasis was evaluated in a phase II clinical trial. During the treatment period (12 weeks), the most common adverse event was injection-site reaction, occurring in 16.7% of patients in the ABT-874 groups and none in the placebo group (p = 0.03). The rate of infection ranged from 23 to 43% in the ABT-874 treatment groups and was 23% in the placebo group, with the most common infection being nasopharyngitis; incidence was 7 to 17% for ABT-874 and 3% for placebo. There were no statistically significant differences for the rate of infections between treatment and placebo groups. No serious infections were reported, and no deaths occurred [824563], [883346].

**Patent summary**
ABT-874 was first claimed in US-06914128 by Abbott (formally BASF AG) and the Genetics Institute LLC (part of Wyeth, which collaborated with Cambridge Antibody to develop other agents). This patent was granted and has an expiry date in March 2020. Also originating from Abbott and Wyeth, and a member of the same patent family, WO-00056772 discloses human antibodies binding human IL-12, methods for their production and their use in IL-12-related diseases, such as RA, CD and MS. Both cases list Cambridge Antibody (now part of AstraZeneca plc) as an affiliate.

Subsequent claims are made by Abbott in WO-200701462, which discloses methods for the synthesis of ABT-874, and by Wyeth in WO-2007076062, which discloses reduced viscosity formulations of ABT-874 and other mAbs.
Current opinion

As anticipated, blockade of the binding of IL-12/IL-23 to their shared receptor IL-12Rβ1 by ABT-874 has resulted in significant clinical efficacy in the treatment of CD and psoriasis in phase II clinical trials. The drug is well tolerated and significantly inhibits the production of proinflammatory cytokines, including IL-12, IFN-γ, TNFα, IL-23 and IL-17, by mononuclear cells. The efficacy and safety of ABT-974 in MS and RA has not been reported, even though the clinical trials have been completed (the MS trial) or implemented for more than 5 years (the RA trial). The reasons for this are unknown.

Results from animal studies have suggested that IL-12 has a biphasic nature as both a proinflammatory and anti-inflammatory mediator during the onset and progression of chronic inflammation. IL-12-deficient p35−/− mice developed more severe collagen-induced arthritis and an increase in IL-17-producing CD4+ T-cells, as well as elevated mRNA expression of the proinflammatory cytokines TNFα, IL-1β, IL-6 and IL-17 in affected tissues [865735]. A low dose of IL-12 may act as a proinflammatory mediator able to drive inflammatory responses in collagen-induced arthritis, whereas a high dose of IL-12 may attenuate arthritic inflammation [865741]. In contrast, IL-23 has a consistent proinflammatory effect [693823], [865734]. Therefore, the clinical efficacy of ABT-874 may predominantly be the result of inhibition of IL-23, rather than IL-12. This needs to be confirmed by clinical studies.

Furthermore, studies using IL-12 knockout mice have suggested that IL-12, through induction of IFN-γ, plays a key role in the host defense of mice against a variety of intracellular bacterial, viral, fungal and parasitic pathogens [865729], [768923]. Studies in individuals with genetic deficiencies in p40 have demonstrated that these patients display a syndrome characterized by predisposition to infection by BCG, non-tuberculous mycobacteria and Salmonella [768923], [865729]. Vigilance for the occurrence of such infections in patients treated with anti-IL-12 p40 agents is warranted, although no increased susceptibility to infections has been reported in ABT-874 trials. Compared with IL-12, IL-23 may play a limited role in host defense [768931]; therefore, antagonists of IL-23 p19 represent viable candidates not only to ameliorate inflammation, but also leave the IL-12/IFN-γ axis intact, thereby being less likely to compromise immunity to these opportunistic pathogens.

Endogenous IL-12 can resist transplantable tumors in most mice and carcinogenesis-induced fibrosarcoma in mouse tumor models. IL-12 treatment inhibits the establishment of tumors or induces the regression of established tumors [768923]. Possible liability to increased incidence of tumors should be monitored over the long term in patients treated with anti-IL-12 p40 agents, including ABT-874, in future clinical studies.

Thus far, several other agents targeting the IL-12/23 pathway have been developed. Ustekinumab (CNT0-1275; Centocor Inc/Janssen-Cilag Ltd) is another fully human IgG1 antibody that has a high affinity for IL-12 p40 and potently inhibits the biological activity of IL-12 and IL-23; it appears to be highly effective and is well tolerated in the treatment of psoriasis, as reported in phase II and III clinical trials [764442]. A phase II clinical trial of ustekinumab in the treatment of CD has also been initiated. The comparability in clinical efficacy and safety between ustekinumab and ABT-874 is unknown. Another comparable drug is apilimod (STA-5326; Synta Pharmaceuticals Corp), an oral small molecule that inhibits IL-12 and IL-23 production through the prevention of nuclear translocation of c-Rel. Preliminary clinical data have suggested that apilimod is effective and safe in the treatment of CD and psoriasis, but seems to have less clinical benefit than ABT-874 or ustekinumab for psoriasis treatment [753334]. An antibody (SMART anti-IL-12 antibody) that is specific for IL-12p70 and not for IL-23 was developed by Protein Design Labs, but has been discontinued possibly because blockage of IL-12 alone is unlikely to be sufficient to achieve efficacy.

There have been no reports about the comparability between IL-12/IL-23 inhibitors and other biological antagonists, such as TNFα and IL-6 inhibitors, in the treatment of the autoimmune diseases. IL-12/IL-23 inhibitors have the potential to be more effective as a consequence of their ability to suppress various pathologically implicated cytokines (IL-12, IL-23, IL-17, IL-6 and TNFα), but conversely, are less safe because of their abrogation of the protective function of IFN-γ. The potential success of these approaches remains to be determined in future clinical trials. In summary, ABT-874 is well tolerated and has significant clinical benefit in the treatment of CD and psoriasis. Its efficacy and safety in the treatment of these and other autoimmune diseases remain to be proven by ongoing phase II and III clinical trials.

Licensing

Abbott Laboratories

In August 1993, Cambridge Antibody and Knoll Pharmaceuticals Ltd (now Abbott) initiated a broad collaboration, giving Abbott the right to select up to six target antigens for which Cambridge Antibody would develop human antibody therapeutics. Cambridge Antibody would receive fees, milestones and royalties on the successful development of any products from this collaboration [525630]. By July 1999, Cambridge Antibody had, in conjunction with BASF Pharma (now Abbott), isolated and optimized ABT-874, with Abbott responsible for further development and marketing [331466], [525630]. In October 2003, Cambridge Antibody received the first payment of royalties from Abbott on sales of a drug (adalimumab) derived from the agreement in the 6-month period ended June 30, 2003. Abbott paid royalties at the minimum level described in the license agreement, which Cambridge Antibody believed was incorrect. The companies started a formal dispute resolution procedure [508894]. In October 2005, Cambridge Antibody and Abbott came to a royalty agreement over adalimumab and
cancelled their Court of Appeal hearings. Abbott would pay Cambridge Antibody: US $255 million to be passed on to licensors (the Medical Research Council, Scripps Institute and Stratagene Corp) in lieu of their entitlement to royalties from January 01, 2005, onwards; five annual sales-contingent payments of US $9.375 million from January 2006, of which US $2 million would go to the licensors; royalties of 2.688% from 01 January 2005; and royalties of 4.75% on future sales of ABT-874 [630430].

### Development status

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### Literature classifications

#### Chemistry

**Study type** | **Result** | **Reference**
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**Synthesis** | Antibodies against IL-12 were isolated from scFv phage display libraries prepared from human tonsil cells, peripheral blood lymphocytes and bone-marrow lymphocytes. The Joe 9 fragment was optimized by mutagenesis of the heavy and light chain CDRs and reassortment of the panel of fragments. The Y61 antibody demonstrated improved binding affinity and was optimized by two amino acid substitutions to yield the IgG1 antibody ABT-874. | 889923

#### Biology

**Study type** | **Effect studied** | **Model used** | **Result** | **Reference**
---|---|---|---|---
**In vitro** | Binding affinity | ABT-874 binding (presumed to be to recombinant human IL-12; few details are available). | ABT-874 bound IL-12 with a $K_{<\text{d}}$ value of $5 \times 10^4$ M$^{-1}$, a $K_{\text{on}}$ value of $5.1 \times 10^3$ s$^{-1}$ and a $K_{\text{off}}$ value of 100 pM. The half-life of the antibody/protein complex was approximately 300 min. ABT-874 bound to the p40 subunit of IL-12, and bound human IL-12 and IL-23 with comparable affinities. | 594620

**Ex vivo** | Activity | ABT-874 incubated with IL-12-stimulated PHA-activated lymphoblasts and IL-12 protein from various species (details not disclosed). | ABT-874 inhibited lymphoblast proliferation ($IC_{50}$ value ~ 10 pM) and suppressed IFN$\gamma$ production ($IC_{50}$ value ~ 5 pM). ABT-874 blocked the function of human, rhesus monkey, cynomolgus monkey and baboon IL-12 ($IC_{50}$ values = 5, 10, 10 and 15 pM, respectively); it was approximately 70-fold less active against canine IL-12 than human IL-12 and did not react with mouse or rat IL-12. | 594620

**In vivo** | Efficacy | Cynomolgus monkeys treated with ABT-874 (0.05, 0.2 or 1.0 mg/kg either sc or iv) before IL-12 stimulation. | ABT-874 prevented human IL-12-induced leukopenia and thrombocytopenia, and dose-dependently suppressed neopterin production ($ED_{50}$ value < 0.05 mg/kg). A 1 $\mu$g/ml serum concentration of ABT-874 inhibited approximately 90% of IL-12-induced neopterin. The two routes of administration were comparably effective. | 889923

**In vivo** | Efficacy | Mice treated with ABT-874 (16 ng/kg to 50 µg/kg ip, on days 0, 2 and 4) and stimulated with chimeric IL-12 protein composed of murine p35 and human p40 subunits (5 mg ip, on days 1 to 4). | ABT-874 dose-dependently inhibited IFN$\gamma$ production ($ED_{50}$ value ~ 1 $\mu$g/kg). | 594620

**In vivo** | Efficacy | A surrogate rat anti-mouse-IL-12 antibody C17.15 was administered to mice in models of collagen-induced arthritis (six doses of 10 mg/kg ip on alternative days) and experimental trinitrobenzene sulfonic acid-induced colitis (single iv dose of 0.1, 0.25, 0.5 or 0.75 mg). | C17.15 significantly delayed the onset and inhibited the severity of experimental arthritis. Histological indicators of experimental colitis were reversed by C17.15 treatment; body weight was increased, and IFN$\gamma$ secretion and IL-12 production were decreased. | 889923
### Pharmacokinetics

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<td>In vivo</td>
<td>Pharmacokinetics</td>
<td>Phase I trial in healthy volunteers (n = 64) administered ABT-874 (0.1 to 5.0 mg/kg sc or iv)</td>
<td>C[C]max and AUC values increased linearly with increasing doses and the terminal phase half-life was approximately 9 days. A dose of 1 mg/kg was required to maintain a serum antibody concentration of 1 µg/ml.</td>
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### Clinical

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<td>Safety</td>
<td>A phase I, double-blind, crossover trial in healthy male volunteers (n = 64) administered ascending doses of ABT-874 (0.1 to 5.0 mg/kg) or placebo.</td>
<td>ABT-874 did not increase complement fragment C3a at 15 min post-dosing. The most common adverse events were mild or moderate headache and common cold/bronchitis. ABT-874 was well tolerated and no individuals withdrew from the study as a result of adverse events.</td>
<td>889923</td>
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<tr>
<td>Safety and efficacy</td>
<td>A phase II, double-blind trial in patients (n = 79) with moderate CD were randomly assigned to receive seven weekly injections (sc) of ABT-874 (1 or 3 mg/kg) or placebo, either with a 4-week interval between the first and second injection (cohort 1) or with no interruption (cohort 2).</td>
<td>In cohort 1, remission was achieved 4 weeks after the first injection, respectively, in 0, 19 and 12% of patients receiving placebo, 1 or 3 mg/kg; 38, 31 and 44% of patients after 9 weeks dosing, and 13, 19 and 50% of patients at the 18-week follow up experienced remission in the respective groups. In cohort 2, a remission was achieved, respectively, in 0, 8 and 38% of patients from placebo, 1 or 3 mg/kg at 7 weeks and 0, 13 and 38% at 18 weeks, respectively. Only the clinical response rate in the 3-mg/kg group at 7 weeks in cohort 2 was significantly superior to placebo (75 versus 25%, respectively, p = 0.03). ABT-874 was well tolerated, causing generally mild injection-site reactions.</td>
<td>578232</td>
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<tr>
<td>Safety and efficacy</td>
<td>A phase II, double-blind, placebo-controlled trial in patients (n = 180) with moderate-to-severe plaque psoriasis, randomized to receive: (i) ABT-874 (100 mg) every other week for 12 weeks, (ii) a single dose of ABT-874 (200 mg) dose at week 0, (iii) ABT-874 (200 mg) every week for 4 weeks, (iv) ABT-874 (200 mg) every other week for 12 weeks, (v) ABT-874 (200 mg) every week for 12 weeks, or (vi) placebo.</td>
<td>A PASI 75 improvement was achieved in 93, 63, 90, 93 and 90% of patients in the respective groups compared with 3% of those receiving placebo (all p &lt; 0.001). More than 50% of the patients in the ABT-874 groups (except group ii) achieved a 90% improvement in skin clearance, compared with none of those receiving placebo. The most common adverse event was injection-site reaction and there were no statistically significant differences in rates of infections between treatment and placebo groups.</td>
<td>883346</td>
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### Associated patent

**Title** Human antibodies that bind human IL-12 and methods for producing.  
**Assignee** BASF AG, Du Fou SL, Genetics Institute Inc  
**Publication** WO-00056772 28-SEP-00  
**Priority** US-1999126603 25-MAR-99  

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