Treating Acne With Topical Antibiotics

Dear Editor,

I write to you to express concern about the recently published article by Bonati and Dover, *Treating acne with topical antibiotics: current obstacles and the introduction of topical minocycline as a new treatment option.*[1] In articles of this type, it is fully understood that the intent behind presenting comparisons between established and/or emerging products is to further educate the dermatology community on pharmaceutical innovation occurring within the specialty. The article in question seeks to draw comparisons between two emerging topical products each containing minocycline at varying concentrations (BPX-01 and FMX101) and each being evaluated for the treatment of acne vulgaris. My primary concerns are specifically the following:

In Table 2, clinical study data is summarized from one Phase 2b study (N=225) evaluating BPX-01 and three Phase 3 studies (N=2,468) evaluating FMX101.[3,4] What is absent from the article is that the data presented for BPX-01 2% for IGA treatment success was not statistically different from vehicle in this study. Equally, vehicle data from either clinical program has not been presented nor any statistical comparisons made at all. This is a key omission as the impact of a positive (or negative) vehicle effect is a well-established phenomenon in topical therapy irrespective of the disease under study and an important consideration in assessing the overall clinical utility of a product. Vehicle composition is as important at times as the pharmacologically active compound(s) as a recent article published in JDD outlines.[5]

Table 3 and corresponding narrative presents preclinical data evaluating systemic exposure of minocycline ofBPX-01 1 %, MNC-L 4%, and oral minocycline. Only BPX-01 2% clinical efficacy data is discussed in this article and therefore any inference linking low exposure with potential safety is meaningless from a clinical utility context. The use of data from a lipophilic, experimental formulation (MNC-L 4%) to draw inference on applicability to FMX101 4% is misleading, particularly when the composition of this experimental formulation was not disclosed.

Figure 3 provides a selective presentation of percent reduction of inflammatory lesion count reduction in clinical studies, again, excluding vehicle data and comparator statistics. Data from BPX-01 1%, which was also evaluated in this study, is not included and was not statistically significantly different from vehicle at week 12.[2] Specific week 2 data is not overtly presented in the plot and, again, was not statistically different from vehicle yet a statement of ">25% reduction" was included and the article concludes that BPX-01 2% is reported to have ... "a greater and quicker reduction than FMX101". The equivalent evaluation in the FMX101 clinical program was not completed at this timepoint. The authors go on to state for FMX101 that"... lesion counts began to separate after 3 weeks of treatment". This is inaccurate, the first post-baseline timepoint for this assessment was at week 3 and FMX101 was found to be statistically superior to vehicle. Data for BPX-01 at week 2 in the quoted Phase 2b study was not statistically different from vehicle. Data from FMX101 phase 3 program was not presented in equivalent plots in Figure 3 and demonstrates a lack of fair balance.

The statement that minocycline exposure as "undetectable" in 251 subjects from a study evaluating minocycline exposure when dosed as BPX-01 is a misrepresentation of the facts as the term should be "unquantifiable". The assay lower limit of quantification (LLOQ) is presented as 10 ng/ml, which is inappropriately high for dermal applications 5 and approximately 40-fold higher than the equivalent used to assess minocycline exposure when dosed as FMX101 (0.27 ng/ml).[7] An LLOQ of 10 ng/ml is most definitely not a "highly sensitive assay" and has not been for a great many years. Reference 35 is miss-referenced in the article as it relates to oral minocycline product labelling and, as positioned, implies that oral minocycline was assessed in these studies. It was not.

Moreover, minocycline exposure when dosed orally was assessed in the corresponding study with FMX101 in a two-period, crossover study design and therefore a more meaningful comparison.[7] No study information is provided in relation to the actual dose the subjects received, eg, grams per day, in these comparisons.The data presented for FMX101 was based on a maximum use safety study in subjects aged 18 years and older with a diagnosis of moderate-to-severe acne vulgaris using an inextremis dose of 4 grams per day for 21 days. The equivalent dosing used in the BPX-01 Phase 2b study is assumed to be 1 gram per day although not clear from the corresponding reference.

As it relates to the effect of ethanol on the disease state under study, ... the sequence of "ethanol...rapidly evaporates from the skin" "Ethanol also acts as an antimicrobial, exceeding the MIC and MBC for P acnes", " ... enter the pilosebaceous unit, where inflammatory and acne begin" is contradictory. If ethanol rapidly evaporates, one assumes that very little if any will enter the pilosebaceous unit to affect a meaningful antimicrobial action against C. acnes where, as the authors state, "inflammation and acne begin". The lack of vehicle clinical efficacy or safety information further clouds these statements. Although ethanol is referred to frequently within the article on its putative impact on acne vulgaris and beneficial effect on product formulation, at no point is there any discussion on the potential impact of the long-term use of primary alcohols on dermal integrity, eg, the potential for a deleterious effect on the stratum corneum and cutaneous adverse events.

Finally, like it's pathogenesis, the clinical presentation of acne vulgaris is multi-factorial although there is no discussion of either treatments respective impact on comedonal acne. Again, this speaks to a degree of selectivity in clinical data presentation as the effect on non-inflammatory lesion reduction in the

phase 2b study for BPX-01 2% was not statistically different from vehicle at week 12. On the contrary, there were statistically significant reductions in non-inflammatory lesion counts at the same timepoint in all phase 3 studies evaluating FMX101.

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References:

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Response

Dear Editor,

Our primary goal was to submit a non-biased article reviewing two topical minocycline formulations that purport to treat acne while reducing antibiotic resistance. Statements made regarding each formulation were based on the most current available data at the time of submission. The article describes data from pre-clinical and clinical trials of each formulation, respectively, but no head-to-head studies have been performed. Comparisons between the two products should be done with caution due to varying stages of research and preliminary formulations that may not represent finalized products. We would like to re-emphasize that both investigational drugs hold promise for effectively treating acne, reducing systemic antibiotic exposure, and ideally lowering rates of antibiotic resistance.

In response to queries about Table 2, we would like to clarify that IGA results in neither the BPX-01 phase 2 study or the FMX101 study 04 showed statistical significance. This is not unexpected, as the studies were likely powered for a different primary endpoint, the change in inflammatory lesions from baseline at week 12. Vehicle composition was presented in this table to clarify which formulations were tested during clinical trials. Final formulations and vehicles may differ.

In response to queries about Table 3, readers should be reminded that MNC-L 4% was a non-foam, lipophilic formulation of topical minocycline that should not be considered an early version of FMX101. As described in the text and table footnotes, MNC-L 4% was designed solely for the purposes of testing lipophilic versus hydrophilic penetrance.

Figure 3 is a presentation of inflammatory lesion counts from the most recent phase II BPX-01 clinical trial and from an oral minocycline phase III trial. Unfortunately, the FMX101 trial data was not included due to a different visit and assessment schedule (3, 6, 9, and 12-weeks) than that of BPX-01 and the oral minocycline trial, which had the same visit and assessment schedule (2, 4, 6, 8, and 12-weeks). As a result, conclusions cannot be made about time to improvement between BPX-01 and FMX101 from this data set. The statement, "BPX-01 trials reported a quicker reduction than FMX101 in its respective trial" was unintentionally misleading given the differing 2-week versus 3-week timepoints.

In response to the concern of our use of the term "undetectable" rather than "unquantifiable" minocycline levels, we would like to clarify that "undetectable" does not imply a zero-level of minocycline in the plasma, but rather, a level so low it cannot be detected by the assay. A more appropriate term may have been "unquantifiable." It should also be mentioned that the 10ng/ml LLOQ mentioned in the letter to the editor was taken from the FDA draft guidelines on maximal use study parameters for OTC products. This LLOQ may

not be applicable to prescription medications such as FMX101 and BPX-01. However, both products were found to have approximately 800-times less systemic absorption than oral minocycline.

In regards to reference number 35, this citation refers to the average plasma concentration produced with a single dose of oral minocycline (758 ng/ml). Placing the citation lower down in the paragraph may have provided more specificity regarding the reference.

In response to the mention of a two-period, crossover study of FMX101 and oral minocycline, we chose to discuss the phase II trial of BPX-01 because it tested a single-use 1g application of the topical drug for the purpose of comparing a single 100mg dose of oral minocycline. The FMX101 study referenced by the letter's author was a maximal use trial (MUSE) for safety, which was deemed less relevant for comparing systemic exposure with a single dose application. BPX-01 has not yet conducted a MUSE trial for head-to-head comparison with FMX101.

In response to queries about the action of ethanol in BPX-01, ethanol is a well-known solvent that is miscible with lipids and possesses a rapid evaporative quality. We acknowledge this paradox might raise questions about its usefulness in acne treatment. The statements regarding ethanol's ability to penetrate the pilosebaceous unit and exert antimicrobial action against P. acnes was taken from the 2018 research presentation of Del Rosso JQ et al, entitled, *"The benefits of ethanol in a drug delivery vehicle for topical acne treatment."* This is cited in our reference section. Del Rosso's work made reference to "the solvent distribution coefficient properties of ethanol that enable it to penetrate and enhance the penetration of other dissolved molecules into the skin."[1,2] Further evidence regarding the use of ethanol in BPX-01 as the major excipient was seen in their phase IIa and IIb trials, where the vehicle arm showed a 65.3% reduction in P. acnes and a 43.8% reduction of inflammatory lesions at week 12, respectively.[3] These benefits cannot be linked directly to ethanol however, as the vehicle contained other excipients or components.

To our knowledge no studies have been published evaluating the long-term impact of ethanol on the skin, although many prescription and over-the-counter products utilize ethanol without worrisome long-term sequelae, including hand sanitizers and facial toners.

In regards to non-inflammatory acne, we chose not to discuss the effects of either formulation on comedonal acne. This is because FMX101 and BPX-01 trials have been focused on moderate to severe inflammatory acne as a primary endpoint. Of note, absolute change in non-inflammatory lesion count at week-12 was a secondary endpoint in the FMX101 phase III numbers 22, 04, and 05 trials and showed statistically significant reductions. Change in non-inflammatory lesion count was an exploratory endpoint in the BPX-01 phase IIb trial. We would welcome any additional information regarding either product's intention of studying comedonal acne as a primary endpoint.

We sincerely hope this response addresses the questions and concerns of the response letter author. We are encouraged by the progress made in both formulations of topical minocycline and applaud both company's efforts to reduce antibiotic resistance while effectively treating such a ubiquitous condition.

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