A Systematic Review of Deucravacitinib as a Novel Systemic Therapy for Moderate to Severe Plaque Psoriasis

Fiosanda Rizky Nugrahanti[a], Evy Ervianti[b], Primasitha Maharani Harsoyo[a], Rayi Megasari Putri[a]

[a] *fiosanda14@gmail.com*
[a] *Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia*

[b]*Department of Dermatology and Venereology, Faculty of Medicine Universitas Airlangga/Dr. Soetomo General Hospital Surabaya, Indonesia*

Abstract

Psoriasis is a chronic skin disease which to date, available treatments can only prevent symptoms' remission. Plaque psoriasis is the most common type. Moderate to severe plaque psoriasis are commonly treated with systemic agents which bring systemic side effects that are unfavourable to patients. Researchers and clinicians are now looking at a novel highly selective TYK2 inhibitor agent, Deucravacitinib, which carries a lot less systemic side effects. We aim to review its efficacy on current studies available. We performed systematic review conducted from MEDLINE, ScienceDirect, and ProQuest library. The authors screened the articles based on inclusion criteria: (1) Trials including patients with moderate-to-severe plaque psoriasis for more than six months; (2) Deucravacitinib as interventional therapy; (3) Human studies that have PASI score as an outcome; (4) Written in English. PASI, sPGA, and DLQI score improvements are outcomes measured in this review. Three randomized control trials (RCT) studies involving 1,943 patients were included. PASI75, PASI90, sPGA 0/1, and DLQI 0/1 achievements in all studies were significantly higher in subjects receiving Deucravacitinib compared to placebo and Apremilast—other active comparator. Deucravacitinib has been proven to be more efficacious in treating moderate to severe plaque psoriasis, even compared to another active biologic agent, Apremilast.

Keywords : Plaque Psoriasis; Psoriasis vulgaris; Deucravacitinib; Apremilast; Psoriasis Area and Severity Index; static Physician's Global Assessment; Dermatology Life Quality Index

1. Introduction

Psoriasis is a chronic, systemic, immune-mediated disease that is mainly characterized by epidermal growth and differentiation impairment. According to the World Psoriasis Day consortium, 125 million people worldwide have psoriasis—this accounts for 2 to 3 percent of the global population (Armstrong et al., 2021). It has a bimodal distribution for the age of onset, one is peaking at 30-39 years and the second is peaking at 60-69 years (Parisi et al., 2013).

To this day, the treatment for psoriasis is limited to prevent symptoms' remission, so psoriasis has been widely heralded as a lifetime disease. Although psoriasis very rarely causes emergency, it still affects people's quality of life. Forty percent of people who have psoriasis reported that their disease is a problem in their everyday life (Stern et al., 2004). Patients who have moderate to severe psoriasis reported to experience a bigger problem and that this disease has gotten them a more negative impacts in their life (Gelfand et al., 2004).

A recent study by Gotlieb et al (2019) revealed that women with psoriasis are reported to experience more burden compared to men having the same disease, reporting lower levels of happiness (women: 18.5%; men: 11.3% lower vs. general population) and are more likely to experience stress (women: 60%; men: 42%), loneliness (women: 25-28%; men: 19-24%), stigmatization (Feelings of Stigmatization Questionnaire score; women: 93.2; men: 78.0), and reduced sexual activity (women: 33%; men: 19%) compared to men (Gottlieb et al., 2019).

Psoriasis comes in several types, each with distinct clinical characteristics. The main variants of psoriasis include plaque psoriasis, pustular psoriasis, guttate psoriasis, and erythrodermic psoriasis (Armstrong & Read, 2020). Plaque psoriasis is by far the most common subtype, accounting for approximately 90% of cases (Boehncke & Schön, 2015). It is mainly characterised by a sharply demarcated erythematous plaques with silvery squama. Elbows, knees, head, intergluteal fold, palmar, and plantar are the most common area to develop plaque psoriasis, although sometimes it can also affect genital area as well (Gudjonsson & Elder, 2019). Up to 50% patients also having nail involvement in psoriasis, with pitting, onycholysis, and oil-drop discoloration being the most seen nail changes (Rigopoulos et al., 2021).

While psoriasis might be known for a skin disease, psoriasis can also develop into systemic co-morbidities. Recent studies have suggested that there are risk of diabetes, likelihood of insulin resistance, and diabetic complications increases with greater psoriasis severity, as defined by treatment patterns or BSA body surface area involved, independent of traditional risk factors. The mechanism is not yet known, but it is suggested that common inflammatory pathways, cellular mediators, and genetic susceptibility may contribute to these findings (Takeshita et al., 2017).

The treatment of psoriasis is mainly based on the severity of the disease. Mild psoriasis only requires topical therapy while moderate to severe psoriasis often need systemic therapy. Systemic therapy of psoriasis varies from conventional, non-biologic agents to relatively-newer and more selective biologic agents. To date, the conventional systemic therapy regimes often bring adverse effects, end-organ toxicity, drug interactions, and the need for close laboratory monitoring (Balak et al., 2020; Boehncke & Schön, 2015; Rendon & Schäkel, 2019). Apremilast, an oral PDE4 inhibitor, remains to be of limited efficacy (Papp et al., 2015). Biological agents available are currently in parenteral preparations which present risk of infection, immunogenicity, and decreasing efficacy over time (Balogh et al., 2020; Kalb et al., 2015).

Deucravacitinib, a novel oral biologic agent which selectively inhibits TYK2, could answer the limitations of the current moderate to severe psoriasis systemic therapy. Its inhibition mechanism of TYK2 is highly selective and shows minimal to no inhibition of JAK 1/2/3. This high selectivity for TYK2 is expected to grant Deucravacitinib a better safety profile, compared to other less selective JAK inhibitors, with fewer adverse effects generally associated with the other three members of the JAK family, such as hyperlipidemia, renal (increased serum creatinine levels) and hepatic abnormalities (increased liver enzyme levels), hematologic changes (anemia, thrombocytopenia, lymphopenia, and neutropenia), and infections, particularly herpes zoster and opportunistic infections (especially tuberculosis) (Chimalakonda et al., 2021; Schwartz et al., 2017). Thus, Deucravacitinib may be a more effective and safer treatment for psoriasis (Estevinho et al., 2023).

Despite a number of reviews about the newly discovered agent Deucravacitinib, a systematic review has not been performed. Therefore, we aim to review current available studies on the efficacy of Deucravacitinib as the treatment for moderate to severe psoriasis.

2. Materials and Methods

2.1. Search strategy and selection criteria

We performed systematic review in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline (Page et al., 2021).

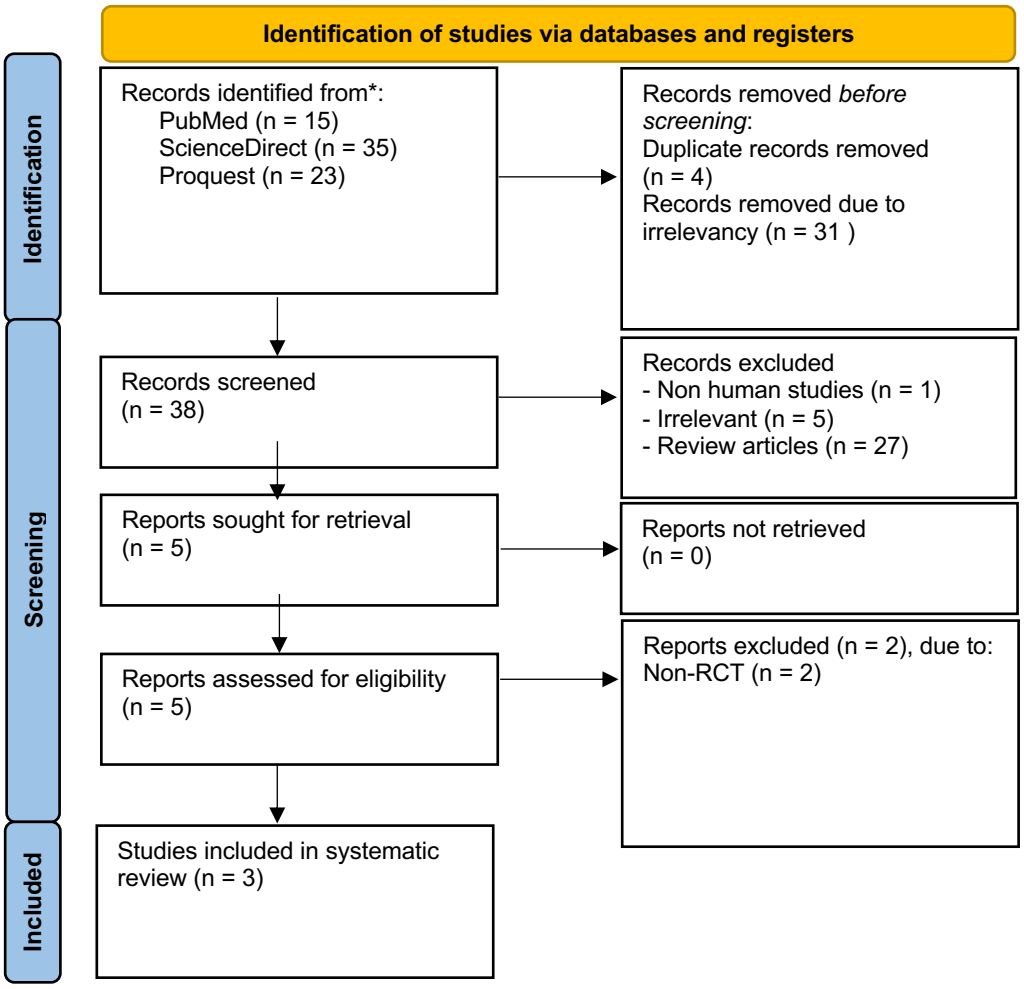

Figure I. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

The authors screened the articles based on inclusion criteria: (1) Trials including patients with moderate-to-severe plaque psoriasis for more than six months; (2) Deucravacitinib as interventional therapy; (3) Human

studies that have PASI score as an outcome; (4) Written in English. Three randomized control trials (RCT) studies were included. Review articles, unpublished articles, conference abstracts, and irrelevant articles were excluded from this study. The literature search was carried out by authors through the databases (PubMed, ScienceDirect, and ProQuest) using keywords "((Deucravacitinib) AND (Plaque Psoriasis))".

2.2. Data extraction and quality assessment

The authors extracted data from selected studies into the evidence table. We evaluated the information including first authors' names and publication year, study design, sample size, patient age, Deucravacitinib intervention, and several outcomes (PASI score, sPGA score, BSA involvements, DLQI score). The risk of bias was accessed using Cochrane risk of bias tool for randomized trial (RoB ver.2). Randomisation, intended interventions, missing outcomes, measurement of outcomes, and selective reporting were assessed in ROB ver.2 tools and rated as low and some concerns (Sterne et al., 2019).

3. Results

3.1. Search results

The search results identified 73 articles. 35 articles were removed due to duplicates. We screened 38 articles from abstracts and titles. Thirty three studies were excluded due to non-human studies, irrelevant, and article reviews. The screening results obtained 5 studies that were assessed for eligibility, resulting two studies that were excluded because they were the analysis of one clinical trial study and as a result there were three studies included in this systematic review.

3.2. Included studies' characteristics

This systematic review included a total of 1,943 patients which consisted of 67.98% male patients and the other 32.02% patients were female. There were 1,065 (54.81%) patients who received Deucravacitinib and 466 (23.98%) patients who received placebo. Two of the included studies used Apremilast as the active comparator, with a total of 422 (21.71%) patients. Those studies were the phase three trial studies (Armstrong et al., 2023; Strober et al., 2023).

These studies enrolled moderate-to-severe plaque psoriasis patients who had had the disease for 6 months or longer. The criteria for moderate-to-severe psoriasis included three main categories, the first one is a 10% or more of body-surface area (BSA) affected (calculated by measuring the area affected with patients' handprint which represents 1% involvement of BSA of each palm (Thomas & Finlay, 2007), secondly is a

Psoriasis Area and Severity Index (PASI) score 12 or higher (this scoring method measures erythema, induration, and the scaliness of the lesions in four divided areas of the body), and lastly a static Physician Global Assessment (sPGA) score of 3 or higher (this scoring has the same measurements as the previous one but the physician's scoring the current severity from each lesion) (Feldman & Krueger, 2005).

Five different doses of Deucravacitinib were used in one phase 2 trial; 3 mg every other day, 3 mg daily, 3 mg twice daily, 6 mg twice daily, and 12 mg daily—compared to placebo. The result of the efficacy were then used to determine the dosage needed for the phase 3 trials, that is 6 mg daily, which were compared with placebo and an active comparator, Apremilast 30 mg twice daily (Armstrong et al., 2023; Strober et al., 2023). Duration of intervention ranges from 12 to 52 weeks.

This systematic review demonstrated the endpoints that were commonly used in measuring the success of psoriasis' therapy in all studies involved, being the primary endpoint is PASI75, defined by 75% reduction of PASI score from baseline, and other secondary endpoints such as sPGA (static Physician Global Assessment) score of 0 or 1, and DLQI (Dermatology Quality of Life Index) score of 0 or 1.

3.3. Endpoints

3.3.1. PASI75

Table I. PASI75 outcomes mentioned in all studies reviewed

References	Study Design	Patients	Intervention and Comparison Dosage	PASI75
Papp, 2018	Randomized controlled trial (Phase 2)	267	Deucravacitinib 3 mg every other day	9%
			Deucravacitinib 3 mg daily	39%
			Deucravacitinib 3 mg twice daily	69%
			Deucravacitinib 6 mg twice daily	67%
			Deucravacitinib 12 mg daily	75%
			Placebo	7%
Armstrong, 2022	Randomized controlled trial (Phase 3)	666	Deucravacitinib 6 mg daily	58.4%
			Apremilast 30 mg twice daily	35.1%
			Placebo	12.7%
Strober, 2023	Randomized controlled trial (Phase 3)	1020	Deucravacitinib 6 mg daily	53%
			Apremilast 30 mg twice daily	39.8%
			Placebo	9.4%

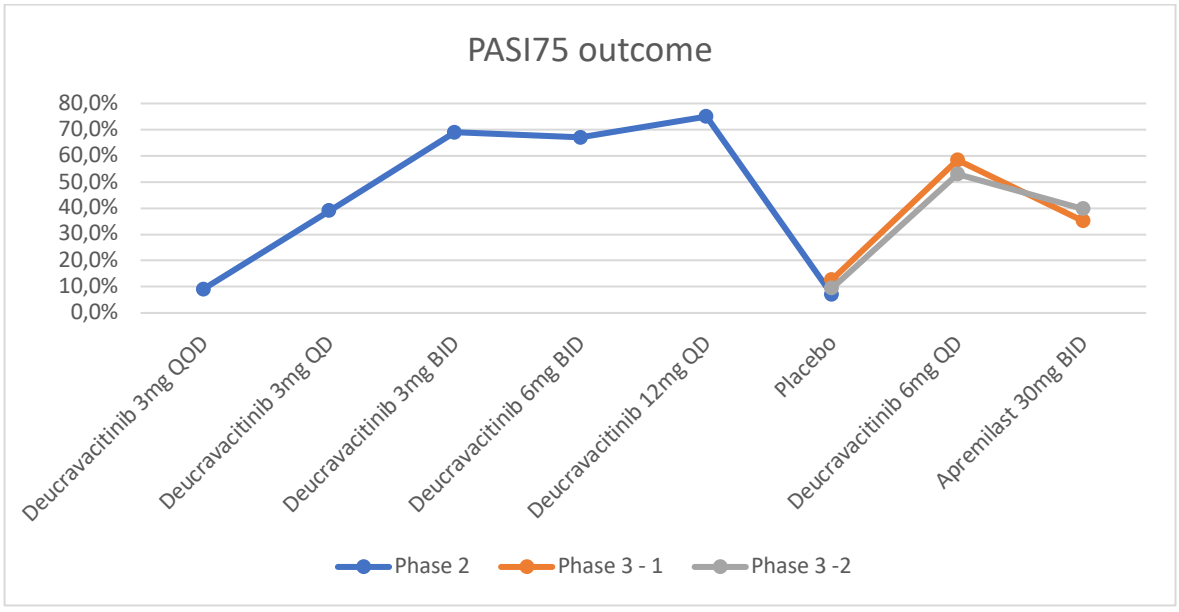

Figure 2. PASI75 outcome

3.3.2. PASI90

Table II. PASI90 outcomes mentioned in all studies reviewed

References	Study Design	Patients	Intervention and Comparison Dosage	PASI90
Papp, 2018	Randomized controlled trial (Phase 2)	267	Deucravacitinib 3 mg every other day	7%
			Deucravacitinib 3 mg daily	16%
			Deucravacitinib 3 mg twice daily	44%
			Deucravacitinib 6 mg twice daily	44%
			Deucravacitinib 12 mg daily	43%
			Placebo	2%
Armstrong, 2022	Randomized controlled trial (Phase 3)	666	Deucravacitinib 6 mg daily	35.5%
			Apremilast 30 mg twice daily	19.6%
			Placebo	4.2%
Strober, 2023	Randomized controlled trial (Phase 3)	1020	Deucravacitinib 6 mg daily	27.0%
			Apremilast 30 mg twice daily	18.1%
			Placebo	2.7%

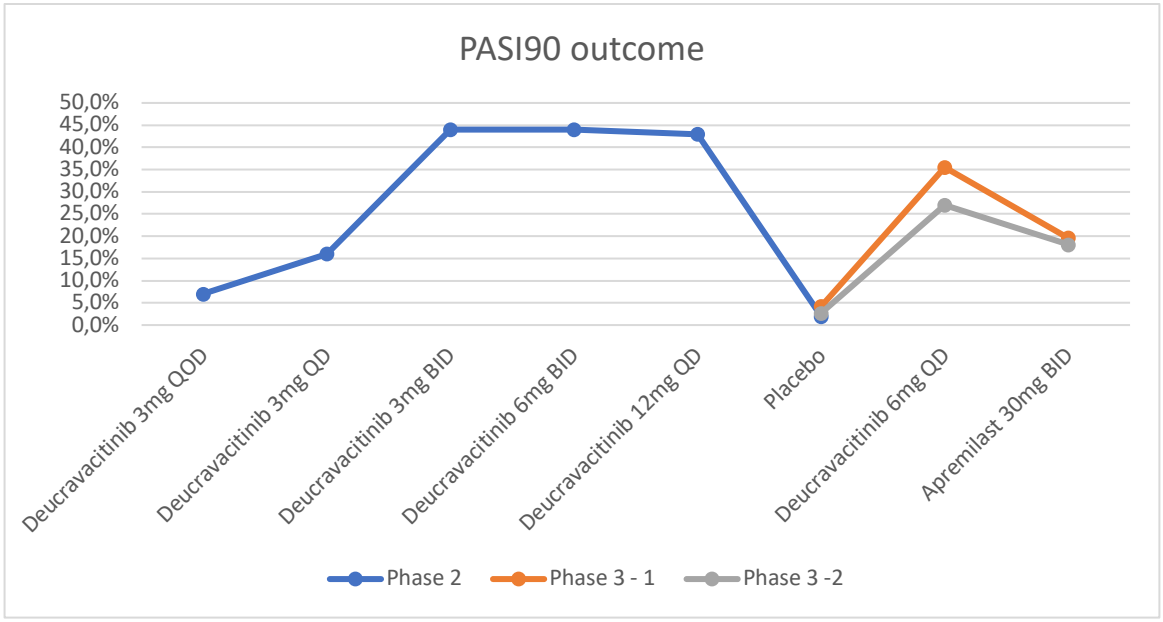

Figure 3. PASI90 outcome

3.3.3. sPGA 0/1

Table III. sPGA score of 0/1 achieved in all studies reviewed

References	Study Design	Patients	Intervention and Comparison Dosage	sPGA 0/1
Papp, 2018	Randomized controlled trial (Phase 2)	267	Deucravacitinib 3 mg every other day	20%
			Deucravacitinib 3 mg daily	39%
			Deucravacitinib 3 mg twice daily	76%
			Deucravacitinib 6 mg twice daily	64%
			Deucravacitinib 12 mg daily	75%
			Placebo	7%
Armstrong, 2022	Randomized controlled trial (Phase 3)	666	Deucravacitinib 6 mg daily	53.6%
			Apremilast 30 mg twice daily	32.1%
			Placebo	7.2%
Strober, 2023	Randomized controlled trial (Phase 3)	1020	Deucravacitinib 6 mg daily	49.5%
			Apremilast 30 mg twice daily	33.9%
			Placebo	8.6%

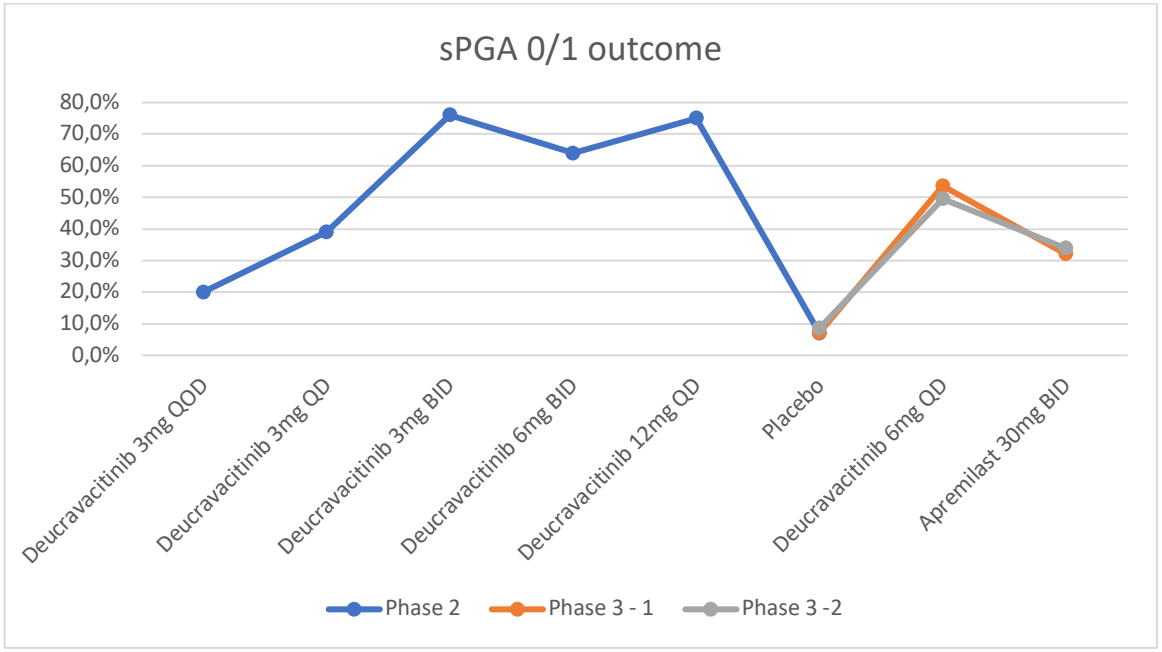

Figure 4. sPGA 0/1 outcome

3.3.4. DLQI 0/1

Table IV. DLQI score of 0/1 achieved in all studies reviewed

References	Study Design	Patients	Intervention and Comparison Dosage	DLQI 0/1
Papp, 2018	Randomized controlled trial (Phase 2)	267	Deucravacitinib 3 mg every other day	16%
			Deucravacitinib 3 mg daily	16%
			Deucravacitinib 3 mg twice daily	42%
			Deucravacitinib 6 mg twice daily	60%
			Deucravacitinib 12 mg daily	64%
			Placebo	4%
Armstrong, 2022	Randomized controlled trial (Phase 3)	666	Deucravacitinib 6 mg daily	41.0%
			Apremilast 30 mg twice daily	28.6%
			Placebo	10.6%
Strober, 2023	Randomized controlled trial (Phase 3)	1020	Deucravacitinib 6 mg daily	37.6%
			Apremilast 30 mg twice daily	23.1%
			Placebo	9.8%

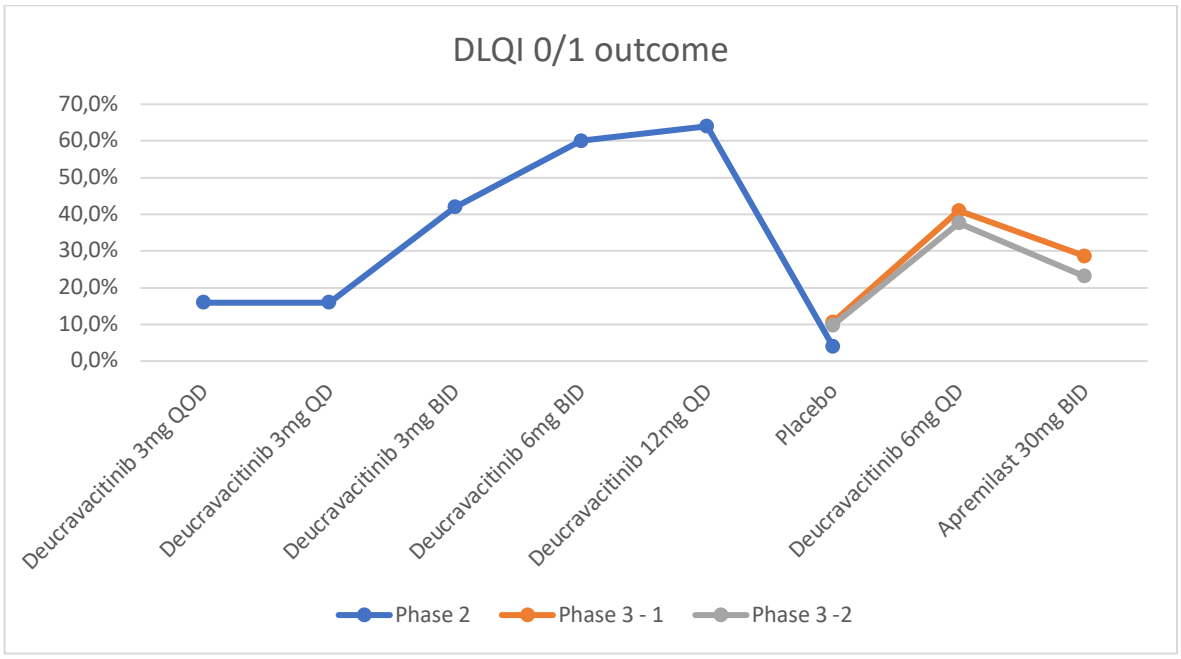

Figure 5. DLQI 0/1 outcome

4. Discussion

This systematic review of three trials using a novel biological agent Deucravacitinib, which involved a total of 1,943 patients, is showing a positive result. As seen in the phase 2 trial, although the first two minimum doses showed no significant result compared to placebo (3 mg every other day and 3 mg daily, respectively), three other larger doses showed better outcomes. As much as 69% of patients receiving 3 mg twice daily dose of Deucravacitinib achieved PASI75, a 75% reduction of PASI score from baseline. A positive result is also seen in patients receiving higher doses, which were 67% of PASI75 in patients with 6 mg twice daily and 75% of PASI75 in patients with 12 mg daily dose. This result is higher compared to only 7% of patients reaching PASI75 in placebo group (Papp et al., 2018). Results from the former phase 2 trial were then brought to the first two phase 3 trials to determine the amount of Deucravacitinib dose selected to be compared with placebo and the active comparator, another biologic agent, Apremilast, that was 6 mg daily dose. The results from the first and second phase 3 trial showed positive results as well, that were the achievement of PASI75 58.4% and 53.0% respectively. As a comparison, only 12.7% patients from the first phase 3 trial and 9.4% patients from the second phase 3 trial in placebo group achieved PASI75. Apremilast as the active comparator were in the middle between the placebo and Deucravacitinib group, as many as 35.1% patients from the first phase 3 trial and 39.8% patients from the second phase 3 trial achieved PASI75. (Fig 2)

All three trials also measured PASI90 outcomes, which is a 90% reduction of PASI score from baseline. Phase 2 trials discovered that the first two lowest doses of Deucravacitinib showed minimum achievement of PASI90, only 7% patients in the 3 mg every other day group and 16% in 3 mg daily group, although this number is larger than the placebo group which only 2% patients achieved PASI90. The other three larger doses showed positive results, 44% of patients achieved PASI90 in both 3 mg twice daily and 6 mg twice daily, and 43% in 12 mg daily group. The results from two phase 3 trials showed the same trend like the previous outcome mentioned. As many as 35.5% patients in the Deucravacitinib group from the first phase 3 trial achieved PASI90, higher than the Apremilast group which only 19.6% patients achieved PASI90. Only 4.2% of patients from the placebo group achieved PASI90. The second phase 3 trial resulted as many as 27.0% subjects receiving Deucravacitinib 6 mg daily achieved PASI90, while there were only 2.7% patients from the placebo group and 18.1% patients from the Apremilast group achieved PASI90. (Fig 3)

sPGA (static Physician Global Assessment) score of 0 (clear) or 1 (almost clear) was also the outcome measured in these trials. There were only 7% patients in placebo group achieving sPGA score 0/1, while two lowest doses of Deucravacitinib also showed minimal result, 20% patients in 3 mg every other day group and 39% patients in 3 mg daily group. The expected results are seen in three larger doses, 76% patients in 3 mg

twice daily group, 64% patients in 6 mg twice daily group, and 75% patients in 12 mg daily group. The results seen on both phase 3 trials showed consistency. In the first phase 3 trial, 7.2% patients in placebo group achieved sPGA score 0/1, while there are 53.6% and 32.1% patients in Deucravacitinib 6 mg daily and Apremilast group respectively achieved sPGA score of 0 or 1. From the second phase 3 trial, 8.6% patients from the placebo group achieved sPGA 0/1, while there were 49.5% patients in Deucravacitinib 6 mg daily dose group and 33.9% patients from Apremilast group achieved sPGA 0/1. (Fig 4)

The last outcome measured was DLQI (Dermatology Life Quality Index) score 0/1. Only 4% patients from the placebo group in phase 2 trial who achieved such outcome. Two lowest dose groups also showed minimum results, only 16% patients showed DLQI 0/1 in both 3 mg every other day dose group and 3 mg daily dose group. Higher dose groups achieved more likeable results, the people achieved DLQI 0/1 in 3 mg twice daily dose group, 6 mg twice daily dose group, and 12 mg daily dose group are 42%, 60%, and 64% respectively. In the first phase 3 trial, 10.6% patients from placebo group achieved DLQI 0/1, while there were 41.0% in Deucravacitinib 6 mg daily dose group and 28.6% patients in Apremilast group achieved such outcome. The second phase 3 trial showed similar results, being only 9.8% in the placebo group achieved DLQI 0/1, while 37.6% patients in Deucravacitinib group and 23.1% patients in Apremilast group achieved such outcome. (Fig 5)

5. Conclusions

The use of a novel highly selective biologic agent is by date proven to be more efficacious, even compared in other active comparator, in treating moderate-to-severe plaque psoriasis. Using PASI75 as the main outcome measured in all studies, we can see the achievement of PASI75 in groups treated with Deucravacitinib is higher than the group receiving placebo as we can see in Figure 2. This result is consistent in three other outcomes mentioned in all studies, those are PASI90 achievement, sPGA score 0 or 1 (clear or almost clear) and the achievement of DLQI score of 0 or 1, as seen on Figure 3, Figure 4, and Figure 5 respectively. Although there are still numerous clinical trials going (POETYK PSO-3 [NCT04167462], POETYK PSO-4 [NCT03924427], and POETYK PSO-LTE [NCT04036435]), these three trials have shown positive result for the use of Deucravacitinib. If the results in ongoing trials are consistent, treating moderate-to-severe plaque psoriasis with this new agent could be favourable, since Deucravacitinib poses less adverse effects thanks to its highly selectivity towards TYK2. At this moment, we surely still have to wait for the ongoing trials to finish and see the results.

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