Repeated Insult Patch Study: Comments on Scientific Issues

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Product A - Demographics

- Two sub-studies
- Healthy volunteers aged 18-70
- Study 1 (DS104005): n=116; 77% women; 95% under 65; 19% minority;
- Study 2 (DS104105): n=130; 81% women; 91% under 65; 35% minority (31% Hispanic)

Study Protocol: Change Exposure

- Begin with occlusive patches applied to the same skin area;
- Upon observing “P” or “PV” with no erythema, or “?”, or “+”, switch to semi-occlusive patch and apply patch to the same area;
- Upon observing “D”, “++”, or ”+++”, switch to semi-occlusive patch and apply patch to an unexposed area;
- Upon observing “P” or “PV” with no erythema, or any of the “?”, “+”, “D”, “++”, and ”+++” under semi-occlusive, apply patch to a new area;
- Maximum two changes of the exposure conditions allowed

Results

No positive reactions observed prior to subjects' withdrawals: lack of evidence of non-random attrition

Results Downplayed

Grading of subject #55 of Study 1:

- Response in induction phase: -,+,++,+,+,+,x,+,?,? (switched to semi-occlusive patch after third application)
- Response in challenge phase: ?,?

Additionally, there 8 “?” readings among three subjects in study 1

No positive reaction observed in study 2

Product B

- Positive responses from Subject #55 on 2nd ("+") and 3rd ("++") grading, and switched to new site with semi-occlusive patch
- Readings missing from the redacted report;
- Additionally, there were 9 observations of "?" from three subjects, of whom two also showed "?" to product A;

Limitation

- Data reliability (grading): measurement error due to rater difference not quantified due to the study protocol
- No information available on dose-mixture of all ingredients: cannot evaluate potential synergistic effects on sensitization

Concern on Study Population

- Would “established” subjects develop resistance to the testing compounds especially they are structurally similar?
- How to obtain a representative sample (e.g. not overwhelmingly women)

Concerns on Data Analysis

- One subject showed a persistent pattern of sensitizing symptom (ranging from “?” to “++” under both occlusive and semi-occlusive patch) to BOTH products from 3rd patch onward (need to verify with product B);
- 1 positive case out of 210 cannot be dismissed statistically as no evidence
  - If the same study (n=210) were repeated, 63% of the times we would see at least one subject with the positive reaction;
  - if the study were repeated with n=482, 90% of the times we would see at least one subject with the positive reaction;
- The conclusion of “no evidence of sensitization” without accounting for these observations (i.e. subject #55) is not a concise statement

Recommendation

- To consider multiple raters to independently evaluate each subject
- To statistically quantify the chance of meaningful (timed) patterns of positive reactions of the same subject
- To develop standards for data reporting and analysis in accordance to repeated outcome data

  - not to ignore attrition

  - to consider subject as well as data point as unit of analysis
- To require analysis that differentiates outcome of a susceptible sub-population (incidence of severe reaction) from the average