# The BRodalumab Assessment of Hazards:

# A Multinational Safety (BRAHMS) study in electronic healthcare databases

EMEA/H/CH003959/MEA/002

## Progress report, Q2 2021

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# Introduction

With reference to the adopted PASS protocol via the Post Authorisation Measure EMEA/H/CH003959/MEA/002.

The BRAHMS study is an observational post-authorisation safety study aiming to evaluate potential excess risks associated with the use of brodalumab in the treatment of psoriasis with regards to 1) serious infections, 2) suicidal attempts, 3) major adverse cardiac events (MACE) and 4) malignancies.

LEO Pharma A/S is the funder of the BRAHMS study while Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark is the coordinating study entity.

The main purpose of the annual progress reports for this study is to monitor the accumulation of subjects exposed to brodalumab, to evaluate their treatment persistence, which is important to confirm assumptions about the study's statistical power, and finally, to provide an update on the BRAHMS collaboration.

The number of individuals exposed to brodalumab is accumulating. However, data are still too scarce to evaluate persistence to treatment. The focus of this report is therefore mainly to document the progress in establishing the cross-country collaboration and application for data access as well as to monitor/estimate the accumulation of subjects exposed to brodalumab in the study databases.

# Status on the BRAHMS research collaboration

**Collaborating sites**

Collaborating sites of the BRAHMS study are listed below.

Amendments to the Annual Progress Report 2020:

From October 2020 onwards, University of Verona replaces University of Messina.

**Table 1.** Collaborating sites, currently part of the BRAHMS collaboration

| Country | Department, Institute | Abbreviation | Role |
|---|---|---|---|
| Denmark | Clinical Pharmacology and Pharmacy, University of Southern Denmark, Odense | SDU | Coordinating entity |
| Sweden | Centre for Pharmacoepidemiology, Clinical Epidemiology Division, Karolinska Institutet, Stockholm | KI | Collaborator |
| Norway | Norwegian Institute of Public Health, Department of Chronic Diseases and Ageing, Oslo | NIPH | Collaborator |
| Germany | Leibniz Institute for Prevention Research and Epidemiology - BIPS GmbH, Bremen | BIPS | Collaborator |
| The Netherlands | The PHARMO Institute, Utrecht | PHARMO | Collaborator |
| Italy | Agenzia Regionale di Sanità, Tuscany | ARS | Collaborator |
| Italy | Department of Epidemiology, ASL Roma 1, Lazio Regional Health Service | Lazio | Collaborator |
| Italy | Department of Diagnostics and Public Health, University of Verona | Verona | Collaborator |
| Italy | Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina | Messina | Collaborator |

**Meetings**

Three annual meetings and a mid-year meeting have been conducted by the SDU since kick-off of the study collaboration in 2018.

**Table 2.** Annual- and mid-year meetings held in the BRAHMS collaboration.

| Location and date | Purpose of meeting | Participants* |
|---|---|---|
| Annual meeting<br>Denmark<br>November 12th and 13th, 2018 | Kick-off meeting.<br>Initiate and optimize the BRAHMS research collaboration<br>Understand data structure in collaborating countries | SDU<br>KI<br>NIPH<br>PHARMO<br>ARS<br>Lazio<br>Messina<br>University of Eastern Finland<br>[redacted] (dermatologist)<br>LEO Pharma A/S |
| Annual meeting<br>Italy<br>September 30th and October 1st, 2019 | Optimize the BRAHMS research collaboration<br>Understand data structure in collaborating countries<br>Agree on how to ensure validity of data<br>Develop a common data model | SDU<br>KI<br>NIPH<br>BIPS<br>PHARMO<br>ARS<br>Lazio<br>Messina<br>[redacted] (dermatologist)<br>LEO Pharma A/S |
| Mid-year meeting<br>Norway<br>May 27th and 28th, 2020<br>Due to the corona pandemic changed to an online event | Present and discuss the architecture of the common data model and the composite component framework, which constitutes the basis for future work on the statistical analysis plan. | SDU<br>KI<br>NIPH<br>BIPS<br>PHARMO<br>ARS<br>Lazio<br>Messina<br>[redacted] (dermatologist)<br>LEO Pharma A/S |
| Annual meeting<br>Online event | Present and discuss the statistical analysis plan and the building of study variables. | SDU<br>KI<br>NIPH |

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|---|---|---|
| December 7th and 9th, 2020 | | BIPS<br>PHARMO<br>ARS<br>Verona<br>Messina<br>[redacted] (dermatologist)<br>LEO Pharma A/S |

*Names on participants can be found in Appendix A

Two webinars have been conducted; one by [redacted] (ARS) on May 9, 2019 concerning the validity of data on suicides and one by [redacted] (SDU) on June 18, 2019 concerning the development of a common data model.

Regular online meetings with 3 months intervals have been conducted with each collaborating site to ensure progress and to discuss fundamental questions, milestones and deadlines.

**Committees**

A task force was established on October 1st, 2019, focusing on how to validate data on suicide attempts in a uniform manner across countries. Members: [redacted] (ARS), [redacted] (BIPS), [redacted] (SDU), Jesper Hallas (SDU) and [redacted] (SDU).

A steering committee was established on June 20th, 2019. Members: [redacted] (NIPH), Jesper Hallas (SDU), and [redacted] (SDU).

A publication committee was established on November 1, 2019. Members: [redacted] (KI), [redacted] (BIPS), [redacted] (NIPH, [redacted] (PHARMO), [redacted] (Messina), Jesper Hallas (SDU) and [redacted] (SDU).

**Common Data Model and data transformation**

A final version the Common Data Model (CDM) has been completed. This has happened through an iterative process of development and review by collaborators. The transformation of raw source data can now be initiated at the sites where data are available. As transformation progresses, we expect that the CDM will require ongoing adjustments. A transformation documentation document and a Quality Assurance (QA) package for confirming CDM compliance following transformation has also been completed.

**Statistical Analysis Plan**

A first draft of the statistical analysis plan (SAP) has been sent to collaborators. The completion of the SAP will be done through an iterative process of development and review by collaborators. The SAP is expected to be finalized late 2021 in due time for the preparation of the interim report.

A framework for how to build site-dependent algorithms for each study variable has been developed and a list of study variables has been presented. Collaborators will initiate the task of building site-dependent algorithms for these study variables during Q2 2021.

**Agreements on co-financed research**

Agreements on co-financed research between SDU and research partners have been signed by all current collaborators

- Centre for Pharmacoepidemiology, Clinical Epidemiology Division, Karolinska Institutet, Stockholm, Sweden
- Norwegian Institute of Public Health, Department of Chronic Diseases and Ageing, Norway
- Leibniz Institute for Prevention Research and Epidemiology – BIPS GmbH, Bremen, Germany
- PHARMO Institute N.V., the Netherlands
- Agenzia Regionale di Sanità, Tuscany, Italy
- Department of Epidemiology, ASL Roma 1, Lazio Regional Health Service, Italy
- Department of Diagnostics and Public Health, University of Verona, Italy

## Status on data access in collaborating countries and regions

**Table 3.** Status on data access in collaborating countries and regions.

| **Country** | **Status** |
|---|---|
| Denmark | Data access has been approved. Data from 1995 to 2019 are available including data on brodalumab dispensing from October 2017 to May 2019 |
| Norway | Application for the approvals for the full linked data (ethics, DPIA, data order) is in progress |
| Sweden | To ensure suitable data coverage for the interim report, data will be applied for in 2022. Ethical approval has been received. |
| The Netherlands | Data access has been approved and data from the high budget impact medication (e.g. where brodalumab is registered) is currently available in PHARMO from January 1st 2017 to December 31st 2019 |
| Germany | Data access has been approved for the data from 2004-2026. Data on brodalumab dispensations are currently available from January 1st 2017 to December 31st 2018. Data for 2017 are available from all 4 statutory health insurances participating in The German Pharmacoepidemiological Research Database (GePaRD), whereas data for 2018 are available from 2 statutory health insurances (covering about 50% of persons in GePaRD). |
| Italy | |
| Palermo | The study is notified to the local Ethical Committee.<br>Extraction of data till the end of 2019 is ongoing. |
| Caserta | The study will be notified to the local Ethical Committee of Verona.<br>Claims data covering until 31st December 2018 are available. Extraction of data until 31st December 2020 is ongoing. |
| Veneto | The study will be notified to the Ethical Committee of Verona |
| Lazio | The study has been approved. Data until April 2020 are available. |
| Tuscany | The study has been approved. Data until September 2020 are available. |

## Number of subjects exposed to brodalumab in the databases

**Table 4.** Number of subjects exposed to brodalumab in available databases. Of note, data are not yet available from all databases. The BRAHMS population consists of patients with moderate to severe psoriasis who are treated with either brodalumab or one of the active comparators included in the BRAHMS study.

| **Country** | **Population covered by databases** | **Population in which brodalumab users are identified** | **Data coverage of brodalumab** | **Number of unique users of brodalumab** |
|---|---|---|---|---|
| Denmark | Nationwide, 5.7 million individuals | Restricted to the BRAHMS population | October 1st 2017 to May 22nd 2019 | 19 |
| Norway | Nationwide, 5.4 million individuals | Among all users of biologics, not restricted to the BRAHMS population | September 2018 – January 2021 | 103 |
| Sweden | Nationwide, 10.1 million individuals | Among all users of biologics, not restricted to the BRAHMS population | January 1st 2017 to December 31st 2020 | 1 (2017)<br>18* (2018)<br>49* (2019)<br>76* (2020) |
| The Netherlands | 19 % of the Dutch population is covered by databases in PHARMO, approx. 3 million individuals | Among all users of biologics at Dutch hospitals covered by the databases in PHARMO (50% of Dutch hospitals) and among all persons in the GP Database | January 1st 2017 to December 31st 2019. | 15 (HBIM)**<br>9 (GP) ** |
| Germany | 17% of the German population is covered by GePaRD, approx. 20 million individuals | Among all members of 4 statutory health insurances***<br>Not restricted to the BRAHMS population | January 1st 2017 to December 31st 2018 | 228 |
| Italy | | | | |
| Palermo | Regional data, 1.3 million individuals | NA | NA | No data available |
| Caserta | Regional data 1.1 million individuals | Among any user of biologics, not restricted to the BRAHMS population | May 2019 – December 2020 | 34 |

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|---|---|---|---|---|
| Veneto | Regional data, 4,9 million individuals | Among all users of biologics, not restricted to the BRAHMS population | NA | No data available |
| Lazio | Regional data, 5.7 million individuals | Among all users of biologics, not restricted to the BRAHMS population | May 2019 – April 2020 | 74 |
| Tuscany | Regional data, 3.6 million individuals | Among all users of biologics, not restricted to the BRAHMS population | May 2019 – September 2020 | 1 |

*Unique users within the specific calendar year. Data on unique users across calendar years are currently not available.

**15 patients registered in the register of High budget impact medication and 9 patients in the GP database. There is a potential overlap between these registries.

*** Data from two health insurances are still missing for 2018.

The collaboration with the University of Verona, Italy has replaced the collaboration with the University of Messina. Thereby data from the region of Veneto, Italy, will be available for the BRAHMS study and will most likely replace data from Palermo and Caserta. Since the region of Veneto is considerably larger than the regions of Palermo and Caserta, this is in any case expected to lead to a higher number of subjects exposed to brodalumab available for the study in Italy. The inclusion of the region of Veneto will also at least in part compensate for the Finnish data no longer being included.

## Conclusion

The BRAHMS study is progressing as planned in terms of building organization, completion of research agreements, development of the common data model and the statistical analysis plan, and in terms of data coverage. The number of registered brodalumab users is currently rather low. This may, at least to some extent, be explained by a reluctance towards initiating new biological therapy during the current covid-19 pandemic. Furthermore, there is a delay in data availability in some countries and the actual number of individuals eligible for the BRAHMS study is expected several folds higher than indicated by the current number of brodalumab users. For example, we only have access to data from 2018 from 2 out 4 SHIs in the German GePaRD database, where we expect to find the highest number of brodalumab users over time. In addition, the covid-19 pandemic has caused a marked delay in data access in some countries. In conclusion, the actual, current number of brodalumab users is likely to be considerably higher than indicated by this report.

# Appendix A

**Table A.** Meeting participants

| | Participants |
|---|---|
| Annual meeting<br>Denmark<br>November 12th and 13th, 2018 | SDU (Lead investigator Jesper Hallas, Lead investigator [redacted], Lead project manager [redacted], Lead data manager [redacted], Lead project coordinator [redacted])<br>KI (Local project coordinator [redacted], Local principal investigator [redacted])<br>NIPH (Local project coordinator [redacted])<br>BIPS (Local project coordinator [redacted], Statistician [redacted])<br>PHARMO (Local project coordinator [redacted], Local data analyst [redacted])<br>ARS (Local project coordinator [redacted])<br>Lazio (Local project coordinator [redacted])<br>Messina (Local project coordinator [redacted], Dermatologist [redacted], Local data analyst [redacted], Pharmacologist [redacted])<br>University of Eastern Finland (Local project coordinator [redacted])<br>[redacted] (dermatologist)<br>LEO Pharma A/S ([redacted] and [redacted]) |
| Annual meeting<br>Italy<br>September 30th and October 1st, 2019 | SDU (Lead investigator Jesper Hallas, Lead project manager [redacted], Lead data manager [redacted], Lead project coordinator [redacted])<br>KI (Local project coordinator [redacted], Statistician [redacted])<br>NIPH (Local project coordinator [redacted], Statistician [redacted], Local principal investigator [redacted])<br>BIPS (Local project coordinator [redacted], Pharmaco-epidemiologist [redacted])<br>PHARMO (Local project coordinator [redacted], Local data analyst [redacted]) |

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|---|---|
| | ARS (Local project coordinator [redacted], Local data analyst [redacted])<br>Lazio (Local project coordinator [redacted])<br>Messina (Local project coordinator [redacted], Dermatologist [redacted], Local data analyst [redacted], Pharmacologist [redacted]).<br>[redacted] (dermatologist)<br>[redacted] (representative from LEO Pharma A/S) |
| Mid-year meeting<br>Online event<br>May 27th and May 28th 2020 | SDU (Lead investigator Jesper Hallas, Lead project manager [redacted], Lead data manager [redacted], Lead project coordinator [redacted])<br>KI (Local project coordinator [redacted], Statistician [redacted])<br>NIPH (Local project coordinator [redacted], Statistician [redacted], Local principal investigator [redacted])<br>BIPS (Local project coordinator [redacted], Pharmaco-epidemiologist [redacted], Local principal investigator [redacted])<br>PHARMO (Local project coordinator [redacted], Local data analyst [redacted])<br>ARS (Local project coordinator [redacted], Local data analyst [redacted])<br>Lazio (Local project coordinator [redacted], Statistician [redacted])<br>Messina (Local project coordinator [redacted], Dermatologist [redacted], Local data analyst [redacted], Local data analyst [redacted], Statistician [redacted]).<br>[redacted] (dermatologist)<br>[redacted] (representative from LEO Pharma A/S) participated. |
| Annual meeting<br>Online event<br>December 7th and 9th, 2020 | SDU (Lead investigator Jesper Hallas, Lead project manager [redacted], Lead data manager [redacted], Lead project coordinator [redacted])<br>KI ((Local project coordinator [redacted], Statistician [redacted], pharmocoepidemiologist [redacted]) |

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|---|---|
| | NIPH (Local project coordinator [redacted], Statistician [redacted], Local principal investigator [redacted])<br><br>BIPS (Local project coordinator [redacted], Pharmaco-epidemiologist [redacted], Statistician [redacted])<br><br>PHARMO (Local project coordinator [redacted], Local data analyst [redacted])<br><br>ARS (Local project coordinator [redacted], Local data analyst [redacted])<br><br>Lazio ((Local project coordinator [redacted], Statistician [redacted], Local data analyst [redacted], Statistician [redacted])<br><br>Verona ((Local project coordinator [redacted])<br><br>Messina (Dermatologist [redacted], Local data analyst [redacted], Pharmacologist [redacted], Pharmacist [redacted]).<br><br>[redacted] (dermatologist)<br><br>[redacted] (representative from LEO Pharma A/S) |