P-CID Study Synopsis

STUDY TITLE	A prospective outcome study on patients with profound combined immunodeficiency
ABBREVIATED TITLE	**P-CID**
STUDY NUMBER/DRKS	DRKS00000497
INDICATION/ MAIN DIAGNOSIS	Combined immunodeficiencies (CID) are a heterogeneous group of inherited immune disorders with impaired T cell development and/or function manifesting through increased susceptibility to infections and/or immune dysregulation. They can be delineated from SCID by their manifestation beyond the first year of life. **Profound CID (P-CID)** is a potentially life-threatening form of CID, in which SCT is a relevant consideration at diagnosis.
TRIAL OBJECTIVES	The primary objective of the study is to provide natural history data on patients with P-CID, irrespective of whether they undergo HSCT or not. The goals are to determine **survival, the frequency of severe events and quality of life 5 years after study inclusion**. The secondary objective is to develop a **risk model for P-CID** patients. The model is developed from a set of clinical and laboratory parameters obtained at diagnosis, at study inclusion and yearly thereafter. The tertiary objectives of this study are to determine the **effects of donor, recipient and treatment factors on the outcome of HSCT**. The goal is to determine the quality of engraftment and immunological reconstitution and to determine the effects of these parameters on clinical outcome.
MAIN HYPOTHESIS	P-CID patients undergoing early HSCT have a better 5-year survival than patients who undergo late HSCT or are not transplanted.
STUDY DESIGN	Prospective international multicenter cohort study (observational study). Enrolled patients will be evaluated and treated according to local institutional protocols. They will receive comparable baseline and follow-up evaluations across all participating centres, irrespective of the therapeutic strategy at the individual site. There will be 6 study visits (scheduled yearly) for all patients. Because of the variable history prior to study inclusion, a morbidity score is determined for each patient at study visit 1. For those patients undergoing HSCT, an additional 6 months post-HSCT visit will be documented. The study visits will document immunological parameters, severe events including major infections and major manifestations of immune dysregulation, severe transplant-related events and quality of life.
ENDPOINTS	The **primary** endpoint is overall survival determined after year 5. The event analysed is death from any cause. The time to this event is the time from the first major infection or major manifestation of immune dysregulation (documented retrospectively at the time of study entry) to death. The **secondary** endpoint is the time point of HSCT. The time to this event is the time from the first major infection or major manifestation of immune dysregulation to HSCT. **Tertiary** endpoint is the frequency of major infections or major manifestations of immune dysregulation during the observation period. These endpoints will be used as prognostic factors in combination with a set of potentially predictive biomarkers in survival models in order to establish a risk model for P-CID patients. In addition, within this study, all patients undergoing HSCT will be

	analyzed with a second set of endpoints to evaluate of the outcome of SCT. Primary endpoint is overall survival after 6 months and 1 year of follow up **Secondary** endpoints are engraftment, immune reconstitution and clinical outcome assessed at 6 and 12 months after HSCT.	
TIMETABLE	Start of Study:	07/2011
	Duration of the Study:	06/2021
	Evaluation of Pilot Phase:	06/2013
	First Statistical evaluation:	06/2016
	Final Evaluation:	06/2021
SAMPLE SIZE	We assume that 40 patients/year (a total of 200 patients) will be included. Of these, it is estimated that 40% (80 patients) will receive primary HSCT, 30% (60 patients) secondary HSCT and 30% (60 patients) no HSCT. It should be stated that the main trial objectives can also be achieved, if less patients are recruited. The characteristics of the patient cohort (presence and variability of molecular diagnosis, variability in decision to transplant) are difficult to foresee. Evaluation of a pilot phase (until 06/2013) will provide this information. It will then be evaluated to which degree patients can be matched by the morbidity score obtained at study entry for the outcome studies. To determine, how many patients will be needed to compare outcome in those undergoing 1° vs. 2° vs. no HSCT, sample size calculations have been performed. Assuming a reference 5-year-mortality of 20%, 60 patients in each of the 3 groups will allow detecting a relative risk of 2.2 with a power of 80%.	
STATISTICAL ANALYSIS	The risk and prognostic factors for the need of HSCT and the impact of HSCT on death will be analysed with survival analysis using multistate models. Left-truncation (delayed entry) will be addressed. Appropriate regression models will be applied. The impact of HSCT on the frequency of severe events (infections, severe manifestations of immune dysregulation, transplant-related complications) will be examined using models for analysing recurrent events.	
INCLUSION CRITERIA	Clinical and immunological criteria determine inclusion irrespective of the genetic diagnosis. **T cell criteria (2 out of 4)** o Reduced T cell counts (CD4 : <700, if <2y ; <500, if 2-4y ; <300, if >4y ; CD8 : <350, if <2y ; <250, if 2-4y ; <150, if >4y) o Reduced thymic function (CD45RA+CD62L+ *or* CD45RA+CD31+ of CD4+ <30% <2y, <25% 2-6y, <20% >6y) o Impaired T cell proliferation (PHA response <30% of lower limit of normal) o Elevated fraction of γ/δ T cells (>15% of total CD3+ T cells) **AND Clinical criteria** • At least one major infection criteria (viral, bacterial, opportunistic) OR • At least one major immune dysregulation criteria (granulomas, lymphoproliferative disease, unexplained interstitial lung disease, inflammatory bowel disease, autoantibody mediated disease, vasculitis) OR • At least one malignancy criteria (lymphoid malignancies and virally induced malignancies) **AND Age >= 1yr and <= 16yr at study inclusion**	
EXCLUSION CRITERIA	• No written consent available No written informed consent of patient or parents in case of minors available or no assent of minor if applicable	

	• Patients with a clinical diagnosis of SCID or Omenn syndrome within the first year of life • P-CID Patients for whom decision for HSCT is taken at age <1yr • Patients with Wiskott-Aldrich syndrome and CD40 Ligand Deficiency, because disease-specific prognosis and treatment data are available • Patients undergoing gene therapy or ADA enzyme replacement will be followed using the same parameters, but will not be included in the analysis

Flow Chart of Study Protocol

	Pre-Study: Clinical Work-Up according to Local Center Practice	Baseline-Study Start	Month 12 ±3	Month 24 ±3	Month 36 ±3	Month 48 ±3	Month 60 ±3	yearly
Visits	**-**	**1**	**2**	**3**	**4**	**5**	**6**	**x**
Signed Study Informed Consent		x						
Signed Informed Consent SCETIDE register[1]		x (group 1)	x (when entering group 2)					
Study Forms								
P-CID Eligibility Form		x						
P-CID Visit 1		x						
P-CID Visit 2+			x	x	x	x	x	x
QoL Form (age-related)		x	x	x	x	x	x	x
P-CID SCETIDE Initial Report suppl.[1]		x (Visit SCT1: 6 months after HSCT)[3]						
Medical History								
Assessment Infectious Disease	x	x	x	x	x	x	x	x
Assessment Immune Dysregulation	x	x	x	x	x	x	x	X
Malignancies/other Manifestations	x	x	x	x	x	x	x	X
Treatment for CID	x	x	x	x	x	x	x	x

[1] only group 1 and 2 (HSCT patients)
[2] if not performed previously
[3] HSCT will be reported to study coordination immediately. P-CID SCETIDE Initial Report supplement is due 6 months post transplant. The study coordinator will then inform the study center about (re-)scheduling follow-up visits.

	Pre-Study: Clinical Work-Up according to Local Center Practice	Baseline-Study Start	Month 12 ±1 Month	Month 24 ±1 Month	Month 36 ±1 Month	Month 48 ±1 Month	Month 60 ±1 Month	yearly
Visits	-	1	2	3	4	5	6	x
Laboratory								
CBC with Differential and Platelets	x	x	x	x	x	x	x	x
HIV testing	x							
CMV, EBV status	x	x[1]						
Immune Status Testing								
Quantitative Immunoglobulins (GAME)	x	x	x	x	x	x	x	x
Isohemagglutinin Titers	x	X[1]						
Immunization Response/Vaccine Titers	x	X[1]						
B cell counts Memory B cells	x	X[2]	x	x	x	x	x	x
NK cell counts	x	X[2]	x	x	x	x	x	x
T cell counts Naïve T cells g/d T cells T cell proliferationPBMC Phenotyping, T cell proliferation	x	X[2]	x	x	x	x	x	x
T cell repertoire by Vβ usage		X[3]					x	
TRECs from Dried Blood Filter Spot		x	x	x	x	x	x	x
sCD25		x	x	x	x	x	x	x
Biomaterial								
Frozen PBMC Archive		x	x	x	x	x	x	x
Fibroblast/EBV Cell Line		x						
Serum Archive		x	x	x	x	x	x	X
Registration of (prior) tissue biopsies		x	x	x	x	x	x	

[1]if not performed previously
[2]if not performed within the last 6 months
[3]optional