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31 August 2016

European Commission
SANTE-B4-GL-results-laypersons@ec.europa.eu

Re : Public consultation on "Summary of Clinical Trial Results for Laypersons"

Dear Madam, Sir,

MSD is a subsidiary of Merck & Co. Inc., Kenilworth, NJ, U.S.A. (the "Company"), a global research-based pharmaceutical and healthcare company. The Company is known as MSD outside the United States and Canada. Through a combination of the best science and state-of-the-art clinical development, Merck has produced many important medicines and vaccines. Today the company is actively developing a broad portfolio of small molecules, vaccines and biologic products, including biosimilars, with the goal of improving worldwide patient access to important/life-saving therapies.

As a globally operating company we are conducting clinical trials in multiple regions of the world and internet access will make published information accessible globally. Hence we encourage the EU to collaborate with multiple regulators around the globe to create a lay summary document that is readily understandable for audiences in all countries in which a trial was performed. The value of this new document will be jeopardized if it is written with a specific EU focus and it is not a good use of resources for clinical trial sponsors to write multiple versions of the lay summary for a global clinical trial. Hence, we strongly recommend this guidance be geographically agnostic to the extent possible and that multiregional alignment of lay summary document templates is actively supported.

Further, we appreciate the opportunity to comment on the above referenced document and respectfully provide the following input based on a user test of a clinical trial lay summary that was conducted between January and August 2016 together with LUTO Research Limited. The purpose of this testing was to specifically inform the Public Consultation on "Summary of Clinical Trial Results for Laypersons" with some real world experience. The required time and resources to conduct a user test for a Clinical Trial Lay Summary are quite substantial and it is apparent that such tests might initially be very useful to build up capabilities for writing lay friendly documents, but will be prohibitive for routine use in daily clinical trial operations.

The objective of our User Test was to determine the readability and understandability of

a sample Clinical Trial Lay Summary, by:

- reviewing whether members of the public, across a range of educational backgrounds and health literacy levels, could find and understand key information from the Clinical Trial Lay Summary.
- gathering general feedback on the Clinical Trial Lay Summary from lay readers, informed by them having to use the summary in the first part of the process.

User Testing interviews are normally completed in rounds of ten participants. Within a round, a range of participants are recruited across different genders, age groups and educational backgrounds to provide a representative sample of the readers who may use the material in the real world. For this particular User Test, MSD and Luto also wanted to receive feedback from participants who had higher education degrees and post-graduate qualifications to investigate whether the clear and simple language used in the summary is also appropriate and acceptable for well-educated people.

Luto researchers made a quantitative assessment of whether participants could find and understand the key points of information and collected at the same time other qualitative feedback from participants.

For the testing, MSD provided Luto with a sample Clinical Trial Lay Summary that had been drafted according to the recommendations of the draft guideline and based on the results of a previously completed clinical trial that took place in 2001. However, the draft summary replaced the “headings” (or “elements”) included in Annex V of the EU Clinical Trials Regulation, with lay friendly headings in place of the terminology proposed in the Regulation. This was felt necessary to achieve a better outcome of the test.
A revised version of the sample summary that was further amended based on the experience of the user testing is attached in Annex 1 for illustrative purposes.

Below are our conclusions and recommendations for consideration in the draft guidance document based on the testing results:

- All readers, including those with higher education qualifications, appreciated the clear and straight forward language used in the tested summary.
- To ensure the summary is accessible and navigable by readers of all abilities, consideration should be given to the inclusion of numbered sections, possibly with an index at the start of the document (depending on length of information). Note that this would only apply to the main section headings or “first level” headings. Numbering conventions for sub-headings or “second level” headings such as 1.1, 1.2 (as shown in the consultation document), should not be used as these are confusing for less skilled readers.
- Consideration should be given to the use of more lay friendly headings (like those tested). The headings used in the summary that we tested helped readers to navigate

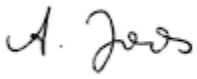
the document and identify the information they needed. It is not clear if the headings suggested in Annex V and the consultation document, for example “Investigational medicinal products used”, would necessarily achieve this goal. Headings and sub-headings should be selected carefully to ensure that they signpost the information beneath appropriately. This testing has shown that even a subtle change in a sub-heading can affect how user’s move around a document.

- Consideration should be given to the amount of detail that is actually necessary for a lay summary of the trial, some examples include:
    - Does the summary need to provide a detailed breakdown of the demographics of the participants in the study?
    - Do readers need to know the official descriptions or titles for outcome measures or can they simply be described in lay language? If both descriptions are required, then the lay description should be included as the priority, with the official name afterwards presented in brackets or quotation marks.
- The summary would benefit from an introductory section that makes it clear to the reader who it has been written for and why it has been written.
- Bullet points are a powerful tool when presenting information in a clear and understandable manner, as they break the text into more manageable chunks for the reader. Care should be taken to ensure that the most important information is presented at the beginning of the bullet point.
- Charts and graphs can be well received by users as they add a visual element to the summary. However, they should only be included if they are simple and clearly demonstrate what they are intending to show. Discussing or testing any chart or graph with lay readers will provide valuable feedback on whether the graph is effective. Numbers or scales should only be included in the chart if they represent a concept that is simple to understand, such as the number of people whose symptoms improved during the study or similar. The graph should also be supported by a simple description of what it is showing.
- It is important that readers of the lay summary understand that it only describes the results of **one study**, and that there may be other studies that have different results. This is noted in the guidance. However, this information may be overlooked if it is included as a single sentence between other paragraphs of text, as per the summary that was tested and the guidance in the consultation. Consideration should be given to whether this information could be presented under a new sub-heading so that it stands out to the reader or if more detail could be added so the reader understands why this is so important.
- Particular care should be taken when designing the layout of a Clinical Trial Lay Summary to ensure that it is effective both on screen and when printed, as members of the public will use the document in different ways. A PDF format is preferred, as users can either download and save this file as needed, or print at their convenience. In both cases the formatting of the document will be preserved.

Our contribution in this letter can be directly published, in whole or in part, with our organisation information. Moreover, nothing within this letter is unlawful or would infringe the rights of any third party in a manner that would prevent its publication.
However, we are currently preparing the publication of the results of our lay summary testing in a scientific journal and hence respectfully request that the attached testing report is not directly published by the Commission.

Should you need additional information or wish to hold further discussions with our company representatives, do not hesitate to contact me.

Yours sincerely,



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Annex 1: MSD sample Clinical Trial Lay Summary
Annex 2: LUTO User Test Report (Annexes available upon request)

Lay Title: How Well Does "Medicine A" Treat Seasonal Allergies?

Official Title: A Multi-Center, Double-blind, Randomized, Parallel-Group Study Investigating the Effect of "Medicine A" in Patients With Seasonal Allergic Rhinitis-Spring 2001 Study

Protocol Number: XX-1234-567 **EudraCT Trial Number:** 2001-123456-01

National Clinical Trial Number: NCT01234567

1. Who did the study and how can I contact them?

The research sponsor was Smith & Jones Company. You can send an email to: ClinicalTrialsDisclosure@SJC.com

2. Where and when did this study take place?

This study took place in the United States and Canada. It started in April 2001 and ended in July 2001.

3. Why was this study done?

This study had 2 purposes:

1. **To look at daytime nose symptoms:** To see how well a drug called "Medicine A" could improve symptoms of seasonal allergies (seasonal allergic rhinitis). This was compared to a "sugar pill" that didn't contain any drug (placebo). The aim was for patients to feel better and have their symptoms improve while taking the drug.
2. **To look at safety:** To look at how safe this drug was when taken for seasonal allergies.

This study was called a Phase 3 study. Phase 3 studies compare new drugs or treatments to the standard treatment or to a placebo.

This summary only shows the results from this one study. Other studies may find different results.

Seasonal allergies

People with seasonal allergies can have symptoms in spring, summer, or early fall. Symptoms are usually caused by sensitivity to pollen in the air. Seasonal allergies affect about 1 out of every 10 people (10%) in the world. Many people who have seasonal allergies also have asthma - a different problem that can make it hard to breathe.

The study looked at the following symptoms of seasonal allergies:

- Daytime nose (nasal) symptoms including stuffy, runny or itchy nose, and sneezing. The study's main goal was to see if "Medicine A" helped improve these nose symptoms.
- Daytime eye symptoms including watery, itchy, red, and puffy eyes.
- Night-time symptoms, such as trouble going to sleep or staying asleep due to a stuffy nose.

4. How was this study done?

Part 1: Patients got a placebo tablet for 3 to 5 days in Part 1 before entering Part 2.

This study compared the new drug to a placebo, also called a "sugar pill." A placebo doesn't contain any drug - but in research, it can make some patients "feel" it's working just because they're taking it. A placebo allows researchers to compare patients who didn't get the drug to patients who did get the drug to see if the patients who got the drug feel differently.

Part 2: Patients were then put in 1 of 3 groups that each received a different tablet. They were put into a group randomly (by chance). This is to make the groups as similar as possible so researchers could compare them.

Each patient had the same chance of being placed in any of these 3 groups:

- **The "Medicine A" Group**
- **The "Medicine B" Group**
- **The Placebo Group**

This study used a "double-blind" method. This means that neither patients nor doctors knew which drug the patients actually got.

How were symptoms measured by researchers?

Diary: During the study, patients used a diary to answer questions about their symptoms every day. They did this when they woke up and in the evening before they took their study drug. These questions asked patients to rate their seasonal allergy symptoms on a scale from better to worse.

Patients' scores: From these ratings, researchers calculated different scores for each patient, and each treatment group.
Researchers then measured how much these scores changed from the start of the study through the end of the study for each treatment group. This allowed them to see how well a drug was working after patients took it for 2 weeks.

5. Who took part in this study?

1,214 men and women with spring seasonal allergies joined this study (764 women and 450 men). 974 patients were white, 95 were black, and 48 were Hispanic. The remaining 97 were African, Asian, European, or Native American. The average age was 36 years.
56 patients left the study before it was finished.

To take part, patients had to:

- Be a male or female between ages 15 and 85
- Have had seasonal allergies for 2 years or more (confirmed by a doctor)
- Show signs or symptoms of seasonal allergies
- Be in good physical and mental health

Patients weren't allowed to take part if:

- They were under age the age of legal consent (18 years old) and consent could not be obtained from their guardian
- They were allergic to "Medicine A", "Medicine B", or any of their components
- They did not have spring seasonal allergies
- They were pregnant or a nursing mother
- They had any major surgery within 4 weeks of the first study visit

6. What treatments did patients receive?

Patients got 1 of these 3 treatments:

- **"Medicine A"** is a prescription drug already approved to treat asthma. This is the drug that researchers were studying to see if it also treated seasonal allergies.
  - Patients took a "Medicine A" 10 mg tablet daily for 2 weeks. (522 patients)
- **"Medicine B"** is a prescription drug approved to treat seasonal allergies. This drug was included in this study as a "positive control", something that's already known to work.
  - Patients took a "Medicine B" 10 mg tablet daily for 2 weeks. (171 patients)
- **Placebo** is a "sugar pill" that doesn't contain any drug.
  - Patients took a placebo tablet daily for 2 weeks. (521 patients)

7. What side effects did patients have?

Serious side effects

No patients in this study had serious side effects. A serious side effect is a medical problem that's life threatening, requires a hospital stay, adds more time to a hospital stay, results in a disability, or results in death.

Other side effects

Some patients in each of the 3 groups had side effects. Side effects are unwanted medical problems that happen during a study. They may or may not be caused by the drug the patient takes for a study. All 3 groups had similar percentages of patients with side effects. They happened in:

- 89 out of 522 patients in the "Medicine A" Group (17%)
- 26 out of 171 patients in the "Medicine B" Group (15%)
- 83 out of 521 patients in the Placebo Group (16%)

Most common side effect

The most common side effect was headache. This table shows how many patients in each group had this side effect:

	Number (%) of patients		
	"Medicine A"	**"Medicine B"**	**Placebo**
Headache	18 out of 522 (3%)	7 out of 171 (4%)	22 out of 521 (4%)

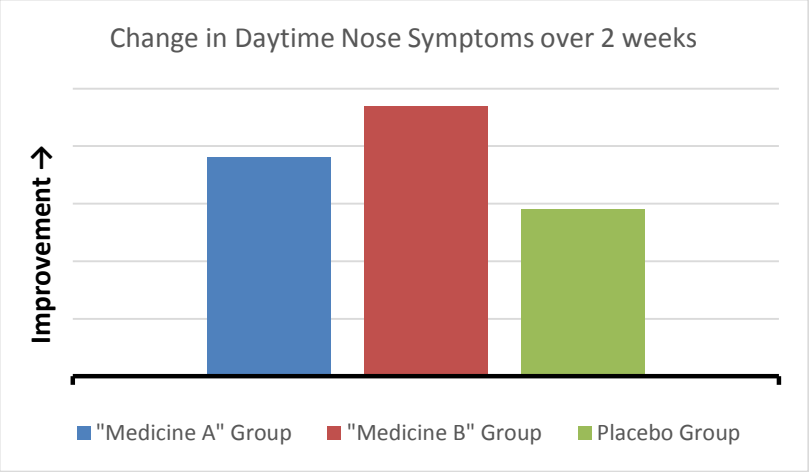
8. What were the results of the study?

Daytime nose symptoms

The study's main goal was to see if "Medicine A" could improve the Daytime Nasal Symptoms Score. The Daytime Nasal Symptoms Score measured 4 nose symptoms during the day: runny nose, itchy nose, stuffy nose, and sneezing.

- In all 3 groups, patients' daytime nose symptoms were better while taking their tablet than before starting their tablet.
- Patients in both the "Medicine A" Group and the "Medicine B" Group had more improvement in daytime nose symptoms than patients in the Placebo Group.
- Not everyone in the "Medicine A" Group and the "Medicine B" Group had these results.

In the below chart, you can see how much each group's daytime nose symptoms changed during the 2 week study. The higher a bar rises above the black line, the more a group's symptoms improved.



Other symptoms

Other findings of the study were similar. For all of the scores listed below that researchers looked at, patients in all 3 groups felt better about their symptoms while taking their tablet than before starting their tablet.

For all scores below, patients in the "Medicine A" Group and the "Medicine B" Group had their symptoms improve more than patients in the Placebo Group:

- Improved seasonal allergy eye symptoms during the day – "Daytime Eye Symptoms Score"
- Improved seasonal allergy symptoms at night – "Night-time Symptoms Score"
- Patients felt better overall about their seasonal allergies – "Patient's Global Evaluation of Seasonal Allergy Symptoms"
- Doctors believed that patients had overall improvement in their seasonal allergies – "Physician's Global Evaluation of Seasonal Allergy Symptoms"
- Patients felt better about how their seasonal allergy symptoms affected their lives – "Rhino-conjunctivitis Quality-of-Life Score"

9. How has this study helped patients?

The study showed that "Medicine A" may help seasonal allergy symptoms without causing serious side effects. As shown by the different ways that the symptoms were measured during the study - these improvements in seasonal allergy symptoms were important to patients.

No further clinical studies of "Medicine A" in seasonal allergic rhinitis are planned at this time.

10. Where can you learn more about this study?

To learn more about this study, visit: https://www.clinicaltrials.gov/ct2/show/NCT01234567

For general information about clinical trials, visit:

- http://www.testingtreatments.org
- https://www.clinicaltrials.gov/ct2/about-studies/learn
- http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm