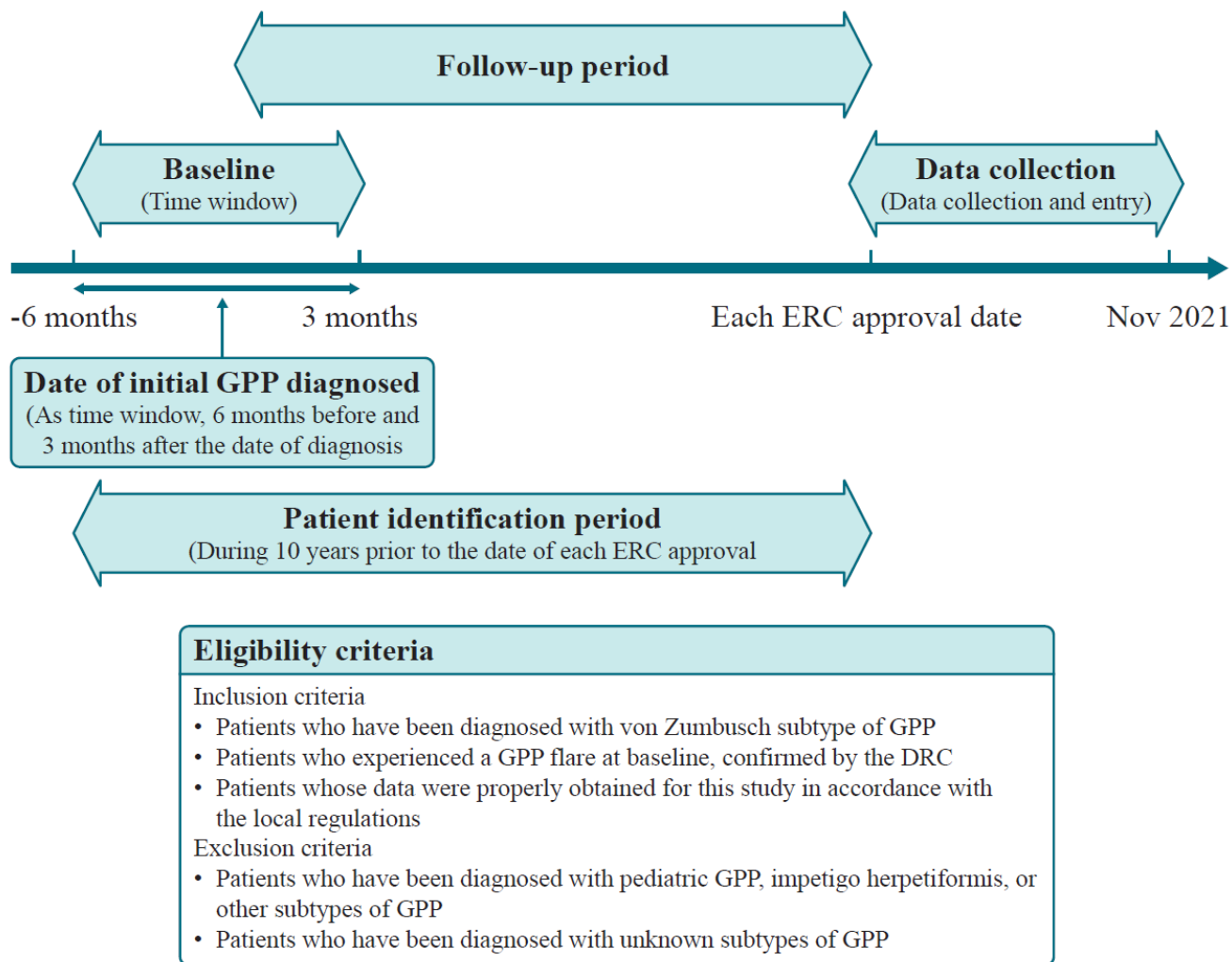


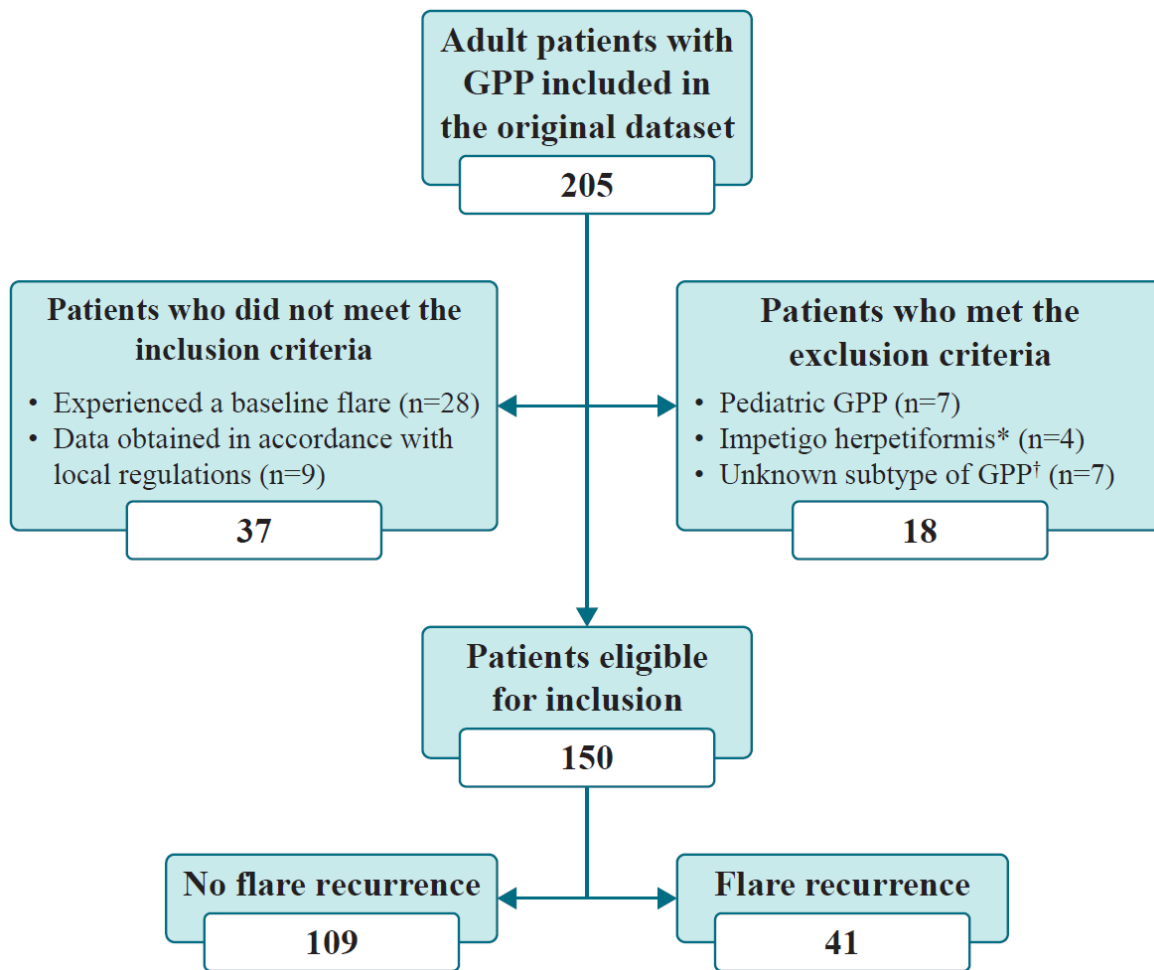
Supplementary material has been published as submitted. It has not been copyedited, or typeset by Acta Dermato-Venereologica

**Fig. S1. Study design and eligibility criteria**



DRC: Data Review Committee; ERC: Ethics Review Committee; GPP: generalized pustular psoriasis.

**Fig. S2. Patient selection flow chart**



\*Of the four patients, three were diagnosed with impetigo herpetiformis at initial diagnosis based on the patient report. One patient was diagnosed with acute GPP (or von Zumbusch type of GPP) at initial diagnosis; however, the diagnosis was changed to impetigo herpetiformis approximately 2.5 months later during the follow-up period, as pregnancy was confirmed to have triggered the onset of the disease. The initial diagnosis was therefore more likely to be impetigo herpetiformis; †Patients who were diagnosed as unknown at initial diagnosis based on the patient report and had no subsequent diagnosis data during the follow-up period, or had diagnosis data several years later.

GPP: generalized pustular psoriasis.

## SUPPLEMENTAL TABLES

**Table SI. Study investigators and Ethics Review Committee approval**

<b>Institute name</b>	<b>Investigator</b>	<b>Results notification number or date</b>	<b>Number segment</b>
Nagoya City University Hospital	Akimichi Morita	70-20-0010	Reference number
Shinshu University Hospital	Ryuhei Okuyama	692	Receipt number
Kyoto University Hospital	Kenji Kabashima	G1316	Receipt number
Yokohama City University Hospital	Yukie Yamaguchi	B210300004	Approval number
University Hospital, Kyoto Prefectural University of Medicine	Koji Masuda	ERB-G-118	Receipt number
Gifu University Hospital	Yoko Muzutani	2021-050	Approval number
Mie University Hospital	Keiichi Yamanaka	H2021-071	Approval number
Kagoshima University Hospital	Takuro Kanekura	480	Receipt number
Kindai University Hospital	Shigeto Yanagihara	R03-095	Receipt number
Osaka City University Hospital	Chiharu Tateishi	2021-141	Approval number
Teikyo University Hospital	Yayoi Tada	21-003	Approval number
Hamamatsu University Hospital	Tetsuya Honda	21-038	Study number
Kumamoto University Hospital	Satoshi Fukushima	1. Ethics Committee for Human Genome and Genetic Analysis Research: 481 2. Ethics Committee of the Department of Epidemiology and General Division of Medical Research: 2307	1, 2: Receipt number
Ehime University Hospital	Kazuki Yatsuzuka	1. Ethics Committee for Human Genome and Genetic Analysis Research: R3-2 2. Clinical Research Ethics Committee: 2106009	1: Approval number 2: Receipt number

University of Ryukyu Hospital	Takuya Miyagi	1820	Permit number
Gunma University Hospital	Masahito Yasuda	IRB2021-003(1894)	Receipt number
Okayama University Hospital	Emi Yokoyama	2105-042	Application number
Jichi Medical University	Mayumi Komine	23-120	Receipt number
Hyogo Medical University	Nobuo Kanazawa	0475 (202107-013)	Receipt (reference) number
Fujita Health University Hospital	Kazumitsu Sugiura	HM21-233	Receipt number
University of Miyazaki Hospital	Masahiro Amano	G-0113	Research number
Iwate Medical University Hospital	Daisuke Watabe	HG2021-017	Receipt number
Nihon University Itabashi Hospital	Koremasa Hayama	RK-210511-12	Reference number
Juntendo University Hospital	Hitoshi Tsuchihashi	2021082	Approval number
Asahikawa Medical University Hospital	Masaru Honma	23131	Approval number
Sapporo Dermatology Clinic	Masatoshi Abe	26/05/2021	Approval date
Hosui General Medicine Clinic	Hajime Iizuka	26/05/2021	Approval date
The Jikei University Hospital	Akihiko Asahina	33-095 (10710)	Receipt number

**Table SII. Patient demographics**

	All	Recurrence of GPP flare	
		Yes	No
Patients, n (%)	<b>150</b> (100.0)	<b>41</b> (27.3)	<b>109</b> (72.7)
Male, n (%)	84 (56.0)	25 (61.0)	59 (54.1)
Female, n (%)	66 (44.0)	16 (39.0)	50 (45.9)
Comorbidities, n (%)	106 (70.7)	30 (73.2)	76 (69.7)
Plaque psoriasis, n (%)	65 (43.3)	20 (48.8)	45 (41.3)
Biologics use during the follow-up period, n (%)	121 (80.7)	36 (87.8)	85 (78.0)
Age, years, mean (SD)	55.5 (17.1)	54.5 (16.7)	55.9 (17.3)
BMI*, kg/m <sup>2</sup> , mean (SD)	24.31 (4.48)	24.03 (5.00)	24.41 (4.29)
Follow-up period <sup>†</sup> , years, mean (SD)	4.16 (2.56)	5.25 (2.37)	3.75 (2.52)

\*BMI information was available for 114 patients; <sup>†</sup>Follow-up period was from the date of the first GPP diagnosis to the date of Ethics Review Committee approval for each respective site.

BMI: body mass index; GPP: generalized pustular psoriasis; SD: standard deviation.

**Table SIII. Retrospective GPP-associated genetic testing results**

	Number of patients	Recurrence of GPP flare	
		Yes	No
Patients with genetic test results, n	35	2	33
<i>IL36RN</i> , n	8	2	6
<i>CARD14</i> , n	2	0	2

GPP: generalized pustular psoriasis.

**Table SIV. Potential factors associated with flare recurrence: class of biologics\***

		Number of patients	Recurrence of GPP flare (%)	Hazard ratio	95% CI		p-value <sup>†</sup>
					Lower	Upper	
TNF inhibitors <sup>‡</sup>	No	130	37 (28.5)				0.2242
	Yes	20	4 (20.0)	0.5264	0.1871	1.4813	
IL-17 inhibitors <sup>§</sup>	No	109	33 (30.3)				0.6227
	Yes	41	8 (19.5)	0.8215	0.3753	1.7981	
IL-23 inhibitors <sup>¶</sup>	No	148	41 (27.7)				0.9901
	Yes	2	0 (0.0)	<0.0001	<0.0001	-	
IL-12/23 inhibitor <sup>**</sup>	No	148	41 (27.7)				0.9905
	Yes	2	0 (0.0)	<0.0001	<0.0001	-	

\*Up to 2 months after the onset of the baseline flare; <sup>†</sup>The Cox proportional hazards model was used (p-values of <0.05 were considered statistically significant); <sup>‡</sup>Adalimumab, certolizumab pegol, and infliximab; <sup>§</sup>Brodalumab, ixekizumab, and secukinumab; <sup>¶</sup>Guselkumab and risankizumab; <sup>\*\*</sup>Ustekinumab.

CI: confidence interval; GPP: generalized pustular psoriasis; IL: interleukin; TNF: tumor necrosis factor.

**Table SV. Severity of baseline GPP flare and treatments\* received**

			All	Biologics‡	Non-biologic systemic therapy				Systemic steroids	GMA	
					Cyclosporine MEPC	Etretinate	Methotrexate	Apremilast			
Severity of baseline GPP flare†	Mild	All	22	7 (31.8%)	8 (36.4%)	10 (45.5%)	5 (22.7%)	2 (9.1%)	3 (13.6%)	1 (4.5%)	
		Recurrence of GPP flare	Yes	9	0 (0.0%)	3 (33.3%)	5 (55.6%)	2 (22.2%)	1 (11.1%)	0 (0.0%)	1 (11.1%)
			No	13	7 (53.8%)	5 (38.5%)	5 (38.5%)	3 (23.1%)	1 (7.7%)	3 (23.1%)	0 (0.0%)
	Moderate	All	44	35 (79.5%)	15 (34.1%)	11 (25.0%)	4 (9.1%)	4 (9.1%)	9 (20.5%)	3 (6.8%)	
		Recurrence of GPP flare	Yes	6	4 (66.7%)	3 (50.0%)	2 (33.3%)	2 (33.3%)	0 (0.0%)	1 (16.7%)	1 (16.7%)
			No	38	31 (81.6%)	12 (31.6%)	9 (23.7%)	2 (5.3%)	4 (10.5%)	8 (21.1%)	2 (5.3%)
	Severe	All	84	63 (75.0%)	23 (27.4%)	49 (58.3%)	11 (13.1%)	5 (6.0%)	30 (35.7%)	26 (31.0%)	
		Recurrence of GPP flare	Yes	26	17 (65.4%)	7 (26.9%)	14 (53.8%)	3 (11.5%)	3 (11.5%)	7 (26.9%)	7 (26.9%)
			No	58	46 (79.3%)	16 (27.6%)	35 (60.3%)	8 (13.8%)	2 (3.4%)	23 (39.7%)	19 (32.8%)

\*From the date of onset of the baseline GPP flare to the date of GPP flare recurrence or to the end of the follow-up period; †As assessed by the Data Review Committee; ‡Biologics included adalimumab, brodalumab, certolizumab pegol, guselkumab, infliximab, ixekizumab, risankizumab, secukinumab, and ustekinumab.

GMA: granulocyte and monocyte adsorption apheresis; GPP, generalized pustular psoriasis; MEPC: microemulsion pre-concentrate.

**Table SVI. Potential factors associated with flare recurrence: multivariate analysis**

		Hazard ratio	95% CI		p-value*
			Lower	Upper	
Age (years), initial diagnosis		0.9821	0.9587	1.0061	0.1425
Sex	Male				0.8605
	Female	0.9263	0.3944	2.1755	
Diabetes mellitus	No				0.0018
	Yes	5.1045	1.8361	14.1910	
BMI (kg/m <sup>2</sup> ) <sup>†</sup>	<20				0.2425
	≥20	0.5833	0.2362	1.4404	
Fever (°C) <sup>‡</sup>	≥38.5				0.0558
	≥37 to <38.5	0.5131	0.1668	1.5786	
	<37	0.2035	0.0530	0.7813	
Experienced GPP flare before baseline	No				0.0080
	Yes	2.8714	1.3176	6.2575	
Severity of baseline GPP flare (as assessed by the Data Review Committees)	Mild				0.1847
	Moderate	0.2544	0.0573	1.1300	
	Severe	0.4479	0.1402	1.4311	
Biologics <sup>§</sup> treatment for GPP after the onset of the baseline GPP flare (up to 2 months)	No				0.1311
	Yes	0.5048	0.2078	1.2261	
Systemic steroids <sup>¶</sup>	No				0.6353
	Yes	0.7998	0.3177	2.0133	

\*The Cox proportional hazards model with time-dependent covariates was used to calculate the p-value; <sup>†</sup>Only included patients with data on both height and weight; <sup>‡</sup>Excluding unknown values; <sup>§</sup>Biologics comprised TNF-inhibitors (adalimumab, certolizumab pegol, and

infliximab); IL-17 inhibitors (brodalumab, ixekizumab and secukinumab); IL-23 inhibitors (guselkumab and risankizumab); and IL-12/23 inhibitor (ustekinumab); ¶From the date of onset of the baseline GPP flare to the date of recurrence of a GPP flare, or to the end of the follow-up.

BMI: body mass index; CI: confidence interval; GPP: generalized pustular psoriasis.

## **SUPPLEMENTAL APPENDICES**

### **APPENDIX S1**

#### *Rationale for sample size and locations of data extraction*

In both the original study (1) and this analysis, sample sizes were not determined based on a statistical hypothesis. Since generalized pustular psoriasis (GPP) is a rare disease, the aim of these descriptive studies was to gather as many cases as possible.

The study population needed to include patients with an accurate diagnosis of GPP; therefore, it was considered appropriate to collect data from specialized facilities only. Data were collected from multiple facilities across Japan to avoid regional bias. Consequently, we were able to include the medical records of 205 patients with GPP from 29 medical facilities.

#### *Definition and time frame of recurrence of flares*

All incidences of GPP flares were reviewed and adjudicated by the Data Review Committee. If no flare-related data were available before the date of GPP diagnosis, any flare within 3 months after the date of GPP diagnosis was classified as the baseline flare. The follow-up period was from the date of GPP diagnosis to the date of Ethics Review Committee approval for each respective site. Recurrence of a GPP flare was defined as when patients with baseline flare(s) experienced a flare during the follow-up period.

## References

1. Morita A, Okubo Y, Imafuku S, Tada Y, Yamanaka K, Sugiura K, et al. Assessment of flare frequency and severity of generalized pustular psoriasis in Japanese patients: A retrospective chart review study. *JEADV Clin Pract* 2023; 2: 261-272.