Peer-review Comments and Author Responses

Reviewer 1.

1. According to Schmitt, 2005, PASI is the gold standard. Is there another or better approach than the Psoriasis Area Severity Index (PASI) to evaluate psoriasis skin lesions? PGA? PSI? SPI? CDLQI? PEST? sPGA-G?

There indeed are other methods to evaluate the severity of psoriasis. We considered PASI the best option due to being already pretty established when assessing the improvement of plaque psoriasis over time and overall use among doctors, including non-dermatologist physicians.

2. *How to improve the study? The external validity and generalizability? Have you considered other risk factors than the diagnosis? Weather? Socio-economic level? Educational level?*

We consider that our study has advantageous features that ensure external validity and generalizability, which break down as follows:

-Target population: This point has been addressed in greater depth in question 8.

Hypericum perforatum: the plant has been acclimatized in many parts of the world; thus, it is easy to buy it on many continents. On one hand, different socio-economic groups can afford it due to its reasonable price, on the other hand, the ointment can be prepared by pharmacists, making its acquisition easy. According to 2 pilot studies it was well tolerated by the patients and the treatment regimen was not a considerable burden. Furthermore, herbal treatments are well-accepted in developing countries (e.g., many nations of America and Asia). Additionally, there is an increasing trend of these treatments in many developed countries (e.g., Germany and the USA, etc.)
Intention-to-treat principle: it will be used because it helps to reflect the real-world data. This point has been addressed in greater depth in question 4.
Assessment tools: PASI has been widely used worldwide. It can be applied by non-dermatologist physicians, a great advantage for its implementation in places where there is a lack of dermatologists.
Inclusion/exclusion criteria: We consider our inclusion/exclusion criteria to be not strict. Allows a reachable study population in other places in the world.
Regarding the point about the weather, the worsening of psoriasis is associated with cold climates while improvement with hotter. However, it is not a constant, the behavior of the disease is unpredictable most of the time and different in each patient, therefore we do not completely consider it as an obstacle to external validity. It would be interesting to compare subgroups in cold and hot climates in phase III studies.

3. Beyond the topic of corticosteroids, are there other treatments to use as control? Vitamin D?

Naturally, there are. Nonetheless, topical corticosteroids remain the mainstay of topical treatment, since other treatments have many downsides:

-Vitamin D analogs (calcipotriene and calcitriol): Skin irritation may cause treatment interruption. To avoid side effects, they can be combined with corticosteroids, however, acidic products such as some topical corticosteroids can inactivate topical calcipotriene. Besides, they are more expensive than many generic potent topical corticosteroids.
-Tar: It is usually prescribed in combination with topical corticosteroids. Notwithstanding, staining of hair, skin, and clothing is a common complaint of many users, additionally, its odor can be perceived as unpleasant.
-Retinoids (tazarotene): Similar to vitamin D analogs, they may irritate, thus they are frequently used in combination with topical corticosteroids.
-Calcineurin inhibitors (tacrolimus and pimecrolimus): They are generally well tolerated and present good efficacy. Nevertheless, in 2006 the FDA placed a black box warning on their package due to the possible association with lymphoma and skin cancer, although this has not yet been proven.
-Anthralin: It is less effective than topical vitamin D or potent topical corticosteroids. Furthermore, it can stain skin and clothing and produce skin irritation.
-Others (tapinarof and roflumilast): They are expensive for many patients. They can cause headaches and gastrointestinal adverse effects, respectively.
Even though there are many alternatives on the market, the cost can be a limiting factor for the combination of agents or corticosteroid substitution. In addition, side effects may be intolerable for some patients, leading to treatment dropout. Although there are many alternative and concomitant treatments, there is still an urgent need for a reasonably priced and well-tolerated treatment to avoid or minimize chronic topical corticosteroid use. Therefore, we strongly believe it is important to perform clinical trials to test Hypericum perforatum since its cost and good tolerance by patients (according to 2 pilot studies) could position it as an attractive topical therapy in the future, however, further studies are needed.

4. If you are dealing with drop-outs, how you can assess the data? Can you explain how intention to treat reflects the real-world data?

In comparison to per-protocol analysis, the intention-to-treat principle (ITT) has important advantages for clinical trials such as preserving the benefits of randomization (the cornerstone of clinical trials). Likewise, it keeps the sample size and minimizes type I errors.
It is also noteworthy to highlight that it also reflects the "real world" since it takes into account non-compliance and protocol deviations, situations that occur regularly in clinical practice with our patients, who do not always follow the indications. Therefore, ITT makes it easier to generalize results, i.e. it increases external validity. In our study, multiple imputation methods will be used to allow ITT analysis.

To give a detailed explanation in the manuscript, we decided to add the phrase in red in the last paragraph of point 2.14 as follows:
- Before: Superiority will be tested using the intention-to-treat principle. Multiple imputation…
- After: Superiority will be tested using the intention-to-treat principle to preserve the generalizability of results by reflecting the reality of clinical practice. Multiple imputation…

5. In our clinical practice, we are dealing with patients with multiple comorbidities and taking a lot of medicine. How to deal with the Hawthorn effect in this study?

We know it is completely impossible to avoid the Hawthorne effect. However, our study has the following characteristics to deal with it:

-Non-invasive assessment of adherence: We decided not to use phone calls or messages to ensure adherence because it can continually trigger and increase the feeling of being observed not only in the physician's office but also in their own homes. In contrast, we assessed adherence by instructing the patients properly, using a diary, and the container emptying inspection. All of them are less invasive techniques and can be carried out in a low-key way to reduce the Hawthorne effect.

-Double-blinding and randomization: the blinding of physicians and patients in our study is of easy implementation, and the placebo is quite difficult to recognize from the active ointment. Therefore, although a certain level of Hawthorne effect is expected (as in all clinical trials), it should occur equally in the intervention and control group, thus avoiding discrepancies that can negatively impact trial results. Both groups will be treated the same by the physicians who will not be available to distinguish the allocation of the patients. Randomization also ensures the Hawthorne effect is equivalent in both groups.

6. *Based on eligibility criteria, why do the authors use ages between 18 and 65 years old? Is there a difference between pre and post-menopausal women? Gender? Race/ethnicity? Comorbidities? Other treatment?*

We chose this age range since immunosenescence has been reported to produce an imbalance between inflammatory and immune reactions in elderly individuals, causing an increase in proinflammatory cytokines levels such as TNF-α, (which is a target of Hypericum perforatum) and also affecting immune cells function.
On the other side, the regulatory capacity of Hypericum in T lymphocytes could be different in pediatrics because their innate and adaptive immune systems
mature gradually during infancy, furthermore, their T lymphocytes present distinct functionality. Pilot studies are still needed to test Hypericum specifically in the pediatric population with psoriasis to confirm this. Therefore, an age range of 18 to 65 years old could lead to more reliable results, since the response to Hypericum could be biased if the pediatric and elderly populations are included in the study.

Regarding the point of postmenopausal women, we have decided to exclude postmenopausal women without systemic hormone therapy on account of the decline of their immune system, and higher levels of pro-inflammatory cytokines such as TNFα. Postmenopausal women using systemic hormone therapy will be included in the study.
According to our search, gender and ethnicity do not seem to show significant differences that could affect the results of the study. Regarding comorbidities, we have mentioned some of the most common immunosuppressive diseases. However, we decided to include the next phrase at the end of the list in point 2.3 “...other immunosuppressive or autoimmune diseases”. Apart from the treatments addressed in our exclusion criteria, we have not found others that could affect our results.

7. In item 12. Data Management: is there a better questionnaire to assess quality of life?

There is a lack of a well-tested and widely accepted health-related quality-of-life instrument specific for psoriasis. Although the Dermatology Life Quality Index (DLQI) has been used in patients with different skin conditions, its strength to assess psycho-social aspects makes it more appropriate for psoriasis than for other diseases. Psoriasis complaints in its mild and moderate forms are mostly psycho-social.

On the other side, there are indeed other instruments available such as the
The Psoriasis Disability Index (PDI) has several similarities with DLQI. We preferred DLQI to PDI because DLQI can be assessed at week 12 of the study, that is when it is planned the end of the intervention and last assessments, using PDI would mean extending the duration of the study, since PDI assesses the quality of life of the last 4 weeks in comparison to DLQI (over the last week), resulting in a higher probability of loss of follow-up. Furthermore, we do not know how long the effect of Hypericum perforatum lasts on the skin, thus using PDI could bias the results. Moreover, there are certified translations of DLQI in several languages which is an advantage taking into account that many people in Canada speak a language other than English.

8. How to deal with different countries/cultures to improve the external validity? Why did you choose a single center?

We chose a single center because Toronto Western Hospital is located in the most populated city of Canada (6,202,225 inhabitants according to the 2021 Census of Population, Canada Statistics) as well as in a country with one of the highest prevalence of psoriasis worldwide, additionally, the fact that it is a referral center facilitates the recruitment of patients from other medical institutions, therefore it is an institution that receives a large population of patients.

Apart from that, Toronto is one of the most ethnically diverse cities in the world with a total visible minority population (Asian, black, arab, Latin American, etc) is about 3,501,275 inhabitants (according to the 2021 Census of Population, Canada Statistics), meaning that about 56% of the population was born outside Canada. It is remarkable to mention that most of these minority groups have similar sizes, making Toronto's population quite heterogeneous.

The high heterogeneity of the population, the privileged location of the hospital, and its functions as a referral center make it possible to perform a phase II single-center study without jeopardizing its external validity. Nevertheless, we are conscious that future phase III studies would benefit from multiple centers.

9. *Please review some grammar errors.*

Thanks for noticing, we reviewed the document to fix grammatical errors.

Reviewer 2

10. *There are some little spelling and grammar mistakes*

Thanks for noticing, we reviewed the document to fix grammatical and spelling errors.

11. *It would be nice, if you explain a little bit more about HT, because for some people like me, it's the first time to hear about this plant and its benefits.*

The next information was added in the third line of the abstract as well as the second line of the third paragraph of point 1.2: "Hypericum perforatum (HP) is a flowering plant that has been used as an herbal medication due to its antimicrobial, wound-healing, and anti-inflammatory properties."

12. *Did you know if HP could interact with some drugs and their metabolism throughout cytochrome P450? Because I found some articles related to this topic when I had to read about HP*

We have already added this in the fifth line of the third paragraph of point 1.2 as follows:

"which also has some interaction with other drugs, as it acts as an inducer on the cytochrome P450"

13. *Flow chart: maybe, the first part of the chart flow could be in one color, and another part of the graphic, after randomization, in a different one. I think it clarifies the stages of the study.*

We made the change in color on the chart flow found in the timeline section, in point 2.9

14. ABSTRACT: I have noticed, that this part is divided into introduction, objectives, methods, discussion, and keywords. I suggest that in some parts of the introduction, maybe, only a sentence, you should explain shortly what is HP and its anti-inflammatory effects, because in my case, I truly did not know the plant. It is also called Saint John wort (for the keywords part).

We have already addressed this as described in comment 2 of reviewer 2.

15. *INTRODUCTION (there is a little error in the sequence of numbers, 2.3 is missing).*

We fixed the number sequence in each of the sections.

16. *CHOICE OF COMPARATORS: the idea is fine, but I have some issues understanding these two paragraphs, so I recommend you re-write them more simply.*

We have already addressed this, by summarizing and better explaining the information in the two paragraphs of point 1.4

17. *INCLUSION/EXCLUSION CRITERIA: INCLUSION: is there another way to establish the severity of Psoriasis besides PASI? I mean, clinical criteria.*

PASI uses clinical criteria (area, redness, and thickness). On the other hand, there are indeed other tools to evaluate the severity of psoriasis, however, we considered PASI as the best option due to

being already pretty established when trying to assess the improvement of plaque psoriasis over time as well as overall use among doctors, including non-dermatologist physicians

18. *EXCLUSION: it would be useful to clarify the PASI classification of the severe form of psoriasis.*

We have already addressed this in the fifth line of the first paragraph of point 2.3.

19. *Also, I have read that HP could interfere with some drug's metabolism through p450 cytochrome. I suppose that is if HP is an oral presentation not local or skin, have you read something about that?*

According to Becker et. al. (Becker, 2,004) when applied on the skin of mice, dermal absorption of hypericin (active component) was concentrated in the stratum corneum, and it was undetectable in plasma. Because of this, we consider there would be no interaction with other drugs.

20. *ADHERENCE: the second paragraph is repeated.*

The repetition of the second paragraph of point 2.8 has been removed

21. *TIMELINE: I wrote a comment above in the flow chart section*

The changes on the flowchart were made, such as the change of color of the boxes in point 2.9.

22. *STATISICAL ANALYSIS: I would re-write the first paragraphs for better understanding. I will make it easier with simpler sentences. Now, when I have read it, seems like separate sentences with no connection. The second paragraph is ok, better than the first one. Also, I agree with the statistical test you have chosen.*

We have re-written the first paragraph for a better understanding of point 2.14

23. *Discussion: The limitation paragraph is more useful to put at the end. It's like the end and conclusion of your trial. "Even when proving a significant decrease in the intervention arm, more studies will be needed to assess the clinical significance of the intervention's effect." This phrase is perfect for the final sentence.*

We have already relocated this paragraph at the end of the discussion as suggested.

24. *Discussion: I would add a paragraph comparing existing knowledge, I mean compare with existing literature, and would enhance the strength of your work.*

We appreciate your recommendation. We consider this to be repetitive. In the section "Mechanisms and existing knowledge" the existing knowledge is mentioned. In the discussion, there is a reference to it: "Previous clinical trials showed promising results in small samples.", which is compared to the study results: "Conducting the PSORIATICUM trial will broaden the knowledge and evidence on the safety and efficacy of HP as a topical treatment."

Reviewer 3

25. *Comment about the title: Study Protocol should be added in the title.*

We have already added “Study protocol” in the title.

26. *Comment about the Abstract in the Introduction: (Does it really? If so, what's the purpose of the trial?)*

We have already made some changes in the text to address this in the fifth line of the first paragraph of the abstract as follows:
- Before: It has shown the ability to decrease… It has shown fewer side effects and lower costs compared to standard treatment.
- After: Pilot studies have reported its ability to decrease with fewer side effects and lower costs compared to the standard of treatment. Larger studies are needed to confirm this.

27. *Comment about mechanisms and existing knowledge in the introduction: Excellent paragraph. Maybe consider putting the 1st and 2nd paragraphs in only one.*

Since the first paragraph is about pathophysiology and the 2nd about epidemiology and treatments we decided to keep them separate.

28. *Comment about the need for a trial in the introduction: Suppression of the hypothalamic-pituitary could be added to the list instead of citing it in a whole sentence. That way, the previous 2 paragraphs could be summarized into only one.*

We have already addressed this in the fourth line of the first paragraph in point 1.3

29. *Comment about the choice of comparators in the introduction: This could be explained in the Methods section.*

We have already addressed this by only keeping the first and second paragraph of point 1.4

30. *Comment about the significance/impact of the study in the introduction: This paragraph does not seem necessary. Maybe some ideas could be added while explaining previous HP.*
We have decided to re-write this paragraph in point 1.6 to be more concise.

31. *Comment about the study design in the material and methods section: Any kind of moisturizer? "against a standardized control vehicle"?*
We have already addressed this by being more specific. The term “a control vehicle” was substituted with the term “a control vehicle ointment” in the fourth line of the first paragraph of point 2.1

32. *Comment about the study setting in the material and methods section: This paragraph is not strictly necessary, as it was previously written, the hospital is a referral center and also affiliated with a well-known University.*
We decided to keep the 2nd paragraph in the study setting section. Although the center is affiliated with a prestigious university, we strongly believe that highlighting its experience in the research field is of high importance to support the success when carrying out the study, since other prestigious institutions could have less experience. On the other hand, the location features such as the high incidence of psoriasis and the city's dense population could facilitate the recruitment and the follow-up of the patients by reducing the patients' burden in terms of mobility and travel expenses. Thus, we considered it important to describe them.

33. *Comment about recruitment strategy in the material and methods section: Recruitment strategy could be summarized. The first sentence is the crucial information.*
We have summarized this paragraph in point 2.4.

34. *Comment about the interventions in the material and methods section: This was already said in the article.*
We have summarized this paragraph in point 2.5.

35. *Comment about the interventions in the material and methods section: The double-dummy concept was already explained in the text.*
Thank you for the observation, the study will be a comparison of an active treatment versus placebo (one intervention per group). As far as we understand, a double-dummy model would test 2 interventions per group (active versus placebo).

36. *Comment about Modification/discontinuation in the material and methods section: This can be summarized. Some topics seem obvious.*
We have summarized and eliminated some of the items in point 2.6

37. *Comment about randomization and blinding in the material and methods section: Great paragraph. Randomization sequence, allocation concealment, and implementation could be summarized with a figure to avoid using too many words and also to make it easygoing.*
We thank you for your recommendation. We tried to make a figure for the information, however, we consider that given the amount of detail about the process, using the figure would take away too much information we consider important.

38. *Comment about randomization and blinding in the material and methods section: This can be explained using the term Double-dummy.*
Thank you for the observation, the study will be a comparison of an active treatment versus placebo (one intervention per group). As far as we understand, a double-dummy model would test 2 interventions per group (active versus placebo).

39. *Comment about randomization and blinding in the material and methods section: From "In this scenario..." to the end of the paragraph is not strictly necessary, but it is really good*
We thank you for your recommendation. We have decided to keep this paragraph.

40. *Comment about adherence in the material and methods section: This improves blinding, but it does not improve adherence.*
We have eliminated the first paragraph in point 2.8

41. *Comment about adherence in the material and methods section: This Double*
We have already eliminated the repetition of the last paragraph in point 2.8.

42. *Comment about sample size calculation in the material and methods section: The past two paragraphs are not necessary.*
The paragraph describing the criteria of PASI 50% and PASI 75% (which were not selected as measurements for this study) was eliminated. The other paragraph was not eliminated since we consider the data described in it important to understand the sample calculation.

43. *Comment about Outcomes in the material and methods section: PASI is a well-known measurement. So, this paragraph is not strictly necessary.*
We have summarized this paragraph by eliminating the detailed description of the PASI score since we agree that it is a well-known measurement.

44. *Comment about Outcomes in the material and methods section: Excellent. However, a paragraph explaining the outcomes is more than enough to satisfy the word limit.*
We have tried to summarize this section as much as possible, leaving the information we considered still important.

45. *Comment about data monitoring in the material and methods section: Data Management and Monitoring could be summarized to satisfy the word limit.*
We have re-written some sentences, and removed as much repetitive information as possible to summarize it.

46. *Comment about interim analysis in the material and methods section: Interim analysis could be summarized to satisfy the word limit. Adverse events were already explained previously in the text.*
We removed the description of how AE would be defined and classified since it had already been mentioned in the text.

47. Comment about Statistical Analysis for Primary and Secondary Outcomes in the material and methods section: What is the severity variable?
The severity variable is the baseline PASI score. The sentence has been rewritten to make it more understandable.

48. Comment about Statistical Analysis for Primary and Secondary Outcomes in the material and methods section: (This has already been mentioned in the text)
The phrase “Incidence, type, and severity of adverse events will also be reviewed as exploratory results” was eliminated from the second paragraph of point 2.14

49. Comment about material and methods section: There were 15 topics inside the Methods section. That's a lot. One possible format could be: Study design; Study setting; Eligibility criteria;

Interventions; Randomization and Blinding; Adherence; Participants' timeline; Sample size calculation; Outcome measures; and Statistical Analysis. Again, so many topics make it easy to look for the information, but it makes reading less easy-going.
We tried to remove subsections and managed to remove Trial Design, Randomization Sequence Generation, Allocation Concealment, Randomization/Implementation, and Missing Data. However, we decided to keep the other 14 since without them we considered the content would be more difficult to understand.

50. Comment in the discussion section: (An interim analysis will be conducted at 50% of enrolment, correct?)

Yes, an interim analysis will be conducted at 50% of enrollment.

51. Comment in the discussion section: I recommend carefully going over the article once more to avoid repetitive content to satisfy the word limit.
We have summarized as much as we could trying to remove any repetitive information where possible.

Reviewer D report:

52. The authors considered PASI as the gold standard according to Schmidtt, 2005. There are novel methods to assess lesions in Psoriasis.
Indeed, there are other methods to assess lesions in psoriasis, for example, the investigator global assessment, NAPSI, and PGA. The use of PASI was preferred as it is more established and widely used when measuring the response to treatment, making it easier to extrapolate and compare the results of the study with other trials.

53. The authors did not explain about intention to treat in real-world data.

In comparison to per-protocol analysis, the intention-to-treat principle (ITT) has important advantages for clinical trials such as preserving the benefits of randomization (the cornerstone of clinical trials), likewise, it keeps the sample size and minimizes type I error. It is also noteworthy to highlight that it also reflects the "real world" since it takes into account non-compliance and protocol deviations, situations that occur regularly in clinical practice with our patients, who do not always follow the indications. Therefore, ITT makes it easier to generalize results, i.e. it increases external validity. In our study, multiple imputation will be used to allow ITT analysis.
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54. How to deal with the Hawthorn effect in this study?

We know it is completely impossible to avoid the Hawthorne effect, however, our study has the following characteristics to deal with it:

-Non-invasive assessment of adherence: We decided not to use phone calls or messages to ensure adherence because it can continually trigger and increase the feeling of being observed not only in the physician's office but also in their own homes. In contrast, we chose to assess adherence by instructing the patients properly, the use of a diary, and the container emptying inspection, all of them are less invasive techniques and can be carried out in a low-key way to reduce even more the Hawthorne effect.
-Double-blinding and randomization: the blinding of physicians and patients in our study is of easy implementation, and the placebo is quite difficult to recognize from the active ointment. Therefore, although a certain level of Hawthorne effect is expected (as in all clinical trials), it should occur equally in the intervention and control group, thus avoiding discrepancies that can negatively impact trial results, since both groups will be treated the same by the physicians who will not be available to distinguish the allocation of the patients. Randomization also ensures the Hawthorne effect is equivalent in both groups.

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On the other side, the regulatory capacity of Hypericum in T lymphocytes could be different in pediatrics because their innate and adaptive immune systems mature gradually during infancy, furthermore, their T lymphocytes present distinct functionality. Pilot studies are still needed to test Hypericum specifically in the pediatric population with psoriasis to confirm this. Therefore, an age range of 18 to 65 years old could lead to more reliable results, since the response to Hypericum could be biased if the pediatric and elderly populations are included in the study.

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57. How to deal with different countries/cultures to improve the external validity? Why did you choose a single center?

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