" LIVE cumulative network meta-analysis : SYStemic pharmacological treatments for chronic plaque PSORIAsis

LIVE-PSOria-SYS

1 SUMMARY

Full title	**LIVE cumulative network meta-analysis : SYStemic pharmacological treatments for chronic plaque PSORIAsis**
Acronym/reference	**LIVE PSORIA-SYS**
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Sponsor	Assistance Publique – Hôpitaux de Paris
Scientific justification	Psoriasis is a chronic, relapsing, inflammatory skin or joint disease that affects 1% to 2% of the population and impairs quality of life. Psoriasis is associated with a higher risk of mortality because of a greater risk of developing severe vascular events such as cardiovascular and cerebrovascular diseases. There is no curative treatment for psoriasis. However, there is an arsenal of therapeutic options proposed in the management of the disease and it is of prime importance that clinicians have evidence-based recommendations before initiating treatment in psoriasis. A recent network meta-analysis (NMA) identified drugs presenting a better compromise between efficacy and acceptability with high-confidence evidence among 19 available drugs (on the market or in development). However, there is still a level of uncertainty as few head to head trials compared systemic treatments against each others and new molecules emerged constantly (in 2017, 4 new biological treatments have been commercialized for psoriasis). Thus, using an innovative and high quality methodology, we aim to perform a living NMA for systemic treatments for psoriasis.
Objective and primary assessment criterion	**Primary Objective** To provide a constantly up-to-date evidence that compares and ranks systemic treatments according to their effectiveness and acceptability (the inverse of serious adverse effects) for moderate-to-severe chronic plaque psoriasis **Primary endpoint** 1. The proportion of participants who achieved clear or almost clear skin, that is, at least PASI-90 (90% improvement in the Psoriasis Area and Severity Index score -PASI-) at the end of the induction phase (remission of the psoriasis flare i.e. between 12 to 24 weeks). The Psoriasis Area and Severity Index score (PASI), which is an outcome instrument used to assess the severity of the psoriasis, is the most common outcome measure used in trials 2. The proportion of participants with serious adverse effects (SAE) at the end of the induction phase (remission of the psoriasis flare i.e. between 12 to 24 weeks). We used the definition of severe adverse effects from the International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, which includes death, life-threatening events, initial or prolonged hospitalization, and adverse events requiring intervention to prevent permanent impairment or damage (http://www.ich.org/home.html)
Secondary objectives and endpoints	**Secondary Objectives** To compare and rank systemic treatments according to the improvement of the quality of life of patients with moderate-to-severe chronic plaque psoriasis

	To compare and rank systemic treatments according to other efficacy outcomes moderate-to-severe chronic plaque psoriasis To compare and rank systemic treatments according to adverse effects for moderate-to-severe chronic plaque psoriasis **Secondary endpoints** 1. Proportion of participants who achieve PASI-75 at induction phase (remission of the psoriasis flare i.e. between 12 to 24 weeks) 2. Proportion of participants who achieve a Physician Global Assessment (PGA) value of 0 or 1 3. Quality of life measured by a specific scale. Available validated scales are the Dermatology Life Quality Index (DLQI), Skindex, Psoriasis Disability Index (PDI), or Psoriasis Symptom Inventory (PSI), others specific scale used in selected trials will be included 4. The proportions of participants with adverse effects (AE)
Experimental design	The Live cumulative NMA of randomized controlled trials is initiated with a conventional NMA. The conventional Cochrane NMA has just been published supported by the DGOS call (PHRCN 140322 / NI 14019). Six methodological steps will then be repeated at regular intervals (every 3 months) to update the NMA over time: adaptive search for treatments and trials, screening of reports and selection of trials, data extraction, assessment of risk of bias, update of the network of trials and synthesis, and finally dissemination.
Trials involved	We will consider trials that included adults (over 18 years of age) with moderate to severe plaque psoriasis (i.e. needed systemic treatment) with or without psoriatic arthritis, at any stage of treatment.
Inclusion criteria	We will include randomized controlled trials
Non-inclusion criteria	Phase I trials Cross-over trials Non-randomized studies
Subject of the study	We will evaluate trials assessing all available systemic drugs for psoriasis, whether already on the market or in development. We will create a research community in psoriasis; including international experts in the field who will help to provide information of new “eligible” drugs.
Number of Trials	12000 trials
Number of potential centers	- International team
Study period	- total duration : 48 months
Statistical analysis	**For all new trials included in the network at each iteration, we will re-run the analyses as follows.** **<u>Measures of treatment effect</u>** For every treatment, we will estimate the ranking probabilities of being at each possible rank for all outcomes, taking into account for the within-trial correlation. We will infer on treatment hierarchy using the surface under the cumulative ranking curve (SUCRA). SUCRA will be expressed as a percentage between 0 (when it is certain a treatment is the worst) to 100% (when it is certain a treatment is the best). The primary unit of analysis will be the participant. **<u>Assessment of heterogeneity and inconsistency</u>** The assessment of statistical heterogeneity in the entire network will be based on the estimated heterogeneity variance parameter (τau-square) estimated from the network meta-analysis models. We will estimate the prediction intervals to assess how much the estimated heterogeneity affects the relative effects with respect to the additional uncertainly anticipated in future studies. When feasible, we will investigate the possible sources of heterogeneity in subgroup analyses and meta-regression. We will assess inconsistency using the loop-specific approach and the side-splitting method. We will also fit the design by treatment interaction model to evaluate the presence of inconsistency in the entire network.

	Assessment of reporting biases To assess reporting biases, we will use an adaptation of the funnel plot that allows to induce all studies of a NMA in the same plot. **Data synthesis** We will perform pair-wise meta-analyses for all outcomes and comparisons, meaning that at least two studies are available, using a random-effects model. We will then employ network meta-analysis to estimate the relative effects for all possible comparisons between any pair of treatments. We will provide a graphical depiction of the evidence network for all outcomes to illustrate the network geometry.
Sources of funding for the trial	National PHRC 2018
Trial will have a Data Monitoring Committee	Not applicable