Treatment with spesolimab, an anti-interleukin-36 receptor antibody, in patients with generalized pustular psoriasis, is associated with the downregulation of biomarkers linked to innate, Th1/Th17 and neutrophilic pathways

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Patrick Baum[1], Sudha Visvanathan[2], Sebastian Bossert[1], Benjamin Lang[1], Ramona Schmid[1], Sandra Garcet[3], Steven J Padula[4], Hervé Bachelez[5], Christian Thoma[1], James G Krueger[3]

[1]Boehringer Ingelheim International GmbH, Biberach, Germany; [2]Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA; [3]Laboratory for Investigative Dermatology, Rockefeller University, NY, USA; [4]Boehringer Ingelheim International GmbH, Ingelheim, Germany; [5]UMR INSERM U1163, Institut Imagine, Paris, France

Background

- Generalized pustular psoriasis (GPP) is a rare, potentially life-threatening, severe multisystemic disease first described by Von Zumbusch in 1910[1]
- GPP is a major therapeutic challenge, with no biologic therapies currently approved in the US or Europe
- Interleukin (IL)-36 appears to be central in the pathogenesis of GPP, as evidenced by the occurrence of GPP in patients who have a defective IL-36 receptor antagonist (IL-36Ra)[2–7]
  - In patients with deficiency of interleukin thirty-six-receptor antagonist (DITRA), loss-of-function mutations in the gene encoding IL-36Ra (*IL36RN*) causes GPP through hyperactivation of the IL-36 signaling pathway
  - Mutations in other genes linked to the IL-36 pathway, including *CARD14* and *AP1S3*, are also associated with GPP
- In a Phase I, multicentre , single-arm, open-label study (ClinicalTrials.gov identifier: NCT02978690), seven patients (three with a homozygous *IL36RN* mutation) presenting with a moderate-to-severe GPP flare were treated with a single intravenous (IV) dose of 10 mg/kg of spesolimab (BI 655130), a humanised anti-IL-36 receptor (IL-36R) monoclonal antibody[8]
  - Spesolimab treatment led to rapid clinical improvements in all patients, irrespective of *IL36RN* mutation status[8]
  - Spesolimab was associated with a good safety and tolerability profile[8]
- Here, we present the molecular effects of IL-36R blockade with spesolimab in patients with GPP from this Phase I study

Methods

- Adult (aged 18–75 years) patients with a known and documented history of GPP, regardless of *IL36RN* mutation status, presenting with a moderate-to-severe GPP flare involving ≥10% of their body surface area with erythema and pustules and a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score ≥3, received a single IV dose of 10 mg/kg spesolimab[8]
- The primary endpoint was the safety and tolerability of spesolimab[8]
- Key secondary endpoints included the proportion of patients with a GPPGA total score of 0 (clear) or 1 (almost clear) and percent change from baseline in Generalized Pustular Psoriasis Area and Severity Index (GPPASI) total score at Week 2[8]
- Patients were monitored for 20 weeks[8]
- Global transcriptome-wide sequencing of RNA from lesional and non-lesional skin biopsy samples and whole blood from all patients were assessed to characterise the cellular and molecular response to spesolimab
  - Skin biopsies were performed at baseline and at Week 1, with an optional biopsy at Week 2
    - RNA sequencing and immunohistochemical (IHC) analysis were performed at baseline for non-lesional and lesional skin, and at Weeks 1 and 2 for lesional skin
  - Whole blood and serum were collected at multiple timepoints
    - RNA sequencing was performed at baseline, and at Weeks 1, 2, and 4
    - Serum samples were assayed for multiple biomarkers utilising the Randox Biochip Array platform at baseline and at Weeks 2, 4 and 12
- Biomarkers associated with GPP were assessed in skin biopsies using IHC at baseline and at Week 1 using a semi-quantitative scoring method

Results

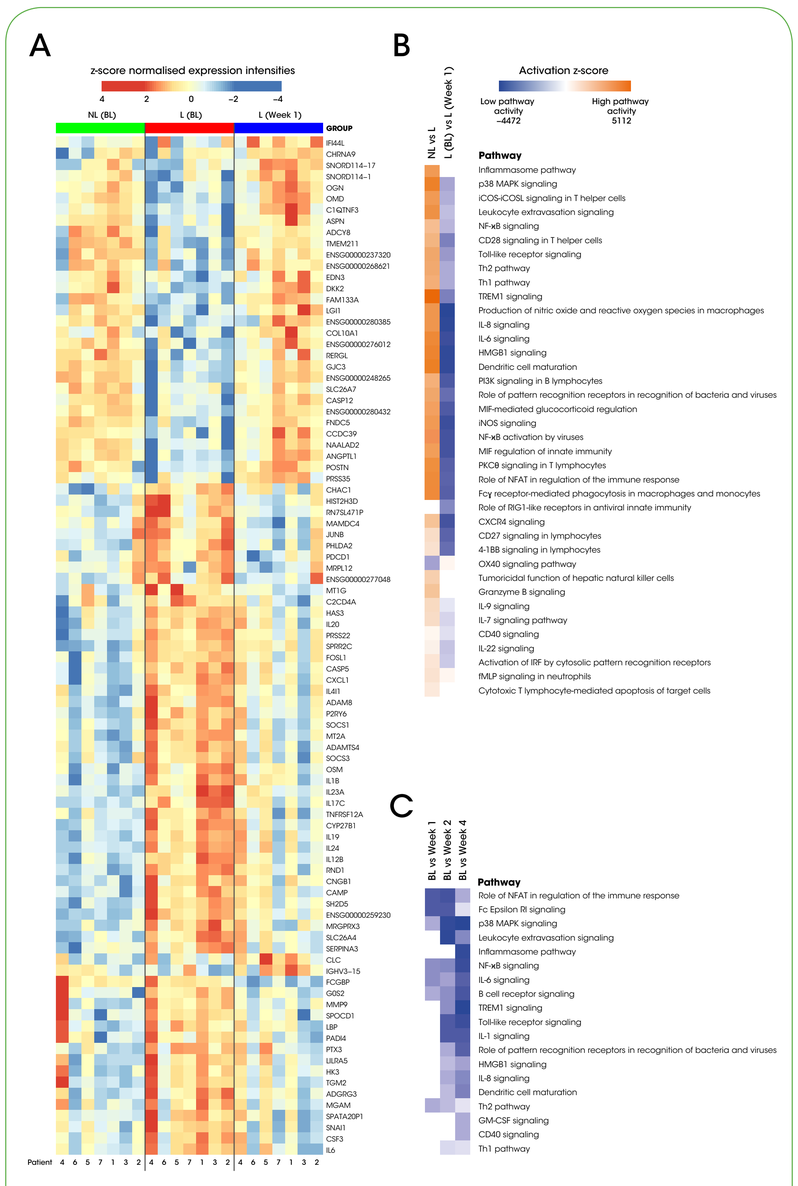
Patients

- In total, seven patients experiencing a moderate-to-severe GPP flare received a single IV dose of 10 mg/kg spesolimab
  - Three patients carried a homozygous *IL36RN* mutation and one patient carried a heterozygous *CARD14* mutation
- All seven patients completed the trial up to Week 20

Biomarker analyses

- At baseline, global transcriptome analysis identified 3276 genes that were differentially expressed (1885 elevated; 1391 decreased) in lesional and non-lesional skin biopsies (adjusted p≤0.05, fold-change ≥2)
  - By Week 1, the expression of 1444 genes in lesional skin reached near non-lesional levels (adjusted p≤0.05, fold-change ≥2; **Figure 1A**)
  - Gene expression for all IL-36 ligands were strongly upregulated (*IL36A*: 90-fold; *IL36B*: 2.6-fold; *IL36G*: 13-fold) in untreated lesional skin versus non-lesional skin from all patients with GPP in this Phase I study
  - Differentially expressed genes were associated with innate (e.g. *IL6, TNFα, CXCL1*) and Th1/Th17–mediated inflammation (e.g. *IL1B, IL12B, IL23A*), and proinflammatory processes of keratinocyte activation (e.g. *IL17C, IL24*)
  - Differentially expressed genes were analysed using Ingenuity Pathway Analysis (IPA); activation z-scores obtained for canonical pathways found that the higher activity in lesional skin at baseline was downregulated by spesolimab by Week 1 **(Figure 1B)**
  - Strong inhibition of T-cell activity was observed following spesolimab treatment; this was consistent with the downregulation of elevated *IL17C* causing inhibition of the feed-forward inflammatory response and strongly affecting T-cell activation
- RNA expression from whole blood detected differentially expressed genes (adjusted p≤0.05, fold-change ≥2) at Weeks 1, 2 and 4 compared with baseline (364, 476 and 563 genes, respectively)
  - Proinflammatory mediators involved in neutrophil activation (e.g. *IL1B, CD177, S100A8/9, S100A12, MMP9, MMP25*) were among the genes most strongly downregulated
  - Differentially expressed genes were analysed using IPA and activation z-scores were derived for canonical immune response pathways; comparisons of activity at baseline with Weeks 1, 2 and 4 post spesolimab treatment show clear and sustained downregulation of immune responses **(Figure 1C)**

Figure 1. Differentially expressed genes in skin and blood following treatment with spesolimab



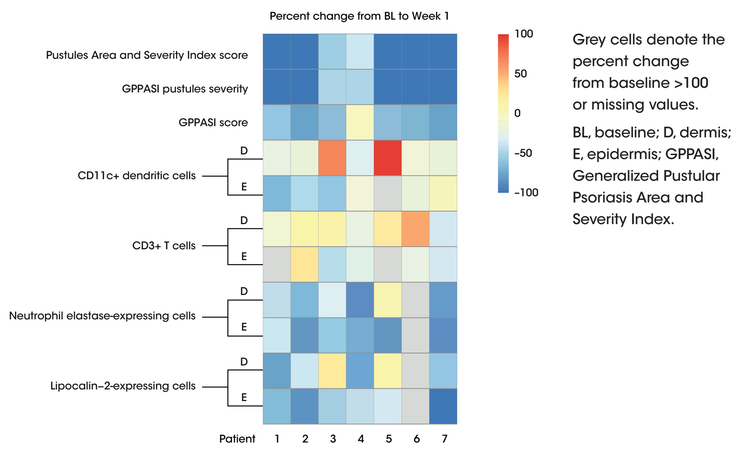
(Panel A) Changes in select genes (n=91; RNA seq) expressed in lesional and non-lesional skin at baseline versus Week 1.

(Panel B) Ingenuity Pathway Analysis of differentially expressed genes in lesional and non-lesional skin at baseline and at Week 1.

(Panel C) Ingenuity Pathway Analysis of differentially expressed genes in blood at baseline and at Weeks 1, 2, and 4.

BL, baseline; L, lesional; NL, non-lesional.

Figure 2. Heatmap of changes in clinical scores and immunohistochemical biomarkers from baseline to Week 1 in each patient following spesolimab treatment



Grey cells denote the percent change from baseline >100 or missing values.

BL, baseline; D, dermis; E, epidermis; GPPASI, Generalized Pustular Psoriasis Area and Severity Index.

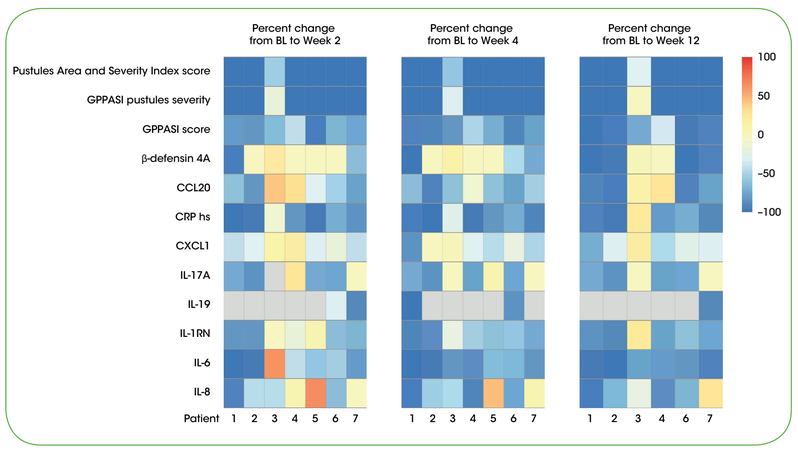
Table 1. Summary of select clinical scores and median immunohistochemical scores over time by patient

Patient no.	Visit	Pustule Area and Severity Index	Pustule Severity Subscore	CD11c+ dendritic cells*		CD3+ T cells*		Neutrophil elastase-expressing cells*		Lipocalin–2-expressing cells*	
				D	E	D	E	D	E	D	E
1	Baseline	2.2	1.8	1112	307	716	60	1109	188	448	211
	Week 1	0	0	861	99	624	220	633	120	105	74
	Week 2	0	0	732	187	327	124	109	15	62	21
2	Baseline	2.5	2.3	664	241	312	66	996	288	217	78
	Week 1	0	0	532	128	344	84	328	49	134	12
	Week 2	0	0	395	102	291	157	17	4	7	2
3	Baseline	2.4	1.5	513	156	317	166	442	78	89	38
	Week 1	1.1	0.8	868	64	359	91	294	33	110	18
	Week 2	1.0	1.0	356	39	175	57	385	40	166	45
4	Baseline	6.8	3.0	1014	252	247	41	794	175	541	187
	Week 1	4.2	1.5	682	214	189	30	108	51	135	106
5	Baseline	7.1	2.8	350	32	167	18	268	17	95	14
	Week 1	0	0	688	95	201	46	284	3	105	9
6	Baseline	3.8	1.8	462	153	177	92	36	1	11	0
	Week 1	0	0	397	125	271	71	172	14	83	16
7	Baseline	2.9	2.8	805	127	434	141	430	16	117	1
	Week 1	0	0	661	128	286	92	83	2	49	0

Week 2 biopsies were optional.
*Number of cells per 1 mm surface length at 100 × magnification.
D, dermis; E, epidermis.

- As early as Week 1, spesolimab treatment selectively decreased the expression of IHC biomarkers, including the number of CD11c+ dendritic cells, CD3+ T cells, neutrophil elastase-expressing cells and lipocalin–2-expressing cells in each patient; these reductions were accompanied by decreases in clinical severity **(Figure 2; Table 1)**
- Treatment with spesolimab led to marked downregulation of select serum biomarkers linked to inflammatory (e.g. C-reactive protein, β-defensin 4A), neutrophilic (e.g. CXCL1, IL-8, IL-6), innate (e.g. IL-19, IL-1RN) and Th17 (e.g. IL-17A, CCL20) pathways as early as Week 2 and through Week 12 in select patients; these reductions were accompanied by decreases in clinical disease severity **(Figure 3; Table 2)**

Figure 3. Heatmap of changes in clinical scores and serum biomarkers from baseline over time in each patient following spesolimab treatment



Grey cells denote the percent change from baseline >100 or missing values. At Weeks 12 and 20, one patient (Patient 5) received methotrexate and was classified as receiving rescue treatment.
BL, baseline; CRP, C-reactive protein; GPPASI, Generalized Pustular Psoriasis Area and Severity Index; IL, interleukin.

Table 2. Summary of select serum biomarkers over time by patient

Patient no.	Visit	IL-19 (ng/mL)	IL-1RN (ng/mL)	β-defensin 4A (ng/mL)	CRP (mg/mL)	IL-6 (ng/mL)	CCL20 (ng/mL)	CXCL1 (ng/mL)	IL-8 (ng/mL)
1	Baseline	2462.1†	993.0	28,804.8†	255.0	209.1	32.6	525.2	526.0
	Week 1	897.4	224.5	28,804.8†	17.3	2.4	20.5	348.1	107.7
	Week 4	37.3*	85.4	513.0	12.0	2.4	12.1	81.6	28.0
2	Baseline	N/A	1310.0	28,804.8†	306.2	188.7	137.7	740.8	51.0
	Week 1	513.6	381.5	28,804.8†	39.0	9.1	24.9	681.7	37.3
	Week 4	37.3*	174.0	28,497.4	4.0	5.1	10.4	728.9	22.5
3	Baseline	N/A	560.6	14,777.9	3.5	14.4	7.1	341.5	24.0
	Week 1	N/A	425.0	13,770.1	3.1	5.2	2.8*	183.9	16.9
	Week 4	N/A	447.8	16,703.0	2.5	2.5	2.8*	342.4	12.6
4	Baseline	611.4	878.8	28,804.8†	139.2	56.4	39.0	380.0	134.6
	Week 1	N/A	525.2	28,804.8†	134.8	212.9	35.7	267.3	7.2
	Week 4	N/A	412.9	N/A	5.0	6.8	34.7	N/A	10.9
5	Baseline	1893.0	402.4	28,804.8†	32.1	41.2	111.8	265.5	18.5
	Week 1	1793.4	187.9	28,804.8†	11.5	15.4	82.8	166.6	30.2
	Week 4	N/A	154.8	28,804.8†	5.7	14.5	43.1	146.9	26.6
6	Baseline	256.7	159.3	28,804.8†	0.5	2.3	38.2	187.4	50.5
	Week 1	268.3	73.6	28,804.8†	0.4	1.8	26.1	148.6	25.6
	Week 4	37.3*	66.7	15,432.0	0.2*	0.7	8.6	145.9	12.4
7	Baseline	324.3	163.2	22,424.8	6.3	14.2	12.1	115.4	8.0
	Week 1	37.3*	56.9	10,667.8	1.6	1.4	10.9	99.4	8.9
	Week 4	N/A	45.0	5917.1	0.6	2.5	5.7	58.1	8.6

Refer to Table 1 for Pustule Area and Severity Index and Pustule Severity Subscore values.
*Lower range of detection; †Upper range of detection.
CRP, C-reactive protein; IL, interleukin; N/A, not available.

Conclusions

- The clinical and biomarker findings from this Phase I, proof-of-concept study with spesolimab support the therapeutic targeting of IL-36R for the treatment of moderate-to-severe GPP
- A single IV dose of spesolimab resulted in strong and rapid downregulation of lesional versus non-lesional biomarkers and serum biomarkers linked to inflammatory, neutrophilic, innate and Th1/Th17 pathways
  - These reductions correlated with decreases in clinical disease severity, highlighting the importance of inhibiting the IL-36 pathway in the skin and blood of patients with GPP
- A multicentre, double-blind, randomised, placebo-controlled, Phase II study (ClinicalTrials.gov Identifier: NCT03782792) is currently ongoing to further investigate the efficacy and safety of spesolimab in patients with GPP

Disclosures

- PB, SV, SB, BL, RS, SG, SJP and CT report being employed by Boehringer Ingelheim. HB reports being an investigator and receiving consultancy and speaker fees for AbbVie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Dermavant, Eli Lilly, Janssen, Leo Pharma, Mylan, Novartis, Pfizer, Sandoz, Sun Pharmaceuticals and UCB. JGK reports receiving grants from, and being an investigator for, Boehringer Ingelheim; personal fees from AbbVie, Baxter, Biogen Idec, Delenex, Kineta, Sanofi, Serono and XenoPort; and grants from Amgen, Bristol-Myers Squibb, Dermira, Innovaderm, Janssen, Kadmon, Kyowa Hakko Kirin, Eli Lilly, Merck, Novartis, Parexel and Pfizer. SG has nothing to disclose.
- This presentation includes discussions of investigational drugs that are not approved for use in humans

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