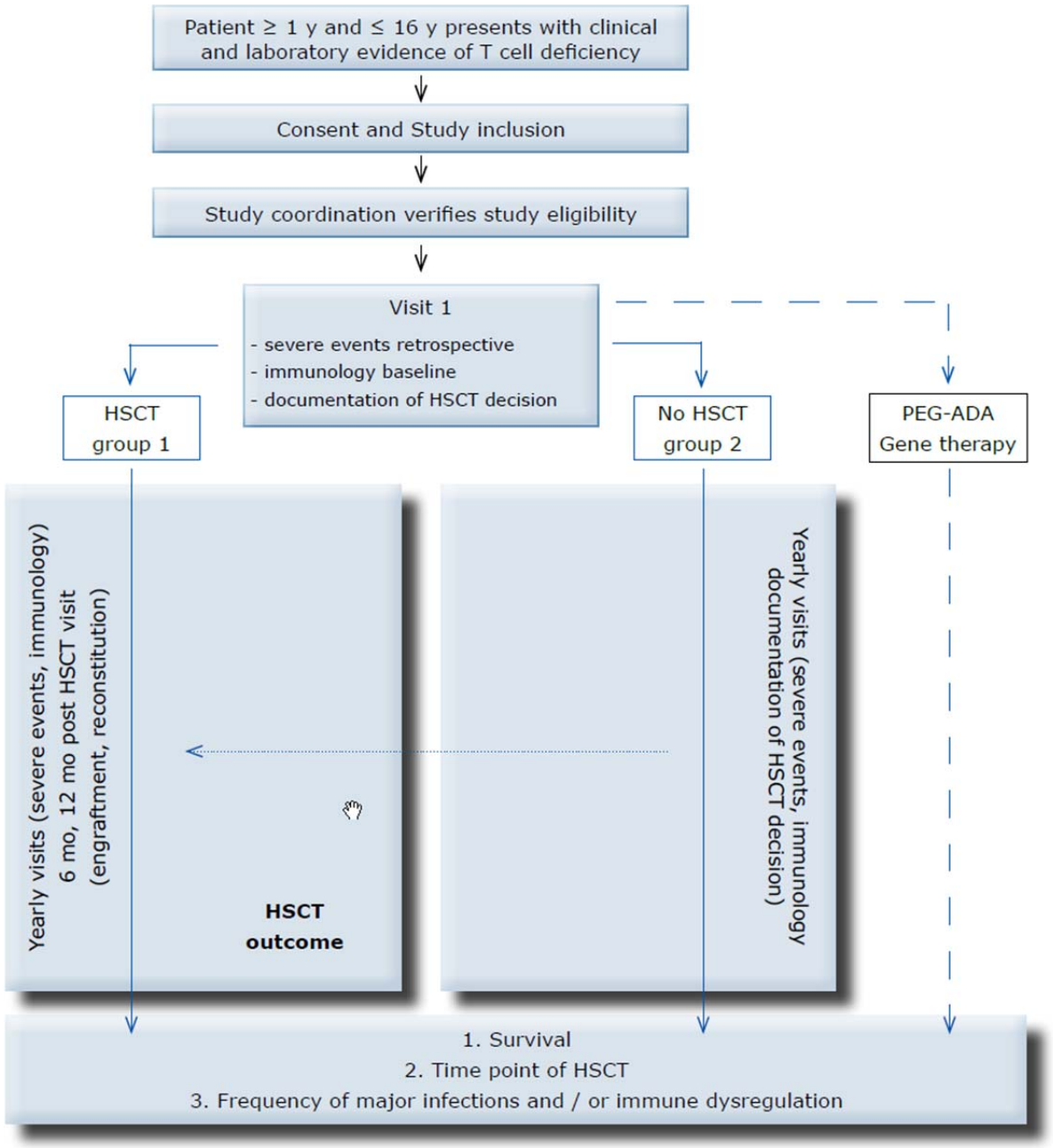
Synopsis

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 (assessed by a morbidity measure) and quality of life 5 years after inclusion of the last patient. The secondary objective of the study is a **matched-pair analysis** of patient pairs with similar age and morbidity measure at study entry, but divergent decision on HSCT during follow-up. The tertiary objective is to develop a **risk model for P-CID** to determine to which extent clinical events and immunologic parameters and their changes are predictive for outcome (survival, morbidity, and QOL). The model is developed from a set of clinical and laboratory parameters obtained at diagnosis, at study inclusion and yearly thereafter. The quarterny 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 HSCT early and with a low morbidity measure 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 at least 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 (summarized in a morbidity measure). These endpoints will be used as prognostic factors in combination with a set of potentially predictive biomarkers or clinical indicator events 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 HSCT. **Primary** endpoint is overall survival after 6 months and 12 months of follow up **Secondary** endpoints are engraftment, immune reconstitution and clinical outcome assessed at 6 and 12 months after HSCT.	
TIMETABLE	Start of Study (FPFV):	11/2011
	Inclusion last patient (LPFV):	11/2018
	Last patient last visit (LPLV):	11/2023
	Evaluation of Pilot Phase:	03/2014
	Final Evaluation (planned):	11/2024
SAMPLE SIZE	We assume that 20 patients/year (a total of 160 patients) will be included. Of these, it is estimated that 60% (96 patients) will receive HSCT and 40% (64 patients) will not receive 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 03/2014) has provided this information. It was concluded that it will be possible to match patients 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 HSCT vs. no HSCT, sample size calculations have been performed. Assuming a reference 5-year-mortality of 20%, 60 patients in each of the 2 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) • 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) • Reduced thymic function (CD45RA+CD62L+ *or* CD45RA+CD31+ of CD4+ <30% <2y, <25% 2-6y, <20% >6y) • Impaired T cell proliferation (PHA or anti CD3 response <30% of lower limit of normal) • 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 ≥ 1 year and ≤ 16 years at study inclusion**
EXCLUSION CRITERIA	• 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, CD40 Ligand Deficiency and Ataxia teleangiectatica, 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 • HSCT prior to study entry

Flow Diagram



Visit Flow Chart

	Pre-Study: Clinical Work-Up according to Local Center Practice	Baseline-Study Start	Month 12 ±3[1]	Month 24 ±3[1]	Month 36 ±3[1]	Month48 ±3[1]	Month 60 ±3[1,2]	Yearly[1,2]
Visits	**-**	**1**	**2**	**3**	**4**	**5**	**6**	**6+x**
Signed Study Informed Consent		x						
Study Forms								
P-CID Eligibility Form		x						
P-CID Visit 1		x						
P-CID Visit 2+			x	x	x	x	x	x
QOL questionnaires (age-related)		x	x	x	x	x	x	x
P-CID SCETIDE Initial Report suppl.[3]		x (Visit SCT1: 6 months after HSCT)[1]						
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

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Visits	-	1	2	3	4	5	6	6+x
Laboratory								
CBC with Differential and Platelets	x	x	x	x	x	x	x	x
HIV testing	x							
CMV, EBV status	x	x[4]						
Immune Status Testing								
Quantitative Immunoglobulins (GAME)	x	x	x	x	x	x	x	x
Immunization Response/Vaccine Titers	x	x[4]						
B cell counts Memory B cells	x	x[5]	x	x	x	x	x	x
NK cell counts	x	x[5]	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[5]	x	x	x	x	x	x
T cell repertoire by Vβ usage		x[6]					x[6]	
sCD25		x	x	x	x	x	x	x
TRECs from Dried Blood Filter Spot		x	x	x	x	x	x	x
Documentation of locally stored 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	x

[1] After transplant the study visits have to be re-scheduled. They are now due yearly after transplant and no longer yearly after baseline study start. The P-CID study coordination will inform the study center about (re-)scheduling follow-up visits.
[2] patients shall be observed at least 60 months, or until study end
[3] only group 1 (HSCT patients). P-CID SCETIDE Initial Report supplement is due 6 months post transplant
[4] if not performed previously [5] if not performed within the last 6 months, [6] optional