Additional file (appendix)

APPENDIX MATERIAL 1: Policy and procedures

Adverse event definition

Adverse events (AEs) include suspected adverse drug reactions, other medical experiences, regardless of their relationship with the intervention drugs, such as injury, surgery, accidents, extensions of symptoms or apparently unrelated illnesses, and significant abnormalities in clinical laboratory values, psychological testing or physical examination findings. Those medical conditions related to the disease under study whose changes during the study are consistent with natural disease progression, or which are attributable to a lack of clinical efficacy of the study interventions, are not considered as AEs and will not be recorded in the case report forms. All other medical conditions that are present at baseline will not be considered as AEs unless a worsening will occur. In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure will be considered an AE rather than the procedure itself. In case of a fatality, the cause of death will be considered an AE, and the death will be the AE "outcome".

Severity of adverse events

The severity of AEs will be defined according to the following categorization: *Grade 1* Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. *Grade 2* Moderate; minimal, local or non invasive intervention indicated; limiting age-appropriate instrumental activities of daily living. *Grade 3* Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living. *Grade 4* Life-threatening consequences; urgent intervention indicated. *Grade 5* Death related to AE.

Causal relationship with the study intervention

The relationship of AE to the study intervention will be considered: *probable*, if a causal relationship is clinically/biologically highly plausible and there is a plausible time sequence between onset of the AE and administration of the investigational product, and there is a reasonable response on withdrawal (i.e., interruption of the infusion); *possible,* if a causal relationship is clinically/biologically plausible and there is a plausible time sequence between onset of the AE and administration of the investigational product; *unlikely,* if a causal relationship is improbable and another documented cause of the AE is most plausible; and *unrelated*, if a causal relationship can be definitively excluded and another documented cause of the AE is most plausible.

Eliciting Adverse Events

Data on AEs will be obtained at scheduled or unscheduled study visits, based on information spontaneously provided by the subject and/or through questioning of the participant. Adverse event data may also be obtained from subject diary cards, but information thus collected must be reviewed and assessed medically before it is transcribed to the case report form. If a physician not involved with the study sees a participant in relation to an AE, the investigator will make every effort to contact the treating physician in a timely manner in order to obtain all information necessary to appropriate reporting of the event.

Serious adverse events

Any serious AE requires expedited reporting to the sponsor safety department, regardless of its relationship to the study intervention. A serious AE is defined as an AE that at any dose results in death is life threatening, is a congenital anomaly or birth defect, results in persistent or significant disability or incapacity and/or requires or prolongs inpatient hospitalization. Hospital admissions for intervention administration, for surgery planned before study entry, for social reasons or for normal disease management (including treatment adjustment) are not to be considered as serious AE according to this criterion. Also medically important conditions, which may not be immediately life threatening or result in death or hospitalization, but are clearly of major clinical significance, have to be considered as serious AE.

Reporting to the institutional review board/independent ethics committee

The investigator will comply with any applicable requirements related to the reporting of serious AEs involving his/her subjects to the Independent Ethics Committee (IEC) that approved the study. In particular, all deaths will be promptly reported to the IEC that approved the study.

In accordance with ICH GCP guidelines, the sponsor will inform the investigator of "findings that could affect adversely the safety of subjects, impact the conduct of the trial or alter the IEC's approval/favorable opinion to continue the trial." In particular and in line with respective regulations and the sponsor policy, the sponsor will inform the investigator of AEs that are both serious and unexpected (i.e. unlisted as per the Ofatumumab or Rituximab Pharmaceutical Company Core Safety Information) and are considered to be possibly or probably related to the administered product by the investigator/reporter. The investigator will keep copies of these safety reports in the investigator file. National regulations with regards to safety reports notifications to investigators will be taken into account. Unless clearly defined otherwise by national or site-specific regulations, and are duly documented, the responsible investigator will promptly notify the concerned IEC of any safety reports provided by the sponsor and provide copies of all related

correspondence to the sponsor. Only when specifically required by regulations, will the sponsor provide appropriate Safety reports directly to the concerned IEC and maintain records of these notifications.

APPENDIX MATERIAL 2: Consent and confidentiality

Consent or assent

Before a children can participate in the study, her or his parents/legal tutor must give written informed consent and the subject provide her/his assent as appropriate for the age. The informed consent process will be in accordance with International Council for Harmonization and Good Clinical Practice, the Declaration of Helsinki and local regulatory requirements. Parents/tutor and minor subject Informed Consent/Assent Forms will be based on a master document provided by the G. Gaslini Institute for submission to the Independent Ethics Committee.

Confidentiality

The investigator will ensure that the subjects' anonymity is maintained. On the case report forms or other documents submitted to the principal investigator, participants will not be identified by their names, but by their assigned identification number and initials. If participant names are included on copies of documents submitted to the principal investigator, the names will be obliterated and the assigned subject numbers added to the documents.

The investigator will keep a separate log of subjects' identification numbers, names, addresses, telephone numbers and hospital numbers (if applicable). Documents not for submission to the principal investigator, such as signed informed Consent /Assent Forms, will be maintained in strict confidence by the investigator.