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Risankizumab for the treatment of moderate to severe psoriasis

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Abstract

Introduction: Psoriasis is a chronic inflammatory skin disorder pathogenically mediated by multiple cytokines, including interleukin (IL)-23, IL-17 and TNF. An emerging class of therapeutics that selectively blocks IL-23 has been developed. Among these new agents, risankizumab is now being investigated in phase III clinical trials, and the preliminary data are promising in inducing an excellent clinical response.

Areas covered: This review aims to describe the pathogenic role of IL-23 in psoriasis and to collect clinical data related to the efficacy and safety of risankizumab, an anti-IL-23p19 agent, in the treatment of psoriasis.

Expert Opinion: Risankizumab showed high response rates in reaching complete or almost complete clearance of psoriasis. When compared to other similarly effective drugs, it may show some advantages related to its mechanism of action (direct blockade of the main pathogenic pathway), safety (no impact on the immune surveillance against *Candida* infection), therapeutic regimen (every-12-week injections), and effectiveness in the treatment of immune-mediated psoriasis comorbid conditions, such as psoriatic arthritis and Crohn's disease.

Keywords: psoriasis, risankizumab, IL-23, pathogenesis, biologic

Drug summary box

Drug name	**Risankizumab**
Phase	**Phase III**
Indicate	**Psoriasis**
Pharmacology description/mechanism of action	**Antibody neutralizing the p19 subunit that constitutes IL-23**
Chemical structure	**Humanized monoclonal IgG1**
Pivotal trial(s)	**ClinicalTrials.gov number: NCT02054481, IMMhance, UltIMMa-1, UltIMMa-2, IMMvent [30-32, 34]**

1.0 Overview of the market

In the last three decades remarkable advances in understanding the pathogenic mechanisms underlying psoriasis manifestations, put the basis for the development of new effective drugs. In particular, monoclonal antibodies and fusion proteins inhibiting different cytokine-mediated signaling have completely revolutionized disease management. Additionally, oral low-molecular-weight compounds have been developed or approved for the treatment of psoriasis, expanding the antipsoriatic therapeutic armamentarium and, thus, creating a "biologic and small molecules jungle", as defined by Megna M et al., where the clinician needs guidance to performed a tailored therapeutic approach [1]. Because psoriasis is a chronic disorder, it requires long-lasting treatment durability in order to suffice better and long-term management. Satisfactory control of the disease over years may be considered the main unmet need that is not obtained in all treated patients, notwithstanding the increasingly higher number of therapeutics available for the treatment of psoriasis. Absolute or relative contraindications, adverse events or predictable class side effects, immunogenicity, and primary lack or secondary loss of efficacy, still represent limitations related to the currently marketed therapeutics. Thereby, the inception of a new class of agents targeting p19IL-23 subunit is considered an additional opportunity for optimally treating psoriasis. These new agents hold high promises in terms of efficacy, drug survival, and safety. Guselkumab, a fully human IgG1λ monoclonal antibody, and tildrakizumab, a high-affinity humanized IgG1k monoclonal antibody, obtained the approval by European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) for the treatment of psoriasis, and guselkumab is the first IL-23 blocker to be marketed. Therefore, risankizumab will represent the third agent, belonging to this biologic class, to face the market.

2.0 Immunopathogenesis of psoriasis

Psoriasis is a chronic inflammatory skin disorder clinically characterized by sharply demarcated, erythematous, and scaly plaques representing the result of a complex pathogenic mechanism, involving the immune compartment and tissue cells. In genetically predisposed subjects, endogenous or environmental factors may trigger an aberrant activation of immune cells that, through the release of pro-inflammatory and proliferative molecular factors, determine the development of psoriatic plaques clinically characterized by erythema and scaliness, possibly associated with itch and skin pain.

The identification of a new subset of T cells producing a pro-inflammatory cytokine, namely interleukin (IL)-17A, has opened new perspectives both in the pathogenesis and therapeutic management of this disease [2]. Indeed, the conventional pathogenic view that considered psoriasis a Th1 disease has been nowadays replaced by an IL-23/IL-17-centered model, wherein IL-17A production stimulated by IL-23 is critically important for the development of psoriasis phenotype [3]. However, even though the current immuno-pathogenic model, supported by various lines of evidence, defines psoriasis as an interleukin (IL)-23/IL-17A-mediated disorder, there are multiple pathways contributing to the pathogenic complexity of psoriasis, particularly in the early steps of the pathogenic cascade, wherein different initiators have been identified [4].

The activation of plasmacytoid dendritic cells (pDCs) by chemerin and TLR agonists could prime the inflammatory cascade of psoriasis through the secretion of IFN-α that, in turn, may potentially activate myeloid dendritic cells (mDCs), inducing the production of crucial pro-inflammatory mediators, including TNF, IL-23, IL-20, and nitric oxide [5-7]. Alternatively, the activation of the pathogenic cascade could be triggered by the presence of auto-reactive T cells recognizing as non-self certain protein antigens derived from keratinocytes (LL37), melanocytes (ADAMSTL-5), or lipid products generated by the activity of phospholipase A2

in mast cells. These auto-reactive T cell clones are able to produce pathogenic cytokines, such as IL-17, TNF, and IFN-γ. Other immune cells, including mast cells and neutrophils, participate in ~~to~~ the early steps of psoriasis pathogenesis through the secretion of large amounts of pro-inflammatory and pro-proliferative mediators. The activation of mDCs that could be triggered not only by pDC-derived IFN-α, but also by TNF and thymic stromal lymphopoietin (TSLP), represents a crucial pathogenic step, as they comprise the major source of IL-23, which is the most potent inducer of IL-17A expression [4].

Various immune cells are able of producing and/or secreting IL-17A. Firstly, T helper cells expressing IL-17A, the so-called Th17 cells, were identified as the most relevant sources of IL-17A in psoriasis and, in addition to this, they are also able to produce also IL-17F and IL-17A/IL-17F heterodimers. Nevertheless, other immune cells, ranging from $CD8^+$ T cells (Tc17 cells) to γδ T cells, innate lymphoid cells 3 (ILC3), mast cells, and neutrophils, have been subsequently described as potential sources of IL-17A leading to the characterization of a large pool of cells markedly infiltrating the psoriatic skin lesions explaining the IL-17A high expression levels detected in skin, serum and tear liquid of psoriatic patients [7]. IL-17A can induce a potent inflammatory response through the activation of tissue fibroblasts, endothelial cells, neutrophils and, in particular, keratinocytes, thus generating reverberating loops that sustain and boost skin inflammation. Skin cells secreting pro-inflammatory cytokines (IL-1β, TNF, IL-17C), antimicrobial peptides (β-defensins, S100A proteins, cathelicidin), chemoattractants, such as CC chemokine ligand 20 (CCL20), chemokine C-X-C motif ligands (CXCLs), and endothelial adhesion molecules (i.e., ICAM-1), stimulate the recruitment and migration of inflammatory cells at the lesional sites [8].

Although other cytokines are involved in the pathogenesis of psoriasis, owing to their pro-inflammatory (i.e., IFN-γ) and/or proliferative activity (i.e., IL-20 cytokine family members), the immune response is genetically oriented towards an IL-23/IL-17 activation [9].

Susceptibility genes, coding for intracellular signal transducers, involved in the IL-23/IL-17 pathway (TYK2, TNFAIP3, TRAF3IP2), or for downstream IL-17-signature molecules (DEFB4) have been identified, as compared to the lack of susceptibility genes related with the IFN-γ signaling pathway [9,10].

In the present review article, we provide an appraisal of current evidence supporting the rationale for considering IL-23 a valid therapeutic target and documenting the suitability of the IL-23 inhibitor risankizumab as a novel biotechnological drug for the therapeutic management of moderate-severe psoriasis.

3.0 Material and Methods

We carried out a search of the English-language literature regarding the pathogenic role of IL-23 in psoriasis and the pre-clinical and clinical development of the IL-23 inhibitor risankizumab for treatment of psoriasis utilizing the following databases: PubMed, Embase, Google Scholar, ResearchGate, and Scopus. Key words used were: ‘‘psoriasis’’, ‘‘psoriasis pathogenesis’’, ‘‘IL-23’’, “ABBV-066”, “BI-655066”, “risankizumab”, “anti-IL-23”, “biological therapies”, and “biologic”. All published articles plus data from recent international meetings were reviewed.

4.0 Role of IL-23 in the pathogenesis of psoriasis

IL-23 is a member of the IL-6/IL-12 cytokine family, which includes other members, such as IL-6, IL-12, IL-27, IL-35, IL-39, and IL-Y [11]. Similarly to IL-12 and all other members of the IL-6/IL-12 family, IL-23 is a heterodimer, consisting of two subunits, p19 and p40. The p40 subunit is common to both IL-23 and IL-12, while the p19 and the p35 subunit take part exclusively to the structure of IL-23 and IL-12, respectively [12]. A plethora of both immune and tissue cells, including keratinocytes and antigen-presenting cells, such as myeloid

dendritic cells, macrophages, and Langerhans cells [13], can produce IL-23 upon exposure to bacterial and fungal products that bind toll-like receptors (TLRs), as well as under chemokine (i.e., TSLP) and cytokine stimulation (i.e, TNF) [14].

Interleukin 23 exerts its biological effects via binding to the IL-23 receptor complex, which is expressed on $CD4^+$, CD8+ and γδ T cell subsets as well as NK cells, neutrophils, mast cells, innate lymphoid cells and macrophages [15]. The activation of this receptor, which comprises two subunits, IL-23Rα and IL-12Rβ1, promotes the phosphorylation of STAT3 and STAT4, mediated by Jak2 and Tyk2 activation, followed by their dimerization and migration into the nucleus, with subsequent activation of NF-κB and RORγt, [16]. In naïve T cells, IL-23 skews their differentiation towards a $ROR\gamma t^+$ T17 phenotype (IL-17-producing T cells), thus inducing and sustaining the Th17 differentiation primed by TGFβ IL-1β, and IL-6, [17], and impairing the differentiation of anti-inflammatory $CD4^+$ T cells (T regulatory cells, Treg cells). Overall, the activity of IL-23 within the T cell compartment favors the differentiation of pro-inflammatory T cells (characterized by the enhanced expression of IL-17A, IL-17F, IL-21 and IL-22), while negatively regulating the development of Treg cells.

Beside the T cell subsets, mast cells, innate lymphoid cells and neutrophils also do express the IL-23 receptor. To potentiate its signaling in a self-amplifying manner, IL-23 stimulates the expression of its own receptor [18]. The immunologic role of IL-23 is of crucial importance against bacterial and fungal pathogens, such as *Candida albicans*, *Klebsiella pneumoniae* and other extracellular bacteria, and its biologic activity is intimately mediated by IL-17A [18,19]. This IL-23/IL-17 immune axis, is also pivotal to the immuno-pathogenesis of psoriasis [7,20,21]. In support of this view, genome-wide association studies have suggested the gene coding for IL-23(p19), IL-12/IL-23(p40), and IL-23 receptor as psoriasis susceptibility genes [10]. In addition, psoriatic skin lesions displayed an overexpression of IL-12(p40) and IL-23(p19), as compared to non-skin lesions, in contrast to IL-12(p35) [21,22]. This increased

expression of IL-23 is due to the marked infiltration of myeloid dendritic cells ($CD11c^+$ dendritic cells) in psoriatic skin lesions, which represent the major source of IL-23 [23]. Likewise, IL-23 serum levels were found to be significantly higher in psoriatic patients than in healthy controls [24].

The pathogenic role of IL-23 has been determined through different functional studies demonstrating that IL-23 is pivotal to the formation of psoriasiform lesions [25]. Imiquimod application on mice skin-induced psoriasiform lesions correlated with a rapid increase in IL-23 expression followed by an increased production of both IL-17A and IL-17F [26]. In this model for the pathogenesis of psoriasis, IL-23 expression is crucial as demonstrated by the occurrence of psoriasiform lesions only in wild type mice and not in IL-23(p19) knockout mice [27]. In line with this evidence, the injection of mAbs, specifically neutralizing human IL-23, prevented or resolved the development of psoriasis lesions [25]. The occurrence of psoriasiform lesions was peculiarly related to IL-23 activity, as suggested by the development of psoriasiform skin lesions after intradermal injection of IL-23 in mice, by contrast with IL-12 stimulation that did not induce similar skin inflammatory lesions [28]. Of note, the pro-inflammatory activity of IL-23 is mediated by different effector cytokines, including IL-17A, IL-22, IL-21 and IL-17F, produced by a wide array of immune cells belonging to both adaptive and innate immunity.

5.0 Targeting the IL-23(p19) subunit of IL-23

Among the four anti-IL23p19 monoclonal antibodies (guselkumab, tildrakizumab, risankizumab, and LY2525623) that are being developed for the treatment of psoriasis, risankizumab, a humanized anti-IL-23p19 monoclonal IgG1, has shown significant clinical results in phase II studies and currently it is being evaluated in phase III trials.

5.1 Selection and molecular validation of risankizumab

Risankizumab is a humanized IgG_1 monoclonal antibody specifically designed to bind, with high selectivity, the p19 subunit of IL-23 over the p40 subunit, interact with high affinity with IL-23 to overcome the high-affinity binding of this interleukin with the IL-23 receptor, hold the ability of ensuring a prolonged neutralization of IL-23 with an administration rate of once monthly, and display favourable biophysical properties. Of note, the DNA sequence coding for the Fc region of risankizumab holds two mutations (L234A and L235A), which reduce greatly the potential for antibody-dependent cell-mediated cytotoxicity [29].

The murine molecular domains, containing the anti-p19 complementarity determining regions (CDRs) to be inserted into the variable region of IgG_1 Fab, were obtained through a screening program of mouse immunization with recombinant hybrid IL-23 (human-p19/mouse-p40). Hybridome methodology was then applied to isolate a pool of candidate monoclonal antibodies endowed with affinity and neutralizing activity on human recombinant IL-23. The murine antibody displaying a K_d <10 pM and an IC_{50} of 8 pM in inhibiting the production of IL-17 stimulated by IL-23 in mouse splenocytes was selected as the lead molecule for humanization with human IgG_1 molecular domains [29]. This procedure allowed the generation of a pool of four candidate anti-IL-23 humanized antibodies, which were transfected into the mouse myeloma NS0 cell line and underwent a large array of validation assays (molecular, cellular and biophysical) aimed at selecting the most suitable biomolecule for entering the clinical development program. In this setting, the antibody BI 655066 (later designated as risankizumab) was identified as the most suitable lead anti-IL-23 monoclonal antibody owing to: very high affinity for human recombinant IL-23 (<10 pM); very high potency in inhibiting IL-17 production induced by human IL-23 in mouse splenocytes (IC_{50}=2 pM); high specificity for the p19 over the p40 subunit; high affinity for FcRn receptors (likely contributing to a high rate of recycling in the blood circulation); low immunogenic potential; favourable biophysical properties, in terms of purity, homogeneity, solubility, low propensity

to aggregate upon concentration and molecular stability; favourable pharmacokinetic properties, as assessed upon single-dose intravenous administration to cynomolgus monkeys [29].

5.2 Phase I trial

A first-in-human, single-rising-dose, multicenter, randomized, double blind, placebo-controlled, proof-of-concept study, included 39 patients receiving risankizumab intravenously (n=18), subcutaneously (n=13) or matched placebo (n=8) [30]. Patients were randomized to receive increasing single doses of risankizumab intravenously or subcutaneously. Treatment response was assessed as Psoriasis Area Severity Index (PASI) score at both week 12 and week 24. After 12 weeks, risankizumab-treated patients achieved at least PASI 75%, 90% and 100% PASI score improvement in 87%, 58% and 16% of patients, respectively. At week 24, the response rates increased, obtaining PASI 75, PASI 90 and PASI 100 response in 71%, 48% and 29% of patients treated with risankizumab, respectively (Table 1). Within the placebo group no meaningful response was observed with the exception of 1 out of 8 patients achieving PASI 75 response at week 24 [30]. Clinical improvement assessed by static Physician Global Assessment (sPGA) in patients receiving risankizumab subcutaneously showed either “clear” or “almost clear” status at both week 12 and week 24 in all subjects [30].

Clinical improvement correlated with major inflammatory cell reductions, from baseline to week 8, of hyperkeratosis with parakeratosis, epidermal acanthosis and generalized inflammation within both dermis and epidermis. Indeed, a decreased expression of keratinocyte layer thickening (K16) and hyperproliferation (Ki67) was observed, as well as a reduced infiltration of dermal T cells (CD3), neutrophils (neutrophil gelatinase lipocalin), and dendritic cells (CD11c and DC-LAMP), along with a decrease in tissue inflammation (□-

defensin 2 and S100A7) [30]. As compared to placebo, risankizumab promoted significant reductions in the expression of genes associated with the IL-23/IL-17 axis (IL23A, IL23R, IL22, IL22RA1, IL22RA2, IL17A, IL17F, IL17RA, and IL17RC), keratinocyte and epithelial cell differentiation (late cornified envelope protein, transglutaminase 1, and cornifelin), tissue inflammation (β-defensin 2, neutrophil gelatinase lipocalin, and S100A7/A8), and the IFN-α pathway (IFIH1, ISG15, IRF7, IFI44, MX1, MX2, STAT1, and TRIM22) (Table 2). Notably, risankizumab suppressed significantly the IL-23 signaling in contrast with IFN-γ mRNA levels that did not vary significantly.

With regard to risankizumab pharmacokinetic (PK) properties, there is currently very limited available information in humans. However, some PK assessments were performed in this trial [30]. After single-dose administrations of risankizumab, by intravenous route at the doses of 0.01, 0.05, 0.25, 1, 3 and 5 mg/kg, or by subcutaneous route, at the doses of 0.25 and 1 mg/kg, blood samples were collected at baseline, on day 1 (0.5, 1, 2, 4, 8 and 16 hours after dosing), on days 2, 3, 7, 14 and 28, as well as every 4 weeks until week 24. The concentrations of free risankizumab in plasma samples were then assayed by means of an ELISA assay. The PK analysis allowed to estimate the following values: area underlying the concentration to time curve $(AUC)_{0\rightarrow\infty}$ 2.9-1650 days•µg/ml and C_{max} (meant as the highest concentration achieved by the drug in plasma following its administration) of 0.3-110 µg/ml, indicating a good and dose-dependent exposure of the body to the biodrug; a terminal phase distribution volume of 10.8 L, suggesting that the distribution of risankizumab remains confined predominantly within the blood circulation, and a clearance of 0.33 L/day, documenting a very low disposition rate of the biodrug from the bloodstream; a plasma half-life ($t_{1/2}$) of 20-28 days, confirming a very high persistence of this monoclonal antibody in the blood compartment, consistently with the profile required to an IgG_1 antibody targeted against a soluble antigen, like IL-23. Following subcutaneous administration, maximal body

exposures to risankizumab were achieved within 4-10 days, with a bioavailability of 59%, as compared with the intravenous route. These PK patterns were consistent with the estimation of exposure-efficacy relationship, which was calculated by a regression of risankizumab doses versus the respective PASI percentage changes from baseline, which showed comparable PASI responses with the intravenous and subcutaneous administrations, along with the achievement of maximal PASI responses at the doses of 0.25 mg/kg or higher [30]. Plasma concentration measurements obtained from 157 subjects with psoriasis enrolled in this phase I trial and in a phase II trial were evaluated together with measures derived from 115 subjects with Crohn's disease enrolled in a phase II trial [31]. This study aimed to assess risankizumab PK, evaluating covariates that may affect in two chronic immune-mediated inflammatory conditions, namely psoriasis and Crohn's disease. Body weight and baseline albumin level represented the two factors statistically correlating with risankizumab clearance, while body weight only had a modest effect on risankizumab exposure, with no significant differences between psoriasis and Crohn's disease populations [31].

With regard to safety, over a 24 week-treatment period, 65% of risankizumab-treated patients experienced an adverse event (AE), as compared to 88% in the placebo group. The most frequently reported AEs were mild-to-moderate upper respiratory tract infections, mild nasopharyngitis, and mild-to-moderate headache. Four serious AEs were recorded, but considered unrelated to the study medication [30].

5.3 Phase II trial

In a 48-week, multicenter, randomized, dose-ranging, phase IIb trial, comparing risankizumab with ustekinumab, patients with mild-to-moderate psoriasis were randomly assigned, in a 1:1:1:1 ratio, to receive: (i) a single dose of risankizumab 18 mg at week 0 (n = 43); (ii) 90 mg (n = 41) or 180 mg (n = 42) of risankizumab at weeks 0, 4, and 16; and (iii) ustekinumab

(n = 40) 45 or 90 mg depending on body weight (<100 or ≥100 kg), at weeks 0, 4 and 16 [32]. The primary endpoint was defined as a 90% or greater reduction from baseline of the PASI score at week 12. This was achieved–in 73% and 81% of patients treated with 90-mg risankizumab and 180-mg risankizumab, respectively, as compared to 40% of ustekinumab-treated patients ($p < 0.001$) [32]. Among the secondary endpoints, PASI 75 response at week 12 was achieved by 63% of patients in the 18-mg risankizumab group, 98% in the 90-mg risankizumab group, 88% in the 180-mg risankizumab group, as compared to 72% of the subjects treated with ustekinumab [32]. The rates of patient achieving skin clearance (100% PASI score) at week 12 were 14%, 41%, 48%, and 18% in the 18 mg, 90 mg, 180 mg risankizumab and ustekinumab groups, respectively (Table 3). Furthermore, 58%, 90%, 88% and 62% of patients scored 'minimal' or 'clear' on sPGA within the 18 mg, 90 mg, 180 mg risankizumab and ustekinumab groups, respectively [30]. At week 24, during the follow-up period, patients achieving at least a PASI 75 response were 53%, 90%, 88%, and 70% of the groups treated with 18, 90, 180 mg risankizumab and ustekinumab, respectively; a PASI 90 achievement was observed in 28%, 63%, 81% and 55% of patients treated with 18 mg, 90 mg, 180 mg risankizumab and ustekinumab, respectively [32]. A complete skin clearance was maintained in 29% of 90-mg risankizumab-treated patients and 26% of 180-mg risankizumab-treated patients for up to 32 weeks after the last administration. Patient-reported outcomes improved during both risankizumab and ustekinumab therapies consistently with decreases in the Dermatology Life Quality Index (DLQI), reaching values of 0-1 (absent or minimal impact on quality of life, QoL) in 72% of patients treated with risankizumab after 12-week treatment, as compared to 53% in the ustekinumab group [32]. Sub-analyses on scalp, fingernail and palmoplantar psoriasis documented a superior efficacy across 90-mg and 180-mg risankizumab groups, as compared to ustekinumab. Through the 48-week observational period, AEs occurred in 81% of 18-mg risankizumab-treated patients, 80% of 90-mg

risankizumab-treated patients, 69% of 180-mg risankizumab-treated patients, and 72% of ustekinumab-treated patients. The most common AE was nasopharyngitis (>10% patients) [32]. Three patients (one in each 18-mg risankizumab, 90-mg risankizumab, and ustekinumab group) withdrew from treatment because of the occurrence of an AE. Serious AEs were recorded in 12% 15%, 0 and 8% of patients included in the 18-mg, 90-mg, 180-mg risankizumab and ustekinumab groups, respectively [32]. Antidrug antibodies were detected in 14% of risankizumab-treated patients. In most cases they were transient, low-titer (<32) or both. Neutralizing antidrug antibodies were found in 3 patients in the multiple-dose risankizumab groups. This trial included also skin tissue analyses. Skin biopsies were taken from 60 risankizumab-treated patients at baseline and week 4, showing: (i) histological improvement of psoriatic lesional skin; (ii) decreased expression of selected genes involved in the IL-23 pathway (IL23R, β-defensin 4B), keratinocyte differentiation (late cornified envelope genes), and downregulation of type-1 interferon pathway-related genes [32].

5.4 Phase III trials

Several trials, with an overall involvement of more than 2000 patients with moderate-to-severe psoriasis, comprise the risankizumab phase III program.

A multicenter, randomized, double-blind, placebo-controlled trial (NCT02672852 [IMMhance]) showed a superior efficacy of risankizumab as compared to placebo, with the achievement of all primary endpoints (PASI 90 response and sPGA 0/1 at week 16) (Table 4). Seventy-three percent of risankizumab-treated patients achieved PASI 90 as compared to 2% in the placebo group, and marked differences between risankizumab therapy and placebo were observed also for other endpoints, including PASI 75 (89% vs 7%), PASI 100 (47% vs 1%), sPGA 0/1 (84% vs 7%), sPGA 0 (46% vs 1%) [33]. After 16-week treatment, patients achieving sPGA 0/1 at week 28 were re-randomized to risankizumab (maintenance regimen)

or placebo (withdrawal regimen). By week 32, any patient who experienced a relapse (defined as sPGA score ≥3) was retreated with risankizumab after 4 weeks and thereafter every 12 weeks. In this second phase, the primary endpoint of sPGA 0/1 at week 52 was achieved in 87% of patients treated continuously with risankizumab, while in patients assigned to a withdrawal regimen sPGA was obtained in 61% of cases. Serious AEs occurred in 2% of risankizumab-treated patients and 8% of placebo-treated patients through week 16. In the second phase of the study, through 104 weeks, 6% of patients in both regimen groups experienced serious AEs. Though no disease-related harmful signals emerged, 1 patient died of intestinal adenocarcinoma and metastatic hepatic cancer. One death was adjudicated as related to a major adverse cardiovascular event (MACE). Two additional MACEs were recorded (one in the placebo and one in the risankizumab group). All three patients had a past history of cardiovascular risk factors.

The clinical outcomes of two replicate head-to-head studies, evaluating risankizumab versus ustekinumab (NCT02684370 [UltIMMa-1] and NCT02684357 [UltIMMa-2]), have been recently published [34]. These randomised, double-blind, placebo-controlled and active comparator-controlled phase III trials stratified patients by weight and previous exposure to TNF inhibitor, and assigned them randomly (3:1:1) to receive 150 mg risankizumab, 45 mg or 90 mg ustekinumab (weight-based per label), or placebo [34]. The study drugs were administered subcutaneously at weeks 0, 4, 16, 28 and 40 for a total study period of 52 weeks. After the 16-week double-blind treatment period, placebo-treated patients were switched to 150 mg risankizumab. The PASI 90 response and sPGA score of 0 or 1 at week 16 represented the co-primary endpoints. These studies included 506 and 491 patients in UltIMMa-1 and UltIMMa-2, respectively, showing higher proportions of patients with previous exposure to biologic therapy (34–41%) [34]. In the UltIMMa-1 trial, the PASI 90 response at week 16 was achieved by a significantly higher rate of patients receiving

risankizumab (75.3%) as compared to both placebo (4.9%) and ustekinumab (42.0%). The other co-primary endpoint (sPGA 0 or 1) at week 16 was achieved by 87.8% of patients receiving risankizumab, as compared to 7.8% and 63.0% of patients treated with placebo and ustekinumab, respectively ($p<0{\cdot}0001$, risankizumab vs. placebo and ustekinumab). At week 16, skin clearance assessed by PASI score improvement (PASI 100 response) was observed in 35.9%, 12.0%, and 0% of patients treated with risankizumab, ustekinumab, and placebo, respectively. Skin improvement reflected an amelioration of QoL, with DLQI 0 or 1 obtained at week 16 in 65.8%, 43.0%, and 7.8% of patients treated with risankizumab, ustekinumab, and placebo, respectively [34].

Similarly, the UltIMMa-2 trial showed that a PASI 90 response was achieved by a significantly higher rate of patients in the risankizumab group, as compared to both placebo and ustekinumab (74.8% vs 2.0% vs. 47.5%). sPGA 0 or 1 at week 16 was obtained in 83.7% of risankizumab-treated patients, as compared to 5.1% and 61.6% of placebo- and ustekinumab-treated patients, respectively [34]. In line with the UltIMMa-1 trial, PASI 100 at week 16 in UltIMMa-2 was achieved by 50.7%, 2.0%, and 24.2% of risankizumab, placebo-, and ustekinumab-treated patients, corresponding to a DLQI response of 0 or 1 at week 16 in 66.7%, 4.1%, and 46.5% of patients [34].

Both the UltIMMa-1 and UltIMMa-2 trials showed sustained responses to risankizumab treatment over 52 weeks, with PASI 90 response observed in 80.6-81.9% of patients, as compared to 44.0-50.5% of ustekinumab-treated patients. PASI 100 at week 52 was recorded in 56.3-59.5% of risankizumab-treated patients, as compared to 21.0-30.3% of ustekinumab-treated patients. The frequency of treatment-emergent adverse events in UltIMMa-1 and UltIMMa-2 was similar across risankizumab, placebo, and ustekinumab groups, throughout the study duration.

Recently published data of another 1:1 randomized, double-dummy, active-controlled phase

III study (NCT 02694523 [IMMvent]), evaluating risankizumab efficacy and safety against adalimumab, reported a PASI 90 response in 72% of patients receiving 150 mg risankizumab as compared to 47% of adalimumab-treated patients [33]. At week 16, a PASI 100 response was observed in 40% of risankizumab-treated patients vs 23% of adalimumab-treated patients, while a sPGA score of clear or almost clear (sPGA 0/1) was achieved by 84% and 60% of patients treated with risankizumab and adalimumab, respectively. The skin improvement induced by risankizumab at week 16 was associated with a significantly greater improvement in DLQI score from baseline as compared to adalimumab [33]. Moreover, at week 16 a significantly higher number of patients treated with risankizumab achieved a DLQI score of 0 or 1 (66%) as compared to adalimumab (49%) ($p<0.001$) [33]. At week 44, patients maintained the benefits achieved with risankizumab. Of note, another multicenter, randomized, open label, efficacy assessor-blinded study comparing risankizumab with secukinumab is ongoing (NCT03478787) [35].

6.0 Regulatory affairs

Risankizumab is being evaluated in phase III trials and on April 25th 2018 the drug company (AbbVie) currently owing risankizumab submitted biologics license application to U.S. FDA for investigational treatment risankizumab for moderate to severe plaque psoriasis. A month later (May 11th 2018) a marketing authorization application for risankizumab was submitted to the EMA with the intention of seeking approval for its use in moderate-to-severe plaque psoriasis.

7.0 Conclusion

Solid evidence supports the concept that IL-23 plays a central role in the immuno-pathogenesis of psoriasis. The ultimate proof of the pathogenic relevance of this interleukin is provided by the striking efficacy of IL-23p19 blockers in patients with psoriasis. In particular, risankizumab has proven to be highly effective in the therapy of psoriasis with high rates of

PASI 90 and PASI 100 responders, exceeding 80% and 55% of patients, respectively, after 52 weeks of treatment. Notably, across four phase III studies (UltIMMa-1 and -2, IMMhance, IMMvent), risankizumab met all co-primary and ranked secondary endpoints without any new safety warning signals [33,34,36]

8.0 Expert opinion

The important role of IL-23 in the immunopathogenesis of psoriasis is well established. Together with IL-17A, IL-23 represents the main axis driving the development of psoriasis phenotype. Targeting this axis, last generation therapeutic agents have allowed to achieve significant clinical advantages as compared to other available antipsoriatic therapies. However, as we are having an increasing number of therapeutics approved for treatment of psoriasis, the "place-in-therapy" for a new agent entering the market is becoming challenging. The high efficacy of anti-IL-17/IL-17-receptor agents, which achieve a significant PASI 90 response in most of the treated patients, has raised the bar of the treatment goal, highlighting the clinical relevance of achieving PASI 90 that correlates with minimal or no impact of the disease on patients' health-related QoL (DLQI 0–1). Hence, to be successful, a novel drug must be competitive with the class of IL-17/IL-17-receptor targeting therapies, with no significant new side effects.

The promising data from Phase II and III trials have profiled the IL-23 blocker risankizumab as a strikingly effective drug, with treatment response levels similar or slightly higher to the majority of currently marketed biologic drugs. Being administered every 12 weeks, risankizumab confers the advantage (not only over the IL-17/IL-17-receptor, but also over the anti-IL-23 guselkumab) of requiring fewer injections per year as well as potentially less physician accesses for patients. In certain countries this feature would have primary relevance, because of insurance or public payer coverage/reimbursement. Moreover,

risankizumab has the advantage of maintaining a fixed dose irrespective of body weight, conversely to ustekinumab that requires dose adjustment based on body weight. Since psoriasis is frequently associated with a wide *spectrum* of comorbid conditions and their presence should have relevant impact on the therapeutic approach, the effects of risankizumab on these conditions will be clinically meaningful. When certain therapeutics are not effective, not recommended, or contraindicated for treatment of psoriasis in the presence of some specific comorbidities, this will limit to their prescriptions. Considering that a significant proportion of psoriasis patients suffer concomitantly of arthritis (up to 42%) and, to a much lower extent, of Crohn's disease (0.5%), the development of risankizumab in the treatment of these conditions could potentially orientate the therapeutic choice towards risankizumab for treatment of these patient subpopulations [37,38]. In this respect, it is noteworthy that risankizumab is currently under phase III testing for both Crohn's disease and psoriatic arthritis, with preliminary data, particularly for Crohn's disease, highly promising, as highlighted also by the Orphan Drug Designation granted by the U.S. FDA to risankizumab for the investigational treatment of Crohn's disease in pediatric patients [39-41].

No safety concerns related to the use of risankizumab have emerged from the phase III trials, even though the occurrence of rare cases of MACEs will make long-term evaluations of this important, class of AEs. Since the clinical development of briakinumab, a fully human monoclonal antibody directed against the IL-12/IL-23p40 subunit, was discontinued due to higher rates of MACEs as compared to placebo, the IL-12/IL-23 inhibition was hypothesized to induce instability of atherosclerotic plaques. However, no warning signals about MACEs have been associated with ustekinumab over the 9 years of clinical usage, which has shown, across national and international registries, the safest profile among the antipsoriatic systemic drugs to date. When compared to ustekinumab, risankizumab is able to inhibit selectively the pathogenic signal mediated by IL-23, thus preserving the IL-12/IFN-γ signaling that is pivotal

to both anti-viral and anti-cancer immune-surveillance. However, the robust safety profile, generated by long-term registry data related to the clinical use of ustekinumab, does not support any advantage of blocking the p19 subunit, in terms of safety implications, as compared to the p40 inhibition [42-45]. By contrast, risankizumab might be advantageous over the IL-17/IL-17-receptor blockers in terms of risk of candida infections. Indeed, no harmful signals, in the short- and mid-term period, have been associated with risankizumab, even though mice models do suggest a central role of IL-23 in candida infections [19,46].

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Megna M, Balato A, Napolitano M, Gallo L, Caso F, Costa L, et al. Psoriatic disease treatment nowadays: unmet needs among the "jungle of biologic drugs and small molecules". Clin Rheumatol. 2018; 37(7): 1739-1741.
2. O'Shea JJ, Steward-Tharp SM, Laurence A, Watford WT, Wei L, Adamson AS, Fan S. Signal transduction and Th17 cell differentiation. Microbes Infect. 2009;11(5):599-611.
3. Hawkes JE, Chan TC, Krueger JG. Psoriasis pathogenesis and the development of novel targeted immune therapies. J Allergy Clin Immunol 2017;140:645-53.
4. Chiricozzi A, Romanelli P, Volpe E, Borsellino G, Romanelli M. Scanning the Immunopathogenesis of Psoriasis. Int J Mol Sci 2018; 19(1). pii: E179
5. Gilliet M, Conrad C, Geiges M, Cozzio A, Thürlimann W, Burg G, et al. Psoriasis triggered by toll-like receptor 7 agonist imiquimod in the presence of dermal plasmacytoid dendritic cell precursors. Arch. Dermatol. 2004; 140: 1490–1495.

** Activation of plasmacytoid dendritic cells by toll-like receptor agonists

6. Albanesi C, Scarponi C, Pallotta S, Daniele R, Bosisio D, Madonna S, et al. Chemerin expression marks early psoriatic skin lesions and correlates with plasmacytoid dendritic cell recruitment. J Exp Med. 2009; 206(1): 249-58.

* Study demonstrating the pathogenic relevance of chemerin in psoriasis

7. Blauvelt A, Chiricozzi A. The Immunologic Role of IL-17 in Psoriasis and Psoriatic Arthritis Pathogenesis. Clin Rev Allergy Immunol. 2018 Aug 14. doi: 10.1007/s12016-018-8702-3. [Epub ahead of print]

8. Chiricozzi A, Nograles KE, Johnson-Huang LM, Fuentes-Duculan J, Cardinale I, Bonifacio KM, et al. IL-17 induces an expanded range of downstream genes in reconstituted human epidermis model. PLoS ONE 2014; 9: e90284.
9. Martin DA, Towne JE, Kricorian G, Klekotka P, Gudjonsson JE, Krueger JG, et al. The emerging role of IL-17 in the pathogenesis of psoriasis: Preclinical and clinical findings. J Invest Dermatol 2013; 133: 17–26
10. Capon F. The Genetic Basis of Psoriasis. Int J Mol Sci. 2017; 18(12): pii: E2526.
11. Hasegawa H, Mizoguchi I, Chiba Y, Ohashi M, Xu M, Yoshimoto T. Expanding diversity in molecular structures and functions of the IL-6/IL-12 heterodimeric cytokine family. Front Immunol. 2016; 7:479.
12. Oppmann B, Lesley R, Blom B, Timans JC, Xu Y, Hunte B, et al. Novel p19 protein engages IL-12p40 to form a cytokine, IL-23, with biological activities similar as well as distinct from IL-12. Immunity. 2000; 13:715–725.
13. Tonini A, Gualtieri B, Panduri S, Romanelli M, Chiricozzi A. A new class of biologic agents facing the therapeutic paradigm in psoriasis: anti-IL-23 agents. Expert Opin Biol Ther. 2018; 18(2):135-148.
14. Liu W, Ouyang X, Yang J, Liu J, Li Q, Gu Y, et al. AP-1 activated by toll-like receptors regulates expression of IL-23 p19. J Biol Chem. 2009; 284(36):24006-24016.
15. Parham C, Chirica M, Timans J, Vaisberg E, Travis M, Cheung J, et al. A receptor for the heterodimeric cytokine IL-23 is composed of IL-12Rbeta1 and a novel cytokine receptor subunit, IL-23R. J Immunol. 2002; 168(11):5699-5708.
16. Cho ML, Kang JW, Moon YM, Nam HJ, Jhun JY, Heo SB, et al. STAT3 and NF-kappaB signal pathway is required for IL-23-mediated IL-17 production in

spontaneous arthritis animal model IL-1 receptor antagonist-deficient mice. J Immunol. 2006; 176(9):5652-5661.

17. Volpe E, Servant N, Zollinger R, Bogiatzi SI, Hupé P, Barillot E, et al. A critical function for transforming growth factor-beta, interleukin 23 and proinflammatory cytokines in driving and modulating human T(H)-17 responses. Nat Immunol. 2008; 9(6):650-657.
18. Langrish CL, Chen Y, Blumenschein WM, Mattson J, Basham B, Sedgwick JD, et al. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. J Exp Med. 2005; 201(2):233-240.
19. Kagami S, Rizzo HL, Kurtz SE, Miller LS, Blauvelt A. IL-23 and IL-17A, but not IL-12 and IL-22, are required for optimal skin host defense against Candida albicans. J Immunol. 2010;185(9):5453-62.

** Relevance of IL-23 against candida infection

20. Chiricozzi A, Saraceno R, Chimenti MS, Guttman-Yassky E, Krueger JG. Role of IL-23 in the pathogenesis of psoriasis: a novel potential therapeutic target? Expert Opin Ther Targets. 2014; 18(5):513-525.
21. Lee E, Trepicchio WL, Oestreicher JL, Pittman D, Wang F, Chamian F, et al. Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. J Exp Med. 2004; 199(1):125-130.

** First evidence of increased IL-23 expression in lesional psoriatic skin.

22. Piskin G, Sylva-Steenland RM, Bos JD, Teunissen MB. In vitro and in situ expression of IL-23 by keratinocytes in healthy skin and psoriasis lesions: enhanced expression in psoriatic skin. J Immunol. 2006;176:1908-1915.
23. Zaba LC, Krueger JG, Lowes MA. Resident and "inflammatory" dendritic cells in human skin. J Invest Dermatol. 2009;129:302-308.

24. Fotiadou C, Lazaridou E, Sotiriou E, Gerou S, Kyrgidis A, Vakirlis E,et al. IL-17A, IL-22, and IL-23 as markers of psoriasis activity: a cross-sectional, hospital-based study. J Cutan Med Surg. 2015;19(6):555-560.

25. Tonel G, Conrad C, Laggner U, Di Meglio P, Grys K, McClanahan TK, et al. Cutting edge: a critical functional role for IL-23 in psoriasis. J Immunol. 2010;185(10):5688-5691.

26. van der Fits L, Mourits S, Voerman JS, Kant M, Boon L, Laman JD, et al. Imiquimod-induced psoriasis-like skin inflammation in mice is mediated via the IL-23/IL-17 axis. J Immunol. 2009; 182(9):5836-45.

27. Nakajima K, Kanda T, Takaishi M, Shiga T, Miyoshi K, Nakajima H et al. Distinct roles of IL-23 and IL-17 in the development of psoriasis-like lesions in a mouse model. J Immunol. 2011;186(7):4481–4489.

28. Chan JR, Blumenschein W, Murphy E, Diveu C, Wiekowski M, Abbondanzo S, et al. IL-23 stimulates epidermal hyperplasia via TNF and IL-20R2-dependent mechanisms with implications for psoriasis pathogenesis. J Exp Med. 2006;203(12):2577-2587.

29. Singh S, Kroe-Barrett RR, Canada KA, Zhu X, Sepulveda E, Wu H, et al. Selective targeting of the IL23 pathway: Generation and characterization of a novel high-affinity humanized anti-IL23A antibody. MAbs. 2015;7(4):778-91.

30. Krueger JG, Ferris LK, Menter A, Wagner F, White A, Visvanathan S, et al. Anti-IL-23A mAb BI 655066 for treatment of moderate-to-severe psoriasis: Safety, efficacy, pharmacokinetics, and biomarker results of a single-rising-dose, randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol. 2015;136(1):116-124.e7

** Mechanistic study showing risankizumab effects on lesion skin gene expression profile, pharmacokinetics, and histopathological features

31. Suleiman AA, Khatri A, Minocha M, Othman AA. Population Pharmacokinetics of the Interleukin-23 Inhibitor Risankizumab in Subjects with Psoriasis and Crohn's Disease: Analyses of Phase I and II Trials. Clin Pharmacokinet. 2018 Aug 20. doi: 10.1007/s40262-018-0704-z. [Epub ahead of print]

32. Papp KA, Blauvelt A, Bukhalo M, Gooderham M, Krueger JG, Lacour JP, et al. Risankizumab versus Ustekinumab for Moderate-to-Severe Plaque Psoriasis. N Engl J Med. 2017;376(16):1551-1560.

** Head-to-head trial testing ustekinumab vs risankizumab, showing superiority of risankizumab in treating psoriasis

33. Blauvelt A, Papp KA, Gooderham M, Langley RG, Leonardi C, Lacour JP, Philipp S, Tyring S, Bukhalo M, Wu JJ, Bagel J, Frankel EH, Pariser D, Flack M, Scherer J, Geng Z, Gu Y, Camez A, Thompson EHZ Efficacy and safety of risankizumab, an interleukin-23 inhibitor, in patients with moderate-to-severe chronic plaque psoriasis: 16-week results from the phase III IMMhance trial. FC – 29 Poster presented at Psoriasis from gene to clinic, 30th November – 2nd December 2017

34. Gordon KB, Strober B, Lebwohl M, Augustin M, Blauvelt A, Poulin Y, et al. Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis(UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. Lancet. 2018;392(10148):650-661.

35. https://clinicaltrials.gov/ct2/show/NCT03478787

36. EUCTR2015□003623□65. BI 655066 (risankizumab) versus adalimumab in a randomised, double blind, parallel group trial in moderate to severe plaque psoriasis to assess safety and efficacy after 16 weeks of treatment and after inadequate adalimumab treatment response (IMMvent) □ BI 655066 (risankizumab) versus adalimumab. www.clinicaltrialsregister.eu/ctr□

search/search?query=eudract_number%3A2015□003623□65/EUCTR2015□003623□65 Date first received: 17 May 2016.

37. Gladman DD1, Antoni C, Mease P, Clegg DO, Nash P. Psoriatic arthritis: epidemiology, clinical features, course, and outcome. Ann Rheum Dis. 2005; 64(2):ii14-7.
38. Cohen AD, Dreiher J, Birkenfeld S. Psoriasis associated with ulcerative colitis and Crohn's disease. J Eur Acad Dermatol Venereol 2009; 23: 561-565.
39. https://news.abbvie.com/news/abbvie-receives-orphan-drug-designation-for-investigational-il-23-inhibitor-risankizumab-from-us-food-and-drug-administration-for-treatment-pediatric-patients-with-crohns-disease.htm
40. Feagan BG, Sandborn WJ, D'Haens G, Panés J, Kaser A, Ferrante M, et al. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's disease: a randomised, double-blind, placebo-controlled phase 2 study. Lancet. 2017; 389(10080): 1699-1709.
41. Mease PJ, Kellner H, Morita A, Kivitz AJ, Papp KA, Aslanyan S, et al. Efficacy and Safety Results from a Phase 2 Trial of Risankizumab, a Selective IL-23p19 Inhibitor, in Patients with Active Psoriatic Arthritis [abstract]. Arthritis Rheumatol. 2017; 69(10)
42. Papp K, Gottlieb AB, Naldi L, Pariser D, Ho V, Goyal K, et al. Safety Surveillance for Ustekinumab and Other Psoriasis Treatments From the Psoriasis Longitudinal Assessment and Registry (PSOLAR). J Drugs Dermatol. 2015;14(7):706-14.
43. Dávila-Seijo P, Dauden E, Carretero G, Ferrandiz C, Vanaclocha F, Gómez-García FJ, et al. Survival of classic and biological systemic drugs in psoriasis: results of the BIOBADADERM registry and critical analysis. J Eur Acad Dermatol Venereol. 2016;30(11):1942-1950.

44. Medina C, Carretero G, Ferrandiz C, Dauden E, Vanaclocha F, Gómez-García FJ, et al. Safety of classic and biologic systemic therapies for the treatment of psoriasis in elderly: an observational study from national BIOBADADERM registry. J Eur Acad Dermatol Venereol. 2015;29(5):858-64.

45. Egeberg A, Ottosen MB, Gniadecki R, Broesby-Olsen S, Dam TN, Bryld LE, et al. Safety, efficacy and drug survival of biologics and biosimilars for moderate-to-severe plaque psoriasis. Br J Dermatol. 2018;178(2):509-519

46. Blauvelt A, Lebwohl MG, Bissonnette R. IL-23/IL-17A dysfunction phenotypes inform possible clinical effects from anti-IL-17A therapies. J Investigative Dermatol. 2015;135:1946-1953.

Table 1. Phase I trial outcomes in psoriatic patients treated with either risankizumab or placebo.

Efficacy Results at Week 24				
	PASI 75**	**PASI 90****	**PASI 100**	**sPGA 0-1**
Risankizumab (n=31)	**71%**	**48%**	**29%**	**100%**
Placebo (n=8)	**13%**	**0%**	**0%**	**0%**

PASI: Psoriasis Area and Severity Index; sPGA: Static Physician Global Assessment

Table 2. Risankizumab effects on psoriasis pathogenic cells.

	Risankizumab effects
Keratinocytes	Reduced expression of K16 and Ki67 (proliferation KC markers), late cornified envelope protein, transglutaminase 1, and cornifelin (differentiation KC markers), IL17RA, and IL17RC IL22RA1, IL22RA2, β-defensin 2, neutrophil gelatinase lipocalin, and S100A7/A8 (immune activation)
T cells	Reduced T cell infiltration and decreased expression of IL23R, IL22, IL17A, IL17F; increased IFN-γ expression
Neutrophils	Reduced expression of neutrophil gelatinase lipocalin
Dendritic cells	Reduced expression of CD11c, DC-LAMP, and IL23A; suppression of IFNα pathway (IFIH1, ISG15, IRF7, IFI44, MX1, MX2, STAT1, and TRIM22)

K16: keratin 16; KC: keratinocytes; IL: interleukin; IFN: interferon.

Table 3. Outcomes derived from 48-week, multicenter, randomized, dose-ranging, phase IIb trial, comparing risankizumab with ustekinumab.

		Head-to-head phase II			
		Single risankizumab 18 mg dose (n = 43)	Multiple risankizumab 90 mg doses (n = 41)	Multiple risankizumab 180 mg doses (n = 42)	Ustekinumab (n = 40)
Week 12	PASI 75	63%	98%	88%	72%
	PASI 90	33%	73%	81%	40%
	PASI 100	14%	41%	48%	18%
	sPGA 0-1	58%	90%	88%	62%
Week 24	PASI 75	53%	90%	88%	70%
	PASI 90	28%	63%	81%	55%

PASI: Psoriasis Area and Severity Index; sPGA: Static Physician Global Assessment

Table 4. Co-primary endpoint results at week 16 across the risankizumab phase 3 psoriasis program.

Study	PASI 90			PASI 100			sPGA (0/1)		
	Placebo	Risankizumab	Ustekinumab	Placebo	Risankizumab	Ustekinumab	Placebo	Risankizumab	Ustekinumab
ultIMMa-1 (PBO n=102, risankizumab n=304, ustekinumab n=100)	5%	75%	42%	0%	35.9%	12.0%	8%	88%	63%
ultIMMa-2 (PBO n=98, risankizumab n=294, ustekinumab n=99)	2%	75%	48%	2.0%	50.7%,	24.2%	5%	84%	62%
IMMhance (PBO n=100, risankizumab n=407)	2%	73%	N/A	1%	47%	N/A	7%	84%	N/A
	Adalimumab	Risankizumab		Adalimumab	Risankizumab		Adalimumab	Risankizumab	
IMMvent (adalimumab n=304, risankizumab n=301)	47%	72%	N/A	23%	40%	N/A	60%	84%	N/A

PASI: Psoriasis Area and Severity Index; sPGA: Static Physician Global Assessment