

Comments on
CPMP Note for Guidance on Clinical Investigation of Medicinal Products
Indicated for the Treatment of Psoriasis
(CPMP/EWP/2454/02, Draft, 20 November 2003)

German Region of the International Biometric Society

Comments:

1. Concomitant medication

The document does not tell anything about the use of concomitant medication in clinical trials. Since many patients with severe psoriasis take medications permanently, it should be stated which concomitant medication is prohibited and in which way this is to be controlled in clinical trials.

2. Washout period

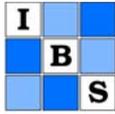
(page 4, 2.1)

A recommended washout period for biologicals should be mentioned, as done for corticosteroids and acitretine.

3. Long-term efficacy and safety

(page 5, 2.6, 2nd paragraph)

The sections 4.2 and 6.1.3 mentioned in this section do not appear in the document.



4. Required results for registration

(page 5, 2.7, 2nd paragraph)

It is not clear whether positive results must be obtained with respect to all endpoints “response to treatment”, “durability of remission/response”, and “relapse and rebound after the end of treatment” in order to be granted the indication “treatment of mild-moderate-severe psoriasis”.

5. Long-term studies required for registration

(page 5, 2.7, 4th paragraph)

It is not clear what is meant by “long-term studies (1-year)”? Does this apply to separate 1-year safety AND efficacy studies or can this requirement be fulfilled in one 1-year study that investigates both safety and efficacy.

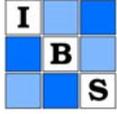
6. Studies required for registration

(page 5, 2.7, and page 9-12, 5.)

The number of pivotal studies required for registration is not mentioned. For example, is one three-arm pivotal trial (new drug, active comparator, vehicle) sufficient for registration?

For therapeutic confirmatory studies involving topicals, both two-arm studies versus placebo (vehicle) and three-arm trials including active comparator and vehicle are mentioned. It is not stated which type of studies are absolutely required for registration and if both types, two studies in one type or a combination thereof is required.

Whereas for topicals both vehicle-controlled and reference- and vehicle-controlled studies are possible, this is not the case for systemically administered agents, where inclusion of a reference arm is mandatory. The question arises as to why there are discrepancies here in the assessment possibilities in topical and systemic administration.



**7. PGA for physician's global assessment of improvement
(page 6, 3.2, 5th paragraph, and page 7, 4.1.1.4)**

There should be a consistent understanding of the use of the PGA throughout the guideline. In some cases it appears to be used in the sense of a static score (section 3.2), in other cases as a change from baseline (section 4.1.1.3). This should be consistently used throughout the guideline.

**8. Definition of wordings in pharmacokinetics
(page 9, 5.1.2)**

It is not clear what is meant by “general pharmacokinetic evaluation” and by “skin reservoir”. These terms should be defined more precisely.

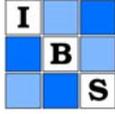
**9. Studies in special populations
(page 9, 5.1.2, and page 13, 6., 4th and 6th paragraph)**

The comments made in section 5.1.2 regarding PK in children and elderly do not seem to be in accordance with those mentioned under section 6 (Studies in Special Populations). There it is stated that “specific studies in children are not warranted” and “In elderly, psoriasis characteristics are similar to those in general adult population and specific trials are generally not necessary.”

**10. Blinding
(page 11, 5.2.5, 3rd paragraph, 2nd sentence)**

On page 11, chapter “Study design”, it is stated “However, in rare cases where blinding may be jeopardised due to the different side-effect profile of available therapies, placebo-controlled studies (blinding possible) and active controlled studies might – if fully justified – be performed separately.”

The advantage of conducting two different trials in such a situation is not comprehensible. If blinding is possible between placebo (P) and a new drug (N), but not between P and an active



comparator (S) and not between N and S, blinding (between P and N) will be possible in a 2-arm trial (between P and N) as well as in a 3-arm trial (with S additionally). In addition, a 3-arm trial has the advantage that a bias (due to the impossibility of blinding between N and S) in favour of N (in comparison to S) will also lead to a bias in favour of P (because P and N are indistinguishable) and therefore to a conservative estimate of the difference between N and S related to the difference between S and P (efficacy of S).

11. Clinical safety evaluations

(page 14, 7.1, 3rd paragraph)

It is not clear whether the statement “Psoriasis patients are generally considered to be at higher risk of developing skin malignancies (and possibly also lymphoproliferative diseases)” refers to an inherent risk based on the disease itself or whether it refers to the higher risk based on the current therapies used in the treatment of psoriasis which can lead to malignancies and lymphoproliferative diseases. This should be specified.