[redacted]

From: [redacted]
Sent: 31 January 2019 17:22
To: EO-PresubmissionConsultation
Subject: Re: Comments Ombudsman Inquiry on EMA pre-submission activities
Attachments: comment enquiry SA_final_3.pdf

Follow Up Flag: ema14
Flag Status: Flagged

Dear Sir, Madam,

There was an error on page 3 of our response. The text should read:

In the USA, developers initiate their contacts with the FDA by submitting an Investigational New Drug (IND) Application before they start the first clinical studies in human.

Please replace our response with this one. Sorry for the inconvenience.

Best regards,

François Houÿez

On 31/01/2019 14:58, François Houÿez wrote:

> Dear Sir, Madam,
>
> Please find a response from Eurordis, the European Organisation for Rare Diseases, to your above-mentioned consultation.
>
> Best regards,
>
> --
>
> François Houÿez
> Treatment Information and Access Director, Health Policy Advisor
>
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>
> 
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>
> Purchase your ticket to attend!
> 12 February, Brussels

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François Houÿez
Treatment Information and Access Director, Health Policy Advisor

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31 January 2019

Comments Ombudsman Inquiry on EMA pre-submission activities

Madam,

In response to your enquiry on the above-mentioned topic, please find the opinion of EURORDIS, the European Organisation for Rare Diseases.

Firstly and foremost, even if the content of pre-submission activities at the European Medicines Agency is not always made public, the debates almost always involve members of the public, i.e. all interested parties: regulators, clinicians, scientists (statisticians, pharmacologists…) and the patients. The developer is sometimes but not always present. More recently, the EMA has started to invite representatives of Health Technology Assessment agencies (HTA) and of payers in some of its discussions, in particular in parallel scientific advice between regulators and HTA.

In 2017, 131 patients participated in Scientific Advice, 46 in Scientific Advisory Group meetings, and 104 participated in scientific committee consultations. For healthcare professionals, 40 participated in Scientific Advisory Group meetings, and 48 in scientific committee consultations. The figures are increasing every year since 2007 when the EMA adopted the Framework of Interactions with Patients and Consumers.

Some organisations criticise the way pre-submission activities are conducted, however they have little experience in these procedures, if any, as they do not act as a network of patients and consumers who take part in these activities. The relative lack of transparency they report largely originates from this ignorance. On the contrary, EURORDIS is organised in such a manner that its members participate in most activities and since the adoption of the Orphan Medicinal Products Regulation back in 1999.

Scientific advice is not mandatory, but EURORDIS considers it corresponds to an ethical requirement, as per principle 21 of the Helsinki Declaration[1]:
21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation.

[1] World Medical Association Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects 64th WMA General Assembly, Fortaleza, Brazil, October 2013

Seeking scientific advice with the objective of submitting adequate data for the marketing authorisation evaluation is one way to respect principle 21 above: EMA experts are an extremely relevant source of information. By obtaining scientific advice, the sponsor reduces the risks that the clinical trials become futile (unable to conclude). Failing to make all efforts to ensure the research has highest chances to conclude whether or not the product is effective and safe is not ethical, as this would result in the recruitment of patients in sub-optimum trials.

1. **Your question: It may happen that EMA staff members and experts who participate in pre-submission activities will be involved in the subsequent scientific evaluation and/or marketing authorisation procedure for the same medicine. To what extent is this a matter of concern, if at all? Are there specific pre-submission activities of particular concern in this regard? How should EMA manage such situations?**

Main points
1. The participation of EMA staff members and experts both in pre-submission activities and in subsequent scientific evaluation is key to ensure consistency in the regulation of pharmaceuticals prior to their authorisation. This intellectual continuity in the regulatory process, from early steps to the surveillance of the marketing authorisation is a benefit to public health: the lifecycle of a medicine is a continuum. In addition to written information, some individuals need to be involved all along this lifecycle.
2. Scientific advice helps minimising the risk that inadequate data are submitted to regulatory authorities when evaluating the benefit/risks ratio.
3. The time gap between the advice given and the benefit/risks evaluation is a long one: experts of EMA staff that participate to both procedures ensure scientific consistency between the moment the advice is given and when assessors evaluate the marketing authorisation: they can explain the context in which the advice was given.

Pre-submission activities of interest to EURORDIS are:

a. Designation of orphan medicinal products by the Committee for orphan medicinal Products (COMP) with an opinion on the significant benefit, and subsequent maintenance of the OMP designation at the time of marketing authorisation. The same COMP member can be the rapporteur for the initial designation and for the opinion on the maintenance of the designation at the time of the marketing authorisation. The rapporteur for the opinion on the designation is the one who knows the dossier the best at the time the COMP needs to confirm the significant benefit for the marketing authorisation and there is a logic to have the same person taking the lead in pre-submission activities and in the marketing authorisation procedure.

b. Opinion on a Compassionate use programme (Article 83 Reg. 726/2004) and subsequent opinion on the benefit/risks ratio. The same member of the Committee for Human Medicinal Products (CHMP) can be the rapporteur for the opinion on the compassionate

use and the rapporteur for the benefit/risks evaluation at the time of marketing authorisation. The rapporteur for the opinion on the compassionate use is the one who knows the dossier the best at the time the CHMP is evaluating the marketing authorisation application.

c. Scientific advice: members of the CHMP, EMA staff and/or patients consulted in scientific advice can participate both in scientific advice and then in the benefit/risks evaluation
d. Protocol assistance (specific to orphan medicinal products): members of the CHMP, EMA staff and/or patients consulted in scientific advice can participate both in scientific advice and then in the benefit/risks evaluation
e. Another situation is for scientific committees (Paediatric Committee PDCO and Committee for Advanced Therapies CAT) with some members who are also members of the CHMP: as provided for in the legislation, this is precisely to ensure scientific communication and consistency between the work of various committees

Firstly, the participation of EMA staff members and experts both in pre-submission activities and in subsequent scientific evaluation is key to ensure consistency in the regulation of pharmaceuticals prior to their authorisation. This intellectual continuity in the regulatory process, from early steps to the surveillance of the marketing authorisation is a benefit to public health: the lifecycle of a medicine is a continuum. In addition to written information, some individuals need to be involved all along this cycle.

Regulatory authorities are not policing the developers of such products, they are regulating their development, decide if they can be used in human, and monitor their use on the market (pharmacovigilance). Regulators are guiding the developers of products on how to best develop and monitor these products. A constant dialogue is necessary; the lifecycle of a product from early phase development to removal from the market can last over decades.

In the USA, developers initiate their contacts with the FDA by submitting an Investigational New Drug (IND) Application before they start the first clinical studies in human. This can precede the evaluation for marketing authorisation by six or eight years, or more. With this, US regulators can interact with the developer as often as needed, mandate changes in clinical trials when regulatory science evolves (over periods of six, eight years or more, methodologies and regulatory guidelines always evolve). Without continuity or when staff/experts change completely, then the FDA would lose track of all changes made to the programme and the reasons why.

Secondly, there are two risks concerning the authorisation of pharmaceuticals:

f. To authorise a product which exposes patients to more risks than initially thought at the time of authorisation (initial positive benefit/risk ratio becomes negative as risks increase)
g. To reject a yet effective product (initial benefit/risk ratio evaluated as negative, hence product not placed on the market)

The latter can happen for example when the developer fails to show a benefit: due to methodological choices, it failed to conduct the clinical trials that could have shown in which patients the product is effective. Rejecting a yet effective product is detrimental to public health.

Scientific advice helps minimising this risk: it increases chances that adequate data are submitted to regulatory authorities when evaluating the benefit/risks ratio.

Thirdly, the time gap between the advice given and the benefit/risks evaluation is a long one: experts of EMA staff that participate to both procedures ensure scientific consistency between the moment the advice is given and when assessors evaluate the marketing authorisation: they can explain the context in which the advice was given. They can also explain the reasoning behind the response given to the developer. Even when written information is available, it does not always capture the intellectual process, the reasoning, the context. Any expert who can explain years later why an advice was given and why it was relevant when it was given if it is not anymore at the time of evaluation (context may have changed in between).

2. Should EMA allow experts from national authorities, who have previously provided scientific advice at national level on a particular medicine, to be involved in EMA's scientific evaluation of the same medicine?

Main points

1. The European regulatory system is a network: a network of national bodies whose work is coordinated by a European agency. Experts from national authorities, including patients, who have provided scientific advice at national level are the ones who know the medicine and the clinical trials in which the medicine was tested the best.
2. Not involving these experts in the benefit/risks evaluation for the marketing authorisation would lower the quality of the evaluation by excluding experts who are the most familiar with the products and the methods chosen for their development.

The European regulatory system is a network: a network of national bodies whose work is coordinated by a European agency. Experts from national authorities, including patients, who have provided scientific advice at national level are the ones who know the medicine and the clinical trials in which the medicine was tested the best:

- They already researched scientific literature and trial registries for other studies in the field, possibly conducted by independent clinical investigators who helped them to generate the advice they gave
- They know better than others what are the weaknesses of the development programmes and the key data on which to focus the evaluation: they are already familiar with the toxicity profile, at the time of evaluation they can further investigate a potential signal they detected in animal studies and that was discussed years before at the scientific advice meeting. In other words, participating to scientific advice helped them do their homework and best prepare for the benefit/risks evaluation at the time of marketing authorisation application.
- Often national experts are from Member States where the clinical trials are conducted. These experts are in the best situation to discuss with clinical investigators and patient

representatives involved in these trials. This can be key for their interpretation of the clinical trials results at the marketing authorisation stage (see example in annexe 1)
Not involving these experts in the benefit/risks evaluation for the marketing authorisation would lower the quality of the evaluation by excluding experts who are the most familiar with the products and the methods chosen for their development.

3. **What precautionary measures should EMA take to ensure that information and views provided by its staff members and experts in the context of pre-submission activities are not, in practice, considered as a "binding" pre-evaluation of data used to support a subsequent application for authorisation?**

Main points

1. The question could be the opposite: are there cases where the CHMP was tied up by a previous scientific advice given? If this would be the case, then there would be reports (EPARs) where the CHMP would have concluded they had an obligation to provide an opinion based on the advice given against their own will.
2. Out of 118 scientific advice requests analysed by EMA[2], the marketing authorisation applicant complied with the advice given in 88 cases, of which the CHMP finally objected to the marketing authorisation in 13 cases (in 15% of cases, the CHMP decided on a negative opinion even if the company adhered to the advice given). This demonstrates CHMP is not dependent on the advice given, even when its members were part of the scientific advice discussions.
3. There are numerous examples where the CHMP based its opinion on the benefit/risks independently of the advice given years before. The advice given is not scientifically binding.
4. Restricting scientific advice to a written procedure would be counter-productive. The more complex the question, the more a direct face-to-face discussion is needed.

The question could be the opposite: are there cases where the CHMP was tied up by a previous scientific advice given? If this would be the case, then there would be reports (EPARs) where the CHMP would have concluded they had an obligation to provide an opinion based on the advice given against their own will.

EURORDIS is not aware of any single case where the CHMP could not object to an advice given and could not make an independent decision. On the contrary, there are evidence that the CHMP is not tied up to any advice given:

Out of 118 scientific advice requests analysed by EMA[3], the marketing authorisation applicant complied with the advice given in 88 cases, of which the CHMP finally objected to the marketing authorisation in 13 cases (in 15% of cases, the CHMP decided on a negative opinion even if the company adhered to the advice given). When the

[2] Hofer M.P., Jakobsson C., Zafiropoulos N., Vamvakas S., Vetter T., Regnstrom J., Hemmings R.J., Regulatory watch: Impact of scientific advice from the European Medicines Agency, Nature Reviews Drug Discovery, Vol 14(5), pp. 302-303.

[3] Hofer M.P., Jakobsson C., Zafiropoulos N., Vamvakas S., Vetter T., Regnstrom J., Hemmings R.J., Regulatory watch: Impact of scientific advice from the European Medicines Agency, Nature Reviews Drug Discovery, Vol 14(5), pp. 302-303.

applicant did not comply with the advice, the rejection rate was logically higher (59%). This demonstrates CHMP is not dependent on the advice given, even when its members were part of the scientific advice discussions.

On the contrary, EURORDIS witnessed CHMP discussions where someone reminded the reason why the advice was given and explained it was not fair vis-à-vis the developer not to follow the advice. This did not at all prevent the CHMP to ignore the advice given.

The evaluation of the benefit/risks is a collective and deliberative discussion. The process corresponds to "deliberative democracy", where deliberation is central to decision-making. It adopts elements of both consensus decision-making and majority rule. Deliberative democracy differs from traditional democratic theory in that authentic deliberation, not mere voting, is the primary source of legitimacy for the decision. In domains of high uncertainty such as the evaluation of medicines, a key condition for success is the consultation with all actors / interested parties.

All participants in scientific advice have an interest: financial interests (the developer), intellectual interests (career development for clinical investigators and other academics or EMA staff), participatory interests (participating in a clinical trial for patients' representatives, or benefiting from the medicine when authorised).

In any case, given the turn-over of EMA staff and scientific committee experts, the reality is that staff or experts involved in pre-submission activities and also involved in the evaluation of benefit/risks are minority. In this deliberative process, in a CHMP committee composed of thirty four members, even if one or two of them were involved in a scientific advice procedure years before, can this really influence the outcome of CHMP discussions? In a deliberative process, a final opinion can hardly be overcome by an individual.

There are numerous examples where the CHMP based its opinion on the benefit/risks independently of the advice given years before. The advice given is not scientifically binding. For example, an advice was given to the developer of a product to treat Spinal Muscular Dystrophy, for the use of an efficacy measurement scale: the experts agreed the developer could use the scale they proposed. At the time of the benefit/risks evaluation, the CHMP rejected the efficacy measurement scientific advice experts had agreed with, as in the meantime the scale had evolved and the one used by the developer was finally outdated.

Restricting scientific advice to a written procedure would be counter-productive. Direct discussions with experts of different horizons and specialties around the table, considering the questions raised and confronting their views with each other, listening to the developer's approach and constraints, is the only method to ensure the responses given are accurate and useful. The more complex the question, the more a direct face-to-face discussion is needed.

4. Is the way in which EMA engages with medicine developers in pre-submission activities sufficiently transparent?

If you believe that greater transparency in pre-submission activities is necessary, how might greater transparency affect: EMA's operations (for example the efficiency of its procedures, or its ability to engage with medicine developers) and medicine developers?

Main points

1. When several competitors seek advice on evaluation guidelines for products targeting patients with a given disease, patients, health care professionals, and learned societies are invited to the workshops. In many cases, they contribute to the preparation of the scientific workshop.
2. Both for scientific advice (SA) and/or for protocol assistance (PA), specific to orphan medicinal products, EURORDIS is satisfied with the transparency of the process as the EMA systematically shares the letters from developers requesting SA or PA with EURORDIS, to help identifying questions and issues where patients should be involved.
3. For example, in 2018, EURORDIS reviewed 168 SA or PA requests for orphan products, and 41 of its members were invited to scientific advice and/or protocol assistance.
4. As scientific advice discussions contain confidential information, the CHMP claims scientific advice letters cannot be released, otherwise industry may stop requesting scientific advice. A developer may propose an innovative method developed in-house or via a partnership with academics at their own expenses, for the qualification of a novel methodology for a medicine development. If this information becomes public, then the EMA will need to compensate the developer who invested in this method to gain an advantage over competitors.

Advice to several companies/developers

When several competitors seek advice on evaluation guidelines for products targeting patients with a given disease, patients, health care professionals, and learned societies are invited to the workshops. In many cases, they contribute to the preparation of the scientific workshop.

Some patients expressed the desire to be better informed on when these workshops are taking place, and more information could inform a larger public who could contribute in writing or by attending the workshops.

This responds to criticism against individual SA that misses the opportunity to set transparent, uniform standards for therapeutic areas which could be applied to all companies and publicly scrutinised. These opportunities exist, uniform standards are discussed for therapeutic areas involving all potential contributors (written consultations on guidelines, scientific workshops e.g.

- Workshop on Haemophilia Registries 08/06/2018[4] and the revision of guidelines on the clinical investigation of recombinant and human plasma-derived factor VIII products
- Workshop on Spinal muscular Atrophy 11/11/2016[5]
- Workshop on ophthalmology in 2012[6]
- Workshop on the development of antisense oligonucleotide therapies for Duchenne muscular dystrophy 25/09/2009[7]…)

Advice to one developer for a given product

Both for scientific advice (SA) and/or for protocol assistance (PA), specific to orphan medicinal products, EURORDIS is satisfied with the transparency of the process as the EMA systematically shares the letters from developers requesting SA or PA with EURORDIS, to help identifying questions and issues where patients should be involved. When the case, EURORDIS informs the EMA on which points patients could be asked questions, identifies patients who could contribute, and organises their participation together with EMA staff. The patients always receive all the information and questions from EMA experts, they can provide comments before each meeting, at the meeting, or after the meeting if necessary. This concertation is in place since 2000.

The same is true for medical experts when the EMA has difficulties identifying them, and EURORDIS can propose experts amongst its contacts.

For example, in 2018, EURORDIS reviewed 168 SA/PA requests for orphan products, and 41 of its members were invited to scientific advice and/or protocol assistance. The same arrangements can be made with all patients and consumers organisations eligible to work with the EMA and who are interested to be involved in scientific advice or protocol assistance.

	Number of finalised SA/PA	Of which orphan products	Number of patients in SA/PA	EURORDIS experts in SA/PA
2017	471	155	131	47
2018	614	168	107	41

As scientific advice discussions contain confidential information, the CHMP claims scientific advice letters cannot be released, otherwise industry may stop requesting scientific advice. The nature of the questions discussed in scientific advice explain this confidentiality requirement; a developer may propose an innovative method developed in-house or via a partnership with academics at their own expenses, for the qualification of a novel methodology for a medicine development. If this information

[4] https://www.ema.europa.eu/en/events/haemophilia-registries-workshop
[5] https://www.ema.europa.eu/en/events/spinal-muscular-atrophy-workshop
[6] See report https://www.ema.europa.eu/documents/report/european-union-regulatory-workshop-ophthalmology-summary-report_en.pdf
[7] https://www.ema.europa.eu/en/events/treat-nmd-workshop-development-antisense-oligonucleotide-therapies-duchenne-muscular-dystrophy

becomes public, then European institutions will have to compensate the developer who invested in this method.

5. Is there a need, in particular, to enhance the transparency of scientific advice EMA provides to medicine developers? Would it, in your opinion, be useful or harmful, for example, if EMA:

- **disclosed the names of the officials and experts involved in the procedures;**
- **disclosed the questions posed in scientific advice procedures;**
- **and/or made public comprehensive information on the advice given.**

If you have other suggestions, for example regarding the timing of the publishing of information on scientific advice, please give details and the reasons for your suggestions.

Main points

1. If the scientific advice letters are published, there is a risk to harm the attractiveness of scientific advice, and developers might decide not to seek advice. The quality of the dossier might decrease, hence more inadequate data could be submitted for the marketing authorisation.
2. On the other hand, developers would continue to seek advice at the FDA, FDA would receive the information they need to evaluate the products, but the EMA would not always get the adequate information needed in Europe. Europe would rely only on results emerging from scientific advice provided by the FDA, with no possibility to orientate the development in line with what European regulators would need.
3. In general, EURORDIS would welcome efforts to inform the public on when a company requests scientific advice or protocol assistance for a given disease. The following information could be made public on the EMA web page: date of letter of request, applicant's name, targeted indication, nature of advice given (in writing or face-to-face meeting).

Disclosing the names of experts and officials involved in the procedures would inevitably expose them to pressure from the pharmaceutical industry, not only the developer in question, but also competitors who could be tempted to learn more.

Disclosing the questions would only be useful if all background information would be made public, otherwise the disclosure would be limited to vague aspects such as "a new evaluation endpoint is proposed" without explaining which one. However, the developer may consider this information as commercially confidential and would ask to be compensated if made public.

Requesting scientific advice is optional and at the cost of the developer (with fee exemptions for orphan medicinal products). The proportion of applications for marketing authorisation that benefited from scientific advice has considerable increased over the years, in the benefit of public health (products benefiting from SA are more likely to receive a positive opinion). This is because of the attractiveness of the procedure, which again is optional, at the discretion of developers.

If the scientific advice letters are published, there is a risk to harm this attractiveness and developers might prefer to renounce to scientific advice. The quality of the dossier might decrease, hence more inadequate data could be submitted for the marketing authorisation.

As a possible consequence, developers would continue to seek advice at the FDA, FDA would receive the information they need to evaluate the products, but the EMA would not always get the adequate information needed in Europe. Europe would rely only on results emerging from scientific advice provided by the FDA, with no possibility to orientate the development in line with what European regulators would need.

In general, EURORDIS would welcome efforts to inform the public on when a company requests scientific advice or protocol assistance for a given disease. The following information could be made public on the EMA web page:

- Date of letter of request
- Developer's name
- Targeted indication
- Nature of advice given (in writing or face-to-face meeting)

If the developer prefers its name to be kept confidential (if they consider the information to be commercially sensitive), it should be justified.

6. What would the advantages and disadvantages be of making scientific advice, given to one medicine developer, available to all medicine developers?

Some consider that individual confidential SA could be used to lower the regulatory bar: this is purely theoretical, not evidence based.

The same argue that confidential SA does not allow a public debate on the scientific requirements of drug development and approval: in fact there is a public debate on scientific requirements (scientific guidelines and methods are open to public consultations). Confidential scientific advice apply when a developer has specific questions on its product and different options for its development. Here the debate is not public; however, regulators, clinicians, scientists, patients' representatives and representatives of the developer debate together. Questions are debated with a public. These are the informed parties which ensure the deliberative democracy aspect of the scientific advice and regulatory process in general.

What would be the added value to enlarge the debate to a larger public?

Another criticism states that confidential SA to individual companies represents an inappropriate use of the sparse resources of regulatory agencies: the EMA collects fees for the scientific advice they provide, from €43,000 to €86,100 (except for orphan medicinal product, where fee exemption is one of the regulatory incentives).

7. **Should EMA be limited to providing scientific advice only on questions not already addressed in its clinical efficacy and safety guidelines?**

The clinical efficacy and safety guidelines are often obsolete the day they are published. Medical progress oblige researchers to constantly revisit the guidelines' recommendations, all methods constantly evolve or new methods are proposed that have never been used in regulatory trials before.

In addition, these guidelines only exist for a minority of diseases, and in the vast majority of cases they are not available.

For example, no guidelines existed on how to use Bayesian methods when they were first proposed for trials in small populations. Without a scientific advice on that method, no developer would have taken the risk to design a Bayesian based statistical analysis plan.

Sincerely,

[redacted]

François Houÿez
Director of Treatment Information and Access
EURORDIS
31 January 2019

Annexe 1

Scientific advice discussed the opportunity to use a placebo in a randomised controlled clinical trial. Due to the high number of pills to be taken daily, the advice was given not to use a placebo:

(1) With no placebo	Experimental product A	Comparator B
Morning		6 pills
Lunch time		6 pills
Evening	1 pill	6 pills
Total	1	18

(2) With a placebo	Experimental product A	Comparator B
Morning	6 pills (placebo of B)	6 pills
Lunch time	6 pills (placebo of B)	6 pills
Evening	1 pill + 6 pills (placebo of B)	6 pills + 1 pill (placebo of A)
Total	19	19

(1) Would inform on the actual efficacy in real life (capturing treatment adherence, higher for A)

(2) Would be more rigorous scientifically speaking, but would fail to compare the actual relative efficacy of A versus B in real life when no placebo is used

Experts present at scientific advice knew the reasoning behind the advice given, and knew they could be difficulties in interpreting the results, as not the most rigorous method was advised.

Marketing authorisation application

A was 50% more effective than B. But in this trial, efficacy of B was much lower than usual. This was due to the Intent to Treat Statistical Analysis, and a higher number of discontinuation in the comparator arm: patients had to take 18 pills a day, and during the trial a new pill for B became available at a higher strength. Trial participants in the comparator arm B left the trial in high numbers to benefit from the new form where they could take only 9 pills and not 18 anymore.

Because experts in scientific advice were aware of potential difficulties with the results interpretation, they were in a better position to investigate and understand the explanation why B was less effective than usual. Indeed patients withdrew consent to leave the trial, and clinical investigators reported thy had left due to an adverse event (reporting a consent withdrawal or a loss-to-follow up is not popular, it

could affect the invitation to participate in future trials, therefore investigators prefer to report an adverse event even if there wasn't any).

Premature discontinuations	Experimental product A (n=422)	Comparator B (n=415)
Adverse event	27*	68
Total discontinuations	90 (21%)*	147 (35%)

* Statistically significant difference from control group, $p<0.05$

Conclusion: the trial methodology explained the difference, and not an intrinsic efficacy difference between products. This could only be explained because same experts who advised on the methodology looked at the results with high caution, as they were aware of potential weaknesses.