## Full protocol title prospective observational study:

"Comparative study of the use of Multigam IV (5% vs. 10%) as substitution therapy in patients with a secondary immunodeficiency due to a hematological disorder to evaluate infusion time, tolerability and satisfaction. A monocentric observational Belgian study."

## Protocol acronym/short title:

MULTISIM/Comparison of Multigam IV 5% and Multigam IV 10% in immunocompromised patients.

## Version and date of final protocol:

Version 3 - 8 September 2017

## Sponsor:

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| | |
|---|---|
| _____ | _____ |
| Principal Investigator | Date |

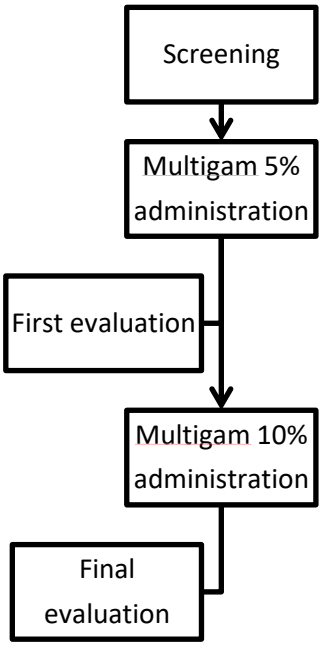
# Table of contents


1. Study synopsis ..... 5
2. Background and rationale ..... 8
3. Study objectives and design ..... 9
   - 3.1 Study objectives ..... 9
   - 3.2 Primary endpoints ..... 9
   - 3.3 Secondary endpoints ..... 9
   - 3.4 Study design ..... 9
   - 3.5 Study diagram ..... 9
   - 3.6 Study flowchart ..... 10
4. Selection and exclusion of participants ..... 10
   - 4.1 Inclusion criteria ..... 10
   - 4.2 Exclusion criteria ..... 10
   - 4.3 Expected duration of study ..... 10
5. Study actions per visit ..... 11
   - 5.1 Study visit 1 ..... 11
   - 5.2 Study visit 2 ..... 11
6. Data collection ..... 11
7. Assessment of efficiency ..... 12
8. Assessment of safety ..... 12
   - 8.1 Specification, timing and registration of safety parameters ..... 12
   - 8.2 Procedures for registration and reporting of adverse events (AE) ..... 12
9. Statistics ..... 15
   - 9.1 Sample size ..... 15
   - 9.2 Analysis ..... 15
10. Direct access to source data and documents ..... 15
11. Ethical and regulatory compliance ..... 15
12. Data handling and management ..... 16
13. Publication policy ..... 16
14. Insurance/compensation ..... 17

15. Financial aspects ..... 17
16. References ..... 17
17. Annex ..... 18

# 1. Study synopsis

| | |
|---|---|
| Clinical trial title | Comparative study of the use of Multigam IV (5% vs. 10%) as substitution therapy in patients with a secondary immunodeficiency due to a hematological disorder to evaluate infusion time, tolerability and satisfaction. A monocentric observational Belgian study. |
| Protocol short title/Acronym | MULTISIM/Comparison of Multigam IV 5% and Multigam IV 10% in immunocompromised patients. |
| Sponsor name | UZ Leuven |
| Principal investigator | Professor dr. Delforge Michel |
| Medical condition or ilness | Secondary immune deficiencies in patients with an underlying hematological disorder. |
| Purpose of the clinical trial | Evaluation of infusion time, safety and tolerance of Multigam 10% compared to Multigam 5%. |
| Primary objective | Assess the administration of Multigam 10% compared to Multigam 5% to shorten the infusion time without additional side effects and loss of quality of care. |
| Secondary objectives | • Evaluate the tolerability and infusion related side effects.<br>• Evaluate patient satisfaction.<br>• Evaluate the number of care actions required.<br>• Evaluate nursing staff satisfaction. |
| Setup | In this non-interventional, monocentric, observational study, the administration of Multigam 10% will be compared with the standard (Multigam 5%) in patients with a secondary immunodeficiency due to a hematological disorder.<br>Patients who are being treated with Multigam because of |

| | |
|---|---|
| | their secondary immunodeficiency will be evaluated for inclusion.<br><br>The last administration of Multigam 5% will serve as a control. During this check, different parameters will be evaluated:<br><br>-Infusion time (hours)<br>-Hospitalization time at the oncological day clinic (hours)<br>-Side effects (via CTCAE v4.03)<br>-Nursing staff care actions<br><br>Subsequently, an identical evaluation will take place at the first administration of Multigam 10% and the satisfaction of the patient and the nursing staff will also be assessed. The results will be analyzed and compared.<br><br>Patients can then receive Multigam 10% or Multigam 5% according to their preference.<br><br>  |
| Endpoints | **Primary:**<br><br>To compare the infusion time (hours) and tolerance of Multigam 10% and the standard administration of Multigam 5%. |

| | |
|---|---|
| | **Secondary:**<br>• Assess the tolerance and patient satisfaction of Multigam 5% vs. Multigam 10% via:<br>- Patient questionnaire<br>- Scoring of side effects via CTCAE v4.03<br>• Assess nursing staff care actions<br>• Assess the satisfaction of the nursing staff (questionnaire)<br>• Patient characterization (age, gender, disorder) |
| Population | 30 patients with a secondary immunodeficiency due to a hematological disorder. |
| Inclusion criteria | • Age ≥ 18 years<br>• Secondary immunodeficiency due to a hematological disorder<br>• Patient received at least 2x Multigam 5%<br>• No side effects (grade 2 or higher according to CTCAE v4.03) during their last 2 Multigam 5% infusions<br>• Patient needs at least 2x Multigam<br>• Signed informed consent form |
| Exclusion criteria | • Patient received less than 2x Multigam 5%<br>• Side effects (grade 2 or higher according to CTCAE v4.03) during their last 2 Multigam 5% infusions<br>• Patient refuses to participate in the study |
| Maximum duration of study/treatment | • 2 months |
| Version and date of final protocol | Version 3 – 8 September 2017 |

## 2. Background and rationale

**Background**

The immune system ensures the detection and elimination of pathogens and even transformed cells. However, normal functioning can be disrupted by a variety of factors. Both primary and secondary causes can lead to an immune deficiency with increased vulnerability for infections (Cooper, et al. 2003, Shinen & Shearer, 2008).

Secondary immune deficiencies can be caused by various diseases (lymphoproliferative disorders, infections, ...) and therapies (immunosuppressants, anti-inflammatory drugs, ...). In lymphoproliferative disorders such as chronic lymphocytic leukemia (CLL) and multiple myeloma (MM), both treatment and the disease itself contribute to a secondary immunodeficiency. In order to strengthen the resistance in these patients, substitution therapy with immunoglobulins can be started in cases of recurrent infections (Friman, et al. 2016). Intravenous gamma globulins (IVIg) are reimbursed in Belgium for patients with CLL and MM with a secondary immunodeficiency that resulted in a life-threatening infection or in repeated episodes of clinically significant infections requiring antibiotics. The dose is 0.4 to 0.5 g / kg every 3 to 4 weeks.

At the UZ Leuven Hematology department, Multigam is being used as standard IVIg substitution therapy. Multigam is an immunoglobulin preparation that is produced from the plasma of human donors. It exists in both 5% and 10% concentrated solution and is administered intravenously.

**Rationale**

The day clinic of the Hematology department at UZ Leuven is experiencing a yearly growth of about 5% in the number of patient contacts. For this reason, we are constantly looking for ways to shorten the time spent at the day clinic to create additional capacity without causing a loss of quality in care. With the arrival of Multigam 10%, patients will be able to switch to this new immunoglobulin solution. This allows patients to be treated independently of the dose and their weight within a shorter period of time.

With this study we want to quantify the transition from Multigam 5% to Multigam 10% in a scientific way. The rationale of this study is to compare and evaluate the administration of both solutions in terms of infusion time, infusion related side effects, patient satisfaction, number of care actions and satisfaction of the nursing staff, and this in about 30 patients.

# 3. Study objectives and design

## 3.1 Study objectives

With this study we want to evaluate the administration of Multigam 10% compared to the standard (Multigam 5%). We want to observe whether there are changes in infusion time and infusion related side effects. In addition, the patient satisfaction, the number of care actions and the satisfaction of the nursing staff will also be evaluated.

## 3.2 Primary endpoints

Comparing the infusion time (hours) and tolerance between Multigam 10% and the standard administration.

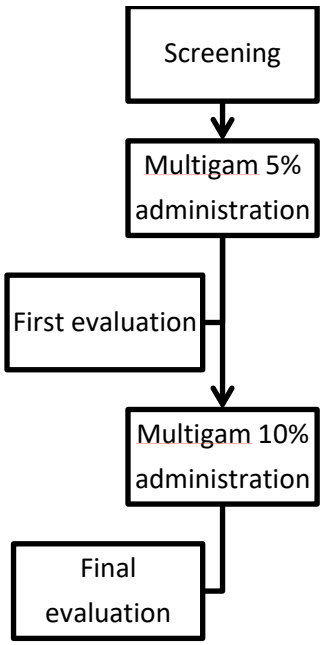
## 3.3 Secondary endpoints

- Assess the satisfaction and therapeutic tolerance of Multigam 5% vs. Multigam 10% via:
  -Patient questionnaire
  -CTCAE v4.03
- Assess the care actions of the nursing staff
- Assess the satisfaction of the nursing staff (questionnaire)
- Patient characterization (age, gender, disorder)

## 3.4 Study design

Prospective - Observational

## 3.5 Study diagram



### 3.6 Study flowchart

| | Study visit 1 (Multigam 5%) | Study visit 2 (Multigam 10%) |
|---|---|---|
| Information and consent form | X | |
| Physical examination<br>AE scoring via CTCAE (v4.03) | X | X |
| Patient questionnaire | | X |
| Questionnaire concerning IVIg administration | X | X |
| Nursing staff questionnaire | | X |

## 4. Selection and exclusion of participants

### 4.1 Inclusion criteria

- Age ≥ 18 years
- Secondary immunodeficiency due to a hematological disorder
- Patient received at least 2x Multigam 5%
- No side effects during their last 2 Multigam 5% infusions
- Patient needs at least 2x Multigam
- Signed informed consent form

### 4.2 Exclusion criteria

- Patient received less than 2x Multigam 5%
- Side effects/intolerance for Multigam 5%
- Patient refuses to participate in the study

### 4.3 Expected duration of study

- Start-up: february 2017
- Recruitment: 4 weeks
- First participant: Q2 2017
- EC submission: Q2 2017
- Final reporting: december 2017

# 5. Study actions per visit

## 5.1 Study visit 1

- Sign information and consent form
- Multigam 5% administration
- Questionnaire concerning IVIg administration
- CTCAE v4.03 scoring during and after infusion

## 5.2 Study visit 2

- Multigam 10% administration
- Questionnaire concerning IVIg administration
- CTCAE v4.03 scoring during and after infusion
- Patient questionnaire
- Nursing staff questionnaire

# 6. Data collection

The following data will be stored in the eCRF:

-Patient characteristics (age, gender and disorder)
-Infusion time (hours)
-Hospitalization time at the oncology day center (hours)
-Safety reporting (collect AEs en SA's according to CTCAE v4.03 criteria)
-Questionnaire concerning IVIg administration (both visits, annex 2)
-Patient satisfaction questionnaire (last visit; annex 1)
-Nursing staff satisfaction questionnaire (last visit; annex 3)

# 7. Assessment of efficiency

**Primary endpoint:**

- **Comparing the infusion time and tolerance**
  Evaluate via time measurements, questioning and AE reporting during both treatments

**Secondary endpoints:**

- **Satisfaction and therapeutic tolerance**
  - Evaluation of satisfaction via questionnaire and tolerance via AE reporting
- **Safety**
  - Evaluate AEs and SAEs via CTCAE v4.03 criteria
- **Care actions**
  - Evaluate the number of nursing actions per patient
- **Satisfaction of nursing staff**
  - Evaluation of satisfaction via questionnaire
- **Patient characterization**
  - Characterization of patients (age, gender, disorder)

# 8. Assessment of safety

## 8.1 Specification, timing and registration of safety parameters

Side effects due to Multigam 5% and Multigam 10% infusion will be reported by the responsible physician and will be registered in the electronic patient record.

## 8.2 Procedures for registration and reporting of adverse events (AE)

8.2.1 Adverse event reporting

8.2.1.1 Adverse event definition

An adverse event (AE) is any unfavorable medical event in a patient or subject of the treated group during an experiment or study and does not necessarily have a causal relationship with the treatment. It may therefore be, regardless of the cause, a new additional disease, a deterioration of a similar disease, an injury or any additional impairment of the patient's health (including laboratory values). Any deterioration (this is any clinically significant unfavorable change in the frequency or intensity of an already existing condition) must be considered an AE.

8.2.1.2 Severity of the AE

To describe and assess the severity of an AE, the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03 is being used. For AEs that are not adequately described in the NCI-CTCAE version 4.03, the following scale is used:

| | | |
|---|---|---|
| Grade 1 | Mild | Transient or mild discomfort; no restriction in physical activity; no medical intervention/therapy required |
| Grade 2 | Moderate | Mild to moderate limitation of activity; limited help may be necessary; no or minimal medical intervention/therapy required |
| Grade 3 | Severe | Noticeable limitation of activity; limited help usually needed; medical intervention/therapy required; hospitalization is possible |
| Grade 4 | Life-threatening | Extreme limitation of activity; significant help required; significant medical intervention/therapy required; hospitalization or care in hospital probable |
| Grade 5 | Death | The event results in death. |

An AE or suspected adverse reaction (ADR) is "unexpected" if it does not appear in the list of the current Summary of Product Characteristics (SmPC) or if it is not listed on the specificity or severity observed.

Abnormal laboratory values must be reported as AE if medical intervention (transfusion, hydration ...) is required or if the event is deemed clinically significant by the attending physician.

8.2.1.3 Duration

The start and stop date will be reported for all AEs. The start date is the first date when the patient / subject was aware of the AE and the end date is the date when the event was completely resolved or returned to baseline.

8.2.1.4 Causality

The investigator must determine the relationship between the administration of the immunoglobulin replacement therapy and the occurrence of an AE as Not suspected or Suspected via following definitions:

| | |
|---|---|
| Not suspected | The temporal relationship between the adverse event and the administration of the immunoglobulin replacement therapy is not causal or small, or other medication, therapeutic interventions or underlying disorders provide sufficient explanation for the observed AE. |
| Suspected | The temporal relationship between the adverse event and the administration of the immunoglobulin replacement therapy is possibly causal and other medication, |

| | |
|---|---|
| | therapeutic interventions or underlying disorders provide insufficient explanation for the observed AE. |

8.2.1.5 Reporting procedure

All AEs are bundled into the eCRF starting from the patient having signed the information and consent form up to and including the last study visit.

All AEs considered to be related to the substitution therapy and all SAEs independent of their relationship must be followed up until they recover, recover with consequences, non-recovery (death by other cause) or death (by the SAE).

8.2.2 Serious Adverse Event reporting

A serious adverse event (SAE) is any AE that meets one of the following criteria:

- death

- life-threatening (this is when, according to the researcher, the patient is exposed to a direct risk of dying from the AE)

- requires hospitalization of patient or extension of existing hospitalization (hospitalization is defined as hospitalization of patient in hospital, regardless of length of stay)

- results in persistence of significant incompetence (a substantial disruption in the patient's ability to perform normal life functions)

- forms an important medical event

Important medical events are defined as events that do not directly threaten the life of the patient or result in death, hospitalization or incompetence, but which do endanger the patient or require medical or surgical intervention to avoid one of the consequences above.

Each SAE, independent of the causal link, that occurs after the patient has signed the information and consent form until the last study visit, must be reported to the sponsor. Each SAE report must be reported to the sponsor within 24 hours of awareness and also by using the Serious Adverse Event form in the eCRF.

# 9. Statistics

## 9.1 Sample size

For this descriptive, semi-quantitative study, the sample size is determined on 30 patients. Based on data in the package leaflet, we expect that the infusion time for Multigam 10% will be shorter than for Multigam 5%. This sample size will also be sufficient to correct for any variability as a result of nursing activities. A sample of 30 patients is sufficient to detect mild side effects. If, unexpectedly, more side effects occur with Multigam 10% administration, we will extend the sample size through an amendment and investigate this further. To evaluate the satisfaction of the patients and the nursing staff, 30 patients are also sufficient to correct for any missing values.

## 9.2 Analysis

The results are reported quantitatively (number of care actions, infusion and hospitalization time) and qualitatively (patient and nursing staff satisfaction). For the number of care actions, infusion time and hospitalization time, a T-test will examine whether both datasets (Multigam 5% and Multigam 10%) differ significantly from each other. The 95% confidence interval will also be determined and Cohen's d will be calculated to estimate the magnitude of the difference between the two variables (effect size, estimate the strength of the difference). For the satisfaction of patients and nursing staff, descriptive statistics will be used.

# 10. Direct access to source data and documents

The researcher / institution will provide direct access to source data and other documents. This access can consist of study-related monitoring, audits, EC review and statutory inspections.

# 11. Ethical and regulatory compliance

The research will be conducted in accordance with the principles of the Helsinki Declaration (current version), the principles of GCP and in accordance with the appropriate legal requirements. This protocol and all related documents will be submitted for review by the Ethics Committee.

The research will be conducted in accordance with the principles of the Helsinki Declaration (current version), the principles of GCP and in accordance with the appropriate legal requirements. This protocol and all related documents will be submitted for review by the Ethics Committee.

The study can and will only be conducted on the basis of prior consent, by the patient or the legal representative, to participate in the study. The participating site will obtain a signed informed consent

document (ICD) for each patient before registering patients and taking part in the study in accordance with the prevailing legislation, regulations and, if necessary, the approval of the (local) Ethics Committee. The participating site will retain the ICDs in accordance with the requirements of the relevant regulatory bodies and laws.

The researcher and the participating site will treat all information and data related to the study as confidential and will not disclose such information to third parties or use the information for any other purpose than the execution of the study. The collection, processing and disclosure of personal data, such as the health of patients and medical information, is subject to compliance with the prevailing protection and processing of personal data (Directive 95/46 / EC and Belgian law of December 8, 1992 on the protection of Secrecy in connection with the Processing of Personal Data).

With **coded** data, a link remains between the data and the individual who provided the information. The research team is obliged to protect the data against disclosure outside the research in accordance with the terms of the research protocol and the informed consent document. The patient name or other items that can be used for identification must be stored separately from the research data and replaced with a unique code to create a new identity for the patient. Note that encrypted data is not anonymous.

## 12. Data handling and management

As part of the responsibilities associated with participation in the study, the researcher agrees to maintain accurate eCRFs and source documents. The researcher or delegate must enter all results collected during the study into eCRFs.

## 13. Publication policy

The results of this study will be published as an abstract or article in which a co-authorship is offered to everyone who has made a significant contribution to the writing of the protocol, the execution of the study and the processing and interpretation of the results. The principal investigator has final responsibility concerning the publication.

## 14. Insurance/compensation

In accordance with the Belgian legislation on experiments on human persons of May 7, 2004, the Sponsor will without fault assume the responsibility of any damage to a study patient, both directly and indirectly related to participation in the study, and will compensate provide through their own insurance.

## 15. Financial aspects

Both Multigam 5% and Multigam 10% are commercially available and are prescribed according to the formulary.

## 16. References

Chinen, J. and Shearer, W. (2008) '6. Secondary immunodeficiencies, including HIV infection',*Journal of Allergy and Clinical Immunology*, 121(2), pp. S388–S392. doi: 10.1016/j.jaci.2007.06.003.

Cooper, M.D. (2003) 'Immunodeficiency disorders', *Hematology, 2003(1)*, pp. 314–330. doi: 10.1182/asheducation-2003.1.314.

Friman, V., Winqvist, O., Blimark, C., Langerbeins, P., Chapel, H. and Dhalla, F. (2016) 'Secondary immunodeficiency in lymphoproliferative malignancies', *Hematological Oncology, 34(3)*, pp. 121–132. doi: 10.1002/hon.2323.

# 17. Annex

**Annex 1: Patient questionnaire**

| | Strongly disagree (1) | Disagree (2) | Neutral (3) | Agree (4) | Strongly agree (5) |
|---|---|---|---|---|---|
| **I experienced fewer side effects with Multigam 10%** | | | | | |
| **I experienced time gain with Multigam 10%** | | | | | |
| **I will therefore have a more productive day** | | | | | |
| **For my own situation I am in favor of using Multigam 10%** | | | | | |

**Annex 2: Questionnaire concerning IVIg administration (to be filled in by nursing staff)**

| | **Multigam 5%** |
|---|---|
| **Infusion time (..hour..minutes)** | Start: …… h …… min<br>Stop: …… h …… min |
| **Number of care actions** | |
| | **Multigam 10%** |
| **Infusion time (..hour..minutes)** | Start: …… h …… min<br>Stop: …… h ……. min |
| **Number of care actions** | |

Care action means both the increase or decrease of infusion rate and any other intervention due to intolerance / complication.

**Annex 3: Nursing staff questionnaire**

| | Strongly disagree (1) | Disagree (2) | Neutral (3) | Agree (4) | Strongly agree (5) |
|---|---|---|---|---|---|
| **I have been able to plan patients more efficiently with Multigam 10%** | | | | | |
| **I have experienced time gain with Multigam 10%** | | | | | |
| **I am in favor of using Multigam 10%** | | | | | |