Taiwan Food and Drug Administration

Assessment Report

Trade Name：喜開悅 75mg 針筒裝注射劑 /
SKYRIZI 75mg / 0.83 ml Pre-filled syringe

Active Ingredient：Risankizumab

License Number：MOHW-BI 001109

Applicant：瑞士商艾伯維藥品有限公司台灣分公司

Approval Date：108/09/27

Indication：
適合接受全身性治療的中度至重度斑塊乾癬成人病人
Skyrizi is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

Background Information

Trade Name	喜開悅 75mg 針筒裝注射劑 / SKYRIZI 75mg / 0.83 ml Pre-filled syringe
Active Ingredient(s)	Risankizumab
Applicant	瑞士商艾伯維藥品有限公司台灣分公司
Dosage Form & Strengths	Pre-filled syringe for injection 75 mg/0.83 ml
Indication	適合接受全身性治療的中度至重度斑塊性乾癬成人病人。 Skyrizi is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.
Posology	150 mg (注射兩針 75 mg)，在第 0 週、第 4 週和之後每 12 週以皮下注射方式投予。 150 mg administered by subcutaneous injection at Week 0, Week 4, and every 12 weeks thereafter
Pharmacological Category **ATC Code**	N/A

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Risankizumab is a humanized antibody which selectively binds to IL-23p19 and therefore inhibits of IL-23 to its receptor. The manufacturer of drug substance is Boehringer Ingelheim GmbH&Co KG located in Germany.

Risankizumab is manufactured using a recombinant CHO cell line and has a molecular weight of approximately 149kD with glycosylation. Detailed description of the origin, history and preparations of cell banks including MCBs, WCBs and EOPs were provided. Adventitious and endogenous agent safety testing, identity and genetic stability for cell banks were conducted based on the recommendations in ICH guidance.

Characterization studies were presented including primary and high order structure, glycosylation, methionine oxidation, deamination, disulfide structure, charge and size heterogeneity, and biological activity analyzed by cell-based assays and SPR. The release specification of risankizumab was provided, as well as the validation of the

analytical methods. The results of comparability studies in terms of the batch release and additional characteristics, and stress studies showed comparable in CMC1 and CMC2 Process.

2.1.2 Drug product

The brand name 喜開悅® contains 2 prefilled syringe (75mg/ 0.83ml per prefilled syringe) with colorless to slight yellow solution. The manufacturer for 喜開悅® is Boehringer Ingelheim Pharma GmbH &Co KG in Germany.

The compositions were listed and the excipients were complied with current Ph. Eur., USP, NF or JP and no novel excipients or animal/human origins were used in the formulation. Manufacturing process/in process controls, process validation, specification and batch analyses were provided and showed that the manufactures of drug product were consistent under proper controls.

The release specification for drug product includes appearance, general tests, identity, heterogeneity, purity/impurity, potency, quantity, functional tests, and microbiological tests and excipient concentrate. The specification is generally acceptable.

Stability studies were conducted under long term and accelerated conditions for pre-filled syringe. The stability data support the shelf life for 2 years at 5 ± 3°C, protected from light.

In conclusion, information on the active substance and drug product is regard as appropriate to support the quality of 喜開悅®.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Risankizumab displayed a high affinity for human (hu) IL-23 and cynomolgus (cyno) IL-23 (Kd of less than 1 pM) with no detectable binding to hu IL-12. *In vitro* cellular assays showed that risankizumab inhibited hu IL-23-mediated STAT3 phosphorylation and the generation of IL-17A induced by hu IL-23 or cyno IL-23. Risankizumab inhibited hu IL-23 induced ear swelling and the induction of IL-17 and IL-22 in the ear tissue in mice. Risankizumab did not

have any notable effects on CNS, cardiovascular or respiratory function following IV or SC administration.

2.2.2 Toxicological Studies

The nonclinical toxicological profile of risankizumab has been evaluated in the GLP compliance repeat-dose study up to 26 weeks in cynomolgus monkeys using QW subcutaneous. Risankizumab was generally well-tolerated in cynomolgus monkeys, no major/apparent organ toxicities were observed at dose levels up to 50 mg/kg/week (~ 20 times the MRHD based on mg/kg comparison).

No genetic toxicology or carcinogenicity studies were conducted with risankizumab. The risk of malignancy from chronic dosing with risankizumab to human is considered to be low. Post-marketing monitor the long-term risk of malignancy in patients with psoriasis will be sufficient at this time.

No effects on female fertility were observed after cynomolgus monkeys subcutaneously administered at doses of up to 50 mg/kg/week for 26 weeks. Risankizumab had no effects on male fertility parameters in sexually mature male cynomolgus monkeys subcutaneously treated with 50 mg/kg/week for 26 weeks.

In an enhanced pre- and postnatal (ePPND) study in cynomolgus monkey received subcutaneously risankizumab at doses of up to 50 mg/kg/week, a dose-dependent increased in offspring losses (combined fetal/infant) was noted in the risankizumab-treated groups (32% and 43% in the 5 mg/kg and 50 mg/kg groups, respectively) compared to the vehicle control group (19%). Although the combined fetal/infant loss (percentage) at the high end of the performing laboratory's background incidence rate for monkeys in the 50 mg/kg/week group (42.9%), it was over two times the increase compared to the control group (19.0%). Therefore, the no observed adverse effect level (NOAEL) for developmental toxicity was identified as 5 mg/kg/week (approximately 2 times the MRHD based on mg/kg comparison).

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

The linear PK range of risankizumab was 18 to 300 mg or 0.25 to 1 mg/kg SC, and 200 to 1200 mg or 0.01 to 5 mg/kg IV, and no time-dependent kinetics were observed. Following SC administration, risankizumab reached C_{max} between 3 and 14 days. With the clinical dosing regimen of 150 mg SC at Weeks 0, 4, and q12w thereafter, the steady-state was achieved by Week 16. As an IgG1 monoclonal antibody, risankizumab was not expected to

undergo metabolism by hepatic metabolic enzymes or renal elimination.

2.3.2 Interaction Studies

In DDI evaluation, repeated administration of risankizumab 150 mg SC every 4 weeks had no effect on the exposures of probe substrates of CYP1A2 (caffeine 100 mg), CYP2C9 (warfarin 10 mg), CYP2C19 (omeprazole 20 mg), CYP2D6 (metoprolol 50 mg) and CYP3A (midazolam 2 mg) in subjects with moderate to severe plaque psoriasis.

2.3.3 Special Populations

Population PK analysis showed risankizumab PK were not significantly affected by liver function markers or serum creatinine. Body weight was correlated with risankizumab clearance. No dose adjustment was recommended for intrinsic covariates since the clinical impact was minimal.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

In this submission, the Sponsor provided four phase III studies (ULTIMMA-1, ULTIMMA-2, IMMHANCE and IMMVENT) to support the efficacy of risankizumab for the claimed indication. The major design features of four studies were summarized as follows:

- **Studies [ULTIMMA-1] and [ULTIMMA-2] (m16008 and m15995)**

Studies [ULTIMMA-1] and [ULTIMMA-2] had the same study design. Both were Phase 3, multi-center, multi-national, randomized, double-blind, double-dummy, placebo and active comparator-controlled, parallel study to compare risankizumab to ustekinumab and placebo in subjects with moderately to severe chronic plaque psoriasis.

The co-primary efficacy endpoints in Part A were in the following:

- Achievement of ≥ 90% reduction from baseline PASI score (PASI 90) at Week 16
- Achievement of an sPGA of clear or almost clear at Week 16

Statistically significantly larger proportions of subjects in the risankizumab groups achieved both PASI 90 and sPGA clear or almost clear at Week 16 compared with the placebo groups (Table 1). Risankizumab was statistically significantly superior to placebo and to ustekinumab for all ranked secondary endpoints (Table 2).

Table 1: Analysis Results of Primary Endpoints in Part A (ITT/Non-Responder Imputation)

Endpoint	Study ULTIMMA-1			Study ULTIMMA-2		
	Placebo	Risankizumab	P-value[a]	Placebo	Risankizumab	P-value[a]

	n/N (%)	n/N (%)		n/N (%)	n/N (%)	
PASI 90 at Week 16	5/102 (4.9%)	229/304 (75.3%)	<0.001	2/98 (2.0%)	220/294 (74.8%)	<0.001
sPGA clear or almost clear at Week 16	8/102 (7.8%)	267/304 (87.8%)	<0.001	5/98 (5.1%)	246/294 (83.7%)	<0.001

Table 2 Statistical Results for Ranked Secondary Endpoints Presented in Rank Order in Part A (ITT)

Ranked Secondary Variable	Study ULTIMMA-1			Study ULTIMMA-2		
	Risankizumab n/N (%)	Comparator n/N (%)	P-value	Risankizumab n/N (%)	Comparator n/N (%)	P-value
1. Proportion of subjects who achieved sPGA clear at Week 16 (versus placebo)	112/304 (36.8%)	2/102 (2.0%)	<0.001	150/294 (51.0%)	3/98 (3.1%)	<0.001
2. Proportion of subjects who achieved PASI 100 at Week 16 (versus placebo)	109/304 (35.9%)	0/102 (0%)	<0.001	149/294 (50.7%)	2/98 (2.0%)	<0.001
3. Proportion of subjects who achieved DLQI score of 0/1 at Week 16 (versus placebo)	200/304 (65.8%)	8/102 (7.8%)	<0.001	196/294 (66.7%)	4/98 (4.1%)	<0.001
4. Proportion of subjects who achieved PSS of 0 at Week 16 (versus placebo)	89/304 (29.3%)	2/102 (2.0%)	<0.001	92/294 (31.3%)	0/98 (0)	<0.001
5. Proportion of subjects who achieved PASI 90 at Week 16 (versus ustekinumab)	229/304 (75.3%)	42/100 (42.0%)	<0.001	220/294 (74.8%)	47/99 (47.5%)	<0.001
6. Proportion of subjects who achieved sPGA clear or almost clear at Week 16 (versus ustekinumab)	267/304 (87.8%)	63/100 (63.0%)	<0.001	246/294 (83.7%)	61/99 (61.6%)	<0.001
7. Proportion of subjects who achieved PASI 100 at Week 16 (versus ustekinumab)	109/304 (35.9%)	12/100 (12.0%)	<0.001	149/294 (50.7%)	24/99 (24.2%)	<0.001
8. Proportion of subjects who achieved sPGA clear at Week 16 (versus ustekinumab)	112/304 (36.8%)	14/100 (14.0%)	<0.001	150/294 (51.0%)	25/99 (25.3%)	<0.001
9. Proportion of subjects who achieved PASI 90 at Week 52 (versus ustekinumab)	249/304 (81.9%)	44/100 (44.0%)	<0.001	237/294 (80.6%)	50/99 (50.5%)	<0.001
10. Proportion of subjects who achieved PASI 100 at Week 52 (versus ustekinumab)	171/304 (56.3%)	21/100 (21.0%)	<0.001	175/294 (59.5%)	30/99 (30.3%)	<0.001
11. Proportion of subjects who achieved sPGA clear at Week 52 (versus ustekinumab)	175/304 (57.6%)	21/100 (21.0%)	<0.001	175/294 (59.5%)	30/99 (30.3%)	<0.001
12. Proportion of subjects who achieved PASI 75 at Week 12 (versus ustekinumab)	264/304 (86.8%)	70/100 (70.0%)	<0.001	261/294 (88.8%)	69/99 (69.7%)	<0.001
13. Proportion of subjects who achieved sPGA clear or almost	250/304 (82.2%)	65/100 (65.0%)	<0.001	242/294 (82.3%)	64/99 (64.6%)	<0.001

clear at Week 12 (versus ustekinumab)						
14. Proportion of subjects who achieved DLQI 0/1 at Week 16 (versus ustekinumab)	200/304 (65.8%)	43/100 (43.0%)	<0.001	196/294 (66.7%)	46/99 (46.5%)	<0.001
15. PSS total score (change from BL) at Week 16 (versus placebo) LS mean change from BL (SE)	–5.608 (0.2254)	0.157 (0.3476)	<0.001	–6.402 (0.2193)	–0.027 (0.3316)	<0.001

- **Study [IMMHANCE] (m15992)**

This was a phase 3, multinational, multicenter, randomized, double-blind, placebo-controlled study to compare risankizumab with placebo in the treatment of moderate to severe chronic plaque psoriasis.

The co-primary efficacy endpoints in Part A1 were in the following:

- achievement of PASI 90 at Week 16
- achievement of sPGA of clear or almost clear (0 or 1) at Week 16

A statistically significantly larger proportion of subjects in the risankizumab group achieved both PASI 90 and sPGA clear or almost clear at Week 16 compared with the placebo group (Table 3). Statistically significant differences in favor of risankizumab were observed for all ranked secondary endpoints (Table 4).

Table 3: Results of Co-Primary Endpoints in Part A1 (ITT/Non-Responder Imputation)

Endpoint	Placebo n/N (%)	Risankizumab n/N (%)	P-value[a]
PASI 90 at Week 16	2/100 (2%)	298/407 (73.2%)	<0.001
sPGA clear or almost clear at Week 16	7/100 (7%)	340/407 (83.5%)	<0.001

[a] Across the strata, *P*-value was calculated from the Cochran-Mantel-Haenszel test adjusted for strata

Table 4 Results of Ranked Secondary Endpoints in Part A1 (ITT/Non-Responder Imputation)

	PBO (N=100)	RZB (N=407)
1.Proportion of subjects who achieved PASI 75 at Week 16	8/100 (8%)	361/407 (88.7%)
P-value	<0.001	
2.Proportion of subjects who achieved PASI 100 at Week 16	1/100 (1%)	192/407 (47.2%)
P-value	<0.001	
3.Proportion of subjects who achieved sPGA of clear at Week 16	1/100 (1%)	189/407 (46.4%)
P-value	<0.001	
4.Proportion of subjects who achieved DLQI 0/1 at Week 16	3/100 (3%)	266/407 (65.4%)
P-value	<0.001	

The primary endpoint and key secondary endpoints in Part B were sPGA of clear or almost

clear at week 52 and at week 104. Results showed that a statistically significantly larger proportion of subjects who were re-randomized to continue risankizumab treatment in Part B achieved sPGA clear or almost clear at week 52 and at week 104 compared with subjects who were withdrawn from risankizumab therapy (Table 5).

Table 5 Results of Primary and key Secondary Endpoints in Part B (ITT/Non-Responder Imputation)

	RZB/RZB/PBO (N=225)	RZB/RZB/RZB (N=111)
Primary endpoint Proportion of subjects who achieved sPGA clear or almost clear at Week 52	138/225 (61.3%)	97/111 (87.4%)
P-value[a]	<0.001	
Secondary endpoint Proportion of subjects who achievement of sPGA of clear or almost clear at Week 104	16/225 (7.1%)	90/111 (81.1%)
P-value[a]	<0.001	

RZB = risankizumab; a. P-value was calculated from the Cochran-Mantel-Haenszel test adjusted for strata.

- **Study [IMMVENT] (m16010)**

This was a phase 3, multi-national, multicenter, randomized, double-blind, double-dummy, active-controlled, parallel-design study to compare risankizumab with adalimumab.

The co-primary efficacy endpoints in Part A were in the following:

- achievement of PASI 90 at Week 16
- achievement of sPGA of clear or almost clear (0 or 1) at Week 16

Statistically significantly larger proportions of subjects in the risankizumab group achieved both PASI 90 and sPGA clear or almost clear at week 16 compared with the adalimumab group (Table 6). For the ranked secondary endpoints in Part A, statistically significant differences in favor of risankizumab were observed in the proportions of subjects who achieved PASI 75 and PASI 100 at week 16 (Table 7).

Table 6: Results of Co-Primary Endpoints in Part A (ITT/Non-Responder Imputation)

Endpoint	Adalimumab n/N (%)	Risankizumab n/N (%)	P-value[a]
PASI 90 at Week 16	144/304 (47.4%)	218/301 (72.4%)	<0.001
sPGA clear or almost clear at Week 16	183/304 (60.2%)	252/301 (83.7%)	<0.001

[a] Across the strata, *P*-value was calculated from the Cochran-Mantel-Haenszel test adjusted for strata

Table 7 Results of Ranked Secondary Endpoints in Part A (ITT/Non-Responder Imputation)

	ADA (N=304)	RZB (N=301)

1.Proportion of subjects who achieved PASI 75 at Week 16	218/304 (71.7%)	273/301 (90.7%)
P-value[a]	<0.001	
2.Proportion of subjects who achieved PASI 100 at Week 16	70/304 (23.0%)	120/301 (39.9%)
P-value[a]	<0.001	

ADA = adalimumab; PASI = Psoriasis Area and Severity Index; RZB = risankizumab
a. Across the strata, *P* value was calculated from the Cochran-Mantel-Haenszel test adjusted for strata.

The primary endpoint and key secondary endpoint in Part B were the achievement of PASI 90 and PASI 100 at week 44 for those subjects who are re-randomized at Week 16. Results showed that a statistically significantly larger proportion of subjects who were re-randomized to risankizumab achieved PASI 90 and PASI 100 at week 44 compared with subjects who were re-randomized to adalimumab (Table 8).

Table 8 Results of Primary and key Secondary Endpoints in Part B (ITT/Non-Responder Imputation)

	ADA/ADA (N=56)	ADA/RZB (N=53)
Primary endpoint Proportion of subjects who achieved PASI 90 at Week 44	12/56 (21.4%)	35/53 (66.0%)
P-value[a]	<0.001	
Secondary endpoint Proportion of subjects who achieved PASI 100 at Week 44	4/56 (7.1%)	21/53 (39.6%)
P-value[a]	<0.001	

ADA = adalimumab; RZB = risankizumab
a. P-value was calculated from the Cochran-Mantel-Haenszel test adjusted for strata.

2.4.2 Safety Results

Major TEAEs/safety concerns include infections, headache, fatigue, arthralgia, injection site reaction and tuberculosis (TB). Due to the pharmacological mechanism and associated safety consideration, risk management plan for latent TB and monitoring hepatitis B/C is required.

2.5 Bridging Study Evaluation

Risankizumab exposures were 22% to 31% higher in healthy Chinese and Japanese subjects compared to healthy Caucasians. After accounting for bodyweight differences, race did not have an impact on risankizumab clearance. And the overall differences in exposure across groups were small compared to the inter-individual variability, and therefore, were not considered to have clinical impact on efficacy or safety.

Bridging study evaluation in clinical section was waived based on subgroup analysis of 100 East Asians (Japan and Korea) in Study M16-008, 65 East Asians (Japan and Korea) in Study M15-992 and 51 Taiwanese in Study M16-010. Efficacy and safety profile were comparable between East Asians and non- East Asians. A Japanese study M16-004 is ongoing, and the

sponsor was requested to submit the study report once available.

2.6 Conclusion

Submitted dossiers for CMC, pharmacology/toxicology, PK/P D were adequate and acceptable. Four adequate and well controlled studies were provided to demonstrate the efficacy of risankizumab for the treatment of adult patients with moderate to severe plaque psoriasis. The overall safety profile was acceptable. A risk management plan (RMP) is required to ensure that the benefits of the drug outweigh the risks.

Approval of risankizumab is recommended. The approved indication is for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

3. Post-Marketing Requirements

(1) A Risk management plan focuses on the latent tuberculosis screening and monitoring of hepatitis B/C.
(2) Submit the study reports of M16-004 and the final reports of M15-992 and M15-997 once available.