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Beyond skin deep: Baseline systemic immune-inflammatory index as predictor of treatment response of HRO350 in mild-to-moderate psoriasis. Results from the HeROPA study

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Introduction

Psoriasis affects roughly 2-4% of the Western population. More than 80% of patients have mild to moderate disease (1). The HeROPA phase 2b clinical trial evaluated the oral investigational medicinal product HRO350 in patients with mild-to-moderate psoriasis (PASI 3-10, sPGA 2-4, BSA ≥3). Severity assessments of psoriasis, including in the HeROPA trial, are predominantly evaluated using PASI. PASI lacks precision for assessing milder psoriasis with lower BSA involvement (2,3). There has recently been an increased interest in biomarkers to complement objective skin assessments in psoriasis. which may be especially useful in patient populations with milder disease. Here we present the main outcome from the HeROPA phase 2b trial along with a *post hoc* stratification utilizing the systemic immune-inflammation index (SII; neutrophils x platelets / lymphocytes) to provide information on systemic effects (4-7). We wanted to investigate if SII as a biomarker could furthermore contribute to improved separation of placebo response in efficacy assessments.

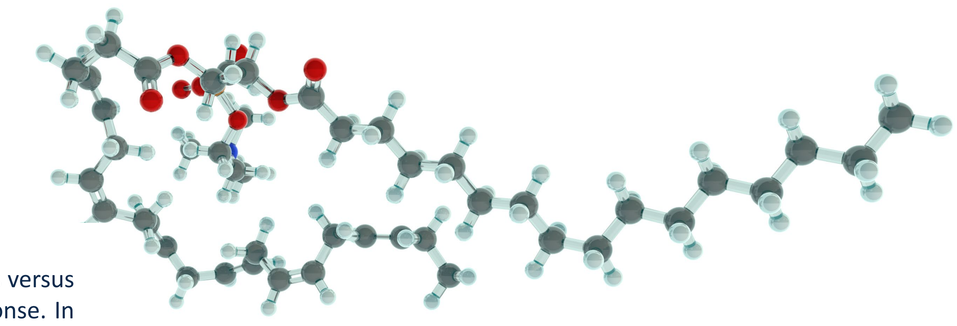
The HeROPA phase 2b trial (NCT06125808) was conducted in five European countries. Patients (N = 521) were randomized (1:1:1) to receive oral HRO350 (active pharmaceutical ingredient [API]: Phospholipid esters from herring roe), IRIS Substance ID: 300000046327) 1050 mg daily, 2100 mg daily, or matching placebo b.i.d. for 52 weeks.

Efficacy results

Key efficacy results:

- High placebo rate in the ITT impacted efficacy assessments and primary endpoint (PASI50) at week 26 was not met in either doses (2100 mg/1050 mg ITT; RD = -3 pp/-9 pp; p = 0.56/0.04)
- The key secondary endpoint sPGA 0/1 indicated a non-significant trend in 2100 mg arm at week 52 (PP; RD = 14 pp; p = 0.07)
- Stratification by baseline SII showed >20% pp improved response rates in several endpoints for patients with low baseline SII vs high baseline SII
- Lower baseline SII (≤ 506) was associated with lower placebo response

Oral API: Phospholipid esters from herring roe (PEHeRo; IRIS Substance ID: 300000046327) contains a complex marine phospholipid matrix for the treatment of mild to moderate psoriasis



The primary endpoint of PASI50 at 26 weeks in HRO350 treatment arms versus placebo was not met partly due to an unexpectedly high placebo response. In the intention-to-treat (ITT) population at week 26, 22% (risk difference [RD] = -2.7 percentage points [pp]; p = 0.56) of patients in the 2100 mg arm and 16% (RD = -8.9 pp; p = 0.04) of patients in the 1050 mg arm achieved PASI50 compared to 25% in the placebo arm.

At week 52 in the per-protocol (PP) population, a non-significant trend was observed in the 2100 mg arm, with 47% (RD = 14 pp; p = 0.07) of the patients achieving sPGA0/1. Other secondary tests included PASI50, PASI75, sPGA, ScPGA, BSA, and sPGAxBSA changes from baseline to all study visits along with mean change analyses, neither of which showed a statistically significant treatment benefit for HRO350.

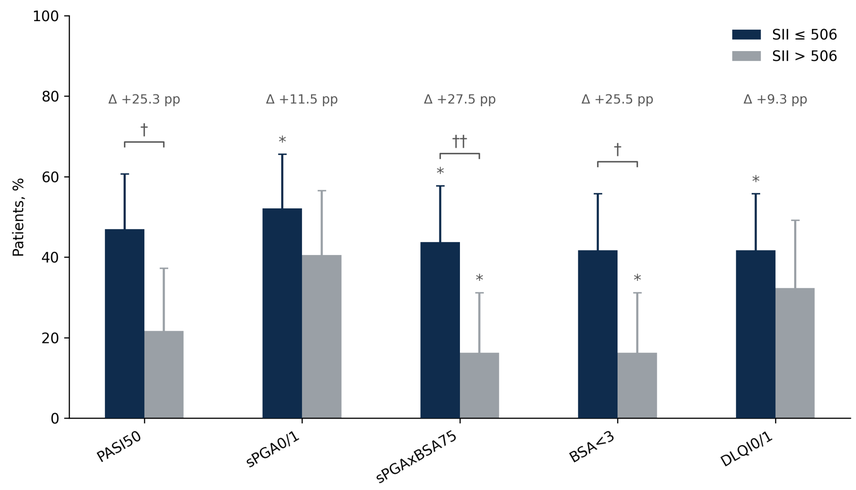
To investigate the high placebo rate using visual assessment tools, the patient population was stratified *post hoc* into two groups: those whose baseline SII was above or below the median SII value of 506. After stratification, the two groups were analysed for their response rates after 52 weeks of treatment towards a set of categorical endpoints: PASI50, sPGA0/1, sPGAxBSA75, BSA <3, and DLQI0/1. These endpoints from the protocol were chosen to cover both psoriasis plaque severity and area, as well as patient quality of life. It should also be noted that patients with baseline DLQI0/1 were included in the DLQI0/1 analysis.

It was observed that response to active treatment (Chart A) was higher, and placebo response (Chart B) was lower in the lower baseline SII group compared to the higher SII group. Specifically, with 9.3 to 27.5 pp higher response rates in the 2100 mg arm and -3.5 to -14.4 pp lower response rates in the placebo arm. Differences between the SII ≤506 and SII >506 groups in the 2100 mg arm were statistically significant at >25 pp for multiple endpoints in the PP population (Chart A). No statistically significant differences between the SII groups were observed in the placebo arm (Chart B).

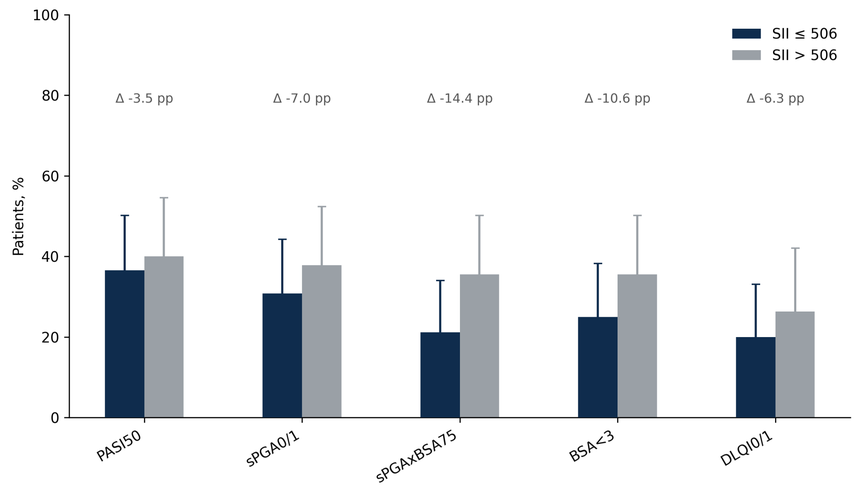
The higher active treatment response rate and lower placebo response rate in the group with baseline SII ≤ 506 led to statistically significant proportions of patients having sPGA0/1 (n: 25/48; RD: 21.3 pp; 95% CI: [2.4, 40.2]; p < 0.05), sPGAxBSA75 (n: 21/48; RD: 22.6 pp; 95% CI: [4.7, 40.4]; p < 0.05), and DLQI0/1 (n: 20/48; RD: 21.7 pp; 95% CI: [3.8, 39.5]; p < 0.05) after 52 weeks of treatment in the PP population.

The PASI50 responder proportions in the whole population made informative assessments of treatment benefit in this study difficult. PASI50 may therefore be an unsuitable endpoint for assessing a mild to moderate psoriasis population over long time periods.

A) Responder rates HRO350 2100 mg arm (PP population)



B) Responder rates placebo arm (PP population)



Bar charts showing absolute proportions for 2100 mg active treatment (A) and placebo (B) in patients with a baseline SII above/below 506 respectively, after 52 weeks of treatment in the PP population. *) p < 0.05 vs placebo (same SII strata), †) p < 0.05 high vs low SII (within-arm), ††) p < 0.01 high vs low SII (within-arm).

Safety

Over 1-year of treatment, a total of 417 patients (80%) reported any adverse event (AE), and 406 patients (78%) experienced a treatment-emergent adverse event (TEAE) with no obvious differences between HRO350 and placebo treatment groups. There was a total of 38 serious adverse events (SAEs), all unrelated to treatment, no SUSARs were observed. The number and nature of the AEs/SAEs that occurred in the study were to be expected considering the large patient population and age range.

The TEAEs reported were generally similar between treatment groups. The most common TEAEs were nasopharyngitis (n = 126; 24.2%), covid-19 (n = 41; 7.9%), psoriasis (n = 33; 6.3%), arthralgia (n = 31; 6.0%) and diarrhoea (n = 31; 6.0%).

The safety data derived from this study shows a favourable safety / tolerability profile for HRO350. The absence of HRO350 related SAEs supports the conclusion that HRO350 is safe and well tolerated.

Conclusion

Treatment benefit from HRO350 compared to placebo was found to be statistically significant across multiple endpoints in patients with baseline SII ≤506. High baseline SII was associated with no treatment benefit versus placebo and moderately increased placebo response compared to lower baseline SII.

Stratifying patients based on baseline SII enhanced treatment effect detection in a patient population prone to high placebo responses and whose disease severity assessments are limited by insufficiently granular clinical assessment tools.

References

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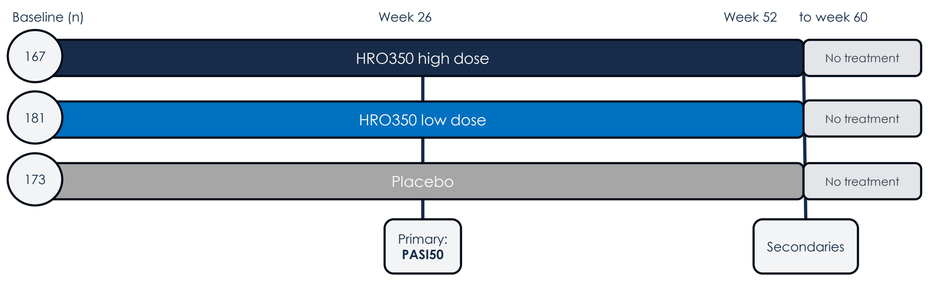
Materials and methods

Study design and treatment: The HeROPA trial (EUCT no.: 2022-501850-12-00; clinicaltrials.gov identifier: NCT06125808) was conducted in clinics and hospitals in Germany, Poland, UK, Norway, and Finland. Patients were randomized (1:1:1) to receive the polar lipid drug candidate HRO350 (API: PEHeRo, IRIS Substance ID: 300000046327) 1050 mg daily, 2100 mg daily, or matching encapsulated vegetable oil placebo for 52 weeks.



Participant selection criteria and recruitment: N = 521 patients (684 screened). Eligible patients were adults (≥18 years) mild-to-moderate plaque psoriasis (PASI 3-10, BSA ≥3, sPGA 2-4). Patients with low white blood cell count, low lymphocyte count, or other pathological complete blood count findings were excluded. ***Post hoc* stratification:** Patients were stratified into two subgroups based on the ITT population baseline SII median (≤ 506 vs. > 506). Categorical efficacy outcomes assessed within these subgroups included sPGA 0/1, PASI50, sPGA×BSA75, DLQI 0/1, and BSA < 3. **Statistical analyses:** Pearson's chi-square test with a 5% level of significance. If the expected counts in any cell in the 2×2 table were less than 5, the Fisher's exact test was used instead. Missingness of data was handled through non-responder imputation. Stratified patients in the PP population were analysed *post hoc* using data as observed and patients in the ITT population were analysed using non-responder imputation. The stratification analyses used Wilson CIs for responder rates and Wald CIs for treatment comparisons.