The BRodalumab Assessment of Hazards:

A Multinational Safety (BRAHMS) study in electronic healthcare databases

EMEA/H/CH003959/MEA/002.4

Progress report, Q2 2020

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Introduction

With reference to the adopted PASS protocol via the Post Authorisation Measure EMEA/H/CH003959/MEA/002 in May 2019

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.

The BRAHMS study is sponsored by LEO Pharma A/S 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.

Since this first progress report is completed shortly after the PRAC assessment of the study protocol, data are 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

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, Unit for Clinical Epidemiology, 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	Servizio Sanitario Regionale del Lazio, Dipartimento de Epidemiologia, Lazio	Lazio	Collaborator
Italy	Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina	Messina	Collaborator

Of note, the planned collaboration with University of Eastern Finland did not proceed due to uncertainties about the reimbursement for Kyntheum® in Finland and an expected low number of individuals treated with Kyntheum® in Finland.

Meetings

Two annual meetings have been conducted by the SDU.

The first annual meeting was held in Denmark, November 12th and 13th, 2018 with participants from SDU (Lead investigator Jesper Hallas, Lead investigator [redacted], Lead project manager [redacted], Lead data manager [redacted], Lead project coordinator [redacted]), KI (Local project coordinator [redacted], Local principal investigator [redacted]), NIPH (Local project coordinator [redacted]), BIPS (Local project coordinator [redacted],

Statistician [redacted]), PHARMO (Local project coordinator [redacted], Local data analyst [redacted]), ARS (Local project coordinator [redacted]), Lazio (Local project coordinator [redacted]), Messina (Local project coordinator [redacted], Pharmacologist [redacted], Local data analyst [redacted], Local data analyst [redacted]), and University of Eastern Finland (Local project coordinator [redacted]). Furthermore, [redacted] (dermatologist) and representatives from LEO Pharma A/S ([redacted] and [redacted]) participated.

The second annual meeting was held in Italy, September 30th and October 1st, 2019 with participants from SDU (Lead investigator Jesper Hallas, Lead project manager [redacted], Lead data manager [redacted], Lead project coordinator [redacted]), KI (Local project coordinator [redacted], Statistician [redacted]), NIPH (Local project coordinator [redacted], Statistician [redacted], Local principal investigator [redacted]), BIPS (Local project coordinator [redacted], Pharmaco-epidemiologist [redacted]), PHARMO (Local project coordinator [redacted], Local data analyst [redacted]), ARS (Local project coordinator [redacted], Local data analyst [redacted]), Lazio (Local project coordinator [redacted]), Messina (Local project coordinator [redacted], Pharmacologist [redacted], Local data analyst [redacted], Pharmacologist [redacted]). Furthermore, [redacted] (dermatologist) and [redacted] (representative from LEO Pharma A/S) participated.
The main themes of the meetings were to understand data structure in collaborating countries, agree on how to ensure validity of data, develop a common data model to, and initiate and optimize the BRAHMS research collaboration.

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 are conducted with each collaborating site to ensure progress and to discuss fundamental questions, milestones and deadlines.

Committees

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

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

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

Common Data Model specification

The specification of the Common Data Model (CDM) is close to completion. This has happened through an iterative process of development and review by collaborators; two rounds of revision have already been performed. The CDM is expected to be finalized before autumn 2020 and transformation of raw source data can begin at select sites where data is already available. A Quality Assurance (QA) package for confirming CDM compliance following transformation is in the pipeline and is expected to be developed in parallel to finalizing the CDM specification. STATA is used as the primary programming language, but it is discussed whether to use R as a secondary option.

Agreements on co-financed research

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

- Centre for Pharmacoepidemiology, Unit for Clinical Epidemiology, 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
- Servizio Sanitario Regionale del Lazio, Dipartimento de Epidemiologia, Lazio, Italy

For the following research partner, an agreement is in the process of being prepared.

- Department of Biomedical and Dental Sciences and Morphofunctional Imaging, University of Messina, Italy

Status on data access in collaborating countries and regions

Table 2. 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
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 2018
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 2017 for 3 out of 4 health insurances participating in The German Pharmacoepidemiological Research Database (GePaRD) (covering about 50% of persons in GePaRD)
Italy	
Palermo	We have currently access to claims data till 31st December 2018 – Currently, extraction of data till the end of 2019 is ongoing
Caserta	We currently have access to claims data till 31st December 2018 – Extraction of data till the end of 2019 will be planned by the end of the month. For both Caserta and Palermo data, the study is notified to the local Ethical Committee. No approval is, however, needed for observational retrospective studies.
Lazio	The study is approved and access is possible on data currently updated to December 2018
Tuscany	The study is approved and access is possible on data currently updated to November 2019

Number of subjects exposed to brodalumab in the databases

Table 3. Number of subjects exposed to brodalumab in available databases at collaborating sites. Of note, for this first progress report data is not available from all databases. The BRAHMS population is patients with moderate to severe psoriasis who are treated with either brodalumab or one the active comparators included in the BRAHMS study.

Country	**Population covered by databases**	**Population in which brodalumab users are identified**	**Data coverage**	**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, 5.2 million individuals	Among all users of biologics, not restricted to the BRAHMS population	September 2018 - October 2019	70
Sweden	Nationwide, 9.9 million individuals	Among all users of biologics, not restricted to the BRAHMS population	January 1st 2017 to December 31st 2018	1 (2017) 18* (2018)
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)***	January 1st 2017 to December 31st 2018.	39**
Germany	17% of the German population is covered by GePaRD, approx. 20 million individuals	Among all users of biologics in 3 out of 4 statutory health insurances covering about half of persons in GePaRD**** Not restricted to the BRAHMS population	January 1st 2017 to December 31st 2017	36
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 2019	34

Lazio	Regional data, 5.7 million individuals	NA	NA	No data available
Tuscany	Regional data, 3.6 million individuals	Among all users of biologics, not restricted to the BRAHMS population	May 2019 – November 2019	0

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

**Number of dispensing. Number of unique users are not available yet.

***In the Netherlands, brodalumab is registered as a high budget impact medication. These medications are solely dispensed at hospitals.

**** Data from one large health insurance are not available yet.

Conclusion

The BRAHMS study is progressing as planned in terms of building organization, negotiations and completions of contracts, development of the common data model, and in terms of data coverage. The number of registered brodalumab users is currently low. This is, however, mainly explained by a delay in the availability of data among the collaborators.