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MONOGRAPH

BRIAKINUMAB

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Human Anti-IL-12/23 Monoclonal Antibody
Treatment of Psoriasis
Treatment of Crohn's Disease

A-796874.0
ABT-874
BSF-415977
J-695
LU-415977
WAY-165772
Ozespa

Immunoglobulin G_1-λ anti-[Homo sapiens interleukin 12 β-subunit (IL12B, IL-12B, IL12 p40, NKSF2, CMLF p40)], Homo sapiens monoclonal antibody; γ_1 heavy chain (1-445) [Homo sapiens VH (IGHV3-30*02(99.00%)-(IGHD)-IGHJ3*01) [8.8.8] (1-115)-IGHG1*03 R120>K(116-445)], (218-216')-disulfide with λ light chain (1'-217')[Homo sapiens V-LAMBDA (IGLV1-44*01 (88.20%)-IGLJ2*01G120>T) [8.3.12] (1'-111')-IGLC2*01 (112'-217')]; (224-224'':227-227'')-bisdisulfide dimer
Immunoglobulin G_1, anti-(human interleukin-12 subunit β (IL-12 subunit p40, CLMF p40 or NKSF2)); human monoclonal γ_1 heavy chain (218-216')-disulfide with human monoclonal λ light chain, dimer (224-224'':227-227'')-bisdisulfide

CAS: 339308-60-0
EN: 272603

SUMMARY

Briakinumab (ABT-874) is a fully human monoclonal antibody targeting the p40 subunit of both interleukin-12 (IL-12) and -23 (IL-23). It is currently being studied in psoriasis and Crohn's disease. Psoriasis is an inflammatory immune-mediated disease that results in erythematous scaly plaques on the body. The pathogenesis is not fully elucidated but is likely driven by Th17 cells, which are activated by IL-23 and other pathways. There are numerous genetic associations with psoriasis, including defects in the p40 subunit of IL-12 and IL-23 and the IL-23 receptor. In up to 20% of patients, psoriatic arthritis may accompany the skin disease. Phase II data and recently published phase III data show very high efficacy for briakinumab in plaque psoriasis, with a 75% improvement in the Psoriasis Area and Severity Index (PASI) in more than 80% of patients. Another anti-p40 antibody, ustekinumab, is currently approved by the FDA for psoriasis. Safety concerns include malignancies, infections and an unexpected increase in major adverse cardiac events (MACE) in briakinumab-exposed patients compared with placebo.

PREPARATION*

Three scFv phage display libraries are screened to isolate IL-12 antibodies. These libraries have been prepared from mRNA derived from human tonsils, tonsil and peripheral blood lymphocytes, and bone marrow-derived lymphocytes. Clone Joe9 is first selected for affinity maturation, and in order to increase its affinity, site-directed mutagenesis on heavy- and light-chain CDR3 is performed. Clones with heavy-chain CDR3 mutations are selected based on their K_{off} rate, and the same procedure is done for the light-chain CDR3 mutated clones. Then, these mutants are combined to form scFvs and the selected scFv clone 101-11 is further mutated on heavy- and light-chain CDR3, obtaining the clone 103-14. Randomized mutagenesis of all light-chain CDRs is then performed and the clone Y61 is selected and subjected to further mutagenesis, to finally obtain briakinumab. To express the whole IgG_1 antibody, a recombinant vector encoding briakinumab heavy and light chains is transfected by the calcium phosphate method into dhfr-CHO cells. Transfectants are selected with methotrexate and two lines, ALP903 and ALP905, are selected to produce briakinumab (1).

BACKGROUND

IL-12 and IL-23 share a common p40 subunit and are both involved in adaptive immune function (2). The effects of IL-12 and IL-23 on inflammation are distinct. IL-12 induces differentiation of naive T cells to T-helper 1 (Th1) cells and activates natural killer (NK) cells (3). IL-23 preferentially stimulates differentiation of naive T cells into effector T-helper cells (Th17), which secrete IL-17, a proinflammatory mediator (4). IL-17 stimulates the production of other cytokines, including IL-22, which leads to keratinocyte proliferation and differentiation, thus producing the clinical phenotype of psoriasis. Psoriatic plaques contain much more IL-23 than IL-12, and genetic linkage in psoriasis has been associated with the IL-23 receptor gene (5, 6). In psoriasis, therefore, IL-23 appears to be the main target of anti-p40 antibodies.

Theoretical safety concerns regarding the IL-12/23 pathway include infections. IL-12 and IL-23 deficiency enhances the susceptibility to

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infectious agents in animal models and humans (3). Humans with IL-12 mutations are susceptible to *Salmonella* and mycobacterial infections but apparently not to other infectious agents (7).

Psoriasis is a T-cell-mediated disease that affects approximately 2% of the population worldwide. Psoriasis has a significant effect on physical and mental function, and may lead to psychosocial and psychological problems (8). Psoriasis should not be considered a disease of the skin alone. Arthritis and other comorbidities, including an independently associated increased risk of cardiovascular disease, make psoriasis more than skin deep (9). Current psoriasis treatments include topical therapy for limited disease and phototherapy and systemic therapies for more widespread involvement (10, 11). Topical therapies are limited by issues with adherence, due to daily or twice-daily application, and local side effects. Oral systemic therapies including methotrexate, ciclosporin and acitretin can be effective in some patients but are limited by side effects and/or efficacy issues. Biologic agents for psoriasis target aspects of the abnormal immune function present in patients with psoriasis (12).

Three TNF inhibitors are approved for use in psoriasis: etanercept, adalimumab and infliximab. TNF inhibitors are also effective in controlling psoriatic arthritis. Alefacept, which targets memory effector T cells, is also approved for use in psoriasis. Efficacy with alefacept, however, is limited. Ustekinumab, an antibody against the p40 subunit of IL-12 and IL-23, has been approved for psoriasis and has shown good efficacy. Some psoriasis patients may be difficult to manage even with biologic therapies. For instance, patients initially treated unsuccessfully with etanercept are less likely to respond to both adalimumab and ustekinumab (13, 14). Many patients initially have a good response to a given therapy, only to lose response over time, and some patients do not respond adequately to any currently available therapies. For these reasons, additional options for psoriasis patients will be necessary to control this systemic disease.

The role of IL-12/IL-23 has also been evaluated in Crohn's disease. The IL-23 receptor gene has been strongly associated with inflammatory bowel disease (15, 16). The Th17 pathway also appears to be paramount in the inflammatory cascade of Crohn's disease (17).

A currently marketed p40 antibody, ustekinumab, is a fully human IgG_{1k} antibody generated in human immunoglobulin transgenic mice. This contrasts with briakinumab, which is a fully human anti-IL-12/23 IgG_1 antibody isolated from a phage display library and optimized in collaboration with Cambridge Antibody Technology (1). The structure of briakinumab is indistinguishable from normal human IgG. Briakinumab binds to the soluble forms of both IL-12 and IL-23 via the shared p40 subunit (18).

PRECLINICAL PHARMACOLOGY

There is minimal information regarding preclinical development and no peer-reviewed publications on the subject. The reported in vitro binding of briakinumab (presumably to IL-12) is characterized by an association rate constant (K_{on}) of $5 \times 10^5\ M^{-1}$, a K_{off} value of $5.1 \times 10^{-5}\ s^{-1}$ and a K_d value of 100 pM. The half-life of the antibody/protein complex is about 300 minutes. Briakinumab apparently binds human IL-12 and IL-23 with similar affinity (19, 20).

PHARMACOKINETICS AND METABOLISM

The pharmacokinetics of briakinumab have been described in normal healthy volunteers (21). A double-blind, randomized, placebo-controlled, crossover study evaluated briakinumab at four different doses by i.v. and s.c. administration in 64 healthy male volunteers. At doses between 0.1 and 5.0 mg/kg i.v. and s.c., the half-life of briakinumab was 8-9 days, the volume of distribution was 8-10 L and the time to reach maximum serum concentrations (C_{max}) was approximately 3-4 days. Bioavailability with s.c. administration ranged between 42% and 62% for the dose range evaluated. The investigators showed a linear relationship between the dose given and C_{max} and AUC. Clearance and volume of distribution at steady state are independent of dose. These findings are consistent with expectations for an IgG_1 antibody.

SAFETY

In a phase II study in psoriasis (see below), the most frequent adverse events were injection-site reactions, nasopharyngitis, upper respiratory tract infections and headache (4, 20). There were no serious infection-related adverse events during the trial. There were two malignancies diagnosed during the trial: ovarian cancer in a placebo-treated patient and nonmelanoma skin cancer in a briakinumab-treated patient.

In the pivotal placebo-controlled phase III trial of briakinumab (see below), six events of malignancy were reported in the briakinumab group in the induction period and none in the placebo group (21). A total of seven major adverse cardiac events (MACEs) were reported in patients on briakinumab and none on placebo. Although there was an overall increase in the number of MACE events in the briakinumab group compared with placebo, it is not clear if this is statistically significant. All MACE events occurred in patients with several underlying risk factors for coronary artery disease, although placebo patients had similar underlying risk factors.

A phase III comparator trial of briakinumab and methotrexate showed that infectious adverse events were similar between the two groups, with four serious infectious events with briakinumab versus three with methotrexate (22). Three malignancies were reported with briakinumab and none with methotrexate. Neither group experienced MACE.

An interim analysis of the long-term safety and efficacy results of an open-label extension of briakinumab in psoriasis was recently reported by Langley et al. (23). The open-label extension study was comprised of patients from the phase II study and the four phase III psoriasis studies detailed in Table I. A total of 2,298 patients had received at least 1 dose of briakinumab as of November 2009. A total of 18 MACE cases were reported in this study population. Seven of these MACE events occurred in a randomized, controlled trial and 11 occurred in the open-label extension study as of November 2009. Of the 18 MACE cases, 11 were nonfatal myocardial infarction, 3 nonfatal cerebrovascular strokes and 4 were cardiovascular deaths. Most of the subjects with MACE had multiple underlying risk factors for coronary artery disease. The open-label extension study has been amended to exclude or discontinue patients with two or more cardiovascular risk factors, unless they have previously failed other sys-

Table I. *Phase III studies of briakinumab in psoriasis.*

Identifier	Trial type	Arm 1	Arm 2	Arm 3	Ref.
NCT00570986	RDBPCT	Placebo	200 mg wks 0 and 4, 100 mg wk 8, then 100 mg every 4 wks	200 mg wks 0 and 4, 100 mg wk 8, then 100 mg every 12 wks	26
NCT00679731	Comparator	200 mg wks 0 and 4, 100 mg wk 8 and 100 mg every 4 wks	Methotrexate 5-25 mg weekly	—	27
NCT00691964	RDBPCT comparator	Placebo	200 mg wks 0 and 4, 100 mg wk 8	Etanercept 50 mg s.c. twice weekly	28
NCT00710580	RDBPCT comparator	Placebo	200 mg wks 0 and 4, 100 mg wk 8	Etanercept 50 mg s.c. twice weekly	29
NCT00626002	Open-label	100 mg every 4 wks for 160 wks	—	—	24

RDBPCT, randomized, double-blind, placebo-controlled trial.

temic therapies, including TNF inhibitors. The overall interim safety results are shown in Table II.

MACE has also been reported in patients on ustekinumab during the placebo-controlled portion of the phase II clinical trials and in patients in the open-label extension study of ustekinumab (24, 25). The numbers are low and are similar to what would be expected in a reference population, such as the Framingham database. The significance of these MACE events is unclear. Further evaluation of post-marketing reports and additional clinical trials will be crucial to determine the risk, if any, posed by both briakinumab and ustekinumab.

CLINICAL STUDIES

In a randomized, placebo-controlled phase II study of briakinumab in psoriasis, patients were randomized into 6 groups of 30 patients each (4, 22). Drug was administered s.c. as follows: one 200-mg dose at week 0; 100 mg every other week for 12 weeks; 200 mg weekly for 4 weeks; 200 mg every other week for 12 weeks; 200 mg weekly for 12 weeks; or placebo. The primary outcome measure was a 75% reduction in the Psoriasis Area and Severity Index (PSAI). The results are shown in Table III. The onset of improvement of psoriasis was rapid, with statistically significant differences versus placebo at week 2 in all treatment groups. This study confirmed the therapeutic efficacy of inhibition of the p40 subunit of IL-12/23 seen in previous studies with ustekinumab.

Recently, phase III data for briakinumab in psoriasis have been presented at several major meetings. Results from a phase III trial comparing two dosing regimens of briakinumab to placebo in patients with moderate to severe psoriasis demonstrated efficacy over 52 weeks (26). Patients (N = 1,465) were randomized 2:1 to briakinumab 200 mg at weeks 0 and 4, followed by 100 mg at week 8, or placebo for 12 weeks. In the maintenance phase, patients with a Physician's Global Assessment of clear or minimal were randomized 2:2:1 to one of three arms: briakinumab 100 mg every 4 weeks, briakinumab 100 mg every 12 weeks or placebo every 4 weeks. At 12 weeks, patients on briakinumab achieved a PASI 75 of 80.7% versus 4.5% for placebo. The 52-week maintenance results revealed PASI 75 results of 82.4%, 46.0% and 9.0%, respectively, for briakinumab every 4 weeks, briakinumab every 12 weeks and placebo. In the initial 12-week period, serious adverse events occurred in 20 (2.0%) briakinumab patients and 6 (1.2%) placebo patients.

Table II. *Interim safety results of open-label extension study of briakinumab (23).*

	Briakinumab patients with events (%) (N = 2,298)	Events (events/ 100 patient-years) (patient-years = 2,904)
Any adverse event	1,673 (72.6)	7,177 (247.1)
Most common adverse events		
Upper respiratory tract infection	313 (13.6)	426 (14.7)
Nasopharyngitis	309 (13.4)	456 (15.7)
Headache	154 (6.7)	220 (7.6)
Arthralgia	133 (5.8)	146 (5.0)
Hypertension	120 (5.2)	126 (4.3)
Any infection	1,045 (45.5)	2,002 (68.9)
Any serious infection	24 (1.0)	20 (1.0)
Opportunistic infections	6 (0.3)	6 (0.2)
Malignancy	37 (1.6)	42 (1.4)
Nonmelanoma skin cancer	28 (1.2)	33 (1.1)
Lymphoma	0	0

In a 52-week comparator phase III study, 317 patients were randomized 1:1 to either briakinumab (200 mg at weeks 0 and 4, followed by 100 mg at week 8 and then every 4 weeks) or methotrexate, titrated from an initial dose of 5 mg up to 25 mg weekly based on efficacy and response (27). At 24 weeks, 81.8% of briakinumab and 39.9% of methotrexate patients had achieved a PASI 75 response. At 52 weeks, the briakinumab group achieved a PASI 75 of 66.2% versus 23.9% for the methotrexate-treated patients (nonresponder imputation; dropout patients considered nonresponders). However, only 27.6% of the methotrexate patients completed 52 weeks compared with 68.8% in the briakinumab group. The majority of discontinuations in the methotrexate group were due to lack of efficacy.

Table III. *Efficacy results of briakinumab in phase II psoriasis clinical trial. Number of responders (%); n = 30 for all 6 groups (4).*

Response	Placebo	200 mg x 1	100 mg every other week	200 mg weekly x 4 weeks	200 mg every other week	200 mg weekly
PASI-50	5 (17)	23 (77)	30 (100)	29 (97)	29 (97)	30 (100)
PASI-75	1 (3)	19 (63)	28 (93)	27 (90)	28 (93)	27 (90)
PASI-90	0	5 (17)	16 (53)	19 (63)	23 (77)	16 (53)

PASI, Psoriasis Area and Severity Index.

Two similar phase III comparator trials have been completed comparing briakinumab to placebo and the TNF fusion protein etanercept (28, 29). Briakinumab was dosed at 200 mg at week 0 and 4, followed by 100 mg at week 8. Etanercept was given as 50 mg twice weekly for 12 weeks, and the placebo arm matched the etanercept dosing schedule. Primary efficacy results (PASI 75) at week 12 for the two studies are presented in Table IV.

Two studies have been performed with briakinumab in Crohn's disease. Seventy-nine patients with active Crohn's disease were given 7 weekly s.c. injections of 1 mg/kg briakinumab, 3 mg/kg briakinumab or placebo with either a 4-week interval between the first and second injection (cohort 1) or no interruption between the injections (cohort 2) (30). Seven weeks of uninterrupted treatment with the dose of 3 mg/kg demonstrated a higher response (Crohn's Disease Activity Index) rate than placebo (75% vs. 25%; $P = 0.03$). The study did not demonstrate significant remission of disease in any study group, although 38% of patients in the 3 mg/kg uninterrupted group showed remission versus 0% for placebo ($P = 0.07$). The authors concluded that treatment with briakinumab may induce clinical responses and remissions in patients with active Crohn's disease. Additionally, cytokine secretion from the mononuclear cells of the colonic lamina propria of study patients was evaluated at baseline and after treatment with briakinumab. Statistically significant decreases in IL-12, interferon gamma and TNF-α were noted after briakinumab treatment.

A multicenter, randomized, double-blind, parallel-group, placebo-controlled dose-ranging phase IIB study comparing the efficacy, safety and pharmacokinetics of i.v. infusions of briakinumab versus placebo in subjects with moderate to severely active Crohn's disease was initiated in 2007 (31). There were three arms: placebo, 400 mg and 700 mg briakinumab i.v. every 4 weeks. This study has been terminated.

In 2004, a multicenter, randomized, double-blind phase II clinical trial in multiple sclerosis (MS) was initiated. Patients received briakinumab or placebo weekly or on alternate weeks for 24 weeks, followed by a 24-week open-label extension period. The primary endpoint was a comparison of gadolinium-enhanced (T1-weighted) images by magnetic resonance imaging (MRI) over the 24-week period (32). A study evaluating the effect of ustekinumab in patients with active MS also failed to show any response (33).

At least 20% of moderate to severe psoriasis patients will develop psoriatic arthritis. The efficacy of briakinumab in psoriatic arthritis has not been reported. A phase II trial of ustekinumab, however, has shown some efficacy in treating psoriatic arthritis (34). The ability of a systemic treatment to control both skin and joint disease is critical in making clinical decisions regarding treatment options.

Table IV. *Results of trials comparing briakinumab and etanercept.*

Trial (Ref.)	Placebo (PASI-75)	Etanercept (PASI-75)	Briakinumab (PASI-75)
M10-315 (28) NCT00710580	6.9%	39.6%	80.6%
M10-114 (27) NCT00691964	7.4%	56.0%	81.9%

Abbott Laboratories, in a report filed with the Securities and Exchange Commission on January 14, 2011, withdrew applications for briakinumab in both the U.S. and the E.U. (35).

DRUG INTERACTIONS

No specific drug interactions have been reported. As briakinumab is an immunosuppressive agent, combination with other agents that suppress the immune system may be of concern. A clinical trial to assess the effect of briakinumab on the cytochrome system is under way in patients with moderate to severe psoriasis. This study will assess the effect of a single dose of briakinumab on the pharmacokinetics of caffeine, tolbutamine, omeprazole, metoprolol and midazolam (36).

SOURCES

Abbott Laboratories (US); originally developed by the former Cambridge Antibody Technology, now MedImmune, which is now part of AstraZeneca.

DISCLOSURES

Dr. Crowley has received research support and served as a consultant for Abbott, Amgen, Centocor, Lilly and Pfizer. He has served on the Speaker's Bureau for Abbott and Amgen.

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