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The ABACHAI clinical trial protocol: Safety and efficacy of abatacept (s.c.) in patients with CTLA-4 insufficiency or LRBA deficiency: A non controlled phase 2 clinical trial

Máté Krausz [a,b,l], Annette Uhlmann [b,c], Ina Caroline Rump [a,b], Gabriele Ihorst [c], Sigune Goldacker [a], Georgios Sogkas [d], Sara Posadas-Cantera [a], Reinhold Schmidt [d], Manuel Feißt [e], Laia Alsina [f], Ingunn Dybedal [g], Mike Recher [h], Klaus Warnatz [a,b], Bodo Grimbacher [a,b,i,j,k,*]

[a] Department of Rheumatology and Clinical Immunology, Center for Chronic Immunodeficiency (CCI), Medical Center, Faculty of Medicine, Albert-Ludwigs-University of Freiburg, Hugstetter Straße 55, 79106 Freiburg, Germany
[b] Institute for Immunodeficiency, Center for Chronic Immunodeficiency (CCI), Medical Center, Faculty of Medicine, Albert-Ludwigs-University of Freiburg, Breisacher Straße 115, 79106 Freiburg, Germany
[c] Clinical Trials Unit, Medical Center, Faculty of Medicine, Albert-Ludwigs-University of Freiburg, Elsaesser Straße 2, 79110 Freiburg, Germany
[d] Hannover Medical School, Klinik für Rheumatologie und Immunologie, Carl-Neuberg-Str. 1, 30625, Hannover, Germany
[e] Medical Center – University of Heidelberg, Institut für Medizinische Biometrie und Informatik, Im Neuenheimer Feld 130.3, 69120, Heidelberg, Germany
[f] Clinical Immunology and Primary Immunodeficiencies Unit, Pediatric Allergy and Clinical Immunology Department, Hospital Sant Joan de Déu, Barcelona, Germany
[g] Oslo University Hospital, Rikshospitalet, Oslo, Norway
[h] Outpatient Internal Medicine Clinic, University Hospital, Basel, Switzerland
[i] DZIF – German Center for Infection Research, Satellite Center Freiburg, Germany
[j] CIBSS – Centre for Integrative Biological Signalling Studies, Albert-Ludwigs University, Schaenzlestraße 18, 79104, Freiburg, Germany
[k] RESIST – Cluster of Excellence 2155 to Hanover Medical School, Satellite Center Freiburg, Germany
[l] Faculty of Biology, Albert-Ludwigs-University of Freiburg, Schaenzlestraße 1, 79104, Freiburg, Germany

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ABSTRACT

Background: Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) insufficiency and lipopolysaccharide-responsive and beige-like anchor protein (LRBA) deficiency are both complex immune dysregulation syndromes with an underlying regulatory T cell dysfunction due to the lack of CTLA-4 protein. As anticipated, the clinical phenotypes of CTLA-4 insufficiency and LRBA deficiency are similar. Main manifestations include hypogammaglobulinemia, lymphoproliferation, autoimmune cytopenia, immune-mediated respiratory, gastrointestinal, neurological, and skin involvement, which can be severe and disabling. The rationale of this clinical trial is to improve clinical outcomes of affected patients by substituting the deficient CTLA-4 by administration of CTLA4-Ig (abatacept) as a causative personalized treatment.

Objectives: Our objective is to assess the safety and efficacy of abatacept for patients with CTLA-4 insufficiency or LRBA deficiency. The study will also investigate how treatment with abatacept affects the patients' quality of life.

*Methods: /*Design: ABACHAI is a phase IIa prospective, non-randomized, open-label, single arm multi-center trial. Altogether 20 adult patients will be treated with abatacept 125 mg s.c. on a weekly basis for 12 months, including (1) patients already pretreated with abatacept, and (2) patients not pretreated, starting with abatacept therapy at the baseline study visit. For the evaluation of drug safety infection control during the trial, for efficacy, the CHAI-Morbidity Score will be used.

* Corresponding author. Department of Rheumatology and Clinical Immunology, Center for Chronic Immunodeficiency (CCI), Medical Center, Faculty of Medicine, Albert-Ludwigs-University of Freiburg, Hugstetter Straße 55, 79106 Freiburg, Germany.

E-mail addresses: mate.krausz@uniklinik-freiburg.de (M. Krausz), annette.uhlmann@uniklinik-freiburg.de (A. Uhlmann), na.caroline.rump@uniklinik-freiburg.de (I.C. Rump), gabriele.ihorst@uniklinik-freiburg.de (G. Ihorst), sigune.goldacker@uniklinik-freiburg.de (S. Goldacker), sogkas.georgios@mh-hannover.de (G. Sogkas), sara.posadas.cantera@uniklinik-freiburg.de (S. Posadas-Cantera), immunologie@mh-hannover.de (R. Schmidt), feisst@imbi.uni-heidelberg.de (M. Feißt), laia.alsina@sjd.es (L. Alsina), idybedal@ous-hf.no (I. Dybedal), Mike.Recher@usb.ch (M. Recher), klaus.warnatz@uniklinik-freiburg.de (K. Warnatz), bodo.grimbacher@uniklinik-freiburg.de (B. Grimbacher).

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Glossary

APC	antigen-presenting cell
BAL	bronchoalveolar lavage
BW	body weight
cCt	cranial computed tomography
CGI-I	Clinical Global Impression – Improvement scale
cMRI	cranial magnetic resonance imaging
CMV	cytomegalovirus
CNS	central nervous system
CSF	cerebrospinal fluid
CT	computed tomography
CTFG	Clinical Trial Facilitation Group
CTLA4	cytotoxic T-lymphocyte-associated protein 4
CVID	common variable immunodeficiency
DFG	Deutsche Forschungsgemeinschaft
DLCO	diffusing capacity for carbon monoxide
DLCOc/VA	diffusing capacity for carbon monoxide corrected for alveolar volume
DMARDs	Disease Modifying Anti-Rheumatic Drugs
DRKS	Deutsches Register Klinische Studien
DSMB	Data Safety Monitoring Board
EBV	Epstein-Barr Virus
eCRF	electronic Case Report Form
EFS	event free survival
EMA	European Medicines Agency
EU	European Union
FDA	United States Food and Drug Administration
FVC	forced vital capacity
GAIN	German Auto-Immunity Network
GLILD	Granulomatous and Lymphocytic Interstitial Lung Disease
HIV	human immunodeficiency virus
HSCT	hematopoietic stem-cell transplantation
IBDQ	Inflammatory Bowel Disease Questionnaire
IMP	investigational medicinal product
IRT	immunoglobulin replacement therapy
IU	international unit
JIA	juvenile idiopathic arthritis
LRBA	lipopolysaccharide-responsive and beige-like anchor protein
mTOR	mechanistic target of rapamycin
NANO	Neurologic Assessment in Neuro-Oncology
OS	overall survival
PVR	polymerase chain reaction
PIRD	primary immune regulatory disorders
RA	rheumatoid arthritis
SGRQ	St. George Respiratory Questionnaire
TLC	total lung capacity

1. Background

1.1. Biological function of the cytotoxic T-lymphocyte antigen-4 protein

The cytotoxic T-lymphocyte antigen-4 (CTLA-4) protein plays an essential role in the regulation of immune responses: it is the antagonist of the co-stimulatory molecule CD28 in the immunological synapse (between antigen-presenting cells and T cells) that leads to sustained T-cell activation, and outcompetes CD28 for the shared ligands CD80 and CD86 by binding them with a higher affinity and avidity [1]. CTLA-4 is expressed constitutively in Treg cells and is upregulated after activation in conventional T-cells. CTLA-4 is mainly localized to intracellular vesicles [2]. Upon activation, it is transported to the plasma membrane, where it gets quickly internalized by clathrin-mediated endocytosis [3]. As its main function, CTLA-4 acts as a cardinal T-cell inhibitory receptor. During the exposure to the extracellular space, CTLA-4 captures its ligands from the surface of antigen-presenting cells (APCs). After this specific binding, the CTLA-4-CD80/86 complex is removed from the plasma membrane by transendocytosis, a process regulated by lipopolysaccharide-responsive vesicle trafficking, beach- and anchor-containing protein (LRBA) [1,4]. As a result, the APC-mediated T-cell activation is downregulated.

1.2. Defects in the CTLA-4 pathway

1.2.1. CTLA-4 deficiency

In patients with severe immune dysregulation syndromes, we and others have identified novel heterozygous germline mutations in *CTLA4* [5–7]. These mutations were either (1) heterozygous nonsense mutations leading to a premature stop codon and loss of the mutated allele and subsequent CTLA-4 haploinsufficiency, or (2) missense mutations affecting either CTLA-4 ligand-binding or CTLA-4 dimerization. As a consequence of these mutations, CTLA-4 expression is impaired on Tregs or cannot bind efficiently to the B7 molecules CD80 and CD86, thereby limiting their efficacy for transendocytosis. As CTLA-4 delivers an inhibitory signal for T cell activation, its insufficiency leads to a sustained and prolonged activation of T cells and their differentiation into an effector memory phenotype. These cells then characteristically infiltrate organs (such as the lung, gastrointestinal tract or the brain tissue), causing a typical lymphocytic infiltrate by both CD4 and CD8-positive T cells. As of today, CTLA-4 deficiency is the one of the most frequent, known genetic cause for common variable immunodeficiency (CVID) [8–10].

The clinical phenotype of patients with *CTLA4* mutations is thus characterized by immune dysregulation, which may manifest anywhere on the spectrum between autoimmunity, autoinflammation, immunodeficiency, and lymphoproliferation. As such, it is one of them main genetic causes of the primary immune regulatory disorders (PIRD) included in the group of syndromes with autoimmunity [11]. The clinical presentation of individual patients is highly diverse. Data from a meta-analysis of one of the largest published patient cohort suggest a penetrance around 70% [12,13]. Surprisingly, some of the mutation carriers do not develop the disease at all, therefore additional genetic, epigenetic and environmental factors are suspected to modify the disease course. The most common clinical features of immune dysregulation are autoimmune cytopenias, enteropathy and lymphoproliferation comprising hepatosplenomegaly and chronic lymphadenopathy. Characteristically lymphocytic or granulomatous organ infiltration occurs in approximately two thirds of patients. Common signs of immunodeficiency include hypogammaglobulinemia, usually associated with recurrent respiratory tract infections, lymphopenia, as well as the reactivation of herpes viruses such as Epstein-Barr virus (EBV) and

cytomegalovirus (CMV). Published data showed an increased frequency of malignancies out of 184 patients with CTLA-4 insufficiency with a prevalence of 12.9% (n = 17), including lymphomas (n = 10) and gastric cancer (n = 5). Out of the 17 cancer entities, 10 were identified as EBV-associated [13].

To summarize, CTLA-4 insufficiency is a complex immune dysregulation syndrome with autoimmunity and lymphoproliferation, with an underlying dysfunction of regulatory T cells.

1.2.2. LRBA insufficiency

As the transendocytosis is regulated by lipopolysaccharide-responsive and beige-like anchor protein LRBA, the CTLA-4 pathway can be indirectly affected by mutations in the *LRBA* gene as well. In patients with an LRBA deficiency, CTLA-4 is synthesized normally, but has an increased turnover, emphasizing the function of LRBA in controlling CTLA-4 trafficking to lysosomes, resulting in recycling of the CTLA-4 protein [4,14]. The clinical phenotypes of CTLA4 insufficiency and LRBA deficiency are therefore similar, however, LRBA-deficiency tends to be more severe. In a meta-analysis of 109 published patients autoimmunity (82%), enteropathy (63%), splenomegaly (57%), and infections (pneumonia, 49%) were identified as the most common clinical manifestations [15].

1.2.3. Current available treatment options for CTLA-4 insufficiency and LRBA deficiency

Treatment options for CTLA-4 insufficiency and LRBA deficiency include immunomodulatory or immunosuppressive therapies such as systemic glucocorticoids, cyclosporine, mycophenolate, anti-CD20 monoclonal antibodies, or cyclophosphamide. In less severe cases, symptom-targeted therapies, such as polyclonal immunoglobulin replacement therapy (IRT) to manage hypogammaglobulinemia, topical steroids to manage skin disease or enteropathy or antibiotics for infections may be sufficient. Systemic but disease-specific therapies, however, targeted to inhibit the inborn signaling-defect, include abatacept (CTLA4-Ig) or mTOR (mechanistic target of rapamycin) inhibitors (the mTOR pathway plays an important role in the regulation of T-cell homeostasis, including Treg responses) [12,16,17]. In treatment-resistant, severe cases, where the immune dysregulation cannot be controlled, hematopoietic stem-cell transplantation (HSCT) may be considered.

Abatacept (Orencia®) is a soluble fusion protein composed of the Fc region of the immunoglobulin IgG1 fused to the extracellular domain of CTLA-4 [18]. Abatacept selectively downregulates the activation of the $CD28^{+}$ T cells. Abatacept inhibits the CD80/86:CD28 co-stimulatory pathway by high affinity binding of the CTLA-4 domain to CD80 and CD86 [18]. Abatacept is available in both intravenous (i.v.) and subcutaneous (s.c.) formulations. Abatacept is an approved treatment for rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), and psoriatic arthritis (PsA) for adult patients since 2005 by the United States Food and Drug Administration (FDA) and 2007 by the European Medicines Agency (EMA), with a good safety profile over more than 10 years of usage [19].

Abatacept treatment is reported to improve the gastrointestinal and lung disease, and alleviate severe autoimmune symptoms in CTLA-4 and LRBA deficiencies [4,12,20]. The rationale of this clinical trial is to substitute the CTLA4-deficient patients by administration of abatacept, the molecule which is not sufficiently produced or turned-over in our patients, as a causative treatment approach.

1.3. Trial purpose and rationale

CTLA-4 insufficiency and LRBA deficiency are severe primary immunodeficiencies with a high mortality. Treatment options are associated with an elevated risk of infections (in case of immunosuppressants and anti-CD20 antibodies), graft versus host disease or death (in case of HSCT). Based on the biological function and previous case reports of abatacept, the molecule is expected to serve as a causative treatment by substituting the dysfunctional CTLA4, thereby reconstituting immune regulation.

Within this prospective, open labeled, single arm phase IIa trial, we strive to prove the concept of treating Treg dysfunction in CTLA4-insufficient or LRBA-deficient patients by administering soluble CTLA4-Ig (abatacept). We will investigate the safety and efficacy of abatacept in such patients.

As discussed before, there are no state-of-the-art control interventions for patients with CTLA4 insufficiency or LRBA deficiency available. As abatacept is approved for patients with e.g. RA, we know that the trial drug is well tolerated with only few side effects (most common ones being infections) [19].

In this trial, 125 mg s.c. abatacept will be applied weekly. This dosing is already approved for indications such RA, JIA) or PsA and has been and is widely used in several clinical trials investigating e.g. cutaneous systemic sclerosis [20], granulomatosis with polyangiitis (ongoing, NCT02108860), IgG4 related disease (completed, NCT03669861), myositis-associated interstitial lung disease (ongoing, NCT03215927), sarcoidosis (ongoing, DRKS00011660) [21], interstitial lung disease, and CVID [22].

2. Methods and analysis

2.1. Study design

This is a multicenter, prospective, open labeled single arm phase IIa trial. Altogether 20 patients are planned to receive the trial medication at two study sites, (1) Medical Center – University of Freiburg (2) Medical Center - University Hannover (MHH). Two patient groups will be included in the trial. (1) Patients already treated with abatacept before registration (*pretreated* with 125 mg abatacept s.c. weekly). For pretreated patients, retrospective data will be collected for a 12-month period before the first application of abatacept, and for the period between first application of abatacept (outside trial) and the trial inclusion. (2) Treatment-naïve patients, starting the abatacept therapy at the baseline study visit (*naive*). For not-pretreated patients, retrospective data will be collected for the 12-month period before trial inclusion (Fig. 1).

2.1.1. Primary objective and endpoint

The primary objective is to assess safety of abatacept in patients with CTLA-4 insufficiency or LRBA deficiency. The primary endpoint is the number of episodes of failed infection control (definition see Table 1) under treatment with abatacept during the one-year trial period.

In addition, the number and characterization of severe infections (definition see Table 1) will be documented retrospectively (where available) for a period of 12 months before first application of abatacept (even if started years ago) for comparison with the 12 months trial period.

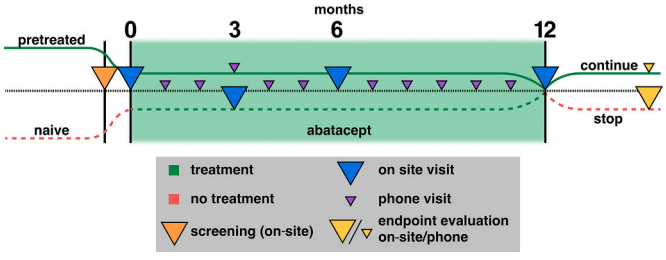

Fig. 1. Treatment schedule.

Table 1
Objectives and related endpoints.

	Objective	Description of endpoints
Primary	Safety assessment of abatacept in patients with CTLA4 insufficiency or LRBA deficiency, measured as the number of episodes of failed infection control during the one year study treatment period	Number of episodes of failed infection control under therapy with abatacept during the trial period of one year. An episode of failed infection control is defined as: • a severe infection, defined as: ○an infection requiring hospitalization OR ○an infection requiring i.v. antibiotic, or i.v. anti-fungal, or i.v. anti-viral treatment OR/AND • the failure to control viral replication. Failure is defined as the occurrence of either EBV viral load ≥5.000 IU/ml or CMV viral load ≥1.000 IU/ml in plasma in two independent measurements within 2 weeks but at least 7 days apart.
Secondary	Safety assessment of abatacept	• Number of severe infections as defined above (i.e. requiring hospitalization, or an infection requiring i.v. antibiotic, i.v. anti-fungal, or i.v. anti-viral treatment). • Characterization (incl. type of pathogen and involved organ system) of severe infections (definition see above) during abatacept trial treatment period. • Number of episodes of failed infection control exceeding 3 months under therapy with abatacept during the trial period of one year. These are as defined above (primary endpoint), with three exceptions: ○primary viral infections which are controlled within 0–3 months. ○hospitalizations which are conducted solely for preventive reasons ○i.v. antibiotic, or i.v. anti-fungal, or i.v. anti-viral treatments which are conducted solely for preventive reasons
Secondary	Efficacy assessment of abatacept	- overall survival (OS) - event free survival (EFS) - treatment failure, defined as any premature termination of treatment for any reason - cumulative steroid dose - cumulative dose of concomitant drugs to alleviate symptoms such as diarrhea medications or pain medication - Clinical Global Impression – Improvement scale (CGI-I) - quality of life measured by SF36 [23] - CHAI-Morbidity Score - laboratory parameters In addition, endpoints dependent on the patient's organ involvement: **Patients with lung involvement:** - lung function parameters - chest computed tomography (CT) scan - St. George Respiratory Questionnaire (SGRQ) [24] - Borg dyspnea scale **Patients with gut involvement (enteropathy):** - stool frequency and quality - Inflammatory Bowel Disease Questionnaire (IBDQ) [25–27] - calprotectin level in stool **Patients with cytopenias:** - number of bleeding episodes and/or number of platelet transfusions needed - Transfusion independency or number of transfusions of red blood cells **Patients with central nervous system (CNS) involvement:** - improvement in neurological assessment, based on neurological examination using the Neurologic Assessment in Neuro-Oncology (NANO) Scale [28] - cranial magnetic resonance imaging (cMRI)/cranial computed tomography (cCT) **Patients with lymphoproliferation:** - spleen size measured by ultrasonography - number of enlarged abdominal + peripheral lymph node groups **Patients with involvement of immune system:** - Absolute total lymphocyte count - Absolute total $CD4^+$ T cell count - Naïve T cells (% of $CD4^+$, CD45RA+) - Activated $CD4^+$ T cells (HLA-DR+ in $CD4^+$) - PD1+ $CD8^+$ cells (%) - Switched memory B cells (CD19/20+, IgM-, $CD27^+$) **Patients with skin involvement:** - percentage of body surface involved - kind and severity of lesions

2.1.2. Secondary objectives and endpoints

The secondary objective is to assess the efficacy of abatacept in patients with CTLA-4 insufficiency or LRBA deficiency. Changes during the treatment in clinical and diagnostic parameters will be monitored as specified in Table 1. Briefly, the secondary endpoints focus on therapy-induced changes in the clinical course, need for concomitant medication, immunological parameters, and patient reported outcomes. Depending on the patient's organ involvement, additional secondary endpoints are defined, as listed in Table 1.

2.2. Patient eligibility

Patients with a molecularly confirmed (genetic and functional testing requested) diagnosis of CTLA-4 insufficiency or LRBA deficiency are eligible for trial enrollment. No gender ratio has been stipulated in this trial as the results of the preclinical and clinical studies did not indicate any gender effect of the trial treatment in terms of efficacy and safety. Patients must have at least one clinically significant CTLA-4 insufficiency or LRBA deficiency-related organ involvement. Patients with severe comorbidities that are not related to the underlying immune-disease, or have (potential) contraindications against abatacept are excluded from participation. Additionally, patients with prior or planned HSCT (within the next 12 months) are excluded as well. The inclusion and exclusion criteria are summarized in Table 2 and Table 3.

Table 2
Inclusion criteria.

Molecular diagnosis of CTLA4 (haplo)-insufficiency or LRBA deficiency with either published mutations or mutations with proven functional effect (impaired CTLA4 staining or CTLA4-dependent transendocytosis)
Age ≥18 years.
IgG serum trough level ≥4 g/l (± IRT): last test result within 3 months at baseline visit.
Signed written informed consent.
Need for intervention on clinical grounds or continued need of therapy with abatacept as evaluated by the treating physician.
One organ system has to be involved. Organ involvements are defined as follows. In case of pretreatment with abatacept, organ involvement should be defined using retrospective data from the period before first application of abatacept.
Patients with lung involvement: • typical radiographic features of Granulomatous and Lymphocytic Interstitial Lung Disease (GLILD) in chest CT scan AND/OR • Lung function impairment (e.g. reduced total lung capacity (TLC), forced vital capacity (FVC), reduced diffusing capacity for carbon monoxide (DLCO), reduced pO2 at rest or exercise-induced) • if possible, bronchoalveolar lavage (BAL)and/or lung biopsy performed to exclude infection and malignancy
Patient with gut involvement (enteropathy): • typical bowel-related symptoms such as recurrent diarrhea, malabsorption, weight loss AND/OR • calprotectin in stool ≥50 μg/g AND • exclusion of infections by stool testing • in case of positive stool testing on current infection, eradication therapy has to be performed before inclusion to trial. Patients with chronic therapy resistant bowel infections can be included. • if possible, inflammation proven with deep bowel biopsy
Patients with cytopenias: • platelets ≤100.000/μl AND/OR • Hb ≤ 10 g/dl
Patients with CNS involvement: • any cerebral lesions in cMRI or cCT • if possible, cerebral spinal fluid (CSF) analysis performed to exclude infection and malignancy
Patients with lymphoproliferation: • spleen maximum cephalocaudal diameter ≥11 cm AND/OR • enlargement of one lymph node group
Patients with involvement of immune system: •Absolute total lymphocyte count •OR/AND≤1000/μl •Absolute total $CD4^+$ T cell count •OR/AND≤500/μl •Naïve ($CD4^+CD45RA+$) T cell % of $CD4^+$ •OR/AND≤20% •CD4 T cell activation, HLA-DR+ in $CD4^+$ •OR/AND≥20% •PD1 expression on $CD8^+$ cells, CD8+PD1+ in % of $CD8^+$ •OR/AND≥25% •Switched memory (CD19/20+, IgM-, $CD27^+$) B cell numbers in % of B cells, CD19/20+, IgM-, $CD27^+$≤6%

Table 2 (*continued*)

Patients with skin involvement: • skin lesions on body surface • eczematous, ulcerative or psoriasis-like skin lesions

Table 3
Exclusion criteria.

1. Patient without legal capacity who is unable to understand the nature, significance and consequences of the trial.
2. Other current immunosuppressive treatments with biologicals or Disease Modifying Anti-Rheumatic Drugs (DMARDs) other than corticosteroids ≤20 mg/day or abatacept. Between treatment with other biologicals or DMARDs and start of abatacept trial treatment the wash out period of the pretreatment must be kept. In case of pre-treatment with rituximab, therapy must be stopped at least 6 months before inclusion to trial.
3. Treatment with systemic steroids (prednisolon) in daily dose >20 mg/day.
4. Active Hepatitis B or tuberculosis infection. For tuberculosis, Quantiferon test is gold standard. In case of a positive Quantiferon test, an active infection has to be excluded by 3 sputum and 3 gastric juice samples, assessed by microscopy, polymerase chain reaction (PCR) and culture. Chest X-ray recommended.
5. Active infection or any major episode of infection requiring hospitalization or treatment with i.v. antibiotics within 30 days prior to baseline.
6. Chronic infection requiring hospitalization or treatment with i.v. antibiotics within 30 days prior to baseline (does not apply for patients already pretreated with abatacept)
7. Acute bacterial or viral infection (patients with a chronic and clinically controlled infection can be included).
8. Patient on antiviral CMV prophylaxis within 28 days prior to baseline visit.
9. Any malignancies within the last 4 years with the exception of basal cell carcinoma and precancerous conditions (does not apply for patients already pre-treated with abatacept).
10. Current or planned pregnancy, nursing period.
11. EBV load of >5.000 IU/ml or CMV load of >1.000 IU/ml in plasma at screening.
12. Receipt of a live virus vaccine within 3 months prior to first application of trial medication.
13. Serious uncontrolled concomitant disease not caused by CTLA-4 insufficiency or LRBA deficiency.
14. Known human immunodeficiency virus (HIV) infection, infectious hepatitis (type A or C) or another uncontrolled infection.
15. Prior HSCT or HSCT planned within next 12 months.
16. Known hypersensitivity to the active substances or any of the excipients.
17. Participation in any other interventional clinical trial within the last 30 days before the start of this trial.
18. Simultaneous participation in other interventional trials; simultaneous participation in registry and diagnostic trials is allowed.
19. Known or persistent abuse of medication, drugs or alcohol.
20. Person who is in a relationship of dependence/employment with the sponsor or the investigator.
21. For women of child bearing potential: Failure to use during treatment with abatacept and at least up to 14 weeks after the last dose of abatacept one of the following safe contraceptive methods that can achieve a failure rate of less than 1% per year. Such methods include: (1) combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), (2) progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), (3) intrauterine device, (4) intrauterine hormone-releasing system (CTFG recommendations, 2014) [29].

2.3. Informed consent

Patients will be recruited from the outpatient clinics of the participating study sites. Patients will be informed about the clinical trial, if they appear to be eligible for the trial. After detailed explanation of the aims and the course the trial, thorough counselling, and answering all questions, patients will be asked for written consent. The investigator must not start any trial-specific procedure before the Informed Consent Form is signed and dated by both the patient and the investigator.

2.4. Concomitant medication

Due to the underlying antibody deficiency, most of the patients are on immunoglobulin replacement therapy (IRT), which is permitted during the trial. Regarding systemic immunosuppression, steroid therapy up to daily dose of 20 mg prednisolone-equivalent is allowed, other immunosuppressive medications (including DMARDs, such as azathioprine or methotrexate and biologicals, such as adalimumab or rituximab) are prohibited. In case of previous immunosuppression, the washout period should be taken into account before study inclusion. Topical corticosteroids such as oral budesonide, inhaled medications (e.g. sympathomimetic or anticholinergic aerosols), as well as medications for comorbidities are allowed during the trial. The patients are advised to document on demand medication (day, dose) in their patient diary. Live vaccines are prohibited during the trial. Additionally, a three months period is mandatory between the last abatacept administration and the consideration of live vaccines.

2.5. Drug administration and monitoring

The trial participants themselves will administer 125 mg abatacept subcutaneously (s.c.) on a weekly basis. The first s.c. injection of the trial medication will be given at the trial site, followed up by a 30-min-long observation period. Here, trial participants will receive detailed education about the handling, the injection and the storage of abatacept. The medication will be provided in pre-filled syringes and handed out to the patients in cooled packs to assure the undisrupted cooling chain. Further injections will be self-administered by the patients at home. Patients are instructed to document each injection in the patient diary. Empty and unused syringes will be collected at the trial sites to check for drug administration compliance.

2.6. Visit schedule and assessments

A detailed visit flowchart is provided in the supplementary materials (Table S1). The schedule lists all assessments needed during the trial and indicates with an "X" when they have to be performed. All data obtained from these assessments must be available in the patient's source record and will be documented in the eCRF as well. The screening evaluation has to be performed within 90 days prior to the first administration of the trial medication. Follow-up visits (either on-site or phone visits) should occur on schedule, visits that occur ±7 days from the scheduled time point are not considered as protocol deviation (Fig. 1). The treatment phase starts with the baseline visit, during the study phase regular onsite and phone visits are planned. The end of treatment visit is scheduled for 12 months after baseline, the end of study visit, after a 3 months follow-up, 15 months after baseline.

2.6.1. Unscheduled visit "Virus control"

As the primary endpoint of the trial is the number of episodes of failed infection control, to confirm an elevated viral replication (EBV ≥5.000I U/ml and/or CMV ≥1.000 IU/ml) that was assessed during a standard trial visit, an unscheduled "Virus control" visit has to be scheduled within the next 7–14 days. Between these two assessments, the trial medication has to be paused. The required list of tests is enumerated in details in Table S1.

2.7. CHAI-Morbidity Score

To better asses longitudinally the clinical efficacy, CHAI-Morbidity-Score (Table 4) will be used The CHAI-Morbidity Score is a longitudinal disease assessment score that was developed based on the experience with the first 130 CTLA-4 insufficiency patients analyzed [12]. The CHAI-Morbidity score allows the longitudinal assessment of individuals with CTLA-4 insufficiency or LRBA deficiency and is based on common clinical and laboratory parameters used to monitor such patients (to

Table 4
CHAI-morbidity score.

Criteria	Score	Description
Lung involvement (GLILD)		
Diagnostic criterion: assessment of diffusion capacity	Severe (3 points)	severe impairment of diffusing capacity corrected for alveolar volume (DLCOc/VA < 50%)
	Moderate (2 points)	moderate impairment of diffusing capacity (DLCOc/VA 50–69%)
	Mild (1 point)	mild impairment of diffusing capacity (DLCOc/VA 70–85%)
	None (0 points)	normal diffusing capacity (DLCOc/VA >85%)
Diagnostic criterion: CT scan (evaluated by radiologist in agreement with immunologist)	Severe (3 points)	GLILD-typical lesions affecting >75% of the lungs in CT
	Moderate (2 points)	GLILD-typical lesions affecting >25%–75% of the lungs in CT
	Mild (1 point)	GLILD-typical lesions affecting ≤25% of the lungs in CT
	None (0 points)	no lesions
Gut involvement (enteropathy)		
Clinical criterion: stool frequency and quality within the last 24 h	Severe (3 points)	≥10 stools
	Moderate (2 points)	≥5 to 9 stools
	Mild (1 point)	≥3 to 4 stools OR any watery stool
	None (0 points)	normal stool consistency AND under 3 stools
Diagnostic criterion: Weight *Reference: weight at baseline*	Severe (3 points)	>10% loss of body weight (BW)
	Moderate (2 points)	5–10% loss of BW
	Mild (1 point)	1–5% loss of BW
	None (0 points)	weight stable
Diagnostic criterion: potassium in serum *(Ref. 3,5 - 5,*1 mmol/l*)*	Severe (3 points)	potassium ≤2,5 mmol/l
	Moderate (2 points)	potassium between 2.51 mmol/l and 2.99 mmol/l
	Mild (1 point)	potassium between 3 and 3.49 mmol/l
	None (0 points)	potassium ≥3.5 mmol/l
Cytopenia		
Diagnostic criterion: Thrombocytopenia	Severe (3 points)	platelets ≤10,000/μl
	Moderate (2 points)	platelets >10,000/μl to 50,000/μl
	Mild (1 point)	platelets >50,000/μl to 100,000/μl
	None (0 points)	platelets >100,000/μl
Diagnostic criterion: Anemia	Severe (3 points)	Hb ≤ 7 g/dl for adults OR pancytopenia
	Moderate (2 points)	Hb 7.1 g/dl to ≤ 9 g/dl for adults
	Mild (1 point)	Hb 9.1 g/dl to ≤ 10 g/dlfor adults
	None (0 points)	Hb > 10 g/dl for adults
CNS involvement		
Diagnostic criterion: cerebral lesions in cMRI/cCT. In case of screening refer to last performed cMRI or cCT before registration.	Severe (3 points)	abnormal CNS imaging with multifocal lesions
	Moderate (2 points)	abnormal CNS imaging with one solitary lesion
	Mild (1 point)	response under therapy with diminishing lesions in size and/or number (not to be assigned at screening)
	None (0 points)	normal CNS imaging without any lesion

(*continued on next page*)

Table 4 (*continued*)

Clinical criterion: neurological impairment (assessment based on neurological examination using the NANO Scale)	Severe (3 points)	≥5 points and/or in case of seizures ≥1/week
	moderate (2 points)	3-4 points and/or in case of seizures ≥1/month
	Mild (1 point)	1-2 point and/or in case of seizures ≥1/year
	None (0 points)	0 points, no seizures
Immune System		
Absolute total lymphocyte count	Severe (3 points)	<500/μl
	Moderate (2 points)	500-749/μl
	Mild (1 point)	750-1000/μl
	None (0 points)	>1000/μl
Absolute total $CD4^+$ T cell counts	Severe (3 points)	<200/μl
	Moderate (2 points)	200-350/μl
	Mild (1 point)	351-500/μl
	None (0 points)	>500/μl
Naïve ($CD4^+CD45RA+$) T cell % of $CD4^+$	Severe (3 points)	<10%
	Moderate (2 points)	10–14.9%
	Mild (1 point)	15–20%
	None (0 points)	>20%
CD4-T cell activation	Severe (3 points)	HLA-DR+ in $CD4^+ \geq 60\%$
	Moderate (2 points)	HLA-DR+ in $CD4^+ \geq 40\%$ but <60%
	Mild (1 point)	HLA-DR+ in $CD4^+ \geq 20\%$ but <40%
	None (0 points)	HLA-DR+ in $CD4^+ < 20\%$
PD1 expression on $CD8^+$ cells	Severe (3 points)	CD8+PD1+ in % of $CD8^+ \geq$ 60%
	Moderate (2 points)	CD8+PD1+ in % of $CD8^+ \geq$ 40% but <60%
	Mild (1 point)	CD8+PD1+ in % of $CD8^+ \geq$ 25% but <40%
	None (0 points)	CD8+PD1+ in % of $CD8^+ <$ 25%
Switched memory (CD19/20+, IgM-, $CD27^+$) B cell numbers in % of B cells	Severe (3 points)	CD19/20+, IgM-, CD27+: <2%
	Moderate (2 points)	CD19/20+, IgM-, CD27+: 2–4%
	Mild (1 point)	CD19/20+, IgM-, CD27+: 4–6%
	None (0 points)	CD19/20+, IgM-, CD27+: >6%
Lymphoproliferation		
Splenomegaly	Severe (3 points)	massive splenomegaly (maximum cephalocaudal diameter >20 cm)
	Moderate (2 points)	moderate splenomegaly (maximum cephalocaudal diameter 15.1–20 cm)
	Mild (1 point)	mild splenomegaly (maximum cephalocaudal diameter 11–15 cm)
	None (0 points)	maximum cephalocaudal diameter <11 cm
Lymphadenopathy	severe (3 points)	generalized lymphadenopathy (enlargement of more than two non-contiguous lymph node groups)
	Moderate (2 points)	localized lymphadenopathy (enlargement of two non-contiguous lymph node groups)
	Mild (1 point)	localized lymphadenopathy (enlargement of one lymph node group)
	None (0 points)	no lymphadenopathy
Lymphoproliferation measured via sIL2 receptor	Severe (3 points)	sIL2-receptor > 1,700U/ml
	Moderate (2 points)	sIL2-receptor > 1200 and ≤1,700U/ml
	Mild (1 point)	sIL2-receptor ≥ 700 and ≤1,200U/ml
	None (0 points)	sIL2-receptor < 700U/ml
Skin involvement		
Distribution	Severe (3 points)	more than 10% of body surface involved
	Moderate (2 points)	more than 5% (but less than 10%) of body surface involved
	Mild (1 point)	skin lesions on less than 5% of body surface
	None (0 points)	no skin lesions
Type of skin lesions	Severe (3 points)	ulcerative lesions, e.g. pyoderma-like skin lesions
	Moderate (2 points)	severe eczematous or psoriasis-like skin lesions, or vesicular skin rash
	Mild (1 point)	mild to moderate eczematous or psoriasis-like skin lesions, or erythematous skin
	None (0 points)	no skin lesions

ensure the score can be calculated for retrospectively collected patient's information). The score assesses the organ involvement of patients by various parameters, including blood work (immunophenotyping) and clinical data (stool frequency). To ensure comparability in case of missing values and between organ systems characterized by 2, 3 or 6 criteria, a mean score value will be calculated for each organ system separately. This approach allows assessing the effect of abatacept on the different organs involved.

Another important aspect of the CHAI-Morbidity Score is the possibility to be calculated in two ways. First, as it is used in this trial, to assess the current state of the disease and treatment. However, we propose another use of the score. A cumulative CHAI-Score can be calculated as well, which can serve as a quantitative assessment of one patient's disease history. In this case, the score should be calculated for each organ using retrospective data from the most severe disease state for that specific organ. This way, the score can be universally used for prospective and retrospective studies as well.

Additionally, to the clinical-laboratory measurements, the patient-reported outcome (measured by three questionnaires) supports the determination of the efficacy. With the combination of these datasets, the ABACHAI study aims to identify the patients, who would mostly benefit from the abatacept treatment.

2.8. Premature termination of the trial

Patients participating in the clinical trial can have his/her trial treatment terminated prematurely at any time, without having to give reasons. Furthermore, the treatment of a patient can or need to be terminated under the following conditions:

- Adverse events (including intercurrent illnesses) which preclude further treatment with the investigational medicinal product (IMP) or make further participation in the clinical trial inadvisable because the informational value of the trial results is impaired.
- Premature termination of the trial treatment is considered to be medically indicated, e.g. because it is subsequently found that inclusion/exclusion criteria were violated.
- Continuation of the trial treatment is unacceptable when the risks outweigh the benefits.
- Pregnancy
- Significant violations of the trial protocol (e.g. taking prohibited medication).

- Lack of compliance on the part of the patient.
- Logistical reasons (patient changes his/her doctor or hospital or moves to another location).
- Worsening of clinical signs of CTLA4 insufficiency of LRBA deficiency that indicates the extension of the therapy beyond abatacept (progress)

2.9. Adverse events and serious adverse events

Adverse events will be documented in the electronic Case Report Form (eCRF) following the participant's written consent until 30 days after the last application of trial medication. Established guidelines and definitions, standard operating procedures as well as applicable laws and regulations will be followed in the documentation and reporting of adverse events.

2.10. Data confidentiality and data management

Information about patients participating in the clinical trial will be kept confidential and managed under the applicable laws and regulations. The data collected during the trial will be stored and evaluated in a pseudonymized form. Data management will be performed with the eCRF system secuTrial® (https://www.secutrial.com/, interActive Systems GmbH), a system in compliance with good clinical practice. Access to the system will be controlled by individually assigned user identification codes and passwords. Access to the data will be limited to authorized and trained staff.

2.11. Statistical analysis

2.11.1. Sample size determination

The determination of the sample size in this orphan disease setting is based on feasibility considerations. As a simplified approach to the analysis of the primary endpoint, number of episodes of failed infection control under therapy with abatacept during the trial period of one year, we consider the width of a two-sided 95% confidence interval for the expected number of episodes, based on the normal approximation of the Poisson distribution. The Poisson distribution is characterized by equality of the expected value and the variance. With this prerequisite, we can determine the size of a two-sided 95% confidence interval. If e.g. four episodes can be expected and the sample size is 20, a two-sided 95.0% confidence interval for the expected number of episodes will extend 0.88 from the observed mean. If six infectious episodes can be expected, a two-sided 95.0% confidence interval for the expected number of episodes will extend 1.07 from the observed mean.

2.11.2. Statistical analysis

Analyses will be based on all patients recruited for the study who received abatacept treatment within the trial.

The primary endpoint (the number of episodes of failed infection control under therapy with abatacept during the trial period of one year) will be counted under trial therapy, which is planned to be one year. In order to account for potential protocol violations or therapy discontinuations, the primary analysis will be performed in terms of an annual incidence rate, thus taking into account that the times under observation may vary. A point estimate and a two-sided 95% confidence interval based on the normal distribution approximation will be presented. All episodes of failed infection control will be tabulated for each patient with detailed information about the type, consequences and further circumstances.

The number of episodes of failed infection control will be compared between the 12 months prior to first treatment with abatacept (where available) and the 12 months during trial treatment by using a Poisson model with patients as random effects and time phase as fixed effect and taking individual differences in risk times into account. The difference will be described by the annual incidence in the two phases, the incidence ratio, and a 95% confidence interval. These analyses will be regarded as descriptive, as the data prior to trial therapy are possibly available for few patients only.

Secondary endpoints of the same type as the primary endpoint (e.g. number of severe infections) will be analyzed in the same way as planned for the primary endpoint.

Further secondary outcomes will be analyzed descriptively. OS and EFS will be described using the Kaplan-Meier method. Rates (e.g. treatment failure rate, defined as the number of treatment failures divided by the number of patients receiving abatacept) will be estimated using the binomial distribution with an exact two-sided 95% confidence interval.

No interim analysis is planned.

2.12. Data Safety Monitoring Board (DSMB)

To assure the safety of participants in the study, an independent Data Safety Monitoring Board (DSMB) has been established with the function to monitor the course of the trial and if necessary to give recommendations to the sponsor/coordinating investigator for discontinuation, modification or continuation of the trial. It is the task of the DSMB to examine whether the process of the trial is acceptable and whether safety of the patients is ensured. For this, the DSMB has to be informed about the adherence to the protocol, the patient recruitment, and the observed adverse events periodically. In the case of an episode of failed infection control (see Table 1 for definitions), the DSMB has to be informed immediately to decide about the continuation of trial medication. The DSMB will be provided with pseudonymized data exports.

2.13. Quality assurance

Onsite Monitoring as well as Risk Based Quality Management will be performed on a regular basis by the Clinical Trials Unit of the Medical Center – University of Freiburg as a continuous measure of quality assurance. Sponsor audits and inspections by regulatory authorities may be conducted at any time.

2.14. Protocol version

The trial was started with the protocol version V2.0 (dated 21.04.2020). Subsequently two amendments were required and therefore the current protocol version is V04 (23.07.2021) including the amendments. Amendments were related to change of coordinating investigator, clarifying inclusion and exclusion criteria, addition of secondary endpoints and elongation of screening period. All study protocols and amendments were positively evaluated by the Ethics Committee of the University of Freiburg and the "Paul-Ehrlich-Institut". All amendments did not conflict with previous inclusion of participants.

All further amendments will be documented, communicated to the funder, the sponsor, the trial centers and the DSMB. Amendments will be reported in resulting publications.

2.15. Ethics approval and patient consent

The trial has been approved by the Ethics Committee of the University of Freiburg (No. 42/20 (FF-MC)) and by the German national competent authority ("Paul-Ehrlich-Institut", Federal Institute for Vaccines and Biomedicines, Langen, Germany). Part of the trial protocol is a patient informed consent form, describing the trial, the tested medicinal product including potential risks, and alternative treatment options (see section 2.3).

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3. Discussion

Genetic defects of the CTLA-4-pathway can lead to rare, but severe systemic immune-mediated diseases. As CTLA-4 insufficiency and LRBA deficiency are rare diseases, many of the therapeutic options are administered off-label. Currently, treatment of these patients is based on the type of organ involvement of the disease and is not linked to disease pathogenesis [30]. The recently published retrospective analysis by Egg et al. [30] proposed organ-specific treatment guidelines. However, as the authors point out, controlled clinical trials are needed for an improved assessment of the various treatment options [30].

Using abatacept in CTLA-4 pathway-defects is a targeted personalized treatment option, replacing the missing or functionally impaired protein. It is currently one of the most commonly used therapeutic agents in these diseases. Egg et al. [30] reported on 29 patients receiving abatacept therapy out of a cohort of 123 clinically symptomatic patients with CTLA-4 insufficiency. Previously published data suggested, that in CVID abatacept may alleviate the autoimmune enteropathy [12,20,31], be effective for treatment of cytopenias [30] or GLILD [22], however, safety studies and lacking and long-term application datasets are currently not available [30].

The ABACHAI trial focuses therefore on the safety and the efficacy of abatacept treatment in patients with CTLA-4 insufficiency or LRBA deficiency. Infections are one of the most common side effects of the therapy with abatacept [18]; therefore, safety was chosen as the primary endpoint for this clinical trial. As worsening of clinical symptoms associated with the underlying immune dysregulation under abatacept treatment may lead to a drop-out of the patient, analysis of ABACHAI needs to account for this to not magnify efficacy data when non-responders are excluded. Results of this clinical trial are expected for 2023.

4. Publication, availability of data and material

Study results will be published in a suitable peer-review journal. Aggregate data and analyses of data will be published. Participant-level data and materials may be made available to the extent permitted by data protection legislation after the study is completed and published.

Author's contributions

BG, CIR, GI, MK, RS designed the trial. AU, BG, CIR, GI, MK wrote the trial protocol and additional documents. BG and KW are the principal investigators. MK, SG, GS are physicians conducting the trial. MF, ID, LA and MR contributed as part of the DSMB. AU is the trail manager, GI is the biostatistician of the trial. All authors contributed to the writing of the manuscript and indorsed its final version.

Declaration for competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The other authors do not have any competing interests.

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Appendix A. Supplementary data

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References

[1] B. Lo, et al., CHAI and LATAIE, New genetic diseases of CTLA-4 checkpoint insufficiency, Blood 128 (2016) 1037–1042.
[2] K.I. Mead, et al., Exocytosis of CTLA-4 is dependent on phospholipase D and ADP ribosylation factor-1 and stimulated during activation of regulatory T cells, J. Immunol. 174 (2005) 4803–4811.
[3] E. Chuang, et al., Interaction of CTLA-4 with the clathrin-associated protein AP50 results in ligand-independent endocytosis that limits cell surface expression, J. Immunol. 159 (1997) 144–151.
[4] B. Lo, et al., Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy, Science 349 (2015) 436–440.
[5] D. Schubert, et al., Autosomal dominant immune dysregulation syndrome in humans with CTLA4 mutations, Nat. Med. 20 (2014) 1410–1416.
[6] H.S. Kuehn, et al., Immune dysregulation in human subjects with heterozygous germline mutations in CTLA4, Science 345 (2014) 1623–1627.
[7] S. Zeissig, et al., Early-onset Crohn's disease and autoimmunity associated with a variant in CTLA-4, Gut 64 (2015) 1889–1897.
[8] H. Abolhassani, L. Hammarström, C. Cunningham-Rundles, Current genetic landscape in common variable immune deficiency, Blood 135 (2020) 656–667.
[9] D.J.A. Bogaert, et al., Genes associated with common variable immunodeficiency: one diagnosis to rule them all? J. Med. Genet. 53 (2016) 575–590.
[10] P. Maffucci, et al., Genetic diagnosis using whole exomesequencing in common variable immunodeficiency, Front. Immunol. 7 (2016).
[11] M. López-Nevado, et al., Primary immune regulatory disorders with an autoimmune lymphoproliferative syndrome-like phenotype: immunologic evaluation, early diagnosis and management, Front. Immunol. 12 (2021).
[12] C. Schwab, et al., Phenotype, penetrance, and treatment of 133 cytotoxic T-lymphocyte antigen 4–insufficient subjects, J. Allergy Clin. Immunol. 142 (2018) 1932–1946.
[13] D. Egg, et al., Increased risk for malignancies in 131 affected CTLA4 mutation carriers, Front. Immunol. 9 (2018).
[14] T.Z. Hou, et al., Identifying functional defects in patients with immune dysregulation due to LRBA and CTLA-4 mutations, Blood 129 (2017) 1458–1468.
[15] S. Habibi, et al., Clinical, immunologic, and molecular spectrum of patients with LPS-responsive beige-like anchor protein deficiency: a systematic review, J. Allergy Clin. Immunol. Pract. 7 (2019) 2379–2386, e5.
[16] D. Benjamin, M. Colombi, C. Moroni, M.N. Hall, Rapamycin passes the torch: a new generation of mTOR inhibitors, Nat. Rev. Drug Discov. 10 (2011) 868–880.
[17] N.M. Chapman, H. Chi, mTOR signaling, Tregs and immune modulation, Immunotherapy 6 (2014) 1295–1311.
[18] European Medicines Agency, Orencia: EPAR - Product Information, 2020. https://www.ema.europa.eu/en/medicines/human/EPAR/orencia#product-information-section.
[19] European Medicines Agency, Orencia (Abatacept): an Overview of Orencia and Why it Is Authorised in the EU, 2019. https://www.ema.europa.eu/en/medicines/human/EPAR/orencia.

[20] S. Lee, et al., Abatacept alleviates severe autoimmune symptoms in a patient carrying a de novo variant in CTLA-4, J. Allergy Clin. Immunol. 137 (2016) 327–330.
[21] D. Khanna, et al., Abatacept in early diffuse cutaneous systemic sclerosis: results of a phase II investigator-initiated, multicenter, double-blind, randomized, placebo-controlled trial, Arthritis Rheumatol. 72 (2020) 125–136.
[22] C. von Spee-Mayer, et al., Abatacept use is associated with steroid dose reduction and improvement in fatigue and CD4-dysregulation in CVID patients with interstitial lung disease, J. Allergy Clin. Immunol. Pract. 9 (2021) 760–770.
[23] M. Bullinger, I. Kirchberger, J. Ware, Der deutsche SF-36 Health Survey Übersetzung und psychometrische Testung eines krankheitsübergreifenden Instruments zur Erfassung der gesundheitsbezogenen Lebensqualität, Z. Gesundh. Wiss. 3 (1995) 21.
[24] J.J. Swigris, et al., The SF-36 and SGRQ: validity and first look at minimum important differences in IPF, Respir. Med. 104 (2010) 296–304.
[25] K.-H. Janke, B. Klump, U. Steder-Neukamm, J. Hoffmann, W. Häuser, Validierung der Deutschen Version (Kompetenznetz „Chronisch entzündliche Darmerkrankungen") des Inflammatory Bowel Disease Questionnaire IBDQ-D TT - validation of the German Version of the Inflammatory Bowel Disease Questionnaire (Competence Network IBD, Psychother Psych Med 56 (2006) 291–298.
[26] K.-H. Janke, et al., Lebensqualität bei chronisch entzündlichen Darmerkrankungen (CED): die deutsche Version des Inflammatory Bowel Disease Questionnaire (IBDQ-D) zur krankheitsspezifischen Lebensqualitätsmessung – erste Anwendung und Vergleich mit anderen internationalen Fas, Gesundheitswesen 67 (2005) 656–664.
[27] W. Häuser, et al., Validation of the inflammatory Bowel disease questionnaire IBDQ-D, German version, for patients with ileal pouch anal anastomosis for ulcerative colitis, Z. Gastroenterol. 42 (2004) 131–139.
[28] L. Nayak, et al., The Neurologic Assessment in Neuro-Oncology (NANO) scale: a tool to assess neurologic function for integration into the Response Assessment in Neuro-Oncology (RANO) criteria, Neuro Oncol. 19 (2017) 625–635.
[29] CTFG (Clinical Trial Facilitation Group), Recommentdations Related to Contraception and Pregnancy Testing in Clinical Trials, 2014. https://www.hma.eu/ctfg.html.
[30] D. Egg, et al., Therapeutic options for CTLA-4 insufficiency, J. Allergy Clin. Immunol. (2021), https://doi.org/10.1016/j.jaci.2021.04.039.
[31] N.K. Gupta, O. Yilmaz, M. Fisher, V. Yajnik, Abatacept: a new treatment option for refractory adult autoimmune enteropathy, J. Clin. Gastroenterol. 48 (2014) 55–58.