# Clinical Trial Protocol

**An open label phase II study of sirolimus in patients with segmental overgrowth syndrome**

**SIPA-SOS**

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| **EudraCT No.** | 2015-005416-15 |
| **DRKS-No.** | DRKS00010085 |
| **Internal Protocol ID No.** | SIPA-SOS |
| **Protocol Version** | 5.0 / 11.11.2020 |
| **Replaced Protocol Version:** | 4.1 / 02.11.2016 |
| **Development Phase** | Phase II |
| **Sponsor** | **Medical Center - University of Freiburg**<br>represented by the Chief Medical Officer and the Chief Financial Officer<br>Breisacher Str. 153<br>79110 Freiburg, Germany |
| **Coordinating Investigator**<br>(LKP in accordance with AMG) | Dr. med. Friedrich Kapp<br>Medical Center – University of Freiburg<br>Center for Pediatrics<br>Department of Pediatric Hematology and Oncology<br>Mathildenstraße 1<br>79106 Freiburg, Germany |

# Approval of the Clinical Trial Protocol

## An open label phase II study of sirolimus in patients with segmental overgrowth syndrome

**EudraCT No.:** 2015-005416-15

**Protocol Version No:** 5.0 / 11.11.2020

**Coordinating Investigator**
*"Leiter der Klinischen Prüfung/ LKP"*
*(in accordance with German Drug Law)*
Dr. Friedrich Kapp

09.12.2020
Date

[redacted]
Signature

**Biostatistician**
Dr. Claudia Schmoor

10.12.2020
Date

[redacted]
Signature

**Sponsor representative**
delegated to
Dr. Friedrich Kapp

09.12.2020
Date

[redacted]
Signature

# Amendment to protocol version 4.1

## Rationale for substantial amendment

The primary purpose of this amendment was a better definition of inclusion/exclusion criteria and endpoints. Most importantly, stable disease has been removed as successful treatment outcome, obviating the need for the observation period before therapy start. There are administrative modifications (inclusively change of the coordinating investigator and project manager, redistribution of responsibilities for the conduct of the study, update of addresses, introduction of data monitoring committee (DMC), some wording specifications and use of the CTCAE Version 5.0 instead off 4.0.

### Summary of changes to the clinical trial protocol: (relevant changes in bold type)

| Section / Page | Previous wording: | New wording: |
|---|---|---|
| Clinical Trial Protocol / 1, Approval of the CTP / 2, Responsibilities / 22 | Coordinating Investigator:<br>Prof. Dr. med. Jochen Rössler | Coordinating Investigator:<br>Dr. med. Friedrich Kapp |
| Responsibilities/ 22 | Sponsor:<br>….<br>represented by the Chief Medical Officer<br>Hugstetter Str. 49, 79106 Freiburg<br><br>Pharmacovigilance:<br>E-Mail: stuz-pv@uniklinik-freiburg.de | Sponsor:<br>….<br>represented by the Chief Medical Officer **and the Chief Financial Officer**<br>Breisacher Str. 153, 79110 Freiburg<br><br>Pharmacovigilance:<br>E-Mail: zks.pv@list.uniklinik-freiburg.de |
| Approval of the CTP / 2 | Sponsor representative:<br>Prof. Dr. Jochen Rössler | **Sponsor representative:**<br>**Dr. Friedrich Kapp** |
| Investigator Statement / 10 | Investigator Statement | Investigator Statement (ergänzt)<br>I confirm that I and my colleagues were informed by a responsible scientist about the results and expected risks of the pharmacological and toxicological examination associated with the clinical trial.<br>I confirm that I will be responsible for supervising any individual or party to whom I delegate study tasks conducted at the trial site. |
| Synopsis / 17 | Synopsis<br>Primary objective:<br>The study aim is to assess the effect of sirolimus to stabilize or reduce the size of defined progressive target lesions in patients with segmental overgrowth syndrome until 6 months of therapy | Synopsis<br>Primary objective:<br>The study aim is to assess the effect of sirolimus to reduce the size of defined progressive target lesions in patients with segmental overgrowth syndrome until 6 months after start of therapy |

| Section / Page | Previous wording: | New wording: |
|---|---|---|
| Synopsis / 17 | Secondary objectives:…..<br>• To evaluate changes in health-related Quality of Life | **Secondary objectives:…..**<br>• To evaluate changes in health-related Quality of Life<br>• **To evaluate changes in pain** |
| Synopsis / 18, 4.2 / .43 | Inclusion criteria<br>1. Male or female patients aged ≥ 3 years.<br>2. Signed written informed consent (patient ≥ 18 years or person(s) having the care and custody of the patient < 18 years).<br>3. Segmental overgrowth syndrome patients independently of genetic background (that means with/without PTEN germline mutations or with/without AKT/PI3K somatic mutations in an overgrowth lesion).<br>4. Patients who meet clinical criteria for segmental overgrowth syndromes including soft tissue lesion(s) composed of one or several tissue components such as fat, vessels, muscle or connective tissue. The patient must present functional impairment and/or pain due to the segmental overgrowth lesion(s).<br>5. Identification of at least one measurable target lesion (up to 5 target lesions) with longest diameter more than ≥ 50 mm by MRI. The target lesion(s) must be externally visible (photos) and composed by soft tissue (see inclusion criteria no. 4).<br>6. At least one measurable target lesion must show radiological progression (MRI according to response criteria (Appendix 5 and Appendix 6) at the end of the observation period compared to MRI at screening to continue study and enter in the therapeutic period.<br>7. Normal organ and bone marrow function (i.e. transaminase levels < 2.5 x ULN or serum bilirubin < 1.5 x ULN, hemoglobin > 9 g/dL).<br>8. Negative urine pregnancy test in females with a childbearing potential (details see chapter 4.2). | 1. Male or female patients aged ≥ 3 years **(no upper limit).**<br>2. Signed written informed consent (patient ≥ 18 years or person(s) having the care and custody of the patient < 18 years).<br>3. Ability to understand the nature of the trial and the trial related procedures and to comply with them.<br>4. Segmental overgrowth syndrome patients independently of genetic background.<br>**These diagnoses include patients with**<br>• **CLOVES syndrome, Klippel-Trenaunay-Syndrome and other PIK3CA related overgrowth spectrum diseaess**<br>• **Proteus syndrome**<br>• **PTEN hamartoma tumor syndromes including patients with PTEN hamartoma of soft tissue (PHOST)**<br>• **Vascular malformations with significant overgrowth (lesion size of at least 5 cm diameter, externally visible), including but not limited to lymphatic malformations, venous malformations, and fibro-adipose vascular anomaly (FAVA)**<br>5. Patients who meet clinical criteria for segmental overgrowth syndromes including soft tissue lesion(s) composed of one or several tissue components such as fat, vessels, muscle or connective tissue.<br>6. Identification of at least one measurable target lesion (up to 5 target lesions) with longest diameter more than **≥ 30 mm** by MRI. The target lesion(s) must be externally visible (photos) and composed by soft tissue (see inclusion criteria no. 4).<br>7. Normal organ and bone marrow function (i.e. transaminase levels < |

| Section / Page | Previous wording: | New wording: |
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| | 9. If female and of child-bearing potential, documentation of negative pregnancy test prior to enrollment. Sexually active female patients (and female partners of male patients) must use adequate contraceptive measures while on study and for up to 12 weeks after ending treatment (details see chapter 4.2). | 2.5 x ULN or serum bilirubin < 1.5 x ULN, hemoglobin > 9 g/dL).<br>8. Negative urine pregnancy test in females with a childbearing potential (details see section 4.2).<br>9. If female and of child-bearing potential, documentation of negative pregnancy test prior to enrollment. Sexually active female patients, male patients and female partners of male patients must use adequate contraceptive measures while on study and for up to 12 weeks after ending treatment. (details see section 4.2). |
| Synopsis / 19,<br>4.3 / 43-44 | Exclusion Criteria:<br>Patients who do not show progression of defined target lesion (MRI according to response criteria (see Appendix 5 and Appendix 6).<br>Target lesion is accessible for complete surgical removal or present pure cosmetic disturbance and no functional impairment/pain<br>1. Any concurrent therapy with chemotherapy agents or biologic agents or radiation therapy.<br>2. Patients who have received live vaccines in the past 30 days prior to informed consent.<br>3. Patients on medication with CYP3A4 inhibitors/inducers which are not replaced by other equivalent medications for the study period.<br>4. Patients who have known immunodeficiency or HIV seropositivity.<br>5. Patients with known interstitial lung disease, pneumonitis or with bleeding diathesis.<br>6. Patients with prior use of sirolimus or other mTOR inhibitors or any analogue within the last 4 weeks before start of observation period; regardless of therapeutic effect, but with risk assessment due to former side effects.<br>7. Any planned surgery within study period. | Exclusion Criteria:<br>~~**Patients who do not show progression of defined target lesion (MRI according to response criteria (see Appendix 5 and Appendix 6)).**~~<br>~~**Target lesion is accessible for complete surgical removal or present pure cosmetic disturbance and no functional impairment/pain**~~<br>1. Any concurrent therapy with chemotherapy agents or biologic agents or other immunosuppressive therapy or radiation therapy.<br>2. Patients who have received live vaccines in the past 30 days prior to informed consent.<br>3. Patients on medication with CYP3A4 inhibitors/inducers which are not replaced by other equivalent medications for the study period.<br>4. Patients who have known immunodeficiency or HIV seropositivity.<br>5. Patients with known history of prior and/or ongoing malignancy within the last 5 years.<br>6. Patients with known interstitial lung disease, pneumonitis or with bleeding diathesis.<br>7. Patients with prior use of sirolimus or other mTOR inhibitors or any analogue within the last 6 months;<br>8. Any planned surgery within study period related to overgrowth lesions.<br>18. Patients must abstain from donating blood, semen, or sperm during participation in the study until 3 |

| Section / Page | Previous wording: | New wording: |
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| | | months after the end of participation in the study |
| Synopsis / 21,<br>3.1 / 40 | Trial design:<br>This is an open-label, multicenter, single-arm, phase II clinical trial of sirolimus in patients with segmental overgrowth syndrome.<br>Patients will enter an observation period of 6 months to demonstrate progression of at least one lesion (up to 5) and if progression or pain or functional impairment/disfigurement is present will continue a therapy period with sirolimus for 6 months. | Trial design:<br>This is an open-label, multicenter, single-arm, phase II clinical trial of sirolimus in patients with segmental overgrowth syndrome. |
| Synopsis / 20,<br>2. / 39 | Primary End Points:<br>Best response: Complete Remission (CR), Partial Remission (PR) or Stable Disease (SD) until 6 months after baseline (start of study therapy) measured by MRI according to response criteria (Appendix 5 and Appendix 6) | Primary End Points:<br>**Best response: Complete Remission (CR)-or Partial Remission (PR) until 6 months after baseline (start of study therapy) measured by MRI according to response criteria (section 7.5).** |
| Synopsis / 20 | Key secondary endpoints:<br>Changes in quality of life after 3 and 6 months of therapymonths compared to baseline (KINDL® parents und Kid-KINDL®; Lansky/Karnofsky scale, WHOQOL-BREF). | Key secondary endpoints (ergänzt):<br>Changes in quality of life including pain after 3 and 6 months of therapy compared to baseline (KINDL® parents und Kid-KINDL®; Lansky/Karnofsky scale, WHOQOL-BREF)<br>**Changes in pain after 3 and 6 months of therapy compared to baseline by visual pain scales for adults and children.** |
| Synopsis / 20 | Statistical analysis:<br>According to the design, 18 patients will be included in the study. If the observed number of patients with best response CR, PR or SD is 2 or more out of 18, sirolimus will be considered as effective | Statistical analysis:<br>According to the design, 18 patients will be included in the study. If the observed number of patients with best response CR or PR is 2 or more out of 18, sirolimus will be considered as effective |
| Synopsis / 20 | Trial duration:<br>Recruitment period (months): 30<br>First patient in to last patient out (months): 45<br>Duration of the entire trial (months): 51<br>Treatment duration per patient (months):<br>6 months observation period + 6 months therapy period + 3 months Follow-Up | Trial duration:<br>Recruitment period (months): 21<br>First patient in to last patient out (months): 30<br>Duration of the entire trial (months): 36<br>Treatment duration per patient (months):<br>**6 months therapy period + 3 months Follow-Up** |
| Synopsis / 20,<br>3.5 / 42 | Timetable:<br>Enrolment of first patient (FPFV)<br>3rd quarter 2016<br>Enrolment of last patient (registration)<br>1st quarter 2019<br>End of trial for last patient (LPLV) | Timetable:<br>Enrolment of first patient (FPFV)<br>1stquarter 2021<br>Enrolment of last patient (registration)<br>4th quarter 2022<br>End of trial for last patient (LPLV) |

| Section / Page | Previous wording: | New wording: |
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| | 2nd quarter 2020<br>Clinical Study Report (CSR)<br>2nd quarter 2021 | 3rd quarter 2023<br>Clinical Study Report (CSR)<br>1st quarter 2024 |
| Synopsis / 21 | | FUNDERS<br>**The clinical trial will be financed by the Research Innovation Fund of the University of Freiburg and by the Deutsche Forschungsgemeinschaft (DFG). IMP (sirolimus) will be provided free of charge by PFIZER Pharma GmbH** |
| Responsibilities / 22 | Project Coordinator:<br>Dr. Maria Huber<br>Medical Center – University of Freiburg<br>Clinical Trials Unit Freiburg<br>Elsaesser Str. 2, 79110 Freiburg, Germany<br>Phone: +49 761 270-74030<br>Fax: +49 761 270-74250<br>E-Mail: maria.huber@uniklinik-freiburg.de | Project Manager:<br>**Susanne Grüninger**<br>Medical Center – University of Freiburg<br>Clinical Trials Unit Freiburg<br>Elsaesser Str. 2, 79110 Freiburg, Germany<br>Phone: 49 761 270-46940<br>Fax: +49 761 270-46990<br>E-Mail: zkj.sipa-sos@uniklinik-freiburg.de |
| Responsibilities / 22-23 | | **Data Monitoring Committee with members and contacts** |
| 1.3 / 38 | | If residual biomaterial from study patients is made available to the **Hilda Biobank** during the course of the study, it would be possible to link analyses from the biomaterial with clinical data from the study. This will allow the investigators to develop targeted research projects on segmental overgrowth syndromes to gain more knowledge on these rare diseases. |
| 2. / 39 | Objectives and Endpoints<br>… | Objectives and Endpoints:<br>…<br>**To evaluate changes in pain:**<br>**Changes in pain after 3 and 6 months of therapy compared to baseline by visual pain scales for adults and children** |
| 3.1 / 40 | Observation period<br>After patients registration for the study, target lesions will be observed for 6 months and evaluated thereafter and only patients presenting<br>- progression of lesions<br>- presence of functional impairment or pain due to lesions<br>will start the therapy period and take the study medication. If these criteria are not | ~~**Observation period**~~<br>~~After patients registration for the study, target lesions will be observed for 6 months and evaluated thereafter and only patients presenting~~<br>~~- progression of lesions~~<br>~~- presence of functional impairment or pain due to lesions~~<br>~~will start the therapy period and take the study medication. If these criteria are not~~ |

| Section / Page | Previous wording: | New wording: |
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| | detected, patient will exit the study. | ~~detected, patient will exit the study.~~ |
| 6. / 45 | Observation period: plan and procedure | ~~**Observation period: plan and procedure**~~ |
| 7.2 / 54 | Trial schedule:<br>Quality of Life questionnaire (KINDL®) | Trial schedule:<br>Quality of Life questionnaire (KINDL®), Pain scales |
| 7. / 58, 60, 61, 62 | - | Assessments:<br>Pain assessment: The pain scales are to be filled out by the patient him/herself. It is important that the investigator is not influencing the patient in any way |
| 7.5.1 / 62 | Eligibility for evaluation:<br>… The radiological assessment will be performed locally. | Eligibility for evaluation:<br>… The radiological assessment will be performed locally. **Central review of radiological assessment date will be performed at Medical Center – University of Freiburg.** |
| 7.9 / 66 | | Pain assessment:<br>Pain assessment will be done together with QOL-assessment. The pain scales are to be filled out by the patient him/herself. Two age-adapted pain scales for adults/teenagers (≥ 14 years) and children (3-13 years) are provided. |
| 7.10 / 66 | | 7.10 Patient diary |
| 9. / 69-71 | 9.Investigational medicinal product | Gesamtkapitel ergänzt |
| 12.4 / 81 | | Data Monitoring Committee<br>The sponsor will appoint 3 persons (see section “Responsibilities”) not involved in the study and known as experienced in statistics, pediatric onco-hematology and pediatrics to form the DMC. The DMC advises the sponsor and the study management with regard to patient safety in the context of the present clinical trial.<br><br>The DMC will make recommendations regarding continuation, modification or termination of the clinical trial. Further details and procedures are described in the study specific DMC Charter. |
| 13.3 / 82 | Sample size calculation is based on the primary endpoint best response CR, PR or SD 6 months. | Sample size calculation is based on the primary endpoint best response CR or PR 6 months. |
| 13.3 / 82 | The required sample size is 18 patients. If there are 2 or more patients with best response CR, PR or SD, sirolimus will be considered as effective. | The required sample size is 18 patients. If there are 2 or more patients with best response CR or PR, sirolimus will be considered as effective. |
| 13.5.3 / 84 | *Primary endpoint*<br>18 patients will be included in the trial. If the observed number of patients with a best response CR, PR or SD until 6 | *Primary endpoint:*<br>18 patients will be included in the trial. If the observed number of patients with a best response CR or PR until 6 months |

| Section / Page | Previous wording: | New wording: |
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| | months after start of treatment is 2 or more out of 18, sirolimus will be considered as effective and will be evaluated in further trials. With this decision rule, the error probability of regarding sirolimus as effective when the probability of best response CR, PR or SD until 6 months after start of treatment is 2% or lower (type I error α) is less than 5% (one-sided), and the error probability of regarding sirolimus as not effective when the probability of best response CR, PR or SD until 6 months after start of treatment is 20% or higher (type II error β) is less than 10%. The probability of best response CR, PR or SD until 6 months after start of treatment will be estimated with 90% confidence interval (corresponding to the planned test procedure) and with 95% confidence interval based on the exact binomial distribution. | after start of treatment is 2 or more out of 18, sirolimus will be considered as effective and will be evaluated in further trials. With this decision rule, the error probability of regarding sirolimus as effective when the probability of best response CR or PR until 6 months after start of treatment is 2% or lower (type I error α) is less than 5% (one-sided), and the error probability of regarding sirolimus as not effective when the probability of best response CR or PR until 6 months after start of treatment is 20% or higher (type II error β) is less than 10%. The probability of best response CR or PR - until 6 months after start of treatment will be estimated with 90% confidence interval (corresponding to the planned test procedure) and with 95% confidence interval based on the exact binomial distribution. |
| 13.5.4 / 84 | *Secondary endpoints for efficacy*<br>The morphological changes in disfigurement, quality of life, changes in neuropsychological tests, changes in IGFBP-3, IGF, VEGF, and inhibition of mTOR in PBMCs will be analysed descriptively | *Secondary endpoints for efficacy*<br>The morphological changes in disfigurement, quality of life including pain, changes in neuropsychological tests, changes in IGFBP-3, IGF, VEGF, and inhibition of mTOR in PBMCs will be analysed descriptively. |
| 17.1./ 89 | Financing of the trial:<br>The clinical trial will be financed by the Research Innovation Fund of the University of Freiburg. | Financing of the trial:<br>The clinical trial will be financed by the Research Innovation Fund of the University of Freiburg and by the Deutsche Forschungsgemeinschaft (DFG). |
| 17.4. / 90 | Clinical trials registry:<br>The trial will also be registered in a public register. | Clinical trials registry:<br>The trial has been registered in the German Clinical Trials Registry: DRKS00010085 |
| App.4 / 119-121 | na | Appendix 4: WHOQOL-BREF |
| App.5. / 122 | na | Appendix 5 :<br>Pain scales for adults/teenagers and children |

## Investigator Statement

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|---|---|
| **Protocol Short Title:** | SIPA-SOS |
| **EudraCT No.:** | 2015-005416-15 |
| **Protocol Version No:** | 5.0 / 11.11.2020 |
| **Trial Center:** | <Center No. and Name of Trial Center> |
| **Investigator:** | <Name of Investigator> |

I confirm that I have read the Clinical Trial Protocol (CTP) and hereby commit myself to adhere to all actions and terms as specified in the relevant sections of the clinical, ethical and general paragraphs.

I confirm that I and my colleagues will comply with the local legislation (in Germany, the German Drug Law with the appropriate amendments). I further confirm that the Clinical Trial will be carried out in compliance with the Declaration of Helsinki and ICH-GCP guidelines.

I acknowledge that all confidential information in this document will not be used or circulated without the prior written consent of the Sponsor.

Under my supervision I put copies of this CTP and possible updates as well as access to all information regarding the carrying out of this clinical trial at the disposal of my colleagues; in particular I will promptly forward all information from the Sponsor in relation to Drug Safety (SUSARs, update of SmPC) to my colleagues.

I confirm that I and my colleagues were informed by a responsible scientist about the results and expected risks of the pharmacological and toxicological examination associated with the clinical trial.
I will discuss this CTP in detail with my colleagues and ensure that they are comprehensively informed about the trial compound/preparation and the execution of the study.

I confirm that I will be responsible for supervising any individual or party to whom I delegate study tasks conducted at the trial site.
Furthermore I commit myself not to commence patient enrolment before the approval of the competent authorities (CA) and acceptance by the responsible Independent Ethics Committee (IEC).

| Date | Name of Investigator | Signature of Investigator |
|---|---|---|

## Table of Contents

# List of Abbreviations

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|---|---|
| ADR | Adverse drug reaction |
| AE | Adverse Event |
| AKT/PI3K | an intracellular signaling pathway |
| ALT | Alanin-Aminotransferase |
| AMG | German Drug Law (Arzneimittelgesetz) |
| AST | Aspartat-Aminotransferase |
| ATC | Anatomisch-Therapeutisch-Chemischen |
| AUC | Area under blood concentration-time curve |
| BOOP | Bronchiolitis obliterans organising pneumonia |
| BSA | Body surface area |
| CA | Competent Authority |
| cmax | Maximum blood concentration |
| CONSORT | Consolidated Standards Of Reporting Trials |
| CPK | Creatine kinase |
| CR | Complete remission |
| CRA | Clinical Research Associate (Monitor) |
| CRF | Case Report Form |
| CsA | Cyclosporin A |
| CT | Computerised Tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTU | Clinical Trials Unit (Zentrum Klinische Studien, ZKS) |
| CV | Coefficient variation |
| DAMAST | SAS®-based data management system |
| DLT | Dose limiting toxicity |
| DRKS | Deutsches Register Klinischer Studien (German Clinical Trials Register) |
| DSUR | Development Safety Update Report |
| EBV | Epstein-Barr virus |
| EDTA | Ethylene diamine tetraacetic acid |
| EMA | European Medicines Agency |
| EOT | End of Treatment |
| EudraCT | European Union Drug Regulating Authorities Clinical Trials |
| FAS | Full Analysis Set |
| FPFV | First Patient First Visit |
| FU | Follow Up |
| GCP | Good Clinical Practice |
| GCP-V | German Decree of 09-Aug-2004 on the Use of Good Clinical Practices |
| GIST | Gastrointestinal stromal tumour |
| GT (gamma-GT) | Gamma-Glutamyl-Transferase |
| HBV-DNA | Hepatitis-B-Virus Deoxyribonucleic acid |
| HIF | Hypoxia-inducible factors |
| HIV | Human Immunodeficiency Virus- |
| HMG-CoA | Hydroxymethylglutaryl-Coenzym A-Synthase |
| HUS/TTP/TMA | Hemolytic–uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy |
| IB | Investigator’s Brochure |
| ICF | Informed Consent Form |
| ICH-GCP | ICH Topic E6: Guideline for Good Clinical Practice (GCP) |
| IEC | Independent Ethics Committee |
| IGF | Insulin-like growth factors |
| IGFBP-3 | Insulin-like growth factor-binding protein 3 |
| IHC | ImmunoHistoChemistry |

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| IMP | Investigational (Medicinal) Product /study medication |
| ITT | Intention To Treat |
| LAM | Lymphangioleiomyomatosis |
| LDH | Lactate-Dehydrogenase |
| LPLV | Last Patient Last Visit |
| MedDRA | Medical dictionary for regulatory activities |
| MH | Medical History |
| MPD | Molecular pharmacodynamic |
| MRI | Magnetic Resonance Imaging |
| mTOR | mechanistic Target of Rapamycin |
| NCT No | National Clinical Trial (NCT) number, another term for the ClinicalTrials.gov registry |
| p.o. | per os |
| PBMC | Peripheral blood mononuclear cell |
| PD | Progressive disease |
| PHI | Protected Health Information |
| PI | Principal Investigator |
| PJP | Pneumocystis jirovecii pneumonia |
| PK | Pharmacokinetic |
| PML | Progressive multifocal leukoencephalopathy |
| PP | Per-Protocol |
| PR | Partial remission |
| PT | Preferred term |
| PTLD | Post-transplant lymphoproliferative disorder |
| PTEN | Phosphatase and tensin homolog |
| QoL | Quality of Life |
| QOL | Quality of Life Questionnaire |
| RBC | Red Blood cell Count |
| RBQM | Risk Based Quality Management |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAR | Serious Adverse Reaction |
| SAS | Statistical Analysis System |
| SD | Stable disease |
| SDQ | Strengths and Difficulties Questionnaire |
| SDV | Source Data Verification |
| SI | International System of Units |
| SmPC | Summary of product characteristics |
| SOC | System organ class |
| SOP | Standard Operating Procedure |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| tmax | Time to peak blood levels |
| TSC | Tuberous Sclerosis |
| UAR | Unexpected Adverse Reaction |
| ULN | Upper limit of normal |
| US | United States |
| VAS | Visual analogue scale |
| VEGF | Vascular Endothelial Growth Factor |
| WBC | White Blood cell Count |
| WHO | World Health Organization |

# Synopsis

| | |
|---|---|
| **TITLE OF TRIAL** | An open label phase II study of sirolimus in patients with segmental overgrowth syndrome |
| **SHORT TITLE** | SIPA-SOS |
| **PROTOCOL NUMBER** | 5.0 / 11.11.2020 |
| **EUDRACT NO** | 2015-005416-15 |
| **MAIN DIAGNOSIS** | Segmental overgrowth syndrome |
| **PHASE** | Phase II trial |
| **OBJECTIVE(S)** | Primary objective:<br>The study aim is to assess the effect of sirolimus to reduce the size of defined target lesions in patients with segmental overgrowth syndrome until 6 months after start of therapy<br><br>The secondary objectives are (more details see section 2):<br>• To evaluate changes in disfigurement assessed by serial digital photograph<br>• To evaluate changes in health-related Quality of Life<br>• To evaluate changes in pain<br>• To evaluate changes in neuropsychological testing<br>• To evaluate changes in biomarkers<br>• To assess the inhibition of the mTOR pathway<br>• Assessment of safety<br>• Study drug compliance |
| **INTERVENTION(S)** | Experimental intervention: 1,6 mg/m² sirolimus daily over 6 months:<br>patients < 16 years will take twice daily oral 0.8 mg/m²,<br>patients ≥ 16 years will be treated p.o. on a once daily dosage regimen<br>Follow-up per patient: 3 months<br>Duration of intervention per patient: 6 months |

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| **INCLUSION CRITERIA** | 1. Male or female patients aged ≥ 3 years (no upper limit)<br>2. Signed written informed consent (patient ≥ 18 years or person(s) having the care and custody of the patient < 18 years).<br>3. Ability to understand the nature of the trial and the trial related procedures and to comply with them.<br>4. Segmental overgrowth syndrome patients independently of genetic background.<br>These diagnoses include patients with<br>• CLOVES syndrome, Klippel-Trenaunay-Syndrome and other PIK3CA related overgrowth spectrum diseases<br>• Proteus syndrome<br>• PTEN hamartoma tumor syndromes including patients with PTEN hamartoma of soft tissue (PHOST)<br>• Vascular malformations with significant overgrowth (lesion size of at least 3 cm diameter, externally visible), including but not limited to lymphatic malformations, venous malformations, and fibro-adipose vascular anomaly (FAVA)<br>5. Identification of at least one measurable target lesion (up to 5 target lesions) with longest diameter more than ≥ 30 mm by MRI. The target lesion(s) must be externally visible (photos) and composed of soft tissue (with one or several tissue components such as fat, vessels, muscle or connective tissue).<br>6. Normal organ and bone marrow function (i.e. transaminase levels < 2.5 x ULN or serum bilirubin < 1.5 x ULN, hemoglobin > 9 g/dL).<br>7. Negative urine pregnancy test in females with a childbearing potential (details see section 4.2).<br>8. If female and of child-bearing potential, documentation of negative pregnancy test prior to enrollment. Sexually active female patients, male patients and female partners of male patients must use adequate contraceptive measures while on study and for up to 12 weeks after ending treatment. (details see section 4.2). |

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| **EXCLUSION CRITERIA** | 1. Any concurrent therapy with chemotherapy agents or biologic agents or other immunosuppressive therapy or radiation therapy.<br>2. Patients who have received live vaccines in the past 30 days prior to informed consent.<br>3. Patients on medication with CYP3A4 inhibitors/inducers which are not replaced by other equivalent medications for the study period.<br>4. Patients who have known immunodeficiency or HIV seropositivity.<br>5. Patients with known history of prior and/or ongoing malignancy within the last 5 years.<br>6. Patients with known interstitial lung disease, pneumonitis or with bleeding diathesis.<br>7. Patients with prior use of sirolimus or other mTOR inhibitors or any analogue within the last 6 months<br>8. Any planned surgery within study period related to overgrowth lesions.<br>9. Pre-existing chronic wounds.<br>10. Triglycerides > 400 mg/dL (> 4.5 mmol/L) or total cholesterol > 300 mg/dl (> 7.8 mmol/L).<br>11. Creatinine clearance ≤ 60 ml/min (Cockcroft-Gault formula).<br>12. Proteinuria ≥ 30 mg/dl on dipstick and 24 hours proteinuria > 0.8 g/24 hours.<br>13. Intake of St John's Wort and/or grapefruit and grapefruit juice.<br>14. Any severe and/or uncontrolled medical conditions which could cause unacceptable safety risks such as:<br>• Uncontrolled hypercholesterolemia/ hypertriglyceridemia<br>• Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of study drug (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome).<br>15. Patients with a known hypersensitivity to sirolimus or other mTOR inhibitors or any analogs or to its excipients.<br>16. Patients unwilling to or unable to comply with the planned therapeutic regimen or to comply with the study treatment visits including blood sample collection within the protocol.<br>17. Female patients who are pregnant or breast feeding, or patients of reproductive potential who are not using effective birth control methods (see: inclusion criteria). If barrier contraceptives are used, they must be continued throughout the study by both sexes.<br>18. Patients must abstain from donating blood, semen, or sperm during participation in the study until 3 months after the end of participation in the study. |

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| **ENDPOINTS** | Primary efficacy endpoint:<br>Best response: Complete Remission (CR) or Partial Remission (PR) until 6 months after baseline (start of study therapy) measured by MRI according to response criteria (see section 7.5).<br><br>Key secondary endpoints<br>• to be assessed at month 3, 6 and 9:<br>▪ Morphological changes in disfigurement compared to baseline by using a scale for external validation documented by photography.<br>▪ Changes in quality of life compared to baseline (KINDL® parents und Kid-KINDL®; Lansky/Karnofsky scale, WHOQOL-BREF<br>▪ Changes in pain compared to baseline by visual pain scales for adults and children.<br>▪ Changes in neuropsychological tests (Strengths and Difficulties Questionnaire (SDQ) compared to baseline.<br>▪ Changes in IGFBP-3, IGF-1, VEGF compared to baseline values.<br>▪ Inhibition of mTOR in peripheral blood mononuclear cells (PBMCs) assessed by immunoblotting.<br>• Assessment of safety: Safety will be determined by observation of any adverse or serious adverse events. Evaluations will include clinical and laboratory assessments performed at the time points described in the flow chart. Criteria for assessment of safety will be based on standard criteria for monitoring, assessing, and reporting of adverse events (CTCAE criteria v. 5.0).<br>• Study drug compliance measured with patient diary. | |
| **TRIAL DESIGN** | This is an open-label, multicenter, single-arm, phase II clinical trial of sirolimus in patients with segmental overgrowth syndrome. | |
| **STATISTICAL ANALYSIS** | According to the design, 18 patients will be included in the study. If the observed number of patients with best response CR or PR is 2 or more out of 18, sirolimus will be considered as effective. The response probability will be estimated with 90% and with 95% confidence interval based on the exact binomial distribution. Secondary endpoints and safety will be analyzed descriptively. | |
| **SAMPLE SIZE** | To be assessed for eligibility (informed consent): | n = 20 |
| | To be allocated to trial: | n = 18 |
| | To be analysed (these patients will be evaluated for at least 1 visit): | n = 18 |
| **TRIAL DURATION** | Recruitment period (months): | 21 |
| | First patient in to last patient out (months): | 30 |
| | Duration of the entire trial (months): | 36 |
| | Treatment duration per patient (months): | 6 months therapy period + 3 months Follow-Up |
| **TIMETABLE** | Enrolment of first patient (FPFV) | 1st quarter 2021 |
| | Enrolment of last patient (registration) | 4th quarter 2022 |
| | End of trial for last patient (LPLV) | 3rd quarter 2023 |
| | Clinical Study Report (CSR) | 1st quarter 2024 |

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| **PARTICIPATING CENTERS** | 4 to 6 defined German sites, additional sites can join later |
| **FUNDERS** | The clinical trial will be financed by the Research Innovation Fund of the University of Freiburg and by the Deutsche Forschungsgemeinschaft (DFG). IMP (sirolimus) will be provided free of charge by PFIZER Pharma GmbH |

# Responsibilities

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| **Sponsor** | | Medical Center - University of Freiburg<br>represented by the Chief Medical Officer and the Chief Financial Officer<br>Breisacher Str. 153, 79110 Freiburg |
| **Coordinating Investigator**<br>*"Leiter der Klinischen Prüfung / LKP" (in accordance with German Drug Law)* | | **Dr. med. Friedrich Kapp**<br>Medical Center – University of Freiburg<br>Center for Pediatrics<br>Department of Pediatric Hematology and Oncology<br>Mathildenstraße 1, 79106 Freiburg, Germany<br>[redacted] |
| **Biostatistician** | | **Dr. Claudia Schmoor**<br>Medical Center – University of Freiburg<br>Clinical Trials Unit<br>Elsaesser Str. 2, 79110 Freiburg, Germany<br>[redacted] |
| **Project Manager** | | **Susanne Grüninger**<br>Medical Center – University of Freiburg<br>Clinical Trials Unit<br>Elsaesser Str. 2, 79110 Freiburg, Germany<br>[redacted] |
| **Registration Office** | | Medical Center – University of Freiburg<br>Clinical Trials Unit<br>Elsaesser Str. 2, 79110 Freiburg, Germany<br>[redacted] |
| **Pharmacovigilance**<br>SAE-Management | | Medical Center – University of Freiburg<br>Clinical Trials Unit<br>Elsaesser Str. 2, 79110 Freiburg, Germany<br>[redacted] |
| **Monitoring** | | Medical Center – University of Freiburg<br>Clinical Trials Unit<br>Elsaesser Str. 2, 79110 Freiburg, Germany<br>[redacted] |
| **Data management** | | Medical Center – University of Freiburg<br>Clinical Trials Unit<br>Elsaesser Str. 2, 79110 Freiburg, Germany<br>[redacted] |
| **Data Monitoring Committee** | Name:<br>Institution:<br>Profession: | PD Dr. M. Kuhlen, Augsburg, Germany<br>Universitätsklinikum Augsburg<br>Pediatrician, pediatric oncology-hematology |

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| Address: | Stenglinstr. 2<br>86156 Augsburg |
| [redacted] | [redacted] |
| Name: | Dr. K. Häffner, Freiburg, Germany, Chair person |
| Institution: | Universitätsklinikum Freiburg, Klinik für Innere Medizin IV |
| Profession: | Pediatrician, pediatric nephrology |
| Address: | Hugstetter Straße 55, 79106 Freiburg |
| [redacted] | [redacted] |
| Name: | Dr. M. Zimmermann, Hannover,Germany |
| Institution: | Pädiatrische Hämatologie und Onkologie Medizinische Hochschule Hannover (MHH) |
| Profession: | Statistician |
| Address: | Carl-Neuberg-Straße 1, 30625 Hannover, Deutschland |
| [redacted] | [redacted] |

# 1 Background and rationale

## 1.1 Scientific background

Segmental overgrowth syndromes are very rare diseases with an extremely relevant genetic background. In some of them, only about 200 cases are known worldwide, such as for example the Proteus syndrome, which presents with asymmetric and fast growth of extremities. Further overgrowth diseases are the SOLAMEN and the CLOVE syndrome with lipomatosis, vascular malformations and epidermal nevus as well as the Cowden syndrome with multiple hamartomas and the Bannayan-Riley-Ruvalcaba syndrome with lipomatosis and macrocephalus [2.]. The patients with overgrowth syndromes all show close clinical overlap. For several years, clinical criteria (phenotype) for diagnosis and discrimination of these syndromes have been defined and are listed in Table 1.

Results of genetic research can today help to diagnose most of the segmental overgrowth syndromes, which means they can clearly be named. Genes of the PI3K/AKT/PTEN/mTOR signalling pathway have been identified to be causative for some of these syndromes. *PTEN* germline mutations have been known to be present in SOLAMEN, Cowden and Ruvalcaba syndrome patients all showing tissue overgrowth and close clinical overlap. However, very rarely, somatic *PTEN* mutations could be detected in surgical specimen of lipomas or hamartomas of other segmental overgrowth patients. Only recently, recurrent somatic activating mutations of *AKT1* have been identified in overgrowth tissue of Proteus syndrome patients (Lindhurst et al., 2011). Because *AKT1* is also activated by loss-of-function mutations in *PTEN*, patients with syndromes harbouring germline *PTEN* mutations (SOLAMEN, Cowden and Ruvalcaba) and Proteus syndrome patients with activating mutations of *AKT1* show close overlap in clinical manifestations. Furthermore, somatic *PI3KCA* mutations have been described to be responsible for the CLOVE syndrome, again a phenotypically closely related variant of the other overgrowth syndromes (Lindhurst et al., 2012). These genetic results confirmed that patients with overgrowth all share a common feature involving the PI3K/AKT/PTEN/mTOR signal pathway (Table 1).

Next to surgical approaches in functional handicapped patients, a standard medical therapy is not available. Therefore, in most cases, a watch-and-wait strategy is followed. Taking into account the genetic background of segmental overgrowth patients, mTOR is a promising target for a possible medical treatment. For example, because the direct molecular consequence of *PTEN* loss-of-function is an aberrant activation of the mTOR pathway, targeting mTOR holds the promise of a causative treatment in *PTEN*-positive segmental overgrowth patients.

**Table 1: Diseases within the scope of the study**

| Disease groups | Entities | Genetic change |
|---|---|---|
| PIK3CA related overgrowth spectrum diseases | e.g. CLOVES syndrome, Klippel-Trenaunay-syndrome | somatic PIK3CA mutation |
| Proteus syndrome | | Somatic ATK1 mutation |
| PTEN hamartoma tumor syndromes | SOLAMEN, Cowden, Bannayan-Riley-Ruvalcaba syndrome) and PTEN hamartoma of soft tissue (PHOST) | germline PTEN mutations |
| Vascular malformations with significant overgrowth | e.g. lymphatic malformations, venous malformations, and fibro-adipose vascular anomaly (FAVA) | somatic TEK or PIK3CA mutations |

Until today, three case reports have described the successful use of the mTOR inhibitor sirolimus for the therapy of patients with segmental overgrowth and *PTEN* germline mutation (Marsh et al., 2008, Iacobas et al., 2011, Schmid et al., 2014). We have recently started with “off label” use of sirolimus in these patients. First results with successfully treated patients have been presented at the annual meeting of the German Society of Human Genetics in 2011 and the meeting of the International Society on the Studies of Vascular Anomalies in 2012. In one patient with segmental overgrowth syndrome and response to sirolimus, we could identify a *PI3KCA* mutation in one lesion. This case is currently prepared for publication (Rössler et al., unpublished). Interestingly, response on mTOR inhibition could be demonstrated in some patients despite the lack of mutations in the published genes responsible for overgrowth syndromes.

A clinical trial sponsored by the National Cancer Institute tested the ability of sirolimus to decrease the activity of proteins that are regulated by mTOR in both benign and cancerous tumour tissue in Cowden syndrome patients (NCT00971789). Only patients over the age of 18 years were included and multiple biopsies were performed before starting treatment and during therapy with sirolimus.

Currently there are several other investigations on sirolimus in segmental overgrowth syndromes ongoing that also include children:

- NCT02443818 from Dijon, France investigating “Sirolimus Effect on Hypertrophic Syndromes Related Gene PIK3CA (PROMISE)”

In this clinical trial, sirolimus is administered in patients with PI3K mutated lesions after a 6 months period of documented overgrowth. The trial includes patients from 3 years to 65 years.

- NCT02428296 from Bethesda, Maryland, United States, “Study of sirolimus Therapy for Segmental Overgrowth Caused by Somatic PI3K Activation”

Again, patients with PI3K mutated lesions can be included after a 6 months period of documented overgrowth. An age inclusion criterion is 3 years to 65 years.

These trials confirm the rationale for an intervention with sirolimus and combining results will raise evidence to lower the disease burden with segmental overgrowth. SIPA-SOS is directed to segmental overgrowth regardless of mutations and therefore to evaluate treatment options for several phenotypes affecting QoL of patients significantly.

### 1.2 Overview of sirolimus

Sirolimus is the first in class mTOR-inhibitor. Sirolimus has been in clinical development since 1993 as an immunosuppressant in solid organ transplantation.
Sirolimus was approved in the United States on 15-Sep-1999 and in the European Union on 13Mar2001. Currently, sirolimus is registered in approximately 92 countries and is indicated for the prophylaxis of organ rejection in patients receiving a renal transplant
Sirolimus is available as 0.5 mg, 1 mg, and 2 mg oral tablets and 1 mg/ml oral solution.

In 2015 sirolimus gained approval in orphan indication lymphangioleimyomatosis (LAM) by US regulation FDA. This approval is based on results from the Multicenter International Lymphangioleiomyomatosis Efficacy and Safety of Sirolimus (MILES) Trial. The MILES Trial included 89 LAM patients with moderate lung impairment who were randomized to receive sirolimus (dose adjusted to 5-15 ng/ml) or placebo for 12 months, followed by a 12 month observation period. In the trial, those treated with sirolimus for one year experienced stabilization of lung function. Full results of the MILES Trial were published by McCormack et al., *New England Journal of Medicine* 2011. The most common adverse events reported during the study were mucositis, diarrhea, nausea, hypercholesterolemia, acneiform rash and swelling in the lower extremities. The adverse drug reactions observed were consistent with the known safety profile of sirolimus in renal transplant patients, with the exception of weight decreased, which was reported at a greater incidence with sirolimus compared to placebo. Further applications for LAM have been successful in Japan and are under discussion in various other countries worldwide.

Nearly 10,000 cancer patients have been treated with the sirolimus prodrug Temsirolimus (Torisel®) in either Pfizer sponsored, or non-Pfizer-sponsored clinical studies for renal cell

cancer. Temsirolimus/ sirolimus is being investigated as an anticancer agent based on its potential to act

- directly on the tumor cells by inhibiting tumor cell growth and proliferation and/or
- indirectly by inhibiting angiogenesis leading to reduced tumor vascularity (via potent inhibition of tumor cell VEGF production and VEGF-induced proliferation of endothelial cells).

Torisel® gained approval for first-line treatment of advanced renal cell carcinoma and also for refractory mantle cell lymphoma.

### *1.2.1 mTOR pathway*

At the cellular and molecular level, sirolimus acts as a signal transduction inhibitor. Sirolimus selectively inhibits mTOR (mammalian target of rapamycin), a key protein kinase present in all cells which regulates cell growth, proliferation and survival. mTOR is mainly activated via PI3K through AKT and the tuberous sclerosis complex (TSC1/2). Mutations in these components or in *PTEN*, a negative regulator of PI3K, may result in their dysregulation. Abnormal functioning of various components of the signaling pathways contributes to the pathophysiology of numerous human cancers. Various preclinical models have confirmed the role of this pathway in tumor development. The main known functions of mTOR include the following (Bjornsti and Houghton 2004):

- mTOR functions as a sensor of mitogens, growth factors and energy and nutrient levels, facilitating cell-cycle progression from G1 to S phase under appropriate growth conditions.
- The mTOR pathway itself is frequently dysregulated in many human cancers, and oncogenic transformation may sensitize tumor cells to mTOR inhibitors.
- The mTOR pathway is involved in the production of pro-angiogenic factors (i.e. VEGF) and inhibition of endothelial cell growth and proliferation.
- Through inactivating eukaryotic initiation factor 4E binding proteins and activating the 40S ribosomal S6 kinases (i.e., p70S6K1), mTOR regulates protein translation, including the HIF-1 proteins. Inhibition of mTOR is expected to lead to decreased expression of HIF-1.

The PI3K/AKT/mTOR pathway is known to be dysregulated in numerous proliferative disorders including cancer. Molecular epidemiological studies have also shown that activation of the PI3K/AKT/mTOR pathway is frequently associated with worsening prognosis through resistance to treatment, disease extension and disease progression. A variety of preclinical models have confirmed the role of this pathway in tumor development. It has also been demonstrated that constitutional activation of kinases such as AKT can lead to inexorable development of cancers resembling those which in patients are characterized by frequent activation of the same kinases.

This is complemented by the demonstration of the antitumor activity of kinase inhibitors acting on the pathway in vitro and in vivo preclinical models.

### *1.2.2 Preclinical data*

In vitro immunological studies demonstrate that sirolimus is a potent inhibitor of lymphocyte activation and antibody production. These immunological effects of sirolimus result in potent anti-graft-rejection activity in a variety of animal models, ranging from rodents to primates, and for both heterotopic and orthotopic organ grafting. Sirolimus was found to be very effective in reversing ongoing graft rejection in a rodent model. Sirolimus has also been demonstrated to be effective in the animal models of bone marrow and islet cell transplantation.

In repeated-dose toxicity studies in rats and monkeys, the majority of compound-related findings that occurred were similar to those seen for other compounds of immunosuppression, such as CsA and Tacrolimus, or were secondary to long-term immunosuppression. However, certain toxicities seen with CsA and Tacrolimus, notably neurotoxicity and nephrotoxicity, are not seen with sirolimus. It is hypothesized that these toxicities are mediated through the ability of CsA and Tacrolimus, but not sirolimus, to inhibit the phosphatase activity of calcineurin. Most of the effects seen in nonclinical studies have not been observed in controlled clinical studies in which sirolimus was administered under the proposed therapeutic regimen. In nonclinical studies, the sirolimus-induced decrease in testosterone levels were considered likely explanations for the effects on male reproductive organs (decreased weights, testicular atrophy and degeneration, and decreased sperm counts) and on bone (osteopenia). Decreases in testosterone levels (males) and bone density have not been seen in renal transplant patients given sirolimus. When sirolimus was administered in combination with CsA, increased toxicities were observed: renal basophilia; pancreatic islet cell vacuolation and associated hyperglycemia; thymic and testicular tubular atrophy; myocardial degeneration and accumulation of pulmonary alveolar macrophages; and fetal mortality and development. The increased severity of these effects was attributed to the significant increases in exposure levels of each compound and associated biological activity when the compounds were given in combination. In a phototoxicity study in rabbits given sirolimus, there was no evidence that exposure to UV light induced a photo-mediated toxicologic response to sirolimus; furthermore, there was no melanin binding to the pigmented tissues of rats. Sirolimus is neither a mutagen nor a clastogen and does not pose a genotoxic risk to humans. In carcinogenicity studies, sirolimus resulted in increased incidences of lymphoma in mice, hepatocellular tumors in male mice, granulocytic leukemia in female mice, and testicular interstitial cell adenoma in male rats. The results of genotoxicity tests on sirolimus were negative, and each of these neoplasms can be related to immunosuppression. Therefore, these neoplasms are considered to be secondary to the pharmacologic effects of sirolimus and

to be nongenotoxic in origin. The increased risk of lymphoma, and of other malignancies, is a well-known complication of immunosuppression in transplant patients. Sirolimus does not appear to further increase this risk based upon the clinical information available to date. Although sirolimus is not considered to pose a teratogenic risk, it is not recommended for use in pregnant women because of its embryo/fetal toxicity. Overall, based on the results of the toxicity and drug metabolism studies, sirolimus does not appear to pose an increased risk for human use under the proposed therapeutic regimen compared with that of other marketed immunosuppressive agents.

### *1.2.3 Pharmacokinetics / pharmacodynamics*

The pharmacokinetic characteristics of sirolimus have been extensively investigated in humans in the context of the drug's development as an immunosuppressant in solid organ transplantation where sirolimus was administered once daily as a part of a glucocorticoid containing immunosuppressive regimen with or without cyclosporin A. Although some pharmacokinetic data is available for sirolimus in both children and adolescents, many of these data were accrued in the context of renal failure, concurrent ciclosporin A treatment and/or renal transplantation, with dosing aimed at achieving adequate plasma levels for immunosuppression. In contrast the target plasma concentration of this trial will be below or at the lower end of this range. Furthermore, clearance of sirolimus in children is higher and has been shown to affect plasma concentrations; this may necessitate twice daily dosing in patients below the age of 16 years.

The 0.5 mg tablet is not fully bioequivalent to the 1 mg, 2 mg and 5 mg tablets when comparing Cmax. Multiples of the 0.5 mg tablets should therefore not be used as a substitute for other tablet strengths.

In healthy subjects, the mean extent of bioavailability of sirolimus after single-dose administration of the tablet formulation is about 27% higher relative to the oral solution. The mean Cmax was decreased by 35%, and mean tmax increased by 82%. The difference in bioavailability was less marked upon steady-state administration to renal transplant recipients, and therapeutic equivalence has been demonstrated in a randomised study of 477 patients. When switching patients between oral solution and tablet formulations, it is recommended to give the same dose and to verify the sirolimus trough concentration 1 to 2 weeks later to assure that it remains within recommended target ranges. Also, when switching between different tablet strengths, verification of trough concentrations is recommended.

In 24 healthy volunteers receiving Sirolimus tablets with a high-fat meal, Cmax, tmax and AUC showed increases of 65%, 32%, and 23%, respectively. To minimise variability, Sirolimus tablets

should be taken consistently with or without food. Grapefruit juice affects CYP3A4-mediated metabolism and must, therefore, be avoided.

Sirolimus concentrations, following the administration of Sirolimus tablets (5 mg) to healthy subjects as single doses are dose proportional between 5 and 40 mg.

Clinical studies of Sirolimus did not include a sufficient number of patients above 65 years of age to determine whether they will respond differently than younger patients. Sirolimus tablets administered to 12 renal transplant patients above 65 years of age gave similar results to adult patients (n=167) 18 to 65 years of age.

Initial therapy (2 to 3 months post-transplant): In most patients receiving Sirolimus tablets with a loading dose of 6 mg followed by an initial maintenance dose of 2 mg, whole blood sirolimus trough concentrations rapidly achieved steady-state concentrations within the recommended target range (4 to 12 ng/ml, chromatographic assay). Sirolimus pharmacokinetic parameters following daily doses of 2 mg Sirolimus tablets administered in combination with ciclosporin microemulsion (4 hours prior to Sirolimus tablets) and corticosteroids in 13 renal transplant patients, based on data collected at months 1 and 3 after transplantation, were: Cmin,ss 7.39 ± 2.18 ng/ml; Cmax,ss 15.0 ± 4.9 ng/ml; tmax,ss 3.46 ± 2.40 hours; AUC,ss 230 ± 67 ng·h/ml; CL/F/WT, 139 ± 63 ml/h/kg (parameters calculated from LC-MS/MS assay results). The corresponding results for the oral solution in the same clinical study were Cmin,ss 5.40 ± 2.50 ng/ml, Cmax,ss 14.4 ± 5.3 ng/ml, tmax,ss 2.12 ± 0.84 hours, AUC,ss 194 ± 78 ng·h/ml, CL/F/W 173 ± 50 ml/h/kg. Whole blood trough sirolimus concentrations, as measured by LC/MS/MS, were significantly correlated (r2=0.85) with AUC,ss.

Based on monitoring in all patients during the period of concomitant therapy with ciclosporin, mean (10th, 90th percentiles) troughs (expressed as chromatographic assay values) and daily doses were 8.6 ± 3.0 ng/ml (5.0 to 13 ng/ml) and 2.1 ± 0.70 mg (1.5 to 2.7 mg), respectively (see section 4.2).
Sirolimus is mainly metabolized by CYP3A4 in the liver and to some extent in the intestinal wall. Sirolimus is also a substrate of P-glycoprotein (P-gp). Therefore, absorption and subsequent elimination of systematically absorbed sirolimus may be influenced by concomitant medications that interact with CYP3A4 and/or P-glycoprotein. *In vitro* studies showed that sirolimus is a competitive inhibitor of CYP3A4 substrates, potentially increasing the concentrations of concomitant medications eliminated by these enzymes. In patients following kidney transplantation, strong inhibitors of CYP3A4 (azole's, antifungal's, cyclosporine, erythromycin) have been shown to reduce the clearance of sirolimus therapy thereby increasing sirolimus blood levels. Similarly, rifampicin, a strong inducer of CYP3A4, increases the clearance of

sirolimus thereby reducing sirolimus blood levels. Caution should be exercised when co-administering sirolimus with CYP3A4 inhibitors or inducers.

Sirolimus pharmacokinetics in transplant patients was investigated in special populations such as subjects with hepatic or renal impairment, various ethnic groups and pediatric renal transplant patients.
In patients with hepatic impairment, it is recommended that the maintenance dose of Sirolimus be reduced by approximately one-third to one-half. It is not necessary to modify the Sirolimus loading dose. In subjects with hepatic impairment, it is recommended that sirolimus whole blood trough levels be monitored. Based on clinical PK data, the Sirolimus dosage need not be adjusted because of impaired renal function. Age, weight (both over the adult range) and gender do not affect the pharmacokinetics of sirolimus to a clinically relevant extent.
The safety and efficacy of Sirolimus in pediatric patients below the age of 13 years have not been established. Safety and efficacy information from a controlled clinical trial in pediatric and adolescent (<18 years of age) renal transplant recipients judged to be at high immunologic risk, defined as a history of 1 or more acute rejection episodes and/or the presence of chronic allograft nephropathy, do not support the chronic use of Sirolimus oral solution or tablets incombination with CNIs and corticosteroids, because of the increased risk of lipid abnormalities and deterioration of renal function associated with these immunosuppressive regimens, without increased benefit with respect to acute rejection, graft survival, or patient survival.

### *1.2.4 Adverse reactions*

ADRs are listed in the following table according to CIOMS frequency categories, as defined in MedDRA System Organ Class. Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); not known (cannot be estimated from the available data).
The list of ADRs is based on experience from clinical trials and on postmarketing experience.

The most commonly reported adverse reactions (occurring in >10% of patients) are thrombocytopaenia, anaemia, pyrexia, hypertension, hypokalaemia, hypophosphataemia, urinary tract infection, hypercholesterolaemia, hyperglycaemia, hypertriglyceridaemia, abdominal pain, lymphocoele, peripheral oedema, arthralgia, acne, diarrhoea, pain, constipation, nausea, headache, increased blood creatinine, and increased blood lactate dehydrogenase (LDH).
The incidence of any adverse reaction(s) may increase as the trough sirolimus level increases.

The following list of adverse reactions is based on experience from clinical studies and on postmarketing experience.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Most patients were on immunosuppressive regimens, which included Sirolimus in combination with other immunosuppressive agents.

**Table 2 Sirolimus adverse reactions**

| System organ class | Very common (≥1/10) | Common (≥1/100 to <1/10) | Uncommon (≥1/1,000 to <1/100) | Rare (≥1/10,000 to <1/1,000) | Frequency not known (cannot be estimated from available data) |
|---|---|---|---|---|---|
| Infections and infestations | Pneumonia; Fungal infection; Viral infection; Bacterial infection; Herpes simplex infection; Urinary tract infection | Sepsis Pyelonephritis; Cytomegalovirus infection; Herpes zoster infection | *Clostridium difficile* colitis; Mycobacterial infection (including tuberculosis); Epstein-Barr virus infection | | |
| Neoplasms benign, malignant and unspecified (including cysts and polyps) | | Non-melanoma Skin cancer | Lymphoma; malignant melanoma; post-transplant lymphoproli-ferative disorder | | Neuroendocrine carcinoma of the skin |
| Blood and lymphatic system disorders | Thrombocytopaenia Anaemia; Leucopenia | Haemolytic uraemic syndrome; Neutropaenia | Pancytopaenia; Thrombotic thrombo-cytopaenic purpura | | |
| Immune system disorders | | Hypersensitivity (including angioedema, anaphylactic reaction, and anaphylactoid reaction) | | | |
| Metabolism and nutrition disorders | Hypokalaemia Hypophosphataemia; Hyperlipidaemia (including Hypercholeste-rolaemia); Hyperglycaemia Hypertriglyceridaemia Diabetes mellitus | | | | |
| Nervous system disorders | Headache | | | | Posterior reversible encephalopathy syndrome |

| System organ class | Very common (≥1/10) | Common (≥1/100 to <1/10) | Uncommon (≥1/1,000 to <1/100) | Rare (≥1/10,000 to <1/1,000) | Frequency not known (cannot be estimated from available data) |
|---|---|---|---|---|---|
| Cardiac disorders | Tachycardia | Pericardial effusion | | | |
| Vascular disorders | Lymphocele Hypertension | Venous thrombosis (including deep vein thrombosis) | Lymphoedema | | |
| Respiratory, thoracic and mediastinal disorders | | Pulmonary embolism; Pneumonitis; Pleural effusion; Epistaxis | Pulmonary haemorrhage | Alveolar proteinosis | |
| Gastrointestinal disorders | Abdominal pain; Diarrhoea; Constipation; Nausea; | Pancreatitis; Stomatitis; Ascites | | | |
| Hepatobiliary disorders | Liver function test abnormal (including alanine aminotransferase increased and aspartate amino-transferase increased) | | Hepatic failure | | |
| Skin and subcutaneous tissue disorders | Rash; Acne | | Dermatitis exfoliative | Hypersensitivity vasculitis | |
| Musculoskeletal and connective tissue disorders | Arthralgia | Osteonecrosis | | | |
| Renal and urinary disorders | Proteinuria | | Nephrotic syndrome; Focal segmental glomerulo-sclerosis | | |
| Reproductive system and breast disorders | Menstrual disorder (including amenorrhoea and menorrhagia) | Ovarian cyst | | | |
| General disorders and administration site conditions | Oedema; Oedema peripheral; Pyrexia; Pain; Impaired healing | | | | |
| Investigations | Blood lactate dehydrogenase increased; | | | | |

| System organ class | Very common (≥1/10) | Common (≥1/100 to <1/10) | Uncommon (≥1/1,000 to <1/100) | Rare (≥1/10,000 to <1/1,000) | Frequency not known (cannot be estimated from available data) |
|---|---|---|---|---|---|
| | Blood creatinine increased; | | | | |

Source: SmPC Rapamune® June 2019

For further details on adverse reactions please refer to the current version of the SmPC.

*Neoplasms benign, malignant and unspecified*

Immunosuppression increases the susceptibility to the development of lymphoma and other malignancies, particularly of the skin. However, in most reported cases, immunosuppression was not realized by sirolimus monotherapy, but in combination with other immunosuppressive agents. In a study using sirolimus as single immunosuppressive therapy for lymphangioleiomyomatosis, no increase in lymphoma or malignancy was reported ([18.]). There are reports available on protective anti-tumor effect of sirolimus for skin cancers and hepatocellular cancer relapses ([7.]). However, this has to be further evaluated ([11.]).

The ongoing sirolimus trial for overgrowth patients as well as the recently published study results on sirolimus therapy for complicated vascular anomalies did not report on lymphoma or induced malignancies ([1.]).

*Infections and infestations*

Sirolimus is an immunosuppressant and consequently patients taking the drug are at an increased risk of infection. This may be the case even if the patient has a normal white cell count. Physicians and patients/carers should be aware of this risk, and vigilant for signs and symptoms of infection. Prompt treatment with appropriate anti-infectives should be given as clinically appropriate.

Cases of BK virus-associated nephropathy, as well as cases of JC virus-associated progressive multifocal leukoencephalopathy (PML), have been reported in patients treated with immunosuppressants, including Sirolimus.

*Reproductive system and fertility*

Impairments of sperm parameters have been observed among some patients treated with Sirolimus. These effects have been reversible upon discontinuation of Sirolimus in most cases.

Ovarian cysts and menstrual disorders (including amenorrhoea and menorrhagia) have been reported. Patients with symptomatic ovarian cysts should be referred for further evaluation. The incidence of ovarian cysts may be higher in premenopausal females compared to postmenopausal females. In some cases, ovarian cysts and these menstrual disorders have resolved upon discontinuation of Sirolimus.

Overall, there is limited knowledge about future fertility in prepuberty children treated by sirolimus.

Hepatoxicity has been reported. The risk may increase as the trough sirolimus level increases. Rare reports of fatal hepatic necrosis have been reported with elevated trough sirolimus levels.

Cases of interstitial lung disease (including pneumonitis and infrequently bronchiolitis obliterans organising pneumonia (BOOP) and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred in patients receiving immunosuppressive regimens including Sirolimus. In some cases, the interstitial lung disease has resolved upon discontinuation or dose reduction of Sirolimus. The risk may be increased as the trough sirolimus level increases.

Impaired healing following transplant surgery has been reported, including fascial dehiscence, incisional hernia, and anastomotic disruption (e.g., wound, vascular, airway, ureteral, biliary).

In patients with delayed graft function, sirolimus may delay recovery of renal function.

The concomitant use of sirolimus with a calcineurin inhibitor may increase the risk of calcineurin inhibitor-induced HUS/TTP/TMA.

Focal segmental glomerulosclerosis has been reported.

There have also been reports of fluid accumulation, including peripheral oedema, lymphoedema, pleural effusion and pericardial effusions (including haemodynamically significant effusions in children and adults) in patients receiving Sirolimus.

### *1.2.5 Clinical pediatric trials*

Controlled clinical studies with posology comparable to that currently indicated for the use of sirolimus in adults have not been conducted in children or adolescents below 18 years of age.

#### *1.2.5.1 Sirolimus in renal transplant children*

Safety was assessed in a controlled clinical study enrolling renal transplant patients below 18 years of age considered of high immunologic risk, defined as a history of one or more acute allograft rejection episodes and/or the presence of chronic allograft nephropathy on a renal biopsy. The use of Sirolimus in combination with calcineurin inhibitors and corticosteroids was associated with an increased risk of deterioration of renal function, serum lipid abnormalities

(including, but not limited to, increased serum triglycerides and cholesterol), and urinary tract infections. The treatment regimen studied (continuous use of Sirolimus in combination with calcineurin inhibitor) is not indicated for adult or pediatric patients.

In another study enrolling renal transplant patients 20 years of age and below that was intended to assess the safety of progressive corticosteroid withdrawal (beginning at six months post-transplantation) from an immunosuppressive regimen initiated at transplantation that included full-dose immunosuppression with both Sirolimus and a calcineurin inhibitor in combination with basiliximab induction, of the 274 patients enrolled, 19 (6.9%) were reported to have developed post-transplant lymphoproliferative disorder (PTLD). Among 89 patients known to be Epstein-Barr virus (EBV) seronegative prior to transplantation, 13 (15.6%) were reported to have developed PTLD. All patients who developed PTLD were aged below 18 years.

Based on initial trials conducted in the US, the FDA approved indication for Sirolimus use in kidney transplant recipients includes adolescent with age from 13 years and higher age. Very few patients below 18 years old were studied and the documentation is considered insufficient for a pediatric indication for sirolimus. The cumulative frequency of investigator-reported AEs and SAEs was similar in both groups; the types of events were consistent with the known safety profile of sirolimus. Vital signs and laboratory tests were similar in both treatment groups and not clinically meaningful. In addition, no unexpected or unusual safety events were identified that would preclude the use of sirolimus in pediatric or adolescent renal allograft recipients. In summary findings indicate that, for the renal transplant population, the overall safety profile of sirolimus in children and adolescents is similar to that for adults.

There is insufficient experience to recommend the use of Sirolimus in children and adolescents in renal transplantation.

*1.2.5.2. Sirolimus in children with other rare diseases*

Data from very young children are available from a team in London, published in the NEJM in 2014 on the effectiveness of sirolimus in four infants with severe hyperinsulinemic hypoglycemia ([27.]). These children were 7, 8, 11 and 16 weeks of age old when treatment was started. No severe side effect was noted during a sirolimus therapy that lasted for 36, 41, 44 and 45 weeks.

Another case series of six autoimmune lymphoproliferative syndrome (ALPS) patients treated with sirolimus reports on one child aged 4 years when therapy was started. Treatment was realized at time of publication for 5 months [29.]. No major side effect could be detected. Later, this group performed a clinical study with sirolimus in ALPS patients. They included 30 patients; detailed data on age of start of therapy is not available in the recent publication in Blood in 2016.

The median age of all at the start of sirolimus was 11 years with a range from 1.8 to 21 years [4.].

Finally, there is data available on children treated with sirolimus for complicated vascular anomalies. In a phase II trial for patients with complicated vascular anomalies to determine the efficacy and safety of treatment with sirolimus recently published [1.], 57 patients were treated with a median age of 8.1 years. Detailed data on age range is not available. The same authors reported on sirolimus for the same indication in a case series of 6 patients in 2011, including a child of 7 and another of 11 months. Therapy was realized for 12 and 27 months without any major toxicity [8.] In addition, six patients reported by the University Hospital in Graz, Austria were treated with sirolimus for complicated vascular anomalies, all of them started therapy under the age of 2 years (four children at time of birth, and two others at the age of 10 and 13 months). Therapy lasted 3 to 56 months without major side effects ([13.]).

In summary, data on young children treated with sirolimus is limited. However, in recent years for very specific rare conditions, sirolimus has been safely used to treat children of young age.

*1.2.6. Long term toxicity of sirolimus*

Sirolimus is used in pediatric hematology and oncology for second line treatment in multiple cancers in combination with other targeted drugs. Furthermore, it is used in the field of bone marrow transplantation as second line treatment for GvH disease. Although immunosuppression by sirolimus harbours a risk of secondary malignancies, no data is today available on induction of secondary malignancies due to sirolimus therapy in this patient group.

Furthermore, sirolimus used as approved immunosuppressive drug after organ transplantation. A recent review and metaanalysis investigated the effect of sirolimus on development of cancer and on survival among transplant recipients using data from randomized trials (Knoll et al., 2014). Sirolimus was associated with a reduction in the risk of malignancy and non-melanoma skin cancer in transplant recipients. The benefit was most pronounced in patients who converted from an established immunosuppressive regimen to sirolimus.

## 1.3 Trial purpose and rationale

Until today, the only therapeutic approach in segmental overgrowth syndromes is by surgery only. Lesions showing overgrowth leading to handicap or discomfort is excised or reduced if possible. Operations have to be repeated regularly as overgrowth is continuously present during lifetime in the patients. A medical treatment, eventually administered continuously during lifetime that could replace the regular surgical procedures has not been available. Three single case

reports showed response of overgrowth lesions in patients with PTEN germline mutations to the mTOR inhibitor sirolimus. In addition, our case report on a patient with a somatic PI3K mutation in an overgrowth lesion showed as well response to sirolimus (Rössler et al., manuscript in preparation). To scientifically investigate the efficacy of mTOR inhibition to stop overgrowth in segmental overgrowth lesions, a clinical trial has to be realized.

In “pubmed” no clinical trial is reported using sirolimus in segmental overgrowth syndrome patients. In the database “clinicaltrial.gov” ongoing clinical trials using sirolimus in segmental overgrowth patients are available, but also including patients with vascular malformations only, w/o phenotype of overgrowth. Furthermore, the company Pfizer has no information on any planned or ongoing clinical trials on sirolimus and segmental overgrowth syndrome patients as main phenotype. In the planned clinical trial SIPA-SOS, we propose to study the therapeutic effect of sirolimus on target lesions in segmental overgrowth patients 3 years of age with no upper limit, independently of presence of mutations in the genes of the PI3K/AKT/PTEN/mTOR signal pathway. In the phase II trial design a dose and target blood level range of sirolimus for children and adults based on literature and own experience was chosen. A firstradiological response assessment will be performed at the end of therapy after 6 months, a second response assessment after 9 months to assess for regrowth of the lesion(s). Quality of life, neurophysiological tests and pain scales as well as photographs will be compared to baseline to further evaluate efficacy of sirolimus therapy.

**Risk-Benefit assessment**

As outlined above, treatment options for segmental overgrowth patients are very limited. According to data that have been generated by different clinical research groups, treatment with sirolimus offers a safe and promising approach for segmental overgrowth patients that would until now receive sole best supportive care by repetitive surgical interventions. Because overgrowth is observed throughout lifetime and especially in periods of intensive body growth, effective medical treatment should be introduced as early as possible. Thus, the investigators believe that the amount of benefit clearly outweighs the amount of risk for the individual patient.
If residual biomaterial from study patients is made available to the Hilda Biobank during the course of the study, it will be possible to link analyses from the biomaterial with clinical data from the study. This will allow the investigators to develop targeted research projects on segmental overgrowth syndromes to gain more knowledge on these rare diseases.

# 2 Objectives and endpoints

**Table 3: Objectives and related endpoints**

| | Objective | Endpoint |
|---|---|---|
| **Primary** | To assess the effect of sirolimus to reduce the size of defined target lesions in patients with segmental overgrowth syndromes. | Best response: Complete Remission (CR), or Partial Remission (PR) until 6 months after start of therapy period (baseline) measured by MRI according to response criteria (see section 7.5). |
| **Secondary** | To evaluate changes in disfigurement assessed by serial digital photograph | Morphological changes in disfigurement compared to baseline by using a scale for external validation documented by photography after 3, 6 and 9 months of therapy |
| | To evaluate changes in health-related Quality of Life | Changes in Quality of life after 3, 6 and 9 months of therapy compared to baseline (for patients ≥ 4 and ≤ 17 years of age by KINDL® parents and Kiddy-KINDL® Kids 4-6 years, Kid-KINDL® Kids 7-13 years, Kiddo-KINDL® Teenager 14-17 years, and for patients ≥ 18 by WHOQOL-BREF as well as Lansky (<16 years)/Karnofsky scale) |
| | To evaluate changes in pain | Changes in pain after 3, 6 and 9 months of therapy compared to baseline by visual pain scales for adults and children |
| | To evaluate changes in neuropsychological testing compared to baseline values. | Changes in neuropsychological tests (using Strengths and Difficulties Questionnaire (SDQ) Kids (6-11 years), Parents and Erwachsene ≥ 18 years after 3, 6 and 9 months of therapy compared to baseline. |
| | To evaluate changes in biomarkers compared to respective baseline values. | Changes in IGFBP-3, IGF-1, VEGF compared to baseline values after 3, 6 and 6 9 months of therapyafter start of study treatment (baseline). |
| | To assess the inhibition of the mTOR pathway. | Inhibition of mTOR in PBMCs assessed by immunoblotting after 3, 6 and 6 9 months after start of study treatment (baseline). |
| | Assessment of safety. | Safety will be determined by observation of any adverse or serious adverse events. Evaluations will include clinical and laboratory assessments performed at the time points described in the flow chart. Criteria for assessment of safety will be based on standard criteria for monitoring, assessing, and reporting of adverse events (CTCAE criteria v. 5.0). |

| | **Objective** | **Endpoint** |
|---|---|---|
| | Study drug compliance. | Study drug compliance measured with patient diary. |

# 3 Clinical trial plan

## 3.1 Trial design

This is an open-label, multicenter, single-arm, phase II clinical trial of sirolimus in patients with segmental overgrowth syndrome.

## 3.2 Treatment arm

This is a single arm study with sirolimus 1.6 mg/m² daily, divided in two doses for patients aged ≤16 years and one dose >16 years over 6 months.

## 3.3 Treatment duration

Patients will be on sirolimus therapy for 6 months.

## 3.4 Flow Chart (s. detailed Flow Chart in 7.1)

| | |
|---|---|
| Screening Day -28 till Day 0 | Patient's registration via fax<br>(after obtained informed consent<br>and fulfilled eligibility criteria)<br>MRI<br>Photo assessment |
| | ⇩ |
| Day 0 /Visit 1 | Photo assessment<br>Baseline exams |
| Day 0/Month 0 till Month 6 | Sirolimus treatment 6 months |
| | ⇩ |
| Day 14 / Visit 2 | Sirolimus serum level |
| | ⇩ |
| Month 3 / Visit 3 | Patient visit 3 months after start of treatment |
| | ⇩ |
| Month 6 / Visit 4 | End of treatment examination (EOT):<br>MRI<br>Photo assessment<br>Response exams |
| | ⇩ |
| Month 9 / Visit 5 | Follow Up Visit<br>MRI<br>Individual end of study<br>(EOS) |

### 3.5 Trial timetable

| | |
|---|---|
| Enrolment of first patient (FPFV) | 1st quarter 2021 |
| Enrolment of last patient (registration) | 4th quarter 2022 |
| End of trial for last patient (LPLV) | 3rd quarter 2023 |
| Clinical Study Report (CSR) | 1st quarter 2024 |
| Treatment duration per patient | 6 months (+ 3 months Follow Up) |

### 3.6 Participating sites

In this German clinical trial, approximately 4 to 6 sites, which meet the structural and personnel requirements for performing the planned regular trial-related investigations will be opened for recruitment of patients. If necessary, additional qualified sites can be included during trial conduct by amendment.

### 3.7 Number of patients

18 patients will be included in the trial. Due to the fact of rare disease in this study a recruitment of at least 6 patients per 6 months over all sites is envisioned.

## 4 Trial population and selection criteria

### 4.1 Target population / main diagnosis

#### 4.1.1 Target population

Patients aged ≥ 3 year with no upper limit with segmental overgrowth syndrome of both genders will be enrolled into this trial. Patients will only be allowed to enter the trial if they or respectively the person(s) having the care and custody provide written informed consent about the participation (following full explanation of the trial) and if the physician has verified that the patient meets all of the inclusion criteria and none of the exclusion criteria.

#### 4.1.2 Gender distribution

No gender ratio has been stipulated in this trial as the results of the preclinical and clinical studies did not indicate any difference in the effect of the trial treatment in terms of efficacy and safety.

### 4.2 Inclusion criteria

For inclusion into the trial, patients must fulfill all of the following criteria:

1. Male or female patients aged ≥ 3 years (no upper limit).
2. Signed written informed consent (patient ≥ 18 years or person(s) having the care and custody of the patient < 18 years).
3. Ability to understand the nature of the trial and the trial related procedures and to comply with them.
4. Segmental overgrowth syndrome patients independently of genetic background

   These diagnoses include patients with:
   - CLOVES syndrome, Klippel-Trenaunay-Syndrome and other PIK3CA related overgrowth spectrum diseases
   - Proteus syndrome
   - PTEN hamartoma tumor syndromes including patients with PTEN hamartoma of soft tissue (PHOST)
   - Vascular malformations with significant overgrowth (lesion size of at least 3 cm diameter, externally visible), including but not limited to lymphatic malformations, venous malformations, and fibro-adipose vascular anomaly (FAVA)
5. Identification of at least one measurable target lesion (up to 5 target lesions) with longest diameter more than ≥ 30 mm by MRI. The target lesion(s) must be externally visible (photos) and composed of soft tissue (with one or several tissue components such as fat, vessels, muscle or connective tissue).
6. Normal organ and bone marrow function (i.e. transaminase levels < 2.5 x ULN or serum bilirubin < 1.5 x ULN, hemoglobin > 9 g/dL).
7. Negative urine pregnancy test in females with a childbearing potential.

   A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
8. If female and of child-bearing potential, documentation of negative pregnancy test prior to enrollment. Sexually active female patients, male patients and female partners of male patients must use adequate contraceptive measures while on study and for up to 12 weeks after ending treatment.

### 4.3 Exclusion criteria

Patients eligible for this trial must not meet any of the following criteria:

1. Any concurrent therapy with chemotherapy agents or biologic agents or other immunosuppressive therapy or radiation therapy.
2. Patients who have received live vaccines in the past 30 days prior to informed consent.
3. Patients on medication with CYP3A4 inhibitors / inducers which are not replaced by other equivalent medications for the study period.
4. Patients who have known immunodeficiency or HIV seropositivity.
5. Patients with known history of prior and/or ongoing malignancy within the last 5 years.

6. Patients with known interstitial lung disease, pneumonitis or with bleeding diathesis.
7. Patients with prior use of sirolimus or other mTOR inhibitors or any analogue within the last 6 months;
8. Any planned surgery within study period related to overgrowth lesions..
9. Pre-existing chronic wounds.
10. Triglycerides > 400 mg/dl (> 4.5 mmol/l) or total cholesterol > 300 mg/dl (>7.8 mmol/L).
11. Creatinine clearance ≤ 60 ml/min (Cockcroft- Gault formula).
12. Proteinuria ≥ 30 mg/dl on dipstick and 24 hours proteinuria > 0.8 g/24 hours.
13. Intake of St John's Wort and/or grapefruit and grapefruit juice.
14. Any severe and/or uncontrolled medical conditions which could cause unacceptable safety risks such as:
    - uncontrolled hypercholesterolemia/hypertriglyceridemia.
    - Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of study drug (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome).
15. Patients with a known hypersensitivity to sirolimus or other mTOR inhibitors or any analogs or to its excipients.
16. Patients unwilling to or unable to comply with the planned therapeutic intervention or to comply with the study treatment visits including blood sample collection within the protocol.
17. Female patients who are pregnant or breast feeding, or patients of reproductive potential who are not using effective birth control methods. If barrier contraceptives are used, they must be continued throughout the study by both sexes (see also 4.2).
18. Patients must abstain from donating blood, semen, or sperm during participation in the study until 3 months after the end of participation in the study.

# 5 Enrolment and patient registration

## 5.1 Patient eligibility

If a patient appears to be eligible for the trial, the investigator will inform the patient and/or person(s) having the care and custody about the trial and ask the patient or respectively person(s) having the care and custody for his/her written consent. It is imperative that written consent is obtained prior to any trial-specific procedures. The investigator will then record the details of these trial patients on the following trial-specific lists:

- Subject Screening log: for the documentation of the trial patients who were checked for eligibility before the clinical trial. The following will be entered: the identification code, the dates of written consent, screening and as well as details of whether the patient was enrolled in the trial and, if not, the reason for not enrolling the patient.

- Subject identification log: A confidential log of the names of all trial patients with the identification code assigned to each patient at the time of enrolment in the clinical trial. With this list, the identity of each patient can be revealed. The list must be kept confidential and must not leave the institution. It must remain at the trial center and must not be copied or otherwise passed on. Monitors, auditors and representatives of authorities must be allowed to inspect the list on request.

### 5.2 Patient registration

The patient identification code assigned for the trial will be entered on the registration form and the questions on inclusion and exclusion criteria on the form will be answered. The fully completed form will then be faxed to the central trial office (CTU) for registration:

Clinical Trials Unit
Medical Center - University of Freiburg
Fax: +49 761 270-74390

Registration times:
Monday to Friday from 9:00 to 16:30

The central trial office will review the patient's details on the registration fax. It will then confirm the patient's enrolment in the trial by fax.

## 6 Treatment period: plan and procedure

The investigator will instruct the patient, respectively person(s) having the care and custody to take the investigational product as per protocol. All dosages prescribed and dispensed to the patient and any dose change or interruption must be recorded in patients' diary, patients chart, CRFs and/or on drug accountability forms, as appropriate. Therefore patients will be instructed to bring along their medication to every visit.

### 6.1 Dosing regimen and investigational product administration

**Table 4: Treatment schedule**

| IMP | Pharmaceutical form and route of administration | Dose/ Frequency | Duration |
|---|---|---|---|
| **Sirolimus** | tablets<br>alternatively<br>suspension ml | 1.6 mg/m² daily<br>(divided in two doses in the morning and evening for patients aged <16years) | 6 months |

### 6.2 Dosing and treatment schedule

Patients will be instructed to take their individual dose of sirolimus orally with a glass of water daily at the same time each day immediately after a meal.

Patients below the age of 16 years take twice daily (morning and evening) oral 0.8 mg/$m^2$ sirolimus (0.5; 1 mg tablets, alternatively suspension (concentration 1 mg/ml). The target sirolimus blood level is 3-8 ng/ml, regular dose adjustment should be performed. Patients of higher age (≥ 16 years) will be treated on an once daily dosage regimen (1,6 mg/ $m^2$ daily). Sirolimus should be swallowed whole with a glass of water and the tablets should not be chewed or crushed. If the tablets cannot be swallowed, the tablets should be alternatively replaced with suspension (concentration 1 mg/ml). Immediately prior to administration, the contents should be stirred gently until the suspension has disintegrated into a solution. The contents should then be drunk by the patient. Afterwards, the glass should be rinsed with an additional 30 ml of liquid and drunk by the patient. If vomiting occurs no attempt should be made to replace the dose. Sirolimus will be taken daily (max. 6 months) except in case of unacceptable toxicity or discontinuation from the study for any other reason ().

### 6.3 Dose calculation modification and dose delay

For calculating the body surface area (BSA), in $m^2$, following formula should be used (Dubois and Dubois 1916): BSA= (weight [kg]0.425 × height [cm]0.725) × 0.007184.

For necessary rounding to facilitate or accommodate convenient dosing, with respect to available formulations of 0.5 and 1mg tablets, a 20% tolerance is allowed and in order to avoid overdosing rounding to lower feasible dose is recommended.

The relationship between sirolimus through concentrations and dose has been elaborated, and shown in previous studies to be linear, consistent with the dose proportionality seen with AUC, providing the quantitative basis for adjusting the sirolimus dose as needed to achieve the desired 3-8 ng/ml trough target concentration. Sirolimus whole blood concentrations (pre-dose) should be assessed 2 weeks after commencing treatment. Dosing should be titrated to attain trough concentrations of 3 to 8 ng/ml. If concentrations are below 3 ng/ml, the daily dose may be increased by 1.0 mg/$m^2$ every 2 weeks, subject to tolerability.

The investigator then decides whether to change or maintain the sirolimus dose according to following guidelines:

- If the pharmacokinetic (PK) value is within the range of 3-8 ng/ml the current sirolimus dose should be maintained.

- If the PK value is below 3 ng/ml, the current sirolimus dose should be increased with respect to current dose level and available formulation. In most patients dose adjustments can be based on simple proportion:

  new sirolimus dose = current dose x (target concentration/current concentration)

  The investigator will only consider increasing the dose if the current dose is well tolerated. The maximum dose should not exceed 10 mg/d.

- If the PK value is above 8 ng/ml the current sirolimus dose must be reduced with respect to current dose level and available formulation. In most patients dose adjustments can be based on simple proportion:

  new sirolimusdose = current dose x (target concentration/current concentration).

  In some patients with minimal doses an every other day regimen had to be considered.

For the case of dose adjustments sirolimus through blood levels (pre-dose) will be assessed 1-2 weeks after any dose increase to a new level, or any decrease in an enzyme-inducing drug, or any increase in an enzyme-inhibiting drug. At investigator's discretion additional measurements may be allowed, especially if side effects occur.

### 6.3.1 Known undesirable adverse reactions of sirolimus

Adverse reactions most frequently observed with sirolimus are rash, stomatitis /oral mucositis, non-infectious pneumonitis, fatigue, headache, anorexia, nausea, vomiting, diarrhea, and infections. Overall, the most frequently observed laboratory abnormalities include neutropenia, thrombocytopenia, hypercholesterolemia, and/or hypertriglyceridemia. The majority of these AEs have been of mild to moderate severity (CTCAE grade 1-2). For further details please refer to the current version of SmPC.
Recommendations for dose adjustments, should any of these treatment-related adverse events occur, are given in Table 5.

**Management of infections**

Sirolimus has immunosuppressive properties and may predispose patients to bacterial, fungal, viral or protozoan infections, including infections with opportunistic pathogens. Localized and systemic infections, including pneumonia, other bacterial infections, invasive fungal infections, such as aspergillosis, candidiasis, or pneumocystis jirovecii pneumonia (PJP) and viral infections including reactivation of hepatitis B virus, have been described in patients taking sirolimus. Some of these infections have been severe (e.g. leading to sepsis, respiratory or hepatic failure)

and occasionally have had a fatal outcome. Physicians and patients should be aware of the increased risk of infection with sirolimus. Treat pre-existing infections prior to starting treatment with sirolimus. There is no clear evidence or consensus, whether the prophylactic use of cotrimoxazol is needed during therapy with sirolimus for vascular malformations. We would recommend antibiotic prophylaxis with cotrimoxazol but this is not required. While taking sirolimus, be vigilant for symptoms and signs of infection; if a diagnosis of infection is made, institute appropriate treatment promptly and consider interruption or discontinuation of sirolimus.

The risk for a EBV primary infection in EBV negative patients and the risk for EBV reactivation in EBV positive patients is very rare under the therapy with sirolimus (≥1/1,000 to <1/100) but can lead to EBV lymphoma or Post Transplant Lymphoma Disease (PTLD). EBV negative patients have a higher risk for primary EBV infection under sirolimus and development of PTLD than EBV positive patients [9.], [19.]. Therefore, during the therapy period in the study, EBV serology is closely monitored and if acute EBV infection is diagnosed, therapy should be stopped immediately.

If a diagnosis of invasive systemic fungal infection is made, discontinue sirolimus and treat with appropriate antifungal therapy. Cases of PJP, some with fatal outcome, have been reported in patients who received sirolimus. PJP may be associated with concomitant use of corticosteroids or other immunosuppressive agents. Prophylaxis for PJP should be considered when concomitant use of corticosteroids or other immunosuppressive agents are required.

**Management of stomatitis/oral mucositis/mouth ulcers**

Stomatitis/oral and/or mucositis/mouth ulcers due to sirolimus should be treated using appropriate locally available supportive care. Please follow the paradigm below for treatment of stomatitis/oral and/or mucositis/mouth ulcers:

1. For Grade 1, conservative measures such as non-alcoholic mouthwash or salt water (0.9%) mouth wash several times a day until resolution are to be used.

2. For Grade 2 or 3 the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as, benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol) with or without topical corticosteroids, such as triamcinolone oral paste 0.1%.

3. Agents containing hydrogen peroxide, iodine, and thyme derivatives may tend to worsen mouth ulcers. It is preferable to avoid these agents.

4. Antifungal agents must be avoided unless a fungal infection is diagnosed. In particular, systemic imidazole antifungal agents (ketoconazole, fluconazole, itraconazole, etc.) should be avoided in all patients due to their strong inhibition of sirolimus metabolism leading to higher exposures. Therefore, topical antifungal agents are preferred if an infection is diagnosed. Similarly, antiviral agents such as acyclovir should be avoided unless a viral infection is diagnosed.

Stomatitis/oral and/or mucositis should be appropriately graded using the functional grading given on the CTCAE for Adverse Events, version 5.0.

**Management of hyperlipidemia and hyperglycemia**

Treatment of hyperlipidemia should take into account the pre-treatment status and dietary habits. Blood tests to monitor hyperlipidemia must be taken in the fasting state. Grade 2 or higher hypercholesterolemia (>300 mg/dl or 7.75 mmol/l or Grade 2 or higher hypertriglyceridemia (>2.5 x ULN) should be treated with a statin (HMG-CoA reductase inhibitor), fibrate, or appropriate lipid-lowering medication in addition to diet. Patients should be monitored clinically and through serum biochemistry as required in the product label/data sheets for HMG-CoA reductase inhibitors.

Note: Concomitant therapy with fibrates and HMG-CoA reductase inhibitors are associated with an increased risk of a rare but serious skeletal muscle toxicity manifested by rhabdomyolysis, markedly elevated creatine kinase (CPK) levels and myoglobinuria, acute renal failure and sometimes death. The risk versus benefit ratio should be determined for individual patients based on their risk of cardiovascular complications of hyperlipidemia.

Hyperglycemia has been observed in patients receiving sirolimus therapy. Monitoring of fasting serum glucose is recommended prior to the start of sirolimus therapy and periodically thereafter. Optimal glycemic control should be achieved before starting trial therapy.

**Management of hematological parameters**

Decreased hemoglobin, lymphocytes, platelets, and neutrophils have been reported in patients treated with sirolimus. Monitoring of complete blood count is recommended prior to the start of sirolimus therapy and periodically thereafter.

**Management of hepatic impairment**

Sirolimus was administered as a single, oral dose to subjects with normal hepatic function and to patients with Child-Pugh classification A (mild), B (moderate), or C (severe) hepatic impairment. Compared with the values in the normal hepatic function group, the patients with mild, moderate, and severe hepatic impairment had 43%, 94%, and 189% higher mean values for sirolimus

AUC, respectively, with no statistically significant differences in mean Cmax. As the severity of hepatic impairment increased, there were steady increases in mean sirolimus t1/2, and decreases in the mean sirolimus clearance normalized for body weight (CL/F/kg).
The maintenance dose of sirolimus could be reduced by approximately one third in patients with mild-to-moderate hepatic impairment and should be reduced by approximately one half in patients with severe hepatic impairment.

**Management of diarrhea**

Diarrhea attributed to sirolimus toxicity may be treated with loperamide. Other medications for diarrhea may be used as needed.

**Management of non-infectious pneumonitis**

Both asymptomatic radiological changes (Grade 1) and symptomatic non-infectious pneumonitis (Grade 2 = not interfering with activities of daily living and Grade 3 = interfering with activities of daily living and oxygen indicated) have been noted in patients receiving sirolimus therapy. Non-infectious pneumonitis has been associated with sirolimus and other mTOR inhibitors (Atkins, et al 2004). If non-infectious pneumonitis develops (or patients with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnea), a consultation with a pulmonologist should be considered. Patients should be advised to report promptly any new or worsening respiratory symptoms. If the patient develops Grade 3 pneumonitis, treatment with sirolimus must be interrupted and the patient treated as medically indicated (short course corticosteroids, oxygen, etc). Management of non-infectious pneumonitis suspected to be associated with sirolimus and dose modification instructions are provided in Table 5 and Table 7.

### 6.3.2 Sirolimus dose level modification/interruption guidelines in case of suspected toxicity

Dose adjustments are permitted for any adverse event suspected to be related to sirolimus in those patients unable to tolerate their individual once daily oral dose. If administration of sirolimus must be interrupted because of unacceptable toxicity, study drug dosing will be interrupted or modified according to the guidelines in, Table 5, Table 6, Table 7.

In addition, if any surgery is planned, trial therapy should be stopped.

If treatment is interrupted due to toxicity, study drug should not be resumed unless recovery to grade ≤1 is achieved in less than 6 weeks. Then it could be reintroduced at the initial dose or a lower dose level depending on the toxicity type and grade (see Table 5 and Table 6).

All interruptions or dose modifications must be recorded on the Dosage Administration Record page of the CRF. If treatment is interrupted for 6 weeks or more, the patient should be discontinued from the study.

**Table 5: Sirolimus dose modification guidelines for non-hematologic toxiticities (Overview)**

| Adverse Drug Reaction | Severity[1] | Sirolimus Dose Adjustment[2] and Management Recommendations |
|---|---|---|
| Non-infectious pneumonitis | Grade 1<br>Asymptomatic, radiographic findings only | No dose adjustment required.<br>Initiate appropriate monitoring. |
| | Grade 2<br>Symptomatic,<br>not interfering with ADL[3] | Consider interruption of therapy, rule out infection and consider treatment with corticosteroids until symptoms improve to Grade ≤ 1.<br>Re-initiate sirolimus at a lower dose.<br>Discontinue treatment if failure to recover within 4 weeks. |
| | Grade 3<br>Symptomatic,<br>interfering with ADL[3]<br>$O_2$ indicated | Interrupt sirolimus until symptoms resolve to Grade ≤ 1. Rule out infection and consider treatment with corticosteroids.<br>Consider re-initiating sirolimus at a lower dose.<br>If toxicity recurs at Grade 3, consider discontinuation. |
| | Grade 4<br>Life-threatening,<br>ventilatory support indicated | Discontinue sirolimus, rule out infection, and consider treatment with corticosteroids. |
| Stomatitis | Grade 1<br>Minimal symptoms,<br>normal diet | No dose adjustment required.<br>Manage with non-alcoholic or salt water (0.9%) mouthwash several times a day. |
| | Grade 2<br>Symptomatic but can eat and swallow modified diet | Temporary dose interruption until recovery to Grade ≤ 1.<br>Re-initiate sirolimus at the same dose.<br>If stomatitis recurs at Grade 2, interrupt dose until recovery to Grade ≤ 1. Re-initiate sirolimus at a lower dose.<br>Manage with topical analgesic mouth treatments (e.g., benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[4] |
| | Grade 3<br>Symptomatic and unable to adequately eat or hydrate orally | Temporary dose interruption until recovery to Grade ≤ 1.<br>Re-initiate sirolimus at a lower dose.<br>Manage with topical analgesic mouth treatments (e.g., benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol or phenol) with or without topical corticosteroids (i.e. triamcinolone oral paste).[4] |
| | Grade 4<br>Symptoms associated with life-threatening consequences | Discontinue sirolimus and treat with appropriate medical therapy. |
| Other non-hematologic toxicities (excluding metabolic events) | Grade 1 | If toxicity is tolerable, no dose adjustment required.<br>Initiate appropriate medical therapy and monitor. |
| | Grade 2 | If toxicity is tolerable, no dose adjustment required.<br>Initiate appropriate medical therapy and monitor.<br>If toxicity becomes intolerable, temporary dose interruption until recovery to Grade ≤ 1. Re-initiate sirolimus at the same dose.<br>If toxicity recurs at Grade 2, interrupt sirolimus until recovery to Grade ≤ 1. Re-initiate sirolimus at a lower dose. |
| | Grade 3 | Temporary dose interruption until recovery to Grade ≤ 1.<br>Initiate appropriate medical therapy and monitor.<br>Consider re-initiating sirolimus at a lower dose.<br>If toxicity recurs at Grade 3, consider discontinuation. |
| | Grade 4 | Discontinue sirolimus and treat with appropriate medical therapy. |
| Metabolic events (e.g. hyperglycemia, dyslipidemia) | Grade 1 | No dose adjustment required.<br>Initiate appropriate medical therapy and monitor. |
| | Grade 2 | No dose adjustment required.<br>Manage with appropriate medical therapy and monitor. |

| Adverse Drug Reaction | Severity[1] | Sirolimus Dose Adjustment[2] and Management Recommendations |
|---|---|---|
| | Grade 3 | Temporary dose interruption.<br>Re-initiate sirolimus at a lower dose.<br>Manage with appropriate medical therapy and monitor. |
| | Grade 4 | Discontinue sirolimus and treat with appropriate medical therapy. |

[1] Severity Grade description: 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening symptoms.
[2] If dose reduction is required, the suggested dose is approximately 50% lower than the dose previously administered.
[3] Activities of daily living (ADL)
[4] Avoid using agents containing alcohol, hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

**Table 6: Sirolimus dose modification guidelines for hematologic toxicities**

| Toxicity | Actions |
|---|---|
| Thrombocytopenia<br>Platelet count | • ≥ 75000/mm$^3$: no change<br>• 50000/mm$^3$ to 75000/mm$^3$: Hold study drug until recovery to ≥ 75000/mm$^3$<br>Reintroduce study drug at the same dose level<br>• < 50000/mm$^3$: Hold study drug until recovery to ≥ 75000/mm$^3$ |
| Absolute Neutrophil Count (ANC) | • ≥ 1000/mm$^3$: no change<br>• 500/mm$^3$ to 1000/mm$^3$: Hold study drug until recovery to ≥ 1000/mm$^3$<br>Reintroduce study drug at the same dose level<br>• < 500/mm$^3$: Hold study drug until recovery to ≥ 1000/mm$^3$ |
| Febrile neutropenia | Hold further dosing until ANC ≥ 1250/mm$^3$ and no fever. |
| Toxicity requiring interruption for > 6 weeks | Discontinue study treatment |
| Physicians should always manage patients according to their medical judgment based on the particular clinical circumstances | |

**Table 7: Management of non-infectious pneumonitis**

| Worst grade | Required Investigations | Management of Pneumonitis | Sirolimus Dose Adjustment |
|---|---|---|---|
| **Grade 1** | CT scans with lung windows. Repeat chest x-ray/CT scan every 12 weeks until return to baseline | No therapy required | Administer 100% of sirolimus dose |
| **Grade 2** | CT scans with lung windows. Repeat chest at least every 12 weeks until return to within normal limits | Symptomatic only. Consider corticosteroids if cough is troublesome | Reduce study treatment dose by 1 dose level until recovery to ≤ Grade 1. Study treatment may also be interrupted if symptoms are troublesome. Patients will discontinue study treatment if they fail to recover to < Grade 1 within 3 weeks |
| **Grade 3** | CT scan with lung windows. Repeat at least every 8 weeks until return to within normal limits. Bronchoscopy with biopsy and/or BAL is recommended | Prescribe corticosteroids if infective origin ruled out. Taper as medically indicated | Hold treatment until recovery to ≤ Grade 1. May restart treatment within 3 weeks at a reduced dose if evidence of clinical benefit. |
| **Grade 4** | CT scan with lung windows and required pulmonary function testing including spirometry, DLco, and room air O2 saturation at rest. Repeat at least every 8 weeks until return to within normal limits. Bronchoscopy with biopsy and/or BAL is recommended if possible. | Prescribe corticosteroids if infective origin ruled out. Taper as medically indicated | Discontinue treatment |
| **Physicians should always manage patients according to their medical judgment based on the particular clinical circumstances.** | | | |

### 6.4 Concomitant medication

The patient must notify the investigational site about any new medications he/she takes after the start of the trial medication. All medications (other than investigational product) and significant non-drug therapies (including physical therapy and blood transfusions) administered since start of screening must be listed in the CRF.

Patients must be instructed not to take any additional medications (over-the-counter or other products) during the study without prior consultation with the investigator. The following guidelines must be adhered to during the study:

- Investigational or commercial anti-proliferative agents other than study drug (including other mTOR inhibitors, e.g., Everolimus, Temsirolimus) are prohibited.
- Co-administration with moderate or strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir, erythromycin, fluconazole) or inhibitors of P-glycoprotein (PgP) must be avoided (see Appendix 6)
- Co-administration with strong inducers of CYP3A4, other than anti-epileptics, must be avoided
- Seville orange, star fruit, grapefruit and their juices affect P450 and PgP activity. Concomitant use should be avoided.

Sirolimus may affect patient response to vaccinations making the vaccination less effective. As sirolimus is an immunosuppressant, live vaccines must be avoided while a patient is treated with sirolimus.

Otherwise, the use of other concomitant medication/therapy deemed necessary for the care of the patient is allowed. The investigator should instruct the patient to notify the study site about any new medications he/she takes after the start of the study drug. All medications (other than study drug) and significant non-drug therapies (including blood transfusions) administered after the patient starts study drug sirolimus must be listed on the Concomitant Medications/Significant Non-drug Therapies page of the CRF.

## 7 Visit schedule and assessments

### 7.1 Flow and visit schedule

The schedule of assessment lists all of the assessments and indicates with an “X” the visits when they have to be performed (Table 8). All data obtained from these assessments must be supported in the patient’s source documentation.

### 7.2 Visit and assessment windows

Screening evaluations has to be performed within 28 days prior to start of therapy.

During the course of the trial visits and test procedures should occur on schedule whenever possible; visits that take place ± 7 respectively ± 14 days from the scheduled date will not constitute protocol deviation.

**Table 8: Trial schedule and Assessments**

| **PERIODS**[1] | **Name** | **SCREENING** | | **TREATMENT** | | | | **FOLLOW UP** |
|---|---|---|---|---|---|---|---|---|
| | **Duration** | **28 days** | | **6 months** | | | | **3 months** |
| **VISITS** | **Name** | **Screening** | **Visit 1 (Start of treatment)** | **Visit 2** | **Dosage administration record** | **Visit 3** | **Visit 4 (EOT)** | **Visit 5 (EOS)** |
| | **Time** | **Day-28 until Day 0** | **Day 0** | **Day 14 (Day 10-14)** | **D1-D14 after start of treatment** | **Month 3** (± 7 days) | **Month 6** (± 7 days) | **Month 9** (± 14 days) |
| **Informed Consent**[2] | | X | | | | | | |
| **Inclusion / Exclusion Criteria** | | X | | | | | | |
| **Demographics**[3] | | X | | | | | | |
| **Registration**[4] | | X | | | | | | |
| **Medical history**[5] | | X | | | | | | |
| **Dispense study drug** | | | X | | | X | X | |
| **Dosage administration record** | | | | | X | X | X | |
| **Drug Accountability** | | | | | X | X | X | |
| **Physical Examination (incl. height, weight)**[6] | | X | X | | | X | X | X |
| **Vital signs (pulse, blood pressure, body temp)** | | X | X | | | X | X | X |
| **Performance Score (Lansky / Karnofsky)** | | X | X | | | X | X | X |
| **Laboratory tests (haematology, clinical chemistry, EBV serology (IgM and IgG) and EBV PCR**[7] | | X | | | | X | X | X |
| **Coagulation** | | X | | | | X | X | X |
| **HIV test** | | X | | | | | | |
| **Pregnancy test**[8] | | X | | | | | | |
| **Sirolimus serum levels**[9,10] | | | | X | | X | X | |
| **PBMC and serum collection to evaluate mTOR inhibition and biomarkers**[11] | | X | | | | X | X | X |
| **MRI target lesion**[12] | | X | | | | | X | X |
| **Photo target lesion** | | X | | | | X | X | X |
| **Neuropsychological tests (SDQ)** | | | X | | | X | X | X |
| **Adverse Events**[13] | | | | X | | X | X | X |
| **Concomitant Medication**[14] | | X[15] | | X | | X | X | X |
| **Quality of Life questionnaire (KINDL®)**[15]**, pain scales** | | | X | | | X | X | X |

| **PERIODS**[1] | **Name** | **SCREENING** | | **TREATMENT** | | | | **FOLLOW UP** |
|---|---|---|---|---|---|---|---|---|
| | **Duration** | **28 days** | | **6 months** | | | | **3 months** |
| **VISITS** | **Name** | **Screening** | **Visit 1 (Start of treatment)** | **Visit 2** | **Dosage administration record** | **Visit 3** | **Visit 4 (EOT)** | **Visit 5 (EOS)** |
| | **Time** | **Day-28 until Day 0** | **Day 0** | **Day 14 (Day 10-14)** | **D1-D14 after start of treatment** | **Month 3** (± 7 days) | **Month 6** (± 7 days) | **Month 9** (± 14 days) |
| **Questionnaire (WHO QOL-BREF)**[16] | | | | | | X | X | X |
| **Patient diary** | | | X | X | | X | X | X |

[1] Procedures during study treatment period will be performed for each patient according to Table 4 for a maximum of 6 months after start of medication.

[2] Informed consent must be obtained by patient and/or person(s) having the care and custody of the child. Patient ≥ 7 years would be included in the decision for study participation.

[3] Demographic data includes date of birth and sex.

[4] Patients will be registered after signing informed consent.

[5] Information about relevant medical history includes disease history (first diagnosis, relapse, prior treatment of segmental overgrowth syndrome) and family history.

[6] Physical Examination includes general appearance, skin, neck including thyroid, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes. Abnormal findings during screening will be documented as medical history. New findings during treatment will be documented as adverse event.

[7] Local lab: The following laboratory parameters will be determined locally during study: complete blood count (CBC) including total white blood cell (WBC), neutrophil count, RBC, lymphocyte, monocyte, eosinophil, basophil counts, hemoglobin (Hgb) and a platelet count. Blood chemistry comprises creatinine, urea, uric acid, sodium, calcium, potassium, glucose, total bilirubin, alkaline phosphatase, ALT, AST, LDH, gamma-GT, total protein, albumin, triglycerides, cholesterine. Local lab results during study treatment period will not be captured in the CRF, if clinically relevant abnormal laboratory values will be captured as adverse event (only screening will be documented in the CRF).

[8] Pregnancy test must be performed by urine analysis within 7 days before day 1 (only female patients of child-bearing potential).

[9] Sirolimus serum level must be between 3-8 ng/ml. Additional measurements of sirolimus serum level between the study visits are not necessary.

[10] First sirolimus serum level measurement after 14 days (Day 10-14, from day 1).

[11] Blood has to be collected for centrally performed immunoblotting and evaluation of serum biomarkers (IGFBP-3, IGF, VEGF).

[12] MRI target lesion will be evaluated according response criteria, see chapter 7.5-

[13] AEs will be captured retrospectively each time the patient presents him/herself for study treatment period and will cover the time in-between visits. However, spontaneously reported or detected AEs at other time points will be captured as well. The AE/SAE reporting period for this trial begins after first intake of medication within the study until 30 days after the last study medication of the patient. Afterwards only AEs/SAEs related to the IMP have to be documented in the CRF

[14] All medications taken within 28 days of screening visit should be reported in the CRF.

[15] Only by patient´s ≥ 3 and ≤ 17 years of age.

[16] Only patients ≥ 18 years

## 7.3 Screening and registration

The investigator is obliged to give the patient respectively person(s) having the care and custody thorough information about the trial and the trial related assessments, the patient respectively person(s) having the care and custody should be given ample time to consider his or her participation. The investigator must not start any trial specific procedure before Informed Consent Form (ICF) is signed and dated by patient respectively person(s) having the care and custody and investigator.

### 7.3.1 Screening

After having been informed about the trial and after having given their written Informed Consent, patients have to pass the examinations listed in section 7.3.3 prior to registration. Results of examinations routinely performed due to segmental overgrowth syndrome will be accepted, if they were done within 28 days prior to registration.

Patients must meet all inclusion criteria and none of the exclusion criteria to be considered eligible.

Patients considered eligible by the investigator should be registered to the trial via fax (see section 5.2).

### 7.3.2 Data to be collected on screening failures

Patients who are screened and do not meet all entry criteria will not be entered into the study. Such patients are considered to be screening failures. The reason for not being started on sirolimus will be entered on the screening log.

### 7.3.3 Assessments at screening (within 28 days)

The following examinations and lab tests will be performed within 28 days prior to Day 0:

| Assessment | Includes |
|---|---|
| Inclusion/exclusion criteria | Patient eligibility is to be assessed including serum pregnancy test in females of child-bearing potential. |
| Demographics | Demographic data that will be collected on patient characteristics at screening include: date of birth, sex, childbearing potential. |
| Medical History | At screening relevant past medical history including date of diagnosis of segmental overgrowth syndrome, assessments of any current medical conditions and any other relevant previous and concomitant disease will be collected initially have to be documented in the CRF. |
| Physical examination | Thorough physical/medical examination includes, but is not limited to cardiovascular, gastrointestinal, hepatobiliary, respiratory, musculoskeletal, genitourinary/renal and other organ systems.<br>Physical examination incl. height, weight and performance status. |
| Vital signs | The vital sign data must be taken at screening and all subsequent visits. Results must be present on the patient's chart and recorded onto the CRF pages. The vital signs include: body temperature, pulse rate and systolic/diastolic blood pressure.<br>Blood pressure will be measured according to the National Institutes |

| Assessment | Includes |
|---|---|
| | of Health, National Heart, Lung, and Blood Institute Guidelines [NIH 1997] with the following standardized techniques:<br>• Patients are seated in a chair; blood pressure measurement begins after at least 5 minutes of rest,<br>• The appropriate cuff size is used to ensure accurate measurement, measurements will be taken preferably with a mercury sphygmomanometer. Only one reading is required. |
| Performance Score | Lansky (< 16years) / Karnofsky |
| Hematology | Haematology includes assessment of haemoglobin, platelet count, a complete red blood cell count (RBC), total white blood cell count (WBC) and differential count including neutrophils, lymphocytes, monocytes, eosinophils and basophils. |
| Virology | EBV serostatus and EBV PCR |
| Biochemistry | Blood chemistry comprises creatinine, urea, uric acid, sodium, calcium, potassium, glucose, total bilirubin, alkaline phosphatase, ALT, AST, LDH, gamma-GT, total protein, albumin, triglycerides, cholesterine |
| Coagulation | Quick, INR, PTT, D-Dimere, Fibrinogen |
| Pregnancy test | Blood or urine, within 7 days prior to day 1 (only female patients of child-bearing potential). |
| MRI assessment | Evaluation according to RECIST criteria 1.1. longest diameter [mm] of each target diameters at screening. |
| Photo assessment | A photo for the target lesion will be performed. The same perspective will be used when photos are repeated during the appropriate visits (see section 7.6) |
| Concomitant medication | Record all concomitant medications and/or non-drug therapies (including the reason for administration) within 28 days of screening. |

### 7.3.4 Check of eligibility Day 0 (Visit 1/Start of therapy)

The following examinations and lab tests will be performed on Day 0:

| Assessment | Includes |
|---|---|
| Physical examination | Thorough physical/medical examination includes, but is not limited to cardiovascular, gastrointestinal, hepatobiliary, respiratory, musculoskeletal, genitourinary/renal and other organ systems.<br>Physical examination incl. height, weight and performance status. |
| Vital signs | The vital sign data must be taken at screening and all subsequent visits. Results must be present on the patient's chart and recorded onto the CRF pages. The vital signs include: body temperature, pulse rate and systolic/diastolic blood pressure.<br>Blood pressure will be measured according to the National Institutes of Health, National Heart, Lung, and Blood Institute Guidelines [NIH 1997] with the following standardized techniques:<br>• Patients are seated in a chair; blood pressure measurement begins after at least 5 minutes of rest, |

| Assessment | Includes |
|---|---|
| | • The appropriate cuff size is used to ensure accurate measurement, measurements will be taken preferably with a mercury sphygmomanometer. Only one reading is required. |
| Performance Score | Lansky (< 16years) / Karnofsky |
| Neuropsychological evaluation | The neuropsychological test Strength and Difficulties Questionaire (SDQ) is to be filled out. It is important that the investigator is not influencing the patient in any way. |
| Concomitant medication | Record all concomitant medications and/or non-drug therapies (including the reason for administration). |
| QoL | The KINDL® is to be filled out by the patient him/herself respectively person(s) having the care and custody (only for patients ≥ 3 and ≤ 17 years of age). Patients ≥18 years of age will fill out the WHOQOL-BREF. It is important that the investigator is not influencing the patient in any way. |
| Pain assessment | The pain scales are to be filled out by the patient him/herself. It is important that the investigator is not influencing the patient in any way |

Patients considered eligible by the investigator once all screening procedures are complete will be registered to the trial (see section 5.2).

### 7.4 Treatment period

Following inclusion of trial and initiation of trial treatment, the patient should visit the study site at day 14, months 3 and 6 after treatment start. For details see sections below.

#### 7.4.1 Assessments on Day 1 until Day 14 after start of therapy (Visit 2)

The following assessments have to be performed:

| Assessment | Includes |
|---|---|
| Dispense study drug | Explain daily intake of individual dose of sirolimus orally |
| Dosage administration record | Record of dosage administration deviation |
| Drug accountability | Record of dispensed and returned medication |
| Sirolimus serum levels | If this level is into the defined range (3-8 ng/ml) next level is performed on next visit, if not see section 6.3. Recording of dose and corresponding level will be done in the case report form. |

### 7.4.2 Assessments at Month 3 (Visit 3)

| Assessment | Includes |
|---|---|
| Physical examination | Thorough physical/medical examination includes, but is not limited to cardiovascular, gastrointestinal, hepatobiliary, respiratory, musculoskeletal, genitourinary/renal and other organ systems.<br>Physical examination incl. height, weight and performance status. |
| Vital signs | The vital signs include: body temperature, pulse rate and systolic/diastolic blood pressure. Blood pressure will be measured according to the National Institutes of Health, National Heart, Lung, and Blood Institute Guidelines [NIH 1997] with the following standardized techniques:<br>• Patients are seated in a chair; blood pressure measurement begins after at least 5 minutes of rest,<br>The appropriate cuff size is used to ensure accurate measurement, measurements will be taken preferably with a mercury sphygmomanometer. Only one reading is required. |
| Hematology | Haematology includes assessment of haemoglobin, platelet count, a complete red blood cell count (RBC), total white blood cell count (WBC) and differential count including neutrophils, lymphocytes, monocytes, eosinophils and basophils.<br>If clinically relevant abnormal laboratory values will be captured in the CRF as adverse event. |
| Virology | EBV serostatus and EBV PCR |
| Biochemistry | Blood chemistry comprises creatinine, urea, uric acid, sodium, calcium, potassium, glucose, total bilirubin, alkaline phosphatase, ALT, AST, LDH, gamma-GT, total protein, albumin, triglycerides, cholesterine.<br>If clinically relevant abnormal laboratory values will be captured in the CRF as adverse event. |
| Coagulation | Quick, INR, PTT, D-Dimere, Fibrinogen |
| Performance Score | Lansky (< 16years) / Karnofsky |
| Sirolimus serum levels | If this level is into the defined range (3-8 ng/ml) next level is performed on next visit, if not see section 6.3. Recording of dose and corresponding level will be done in the case report form. |
| Dispense study drug | Daily Intake of individual dose of sirolimus orally |
| Dosage administration record | Record of dosage administration deviation |
| Drug accountability | Record of dispensed and returned medication |
| PBMC and serum collection | Translation project: Evaluation of mTOR inhibition an biomarkers |
| Photo assessment | A photo for the target lesion will be performed. The same perspective will be used when photos are repeated during the appropriate visits (see section 7.6). |

| Assessment | Includes |
|---|---|
| Neuropsychological evaluation | The neuropsychological test Strength and Difficulties Questionnaire (SDQ) is to be filled out. It is important that the investigator is not influencing the patient in any way. |
| Concomitant medication | Record all concomitant medications and/or non-drug therapies (including the reason for administration). |
| QoL | The KINDL® is to be filled out by the patient him/herself respectively person(s) having the care and custody (only by patient's ≥ 3 and ≤ 17 years of age). Patients ≥18 years of age will fill out the WHOQOL-BREF. It is important that the investigator is not influencing the patient in any way |
| Pain assessment | The pain scales are to be filled out by the patient him/herself. It is important that the investigator is not influencing the patient in any way |
| Adverse Events | See section 10.1 |
| Patient diary | Record of AEs and Comed |

### 7.4.3 Assessments at Month 6 (Visit 4/ End of treatment EOT)

Patients who discontinue treatment before month 6 should be scheduled for an end of treatment (EOT) within 14 days after last administration of investigational product, at which the following assessments will be performed:

| Assessment | Includes |
|---|---|
| Physical examination | Thorough physical/medical examination includes, but is not limited to cardiovascular, gastrointestinal, hepatobiliary, respiratory, musculoskeletal, genitourinary/renal and other organ systems.<br>Physical examination incl. height, weight. |
| Vital signs | The vital signs include: body temperature, pulse rate and systolic/diastolic blood pressure. Blood pressure will be measured according to the National Institutes of Health, National Heart, Lung, and Blood Institute Guidelines [NIH 1997] with the following standardized techniques:<br>• Patients are seated in a chair; blood pressure measurement begins after at least 5 minutes of rest,<br>The appropriate cuff size is used to ensure accurate measurement, measurements will be taken preferably with a mercury sphygmomanometer. Only one reading is required. |
| Performance Score | Lansky (< 16years) / Karnofsky |
| Sirolimus serum levels | If this level is into the defined range (3-8 ng/ml) next level is performed on next visit, if not see section 6.3. Recording of dose and corresponding level will be done in the case report form. |
| Drug accountability | Record of dispensed and returned medication |
| Virology | EBV serostatus and EBV PCR |
| PBMC and serum collection | Translation project: Evaluation of mTOR inhibition an biomarkers |
| Hematology | Haematology includes assessment of haemoglobin, platelet count, a |

| Assessment | Includes |
|---|---|
| | complete red blood cell count (RBC), total white blood cell count (WBC) and differential count including neutrophils, lymphocytes, monocytes, eosinophils and basophils.<br>If clinically relevant abnormal laboratory values will be captured in the CRF as adverse event. |
| Biochemistry | Blood chemistry comprises creatinine, urea, uric acid, sodium, calcium, potassium, glucose, total bilirubin, alkaline phosphatase, ALT, AST, LDH, gamma-GT, total protein, albumin, triglycerides, cholesterine.<br>If clinically relevant abnormal laboratory values will be captured in the CRF as adverse event. |
| Coagulation | Quick, INR, PTT, D-Dimere, Fibrinogen |
| MRI assessment | Evaluation according response criteria (see section 7.5. |
| Photo assessment | A photo for the target lesion will be performed. The same perspective will be used when photos are repeated during the appropriate visits (see section 7.6). |
| Neuropsychological evaluation | The neuropsychological test SDQ is to be filled out. It is important that the investigator is not influencing the patient in any way. |
| Concomitant medication | Record all concomitant medications and/or non-drug therapies (including the reason for administration). |
| QoL | The KINDL® is to be filled out by the patient him/herself respectively person(s) having the care and custody (only by patient's ≥ 3 and ≤ 17 years of age). Patients ≥18 years of age will fill out the WHOQOL-BREF. It is important that the investigator is not influencing the patient in any way |
| Pain assessment | The pain scales are to be filled out by the patient him/herself. It is important that the investigator is not influencing the patient in any way |
| Adverse Events | see section 10.1. |
| Patient diary | Record of AEs and Comed |

### 7.4.4 Assessments at Month 9 (Visit 5/Follow Up Visit/End of Study EOS)

One Follow up visit will be done 3 months after End of Treatment Visit (EOT). The following assessments will be performed:

| Assessment | Includes |
|---|---|
| Physical examination | Thorough physical/medical examination includes, but is not limited to cardiovascular, gastrointestinal, hepatobiliary, respiratory, musculoskeletal, genitourinary/renal and other organ systems.<br>Physical examination incl. height, weight and performance status. |
| Vital signs | The vital signs include: body temperature, pulse rate and systolic/diastolic blood pressure. Blood pressure will be measured according to the National Institutes of Health, National Heart, Lung, and Blood Institute Guidelines [NIH 1997] with the following standardized techniques: |

| Assessment | Includes |
|---|---|
| | • Patients are seated in a chair; blood pressure measurement begins after at least 5 minutes of rest,<br>The appropriate cuff size is used to ensure accurate measurement, measurements will be taken preferably with a mercury sphygmomanometer. Only one reading is required. |
| Hematology | Haematology includes assessment of haemoglobin, platelet count, a complete red blood cell count (RBC), total white blood cell count (WBC) and differential count including neutrophils, lymphocytes, monocytes, eosinophils and basophils.<br>If clinically relevant abnormal laboratory values will be captured in the CRF as adverse event. |
| Biochemistry | Blood chemistry comprises creatinine, urea, uric acid, sodium, calcium, potassium, glucose, total bilirubin, alkaline phosphatase, ALT, AST, LDH, gamma-GT, total protein, albumin, triglycerides, cholesterine.<br>If clinically relevant abnormal laboratory values will be captured in the CRF as adverse event. |
| Coagulation | Quick, INR, PTT, D-Dimere, Fibrinogen |
| MRI assessment | Evaluation according response criteria (see section 7.5) |
| Photo assessment | A photo for the target lesion will be performed. The same perspective will be used when photos are repeated during the appropriate visits (see section 7.6). |
| PBMC and serum collection | Translation project: Evaluation of mTOR inhibition an biomarkers |
| Adverse events | See section 10.1 |
| Neuropsychological evaluation | The neuropsychological test SDQ is to be filled out. It is important that the investigator is not influencing the patient in any way. |
| Concomitant medication | Record all concomitant medications and/or non-drug therapies (including the reason for administration). |
| QoL | The KINDL® is to be filled out by the patient him/herself respectively person(s) having the care and custody (only by patient's ≥ 3 and ≤ 17 years of age). Patients ≥18 years of age will fill out the WHOQOL-BREF. It is important that the investigator is not influencing the patient in any way |
| Pain assessment | The pain scales are to be filled out by the patient him/herself. It is important that the investigator is not influencing the patient in any way |

## 7.5 Criteria for tumour assessment and response

### 7.5.1 Eligibility for evaluation

Patients with a measurable disease by MRI assessed by RECIST 1.1 according to defined response criteria before the start of study treatment are eligible for response evaluation (see 7.5.3). The radiological assessment will be performed locally. Data has to be pseudonymized and sent to Medical Center – University of Freiburg for Central review of radiological assessment

Response and progression of segmental overgrowth syndrome will be assessed by MRI. At least one measurable target lesion (up to 5 target lesions) with more than by MRI ≥ 30 mm needs to be present. One or more target lesions (up to 5) will be defined by the investigator at the recruiting trial center. The MRI focusing on these lesions will be performed at screening and repeated at month 6 and month 9.

### 7.5.2 Criteria for Measurable Lesions

Measurable lesions are lesions that can be accurately measured in at least one dimension with longest diameter at least 30 mm using MRI techniques. A maximum of 5 lesions can be defined as target lesions. The target lesions must be externally visible (photos). A sum of the longest diameter of all target lesions will be calculated and reported as the baseline sum of the longest diameter. This will be used as reference by which to characterize the overgrowth syndrome.

Suggested MRI sequences:

coronal fat-suppressed T2 weighting and T1[SG1] sequences, axial T2 sequence with fat saturation, coronal and axial T1 with contrast enhancement and with fat saturation Contrast enhancement can be omitted if it does not provide additional information compared to the other sequences in screening MRI.

### 7.5.3 Definition of Measurable Lesion Response

Target lesions will be measured in the dimension showing the longest diameter..

**Response Evaluation Criteria (according to RECIST 1.1):**

**Definition of a measurable lesion:**

- At least one lesion which can be measured in at least one dimension
- Measurement of the longest diameter, using MRI techniques ≥ 30 mm

**General guidelines:**

- During the study the same investigations and the same measuring techniques
- Measurements with pictures are preferred to clinical measurements

**Baseline of measurable lesions:**

- Estimation of the total overgrowth mass
- As shortly as possible prior to therapy start (≤ 4 weeks): identification of all measurable lesions
- A maximum of 5 target lesions
- Representative of all organs
- Sum of the largest diameters (this sum is the reference for objective tumor response)

**Evaluation of target lesions**

| **Sum of all diameters** | | *comparison with* |
|---|---|---|
| Complete response CR | Disappearance of all measurable lesions<br>No new lesions | |
| Partial response PR | ≥ 30% decrease in the sum of longest diameters<br>No new lesions may occur or individual lesions progress. | Baseline prior to therapy start |
| Progressive disease PD | ≥ 20% increase in the sum of longest diameters or in at least one new lesion or the appearance of new lesions.<br>If a target lesion disappears and the progression of a lesion or the appearance of new lesions is observed elsewhere at the same time, this is also documented as a progressive disease. | Minimum = smallest sum of longest diameters at baseline or subsequent to therapy start |
| Stable disease SD | Neither a partial nor a complete response in the absence of progression. | |

### 7.5.4 Best Overall Response

| **Target lesion** | **Overall Response (OR)** |
|---|---|
| CR | CR |
| CR | PR |
| PR | PR |
| SD | SD |
| PD | PD |
| - | PD |

| | |
|---|---|
| **New lesion** | PD |

### 7.6 Photo assessment and evaluation

A photo of at least one target lesion will be performed (the lesion must also be visible with MRI). The same perspective (surrounding, light, and distance to camera) will be used when photos are repeated during the appropriate visits. A photo standardization document will be filled in and checked at every photo taken during visits. This guarantees standardized photos in every patient. There are clear standard for all patients in the trial.
A central photo evaluation will be performed using a scale for external validation. In particular, the photographs will be taken at baseline, at 3, 6 and 9 months of sirolimus therapy.

Independent readers (3 experts in the field of pediatric dermatology/oncology and radiology) will be presented paired groups of photographs of month 3, 6 and 9 as compared to baseline.. The paired groups will be placed side by side (with the timepoint blinded to the readers) and the readers will be asked to assess whether or not the target lesion has been responded on therapy in the photographs to the right using a VAS. The VAS presents along a 100 mm line, indicating ‘no response’ as 0 to ‘complete response (external disappearance)’ as 100.

### 7.7 Neuropsychological evaluation

The Strengths and Difficulties Questionnaire (SDQ) is a brief behavioral screening questionnaire. It exists in several versions to meet the needs of researchers, clinicians and educationalists. All versions of the SDQ ask about 25 attributes, some positive and others negative.
The same 25 items are included in questionnaires for completion by the parents or teachers of 4-16 year olds (Goodman, 1997).
Questionnaires for self-completion by adolescents ask about the same 25 traits, although the wording is slightly different (Goodman et al, 1998). This self-report version is suitable for young people aged around 11-16, depending on their level of understanding and literacy and for adults.

### 7.8 Quality of Life

The KINDL® is a generic instrument for assessing Health-Related Quality of Life in children and adolescents aged 3 years and older. The KINDL® provides 24 items and thus is a short, methodologically suitable, psychometrically sound and flexible measure of Health-Related Quality of Life in children and adolescents.
Three different versions of the instrument suitable for different age groups and developmental stages are provided. The KINDL® can be used for children and adolescents between 3 and 17 years of age. Additionally, each version of the questionnaire can be completed both by children and adolescents, and also by their parents.

Adult patients will fill out the WHOQOL-BREF questionnaire. The WHOQOL-BREF instrument comprises 26 items, which measure the following broad domains: physical health, psychological health, social relationships, and environment.

### 7.9 Pain assessment

Pain assessment will be done together with QOL-assessment. The pain scales are to be filled out by the patient him/herself. Two age-adapted pain scales for adults/teenagers (≥ 14 years) and children (3-13 years) are provided

### 7.10 Patient diary

A patient diary covering the six months therapy period, will be provided which the patient/parents or legal guardians has/have to complete and to bring along at each study visit. At each onsite visit the site staff will collect the original hard copy of the diary, make a copy of it and transfer data into the CRF. The copies of the diary will be kept in the ISF during the trial. At the end oft he trial the original hard copy of the diary will be kept with the trial documents and archived. The following information will be collected in the diary:

- Frequency and amount of sirolimus application (tablets or solution)
- Documentation of complaints (AEs)
- Documentation of new concomitant medication

### 7.11 Additional data collection/ Translational program

Overgrowth syndromes are caused by somatic mutations of genes involved in the mTOR signaling pathway that have been recently identified. Germline DNA and (if available) somatic DNA will be collected and studied by Sanger sequencing available in our genetic laboratory. These diagnostic tests are not part of the clinical study protocol and patients will be asked separately for informed consent. Response to mTOR inhibition in overgrowth syndromes is not clear today and will be addressed in this clinical trial. To further understand the mechanism of growth inhibition, we plan to perform biomarker analysis as a translational program of the study. Blood has to be collected for centrally performed immunoblotting (mTOR phosphorylation study by using commercially available antibodies: α-mTOR and phosphor-Ser-2448-specific mTOR antibodies) as well as evaluation of serum biomarkers (commercially available ELISA kits for IGFBP-3, IGF-1 and VEGF measurement).

Therefore 1 ml EDTA, the supernatant of 1 ml EDTA, 5 native peripheral blood smears and the supernatant of 2 ml serum, have to be sent to Freiburg from the local trial center after every blood collection visit.

More details are described in the laboratory manual (stored in the ISF).

# 8 Discontinuation criteria

## 8.1 Premature termination of treatment or the entire trial

The sponsor/coordinating investigator is under obligation to monitor the progress of the clinical trial with regard to safety-relevant developments and, if necessary, initiate the premature termination of the treatment or the entire clinical trial.

Discontinuation can be necessary due to intolerable toxicity, withdrawal of consent, death or termination of the trial due to other reasons. The patient will be observed for another 3 months without study medication.

The treatment or the entire clinical trial must be terminated prematurely if:

- the benefit-to-risk ratio for the patient changes markedly,
- the sponsor/coordinating investigator considers that the termination of the trial is necessary,
- indications arise that the trial patients' safety is no longer guaranteed,
- the questions(s) addressed in the trial can be clearly answered on the basis of results of another trial on the same subjects,
- an insufficient recruitment rate makes a successful conclusion of the clinical trial appear impossible.

If the clinical trial is prematurely terminated or suspended for any reason, the investigator should promptly inform the trial patients and ensure appropriate therapy and follow-up for the patients. Where required by the applicable regulatory requirements, the competent authority(ies) and the ethic committee(s) will also be informed (this is usually done by the sponsor).

## 8.2 Premature termination of the trial at one of the trial centers

Both the investigator and the sponsor have the right to terminate the trial at one of the centers.

The clinical trial can be terminated prematurely at his center by the investigator if, for instance unforeseeable circumstances have arisen at the trial center which preclude the continuation of the clinical trial, the investigator considers that the resources for continuation are no longer available, the investigator considers that the continuation of the trial is no longer ethically or medically justifiable.

The Sponsor can initiate the exclusion of a center from further participation if, for instance, patient recruitment is inadequate, serious problems arise with regard to the quality of the collected data which cannot be resolved.

Premature termination at one of the trial centers does not automatically mean a termination of the trial for already enrolled trial patients. A separate decision on further treatment must be made for each patient, depending on the overall situation. Adequate further treatment and

follow-up of already enrolled trial patients must be ensured. The documentation of already enrolled trial patients will be reviewed for completeness and plausibility. Queries may be raised for further clarification before the center is closed. These queries must be answered properly by the center. The competent authority and ethics committee(s) must be duly notified of the center's closure, including reasons, within the specified period. The trial center concerned will be closed in stages by the CRA when a decision has been made on the further treatment of the patients concerned.

## 8.3 Discontinuation criteria for individual trial patients

It has to be distinguished if trial treatment of a patient has been stopped prematurely or if the trial participation of a patient was stopped prematurely.

In the case trial treatment of a patient has been stopped prematurely, the follow-up visit and the assessment of the trial endpoints are essential to enable an analysis of the full analysis set according to the intention-to-treat principle. Further visits, follow-up and documentation should always be striven for/ensured in this case. This includes the follow-up of AEs, the time of termination, the results available at that time and, if known, the documentation of the termination of treatment on the CRF and in the medical record, giving reasons, a final examination and documentation according to the protocol (if possible).

The documentation should be completed as far as possible under these circumstances, e.g. a final examination and documentation according to the protocol (if possible), a documentation of the premature trial termination on the CRF and in the medical record, giving reasons, appropriate further treatment and follow-up outside the trial should be ensured.

### 8.3.1 Premature discontinuation of trial treatment

The trial patient can have his/her trial treatment terminated prematurely at any time, without having to give reasons.

The investigator responsible for the trial has the right to terminate the treatment of a patient according to the following conditions:

- Adverse events (including intercurrent illnesses) which preclude further treatment with the investigational medicinal product 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 or lack of compliance on the part of the patient (e.g. taking prohibited medication).
- Logistical reasons (patient changes his/her doctor or hospital or moves to another location).

### 8.3.2 Premature termination of trial participation

The trial patient respectively person(s) having the care and custody can withdraw his/her consent at any time, without having to give reasons, and have his/her entire trial participation terminated prematurely. However, the prerequisite for this is that the patient actively terminates trial participation by withdrawing his/her consent for the follow-up and documentation.
The responsible investigator may only withdraw a patient from participation in the trial for the following reasons:

- Loss of contact
- Extreme circumstances arise which make any trial-relevant follow-up impossible

# 9 Investigational medicinal product

## 9.1 Investigational medicinal product

The investigational products used in this trial are characterised as follows:

| | |
|---|---|
| Proprietary name: | Rapamune® |
| Name of substance: | **Sirolimus** |
| Manufacturer: | PFIZER Pharma GmbH |
| Approved indications: | immunosuppressant; rejection prophylaxis in kidney transplant recipients |
| Dosage form: | Tablets, suspension |
| Strength: | 0.5 mg, 1 mg; 1mg/ml |
| Dose: | The recommended starting dose of sirolimus is: 1.6 mg/m$^2$ (divided in two doses if patients age is below 16 years) |

For further characteristics, see corresponding SmPC. For this trial the current version of the summery of product characteristics will be valid.

## 9.2 Packaging and labelling

Pfizer Pharma GmbH will provide local market product of sirolimus (Rapamune) free of charge to the sites. Patients will receive the commercial formulation (Rapamune®). Each commercial pack of Rapamune® contains 30 tablets of sirolimus (0,5mg or 1mg). Each commercial bottle of solution contains 60ml sirolimus.
As trial medication is marketed medication, please refer to the respective Summary of Product Characteristics (Fachinformation) for details on administration, storage conditions, contra-indications, precautions, drug interactions and possible side effects.
As trial medication is marketed medication, there will be no trial-specific labelling.

### 9.3 Supply and ordering

The sites will order the trial medication for each study patient by fax from Pfizer Pharma GmbH. Detailed instructions on the ordering and shipment of trial medication will be provided in the ISF.

### 9.4 Receipt and storage

Trial treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated study personell have access. Upon receipt, all trial medication should be stored according to the instructions specified in the package insert/SmPC. Clinical supplies must be dispensed only in accordance with the protocol.

### 9.5 Dispensing

Trial medication will be dispensed with no trial specific labelled market packs. Patients will receive instructions by an authorized person at the investigator site for transport, storage and application at home as well for the need to return used packages and unused drug at each study visit. A written information concerning storage and handling conditions is part of the patient diary which will be handed out to the patient.. For Rapamune® solution appropiate transport cool bags with cold packs will be provided. Patients will be provided with adequate supply of sirolimus for self-administration at home until at least their next scheduled study visit.

### 9.6 Return and Destruction

The investigator and/or the study nurse maintain records of the use of the trial medication by the individual trial patients, and the return of unused IMP. The site will ensure destruction of the trial medication as per local practices and regulations at the conclusion of the trial, as appropriate during the course of the trial, and after completed drug accountability checks. Onsite destruction has to be performed only after approval and release by the sponsor. Records of the destruction must be maintained.

### 9.7 Drug compliance and accountability

Study patients are obligated to document all applications into a patient diary. Patient’s trial treatment compliance will be assessed by the investigator or designee at each visit by means of drug accountability and by checking the patient diary and resolve discrepancies between drug accountability and patient diary. This information must be documented on the appropriate drug accountability forms by study personnel and entered in the source document at each patient visit to accurately determine the patient’s drug exposure throughout the trial.

The investigator or designee must maintain an accurate record of the shipment and dispensing of investigational product in a drug accountability log. Drug accountability will be checked by the CRA as stated in the study specific monitor manual during site visits and at the completion of the

trial. Patients will be asked to return all used and unused trial medication and packaging to the site at the end of the trial at Visit 4 or at the time of drug discontinuation After end of trial further treatment is at the discretion of the investigator.

The investigator or designee must maintain records of the delivery of the IMP, the stocks at the study site, the use by the individual trial patients, and, the GCP-compliant central destruction. The investigator should ensure that the IMP is only used according to this protocol.

The investigator bears the responsibility for the proper storage in an appropriate place to which unauthorised persons have no access.
The investigator may only dispense the IMP to patients who have been enrolled in the study. The dispensing of the IMP to patients outside of this clinical trial is not permitted.
The investigator or designee should explain the correct use of the IMP to each trial patient and check at regular intervals that each patient is following the instructions correctly.

# 10 Safety monitoring and reporting

## 10.1 Adverse events (AEs)

### 10.1.1 Definition of AEs

An adverse event (AE) is any untoward medical occurrence in a patient administered any dose of a pharmaceutical product and which does not necessarily have to have a causal relationship with the use of the product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the product.

- Irrespective of any causal relationship, all AEs spontaneously reported by the patient or observed by the investigator will be continuously documented in the medical record and on the designated case report form (AE CRF page).
- All AEs must be described by diagnosis or, if an underlying diagnosis is not known, by symptoms or medically significant laboratory or instrumental abnormalities. The AEs will be documented as shown in the section below.
- Laboratory parameters outside the normal range, which are judged by the investigator to be clinically significant (those which require concomitant therapy or procedures, changes in trial treatment or further diagnostic measures), will be recorded as an AE in the CRF. This does not hold true if the laboratory abnormality in the view of the investigator is caused by the underlying disease.
- Symptoms, medically significant laboratory, or instrumental (e.g. electrocardiographic) abnormalities of a pre-existing disease should not be considered an AE. However,

occurrences of new symptoms or laboratory or instrumental abnormalities, as well as worsening of pre-existing ones, are considered AEs.

- In order to monitor the conditions of the patients from the time the patients receive the first dose of investigational product, the investigator is requested to report any untoward clinical event on the AE-page of the CRF. Any untoward medical occurrence, which occurs after the period of patient follow-up defined in the protocol, is not considered an AE.
- All AEs, no matter how intense, are to be followed up by the investigator in accordance with good clinical practice until resolved or judged no longer clinically relevant, or in case of a chronic condition, until it is fully characterized.
- As in this trial the participants suffer from segmental overgrowth syndrome, which is characterized by a constant disease progression, AEs judged by the investigator to belong to the disease course (e.g. progressive overgrowth, coagulopathy in case of venous malformations, oozing from lymphatic malformations) do not have to be documented in the CRF since disease progression representing efficacy endpoint in the study will be collected on the special CRF pages; details on SAE reporting related to disease progression see section 10.1.4.

### 10.1.2 Definition of AEs of special interest

A study subject who develops abnormal values in aspartate transaminase (AST) or alanine transaminase (ALT) or both, concurrent with abnormal elevations in total bilirubin and no other known cause of liver injury, would be classified as a **Hy's Law Case**. The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT baseline values within the normal range who subsequently present with **AST or ALT** greater ≥ three times the ULN (upper limit of normal) concurrent with a **total bilirubin** greater ≥ two times the ULN with no evidence of hemolysis and an **alkaline phosphatase** ≤ two times the ULN or not available.

- Patients with pre-existing AST or ALT baseline values above the normal range who subsequently present with **AST or ALT** ≥ two times the baseline values and ≥ three times the ULN, or ≥ eight times the ULN (whichever is smaller) concurrent with a **total bilirubin** of ≥ two times the ULN and increased by one ULN over baseline or ≥ three times the ULN (whichever is smaller) with no evidence of hemolysis and an **alkaline phosphatase** ≤ two times the ULN or not available.

These cases are treated like SAEs and have to be reported within 24 hours on the SAE reporting form.

### 10.1.3 Documentation of AEs

Adverse events (including AEs of special interest) have to be documented in the CRF starting from the date of first administration and until 30 days after the last administration of investigational product. Afterwards only SAEs judged by the investigator to be related to the IMP have to be documented in the CRF.

- Characterization of the event
- Onset date
- End date
- Severity according to the current version of CTCAE
- Relationship to the investigational medicinal product

  *Note:*

  *According to the CIOMS VI Working group the causal relationship between the investigational product and the adverse event should be characterized as "related" or "not related" (the various gradients of relatedness offer little or no advantages in data analysis or regulatory reporting).*

  *The expression "related" means, that there is evidence or argument to suggest a reasonable causal relationship between the event and the administration of the study drug, e.g. close temporal connection, exclusion of other causes.*

  *The assessment "not related" is appropriate, if the SAE is clearly or most likely explained by other causes even if a potential relationship between study drug and the SAE cannot be completely excluded.*
- Serious or non-serious
- Action taken with investigational medicinal product
- Outcome

### 10.1.4 Definition and documentation of serious adverse events (SAEs)

A Serious Adverse Event (SAE) is any untoward medical occurrence that:

- results in the death of the patient,
- is life-threatening,
- requires inpatient hospitalization of the trial patient or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect,
- other medically important condition.

A hospitalization meeting the regulatory requirement for the “serious” criteria is any inpatient hospital admission that includes a minimum of an overnight stay in a healthcare facility, unless hospitalization is for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under trial and has not worsened since signing the informed consent
- Social reasons and respite care in the absence of any deterioration in the patient’s general condition
- Elective hospitalizations for administering the investigational product or any other trial assessment

Patients may be hospitalized throughout the treatment phase of this trial according to the institution’s policy. Hospitalizations will, therefore, be treated as SAEs only if serious or unexpected events caused either their prolongation or a re-admission as in-patient after the patient had already been discharged.

Other conditions which, in the investigator's opinion, may not be immediately life-threatening or result in hospitalization, but may jeopardize the patient’s safety or may require intervention to prevent one of the other outcomes listed in the definition above, may also be considered serious. Examples of such conditions include: allergic bronchospasm requiring treatment in an emergency room or at home; unexpected convulsions (i.e. convulsions which cannot be explained by the underlying illness) that do not result in hospitalization; development of investigational product dependency or drug abuse; suspected transmission of infectious agents by medicinal product, etc.

**Documentation of SAEs**

All SAEs (with the exception of the special situation described below) that occur starting from the first administration and until 30 days after the last administration of the IMP will be documented in the CRF and on the provided SAE reporting form. Afterwards only SAEs related to IMP have to be documented in the CRF and reported as SAE.

*Exceptions from this principle rule*

Events judged by the investigator as being due to disease progress will not be recorded and reported as SAE, except for those leading to death. A fatal disease progress has to be notified as an SAE.

Disease progress will only be documented on the specific CRF pages. Nevertheless, the investigator must fax the CRF page designated for documentation of the disease progress to CTU Pharmaco-/Vigilance within 3 working days after knowledge.

*Death*

Please note that “death” is an outcome of an SAE and not an SAE per se. Only in cases where the clinical circumstances before the death are not known (i.e. patient died without determinable cause of death), then the diagnosis “death” itself should be reported as a SAE. In case an already notified SAE has a fatal outcome, a follow up SAE notification has to be done.
In case of a patient’s death the CRF-page designated for premature study termination has to be faxed to the SAE Management Center within 3 working days of the site’s knowledge.

The SAE report form will be processed as described in the section below.

### 10.1.5 Reporting requirements

#### *10.1.5.1 Investigator requirements for SAE Reporting*

The following adverse events must be reported on the SAE reporting from and send by investigator to the sponsor:

- SAEs
- AEs of special Interests independent from their seriousness (see definition in section 10.1.2)

The events mentioned above must be reported by fax to the following address within **24 hours** after knowledge by the investigator:

**Pharmacovigilance**
Clinical Trials Unit
Medical Center - University of Freiburg
Elsaesser Str. 2, 79110 Freiburg
**SAE Fax No.:**
[redacted]

According to section 12, subsection 6 GCP-V, in the event of the death of a patient the investigator must submit all information to the competent ethics committee, the other ethics committees involved, the competent authority and the sponsor, that is required for the fulfilment

of their duties (note that personal data must be transmitted using the trial-specific patient identification number, i.e. in pseudonymised form).

*10.1.5.2 Sponsor requirements for SAE reporting*

**SUSAR definition:**

The sponsor's expedited reporting requirements are particularly relevant to suspected unexpected serious adverse reactions (SUSARs). The definition is a combination of the definitions of serious adverse reaction (adverse reaction that results in death, is life-threatening, requires inpatient hospitalization or prolongation of hospitalization, results in persistent or significant disability/incapacity, causes congenital anomaly/birth defect) and unexpected adverse reaction (an adverse reaction, the nature or severity of which is not consistent with the applicable summary of product characteristics (SmPC) for the investigational medicinal product).

*Reporting Requirements:*

The sponsor's reporting requirements are divided into expedited reporting and reporting that must be performed on request or annually.

The sponsor's *expedited reporting* requirements to competent ethics committee(s), competent authority and, in the first two cases described below involved investigators, comprise the following:

- All SUSARs that are life-threatening or result in death must be reported within 7 days after knowledge by the sponsor (section 13 (3) of GCP-V),
- All other SUSARs must be reported within 15 days after knowledge by the sponsor (section 13 (2) of GCP-V),
- All circumstances requiring a review of the benefit/risk evaluation of the investigational medicinal product must be reported within 15 days after knowledge (e.g. expected serious adverse reaction with unexpected outcome, increased incidence of expected serious adverse reactions, SUSARs after the end of the patient's participation in the clinical trial, events in connection with the trial conduct or the development of the investigational medicinal product which may affect the safety of the trial patients) (section 13 (4) of GCP-V).

**Development Safety Update Report (DSUR):**

In addition to the expedited reporting, the sponsor shall submit an annual report **once a year** or on request throughout the clinical trial period, according to section 13, subsection 6 GCP-V and ICH guideline E2F.

The aim of the DSUR is to concisely describe all new safety information relevant for one or several clinical trial(s), to assess the safety conditions of subjects included in the concerned trial(s) and to evaluate whether the benefit / risk ratio is still favorable.

To fulfill these requirements the investigator must fax the CRF page designated for premature treatment/study discontinuation to the SAE Management Center within 3 working days after knowledge.

#### 10.1.5.3 Pregnancy

Any pregnancy (female trial participant or female partner of male trial participant) that occurs during trial participation must be reported. To ensure patient safety each pregnancy must be reported to CTU Pharmaco-/Vigilance within 24 hours of learning of its occurrence. The pregnancy should be followed up by sponsor and investigator to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence/absence of any birth defects, congenital abnormalities or maternal and newborn complications. Pregnancy has to be documented on the pregnancy reporting form.

Highly effective birth control methods include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
- progestogen-only hormonal contraception associated with inhibition of ovulation
- intrauterine device (IUD)
- intrauterine hormone-releasing system ( IUS)
- bilateral tubal occlusion
- vasectomised partner
- sexual abstinence

# 11 Data handling and data management

## 11.1 Data confidentiality

Information about trial patients will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed patient authorization informing the patient of the following:

- what protected health information (PHI) will be collected from patients in this trial;
- who will have access to that information and why;
- who will use or disclose that information;
- the rights of a research patient to revoke their authorization for use of their PHI.

In the event that a patient revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. For patients that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the patient is alive) at the end of their scheduled trial phase.

The data collection system for this trial uses built-in security features to prevent unauthorized access to confidential participant information. Access to the system will be controlled by individually assigned user identification codes and passwords, made available only to authorized personnel who have completed prerequisite training.

## 11.2 Documentation of trial data

### 11.2.1 Documentation in medical records

The investigator will record the participation in the trial, the frequency of the trial visits, the relevant medical data, the concomitant treatment and the occurrence of adverse events in the medical record of each trial patient.

### 11.2.2 Documentation in CRF

The investigator, or a deputy who is designated by the investigator, will document the trial data on a trial-specific case report form (CRF) as promptly as possible.

Hard copy CRFs will be used in this trial. The hard copy CRFs consist of 2-layer Non-Carbon-Required paper (NCR paper). For further details please refer to the CRF completion Instructions.

Corrections and subsequent changes to CRF pages must be made according to the ICH-GCP guidelines provided in the CRF Completion instructions at the beginning of each CRF-folder.

Any queries on the part of Data Management staff will be sent to the site on special forms for subsequent correction (and will be reminded via the CRA, if necessary). The query forms should be completed close to the times of the planned monitoring visits or at the times specified by the trial coordinator (e.g. for interim analyses). The query forms which contain the corrections must be confirmed by the dated signature of the investigator (not the Study Nurse) in the designated places. They will usually be collected by the CRA at the visits.

## 11.3 Data management

The data management will be performed with DAMAST Version 3.2, a proprietary data management system based on the software package SAS, which is developed, validated and maintained by the Clinical Trials Unit (CTU). Details on data management (procedures,

responsibilities, data corrections, if any, which may be made by Data Management staff themselves, etc.) will be described in a data management manual prior to the trial. During the trial, the performance of data management will be documented. The technical specifications (variable names, attributes and data entry checks) of the database will be described in a corresponding plan. Before any data entry is performed, the trial database will be validated. Double data entry will be performed by two different persons (with the exception of free text). The comparison of both entries and the resolution of discrepancies are only performed by trained staff. An audit trail will be created to provide an electronic record of which data were entered or subsequently changed, by whom and when.

SAS software will be used to review the data for completeness, consistency and plausibility. The checks to be programmed will be specified beforehand in a data validation plan. After running the check programs, the resulting queries will be sent to the investigator for review of his/her data. Answered queries will also be entered twice, verified and the updated data will then be transferred to the database. All programs which can be used to influence the data or the data quality will be validated (e.g. check programs, programs for upload of external data).

### 11.4 Data coding

Concomitant medications or procedures entered into the database will be coded using the WHO Drug Reference List. Adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology in its latest version.

## 12 Quality assurance

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted, data is generated, documented (recorded), and reported in compliance with the protocol, ICH-GCP, and the applicable regulatory requirement(s).

### 12.1 Monitoring procedure

The monitoring is performed by the CRAs of the CTU, Medical Center - University of Freiburg. Risk-based monitoring will be done according to ICH-GCP E6 (R2) and standard operating procedures (SOPs) to verify that patients' rights and wellbeing are protected, reported trial data are accurate, complete and verifiable from source documents and that the trial is conducted in compliance with the currently approved protocol and any necessary amendments, with ICH-

GCP and with the applicable regulatory requirements to ensure patient´s safety and integrity of clinical trial data.

The investigator will accept monitoring visits before, during and after the clinical trial. Prior to patient recruitment, a site initiation visit at each site is conducted in order to train and introduce the investigators and their staff to the trial protocol, essential documents, handling of investigational product and related trial specific procedures, ICH-GCP and national/local regulatory requirements.

During the trial, the CRA will visit the site regularly during the trial depending on the recruitment rate and quality of data on the basis of a risk based quality management process (RbQM). During these on-site visits, the CRA verifies that the trial is conducted according to the trial protocol, trial specific procedures, ICH-GCP and national/local regulatory requirements. The presence of signed informed consents, eligibility of patients, primary endpoint, handling of investigational product and documentation/reporting of safety data (e.g. AE/SAE) will be verified by the CRA. The CRA also performs source data verification (SDV), source data review (SDR) and drug accountability checks to ensure that the clinical trial data, which are recorded and documented in the source data and CRFs, are complete and accurate and to ensure the smooth flow of the processes, which have been agreed upon. Extent of source data verification and monitor visit frequency will be adapted for individual sites in case of lack of data quality or a high number of protocol violations. All trial specific monitoring procedures, monitoring visit frequency and extent of SDV will be predefined in a trial specific monitoring manual. The investigator must maintain source documents for each patient in the trial, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments (see section 7). All information recorded on the CRFs must be traceable to source documents in the patient's file. The investigator must also keep the original signed informed consent form (a signed copy is given to the patient).

The investigator must give the CRA access to all relevant source documents to confirm their consistency with the CRF entries.

### 12.2 Source data

Source data as defined by ICH-GCP include original documents, data, and records such as hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, patient´s questionnaires, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, X-rays, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial.

Source data verification will be performed in order to verify the accuracy and completeness of the entries on the case report form (CRF) by comparing them with the source data, and to ensure and increase the quality of the data. All data which are subject to SDV must have been entered in the medical record or, in the case of source documents, enclosed with the medical record. The investigators will grant the CRA access to the medical records for the performance of SDV.
Extent of Source Data verification will be specified in the in the monitoring manual.

### 12.3 Auditing procedures and inspections

According to the ICH-GCP guidelines, audits will be performed in frame of a quality assurance system. Audits and/or inspections may be conducted by the sponsor, authority(ies) or an independent external party.
The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements. All persons who conduct an audit undertake in writing to treat all data related to medical secrecy or which could reveal the patient's identity in absolute confidence, and to restrict the use of such data to the purposes agreed by the patient in writing.
Proposed dates for sponsor's audit, characteristics of the selected patients and further information will be transmitted to the investigator by the CRA in a timely manner.
The investigator will inform the CTU immediately of an inspection requested by a regulatory authority. The investigator is responsible for availability of source data/documents to audit/inspections.

### 12.4 Data Monitoring Committee (DMC)

The sponsor will appoint 3 persons (see section "Responsibilities") not involved in the study and known as experienced in statistics, pediatric onco-hematology and pediatrics to form the DMC. The DMC advises the sponsor and the study management with regard to patient safety in the context of the present clinical trial. The DMC will make recommendations regarding continuation, modification or termination of the clinical trial. Further details and procedures are described in the study specific DMC Charter.

## 13 Biostatistical planning and analysis

Before the start of the final analysis a detailed statistical analysis plan (SAP) will be prepared. This will be completed during the 'blind review' of the data, at the latest. This blind review, i.e. a

checking and assessment of the data, will be performed after the end of the recruitment period and the planned follow-up period. If the SAP contains any changes to the analyses outlined in the trial protocol, they will be marked as such, and reasons for amendments will be given.
All statistical programming for analysis will be performed with the Statistical Analysis System (SAS).

### 13.1 Trial design

For details on trial design see section 3.1 of the protocol.

### 13.2 Objectives and endpoints

For details on endpoints see section 2 of the protocol.

### 13.3 Sample size calculation

Sample size calculation is based on the primary endpoint best response CR or PR until 6 months after start of treatment. Calculations are performed using the exact binomial distribution and are based on the following assumptions and requirements:

- A medical therapy for segmental overgrowth syndrome is not available. In most cases, a watch-and-wait strategy is followed. Without treatment, the probability of response is considered to be near zero. As a consequence, any improvement in best response rate is considered relevant.
- The treatment with sirolimus is considered to be not sufficiently effective if the best response rate is 2% or lower.
- The study should have sufficient power to show that treatment with sirolimus is effective when it leads to a best response rate of 20% or higher.
- The type I error rate α, i.e. the error probability of regarding sirolimus as active when it is inactive (probability of best response CR or PR is 2% or lower), is set to 5% (one-sided).
- The type II error rate β, i.e. the error probability of regarding sirolimus as inactive when the probability of best response CR or PR is 20% or higher, is set to 10%, i.e. the power is set to 90%.

The required sample size is 18 patients. If there are 2 or more patients with best response CR or PR, sirolimus will be considered as effective.

### 13.4 Definition of populations included in the analyses

Efficacy analyses will be performed primarily in the full analysis set (FAS) according to the intention-to-treat (ITT) principle. This means that the patients will be included in the analyses, if

treatment with sirolimus was started, irrespective of whether they discontinued the treatment or whether other protocol violations are revealed.
The per-protocol (PP) population is a subset of the FAS and is defined as the group of patients who had no major protocol violations, received the treatment and underwent the examinations required for the assessment of the endpoints according to the protocol. The analysis of the PP population will be performed for the purpose of a sensitivity analysis.

## 13.5 Methods of analysis

### 13.5.1 Patient demographics/other baseline characteristics

Demographic and other baseline data (including disease characteristics) will be summarized descriptively in the FAS.
Continuous data will be summarized by arithmetic mean, standard deviation, minimum, 25% quantile, median, 75% quantile, maximum, and the number of complete and missing observations. If appropriate, continuous variables can also be presented in categories.
Categorical data will be summarized by the total number of patients in each category and the number of missing values. Relative frequencies are displayed as valid % (number of patients divided by the number of patients with non-missing values).

### 13.5.2 Treatments

13.5.2.1 Trial medication

Duration of treatment with sirolimus, cumulative dose and dose intensity will be summarized. The number of patients with dose changes/interruptions will be presented. Trial medication compliance will be analyzed using patient diaries.
Reporting of trough concentrations, plus corresponding doses taken by the patients for the study by study visit – assuring that goal of maintaining values in therapeutic range was achieved, will be analyzed.

13.5.2.2 Concomitant medication

The concomitant medication will be summarized by ATC level 1/2/4. In each table, patients will be counted once, if they took at least one medication from the respective ATC level. The number of patients and the percentage of the total number of patients in FAS will be given.

### 13.5.3 Primary endpoint

18 patients will be included in the trial who start sirolimus treatment. If the observed number of patients with a best response CR or PR until 6 months after start of treatment is 2 or more out of 18, sirolimus will be considered as effective and will be evaluated in further trials. With this decision rule, the error probability of regarding sirolimus as effective when the probability of best

response CR or PR until 6 months after start of treatment is 2% or lower (type I error α) is less than 5% (one-sided), and the error probability of regarding sirolimus as not effective when the probability of best response CR or PR until 6 months after start of treatment is 20% or higher (type II error β) is less than 10%. The probability of best response CR or PR - until 6 months after start of treatment will be estimated with two-sided 90% confidence interval (corresponding to the planned test procedure) and with two-sided 95% confidence interval based on the exact binomial distribution.

### 13.5.4 Secondary endpoints for efficacy

The morphological changes in disfigurement, quality of life, pain, changes in neuropsychological tests, changes in IGFBP-3, IGF-1, VEGF, and inhibition of mTOR in PBMCs will be analysed descriptively.

### 13.5.5 Safety parameters

All safety parameters (adverse events, laboratory assessments, vital signs) will be listed by center and patient and displayed in summary tables.

#### 13.5.5.1 Adverse events

The incidence of AEs defined by preferred term (PT) according to MedDRA will be calculated as the number of patients who experienced at least one AE with the respective PT in percentage of the total number of patients in the safety population. In the incidence tables the PTs will be grouped by system organ class (SOC) according to MedDRA. Additionally, the incidence of AEs defined by SOC will be calculated as the number of patients who experienced at least one AE in the respective SOC as percentage of the total number of patients in the safety population.
Each table will be produced for the following AE-sets:

- all AEs
- AEs being at least severe
- AEs possibly related to investigational product
- AEs possibly related to investigational product being at least severe (toxicity)
- Serious Adverse Events (SAEs)
- SAEs possibly related to investigational product
- SAEs leading to death
- SAEs possibly related to investigational product leading to death

#### 13.5.5.2 Laboratory data

Laboratory data will be presented in the measured units (or in SI units, being converted from the original units, if necessary). Values outside the investigator's reference range will be flagged as above or below the reference range in the listings. Shift tables for all parameters will also be generated.

#### 13.5.5.3 Other safety data

Summary tables for vital signs will be produced by visit.

### 13.6 Interim analysis

No Interim analysis is planned.

## 14 Ethical and legal principles

### 14.1 Regulatory and ethical compliance

This clinical trial was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

### 14.2 Responsibilities of the investigator and IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Independent Ethics Committee (IEC) before trial start. A signed and dated statement that the protocol and informed consent have been approved by the IEC must be given to sponsor before initiation of the trial. Prior to start of the trial, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the trial in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to sponsor monitors, auditors, sponsor Clinical Quality Assurance representatives, designated agents of sponsor, IECs and regulatory authorities as required.

### 14.3 Informed consent procedures

Before enrolment in the clinical trial, the patient respectively person(s) having the care and custody will be informed that participation in the clinical trial is voluntary and that he/she may

withdraw from the clinical trial at any time without having to give reasons and without penalty or loss of benefits to which the patient is otherwise entitled.

The treating physician will provide the patient respectively person(s) having the care and custody with information about the treatment and the possible risks involved. At the same time, the nature, significance, implications, expected benefits and potential risks of the clinical trial and alternative treatments will be explained to the patient respectively person(s) having the care and custody. During the informed consent discussion, the patient respectively person(s) having the care and custody will also be informed about the insurance cover that exists and the insured's obligations. The patient respectively person(s) having the care and custody will be given ample time and opportunity to obtain answers to any open questions. All questions relating to the clinical trial should be answered to the satisfaction of the patient respectively person(s) having the care and custody. In addition, the patient respectively person(s) having the care and custody will be given a patient information sheet which contains all the important information in writing.

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| The patient's written consent must be obtained before any trial-specific tests/treatments. For this purpose, the written consent form will be personally dated and signed by the trial patient respectively person(s) having the care and custody and the investigator conducting the informed consent discussion. |

By signing the consent form, the patient respectively person(s) having the care and custody agrees to voluntarily participates in the clinical trial and declares his/her intention to comply with the requirements of the clinical trial and the investigator's instructions during the clinical trial. By signing the form, the patient respectively person(s) having the care and custody also declares that he/she agrees to the recording of personal data, particularly medical data, for the trial, to their storage and codified (“pseudonymized”) transmission to the sponsor, to the competent authority or the competent authority, and further agrees that authorized representatives of the sponsor Medical Center - University of Freiburg, who are bound to confidentiality, and national or foreign competent authorities may inspect his/her personal data, particularly medical data, which are held by the investigator.

After signing, the patient respectively person(s) having the care and custody will be given one copy of the signed and dated written consent form and any other written information to be provided to the patients.

In the case of substantial amendments, the patient respectively person(s) having the care and custody must be informed with an appropriate revised patient information/consent form. Changed trial procedures can only be carried out if they have been approved by the competent authority and the leading Ethics Committee, and if the patient respectively person(s) having the care and custody has been appropriately informed and has given his/her written consent.

### 14.4 Patient insurance

All trial subjects enrolled are insured against injury caused by their participation in the study in accordance with § 40 AMG under the group insurance contract of the Albert-Ludwigs-Universität Freiburg. The name of the insurance company:

**HDI Global SE**
Riethorst 2
30659 Hannover
represented by the Office Düsseldorf
Am Schönenkamp 45, 40599 Düsseldorf

Policy-No.: [redacted]

The investigator, or an individual who is designated by the investigator, will inform the subject of the existence of the insurance, including the obligations arising from it. The trial subjects must be afforded access to insurance documents and provided with a copy of the general conditions of insurance on request.

### 14.5 Confidentiality of trial documents and patient records

The investigator must ensure pseudonymity of the patients; patients must not be identified by names in any documents submitted to sponsor. Signed informed consent forms and patient enrolment log must be kept strictly confidential to enable patient identification at the site.

### 14.6 Financial disclosure

Financial disclosures should be provided by trial personnel who is directly involved in the treatment or evaluation of patients at the site - prior to trial start.

## 15 Trial documents and archiving

### 15.1 Trial documents/investigator site file

The investigator will be given an investigator site file containing all the necessary essential trial documents for the initiation of the trial at his/her site. The essential documents include a list on which the investigator will enter all appropriately qualified persons to whom he/she has delegated important trial-related tasks.

The investigator, or an individual who is designated by the investigator, will be responsible for the maintenance and completeness of the trial documents during the clinical trial. At the request of the CRA, auditor, ethics committee or competent authority(ies), the investigator shall make

available all the requested trial-related records for direct access. Essential documents must not be removed permanently.

### 15.2 Archiving

After completion of the clinical trial, the essential trial documents - as defined by ICH-GCP E6 section 8 - from clinical trials will be retained at the trial site for a sufficient period so that they will be available for audits and inspections by the authorities.

The investigator will be responsible for the storage. The following retention periods will apply after the completion/termination of the clinical trial:

- The above-mentioned essential documents must be retained for at least 10 years (section 13, subsection 10 GCP-V); the identification codes of studies submitted for investigational product approval must be retained also for at least 10 years (2001/83/EC).
- The medical records and other source documents must be retained for the longest possible period allowed by the hospital, the institution or the private practice.

The investigator/the institution should take measures to prevent accidental or premature destruction of these documents. The sponsor will notify the investigator in writing when the trial-related essential documents are no longer required

## 16 Protocol adherence and amendments

### 16.1 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact sponsor or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the trial this must be considered a protocol amendment, and unless such an amendment is agreed upon by sponsor and approved by the IEC it cannot be implemented.

### 16.2 Amendments to the protocol

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by sponsor, CA where required, and the IEC.

Only changes of the protocol that are required for patient safety may be implemented prior to IEC approval. Regardless the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this trial, even if this action represents a deviation from the protocol. In such cases, the sponsor should be notified as soon as possible of this action; the IEC should be informed correspondingly.

# 17 Administrative Agreements

## 17.1 Financing of the trial

The clinical trial will be financed by the *Research Innovation Fund* of the University of Freiburg and by the Deutsche Forschungsgemeinschaft (DFG).
Free of charge supply by Pfizer Pharma will be provided.

### 17.1.1 Trial agreement/investigator compensation

According to ICH-GCP 4.9.6, a trial agreement on the conduct of the clinical trial and the compensation for conducting the trial will be signed between the sponsor of the clinical trial and the investigators including their heads of administration.

### 17.1.2 Reimbursement of trial patients

There is no payment planned for patients.

## 17.2 Trial language

The protocol is in English. All remaining forms are in German.

## 17.3 Trial reports

After completion of the analysis by the responsible biostatistician, the coordinating investigator will prepare and sign the final integrated medical and statistical report jointly with the biostatistician.
Except when required by law, no one will disclose a result of the clinical trial to third parties unless all parties involved have first agreed on the results of the analysis and their interpretation.
The final trial report will be written and signed in co-operation between the coordinating investigator and the CTU of Medical Center - University of Freiburg.

## 17.4 Clinical trials registry

The trial has been registered in the German Clinical Trials Registry: DRKS00010085

## 17.5 Publication of trial protocol and results

The sponsor assures that the key design elements of this protocol will be posted in a publicly accessible clinical trials registry such as DRKS. In addition, upon trial completion the results of

this trial will be submitted for publication and/or posted in a publicly accessible database of clinical trial results.

Reporting guidelines will be taken into account (see www.equator-network.org), e.g. the CONSORT statement should be adhered to in the preparation of papers on the results of randomised studies.

Each publication of trial results will be in mutual agreement between the principal investigator, the other investigators involved and the CTU. All data collected in connection with the clinical trial will be treated in confidence by the coordinating investigator and all others involved in the trial, until publication. Interim data and final results may only be published (orally or in writing) with the agreement of the coordinating investigator and the CTU. This is indispensable for a full exchange of information between the above-named parties, which will ensure that the opinions of all parties involved have been heard before publication. The agreement, which does not include any veto right or right of censorship for any of the parties involved, may not be refused without good reason.

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# Appendices

## Appendix 1 Relevant Guidelines and Laws

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| Declaration of Helsinki | http://www.wma.net/en/30publications/10policies/b3/<br>https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/ |
| ICH-GCP Guidelines | http://www.ich.org |
| EMA Guidelines | http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/landing/human_medicines_regulatory.jsp&mid=WC0b01ac058001ff89 |
| AMG/GCP-V | http://www.gesetze-im-internet.de |
| Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 | http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm |
| RECIST Version 1.1<br>(Eisenhauer et al. 2017) | https://www.ncbi.nlm.nih.gov/pubmed/19097774 |

## Appendix 2 Performance Status

| Karnofsky Scale (recipient age ≥ 16 years) | | Lansky Scale (recipient age <16 years) | |
|---|---|---|---|
| **Able to carry on normal activity; no special care is needed** | | **Able to carry on normal activity; no special care is needed** | |
| **100** | Normal, no complaints, no evidence of disease | **100** | Fully active |
| **90** | Able to carry on normal activity | **90** | Minor restriction in physically strenuous play |
| **80** | Normal activity with effort | **80** | Restricted in strenuous play, tires more easily, otherwise active |
| **Unable to work, able to live at home cares for most personal needs, a varying amount of assistance is needed** | | **Mild to moderate restriction** | |
| **70** | Cares for self, unable to carry on normal activity or to do active work | **70** | Both greater restrictions of, and less time spent in active play |
| **60** | Requires occasional assistance but is able to care for most needs | **60** | Ambulatory up to 50% of time, limited active play with assistance/supervision |
| **50** | Requires considerable assistance and frequent medical care | **50** | Considerable assistance required for any active play, fully able to engage in quiet play |
| **Unable to care for self, requires equivalent of institutional or hospital care, disease may be progressing rapidly** | | **Moderate to severe restriction** | |
| **40** | Disabled, requires special care and assistance | **40** | Able to initiate quite activities |
| **30** | Severely disabled, hospitalization indicated, although death not imminent | **30** | Needs considerable assistance for quiet activity |
| **20** | Very sick, hospitalization necessary | **20** | Limited to very passive activity initiated by others (e.g., TV) |
| **10** | Moribund, fatal process progressing rapidly | **10** | Completely disabled, not even passive play |

## Appendix 3 QOL

KINDL® parents (3-6 years)

ID: __ __ __ __ __

# Fragebogen zur Lebensqualität von Kindern

Kiddy-KINDL
3 – 6 Jahre
Elternversion

Sehr geehrte Mutter, sehr geehrter Vater,

vielen Dank, dass Sie sich bereit erklärt haben, diesen Bogen zum Wohlbefinden und zur gesundheitsbezogenen Lebensqualität Ihres Kindes auszufüllen.

Bei den nun folgenden Fragen möchten wir Sie bitten, folgende Instruktionen zu beachten.

- Lesen Sie bitte jede Frage genau durch,
- überlegen Sie, wie Ihr Kind sich in der letzten Woche gefühlt hat,
- kreuzen Sie die Antwort an, die für Ihr Kind am besten zutrifft.

Ein Beispiel:

In der letzten Woche ...

| | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| ... hat mein Kind sich wohl gefühlt. | ☐ | ☐ | ☐ | ☒ | ☐ |

Mein Kind ist ein: Mädchen ☐ Junge ☐ Alter des Kindes: __ __ Jahre

Sie sind: Mutter ☐ Vater ☐ Sonstiges _____?

Ausfülldatum: __ / __ / __ (Tag / Monat / Jahr)

## 1. Körperliches Wohlbefinden

| *In der letzten Woche ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... hat mein Kind sich krank gefühlt | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... hatte mein Kind Kopfschmerzen oder Bauchschmerzen | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... war mein Kind müde und schlapp | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... hatte mein Kind viel Kraft und Ausdauer | ☐ | ☐ | ☐ | ☐ | ☐ |

## 2. Seelisches Wohlbefinden

| *In der letzten Woche ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... hat mein Kind viel gelacht und Spaß gehabt | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... hatte mein Kind zu nichts Lust | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... hat mein Kind sich allein gefühlt | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... hat mein Kind sich ängstlich oder unsicher gefühlt | ☐ | ☐ | ☐ | ☐ | ☐ |

## 3. Selbstwert

| *In der letzten Woche ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... war mein Kind stolz auf sich | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... fühlte mein Kind sich wohl in seiner Haut | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... mochte mein Kind sich selbst leiden | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... hatte mein Kind viele gute Ideen | ☐ | ☐ | ☐ | ☐ | ☐ |

## 4. Familie

| *In der letzten Woche ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... hat mein Kind sich gut mit uns als Eltern verstanden | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... hat mein Kind sich zu Hause wohl gefühlt | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... hatten wir schlimmen Streit zu Hause | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... fühlte mein Kind sich durch mich bevormundet | ☐ | ☐ | ☐ | ☐ | ☐ |

## 5. Freunde

| *In der letzten Woche ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... hat mein Kind mit Freunden gespielt | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... ist mein Kind bei anderen „gut angekommen“ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... hat mein Kind sich gut mit seinen Freunden verstanden | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... hatte mein Kind das Gefühl, daß es anders ist als die anderen | ☐ | ☐ | ☐ | ☐ | ☐ |

## 6. Vorschule / Kindergarten

| *In der letzten Woche ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... hat mein Kind die Aufgaben in der Vorschule/ im Kindergarten gut geschafft | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... hat meinem Kind die Vorschule/ der Kindergarten Spaß gemacht | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... hat mein Kind sich auf die Vorschule/ den Kindergarten gefreut | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... hat mein Kind bei kleineren Aufgaben oder Hausaufgaben viele Fehler gemacht | ☐ | ☐ | ☐ | ☐ | ☐ |

## 7. Weitere wichtige Fragen

| *In der letzten Woche ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... war mein Kind schlecht gelaunt und quengelig | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... hat mein Kind mit Appetit gegessen | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... konnte ich geduldig und verständnisvoll mit meinem Kind umgehen | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... war mein Kind angestrengt | ☐ | ☐ | ☐ | ☐ | ☐ |
| 5. ... konnte mein Kind gut schlafen | ☐ | ☐ | ☐ | ☐ | ☐ |
| 6. ... ist mein Kind viel herumgetobt und hat sich bewegt | ☐ | ☐ | ☐ | ☐ | ☐ |
| 7. ... hat mein Kind schnell geweint | ☐ | ☐ | ☐ | ☐ | ☐ |
| 8. ... war mein Kind fröhlich und gut gelaunt | ☐ | ☐ | ☐ | ☐ | ☐ |
| 9. ... konnte sich mein Kind gut konzentrieren und war aufmerksam | ☐ | ☐ | ☐ | ☐ | ☐ |
| 10. ... ließ sich mein Kind leicht ablenken und war zerstreut | ☐ | ☐ | ☐ | ☐ | ☐ |
| 11. ... war mein Kind gern mit anderen Kindern zusammen | ☐ | ☐ | ☐ | ☐ | ☐ |
| 12. ... habe ich mit meinem Kind geschimpft | ☐ | ☐ | ☐ | ☐ | ☐ |
| 13. ... habe ich mein Kind gelobt | ☐ | ☐ | ☐ | ☐ | ☐ |
| 14. ... hatte mein Kind Schwierigkeiten mit Lehrern, Kindergärtnerinnen oder anderen Betreuungspersonen | ☐ | ☐ | ☐ | ☐ | ☐ |
| 15. ... war mein Kind nervös und zappelig | ☐ | ☐ | ☐ | ☐ | ☐ |
| 16. ... war mein Kind frisch und munter | ☐ | ☐ | ☐ | ☐ | ☐ |
| 17. ... hat mein Kind wegen Schmerzen gejammert | ☐ | ☐ | ☐ | ☐ | ☐ |
| 18. ... war mein Kind kontaktfreudig | ☐ | ☐ | ☐ | ☐ | ☐ |
| 19. ... klappte alles, was mein Kind anfing | ☐ | ☐ | ☐ | ☐ | ☐ |
| 20. ... war mein Kind schnell unzufrieden | ☐ | ☐ | ☐ | ☐ | ☐ |
| 21. ... hat mein Kind heftig geweint | ☐ | ☐ | ☐ | ☐ | ☐ |
| 22. ... wurde mein Kind leicht wütend | ☐ | ☐ | ☐ | ☐ | ☐ |

**Vielen Dank für Ihre Mitarbeit!**

KINDL® parents (7-17 years)

ID: __ __ __ __ __

# Fragebogen zur Lebensqualität von Kindern & Jugendlichen

Kid- und Kiddo-KINDL$^R$
Elternversion

Sehr geehrte Mutter, sehr geehrter Vater,

vielen Dank, dass Sie sich bereit erklärt haben, diesen Bogen zum Wohlbefinden und zur gesundheitsbezogenen Lebensqualität Ihres Kindes auszufüllen.

Bitte beachten Sie beim Beantworten der Fragen folgende Hinweise.

- ⇨ Lesen Sie bitte jede Frage genau durch,
- ⇨ überlegen Sie, wie Ihr Kind sich in der letzten Woche gefühlt hat,
- ⇨ kreuzen Sie **in jeder Zeile** die Antwort an, die für Ihr Kind am besten zutrifft.

Ein Beispiel:

| In der letzten Woche ... | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| ... hat mein Kind gut geschlafen. | ☐ | ☐ | ☐ | ☒ | ☐ |

Mein Kind ist ein: ☐ Mädchen ☐ Junge

Alter des Kindes: _____ Jahre

Sie sind: ☐ Mutter ☐ Vater ☐ Sonstiges: _____

Ausfülldatum: __ / __ / __ (Tag / Monat / Jahr)

**1. Körperliches Wohlbefinden**

| *In der letzten Woche ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... hat mein Kind sich krank gefühlt | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... hatte mein Kind Kopfschmerzen oder Bauchschmerzen | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... war mein Kind müde und schlapp | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... hatte mein Kind viel Kraft und Ausdauer | ☐ | ☐ | ☐ | ☐ | ☐ |

**2. Seelisches Wohlbefinden**

| *In der letzten Woche ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... hat mein Kind viel gelacht und Spaß gehabt | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... hatte mein Kind zu nichts Lust | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... hat mein Kind sich allein gefühlt | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... hat mein Kind sich ängstlich oder unsicher gefühlt | ☐ | ☐ | ☐ | ☐ | ☐ |

**3. Selbstwert**

| *In der letzten Woche ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... war mein Kind stolz auf sich | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... fühlte mein Kind sich wohl in seiner Haut | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... mochte mein Kind sich selbst leiden | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... hatte mein Kind viele gute Ideen | ☐ | ☐ | ☐ | ☐ | ☐ |

**4. Familie**

| *In der letzten Woche ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... hat mein Kind sich gut mit uns als Eltern verstanden | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... hat mein Kind sich zu Hause wohl gefühlt | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... hatten wir schlimmen Streit zu Hause | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... fühlte mein Kind sich durch mich bevormundet | ☐ | ☐ | ☐ | ☐ | ☐ |

**5. Freunde**

| *In der letzten Woche ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... hat mein Kind etwas mit Freunden zusammen gemacht | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... ist mein Kind bei anderen „gut angekommen“ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... hat mein Kind sich gut mit seinen Freunden verstanden | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... hatte mein Kind das Gefühl, dass es anders ist als die anderen | ☐ | ☐ | ☐ | ☐ | ☐ |

**6. Schule/Ausbildung**

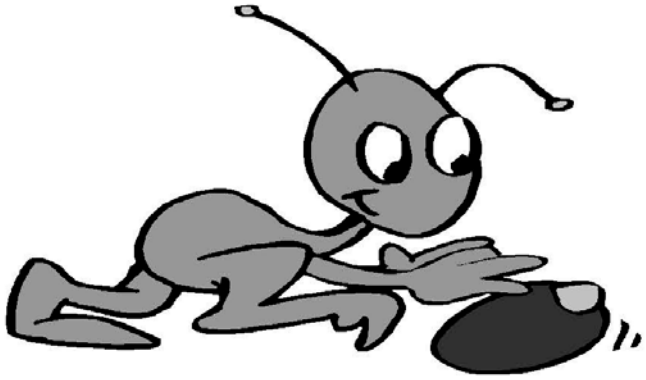
| *In der letzten Woche, in der mein Kind in der Schule/Ausbildung war, ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... hat mein Kind die Aufgaben in der Schule/Ausbildung gut geschafft | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... hat meinem Kind der Unterricht Spaß gemacht | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... hat mein Kind sich Sorgen um seine Zukunft gemacht | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... hatte mein Kind Angst vor schlechten Noten | ☐ | ☐ | ☐ | ☐ | ☐ |

**Vielen Dank für Ihre Mitarbeit!**

Kiddo-KINDL® Teenager (14-17 years)

# Fragebogen für Jugendliche

Kiddo-KINDL ®



**Hallo,**
wir möchten gerne wissen, wie es dir zur Zeit geht. Dazu haben wir uns einige Fragen ausgedacht und bitten dich um deine Antwort.

- ⇨ Lies bitte jede Frage durch,
- ⇨ überlege, wie es in der letzten Woche war,
- ⇨ kreuze **in jeder Zeile** die Antwort an, die am besten zu dir passt.

**Es gibt keine richtigen oder falschen Antworten.**
**Wichtig ist uns deine Meinung.**

| Ein Beispiel: | nie | selten | manch-mal | oft | Immer |
|---|---|---|---|---|---|
| In der letzten Woche habe ich gerne Musik gehört | ☐ | ☐ | ☐ | ☒ | ☐ |

Bogen ausgefüllt am:

_____
Tag/Monat/Jahr

**Bitte sage uns zunächst etwas zu dir. Kreuze an oder trage ein !**

Ich bin ein ☐ Mädchen ☐ Junge

Ich bin _____ Jahre alt

Wie viele Geschwister hast du? ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ über 5

Welche Schule besuchst du? ☐ Grundschule ☐ Hauptschule ☐ Realschule
☐ Gesamtschule ☐ Gymnasium ☐ Sonderschule
☐ privater Unterricht

**1. Zuerst möchten wir etwas über deinen Körper wissen, ...**

| *In der letzten Woche ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... habe ich mich krank gefühlt | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... hatte ich Schmerzen | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... war ich müde und erschöpft | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... hatte ich viel Kraft und Ausdauer | ☐ | ☐ | ☐ | ☐ | ☐ |

**2. ... dann etwas darüber, wie du dich fühlst ...**

| *In der letzten Woche ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... habe ich viel gelacht und Spaß gehabt | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... war mir langweilig | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... habe ich mich allein gefühlt | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... habe ich mich ängstlich oder unsicher gefühlt | ☐ | ☐ | ☐ | ☐ | ☐ |

**3. ... und was du selbst von dir hältst.**

| *In der letzten Woche ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... war ich stolz auf mich | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... fühlte ich mich wohl in meiner Haut | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... mochte ich mich selbst leiden | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... hatte ich viele gute Ideen | ☐ | ☐ | ☐ | ☐ | ☐ |

**4. In den nächsten Fragen geht es um deine Familie ...**

| *In der letzten Woche ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... habe ich mich gut mit meinen Eltern verstanden | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... habe ich mich zu Hause wohl gefühlt | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... hatten wir schlimmen Streit zu Hause | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... fühlte ich mich durch meine Eltern eingeschränkt | ☐ | ☐ | ☐ | ☐ | ☐ |

**5. ... und danach um Freunde.**

| *In der letzten Woche ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... habe ich etwas mit Freunden zusammen gemacht | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... bin ich bei anderen „gut angekommen“ | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... habe ich mich mit meinen Freunden gut verstanden | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... hatte ich das Gefühl, dass ich anders bin als die anderen | ☐ | ☐ | ☐ | ☐ | ☐ |

**6. Nun möchten wir noch etwas über die Schule/Ausbildung wissen.**

| *In der letzten Woche, in der ich in der Schule/Ausbildung war, ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... habe ich die Aufgaben in der Schule/Ausbildung gut geschafft | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... hat mich der Unterricht interessiert | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... habe ich mir Sorgen um meine Zukunft gemacht | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... habe ich Angst vor schlechten Noten gehabt | ☐ | ☐ | ☐ | ☐ | ☐ |

**VIELEN DANK FÜR DEINE MITARBEIT!**

Kiddy-KINDL® Kids (4-6 years)


Hallo,

wir möchten gerne wissen, wie es dir zur Zeit geht und wie du dich fühlst. Dazu haben wir uns einige Fragen ausgedacht und bitten dich um deine Antwort.

- ⇨ Ich lese dir jede Frage vor,
- ⇨ Du überlegst, wie es letzte Woche war und
- ⇨ sage mir dann die Antwort, die für dich am besten passt.

Es gibt keine richtigen oder falschen Antworten. Wichtig ist uns deine Meinung.

Bogen ausgefüllt am:

_____
Tag/Monat/Jahr

**Bitte sage mir zunächst etwas zu dir**

| | |
|---|---|
| Bist du ein | ☐ Mädchen oder ein ☐ Junge? |
| Wie alt bist du? | _____ Jahre |
| Wie viele Geschwister hast du? | ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ über 5 |
| Gehst du in den Kindergarten oder in die Vorschule? | ☐ Kindergarten<br>☐ Vorschule<br>☐ nichts von beidem |

Ich lese dir jetzt ein Beispiel vor:
Wenn du den Satz hörst: „In der letzten Woche habe ich Lust auf Eisessen gehabt",
kannst **du** mir sagen, wie häufig das bei **dir** war?
Es gibt 3 Möglichkeiten zu antworten: **nie, manchmal und ganz oft**.
Also: wie war das bei **dir**?
Würdest **du** sagen: In der letzten Woche habe ich...
**nie** Lust auf Eisessen gehabt,
habe ich **manchmal** Lust auf Eisessen gehabt oder
habe ich **ganz oft** Lust auf Eisessen gehabt

***Antwort des Kindes! Wenn der Eindruck besteht, dass das Kind das Antwortschema verstanden hat weiter mit Frage 1, ansonsten Beispiel wiederholen.***

Das machst du sehr gut. Jetzt geht es los.

**1. Zuerst möchten wir etwas über deinen Körper wissen, ...**

| *In der letzten Woche ...* | nie | manchmal | ganz oft |
|---|---|---|---|
| 1. ... habe ich mich krank gefühlt | ☐ | ☐ | ☐ |
| 2. ... hatte ich Kopfweh oder Bauchweh | ☐ | ☐ | ☐ |

**2. ... dann etwas darüber, wie du dich fühlst ...**

| *In der letzten Woche ...* | nie | manchmal | ganz oft |
|---|---|---|---|
| 1. ... habe ich viel gelacht und Spaß gehabt | ☐ | ☐ | ☐ |
| 2. ... war mir langweilig | ☐ | ☐ | ☐ |

**3. ... und was du selbst von dir hältst.**

| *In der letzten Woche ...* | nie | manchmal | ganz oft |
|---|---|---|---|
| 1. ... war ich stolz auf mich | ☐ | ☐ | ☐ |
| 2. ... mochte ich mich selbst leiden | ☐ | ☐ | ☐ |

**4. In den nächsten Fragen geht es um deine Familie ...**

| *In der letzten Woche ...* | nie | manchmal | ganz oft |
|---|---|---|---|
| 1. ... habe ich mich gut mit meinen Eltern verstanden | ☐ | ☐ | ☐ |
| 2. ... habe ich mich zu Hause wohl gefühlt | ☐ | ☐ | ☐ |

**5. ... und danach um Freunde.**

| *In der letzten Woche ...* | nie | manchmal | ganz oft |
|---|---|---|---|
| 1. ... habe ich mit Freunden gespielt | ☐ | ☐ | ☐ |
| 2. ... habe ich mich mit meinen Freunden gut verstanden | ☐ | ☐ | ☐ |

**6. Nun möchte ich noch etwas über die Vorschule/den Kindergarten wissen.**

| *In der letzten Woche, in der ich in der Vorschule/im Kindergarten war, ...* | nie | manchmal | ganz oft |
|---|---|---|---|
| 1. ... habe ich die Aufgaben in der Vorschule/im Kindergarten gut geschafft | ☐ | ☐ | ☐ |
| 2. ... hat mir die Vorschule/der Kindergarten Spaß gemacht | ☐ | ☐ | ☐ |

**VIELEN DANK FÜR DEINE MITARBEIT!**

Kid-KINDL® Kids (7- 13 years)


**Hallo,**

wir möchten gerne wissen, wie es dir zur Zeit geht. Dazu haben wir uns einige Fragen ausgedacht und bitten dich um deine Antwort.

- ⇨ Lies bitte jede Frage durch,
- ⇨ überlege, wie es in der letzten Woche war,
- ⇨ kreuze **in jeder Zeile** die Antwort an, die am besten zu dir passt.

**Es gibt keine richtigen oder falschen Antworten.**
**Wichtig ist uns deine Meinung.**

| Ein Beispiel: | nie | selten | manch-mal | oft | Immer |
|---|---|---|---|---|---|
| In der letzten Woche habe ich gerne Musik gehört | ☐ | ☐ | ☐ | ☒ | ☐ |

Bogen ausgefüllt am:

_____
Tag/Monat/Jahr

**Bitte sage uns zunächst etwas zu dir. Kreuze an oder trage ein !**

Ich bin ein ☐ Mädchen ☐ Junge

Ich bin _____ Jahre alt

Wieviele Geschwister hast du? ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ über 5

Welche Schule besuchst du? ☐ Grundschule ☐ Hauptschule ☐ Realschule ☐ Gesamtschule ☐ Gymnasium ☐ Sonderschule ☐ privater Unterricht

**1. Zuerst möchten wir etwas über deinen Körper wissen, ...**

| *In der letzten Woche ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... habe ich mich krank gefühlt | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... hatte ich Kopfschmerzen oder Bauchschmerzen | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... war ich müde und schlapp | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... hatte ich viel Kraft und Ausdauer | ☐ | ☐ | ☐ | ☐ | ☐ |

**2. ... dann etwas darüber, wie du dich fühlst ...**

| *In der letzten Woche ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... habe ich viel gelacht und Spaß gehabt | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... war mir langweilig | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... habe ich mich allein gefühlt | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... habe ich Angst gehabt | ☐ | ☐ | ☐ | ☐ | ☐ |

**3. ... und was du selbst von dir hältst.**

| *In der letzten Woche ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... war ich stolz auf mich | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... fand ich mich gut | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... mochte ich mich selbst leiden | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... hatte ich viele gute Ideen | ☐ | ☐ | ☐ | ☐ | ☐ |

**4. In den nächsten Fragen geht es um deine Familie ...**

| *In der letzten Woche ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... habe ich mich gut mit meinen Eltern verstanden | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... habe ich mich zu Hause wohl gefühlt | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... hatten wir schlimmen Streit zu Hause | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... haben mir meine Eltern Sachen verboten | ☐ | ☐ | ☐ | ☐ | ☐ |

**5. ... und danach um Freunde.**

| *In der letzten Woche ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... habe ich mit Freunden gespielt | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... mochten mich die anderen Kinder | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... habe ich mich mit meinen Freunden gut verstanden | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... hatte ich das Gefühl, dass ich anders bin als die anderen | ☐ | ☐ | ☐ | ☐ | ☐ |

**6. Nun möchten wir noch etwas über die Schule wissen.**

| *In der letzten Woche, in der ich in der Schule war ...* | nie | selten | manch-mal | oft | immer |
|---|---|---|---|---|---|
| 1. ... habe ich die Schulaufgaben gut geschafft | ☐ | ☐ | ☐ | ☐ | ☐ |
| 2. ... hat mir der Unterricht Spaß gemacht | ☐ | ☐ | ☐ | ☐ | ☐ |
| 3. ... habe ich mir Sorgen um meine Zukunft gemacht | ☐ | ☐ | ☐ | ☐ | ☐ |
| 4. ... habe ich Angst vor schlechten Noten gehabt | ☐ | ☐ | ☐ | ☐ | ☐ |

**VIELEN DANK FÜR DEINE MITARBEIT!**

SDQ-D Parents (3-17 years)

## Fragebogen zu Stärken und Schwächen (SDQ-D) Eltern[4-16]

Bitte markieren Sie zu jedem Punkt "Nicht zutreffend", "Teilweise zutreffend" oder "Eindeutig zutreffend". Beantworten Sie bitte alle Fragen so gut Sie können, selbst wenn Sie sich nicht ganz sicher sind oder Ihnen eine Frage merkwürdig vorkommt. Bitte berücksichtigen Sie bei der Antwort das Verhalten Ihres Kindes in den letzten sechs Monaten.

Name des Kindes: ..... männlich ☐ weiblich ☐

Geburtsdatum: .....

| | Nicht zutreffend | Teilweise zutreffend | Eindeutig zutreffend |
|---|---|---|---|
| 1. Rücksichtsvoll | ☐ | ☐ | ☐ |
| 2. Unruhig, überaktiv, kann nicht lange stillsitzen | ☐ | ☐ | ☐ |
| 3. Klagt häufig über Kopfschmerzen, Bauchschmerzen oder Übelkeit | ☐ | ☐ | ☐ |
| 4. Teilt gerne mit anderen Kindern (Süßigkeiten, Spielzeug, Buntstifte usw.) | ☐ | ☐ | ☐ |
| 5. Hat oft Wutanfälle; ist aufbrausend | ☐ | ☐ | ☐ |
| 6. Einzelgänger; spielt meist alleine | ☐ | ☐ | ☐ |
| 7. Im allgemeinen folgsam; macht meist, was Erwachsene verlangen | ☐ | ☐ | ☐ |
| 8. Hat viele Sorgen; erscheint häufig bedrückt | ☐ | ☐ | ☐ |
| 9. Hilfsbereit, wenn andere verletzt, krank oder betrübt sind | ☐ | ☐ | ☐ |
| 10. Ständig zappelig | ☐ | ☐ | ☐ |
| 11. Hat wenigstens einen guten Freund oder eine gute Freundin | ☐ | ☐ | ☐ |
| 12. Streitet sich oft mit anderen Kindern oder schikaniert sie | ☐ | ☐ | ☐ |
| 13. Oft unglücklich oder niedergeschlagen; weint häufig | ☐ | ☐ | ☐ |
| 14. Im allgemeinen bei anderen Kindern beliebt | ☐ | ☐ | ☐ |
| 15. Leicht ablenkbar, unkonzentriert | ☐ | ☐ | ☐ |
| 16. Nervös oder anklammernd in neuen Situationen; verliert leicht das Selbstvertrauen | ☐ | ☐ | ☐ |
| 17. Lieb zu jüngeren Kindern | ☐ | ☐ | ☐ |
| 18. Lügt oder mogelt häufig | ☐ | ☐ | ☐ |
| 19. Wird von anderen gehänselt oder schikaniert | ☐ | ☐ | ☐ |
| 20. Hilft anderen oft freiwillig (Eltern, Lehrern oder anderen Kindern) | ☐ | ☐ | ☐ |
| 21. Denkt nach, bevor er/sie handelt | ☐ | ☐ | ☐ |
| 22. Stiehlt zu Hause, in der Schule oder anderswo | ☐ | ☐ | ☐ |
| 23. Kommt besser mit Erwachsenen aus als mit anderen Kindern | ☐ | ☐ | ☐ |
| 24. Hat viele Ängste; fürchtet sich leicht | ☐ | ☐ | ☐ |
| 25. Führt Aufgaben zu Ende; gute Konzentrationsspanne | ☐ | ☐ | ☐ |

Gibt es noch etwas, das Sie erwähnen möchten?
(Bitte hier eintragen!)

**Bitte umblättern**

Würden Sie sagen, daß Ihr Kind insgesamt gesehen in einem oder mehreren der folgenden Bereiche Schwierigkeiten hat: Stimmung, Konzentration, Verhalten, Umgang mit Anderen?

| Nein | Ja, leichte Schwierigkeiten | Ja, deutliche Schwierigkeiten | Ja, massive Schwierigkeiten |
|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ |

Falls Sie diese Frage mit "Ja" beantwortet haben, beantworten Sie bitte auch die folgenden Punkte:

- Seit wann gibt es diese Schwierigkeiten?

| Weniger als einen Monat | 1-5 Monate | 6-12 Monate | Über ein Jahr |
|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ |

- Leidet Ihr Kind unter diesen Schwierigkeiten?

| Gar nicht | Kaum | Deutlich | Massiv |
|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ |

- Wird Ihr Kind durch diese Schwierigkeiten in einem der folgenden Bereiche des Alltagslebens beeinträchtigt?

| | Gar nicht | Kaum | Deutlich | Schwer |
|---|---|---|---|---|
| Zu Hause | ☐ | ☐ | ☐ | ☐ |
| Mit Freunden | ☐ | ☐ | ☐ | ☐ |
| Im Unterricht | ☐ | ☐ | ☐ | ☐ |
| In der Freizeit | ☐ | ☐ | ☐ | ☐ |

- Stellen die Schwierigkeiten eine Belastung für Sie oder die gesamte Familie dar?

| Keine Belastung | Leichte Belastung | Deutliche Belastung | Schwere Belastung |
|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ |

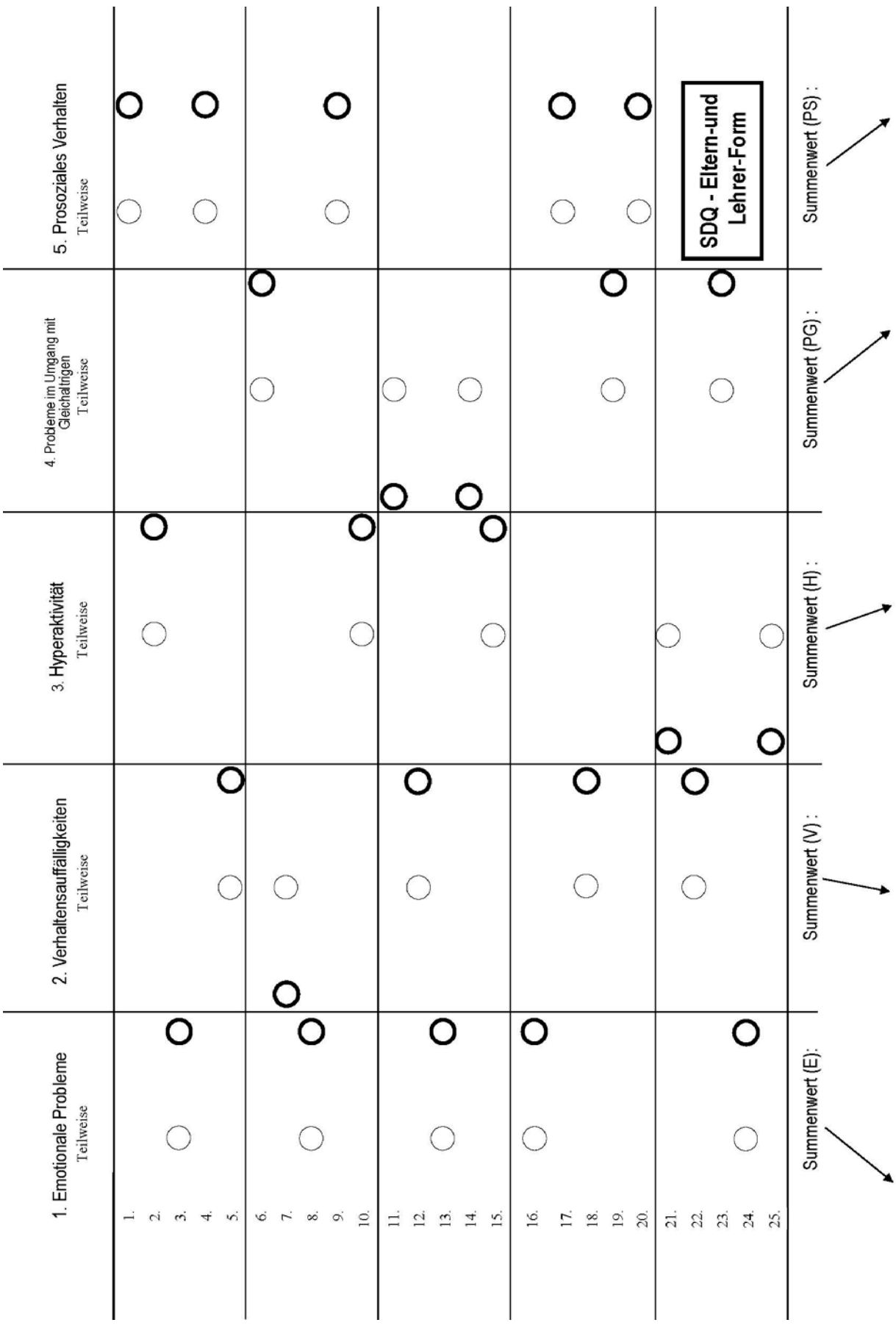
Von wem wurde dieser Bogen ausgefüllt ?

| Vater | Mutter | Andere:..... |
|---|---|---|
| ☐ | ☐ | ☐ |

Heutiges Datum .....

**Bitte überprüfen Sie nochmals, ob alle Fragen beantwortet wurden.**

**Vielen Dank !**


1. Emotionale Probleme
Teilweise
2. Verhaltensauffälligkeiten
Teilweise
3. Hyperaktivität
Teilweise
4. Probleme im Umgang mit Gleichaltrigen
Teilweise
5. Prosoziales Verhalten
Teilweise
SDQ - Eltern-und Lehrer-Form
Summenwert (E):
Summenwert (V) :
Summenwert (H) :
Summenwert (PG) :
Summenwert (PS) :

SDQ-D Kids (11-16 years)

## Fragebogen zu Stärken und Schwächen (SDQ-D)

**Selbst**[11-16]

Bitte markiere zu jedem Punkt "Nicht zutreffend", "Teilweise zutreffend" oder "Eindeutig zutreffend". Beantworte bitte alle Fragen so gut Du kannst, selbst wenn Du Dir nicht ganz sicher bist oder Dir eine Frage merkwürdig vorkommt. Überlege bitte bei der Antwort, wie es Dir im letzten halben Jahr ging.

Dein Name: ..... männlich ☐ weiblich ☐

Geburtsdatum: .....

| | Nicht zutreffend | Teilweise zutreffend | Eindeutig zutreffend |
|---|---|---|---|
| 1. Ich versuche, nett zu anderen Menschen zu sein, ihre Gefühle sind mir wichtig | ☐ | ☐ | ☐ |
| 2. Ich bin oft unruhig, ich kann nicht lange stillsitzen | ☐ | ☐ | ☐ |
| 3. Ich habe häufig Kopfschmerzen oder Bauchschmerzen; mir wird oft schlecht | ☐ | ☐ | ☐ |
| 4. Ich teile normalerweise mit anderen (Süßigkeiten, Spielzeug, Buntstifte usw.) | ☐ | ☐ | ☐ |
| 5. Ich werde leicht wütend; ich verliere oft meine Beherrschung | ☐ | ☐ | ☐ |
| 6. Ich bin meistens für mich alleine; ich beschäftige mich lieber mit mir selbst | ☐ | ☐ | ☐ |
| 7. Normalerweise tue ich, was man mir sagt | ☐ | ☐ | ☐ |
| 8. Ich mache mir häufig Sorgen | ☐ | ☐ | ☐ |
| 9. Ich bin hilfsbereit, wenn andere verletzt, krank oder betrübt sind | ☐ | ☐ | ☐ |
| 10. Ich bin dauernd in Bewegung und zappelig | ☐ | ☐ | ☐ |
| 11. Ich habe einen oder mehrere gute Freunde oder Freundinnen | ☐ | ☐ | ☐ |
| 12. Ich schlage mich häufig; ich kann andere zwingen zu tun, was ich will | ☐ | ☐ | ☐ |
| 13. Ich bin oft unglücklich oder niedergeschlagen; ich muß häufig weinen | ☐ | ☐ | ☐ |
| 14. Im allgemeinen bin ich bei Gleichaltrigen beliebt | ☐ | ☐ | ☐ |
| 15. Ich lasse mich leicht ablenken; ich finde es schwer, mich zu konzentrieren | ☐ | ☐ | ☐ |
| 16. Neue Situationen machen mich nervös; ich verliere leicht das Selbstvertrauen | ☐ | ☐ | ☐ |
| 17. Ich bin nett zu jüngeren Kindern | ☐ | ☐ | ☐ |
| 18. Andere behaupten oft, daß ich lüge oder mogle | ☐ | ☐ | ☐ |
| 19. Ich werde von anderen gehänselt oder schikaniert | ☐ | ☐ | ☐ |
| 20. Ich helfe anderen oft freiwillig (Eltern, Lehrern oder Gleichaltrigen) | ☐ | ☐ | ☐ |
| 21. Ich denke nach, bevor ich handle | ☐ | ☐ | ☐ |
| 22. Ich nehme Dinge, die mir nicht gehören (von zu Hause, in der Schule oder anderswo) | ☐ | ☐ | ☐ |
| 23. Ich komme besser mit Erwachsenen aus als mit Gleichaltrigen | ☐ | ☐ | ☐ |
| 24. Ich habe viele Ängste; ich fürchte mich leicht | ☐ | ☐ | ☐ |
| 25. Was ich angefangen habe, mache ich zu Ende; ich kann mich lange genug konzentrieren | ☐ | ☐ | ☐ |

Gibt es noch etwas, das Du erwähnen möchtest?
(Bitte hier eintragen)

**Bitte umblättern**

Würdest Du sagen, daß Du insgesamt gesehen in einem oder mehreren der folgenden Bereiche Schwierigkeiten hast: Stimmung, Konzentration, Verhalten, Umgang mit Anderen?

| Nein | Ja, leichte Schwierigkeiten | Ja, deutliche Schwierigkeiten | Ja, massive Schwierigkeiten |
|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ |

Falls Du diese Frage mit "Ja" beantwortet hast, beantworte bitte auch die folgenden Punkte:

- Seit wann gibt es diese Schwierigkeiten?

| Weniger als einen Monat | 1-5 Monate | 6-12 Monate | Über ein Jahr |
|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ |

- Leidest Du unter diesen Schwierigkeiten?

| Gar nicht | Kaum | Deutlich | Massiv |
|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ |

- Wirst Du durch diese Schwierigkeiten in einem der folgenden Bereiche des Alltagslebens beeinträchtigt?

| | Gar nicht | Kaum | Deutlich | Schwer |
|---|---|---|---|---|
| Zu Hause | ☐ | ☐ | ☐ | ☐ |
| Mit Freunden | ☐ | ☐ | ☐ | ☐ |
| Im Unterricht | ☐ | ☐ | ☐ | ☐ |
| In der Freizeit | ☐ | ☐ | ☐ | ☐ |

- Findest Du, daß diese Schwierigkeiten anderen (Familie, Freunden, Lehrern usw.) das Leben schwerer machen?

| Gar nicht | Kaum schwerer | Deutlich schwerer | Sehr viel schwerer |
|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ |

Heutiges Datum .....

**Bitte überprüfe nochmals, ob Du alle Fragen beantwortet hast.**

**Vielen Dank !**

1. Emotionale Probleme
Teilweise
2. Verhaltensauffälligkeiten
Teilweise
3. Hyperaktivität
Teilweise
4. Probleme im Umgang mit Gleichaltrigen
Teilweise
5. Prosoziales Verhalten
Teilweise
1.
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23.
24.
25.
Summenwert (E) :
Summenwert (V) :
Summenwert (H) :
Summenwert (PG) :
Summenwert (PS) :
SDQ - Selbst-Form

SDQ-D Erwachsene

## Fragebogen zu Stärken und Schwächen (SDQ-Deu) Selbst 18+

Bitte markieren Sie zu jedem Punkt "Nicht zutreffend", "Teilweise zutreffend" oder "Eindeutig zutreffend". Beantworten Sie bitte alle Fragen so gut Sie können, selbst wenn Sie sich nicht ganz sicher sind oder Ihnen eine Frage merkwürdig vorkommt. Überlegen Sie bitte bei der Antwort, wie es Ihnen im letzten halben Jahr ging.

Dein Name ..... Männlich/Weiblich

Geburtsdatum .....

| | Nicht zutreffend | Teilweise zutreffend | Eindeutig zutreffend |
|---|---|---|---|
| Ich versuche, nett zu anderen Menschen zu sein, ihre Gefühle sind mir wichtig | ☐ | ☐ | ☐ |
| Ich bin oft unruhig; ich finde es schwierig, lange Zeit still zu sitzen | ☐ | ☐ | ☐ |
| Ich habe häufig Kopfschmerzen oder Bauchschmerzen; mir wird oft schlecht | ☐ | ☐ | ☐ |
| Ich teile normalerweise mit anderen (z.B. Essen oder Trinken) | ☐ | ☐ | ☐ |
| Ich werde leicht wütend; ich verliere oft meine Beherrschung | ☐ | ☐ | ☐ |
| Ich bin lieber alleine als mit anderen Menschen zusammen | ☐ | ☐ | ☐ |
| Im Allgemeinen bin ich gewillt zu tun, was andere Menschen von mir verlangen | ☐ | ☐ | ☐ |
| Ich mache mir häufig Sorgen | ☐ | ☐ | ☐ |
| Ich bin hilfsbereit, wenn andere verletzt, krank oder traurig sind | ☐ | ☐ | ☐ |
| Ich bin dauernd in Bewegung und zappelig | ☐ | ☐ | ☐ |
| Ich habe mindestens eine gute Freundin/einen guten Freund | ☐ | ☐ | ☐ |
| Ich schlage mich häufig; ich kann Andere zwingen zu tun, was ich will | ☐ | ☐ | ☐ |
| Ich bin oft unglücklich oder deprimiert; ich muss häufig weinen | ☐ | ☐ | ☐ |
| Andere Menschen mögen mich im Allgemeinen | ☐ | ☐ | ☐ |
| Ich lasse mich leicht ablenken; ich finde es schwer, mich zu konzentrieren | ☐ | ☐ | ☐ |
| Neue Situationen machen mich nervös; ich verliere leicht das Selbstvertrauen | ☐ | ☐ | ☐ |
| Ich bin nett zu Kindern | ☐ | ☐ | ☐ |
| Andere behaupten oft, dass ich lüge oder mogele | ☐ | ☐ | ☐ |
| Ich werde von anderen gehänselt oder schikaniert | ☐ | ☐ | ☐ |
| Ich biete anderen oft meine Hilfe an (Familienangehörigen, Freunden, Kollegen) | ☐ | ☐ | ☐ |
| Ich denke nach, bevor ich handele | ☐ | ☐ | ☐ |
| Ich nehme Dinge, die mir nicht gehören (von zu Hause, von der Arbeit oder anderswo) | ☐ | ☐ | ☐ |
| Ich komme besser mit Menschen aus, die älter sind als ich, als mit Menschen in meinem Alter | ☐ | ☐ | ☐ |
| Ich habe viele Ängste; ich fürchte mich leicht | ☐ | ☐ | ☐ |
| Was ich angefangen habe, mache ich zu Ende; ich kann mich lange genug konzentrieren | ☐ | ☐ | ☐ |

Unterschrift:..... Datum: .....

**Vielen Dank für Deine Hilfe**

## Appendix 4 WHOQOL-BREF

# WHOQOL-BREF

## Deutsche Version

ÜBER SIE

Bevor Sie beginnen möchten wir Sie bitten, einige allgemeine Fragen über Sie selbst zu beantworten: Bitte kreuzen Sie die richtige Antwort an oder füllen Sie das vorgesehene Feld aus.

Was ist Ihr Geschlecht? Männlich Ç0 Weiblich Ç1

Wann sind Sie geboren?

| Tag | Monat | Jahr |
|---|---|---|
| | | |

Was ist Ihr höchster Schulabschluß?

Ç1 Kein Abschluß
Ç2 Hauptschule
Ç3 Mittlere Reife
Ç4 Fachhochschulreife (Dr.)
Ç5 Abitur
Ç6 Fachhochschule
Ç7 Universität
Ç8 Postgraduiert

Wie ist Ihr Familienstand?

Ç1 Allein lebend
Ç2 Verheiratet
Ç3 Mit Partner lebend
Ç4 Getrennt lebend
Ç5 Geschieden
Ç6 Verwitwet

Sind Sie gegenwärtig krank? Ç1 Ja Ç0 Nein

Wenn etwas mit Ihrer Gesundheit nicht in Ordnung ist, was glauben Sie was es ist?

Krankheit/Gesundheitsproblem: _____

### Instruktionen

In diesem Fragebogen werden Sie danach gefragt, wie Sie Ihre Lebensqualität, Ihre Gesundheit und andere Bereiche Ihres Lebens beurteilen. **Bitte beantworten Sie alle Fragen.** Wenn Sie sich bei der Beantwortung einer Frage nicht sicher sind, wählen Sie bitte die Antwortkategorie, die Ihrer Meinung nach am ehesten zutrifft. Oft ist dies die Kategorie, die Ihnen als erstes in den Sinn kommt.

Bitte beantworten Sie alle Fragen auf der Grundlage Ihrer eigenen Beurteilungskriterien, Hoffnungen, Vorlieben und Interessen. Bitte denken Sie bei der Beantwortung der Fragen an Ihr Leben **während der vergangenen zwei Wochen**. So könnte eine Frage zum Beispiel lauten:

| | Überhaupt nicht | Eher nicht | Halbwegs | Überwiegend | Völlig |
|---|---|---|---|---|---|
| Bekommen Sie von anderen Menschen die Unterstützung die Sie brauchen? | 1 | 2 | 3 | 4 | 5 |

Bei dieser Frage sollen Sie das Feld ankreuzen, das am besten ausdrückt, in welchem Umfang Sie während der vergangenen zwei Wochen von anderen Menschen die Unterstützung erhalten haben die Sie brauchen. Wenn Sie während der vergangenen zwei Wochen von anderen Menschen überwiegend die Unterstützung erhalten haben die sie brauchen, kreuzen Sie das Feld mit der Zahl 4 an.

| | Überhaupt nicht | Eher nicht | Halbwegs | Überwiegend | Völlig |
|---|---|---|---|---|---|
| Bekommen Sie von anderen Menschen die Unterstützung die Sie brauchen? | 1 | 2 | 3 | 4 | 5 |

Wenn Sie während der letzten zwei Wochen von anderen Menschen die Unterstützung die Sie brauchen überhaupt nicht erhalten haben, kreuzen Sie das Feld mit der Zahl 1 an.

**Bitte lesen Sie jede Frage, überlegen Sie, wie Sie sich in den vergangenen zwei Wochengefühlt haben, und kreuzen Sie die Zahl auf der Skala an, die für Sie am ehesten zutrifft.**

| | | Sehr schlecht | Schlecht | Mittel-mäßig | Gut | Sehr gut |
|---|---|---|---|---|---|---|
| 1(G1) | Wie würden Sie Ihre Lebensqualität beurteilen? | 1 | 2 | 3 | 4 | 5 |

| | | Sehr unzufrieden | Unzufrieden | Weder zufrieden noch unzufrieden | Zufrieden | Sehr zufrieden |
|---|---|---|---|---|---|---|
| 2(G4) | Wie zufrieden sind Sie mit Ihrer Gesundheit? | 1 | 2 | 3 | 4 | 5 |

In den folgenden Fragen geht es darum, **wie stark** Sie während der vergangenen zwei Wochen bestimmte Dinge erlebt haben.

| | | Überhaupt nicht | Ein wenig | Mittel-mäßig | Ziemlich | Äußerst |
|---|---|---|---|---|---|---|
| 3 (F1.4) | Wie stark werden Sie durch Schmerzen daran gehindert, notwendige Dinge zu tun? | 1 | 2 | 3 | 4 | 5 |
| 4 (F11.3) | Wie sehr sind Sie auf medizinische Behandlung angewiesen, um das tägliche Leben zu meistern? | 1 | 2 | 3 | 4 | 5 |
| 5 (F4.1) | Wie gut können Sie Ihr Leben genießen? | 1 | 2 | 3 | 4 | 5 |
| 6 (F24.2) | Betrachten Sie Ihr Leben als sinnvoll? | 1 | 2 | 3 | 4 | 5 |

| | | Überhaupt nicht | Ein wenig | Mittel-mäßig | Ziemlich | Äußers |
|---|---|---|---|---|---|---|
| 7 (F5.3) | Wie gut können Sie sich konzentrieren? | 1 | 2 | 3 | 4 | 5 |
| 8 (F16.1) | Wie sicher fühlen Sie sich in Ihrem täglichen Leben? | 1 | 2 | 3 | 4 | 5 |
| 9 (F22.1) | Wie gesund sind die Umweltbedingungen in Ihrem Wohngebiet? | 1 | 2 | 3 | 4 | 5 |

| | | Überhaupt nicht | Eher nicht | Halbwegs | Überwiegend | Völlig |
|---|---|---|---|---|---|---|
| 10 (F2.1) | Haben Sie genug Energie für das tägliche Leben? | 1 | 2 | 3 | 4 | 5 |
| 11 (F7.1) | Können Sie Ihr Aussehen akzeptieren? | 1 | 2 | 3 | 4 | 5 |
| 12 (F18.1) | Haben Sie genug Geld, um Ihre Bedürfnisse erfüllen zu können? | 1 | 2 | 3 | 4 | 5 |
| 13 (F20.1) | Haben Sie Zugang zu den Informationen, die Sie für das tägliche Leben brauchen? | 1 | 2 | 3 | 4 | 5 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 14 (F21.1) | Haben Sie ausreichend Möglichkeiten zu Freizeitaktivitäten? | 1 | 2 | 3 | 4 | 5 |

In den folgenden Fragen geht es darum, im welchem Umfang Sie während der vergangenen zwei Wochen bestimmte Dinge erlebt haben oder in der Lage waren, bestimmte Dinge zu tun

| | | Sehr schlecht | Schlecht | Mittel-mäßig | Gut | Sehr gut |
|---|---|---|---|---|---|---|
| 15 (F9.1) | Wie gut können Sie sich fortbewegen? | 1 | 2 | 3 | 4 | 5 |

In den folgenden Fragen geht es darum, wie **zufrieden, glücklich oder gut** Sie sich während der vergangenen zwei Wochen hinsichtlich verschiedener Aspekte Ihres Lebens gefühlt haben.

| | | Sehr unzufrieden | Unzufrieden | Weder zufrieden noch unzufrieden | Zufrieden | Sehr zufrieden |
|---|---|---|---|---|---|---|
| 16 (F3.3) | Wie zufrieden sind Sie mit Ihrem Schlaf? | 1 | 2 | 3 | 4 | 5 |
| 17 (F10.3) | Wie zufrieden sind Sie mit Ihrer Fähigkeit, alltägliche Dinge erledigen zu können? | 1 | 2 | 3 | 4 | 5 |
| 18 (F12.4) | Wie zufrieden sind Sie mit Ihrer Arbeitsfähigkeit? | 1 | 2 | 3 | 4 | 5 |
| 19 (F6.3) | Wie zufrieden sind Sie mit sich selbst? | 1 | 2 | 3 | 4 | 5 |
| 20 (F13.3) | Wie zufrieden sind Sie mit Ihren persönlichen Beziehungen? | 1 | 2 | 3 | 4 | 5 |
| 21 (F15.3) | Wie zufrieden sind Sie mit Ihrem Sexualleben? | 1 | 2 | 3 | 4 | 5 |
| 22 (F14.4) | Wie zufrieden sind Sie mit der Unterstützung durch Ihre Freunde? | 1 | 2 | 3 | 4 | 5 |
| 23 (F17.3) | Wie zufrieden sind Sie mit Ihren Wohnbedingungen? | 1 | 2 | 3 | 4 | 5 |
| 24 (F19.3) | Wie zufrieden sind Sie mit Ihren Möglichkeiten, Gesundheitsdienste in Anspruch nehmen zu können? zu können? | 1 | 2 | 3 | 4 | 5 |
| 25 (F23.3) | Wie zufrieden sind Sie mit den Beförderungsmitteln, die Ihnen zur Verfügung stehen? | 1 | 2 | 3 | 4 | 5 |

In der folgenden Frage geht es darum, **wie oft** sich während der vergangenen zwei Wochen bei Ihnen negative Gefühle eingestellt haben, wie zum Beispiel Angst oder Traurigkeit.

| | | Niemals | Nicht oft | Zeitweilig | Oftmals | Immer |
|---|---|---|---|---|---|---|
| 26 (F8.1) | Wie häufig haben Sie negative Gefühle wie Traurigkeit, Verzweiflung, Angst oder Depression? | 1 | 2 | 3 | 4 | 5 |

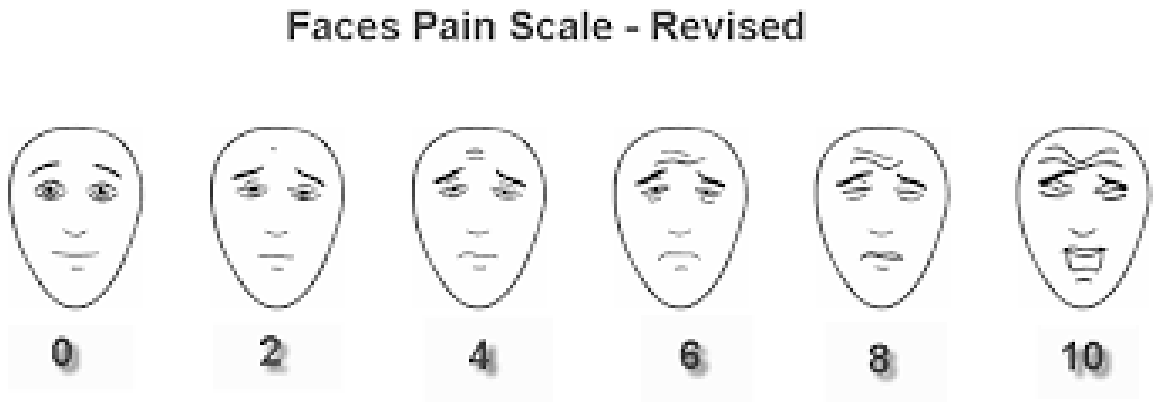
Hat Ihnen jemand beim Ausfüllen dieses Fragebogens geholfen? C1 Ja C0 Nein

Wie lange hat es gedauert, den Fragebogen auszufüllen? _____ Minuten

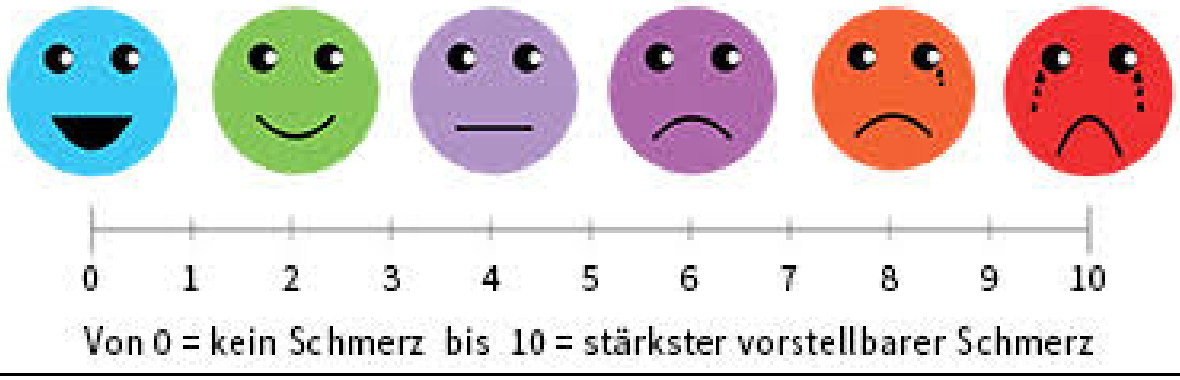
Haben Sie irgend welche Anmerkungen zu diesem Fragebogen?

## Appendix 5 Pain Scales

Adults and teenagers (≥ 14 years):




Children (3-13 years):



# Appendix 6 Clinically relevant drug interactions

## Inducers, and inhibitors of isoenzyme CYP3A

**Inducers**

**Strong inducers:**

avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort

(hypericum perforatum)

**Moderate inducers:**

bosentan, efavirenz, etravirine, genistein, modafinil, nafcillin, ritonavir, [talviraline], thioridazine, tipranavir

**Weak inducers:**

amprenavir, aprepitant, armodafinil (R-modafinil), bexarotene, clobazam, danshen, dexamethasone, Echinacea,garlic (allium sativum), gingko (ginkgo biloba), glycyrrhizin, methylprednisolone, nevirapine, oxcarbazepine, pioglitazone, prednisone, [pleconaril], primidone, raltegravir, rufinamide, sorafenib, telaprevir, terbinafine, topiramate, [troglitazone] , vinblastine

**Inhibitors**

**Strong inhibitors:**

boceprevir, clarithromycin, cobicistat, conivaptan, elvitegravir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, posaconazole (Krishna et al 2009), ritonavir, saquinavir, telaprevir, telithromycin, tipranavir, troleandamycin, voriconazole

**Moderate inhibitors:**

Amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, grapefruit and grapefruit juice (citrus parasidi fruit juice), imatinib, schisandra sphenanthera, tofisopam, verapamil

## Substrates, inducers, inhibitors of PgP and PgP/CYP3A dual inhibitors

**Substrates**

colchicine, digoxin, fexofenadine, indinavir, paclitaxel, talinolol, topotecan, vincristine, everolimus

**Inducers**

rifampin, St John’s wort

**PgP Inhibitors and PgP/CYP3A Dual Inhibitors**

amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, diltiazem, dronedarone, elacridar, erythromycin, felodipine, fexofenadine, fluvoxamine, ginkgo (ginkgo biloba), indinavir, itraconazole, lopinavir, mibefradil, milk thistle (silybum marianum), nelfinavir, nifedipine, nitrendipine, paroxetine, quercetin, quinidine, ranolazine, rifampin, ritonavir, saquinavir, Schisandra chinensis, St John's wort (hypericum perforatum), talinolol, Telaprevir, telmisartan, ticagrelor, tipranavir, tolvaptan, valspodar, verapamil

Reference: Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated 24-Oct-2017 which summarizes DDI data from three sources including the FDA's "Guidance for Industry, Drug Interaction Studies", the University of Washington's Drug Interaction Database, and Indiana University School of Medicine's DrugInteraction Table.