etc.) or any liability under this agreement regarding the National Co-Sponsor's responsibilities and obligations.

4.7. The Sponsor reserves the right to audit the authorised National Co-Sponsor and/or the National representative(s) and the sites for the purpose of compliance with international regulation, national laws and standards (see section 2) in the agreed region on written notice. The National Co-Sponsor will allow regular monitoring and scheduled audit visits in own facilities and in the sites in accordance with GCP guidelines and as required by national/international Authorities. Any such monitoring and audits are to take place at times mutually agreed during business hours and subject to such reasonable conditions relating to occupational health and safety, security and confidentiality as the National Co-Sponsor may require. After consultation with the Sponsor Immunomedics may audit independently in cases concerning primarily safety issues related to Epratuzumab.

4.8. Presence on site is guaranteed to both Parties in case of inspections by national/international Authorities in the agreed region. Any documents of, for and about the inspection will be shared among the Parties.

4.9. The National Co-Sponsor will oblige any investigator, site and subcontractor in the agreed region to cooperate in performing audits or inspections according to 4.7 and 4.8. The Sponsor will, as soon as it becomes aware, advise the National Co-Sponsor of the cessation elsewhere of any trial also investigating the **IMP** or the withdrawal of the said **IMP** from any other market for safety reasons.

4.10. The Sponsor will notify the National Co-Sponsor of any adverse events (including serious adverse events) that occur during the course of the Trial including at overseas sites which may require alteration of the conduct of the Trial, or which may affect the rights, interests, safety or well-being of the participants in the **Trial**.

4.11. The Sponsor will cooperate with the National Co-Sponsor and/or the responsible IEC/IRB in investigating any adverse event (including serious adverse event) arising out of or in connection with the **Trial**.

4.12. The National Co-Sponsor has to certify to the best of his knowledge that he did not and will not use in any capacity the service of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act 1992 and as amended in connection with the trial.

4.13. The National Co-Sponsor will help the Sponsor in collecting from all investigators in the agreed region financial disclosure forms that are required by the FDA under 21 CFR Part 54 to the United States Food and Drug Administration or may become applicable with respect hereto. The National Co-Sponsor will oblige any investigator to supply resp. update such forms during the Trial and for 1 year thereafter.

4.14. Instead of using the MARVIN-System as a remote-data-entry (RDE)-System and Database Japan will make use of their proprietary Ptosh System due to legal obligations. The outlines of the procedures of integrating and reconciling the data from Ptosh and MARVIN and of immediate access to safety data in both EDC-systems are recorded in attachment 4.

5. LIABILITY and INDEMNITY

5.1. The National Co-Sponsor takes out adequate clinical trial insurance as required by applicable regulatory requirements to provide compensation to participants in the trial suffering injury or death or loss caused by the administration of the **IMP** or any clinical intervention or procedure carried out in accordance with the Protocol and all legal requirements laid down by regional regulations. This principle regulation does not prevent the Sponsor from offering a trial-wide solution for adequate insurance in the region.

5.2. According to the decentralized setup of the Trial and also with regard to the obligation in 4.5 liability issues reside first with the National Co-Sponsor being the qualified (legal) person for the agreed region and for the application of its laws in regard to the performance of the Trial. Therefore the National Co-Sponsor shall indemnify, defend and hold harmless the Sponsor and its Representatives, its sites and investigators engaged in the Trial from and against any claims, causes of action, lawsuits, liability, damages and costs that are based upon injury and damage (including death) to any person participating in the Trial in the agreed region. This indemnification also covers claims which are not covered by or exceed the range of the clinical trial insurance which the National Co-Sponsor arranged for according to 5.1..

5.3. The Sponsor shall indemnify, defend and hold harmless the National Co-Sponsor and its Representative and its sites and investigators engaged in the Trial from and against any claims, causes of action, lawsuits, liability, damages and costs that are based upon injury and damage (including death) to any person participating in the Trial in the agreed region to which injury and damage is sustained as a direct result of defects in the design of the Trial unless the injury results from:

5.3.1. a) Failure to use the trial drug in accordance with the Protocol;

5.3.2. b) negligence or wilful misconduct on the part of participating institutions or its sites or investigators;

5.3.3. c) a breach of any applicable law or regulation by participating institutions, its sites or investigators.

5.4. The National Co-Sponsor shall notify the Sponsor promptly upon becoming aware of a claim for which indemnification may be sought hereunder and cooperate with Sponsor in its investigation and defence of any such claim.

6. CONFIDENTIALITY

6.1. Both Parties will ensure the confidential treatment of and not to transfer to third parties any confidential information that will be disclosed to any personnel working in or for the **Trial** eg. Personnel in **Trial** sites in the agreed region, investigators, employees, staff members, agents, authorized representatives, monitors, students or other third persons in the course of the **Trial** and/or afterwards. This obligation shall last for the time of the **Trial** being performed and up to 10 years after its official planned or its unplanned end. Both parties ensure that the above mentioned obligation to confidentiality is extended to and made aware to all before mentioned personnel in similar terms.

6.2. This obligation to confidentiality shall not apply to

- information that was already in the possession of the Parties in receipt of the confidential information concerned before disclosure (except as a result of a breach of this agreement);
- information obtained independently from a third party source that was free to disclose the same;
- information that is in the public domain (except as a result of a breach of this or any other agreement);
- information that is required to be disclosed by law or in fulfilling a legal obligation (eg. Patient insurance) or by any governmental or regulatory authority (eg: Ethics Committees and/or Competent Authorities).
- information that is developed by or on behalf of the National Co-Sponsor entirely independent of any disclosure hereunder
- information the disclosing party has a written permission to transfer by the proprietor of the information and this permission was obtained before transferring
- information as part of a publication published according to section 7

6.3. The Manufacturer of the IMP (Immunomedics) will receive reports on the progress of the **Trial**, a report on the concomitant research projects, all Safety data related to the Epratuzumab arm of the **Trial,** the Safety Monitoring Board reports and the annual Development Safety Update Reports (DSUR). Reports on Monitoring are provided to decide on the necessity of additional Monitoring activities financed by Immunomedics. At the end of the **Trial** Immunomedics is entitled to review the entire trial data set to decide whether they want to buy it. The regulations for confidentiality do not apply to the transfer of these informations to Immunomedics.

6.4. For the purpose of this **Trial** confidential information means

- information which the Parties receive from each other or from others in relation to the **Trial** and which is in writing designated "confidential" (or with similar wording), or the nature of such information itself and/or the circumstances of such information's disclosure reasonably indicate that such information is considered confidential or, if disclosed orally, visually or physically, is designated "confidential" (or with similar wording) at the time of disclosure, or the nature of such information itself and/or the circumstances of disclosure of such information reasonably indicate that such information is considered confidential.
- all information collected in the course of, resulting from, or arising directly out of the conduct of the **Trial,** whether at a study site or elsewhere;
- the protocol, information relating to the protocol, study materials and investigational product; methodology, trade secrets, processes, sequences, structure and organisation of the **Trial**;
- Information about the **IMP**. This is regarded as proprietary information of Immunomedics.
- information, know-how, trade secrets, ideas, concepts, technical and operational information, scientific or technical processes or techniques owned by any participating institutions or their respective personnel before actively entering into this **Trial** ("background");
- information concerning the business affairs of the Parties of this Agreement or its affiliates;

6.5. The National Co-Sponsor must ensure in the agreed region that any personal information arising from the **Trial** regarding **Trial** participants or employees, agents or authorised representatives of

the National Co-Sponsor, is collected, stored, used and disclosed in accordance with the local/National law of Privacy.

7. OWNERSHIP AND USE OF DATA - PUBLICATION

7.1. The collected study data will become or are property of Charité as the chosen **Sponsor** and will be centrally managed within the **Trial**. This also applies to the data from Japan being merged with the data from MARVIN-System as stated in 4.14 above and in attachment 4.

7.2. The Sponsor will not make use of the study data for its own purposes or without prior consent of the **Trial Committee**.

7.3. Publication and other dissemination of results of the **Trial** shall be coordinated by the **Trial** Committee and the Coordinator. It is planned and agreed to publish the results of the **Trial** in a timely manner (and in any event within 15 months) after its completion. This is also the basis for all participating centres in the **Trial**. The National Co-Sponsor shall ensure that all participating centres in the agreed region shall follow this Agreement and therefore shall not publish any part of the data reported from its centres before the final publication of results from the entire **Trial** has been published.

7.4. The Sponsor has given the right to review any manuscript according to 7.3 to the supplier of the **IMP**, which is the company Immunomedics. Therefore the **Sponsor Representative** is obliged to send the **Manufacturer** a copy of the manuscript to be submitted, and shall allow the Manufacturer 60 days from the date of mailing for the review to comment, to identify any proprietary information belonging to Immunomedics to be deleted and to determine whether patent protection should be sought prior to publication for any subject matter. The **Manufacturer** shall give written notification of such determination to the Sponsor Representative and send a proposal of how to solve the issue and within what timelines. The parties agreed that no more delay of publication than 60 days after giving notice through the **Manufacturer** are appropriate. All other forms of publication eg. Posters which might have shorter time intervals on its way to publication or its withdrawal will be dealt with in analogous application of the before mentioned rules.

7.5. The National Co-Sponsor and any participating site in the agreed region may use and present any information concerning the Trial for the purposes of internal training, education, evaluation or discussion without the consent of the Sponsor or the Trial Committee if the use of the data complies with the rules of confidentiality stated in confidentiality section of this agreement.

7.6. National Co-Sponsor agrees not to provide the Trial data to any third party or to use the Trial data in commercially sponsored research without Sponsor's prior written consent. National Co-Sponsor also agrees not to identify, either on a blinded or unblinded basis subjects from this Trial in order to benefit research conducted or sponsored by any third party without Sponsor's prior written consent. National Co-Sponsor agrees to impose the aforementioned obligations on its sites, investigators and subcontractors in the agreed region.

8. INTELLECTUAL PROPERTY

8.1. Each Party shall implement and undertake the conduct of the **Trial** in accordance with this Agreement (including its attachments) and shall bear sole responsibility for ensuring that in conducting and carrying out the **Trial** the parties and their personnel as described in clause 6.1 do not knowingly infringe third party intellectual property rights or background.

8.2. Similar to the regulation in the EU-Project, the **Sponsor** makes no claim for and shall not require the **National Co-Sponsor** or any participating centre to transfer or assign to the **Sponsor** any intellectual property generated out of results of the **Trial** or generated as a consequence of the conduct of the **Trial** in the agreed region and without any participation of the Sponsor in generating the IP. To keep track of all developments with regard to intellectual property issues throughout the **Trial** and to safeguard the rights of Immunomedics as already lined out in the preamble, the National Co-Sponsor and all participating investigators and all personnel in the agreed region working in the **Trial** have to consent

- to disclose fully and promptly to the Sponsor and to the National Co-sponsor any discovery or invention made by the Investigators or any personnel working in the **Trial** in the agreed region. According to his obligation to Immunomedics the Sponsor will transfer these disclosures to Immunomedics.
- to assign to Immunomedics all inventions which are linked to the use of the IMP Epratuzumab in the **Trial**, to its mechanisms, its side-effects or are by other ways or means caused by the IMP in trial setting. Immunomedics shall become the sole owner of this invention upon conditions directly agreed with the inventor resp. her/his institution and according to local law. There will be no claim for co-ownership in regard to these inventions.
- that in case of breach of the regulations about the IMP in section 4.2, the Protocol or any other trial-regulation Immunomedics will have the right to withdraw the IMP from the trial and to claim any results, discoveries or inventions out of such misuse.

The National Co-Sponsor will oblige all investigators and all other personnel in the **Trial** in the agreed region to accept these before mentioned obligations and to take all necessary steps in order to ensure fulfilling these obligations and to cooperate effecting the transfer of inventions directly to Immunomedics.

8.3. .The Sponsor reminds the National Co-Sponsor and agreed with him to give notice of the right of Immunomedics according to 7.4 to any site in the agreed region.

8.4. There is no claim from the Sponsor's side to any background owned by and no restriction to use it for the National Co-Sponsor, the participating centres or their respective personnel.

8.5. If any participating site in the agreed region and/or the National Co-Sponsor identify foreground capable of protection that does not fall under section 8.2 above, notice shall be given to the Sponsor and, if applicable, to the National Co-Sponsor. The Sponsor and the National Co-Sponsor however are not able to ensure that no other party in the **Trial** makes a claim for or does not require foreground resp. intellectual property rights to be transferred to him respectively to be owned jointly. The Sponsor will only help in finding a solution on joint ownership or disputes on intellectual property, but cannot be held responsible.

8.6.

If the National Co-Sponsor successfully applies for intellectual property rights in the results of the **Trial** or intellectual property generated as a consequence of the conduct of the **Trial** in the

agreed region that do not fall under 8.2 above then the National Co-Sponsor agrees to grant the Sponsor a non-exclusive licence to use (but not a right to sub-licence) such intellectual property.

8.7. Only in case that EU-funds from the IntReALL-Project serve for the main part of the costs incurred in conducting the **Trial** and all the investigators or other personnel working for the **Trial** in the agreed region do not want to apply for obvious possible intellectual property rights and if section 8.2 is not applicable the **Parties** shall secure that possible intellectual property rights shall be applied for and assigned to according to the EU-Consortium Agreement. The National Co-Sponsor agrees to execute or procure the execution by its employees, agents and representatives of any documents reasonably necessary to give effect to the assignment.

8.8. For the purposes of this Agreement:

8.8.1. intellectual property means all industrial and intellectual property rights, including but without limitation:

(a) patents, copyright, future copyright, trade business, company or domain names, rights in relation to circuit layouts, plant breeders rights, registered designs, registered and unregistered trademarks, know how, trade secrets and the right to have confidential information kept confidential, any and all other rights to intellectual property which may subsist anywhere in the world; and

(b) any application or right to apply for registration of any of those rights.

8.8.2. background means pre-existing information, techniques, know-how, software and materials (regardless of the form or medium in which they are disclosed or stored) that may be provided by one party or participant to the other for use in the **Trial** (whether before or after the date of this Agreement).

9. GENERAL PROVISIONS

9.1. This agreement may only be modified through a written notice signed by all Parties and specifically referring to this Agreement;

9.2. The invalidity of one or more provisions of this agreement does not affect the validity of the others. The invalid provision is to be replaced by a provision, which, in compliance with the legal prescriptions, suits the purpose best.

9.3. Subject to the consent of the National Co-Sponsor this agreement may be altered/amended or put onto a new basis if the Investigators change their form of organisation and found an association or a foundation/trust to pursue their purposes.

9.4. The intellectual property rights regulation may be changed by a new agreement.

10. CONSENT AND SIGNATURE

10.1. This Agreement contains the following Appendices:

1 Task Allocation List ("TAL")

2 Certificate of Authority

3 Protocol Abstract and documents in force

10.2. New appendices will become valid after signing by the parties.

By signing the page I agree to the terms of the agreement

For the **Sponsor** in Berlin: **Charité –Universitaetsmedizin Berlin**

Represented by

15.10.14

Fabian Hempel Date (dd-mmm-yyyy)

Director of Finance for the Faculty

Dr. Arend von Stackelberg 15.10.2014 Date (dd-mmm-yyyy)

Sponsor Representative

For the **National Co-Sponsor for Japan**

National Hospital Organization Nagoya Medical Center

Represented by: Dr Keizo Horibe

Director of Clinical Research Center 23.10.2014 Date (dd-mmm-yyyy)

Director of the Clinic of Pediatrics

Appendix 1

Task Allocation List (TAL)

	STANDARD RISK, as of Oct 14, 2014	A	B	C	D	E	F	G	H	I	K	L
1	Participants / Tasks — Table: Division of responsibilities: 1 primarily competent and responsible; 2 needs to be consulted; 3 needs to be informed	Sponsor Charité	National Coordinating Institution (NCI)	National Coordinating Investigator (NCI)	Local Sites	[illegible] UM	KKS	Mar-Vin-Group	Oxford	Immunomedics	Ptosh Group: JPLSG	Comments
2	for the country of JAPAN		Clinical Research Center, Nagoya Medical Center	Hidemi Toyoda			central service units				Japan central service unit: Operation Department of Clinical Research Center, Nagoya Medical Center	Lines written in grey colour deal with the investigational product (IMP) Epratuzumab, which is not yet established to be used within the trial in Japan. The parties have agreed to keep these regulations within the agreement in case the IMP becomes available in Japan.
3	**1 Study Preparation**											
4	Selection of the coordinating study site in the participating country	2	1	1								
5	Selection of the participating study sites in the participating country	2	1	1								
6	Search for external co-contractors (e. g. CRAs, pharmacy,...)	1	1	1								
7	System audit of all institutions who take over sponsor responsibilities or rather check quality certificates	1										
8	System audit of national Sites			1								
9	Organization of system audits on behalf of the sponsor	1										
10	Contract for sponsor delegation	1					1					
11	Contract of the between national coordinating Institution and local site/ investigator		1	1								Contract template in English provided by the Sponsor
12	Contract about services provided in the trial	1	1				1	1	1	1		in compliance with IntReALL work programme
13	study financing in the country	1	1									
14	study financing at local sites	3		1	1							
15	**2 Regulatory affairs**											
16	**2.1 Study documents**											
17	Protocol development	1	2	1								
18	Protocol (preparation, formal check)	1	2	1			1					formal check KKS (without biometry)
19	Preparation of patients informed consent (PIC)	1	2	1			1					formal check KKS, template provided by Sponsor
20	PIC local customisation	2	2	1	1							
21	PIC translations (organisation, QC)	2	2	1								
22	Preparation and allocation of the IMPD and IB	2								1		IMPD/ IB for Epratuzumab: Immunomedics
23	Obtain qualification, CVs and Financial Disclosure forms:											
24	- for the national coordinating Institution	2	1	1								
25	- for sites		1	1	1							
26	Application of patient insurance	2		1								
27	**2.2 Study reports / reporting system**											
28	periodic reports / final report	1	1	1			1					KKS for Germany
29	development safety update reports	1	3				1			1		
30	ownership of data	1				TC						follows EU-Grant regulations. T.b.d.
31	Preparation of status reports to the sponsor		1	1			national					
32	Publication	1	1	1		TC						publication of interim results through TC
33	**2.3 Submission**											
34	Application in VHP	1	2	2			1			2		
35	Preparation of applications for national approval (CA/IRB) and check list	2	1	1			2					part of the documents will be supplied centrally
36	Application at the IRB(s)	2	1	1	1		2					different in different countries
37	Application at the national Competent Authorities (CA, e.g. BfArM,PEI)	2	1	1			2					including queries of CA
38	scientific advice at EMA	2					2			1		for Epratuzumab only
39	Notification of the clinical trial to the local / national authority (ies)		1	1								follows national laws
40	Notification of the end or early termination of the CT to the IRB, competent and local authorities	2	1	1	1		2					
41	**2.4 Amendments**											
42	Preparation of amendments incl. changes in documents	1	2	2			1					
43	Application of amendments at the IRB and competent authority	2	1	1	1		2					including queries of CA
44	**3 Logistics**											
45	**3.1 Documents**											
46	Preparation and shipment of Trial Master File (TMF) according to ICH-GCP	2	2				1					1 TMF for each National Coordinating Institution
47	Preparation and shipment Investigator Site File (ISF) according to ICH-GCP in English	2	1									KKS will provide contents of ISF-version to NCRs
48	Coordination and Clearing of sub-contracts with other study sites	2	1	1			2					template will be offered by KKS
49	**3.2 Laboratory - Reference Laboratories**											
50	[illegible]	1					1			1		
51	Organization of national reference laboratories	2	1	1		TC						samples will be sent by local sites to the reference lab
52												
53	[illegible]									1		
54	[illegible]						2			1		
55	[illegible]									1		
56	[illegible]									1		
57	[illegible]									1		
58	[illegible]									1		[illegible]
59	[illegible]									1		[illegible]
60	[illegible]									1		
61	[illegible]									1		
62	[illegible]									1		[illegible]
63	[illegible]									1		
64	**4 Coordination**											
65	**4.1 Registration / Project organization**											
66	Registration of the CT (e. g. clinicaltrials.gov)	1										
67	Project organization - coordination of all participating parties	1	1			TC	national					and TC (Trial Committee)
68	**4.2 Meetings**											
69	Preparation and distribution of newsletters					TC						
70	Organization of telephone conferences incl. protocol					TC						
71	Organization of meetings incl. protocol					TC						
72	Organization/Coordination of sponsor meetings					TC						
73	Organization/Coordination of investigator meetings					TC						
74	Participation in investigator meetings					TC						
75	Follow up of meetings					TC						
76	**4.3 Study material / documentation**											
77	Maintenance and closure of TMF		1	1								
78	Maintenance and closure of ISF		1	1	1							
79	Organization of return/destruction of unused materials		1	1	1							
80	Sample storage incl. temperature control and documentation				1							
81	**5 Monitoring**											
82	Selection / employment of national monitors		1	1			2					
83	Preparation of the monitor manual	1					1					
84	Monitor training (as well as SOP training + GCP)		1	1								
85	Review monitor reports incl. post-processing		1	1			2					all critical findings need to be reported to Sponsor
86	Site monitoring visits incl. monitor reports		1	1								
87	Organization of monitor meetings (via telephone conference)	1	1	1			1					
88	Follow up and resolution of monitoring issues	1	1	1			1					escalation of findings / problems: First national, then Stackelberg/KKS
89	**6 Quality Management**											
90	**6.1 Development and training of SOPs**											
91	International and national coordination	1					1					development, review, approval, periodic update (national, international)
92	Statistics								1			
93	Data base								Marvin		Ptosh	see 7.1
94	Diagnostics								TC			

	STANDARD RISK, as of Oct 14, 2014	A	B	C	D	E	F	G	H	I	K	L
1	Participants / Task — Table: Division of responsibilities: 1 primarily competent and responsible; 2 needs to be consulted; 3 needs to be informed	Sponsor Charité	National Coordinators Representatives (NCR)	National Coord. group investigators	[illegible]	[illegible]	KKS	Marvyn Group	Oxford	Immunomedics	Pirsh Group: JPLSG	Comments
95	7 Data management / eCRF											
96	7.1 CRF/eCRF design and development of a database											Due to legal reasons Japan will use the Pirsh-database in Japan. Pirsh will apply/use the structure of the MARVIN-database. Evaluation and maintenance will be similar to the MARVIN-setup and is agreed between both teams. Data from both systems will be reconciled at least every 6 months by Oxford or on demand. For immediate reporting (e.g. pharmacovigilance) there are procedures in place and still available able to look into both systems. The same applies to central monitoring.
97	CRF design	1						1			1	
98	Setup of a dataset table	1						1			1	
99	Programming incl. plausibility checks (database and design of data entry forms)	1						1			1	
100	Validation of the data base and the data entry forms – with dummy data	1						1			1	
101	Preparation of a data management manual incl. data validation plan	1						1			1	
102	User and rights administration	1						1			1	
103	Data entry per patient				1			1			1	If not done by CRA on site: who coordinates documentaries?
104	Remote Data Entry (RDE) user support (specify details: e.g. hotline, training, training documents), eCRF training							1			1	
105	Database maintenance and change management	1						1			1	
106	Database administration	1						1			1	
107	Status reports							1			1	
108	7.2 Plausibility check											
109	Definition of plausibility checks							1			1	
110	Programming of plausibility checks							1			1	
111	Data clarification / query process							1			1	
112	Data cleaning process							1			1	
113	Data quality checks							1			1	
114	7.3 Data Management / Data Access											
115	administrative decision of data access	1				TC					2	Safety data open for immunomedics, contractually agreed
116	7.4 Data closure											
117	Closure of the database and handover to the biometrician	1				TC		1			1	procedures agreed between Pirsh and MARVIN
118	7.5 Safety database:											established within the MARVIN-system are [illegible]
119	AE / SAE Data entry				1							
120	8 Biometry											
121	8.1 Statistical planning of the study	1							1		3	
122	8.2 Registration/Randomization										1	
123	Generation of randomization codes (list, program)								1		1	
124	Performance of centralised randomization/registration by phone/fax	1							1		3	need to involve Marvin and take over result
125	8.3 Interim analysis (specify number of analysis)											
126	Statistical analysis plan	2				TC			1		3	
127	Performance of analysis incl. preparation of tables, listings and figures (specify details)	2							1			Pirsh will be suited to meet the demands of MARVIN and of the team at Oxford to deliver the Japanese data
128	Validation of the analyzer								1			
129	8.4 Final analysis											
130	Statistical analysis plan	2							1		3	
131	Validation of the analyzer								1			
132	Performance of analysis incl. preparation of tables, listings and figures (specify details)	2							1			Pirsh will meet same demands as MARVIN for data transfer to Oxford
133	Statistical report	2							1		3	
134	9 Pharmacovigilance											
135	9.1 Safety infrastructure / surveillance											
136	development of international safety surveillance management	2					1					
137	Safety manual + SAE-Form		1	1			1					national adaption through NCI necessary
138	Line Listing						1					
139	SAE processing Germany						1					
140	SAE processing international	2	1	1			2					tbd
141	SAE documentation/Notification/Follow-Up	2	2		1		2					SAE reporting on Immunomedics is part of contract
142	SUSAR qualification/documentation/Notification/Follow-Up	1				DSMC	1					
143	SAE case narratives (writing)				1							
144	expedited reporting to IRB / Cas	2	1	1			2					
145	Pregnancy report form if necessary				1							
146	9.2 DMC											
147	Establishing / composition of DMC	1				TC						
148	working procedure of DMC	1										
149	preparing the meetings and (safety) data processing	1					1		1			
150	DMC reports			3			1		1			
151	10 Archiving											
152	Archiving of the TMF/essential documents		1	1								electronic archiving of documents, storage conditions, time period
153	archiving of ISF				1							
154	Electronic archiving of the database							1	1		1	Database versions and data

Appendix 2

Certificate of Authority

Charité – Universitaetsmedizin Berlin – as the Sponsor for the trial

IntReALL SR 2010
International study for treatment of standard risk childhood relapsed ALL 2010. A randomized Phase III Study conducted by the Resistant Disease Committee of the International BFM Study Group

herewith delegates to the ... as the National Co-Sponsor duties as stated and indicated in the Task Allocation List (appendix #1) AL to the National Co-Sponsor: Keizo Horibe, 4-1-1 Sannomaru Naka-ku, Nagoya, Aichi 460-0001 Japan.

The National Co-Sponsor is hereby given authority to represent the Sponsor for the agreed region Japan, all participating institutes in Japanese Pediatric Leukemia/Lymphoma Study Group vis-á-vis third parties and to perform all the duties indicated in the TAL to be assigned to or performed by the National Co-Sponsor and equally from all applicable legal provisions in their recent version, as far as the clinical trial stated above is concerned.

This Authority is given until the completion/termination of the clinical trial or the revocation of the Authority to represent.

For the **Sponsor Charité**
Dr. Arend von Stackelberg

Represented by:
Name

15.10.2014
Date (dd-mmm-yyyy)

Appendix 3

Protocol outline and documents in force

Protocol outline, based on Synopse Version 1.8 from Nov. 1, 2012

Background

Though survival of children with acute lymphoblastic leukemia (ALL) has considerably improved over the past few decades, relapsed ALL remains a leading cause of mortality in children with cancer. Given the rarity of the disease, prospective clinical studies need to be coordinated within an international cooperative group such as the International BFM Study Group (I-BFM-SG). Within the group, over the last few years two different treatment protocols, ALL-REZ BFM 2002 and ALL R3 have been used by most Study groups for treatment of relapsed ALL. Both studies have produced comparable results. In both Studies patients were risk stratified based on duration of first remission, immunophenotype, site of relapse and post induction minimal residual disease (MRD) levels to identify patients who should be transplanted. For non-HR or standard risk (SR) patients both ALL-REZ BFM 2002 and ALL R3 have achieved better results than previous studies. Both protocols have however been primarily used in patients relapsing off different frontline protocols. Thus there is need for a prospective randomized controlled comparison across the Study groups (randomization 1), before a uniform backbone for further studies can be developed. In SR patients, survival may be improved by modifying the consolidation therapy using targeted non-myelotoxic drugs. As ideal candidate, epratuzumab (humanised chimeric anti CD22 antibody) will be randomly tested in combination with conventional chemotherapy (randomization 2). CD22 is well expressed in all B-cell precursor ALL cells. Epratuzumab has been developed in combination phase I and II studies in childhood relapsed ALL and has shown a favourable toxicity profile and moderate antileukemic activity.

Objectives:

Primary objectives:

- Overall: Improvement of event-free survival (EFS) probabilities in childhood relapsed ALL
- Randomisation 1: EFS of Arm A (ALL-REZ BFM 2002) versus B (ALLR3) in SR patients
- Randomisation 2: Influence of epratuzumab on EFS in consolidation of SR patients

Secondary objectives:

- OS of Arm A (ALL-REZ BFM 2002) versus B (ALLR3) in SR patients
- Influence of epratuzumab on OS in consolidation of SR patients
- Rate of second complete remission (CR2) of Arm A versus Arm B
- Rate of SCT performed in Arm A versus Arm B
- Toxicity of randomized SR arms A versus B
- Toxicity of consolidation with versus without epratuzumab
- Improvement of MRD reduction during consolidation with versus without epratuzumab
- Rate of MRD negativity prior to SCT with Arm A vs. Arm B
- Rate of MRD negativity prior to SCT after consolidation with versus without epratuzumab
- Pharmacokinetic of epratuzumab in context with arm A and arm B

Risk group stratification:

Definition of standard risk group:

Late isolated B-cell precursor (BCP) bone marrow (BM) relapse, late/early combined BCP BM relapse, any late/early isolated extramedullary (EM) relapse

Study design:

The IntReALL SR 2010 Study is an inter-group, international multi-centre, treatment optimization Study. It contains the followings branches:

- SR induction/consolidation arm A (ALL-REZ BFM 2002, arm protocol II-IDA) versus B (UK-ALL-R3, arm MITOX): prospective, randomized, open label, phase III Study
- SR consolidation +/- epratuzumab: prospective, randomized, open label, phase III Study

Primary endpoints:

- SR induction/consolidation ALL-REZ BFM 2002 versus UK-ALL-R3 (randomisation 1): 10% pEFS superiority of arm B above a 65% pEFS at 4 years of arm A
- SR consolidation +/- epratuzumab (randomisation 2): 10% pEFS superiority of the arm with epratuzumab above an expected 74% pEFS at 4 years of the standard arm

Statistical analysis:

Analysis of primary outcomes:

- SR induction/consolidation: a cox analysis of treatment effect on EFS adjusting for the factors used in the randomisation stratification
- SR consolidation +/- epratuzumab: a cox analysis of treatment effect on EFS adjusting for the factors used in the randomisation stratification

Analysis of secondary outcomes:

- SR induction/consolidation: comparison of OS, toxicity, rate of CR2, and rate of MRD between treatment groups
- SR consolidation +/- epratuzumab: comparison of OS, toxicity, MRD levels, rate of MRD and evaluation of pharmacokinetic parameters of Epratuzumab

Sample size:

Number of SR patients expected per year: 200
Number for SR induction/consolidation: 306/arm; recruitment 4 years
Number for SR consolidation: 286/arm; recruitment 4 years

Diagnosis and criteria for inclusion/ exclusion:

Inclusion criteria:

- Morphologically confirmed diagnosis of 1st relapsed precursor B-cell or T-cell ALL
- Children less than 18 years of age at inclusion
- Meeting SR criteria: late isolated or late/early combined BCP BM relapse, any late/early isolated extramedullary relapse
- Patient enrolled in a participating centre
- Written informed consent
- Start of treatment falling into the Study period
- No participation in other clinical studies 30 days prior to Study enrolment that interfere with this protocol, except studies for primary ALL

Inclusion criteria specific for the epratuzumab randomization:

- Precursor B-cell Immunophenotype of ALL
- M1 or M2 bone marrow status after induction

Exclusion criteria:

- BCR-ABL / t(9;22) positive ALL
- Pregnancy or positive pregnancy test (urine sample positive for β-HCG > 10 U/l)
- Sexually active adolescents not willing to use highly effective contraceptive method (pearl index <1) until 2 years after end of antileukemic therapy
- Breast feeding
- Relapse post allogeneic stem-cell transplantation
- The whole protocol or essential parts are declined either by patient himself/herself or the respective legal guardian
- No consent is given for saving and propagation of pseudonymized medical data for Study reasons
- Severe concomitant disease that does not allow treatment according to the protocol at the investigator's discretion (e.g. malformation syndromes, cardiac malformations, metabolic disorders)
- Karnovsky / Lansky score < 50%
- Subjects unwilling or unable to comply with the Study procedures
- Subjects who are legally detained in an official institute

Test drug/treatment, dose and mode of administration:

- SR arm A (ALL-REZ BFM 2002 arm Prot II-IDA): Induction: SIA (F1, F2); Post induction: SCA1 and SCA2 ± epratuzumab (8x360mg/m^2/ 1 hrs IV weekly, week 5-12), 5 courses SCA3-7 (R1/2/1/2/1), 24 months maintenance (6MP, MTX) with 6 x TIT / 4 weeks. Cranial irradiation 18Gy for CNS relapse.
- SR arm B (UK-R3, arm mitoxantrone): Induction: SIB (phase I); Post induction: SCB1 and SCB2 (R3-consolidation and intensification) ± epratuzumab (8x360mg/m^2/ 1hrs IV weekly, week 6-13), 2 courses SCB3-4 (R3-interim maintenance 1 and 2), 24 months maintenance (6MP, MTX, 4-weekly VCR/DEX/IT reinduction pulses). Cranial irradiation 18 for CNS disease.
- SCT indications: Any donor Arm A with MRD ≥ 10-3 after SIA, arm B with ≥ 10-4 after SIB. Matched donor any early combined, isolated extramedullary relapse or patients without MRD results. SCT is scheduled at week 16

Documents in force

1. Complete Study protocol (IntReALL SR 2010 version 1.8 of November 1st 2012) and electronic Case Report Forms (CRF)
2. Statistical Analysis Plan, Version 3.2 dated July 12th 2012
3. Investigator's Brochure Epratuzumab dated March 22nd 2012
4. IMPD- Quality Data Epratuzumab dated March 9th 2012
5. PDF file for EudraCT
6. XML file for EudraCT
7. Scientific Advice for Epratuzumab, cover letter dated June 21th 2012
8. Sponsors Response to List of Grounds for Non-acceptance

9. Immunomedics Manufacturing Authorization
10. Immunomedics QP declaration September 26th 2012
11. Epratuzumab SUSAR List June 2010 to September 2012
12. Summary of Interactions as listed in SmPCs, version 1.0 dated November 8th 2012
13. Applications to National Ethics Committees and Approvals
14. Applications to Competent National Authority and Approval
15. Patient and parent information and informed consent form in the national language
16. Insurance statement, i.e. provision for the indemnity or compensation in the event of injury or death attributable to the clinical Study and any insurance or indemnity to cover the liability of the investigator and (co-) sponsor on a national bases
17. Copy of importer authorisation where needed
18. Curriculum vitae /other documents evidencing the qualifications of investigators and sub-investigators

APPENDIX 4: Outline of the access to and the synchronisation and reconciliation of the PTOSH- and the MARVIN System, both employed in the IntReALL-SR 2010 trial

Based on the consultation at the IntReALL 2010 SR Month 24 meeting on 2013.10.31-2013.11.1, attended by Martin Zimmermann, Cristian Ciria, Sharon Love, Tom Groeneveld, Toshiki Saito

General information on the two systems:
PTOSH and MARVIN are both using English as the working language.

Dataset format:
All data fields within both systems appear in the same context in each EDC-system, have the same type, description and code lists and are thus identical.
The data of both systems will be cleared at the end of the study before the transfer of the data to the statistical center. All query-management will therefore be done within the both systems. There will be no transfer of data between the two EDC-systems.
The format for the dataset transfer will be the odm-based xml format for both.
Both systems will transfer their finalized data-set to the statistical center in Oxford.

Patient ID:
Patient's ID is just an incremental number in Ptosh, whereas country code + center code + incremental number is used in MARVIN. The latter will be used for statistics in Oxford.
Ptosh Patient's IDs will therefore be converted to MARVIN-base in Oxford.

Randomization:
Variable block size randomization will be performed in MARVIN with stratifying factors of country groups (4) and site of relapses (3, 3 x 4 = 12 groups) for the first randomization.
Japan has its own stratum within the setting of this trial, randomization will be performed within Japanese cases with the Japanese EDC-system (Ptosh).
Japan will not participate in the second randomization, as Epratuzumab is not yet available in Japan.
At the start of the trial there are procedures in place for the central paper/fax based randomization. As soon as randomization becomes available within the EDC/data base systems going productive the paper based randomization will become the backup-system.

Progress reports:
The local Data Committee in Japan will submit all data regularly (for the startup-phase of the trial every 6 months) or on special request by the Sponsor representative to the Centre for Statistics in Medicine, Oxford. The statistical center will prepare the statistical part of the Data Safety Monitoring reports.

Safety issues / Pharmacovigilance/ Central Monitoring/Availability:
The central trial office at Charité will have direct and immediate access to both systems and

- will be in charge of all safety issues within the trial, the team is given all rights to access both systems thus following the established routines for central SAE-/SUSAR – Management and will be supported by the statistics in Oxford as well
- will be in charge of technical aspects, maintaining a high availability of the systems
- will regularly monitor the progress of the trial and perform central monitoring

Content Trial Master File National

1 Correspondence	Filed	File No.	Comment
1.1 XX	☐	I	
1.2 XX	☐	I	
2 Meetings	**Filed**	**File No**	**Comment**
2.1 XX	☐	I	
2.2 XX	☐	I	
3 Quality management	**Filed**	**File No.**	**Comment**
3.1 Standard Operating Procedures (SOPs)	☒	I	
3.2 Work Instructions	☒	I	
4 Planning and Progress	**Filed**	**File No.**	**Comment**
4.1 XX	☐	I	
5 Financial and Legal	**Filed**	**File No**	**Comment**
5.1 Correspondence	☐	I	
5.2 Clinical Trial Agreements	☐	I	
5.3 Confidentiality Agreement	☐	I	
5.4 Budget	☐	I	
5.5 Contracts (other than local trial sites)	☐	I	
6 Study team	**Filed**	**File No.**	**Comment**
6.1 Contact list	☒	I	Please complete with your national site contacts.
6.2 Delegation of Responsibilities	☒	I	
6.3 Meetings	☐	I	
6.4 Documents **Site X/Y/Z**	This section provides the possibility to organise site related documents per site (if necessary please use a separate binder).		

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6.4.1 Study Team list Site X	☒	I	
6.4.2 Description of Trial Site X	☒	I	
6.4.3 Documents (Investigators + Deputies + further members of the study team) (Site X): CV, FD, GCP-Certificate,	☒	I	
7 Protocol	**Filed**	**File No.**	**Comment**
7.1 Protocol (approved, current), signed	☒	I	
7.1.1 Protocol (relevant previous versions)	☐	I	Please note: There are no relevant previous versions at the moment.
7.2 Synopsis	☒	I	
7.3 Amendments (final and signed)	☐	I	Please note: There are no amendments at the moment.
7.4 File notes	☐	I	
8 Patient Information and Informed Consent	**Filed**	**File No.**	**Comment**
8.1 Site - specific versions	☒	I	Please find the English master version in this section.
8.2 Site X/Y/Z: Patient Information	☐	I	These sections provide you the possibility to file the PICFs according to their sites.
8.2.1 Approved version (current)	☐	I	
8.2.2 Relevant previous versions	☐	I	
8.3 Site X/Y/Z: Informed Consent	☐	I	
8.3.1 Approved version (current)	☐	I	
8.3.2 Relevant previous versions	☐	I	

Content Trial Master File National

9 Further Study Documents	Filed	File No.	Comment
9.1 Recruiting advertisements	☐	I	Please note: There are no recruitment advertisements planned by the sponsor.
9.2 XX	☐	I	
10 CRF and other Documents	**Filed**	**File No.**	**Comment**
10.1 CRF			
10.1.1 eCRF (Manual)	☐	I	Will be sent to you via email.
10.1.2 pCRF (blank)	☒	I	
10.1.3 CRF marked for Monitoring	☒	I	
10.1.4 Data Correction Forms	☐	I	
11 Agreements and Tasks lists	**Filed**	**File No.**	**Comment**
11.1 Monitor	☐	I	
11.2 Data management	☐	I	
11.3 Statistic	☐	I	
11.4 Pharmacy	☐	I	
11.5 Central Laboratory	☐	I	
11.6 Laboratory X	☐	I	
11.7 Companies/ Pharmaceutical Companies/ Foundations	☐	I	
12 Drug	**Filed**	**File No.**	**Comment**
12.1 Investigator's brochure			
12.1.1 Approved Version (current)	☒	II	
12.1.2 Approved Version (relevant previous	☐	II	Please note: There are no

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versions)			relevant previous versions at the moment.
12.2 IMPD	☒	II	
12.3 SmPC	☐	II	Please file here the appropriate SmPCs for your country.
12.4 Manufacturing Authorization / Certificates	☒	II	
12.5 Shipment	☒	II	
12.6 Instructions for Handling	☒	II	
12.7 Storage / Delivery	☐	II	
12.8 Confirmation of receipt	☐	II	
12.9 Acknowledgement of Destruction	☒	II	
12.10 Drug accountability	☒	II	
12.11 Correspondence with Manufacturer	☐	II	
13 Randomisation	**Filed**	**File No.**	**Comment**
13.1 Randomisation list	☐	II	
14 Monitoring	**Filed**	**File No.**	**Comment**
14.1 Monitoring manual / Monitoring plan	☒	II	incl. Note to File
14.2 Initiation Reports	☐	II	
14.3 Monitoring Reports (during the trial)	☐	II	
14.4 Monitoring-Visit Logs	☒	II	
15 Manuals / Instructions / Forms	**Filed**	**File No.**	**Comment**
15.1 XXX	☐	II	

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16 Correspondence	Filed	File No.	Comment
16.1 Correspondence with Sites	☐	II	
16.2 Correspondence with Pharmacy	☐	II	
16.3 General Correspondence	☐	II	
17 Adverse Events/Serious Adverse Events	**Filed**	**File No.**	**Comment**
17.1. Instructions in case of SAEs	☒	II	
17.2. SAE-Form (blank)	☒	II	
17.3. Form Second Assessment (blank)	☒	II	incl. Note to File
17.4. SAE-Notification from the sites	☐	II	
17.5. SAE Second Assessment / SAE Evaluation	☒	II	incl. Note to File
17.6. SUSAR-Report Form (CIOMS I- blank)	☒	II	incl. Note to File
17.7. SUSAR-Reports	☐	II	
17.8. SUSAR-Reports to Ethics Committee and National Authorities	☒	II	incl. Note to File
17.9. Line listing (Lists of SAEs and SUSARs for the EC and NRA)	☐	II	
18 DSMB	**Filed**	**File No.**	**Comment**
18.1 DSMB Instructions	☐	II	Will be sent to you via email.
18.2 DSMB-Reports	☐	II	
18.3 Correspondence with	☐	II	
19 Laboratory	**Filed**	**File No.**	**Comment**
19.1 Laboratory XX			
19.1.1 Certificates (XX)	☒	II	