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ADISINSIGHT REPORT

Spesolimab: First Approval

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Abstract
Spesolimab (spesolimab-sbzo; SPEVIGO®) is an interleukin (IL)-36 receptor antagonist being developed by Boehringer Ingelheim for the treatment of various immune-mediated disorders. In September 2022, spesolimab was approved in the USA for the treatment of generalized pustular psoriasis (GPP) flares in adults. This article summarizes the milestones in the development of spesolimab leading to this first approval for GPP flares.

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Spesolimab (SPEVIGO®): Key points

IL-36 receptor antagonist being developed by Boehringer Ingelheim for the treatment of immune-mediated disorders

Received its first approval on 1 September 2022 in the USA

Approved for the treatment of GPP flares in adults

1 Introduction

Generalized pustular psoriasis (GPP) is a rare and potentially life-threatening disease characterized by extensive eruption of pustules on the skin, with or without systemic inflammation and with or without plaque psoriasis [1–3]. GPP flares may occur de novo or in response to triggers such as infection, stress, pregnancy and discontinuation of corticosteroids [1, 2]. While the frequency and severity of flares is variable between patients, most flares last between 2 and 5 weeks and around half require hospitalization [1]. Complications can be life-threatening, and include sepsis, kidney failure, liver failure and heart failure [1].

The pro-inflammatory role of interleukin (IL)-36 is well studied in a number of inflammatory diseases, including arthritis, inflammatory bowel disease and psoriasis [4]. The IL-36 signaling pathway has been shown to play an important role in the pathogenesis of GPP, thereby providing a basis for the development of targeted therapies for the disease [2, 3].

Spesolimab (spesolimab-sbzo; SPEVIGO®) is an IL-36 receptor antagonist being developed by Boehringer Ingelheim for the treatment of various immune-mediated disorders. Spesolimab was given orphan drug designation by the US FDA in October 2018 for the treatment of GPP flares in adults [5]. In December 2021, the US FDA accepted a biologics license application and granted priority review for spesolimab for the treatment of GPP flares; prior to this, spesolimab had been granted breakthrough therapy designation [6]. On 1 September 2022, spesolimab received its first approval in the USA for the treatment of GPP flares in adults [7]. The recommended dose of spesolimab is 900 mg as an intravenous infusion over 90 min; a second 900 mg dose can be administered 1 week after the initial dose if GPP flare symptoms persist [8].

On 26 September 2022, spesolimab was approved in Japan for the treatment of acute symptoms in GPP [9]. Spesolimab received a positive opinion in the EU in October 2022 for the treatment of flares in adult patients with GPP [10]. The drug is in phase II or III development for GPP in multiple countries worldwide. Spesolimab is also being developed for the treatment of ulcerative colitis (at phase II/III), Crohn's disease, palmoplantar pustulosis (PPP) and hidradenitis

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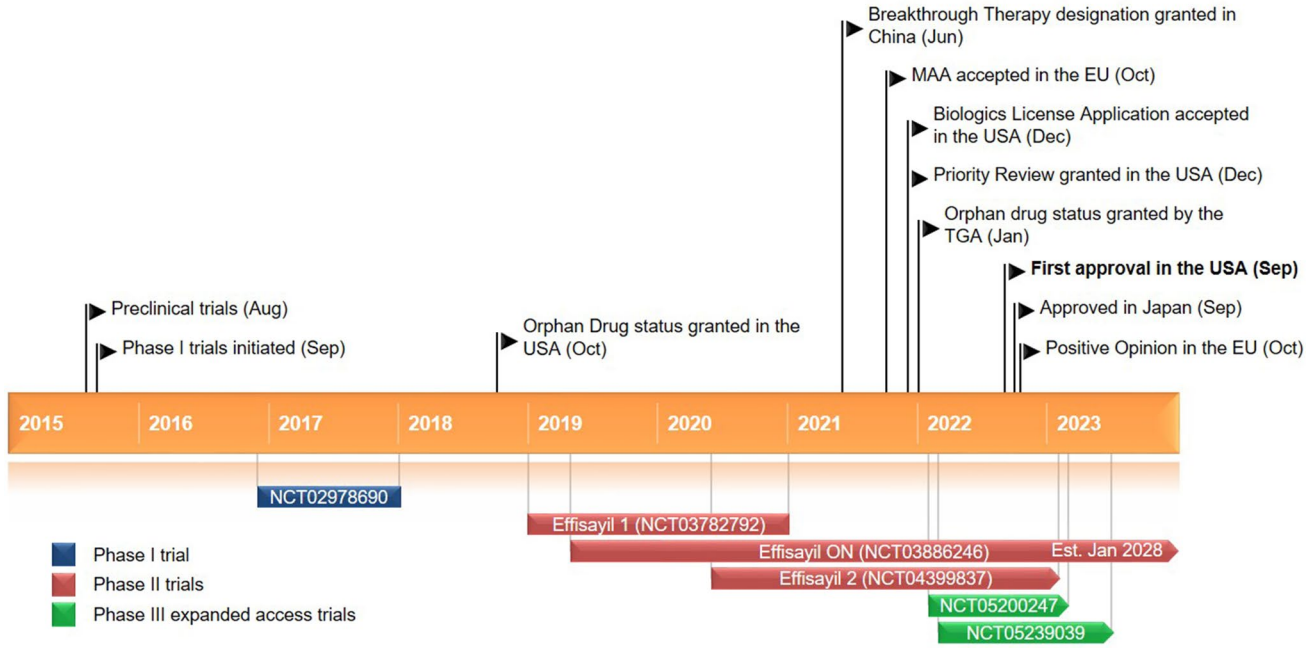

Key milestones in the development of spesolimab, focusing on its use in the treatment of generalized pustular psoriasis. *TGA* Therapeutic Goods Administration

suppurativa (all phase II). Development of spesolimab for the treatment of atopic dermatitis has been discontinued.

2 Scientific Summary

2.1 Pharmacodynamics

Spesolimab is a humanized monoclonal immunoglobulin (Ig) G1 antibody that binds specifically to the IL-36 receptor (IL-36R) [8]. Consequently, the downstream signaling effects of IL-36 are blocked, preventing cognate ligands (IL-36 α, β and γ) from activating IL-36R and preventing downstream activation of pro-inflammatory and pro-fibrotic pathways. Uncertainty exists regarding the exact mechanism by which reduced IL-36R activity improves the symptoms of GPP flares [8]. However, molecular, genetic and preclinical evidence implicates the role of IL-36 pathway dysfunction in the pathogenesis of GPP [11, 12]. This has led to the view that GPP may rely more heavily on the IL-36 pathway, in contrast to plaque psoriasis, which relies on the IL-17 pathway [13].

In a phase I proof-of-concept study (NCT02978690), a single intravenous dose of spesolimab 10 mg/kg led to rapid skin and pustular clearance in patients with a GPP flare ($n = 7$), regardless of the presence of the *IL36RN* mutation ($n = 3$) [14]. Spesolimab was also associated with near normalization of C-reactive protein (from 69.4 mg/dL at baseline to 4.5 mg/dL at week 2); this reduction was sustained until the last measurement at week 4 [14]. In these patients, spesolimab demonstrated rapid normalization/downregulation of a number of commonly dysregulated molecular pathways associated with GPP, with corresponding clinical improvement [11].

2.2 Pharmacokinetics

According to a population pharmacokinetic model, spesolimab demonstrates linear pharmacokinetics over a dose range of 0.3–20 mg/kg [8]. In a typical anti-drug antibody (ADA)-negative patient with GPP, the area under the concentration-time curve from zero to infinity and peak plasma concentration of spesolimab following a single intravenous dose of 900 mg are 4750 µg · day/mL and 238 µg/mL, respectively. Spesolimab has a typical total volume of distribution at steady state of 6.4 L. The expected metabolic pathway for spesolimab involves degradation to small peptides and amino acids by catabolic pathways in the same manner as endogenous IgG. The terminal half-life of spesolimab is 25.5 days. In a typical ADA-negative patient with GPP weighing 70 kg, the clearance of spesolimab is 0.184 L/day. Terminal half-life and clearance are independent of dose [8].

Age, sex and race have no effect on the pharmacokinetics of spesolimab [8]. The effect of hepatic or renal impairment on the pharmacokinetics of spesolimab has not been studied; however, hepatic or renal impairment is not expected to influence elimination of spesolimab. Plasma concentrations of spesolimab are lower in subjects with higher body weight; the clinical relevance of this finding is unknown. No formal drug interaction studies have been performed with spesolimab [8].

Features and properties of spesolimab

Alternative names	BI 655130; spesolimab-sbzo; SPEVIGO
Class	Anti-inflammatories; antipsoriatics; monoclonal antibodies; skin disorder therapies
Mechanism of action	IL-36 receptor antagonists
Route of administration	Intravenous
Pharmacodynamics	Binds to the IL-36 receptor, blocking the downstream signaling effects of IL-36; normalizes C-reactive protein; downregulates commonly dysregulated molecular pathways associated with GPP
Pharmacokinetics	Linear pharmacokinetics over dose range of 0.3–20 mg/kg; typical total volume of distribution 6.4 L; terminal half-life 25.5 days; clearance 0.184 L/day
Most frequent adverse events	Infection, asthenia and fatigue, nausea and vomiting, headache
ATC codes	
WHO ATC code	L04A-C22 (spesolimab)
EphMRA ATC code	A7E (intestinal anti-inflammatory agents); D11 (other dermatological preparations); D5B (systemic antipsoriasis products)

GPP generalized pustular psoriasis, *IL-36* interleukin-36

2.3 Therapeutic Trials

2.3.1 Generalized Pustular Psoriasis

Spesolimab was associated with higher rates of clearance of pustular lesions than placebo in patients with a moderate-to-severe GPP flare participating in the randomized, double-blind, multicentre, phase II Effisayil 1 trial (NCT03782792) [15]. The proportion of patients with a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 0 (no visible pustules) at the end of week 1 (primary endpoint) was 54% with spesolimab versus 6% with placebo ($p < 0.001$). The proportion of patients with a GPPGA total score of 0 or 1 (clear or almost clear skin) at the end of week 1 (key secondary endpoint) was 43% with spesolimab versus 11% with placebo ($p = 0.02$). Similar results were seen in post hoc sensitivity analyses after adjusting for baseline between-group imbalances in sex, race and disease severity [15].

This study enrolled 53 patients aged 18–75 years with a history of GPP [15]. All patients were required to have a GPPGA total score of ≥ 3 (scores range from 0 to 4, with higher scores indicating greater disease severity), new or worsening pustules, a GPPGA pustulation subscore of ≥ 2 [scores range from 0 (no visible pustules) to 4 (severe pustulation)] and ≥ 5% of body surface area with erythema and pustules. Seven patients had *IL36RN* mutations at baseline. Patients were randomized 2:1 to receive a single intravenous dose of spesolimab 900 mg or placebo. Patients in both groups were eligible to receive an open-label dose of spesolimab on day 8, an open-label dose of spesolimab as rescue medication after day 8, or both. At the end of the trial (week 12), all patients were eligible to enter Effisayil ON, a 5-year open-label extension trial of spesolimab (NCT03886246) [15].

2.3.2 Palmoplantar Pustulosis

Early clinical data from a randomized, double-blind, multicentre, phase IIa pilot study (NCT03135548) indicate that spesolimab may be effective for the treatment of PPP [16]. At week 16, the proportion of patients achieving a ≥ 50% reduction from baseline in Palmoplantar Pustulosis Area and Severity Index (PPP ASI50; primary endpoint) was 32% in each of the 300 and 900 mg spesolimab groups and 24% in the placebo group. The risk difference versus placebo was 0.078 (95% CI –0.190, 0.338), indicating that the primary endpoint was not met. In this study, 59 patients aged 18–65 years with PPP were randomized 1:1:1 to receive one of two doses of spesolimab (300 or 900 mg) or placebo intravenously on day 1 and at weeks 4, 8 and 12. All patients had primary, persistent (> 3 months' duration), sterile, macroscopically visible pustules on the palms of the hands and/or soles of the feet. Patients also had active pustulation with a PPP ASI of ≥ 12 (assessed on a scale of 0–72, with higher scores indicating greater disease severity) and a Palmoplantar Pustulosis Physician Global Assessment score of ≥ 3 [scores range from 0 (clear skin) to 4 (very severe lesions)] [16].

2.3.3 Ulcerative Colitis

Spesolimab was associated with low rates of clinical remission in patients with moderate-to-severe ulcerative colitis participating in a randomized, double-blind, multicentre, phase II trial (NCT03482635) [17]. The proportion of patients achieving clinical remission at week 12 (primary endpoint) was 4% with spesolimab 300 mg, 9 and 7% with spesolimab 450 and 1200 mg every 4 weeks, and 0% with placebo. In this study, 98 patients who had failed previous therapy with a tumour necrosis factor (TNF)-α inhibitor and/

or vedolizumab were randomized 1:1:1:1 to receive a single dose of intravenous spesolimab 300 mg at week 0 followed by placebo at weeks 4 and 8, or spesolimab 450 mg, spesolimab 1200 mg or placebo at weeks 0, 4 and 8. Clinical remission was defined as a modified Mayo Clinic Score (MCS) of ≤2, a stool frequency score of 0 or 1, a rectal bleeding score of 0 and a modified endoscopic subscore (mESS) of ≤1 [17].

Another randomized, double-blind, phase IIa trial (NCT03123120) found that spesolimab did not induce mucosal healing in patients with mild-to-moderate ulcerative colitis receiving stable TNF-α inhibitor therapy [17]. At week 12, only two (14%) spesolimab recipients achieved endoscopic improvement (MCS mESS ≤1; primary endpoint); the unadjusted risk difference relative to placebo was – 0.232 (95% CI – 0.568, 0.118). In this study, 22 patients were randomized 2:1 to receive intravenous spesolimab 1200 mg or placebo at weeks 0, 4 and 8 [17].

In an open-label, single-arm, phase IIa exploratory trial (NCT03100864), spesolimab had a limited effect on gene expression in patients with moderate-to-severe, active ulcerative colitis [17]. Very few genes were deregulated between baseline and week 12 (primary endpoint), and no patients achieved total clinical remission (total MCS ≤2 and all subscores ≤1). The study enrolled eight patients who were naïve to advanced therapies or only exposed to and not failing TNF-α inhibitors. All patients received intravenous spesolimab 1200 mg at weeks 0, 4 and 8 [17].

Key clinical trials of spesolimab (Boehringer Ingelheim)

Drug	Indication	Phase	Status	Location(s)	Identifier
Spesolimab	GPP	III	Recruiting	China	NCT05239039
Spesolimab	GPP	III	Recruiting	Japan	NCT05200247
Spesolimab	Ulcerative colitis	II/III	Discontinued	Multinational	NCT03482635; EudraCT2017-004230-28; JapicCTI184052
Spesolimab	GPP	II	Completed	Multinational	NCT03782792; EudraCT2017-004231-37; JapicCTI194575; Effisayil 1
Spesolimab	GPP	II	Active, no longer recruiting	Multinational	NCT04399837; EudraCT2018-003081-14; JapicCTI205387; Effisayil 2
Spesolimab	GPP	II	Recruiting	Multinational	NCT03886246; EudraCT2018-003080-56; Effisayil ON
Spesolimab	Ulcerative colitis	II	Completed	Multinational	NCT03100864; EudraCT2017-000100-20
Spesolimab	Ulcerative colitis	II	Discontinued	Multinational	NCT03123120; EudraCT2016-004572-21
Spesolimab	Ulcerative colitis	II	Active, no longer recruiting	Multinational	NCT03648541; EudraCT2018-000334-35; JapicCTI184200
Spesolimab	Crohn's disease	II	Completed	Multinational	NCT03752970; EudraCT2017-003090-34
Spesolimab	Crohn's disease	II	Active, no longer recruiting	Multinational	NCT04362254; EudraCT2019-001673-93
Spesolimab	Crohn's disease	II	Discontinued	Multinational	NCT05013385; EudraCT2020-005770-99
Spesolimab	PPP	II	Completed	Multinational	NCT04015518; EudraCT2018-003078-28; JapicCTI194902
Spesolimab	PPP	II	Completed	Multinational	NCT03135548; EudraCT2016-004573-40
Spesolimab	PPP	II	Recruiting	Multinational	NCT04493424; EudraCT2020-000189-41; JapicCTI205433
Spesolimab	Hidradenitis suppurativa	II	Completed	Multinational	NCT04762277; EudraCT2020-003672-40
Spesolimab	Hidradenitis suppurativa	II	Active, no longer recruiting	Multinational	NCT04876391; EudraCT2020-005587-55
Spesolimab	GPP	I	Completed	Multinational	NCT02978690; EudraCT2016-001236-35

GPP generalized pustular psoriasis, *PPP* palmoplantar pustulosis

2.4 Adverse Events

Spesolimab was generally well tolerated in patients with GPP [15]. During the first week of treatment in Effisayil 1, adverse events (AEs) occurred in 66% of patients receiving spesolimab and 56% of patients receiving placebo [15]. The most common AEs (occurring in ≥5% of spesolimab recipients and more frequently than in the placebo group) through week 1 were infections (17 vs 6%), asthenia and fatigue (9 vs 0%), nausea and vomiting (9 vs 6%), headache (9 vs 6%), pruritus and prurigo (6 vs 0%), infusion site haematoma and bruising (6 vs 0%) and urinary tract infection (UTI; 6 vs 0%) [8]. The incidence of investigator-defined drug-related AEs was similar in both treatment groups (29% with spesolimab and 28% with placebo) [15]. Through week 12, serious AEs occurred in six (12%) spesolimab recipients; these included drug reaction with eosinophilia and systemic symptoms (DRESS; $n = 2$), drug-induced hepatic injury, UTI, arthritis, worsening chronic plaque psoriasis, influenza and squamous cell carcinoma of the skin (all $n = 1$) [15].

Spesolimab was also generally well tolerated in patients with PPP [16] and ulcerative colitis [17]. In patients with PPP, the incidence of investigator-defined drug-related AEs through 32 weeks was 42% with spesolimab; however, most were mild or moderate in severity [16]. The most common (incidence ≥10%) AEs associated with spesolimab were nasopharyngitis and headache. No clinically relevant treatment-emergent safety signals were observed [16]. In patients with ulcerative colitis, there was no evidence of clinically relevant hypersensitivity or severe, serious or opportunistic infections related to spesolimab [17]. The majority of AEs were mild or moderate in severity, and most serious AEs were a result of the underlying disease or its complications. The most common investigator-defined drug-related AEs were skin rash, nasopharyngitis, headache and acne. There were no unexpected safety concerns [17].

Spesolimab has the potential for immunogenicity. In Effisayil 1, ADAs were detected in 46% of patients who received at least one dose of spesolimab; the median onset was 2.3 weeks after spesolimab administration [15]. The pharmacokinetics of spesolimab were unaffected in subjects with ADA titres <4000, while plasma concentrations of spesolimab were significantly reduced in subjects with ADA titres ≥4000 [8]. There is no indication that ADAs are associated with hypersensitivity events [17].

2.5 Ongoing Clinical Trials

The efficacy and safety of spesolimab for the prevention of GPP flares in patients with a history of GPP is being investigated in Effisayil 2, a randomized, double-blind, multicentre, phase IIb dose-finding trial (NCT0439983). Effisayil ON is an open-label extension study (NCT03886246) that is currently recruiting and plans to assess the long-term efficacy and safety of spesolimab in patients with GPP who participated in previous spesolimab trials. Phase III expanded access programs are underway in China (NCT05239039) and Japan (NCT05200247) to provide spesolimab to patients with GPP flares who have no other treatment options. Several multinational phase II trials are also currently underway in patients with PPP (NCT04493424), hidradenitis suppurativa (NCT04876391) and Crohn's disease (NCT04362254).

3 Current Status

Spesolimab received its first approval on 1 September 2022 in the USA for the treatment of GPP flares in adults [7]. On 26 September 2022, spesolimab was approved in Japan for the treatment of acute symptoms in GPP [9]. On 31 October 2022, spesolimab received a positive opinion in the EU for the treatment of flares in adult patients with GPP [10].

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Declarations

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

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