Drugs (2024) 84:1481–1485
https://doi.org/10.1007/s40265-024-02110-8

ADISINSIGHT REPORT

Vunakizumab: First Approval

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Accepted: 10 October 2024 / Published online: 5 November 2024

Abstract
Vunakizumab (安达静®) is a subcutaneous (SC) recombinant anti-interleukin (IL)-17A humanized monoclonal IgG1/κ antibody being developed by Suzhou Suncadia Biopharmaceutical Co., Ltd (a subsidiary of Jiangsu Hengrui Pharmaceuticals Co., Ltd) for the systemic treatment of autoimmune diseases related to the IL-17 pathway, including psoriasis, ankylosing spondylitis and psoriatic arthritis. In August 2024, vunakizumab was approved in China for the treatment of adult patients with moderate-to-severe plaque psoriasis who are suitable for systemic treatment or phototherapy. This article summarizes the milestones in the development of vunakizumab leading to this first approval for the systemic treatment of moderate-to-severe plaque psoriasis.

Digital Features for this AdisInsight Report can be found at https://doi.org/10.6084/m9.figshare.27199023.

Vunakizumab (安达静®): Key Points

An SC recombinant anti-IL-17A humanized monoclonal IgG1/κ antibody being developed by Suzhou Suncadia, a subsidiary of Jiangsu Hengrui, for the treatment of autoimmune diseases related to the IL-17 pathway

Received its first approval on 20 August 2024 in China

Approved for use in adult patients with moderate-to-severe plaque psoriasis who are suitable for systemic treatment or phototherapy

1 Introduction

The interleukin (IL)-23/IL-17 immunologic pathway is crucial in the pathogenesis of autoimmune disorders. IL-17A, a naturally occurring cytokine that has a key role in normal inflammation and immune responses, has been identified as the main effector cytokine in a number of autoimmune disorders, including plaque psoriasis and spondyloarthritis [which includes psoriatic arthritis and ankylosing spondylitis (AS)]. Consequently, blocking IL-17A or the IL-17 receptor is a therapeutic target of interest [1–4].

Vunakizumab (安达静®), a subcutaneous (SC) recombinant anti-IL-17A humanized monoclonal IgG1/κ antibody, is being developed by Suzhou Suncadia Biopharmaceutical Co., Ltd (a subsidiary of Jiangsu Hengrui Pharmaceuticals Co., Ltd) for the systemic treatment of autoimmune diseases related to the IL-17 pathway, including psoriasis, ankylosing spondylitis and psoriatic arthritis [5–8]. In August 2024, vunakizumab was approved in China for the treatment of adult patients with moderate-to-severe plaque psoriasis who are suitable for systemic treatment or phototherapy [6]. Vunakizumab is available as a prefilled autoinjector pen containing a 120 mg dose. The recommended dose is 240 mg (two 120 mg injections) SC at weeks 0, 2 and 4, and then every 4 weeks. Vunakizumab can be self-injected by the patient after training. Injection sites include the lower abdomen, the legs and the upper arms; different sites should be selected for each injection and if possible, injections should avoid psoriatic lesions [6]. Vunakizumab is contraindicated in patients with active infections of significant clinical significance (e.g., active tuberculosis) [6].

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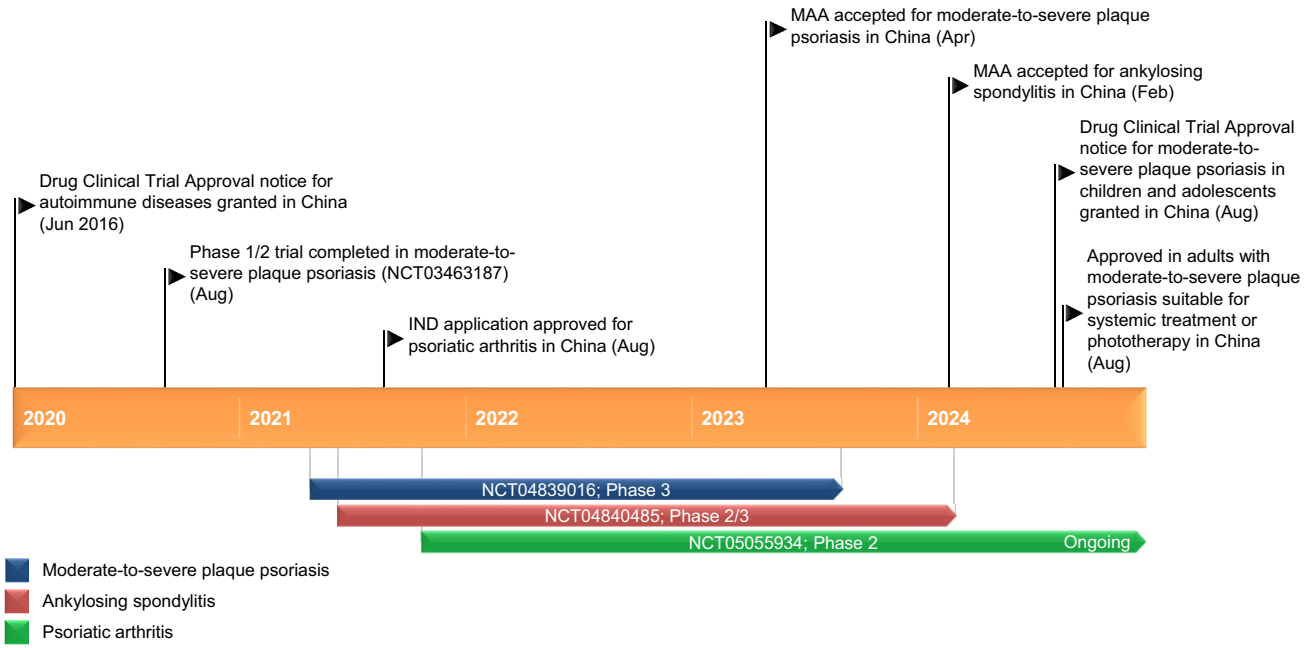

Key milestones in the development of vunakizumab in the treatment of autoimmune diseases related to the IL-17 pathway. *IND* investigational new drug, *MAA* marketing authorization application

2 Scientific Summary

2.1 Pharmacodynamics

Vunakizumab specifically binds to IL-17A, blocking interaction with the IL-17 receptor, which inhibits production of the chemokine CXCL1. Reduced interaction between CXCL1 and its receptor inhibits downstream inflammatory signal transduction and alleviates inflammatory processes [6]. In mouse models of psoriasis, vunakizumab antagonized IL-17 and was as effective as etanercept in improving psoriasis skin lesions [1].

2.2 Pharmacokinetics

The pharmacokinetics of SC vunakizumab are approximately dose proportional over an 8–240 mg dose range. After a single SC injection of vunakizumab 240 mg in patients with plaque psoriasis, the mean C_{max} of 29.5 µg/mL was achieved ≈ 7 days after administration [6]. After SC administration of vunakizumab 240 mg at weeks 0, 2, 4, and 8, the mean C_{trough} at week 12 was 32.6 µg/mL. The mean C_{trough} at steady state from week 12 onwards after administration of vunakizumab 240 mg every 4 weeks was 28.7 µg/mL. Based on population pharmacokinetic analysis, V_d in patients with plaque psoriasis was 3.40 L [6].

Vunakizumab is predicted to be degraded into small peptides and amino acids via the same catabolic pathways as endogenous immunoglobulins [6]. Based on population pharmacokinetic analysis, mean CL/F was 0.236 L/day in patients with plaque psoriasis and was not affected by vunakizumab dose or treatment duration. Patient age and hepatic and renal impairment had no clinically significant effect on the pharmacokinetics of vunakizumab. Population pharmacokinetics predicted that CL/F was ≈ 34% lower and AUC was ≈ 52% higher at the same dose in patients whose weight was in the 5th percentile (50.9 kg) of the study population, and CL/F was ≈ 53% higher and AUC was ≈ 34% lower at the same dose in those at the 95th percentile (95 kg) of the study population [6].

2.3 Therapeutic Trials

2.3.1 Plaque Psoriasis

Vunakizumab improved signs and symptoms of plaque psoriasis in the 52-week, randomized, double-blind placebo-controlled phase 3 trial in patients with moderate-to-severe, chronic disease (NCT04839016) [9]. Significantly more vunakizumab 240 mg recipients ($n = 461$) than placebo recipients ($n = 229$) achieved the co-primary endpoints of ≥ 90% improvement from baseline in the psoriasis area-and-severity index score (PASI 90) [76.8% vs 0.9%; $p < 0.0001$] and a static Physicians Global Assessment (sPGA) score of 0 (clear) or 1 (almost clear) [71.8% vs 0.4%; $p < 0.0001$] at week 12 [9]. A mean PASI reduction of > 50% from baseline was evident at week 2 in vunakizumab recipients [6]. PASI

Features and properties of vunakizumab

Alternative names	安达静, SHR-1314
Class	Anti-inflammatories; Antipsoriatics; Antirheumatics; Monoclonal antibodies
Mechanism of action	IL-17A inhibitor
Route of administration	SC
Pharmacodynamics	Specifically binds to IL-17A, thereby inhibiting the interaction of IL-17A with its receptor. This prevents the production of downstream CXCL1, blocking further signal transduction and alleviating the inflammatory process
Pharmacokinetics	C_{max} 29.5 μg/mL; T_{max} ≈ 7 d; Ctrough,$_{ss}$ 28.7 μg/mL; V_d 3.40 L; CL/F 0.236 L/d
Adverse events	
Most frequent	Upper respiratory tract infection, injection site reactions, hyperuricemia, elevated ALT, hyperlipidemia, elevated triglycerides, elevated uric acid and hypertriglyceridemia
Occasional	New-onset inflammatory bowel disease
ATC codes	
WHO ATC code	L04A-C (Interleukin inhibitors)
EphMRA ATC code	L4C (Interleukin Inhibitors)

90 and sPGA 0/1 response rates with vunakizumab 240 mg were maintained through week 52 [9]. PASI 75, PASI 100 and sPGA 0 responses were also significantly higher with vunakizumab than with placebo at week 12 ($p < 0.0001$ for all comparisons) [9]. The trial comprised a 12-week, double-blind, placebo-controlled induction treatment period, followed by a 40-week, double-blind maintenance period. Eligible patients were randomized to receive SC vunakizumab 240 mg or matching placebo subcutaneously at weeks 0, 2, 4 and 8. At week 12, patients in the placebo group were switched to receive vunakizumab 240 mg at weeks 12, 14 and 16, and then every 4 weeks through week 52, while vunakizumab 240 mg recipients continued treatment every 4 weeks through week 52 [9]. Among the 690 enrolled patients, 44.5% had previously received non-biologic systemic treatment for psoriasis, 22.0% had received phototherapy, and 4.6% had received a biologic agent. At baseline in the vunakizumab arm, median PASI was 20.1, sPGA was moderate (41.2%), severe (49.9%) or very severe (9.0%), and median body surface area (BSA) of psoriasis involvement was 31.0% [6].

Vunakizumab was effective in the treatment of moderate-to-severe plaque psoriasis in a 36-week, randomized, double-blind, placebo-controlled, dose-ranging phase 2 trial (NCT03463187, part B) conducted in China, the USA and Australia [1]. Significantly more patients in the vunakizumab 40 mg ($n = 37$), 80 mg ($n = 38$), 160 mg ($n = 38$) and 240 mg ($n = 37$) groups than in the placebo group ($n = 37$) were PASI 75 responders at week 12 (56.8%, 65.8%, 81.6% and 86.5% vs 5.4%; all $p < 0.001$ vs placebo) [primary endpoint]. PGA 0/1 response rates at week 12 in the 40 mg, 80 mg, 160 mg and 240 mg vunakizumab groups were 45.9%, 47.4%, 60.5% and 73.0% compared with 8.1% in the placebo group [1]. Patients were randomized to receive SC vunakizumab 40, 80, 160 or 240 mg or placebo at weeks 0, 4, 8, and 12. During the remaining 24 weeks, patients in the vunakizumab groups received an additional dose at weeks 16 and 20, while placebo recipients received standard of care treatment. At baseline, the mean PASI score was 21.6–24.0, mean PGA ≥ 4 was 14–21, and mean BSA of psoriasis involvement was 36.4–42.6% [1].

2.3.2 Ankylosing Spondylitis

Treatment with vunakizumab improved signs and symptoms of AS in the 32-week, randomized, double-blind, adaptive, seamless, phase 2/3 study in patients with active disease (NCT04840485) [10]. During the entire phase 2/3 study, significantly more vunakizumab 120 mg recipients ($n = 294$) than placebo recipients ($n = 146$) achieved ≥ 20% improvement in Assessment of Spondyloarthritis International Society (ASAS20) response criteria at week 16 (primary endpoint) [65.6% vs 42.5%; $p < 0.0001$]. The ASAS40 response rate at week 16 was also significantly greater with vunakizumab 120 mg than with placebo (46.3% vs 24.0%; $p < 0.0001$), and ASAS20 and ASAS40 responses with vunakizumab 120 mg were maintained through 32 weeks [10]. Eligible patients ($n = 548$) had active AS and an inadequate response, contraindications, or intolerance to non-steroidal anti-inflammatory drugs; prior anti-tumour necrosis factor therapy was allowed. In the phase 2 part, patients were randomized to receive SC vunakizumab 120 mg or 240 mg or SC placebo at weeks 0, 2, 4, 8 and 12. At week 16, placebo recipients were re-randomized to vunakizumab 120 mg or 140 mg every 4 weeks through 32 weeks and vunakizumab recipients continued their assigned dose every 4 weeks through 32 weeks. A preplanned interim analysis at 16 weeks found that vunakizumab 120 mg was the recommended phase 3 dose. In the phase 3 part, patients were randomized to receive SC vunakizumab 120 mg or placebo at weeks 0, 2, 4, 8 and 12; from week 16, all patients received vunakizumab 120 mg every 4 weeks through week 32 [10].

2.4 Adverse Events

The incidence of adverse reactions reported in vunakizumab 240 mg ($n = 460$) or placebo ($n = 229$) recipients in the 12-week, placebo-controlled part of the 52-week phase 3 trial in patients with moderate-to-severe plaque psoriasis (NCT04839016) were comparable (69.1% vs 71.6%) [9]. The most common adverse reactions (incidence ≥ 1%) were injection site reactions (6.3% vs 2.2%), elevated triglycerides (5.0% vs 2.6%), elevated uric acid (3.9% vs 1.3%), elevated ALT (3.5% vs 3.1%), hypertriglyceridemia (3.3% vs 2.2%), hyperlipidemia (2.8% vs 2.6%), urticaria (2.8% vs 0%), elevated non-HDL cholesterol (2.4% vs 0.9%), hypercholesterolemia (2.2% vs 1.3%), tinea pedis (2.0% vs 0.9%), elevated LDL cholesterol (2.0% vs 0%), elevated total cholesterol (2.0% vs 0%), elevated bilirubin (1.3% vs 0.9%), eczema (1.3% vs 0.4%) and abnormal liver function (1.1% vs 0.4%) [6]. The most common adverse reactions (incidence ≥ 5%) during the entire 52-week treatment period were upper respiratory tract infection, injection site reactions, hyperuricemia, elevated ALT, hyperlipidemia, elevated triglycerides, elevated uric acid and hypertriglyceridemia. The safety profile of vunakizumab through 52 weeks was generally consistent with that at week 12 [6].

In the 32-week, phase 2/3 placebo-controlled trial of vunakizumab in patients with ankylosing spondylitis (NCT04840485), the overall incidence of adverse events in the vunakizumab 120 mg and placebo arms during the 16-week placebo-controlled period were comparable (83.7% vs 81.5%) [10].

The incidence of infections reported in the vunakizumab 240 mg and placebo arms were comparable in the first 12 weeks of the phase 3 trial in moderate-to-severe plaque psoriasis (17.8% vs 18.3%) [6] and in the vunakizumab 120 mg and placebo arms in the first 16 weeks of the phase 2/3 trial in ankylosing spondylitis (37.1% vs 47.3%) [10]. Infection was reported in 38.6% of vunakizumab 240 mg recipients during the 52-week treatment period in the trial in moderate-to-severe plaque psoriasis, with severe infections occurred in 2 (0.3%) patients [6]. In the trials in patients with plaque psoriasis (NCT04839016) and ankylosing spondylitis (NCT04840485), two cases of new-onset inflammatory bowel disease (one case of Crohn's disease and one case of ulcerative colitis, both of which were moderate in severity), were reported in vunakizumab recipients [6, 10]. In the phase 3 trial in moderate-to-severe plaque psoriasis, 5.0% of patients who received vunakizumab for up to 52 weeks developed anti-drug antibodies, 2.4% of which were neutralizing antibodies [6].

2.5 Ongoing Clinical Trials

A placebo-controlled phase 2 trial of vunakizumab in psoriatic arthritis (NCT05055934) is ongoing, and a phase 3 trial of vunakizumab in children and adolescents aged 6–18 years with moderate-to-severe plaque psoriasis planned [7, 8].

3 Current Status

Vunakizumab received its first approval on 20 August 2024 for that treatment of adult patients with moderate to severe plaque psoriasis who are suitable for systemic treatment or phototherapy in China [5–7].

Key clinical trials of vunakizumab (Jiangsu Hengrui Medicine/Suzhou Suncadia Biopharmaceutical)

Drug(s)	Indication	Phase	Status	Location(s)	Identifier
Vunakizumab, placebo	Moderate-to-severe plaque psoriasis	3	Completed	China	NCT04839016; CTR20210753
Vunakizumab, placebo	Moderate-to-severe plaque psoriasis	1/2	Completed	China, USA, Australia	NCT03463187; CTR20190055
Vunakizumab, placebo	Moderate-to-severe plaque psoriasis	2	Terminated	China	NCT04121143; CTR20191914
Vunakinumab	Moderate-to-severe plaque psoriasis	1	Completed	China	NCT03710681; CTR20181599
Vunakinumab, placebo	Ankylosing spondylitis	2/3	Completed	China	NCT04840485; CTR20210745
Vunakinumab, placebo	Ankylosing spondylitis	1	Completed	China	NCT03704428; CTR20180338
Vunakizumab, placebo	Psoriatic arthritis	2	Active	China	NCT05055934; CTR20212347

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40265-024-02110-8.

Declarations

Funding The preparation of this review was not supported by any external funding.

Authorship and Conflict of interest During the peer review process the manufacturer of the agent under review was offered an opportunity to comment on the article. Changes resulting from any comments received were made by the authors on the basis of scientific completeness and accuracy. Susan J. Keam is a contracted employee of Adis International Ltd/Springer Nature, and declares no relevant conflicts of interest. All authors contributed to this article and are responsible for its content.

Ethics Approval, Consent to Participate, Consent to Publish, Availability of Data and Material, Code Availability Not applicable.

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