BIOETHICS COMMITTEE AT THE MEDICAL UNIVERSITY OF LODZ
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RESOLUTION
BIOETHICS COMMITTEE ON THE MEDICAL EXPERIMENT PROJECT
Number RNN/188/20/EC of 14 July 2020

(when corresponding regarding this decision, please refer to the above number and date of the Resolution each time)

Principal investigator and executive:

Prof.dr hab.n.Marek L. Kowalski, MD, Department of Immunology and Allergy, Chair of Clinical Immunology and Rheumatology, Medical University of Lodz,
Pomorska 251, 92-213 Łódź

Co-investigators: Aleksandra Wardzyńska, PhD; Monika Antczak-Marczak, PhD

Study title:

The efficacy of mepolizumab in patients with severe eosinophilic asthma treated in Poland. The real-life observational study

Pursuant to the Act of 5 December 1996 on the professions of doctor and dentist (i.e. Dz. U. of 2017, item 125, as amended.), the Act of 6 September 2001 on Pharmaceutical Law (i.e. Dz. U. of 2016, item 2142, as amended.), the Regulation of the Minister of Health of 2 May 2012 on templates of documents to be submitted in connection with a clinical trial of a medicinal product and on the amount and manner of payment of fees for submitting an application for the initiation of a clinical trial (Journal of Laws of 2012 U. of 2012, item 491), the Act of 20 May 20 IO on Medical Devices (Journal of Laws of 20 I7.item 211 as amended.), Regulation of the Minister of Health of 17 February 2016. on templates of applications submitted in connection with a clinical trial, the amount of fees for submitting applications and the final report on the performance of a clinical trial (Journal of Laws, item 208), Regulation of the Minister of Health and Social Welfare of 11 May 1999. on the detailed rules for the appointment and financing and operation of bioethics committees (Journal of Laws No. 47, item 1). 480), Ordinance No. 8/2015 of 16 February 2015 of the Rector of the Medical University of Lodz on the introduction of the Rules of Procedure of the Bioethics Committee at the Medical University of Lodz and Ordinance No. 57/2017 of 5 February 2015September 2017 of the Rector of the Medical University of Lodz on the appointment of the Bioethics Committee at the Medical University of Lodz after analysing the application, getting acquainted with the draft opinion on the submitted study, in a secret ballot,

The Bioethics Committee at the Medical University of Lodz (fulfilling the obligations of the ICH GCP) resolves as follows:

§1

1. Opinions the request **positively, without reservations** , based on Complex Documents, the list of which is set out in Annex No. 1. The resolution enters into life with the day of taking.

§2

The opinion concerns only the application under consideration, taking into account the submitted draft. Each change and modification requires a separate opinion. The applicant is obliged to inform about any corrections, adverse events and unforeseen circumstances.

An appeal against this resolution shall be lodged through the Bioethics Committee at the Medical University of Lodz to the Bioethics Appeal Committee, within 14 days from the date of receipt of the resolution expressing the opinion.

Chairman of the Bioethics Committee
at the Medical University of Łódź

prof.dr hab.n.med. Józef Drzewoski

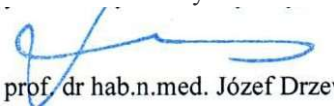
ATTACHMENT NO. 1 TO THE RESOLUTION
BIOETHICS COMMITTEE ON THE MEDICAL EXPERIMENT PROJECT
Number RNN/188/20/EC of 14 July 2020
(when corresponding regarding this decision, please refer to the above number and date *of the Resolution each time)*

Principal investigator and **executive:**
Prof.dr hab.n.med. Marek L. Kowalski, Department of Immunology and Allergy, Department of Clinical Immunology and Rheumatology, Medical University of Lodz, 251 Pomorska Street, 92-213 Lodz
Co-investigators: Aleksandra Wardzyńska, PhD; Monika Antczak-Marczak, PhD
Study title:
The efficacy of mepolizumab in patients with severe eosinophilic asthma treated in Poland. The real-life observational study

The Commission received the following documents:

1. Request to the Bioethics Committee
2. Study protocol
3. List of sites participating in the study
4. CV of Prof.Marek L. Kowalski, MD
5. Consent of the director of the SP ZOZ Central Clinical Hospital of the Medical University of Łódź

Chairman of the Bioethics Committee at the Medical University of Lodz



prof. dr hab.n.med. Józef Drzewoski

NON-INTERVENTIONAL STUDY PROTOCOL

THE EFFICACY OF MEPOLIZUMAB IN PATIENTS WITH SEVERE EOSINOPHILIC ASTHMA TREATED IN POLAND.

THE REAL-LIFE OBSERVATIONAL STUDY

TABLE OF CONTENTS

1. BACKGROUND AND RATIONALE

Mepolizumab is a humanized monoclonal antibody (IgG1, kappa) against IL-5, which mediates the role of the eosinophils in the inflammatory process of the airways. The drug has a high affinity to IL-5 and blocks the binding of IL 5 to the alpha chain of the IL-5 receptor complex expressed on the eosinophil cell surface. At present, mepolizumab is registered in the European Union as an adjunctive therapy in adults and paediatric patients aged 6-17 years with inadequately controlled severe eosinophilic asthma. In Poland mepolizumab has been a reimbursable drug since 1st November, 2017 and is available under the national drug program for adults with severe eosinophilic asthma.

The published results of the clinical trials show that the use of mepolizumab in the treatment of patients with severe eosinophilic asthma reduces the exacerbation rates, as well as decreases the doses of glucocorticosteroids (with the maintenance of asthma control). Moreover, mepolizumab demonstrates: long-term reduction of eosinophilic inflammation, consistent and sustained exacerbation reductions and improvements in asthma control for the duration up to 4.5 years.

The proposed real-life observation study can deliver valuable information about mepolizumab efficacy complementing the results of clinical trials. Multicentre design of the study will allow to collect data from relatively large group of patients treated at least one year within the Polish Drug programme. The added value of this retrospective study relies in the specifics of the Polish drug programme which has unique inclusion criteria with respect to the number of eosinophil cells in blood. (the unique inclusion criteria in the Polish drug programme is ≥350 eos/ul) Therefore we can test the efficacy of mepolizumab in the specific treatment group. To this time no study has been published about the efficacy of mepolizumab in Poland.

2. OBJECTIVES

To evaluate the efficacy of mepolizumab 100 mg SC every 4 weeks in patients with severe eosinophilic asthma who have been treated for at least 12 months in several Polish allergy/asthma centres under the same protocol .

3. RESEARCH METHODOLOGY

3.1. Study Design

Retrospective multicentre observational study will involve 130 patients with severe eosinophilic asthma (SEA) who have been treated in six Severe Asthma Treatment Centres (SATCs) in Poland.

In each SATC all data available in the program questionnaires will be transferred to the Study Data Sheet (questionnaire), and will be send to the study coordinator within 5 months from the study beginning

The start-up meeting including partners from all centres involved will be organized to discuss the study protocol and to unify data collection

The evaluation parameters (exacerbations rate, OCS dose) will be analysed at least at three time points: pre-MEPO, after 24 weeks of MEPO and after 1 year of MEPO administration (some of the outcomes will be observed every 4 weeks, for the details see 'study endpoints' section).

In addition the following parameters which are available in patients' records will be analysed:

- ACQ-5 score (measured at qualification for the treatment and every 4 weeks thereafter)
- AQLQ score (measured at qualification for the treatment and every 4 weeks thereafter)
- Pre-bronchodilator FEV1 (measured at qualification for the treatment and every 4 weeks thereafter)

Research activities will include:

- collecting raw data from the clinical centres (paper version) and constructing a raw dataset (digital version),
- data cleaning, computation of variables,
- statistical analysis typical for pre-post study design (the statistical analysis will be outsourced to the specialized private institute).

Clinical improvements observed at 24 weeks and at 52 weeks of treatment with Mepolizumab will be referred to the following characteristics of patients at baseline:

- demographics,
- presence of comorbidities including the atopic status,
- concomitant pharmacotherapy,
- clinical status,
- eosinophilia.

We will control for mepolizumab use regarding dose, treatment duration and dosing frequency as well as for the safety profile based on the AEs reporting in the medical documentation.

3.2. Data Source / Data Collection

Patients recruited to the study had been treated with mepolizumab between December 2017 and December 2019.
All the data planned to be used in the proposed study were systematically collected in the form of the clinical documentation (paper version) and will be transferred in the study centres into the study Data Sheets.
Collaborating Researchers (Severe Asthma Centres' Leaders) will provide the data input into the dedicated online questionnaire.

3.3. Study Population

130 Patients who were treated with mepolizumab in six severe-asthma clinics in Poland between December 2017 and December 2019 . In the drug program in Poland it was mandatory to conduct the control examinations at the 24^{th} and 52^{nd} week of the treatment . In the proposed study we will use this information to evaluate study endpoints. Only patients who have been treated for at least 52 weeks are included into the study

3.3.1. Inclusion Criteria

- The availability of the complete data

- Duration of treatment with mepolizumab: ≥ 52 weeks
- Satisfying the Polish drug programme inclusion criteria:
  - Age >18
  - Before treatment with mepolizumab (BSAT inclusion criteria):
    - High doses of ICS + one other controlling medication (i.e. LABA)
    - ≥2 exacerbations in the previous year
    - ≥350 eosinophil cells/µl in the blood at the time of qualifying, or in the previous year
    - Pre-bronchodilator FEV1 < 80%

3.3.2. Exclusion Criteria

- Duration of treatment with mepolizumab < 52 weeks
- Lack of complete data

3.4. Variables

The main outcome variables are listed as the primary or secondary endpoints. Asthma exacerbation is defined as in the Polish drug programme (see 3.4.1.1.).

Variables concerning the primary endpoints

- Asthma exacerbations measured at qualification for the treatment (in the period of previous 52 weeks) and at the 24th and 52nd week of the treatment.
- Oral Corticosteroids use dose (documented at qualification for the treatment and at the 24th and 52nd week of the treatment)

Variables concerning the secondary endpoints

- ACQ-5 score (measured at qualification for the treatment and every 4 weeks thereafter)
- AQLQ score (measured at qualification for the treatment and every 4 weeks thereafter)
- Pre-bronchodilator FEV1 (measured at qualification for the treatment and every 4 weeks thereafter)
- Blood eosinophil counts (measured at qualification for the treatment and at the 24th and 52nd week of the treatment)

3.4.1. Outcome Definitions

3.4.1.1. Asthma Exacerbation

Asthma exacerbations, defined according to the Polish drug programme, is *the worsening in asthma requiring (1) use of systemic corticosteroids or (2) increase in dose of OCS for more than 3 days in case of patients who are chronically treated with OCS.*

3.4.2. Exposure Definitions

There are no exposure variables to be defined in this study.

3.5. Sample Size

Retrospective multicentre observational study will involve 130 patients with SEA who have been treated in six severe asthma treatment centres in Poland. The sample includes all individuals who participated in the drug programme in Poland at least for 52 weeks between December 2017 and December 2019

The motivation to focus on this sample was the following:

- a relatively large sample of patients (N=130),
- the unique and complete dataset containing patients' characteristics and treatment results (all severe asthma centres participating in the drug programme are obliged to collect all the data we use in this study),
- the opportunity to study the treatment results under the unique inclusion criteria of the Polish drug programme (≥350 eos/ul) (see 3.3.1).

4. DATA ANALYSIS CONSIDERATIONS

- Exacerbations rates in 24th and 52nd week with comparison to rate of exacerbations during the pre-treatment year. Also the frequency of exacerbations in 6- and 12-month follow-up period will be described as patient count and percentage as categorical variable (0,1,2,3,4+ exacerbations).
- OCS median doses in 24th and 52nd week with comparison to the median dose at baseline
- ACQ-5, AQLQ, FEV1 measured on the monthly basis, the mean score at baseline will be compared with every post-treatment monthly score.
- Blood eosinophil geometric mean in 24th and 52nd week with comparison to the geometric mean at baseline

5. LIMITATIONS

- The real-life observational studies are only complimentary to the clinical trials

6. STUDY CONDUCT, MANAGEMENT & ETHICS

6.1. Ethical Approval and Subject Consent

This study will comply with all applicable laws regarding subject privacy. No direct subject contact or primary collection of individual human subject data will occur. Study results will be in tabular form and aggregate analyses that omits subject identification. The Polish ethics committee approval is required. Any publications and reports will not include subject identifiers.

6.2. Adverse Event (AE), Pregnancy Exposure, and Incident Reporting

The planned study is a retrospective analysis. All the adverse events (AEs) and serious adverse events (SAEs) resulting in therapy termination will be scrutinized and qualitatively analysed.

7. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study results are planned for external distribution (presentation at conferences and publication). The study will be closed upon sign-off of the final report document. Manuscript development activities will follow the final report sign-off. Planned Publication date (manuscript): October 2020.

8. REFERENCES

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