# CLINICAL TRIAL PROTOCOL

Hydroxychloroquine in pediatric ILD

START randomized controlled in parallel-group, then switch placebo to active drug,

and

STOP randomized controlled in parallel-group

to evaluate the efficacy and safety of hydroxychloroquine (HCQ)

Short Title: HCQ in pediatric ILD particularly 4surfdefect

EudraCT: 2013-003714-40

IZKS trial code: 2013-006

final

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## List of abbreviations

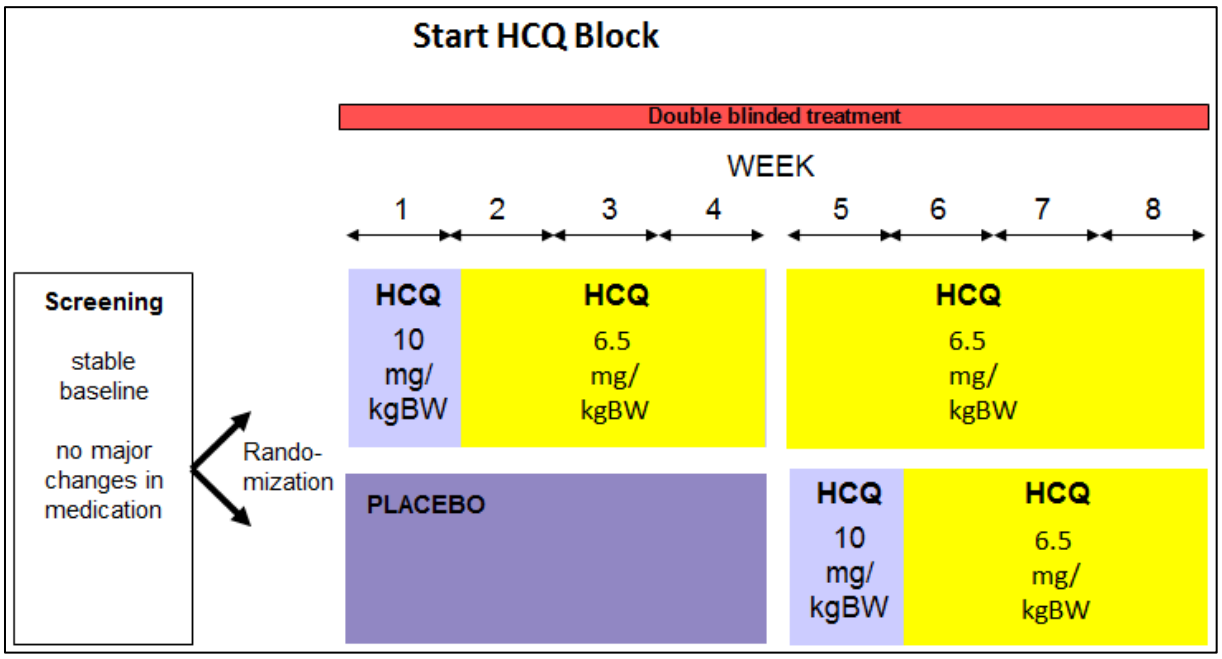
| | |
|---|---|
| 6MWT | 6-minute-walk test |
| ABCA3 | Human ATP-binding cassette transporter, sub-family A, member 3 |
| AE | Adverse event |
| AMG | German drug law (Arzneimittelgesetz) |
| AR | Adverse reaction |
| BAL | Bronchoalveolar lavage |
| BB | Blood count |
| BP | Blood pressure |
| BSPAR | The British Society for Paediatric and Adolescent Rheumatology |
| BW | Body weight |
| chILD | Children's interstitial lung disease |
| CK | Creatine kinase |
| CO2 | Carbon dioxide |
| CPI | Chronic pneumonitis of infancy |
| CQ | Chloroquine |
| Crea | Creatinine |
| CRF | Case report form |
| D | Day |
| DCF | Data clarification form |
| Diff | Differential blood count |
| DIP | Desquamative interstitial pneumonitis |
| DLCO | Diffusing capacity of the lung for carbon monoxide |
| DMC | Data monitoring committee |
| DMP | Data management plan |
| DPLD | Diffuse parenchymal lung disease |
| DZL | German Center of lung research |
| EC/IEC | Ethics committee/Independent ethics committee |
| ECG | Electrocardiogram |
| Echo | Echocardiography |
| ECLA | Extracorporeal lung assist |
| ECLS | Extracorporeal Life Support System |
| ECMO | Extracorporeal membrane oxygenation |
| e-CRF | Electronic case report form |
| EDC | Electronic data capture |
| EDTA | Ethylene diamine tetraacetic acid |
| EMEA | European Medicines Agency |
| FAF | Fundus autofluorescence |
| FDA | Food and Drug Administration |
| FEV1 | Forced expiratory volume in 1 second |
| FiO2 | Fraction of inspired oxygen |
| FVC | Forced vital capacity |
| GCP | Good clinical practice |
| GCP-V | GCP regulation |
| GFR | Glomerular filtration rate |
| gGT | Gamma-glutamic transferase |
| GIP | Giant cell interstitial pneumonia |
| GLI | Global Lung function Initiative |
| GMCSF | Granulocyte macrophage colony-stimulating factor |
| GMCSF-Ra/b | Granulocyte macrophage colony-stimulating factor receptor subunit α and β |
| GOT | Glutamate oxaloacetate transaminase |
| GPT | Glutamate pyruvate transaminase |
| GvHD | Graft-versus-Host-Disease |
| HCQ | Hydroxychloroquine |
| HP | Hypersensitivity pneumonitis |
| ICH | International conference on harmonization of technical requirements for registration of pharmaceuticals for human use |

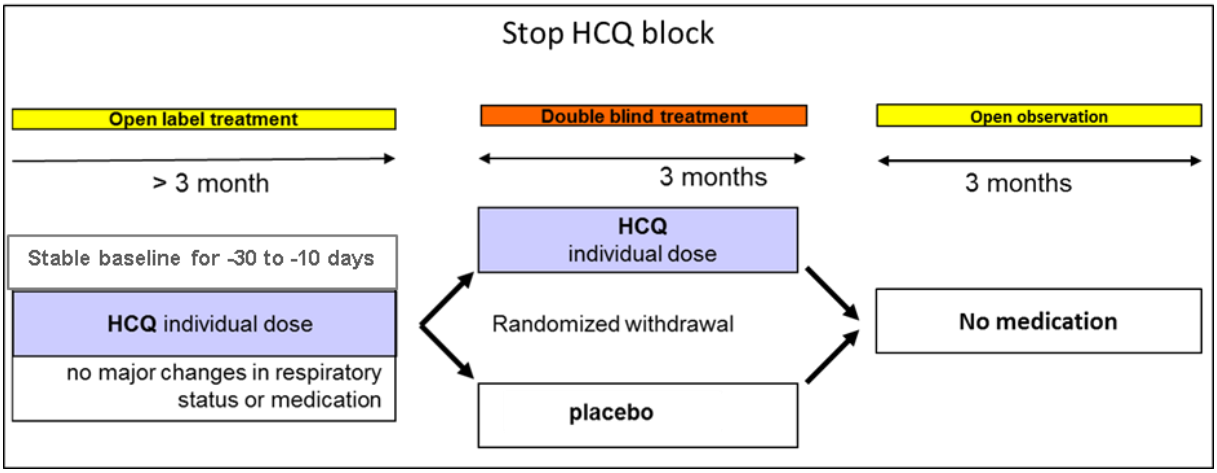
| | |
|---|---|
| IgG | Immunoglobulin G |
| IMP | Investigational medicinal product |
| ILD | Interstitial lung disease |
| IRB | Institutional review board |
| ISRCTN | International standard randomised controlled trial number |
| INN | International non-proprietary name |
| ISF | Investigator site file |
| ITT | Intention to treat |
| IZKS | Interdisciplinary centre for clinical trials |
| Lab | Laboratory |
| LDH | Lactatdehydrogenase |
| LIP | Lymphocytic interstitial pneumonia |
| LKP | Clinical Trial Director according (Leiter der Klinischen Prüfung) |
| MedDRA | Medical dictionary for regulatory activities terminology |
| MDAT | Medical database |
| MPAW | Mean airway pressure |
| NEHI | Neuroendocrine Hyperplasia of Infancy |
| Nkx2-1 | NK2 homeobox 1 gene |
| NO | Nitrogen monoxide |
| NSIP | Nonspecific interstitial pneumonitis |
| PaO2 | Partial pressure of oxygen in arterial blood |
| PcapO2 | Partial pressure of oxygen in capillary blood |
| PAP | Pulmonary alveolar proteinosis |
| pCO2 | Carbon dioxide partial pressure |
| pO2 | Oxygen partial pressure |
| O2 | Oxygen |
| O2-sat | Oxygen saturation |
| OCT | Ocular coherence tomography |
| O.I. | Oxygenation index |
| PEEP | Positive endexspiratory pressure |
| PIP | Positive inspiratory pressure |
| p.o. | Orally |
| PP | Per protocol |
| QOL | Quality of life |
| QC | Quality control |
| QT | QT-intervall in the ECG |
| RDS | Respiratory distress syndrome |
| RR | Respiratory rate |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SAR | Serious adverse reaction |
| SAS | Statistical analysis system |
| SDV | Source data verification |
| SFTPB | Surfactant protein B |
| SFTPC | Surfactant protein C |
| SmPC | Summary of product characteristics |
| SOP | Standard operating procedure |
| SPSS | Statistics program |
| SSL | Secure Sockets Layer |
| SUSAR | Suspected unexpected serious adverse reaction |
| Temp | Body temperature |
| Ti | Inspiration Time |
| TMF | Trial master file |
| TTF1 | Thyroid Transcription Factor-1 |
| UIP | Usual interstitial pneumonitis |
| VA | veno-arterial |
| VV | veno-venous |

# Overview Study plan HCQ

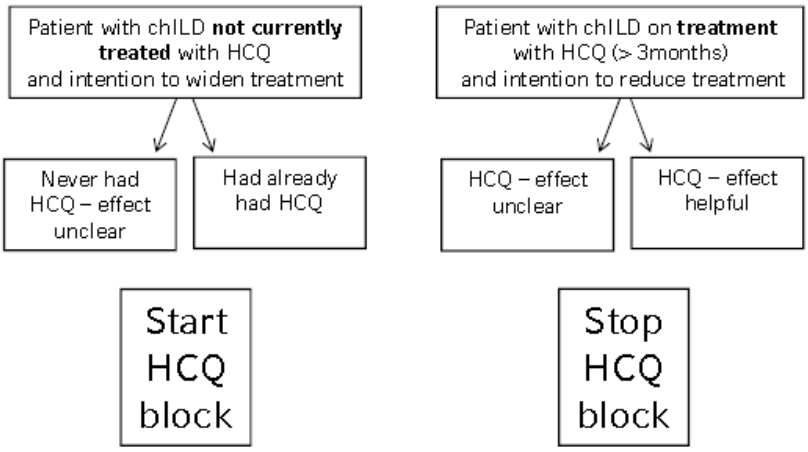
This randomized controlled study is embedded into the European Management Platform for Children´s Interstitial Lung Diseases (chILD). Patients included into this register and biobank are eligible for inclusion into the trials (see 3.5.1).

The study contains two different study blocks:



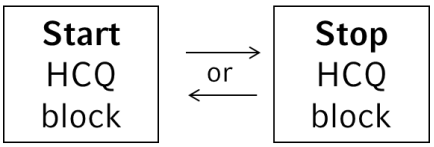
Typical examples for the indication of these blocks:

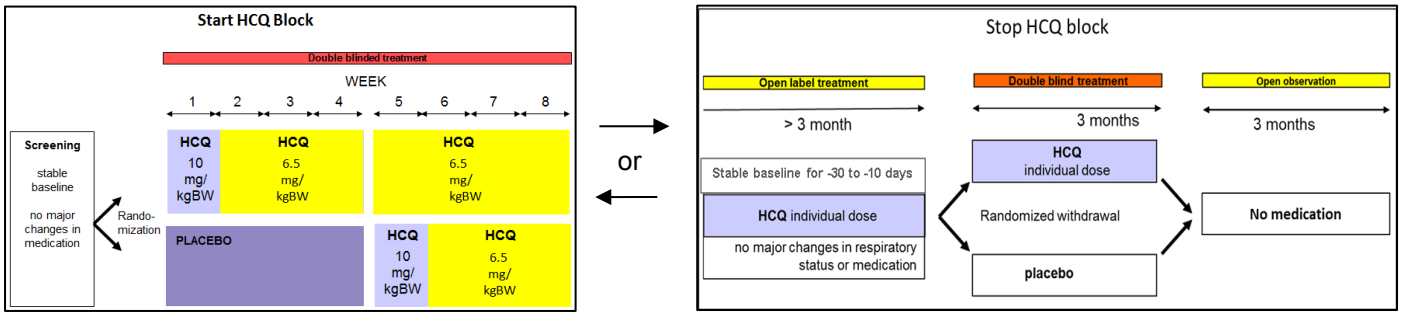



If a patient already had been treated with HCQ longer than 3 months ago, it makes sense to include him/her into the START-HCQ block for several reasons among others, especially for :

- It is not obvious, if there was an effect of the HCQ treatment or not
- It is unclear which dose of HCQ was given or if the patient was compliant
- There are new aspects of the course of the patient's disease
- The child has become substantially (e.g. > 1 year) older

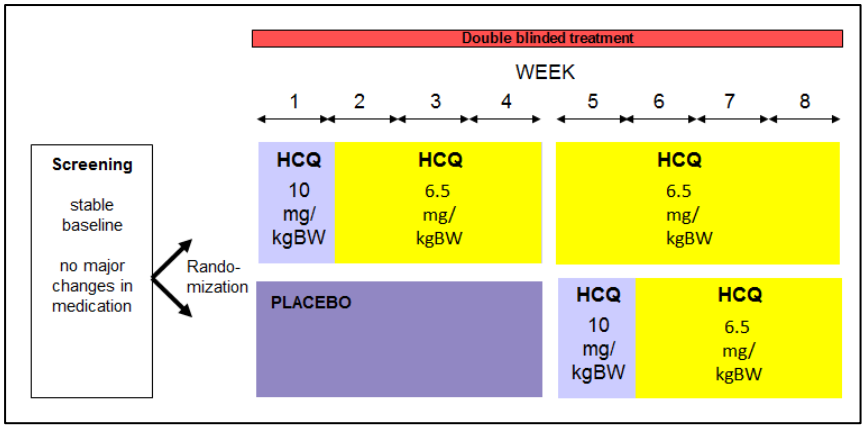
These blocks can be initiated in sequence as needed by the subjects. Each patient can participate in **each block only once**:

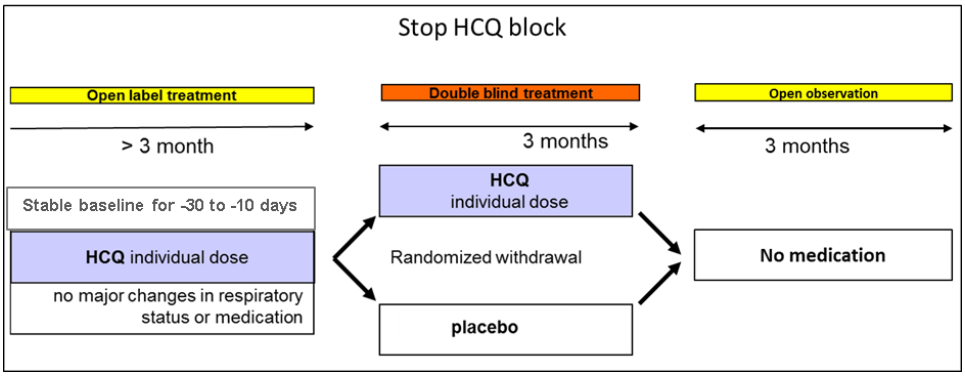


# Synopsis

| | |
|---|---|
| **Title** | Hydroxychloroquine in pediatric ILD. START randomized controlled in parallel-group, then switch placebo to active drug, and STOP randomized controlled in parallel-group to evaluate the efficacy and safety of hydroxychloroquine (HCQ) |
| **Short title** | HCQ in pediatric ILD |
| **EudraCT** | 2013-003714-40 |
| **IZKS trial code** | 2013-006 |
| **Indication** | Diagnosed children´s interstitial lung disease (chILD) in children and adults |
| **Phase** | 2a |
| **Treatments** | Test product: Hydroxychloroquine Sulfate (HCQ), one daily dose in the evening.<br>Reference therapy: Placebo<br>The treatments are organized in START and STOP blocks, which can be initiated in sequence, as needed by the subjects. |

| | ***START* HCQ block** |
|---|---|
| **Block specific inclusion criterion (others see 3.6.1)** | All subjects not currently on HCQ (last dose ≥ 3 months ago) and intention to widen treatment. |
| **Primary objective** | To evaluate the efficacy of HCQ after 28 days of treatment in chILD compared to placebo |
| **Secondary objectives** | To evaluate the efficacy of HCQ after 56 days of treatment in chILD compared to 28 days<br>To evaluate the safety of HCQ after 28 and 56 days of treatment in chILD<br>To evaluate blood levels of HCQ after 28 and 56 days of treatment in chILD |
| **Trial design** |  <br>This is an exploratory Phase 2a, randomized, double-blind, placebo-controlled, parallel-group study and switched placebo to active drug, multicentre, multinational study in subjects with chILD genetically, histologically or clinically diagnosed.<br><br>This study includes:<br>• Screening Period (Day -28 through Day -3)<br>• Treatment Period (Day 1 through Day 56) |

| | |
|---|---|
| | ***STOP* HCQ block** |
| **Block specific inclusion criterion (others see 3.6.1)** | All subjects on chronic (> 3 months) treatment with HCQ (usually 6-10 mg/kg/d or individually tolerated dose) and intention to reduce treatment. |
| **Primary objective** | To evaluate the efficacy of HCQ after 84 days of treatment in chILD compared to placebo |
| **Secondary objectives** | To evaluate the efficacy of chronic (> 3 months) HCQ treatment in chILD compared to placebo<br>To evaluate the safety of HCQ after > 3 months of treatment in chILD<br>To evaluate blood levels of HCQ before and after treatment in chILD |
| **Trial design** |  <br>This is an exploratory Phase 2a, randomized, double-blind, placebo-controlled, parallel-group, multinational withdrawal study in subjects with chILD and treated with hydroxychloroquine.<br><br>This study includes:<br>• History of Open Treatment Period (total of at least 3 months of continuing HCQ treatment until randomization)<br>• Screening Period (Day -30 through Day -10)<br>• Treatment Period (Day 1 through Day 84)<br>• Open observation period (Day 85 through Day 168) |

| | |
|---|---|
| **Trial population** | **In addition to the block specific inclusion criterion the inclusion criteria are:**<br>See 3.6.1 in the protocol<br>Allowed previous medication: see 4.1.10 |
| | **exclusion criteria:** See 3.6.2 |
| **Trial duration** | Until 2024/2025 |
| **Number of subjects** | It is planned to enrol at least 80 subjects |
| **Number of sites** | Up to 100 trial sites are planned to participate |
| **Primary outcome** | **START HCQ block**<br>Relative change trial day 1 (i.e. Visit 2) through day 28 (i.e. Visit 3) and relative change day 28 to day 56 (i.e. Visit 4) active compared to change placebo<br><br>**STOP HCQ block**<br>Relative change day 1 (i.e. Visit 2) through day 84 (i.e. Visit 5): change active compound compared to change placebo<br><br>Oxygenation (see Table 3.3-1) |
| **Secondary outcome** | See 3.4 |
| **Statistical analysis** | ***START* HCQ block and STOP HCQ block**<br><br>The variable assessing the **primary** outcome is the response rate measured by the oxygen saturation in room air.<br><br>Both blocks separately<br><br>a) A difference between the changes in placebo and active phases is considered significant, if the oxygen saturation increases by ≥ 5%.<br><br>b) Patients are defined as responder if the oxygen saturation is increased by 5% compared to baseline. The numbers of responders are counted and compared by Fisher exact test.<br><br>Both blocks together<br><br>c) oxygen saturation and the correspondent responder will be analysed by a linear mixed model (or logistic regression respectively). If indicated, a Bayesian approach will be employed.<br><br>If appropriate, the analyses will be adjusted for the stratification factor of the randomization: age group. |

## Trial schedule

### *START* HCQ block

Table 1-1

| Visit | Screening evaluations and Visit 1 | Visit 2 | Email-/Phone-Visit | Visit 3 | Email-/Phone-Visit | Visit 4 |
|---|---|---|---|---|---|---|
| Action | „Start of baseline“ | “End of baseline” + Day 1 of treatment | Every 7 days at home | End of 1st Tx period | Every 7 days at home | “End of trial” |
| Trial day | -28 to -3 | 1 | 7, 14, 21 (+/- 3) | 28 (-4, +7) | 35, 42, 49 (+/- 3) | 56 (-4, +7) |
| Demographics (e.g. sex, age) | X | | | | | |
| Patient information, informed consent | X | | | | | |
| Previous (last 12 months) and concomitant diseases | X | X | X | X | X | X |
| Previous (last 3 months) and concomitant treatments | X | X | X | X | X | X |
| Inclusion/exclusion criteria | X | X*5 | | | | |
| Pregnancy test K | X* | | | X | | X |
| Randomization a | X | | | | | |
| Trial medication supply to patient | | X | | X | | |
| History (cardiotoxicity, hypoglycaemia) | X | X | | X | | X |
| Physical examination | X | X | | X | | X |
| Vital signs (BP, pulse, temp) b | X | X | | X | | X |
| ECG | X* | | | X | | X |
| Ophthalmologic review J | X* | | | | | X |
| Lab c (GOT/GPT/Crea/Potassium/CK/gGT/LDH/BB/ DIFF / HCQ drug level, blood glucose) | X* | | | X | | X |
| $pO_2$, $pCO_2$ (capillary) | X | X*3 | | X*3 | | X*3 |
| $O_2$-sat e, in room air | X | X | X | X | X | X |
| Respiratory rate, in room air | X | X | X | X | X | X |
| Retractions | X | X | X | X | X | X |
| Coughing | X | X | X | X | X | X |
| Oxygen demand | X | X | X | X | X | X |
| Chest x-ray | X*2 | | | X*4 | | |

| Visit | Screening evaluations and Visit 1 | Visit 2 | Email-/Phone-Visit | Visit 3 | Email-/Phone-Visit | Visit 4 |
|---|---|---|---|---|---|---|
| Pulmonary hypertension (Echo) [j] | X* | | | | | |
| Quality-of-life [i] | X* | | | X | | X |
| Health Economics [h] | X* | | | X | | X |
| Weight for height [b] | X* | X | | X | | X |
| Clinical course of lung disease | X[*6] | X[*6] | X[*6] | X[*6] | X[*6] | X[*6] |
| Exacerbation [o] | X[*7] | X[*7] | X[*7] | X[*7] | X[*7] | X[*7] |
| Adverse events | X | X | X | X | X | X |
| Drug accountability | | | | X | | X |
| Additionally in children > 5 years | | | | | | |
| Spirometry / Bodyplethysmography [d] | X | X | | X | | X |
| 6 minute walking distance (meter) [g] | X | X | | X | | X |
| $O_2$-saturation before and after 6MWT | X | X | | X | | X |
| Borg scale [f] | X | X | | X | | X |
| Additionally in ventilated patients [m] | | | | | | |
| Oxygenation index (OI) [n] | X | X | X | X | X | X |
| Duration (h) of mechanical ventilation | X | X | X | X | X | X |
| NO (%), ECLS (VV/VA/ECLA/Flow/time since insertion) | X | X | X | X | X | X |

X* Tests must be done before first drug dosing
X[*2] Test can be done according to the opinion of the treating physician
X[*3] Puncture site should be warm and well perfused[P].
X[*4] Chest x-ray is recommended if clinically indicated e.g. to answer the question if the disease is stable
X[*5] Re-check inclusion criteria 1

X[*6] (since last visit): Healthy / Sick-better / Sick-same / Sick-worse / Patient died

X[*7] Pulmonary exacerbation is defined as sustained worsening of the patient's condition from stable state and beyond normal day to day variations. The exacerbation is rated as indicated below [o].

## ***STOP*** **HCQ block**

Table 1-2

| Visit | Visit 1 + Screening | Visit 2 | Email-/Phone-Visit | Visit 3 | Email-/Phone-Visit | Visit 4 | Email-/Phone-Visit | Visit 5 | Email-/Phone-Visit | Visit 6 | Email-/Phone-Visit | Visit 7 | Email-/Phone-Visit | Visit 8 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Action | „Begin of baseline“ | “End of baseline” + Day 1 of withdrawal treatment | 2 weeks of withdrawal, at home | 4 weeks of withdrawal treatment | 6 weeks of withdrawal, at home | 8 weeks of withdrawal treatment | 10 weeks of withdrawal, at home | “End of trial” after 12 weeks of withdrawal treatment | 2 weeks of open observation at home | Follow up after 4 weeks of open observation | 6 weeks of withdrawal, at home | Follow up after 8 weeks of open observation | 10 weeks of withdrawal, at home | Follow up after 12 weeks of open observation |
| Trial day | -30 to -10 | 1 | 14 (-7, +7) | 28 (-7, +7) | 42 (-7, +7) | 56 (-7, +7) | 70 (-7, +7) | 84 (-7, +7) | 98 (-7, +7) | 112 (-7, +7) | 126 (-7,+7) | 140 (-7, +7) | 154 (-7, +7) | 168 (-7, +7) |
| Demographics (e.g. sex, age) | X | | | | | | | | | | | | | |
| Patient information, informed consent | X | | | | | | | | | | | | | |
| Previous (last 12 months) and concomitant diseases | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Previous (last 3 months) and concomitant treatments | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Inclusion/exclusion criteria | X | X[*5] | | | | | | | | | | | | |
| Pregnancy test [K] | X* | | | X | | X | | X | | | | | | |
| Randomization [a] | X | | | | | | | | | | | | | |
| Trial medication supply to patient | | X | | X | | X | | | | | | | | |
| History (cardiotoxicity, hypoglycaemia) | X | X | | X | | X | | X | | X | | X | | X |
| Physical examination | X | X | | X | | X | | X | | X | | X | | X |
| Vital signs (BP, pulse, temp) [b] | X | X | | X | | X | | X | | X | | X | | X |
| ECG | X* | | | | | | | X | | | | | | X |
| Ophthalmologic review[J] | X* | | | | | | | | | | | | | X[*8] |
| Lab [c] (GOT/GPT/Crea/Potassium/CK/gGT/LDH/BB/DIFF / HCQ drug level, blood glucose) | X* | | | X | | X | | X | | X (only HCQ drug level) | | X (only HCQ drug level) | | X (only HCQ drug level) |
| $pO_2$, $pCO_2$ (capillary) | X | X[*3] | | X[*3] | | X[*3] | | X[*3] | | X[*3] | | X[*3] | | X[*3] |
| $O_2$-sat [e], in room air | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Respiratory rate, in room air | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

| Visit | Visit 1 + Screening | Visit 2 | Email-/Phone-Visit | Visit 3 | Email-/Phone-Visit | Visit 4 | Email-/Phone-Visit | Visit 5 | Email-/Phone-Visit | Visit 6 | Email-/Phone-Visit | Visit 7 | Email-/Phone-Visit | Visit 8 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Retractions | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Coughing | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Oxygen demand [L] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Chest x-ray | X*[2] | | | | | | | X*[4] | | | | | | |
| Pulmonary hypertension (Echo) [j] | X* | | | | | | | | | | | | | |
| Quality-of-life [i] | X* | | | X | | X | | X | | X | | X | | X |
| Health Economics [h] | X* | | | X | | X | | X | | X | | X | | X |
| Weight for height [b] | X* | X | | X | | X | | X | | X | | X | | X |
| Clinical course of lung disease | X*[6] | X*[6] | X*[6] | X*[6] | X*[6] | X*[6] | X*[6] | X*[6] | X*[6] | X*[6] | X*[6] | X*[6] | X*[6] | X*[6] |
| Exacerbation [o] | X*[7] | X*[7] | X*[7] | X*[7] | X*[7] | X*[7] | X*[7] | X*[7] | X*[7] | X*[7] | X*[7] | X*[7] | X*[7] | X*[7] |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Drug accountability | | | | X | | X | | X | | | | | | |
| Additionally in children > 5 years | | | | | | | | | | | | | | |
| Spirometry / Bodyplethysmography [d] | X | X | | X | | X | | X | | X | | X | | X |
| 6 minute walking distance (meter)[g] | X | X | | | | | | X | | | | | | X |
| $O_2$-saturation before and after 6MWT [g] | X | X | | | | | | X | | | | | | X |
| Borg scale [f] | X | X | | | | | | X | | | | | | X |
| Additionally **in ventilated** patients [m] | | | | | | | | | | | | | | |
| Oxygenation index (OI) [n] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Duration (h) of mechanical ventilation | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| NO (%), ECLS (VV/VA/ECLA/Flow/time since insertion) | X | X | X | X | X | X | X | X | X | X | X | X | X | X |

X* Tests must be done before first drug dosing
X*2 Test can be done according to the opinion of the treating physician
X*3 Puncture site should be warm and well perfused[P]
X*4 Chest x-ray is recommended if clinically indicated e.g. to answer the question if the disease is stable
X*5 Re-check inclusion criteria 1
X*6 (since last visit): Healthy / Sick-better / Sick-same / Sick-worse / Patient died
X*7 Pulmonary exacerbation is defined as sustained worsening of the patient's condition from stable state and beyond normal day to day variations. The exacerbation is rated as indicated below [o]

X*8 This ophthalmologic investigation may be used for patients entering the START block, if START HCQ block is done within 6 months and no HCQ was taken since end of STOP block and the ophthalmological investigation was normal.

[a] Randomization must occur for logistic reasons as soon as possible after concluding all screening investigations and including the patient into the study. This secures delivery of the study medication in time to any study center.

[b] Weight (kg) and height (cm) will be measured with shoes and clothes off. Vital signs will be collected after the patient has been at rest for 5 minutes.

[c] Blood sample should include: Blood count with differential, GOT, GPT, gGT, Creatinine, LDH, Potassium, Creatine kinase, blood glucose.
HCQ drug level (2 ml EDTA blood and 2 ml of Serum blood). Labor Manual will be provided.

[d] Spirometry / Bodyplethysmography will be performed pre-bronchodilator in children age ≥ 5 years. (If a child ≤ 5 years is already able to perform the listed investigations (spirometry or bodyplethysmography), these should also be performed and documented at the discretion of the investigator) The following lung function parameters will be assessed: FEV1 % predicted (recorded in L), FEV 1 (L), FVC % predicted (recorded in L), FVC (L); MEF 75 (L/s); MEF 50 (L/s); MEF 25 (L/s); TLC (L); ITGV (L); RV (L); R eff (kPa*s/L); R eff predicted (%). SOP will be provided.

[e] Measurement of $O_2$-Saturation, respiratory rate and $O_2$ flow (if necessary) in awake patient at rest:

If not on $O_2$: after 5 min at rest, room air, then measure twice over 1 min. each; the measurements have to be at least 1 min. apart; report the stable average value

If on $O_2$:

- BEFORE withdrawal (after 5 min at rest with steady state $O_2$ supplement, measure over 1 minute)
- Then withdraw $O_2$ to obtain steady state $O_2$-Sat. in room air (at least 30 seconds without change). Then measure twice over 1 min. each; the measurements have to be at least 1 min. apart; report the stable average value. If the $O_2$-Sat falls below $SpO_2$<80% place back in oxygen and note as exact value.

Document the time of measurement and state of the patient, usually "awake, at rest". Note: In babies avoid crying, eating, sleeping during measurement.
Note: try to schedule patients at similar time of the day.

[f] Borg-Scale: assessment of dyspnea (0 – 10: 0 = no dyspnea at all, 5 = severe dyspnea, 10 = extremely severe dyspnea)

[g] Standard exercise testing (6-minute-walk test): SOP will be provided

[h] Health economics assessment with the use of a special questionnaire which has to be filled out by the parents or adult patients.

[I] Quality of Life assessment with the use of the questionnaire PedsQL for different age groups which has to be filled out by parents and/or patients

[j] For Electrocardiography (ECG), ophthalmological review and Echocardiography (Echo) please see Chapter 5. If a routine ophthalmological examination was done within 3 month before Visit 1, no additional ophthalmological exam is required.

[k] Pregnancy test only has to be performed in girls of childbearing age and only if sexual relations are known or probable. It is at the discretion and responsibility of the attending physician to decide, whether a pregnancy test is necessary or not. The pregnancy test can be performed in the urine or serum.

[L] The following parameter will also be assessed, if there is **oxygen demand**:
1. O2 via nasal cannula or via face mask: O2-Flow (l/min)
2. on high-flow nasal cannula: Flow air (l/min), O2-Flow (l/min), FiO2

[m] The following parameter will also be assessed on ventilation: ventilation method, duration of ventilation (hours/day/only for non-invasive ventilation), PEEP ($cmH_2O$), $P_{IP}$ ($cmH_2O$), $F_iO_2$, $T_i$ (sec), $M_{PAW}$ ($cmH_2O$) and Oxygenation Index (OI);
In addition, if patients on the heart lung machine (e.g. NO (%), ECLS (VV/VA/ECLA), Flow/time since insertion) will be documented descriptively.

[n] Calculation of Oxygenation Index (OI): $OI = (F_iO_2 * M_{PAW})/P_aO2$
with $M_{PAW}$ = ((frequency * inspiration time)/60) * ((inspiratory pressure ($P_{IP}$) – PEEP) + PEEP))) ; If PaO2 is not available, PcapO2 can be used.)

[o] Start date, End date, Patient returned to baseline function? Y/N
1. Increase in respiratory rate? Y/N/not done.
2. Increase or development of dyspnea ? Y/N
3. Newly developing or increased abnormalities on chest imaging ? Y/N/not done
4. Onset/increase of oxygen demand to attain the individual baseline saturation ? Y/N
5. Need for an additional level of ventilatory support (in addition to oxygen) ? Y/N
6. Decrease in lung function in children able to perform the tests? Y/N/not done. Give before and after FEV1 (% predicted) _____, FVC (%)_____
7. Reduced exercise tolerance (history or in tests)? Y/N

Additional info: 1. Was the patient hospitalized? Y/N, 2. New feeding problem? Y/N, 3. New failure to thrive/weight lost? Y/N, 4. Was there a change in treatment ? Y/N

Cause/trigger (multiple selection possible), 1. Infection? Y/N, 2. Exposure to environmental irritant? Y/N, 3. Aspiration ? Y/N, 4. Extra-pulmonary processes? Y/N, 5. Changes of treatment prior worsening? Y/N, 6. Poor treatment adherence ? Y/N, 7. Side effect of current medication? Y/N, 8. Psychosocial factors? Y/N. 9. Other? Y/N. Give detail:_____

[P] Capillary blood sample is obtained by the use of a warm, moist towel at a temperature not higher than 42 °C on a puncture site not longer than three to five minutes or use of other vasodilator agent (e.g. Finalgon). Puncture site: Fingertip is recommended (rarely ear lobe or in neonates/infants, heel). If an arterial sample is available, this can substitute the capillary sample.

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# 1 INTRODUCTION

## 1.1 Scientific background

The problem

Interstitial lung disease in children (chILD) is a very rare condition. It is a group of over 200 different entities that affect the parenchyma of the lung and lead to a chronic lung disease. The natural course of many of these diseases is connected to a high morbidity and mortality. Often the children are dependent on oxygen for a long period of time or demand mechanical ventilation (Griese 2009).

No successfully proven pharmacological treatments are available up-to-date. The symptomatic treatment in general consists of oxygen supplementation if necessary, adequate nutrition adapted to the high energy demand due to the increased breathing effort, as well as immunization against respiratory pathogens to prevent exacerbations through respiratory infections.

The current pharmacological treatment regimens are mainly dependent on the treating physician's expertise. Common treatment options include the treatment with steroids, hydroxychloroquine (HCQ) and macrolide antibiotics. All three substances are often used in chILD, although so far no controlled study has shown a benefit. In some cases treatment consist of other agents such as azathioprine, cyclophosphamide, cyclosporine or methotrexate (Clement 2010).

## 1.2 Trial rationale

The impact

So far, there exist no controlled studies to evaluate the efficacy of the different treatment options in chILD. In practice beside steroids hydroxychloroquine and macrolide antibiotics are often used drugs for the treatment of chILD (Clement 2010).

Due to the rareness of the diseases only international studies can collect sufficient numbers of patients. Therefore we will use the European wide project on chILD, the chILD-EU project, to implement a randomized controlled study to evaluate the pharmacological treatment of chILD.

This international study will address all these issues and will help to create new knowledge for everyday care in this broad group of pediatric interstitial lung diseases.

With this study we aim to

- Evaluate the efficacy of hydroxychloroquine against placebo in chILD
- Evaluate the safety of mid-term use of hydroxychloroquine
- Be able to make a decision on the risk and benefit of the use of hydroxychloroquine
- Help standardizing the pharmacological treatment of chILD

Currently HCQ is used off-label in a wide range of clinical severity, ranging from respiratory insufficiency to minimal respiratory symptoms. So far it is not predictable which patients will respond to the treatment and which will not. Due to this fact and due to the rareness of the diseases the goal of this exploratory study is to include patients with different symptoms and a wide range of clinical severity to sample as much information about this topic as possible to improve the treatment of this group of patients. Therefore, the character of this study is explorative and not confirmative.

## 1.3 Treatments and rationale for dose selection

Pharmacological treatment of chILD – literature review

Performing a literature review concerning the pharmacological treatment of chILD we found only case reports and small series. There exist no standards for the pharmacological treatment of patients with chILD, as well as randomized controlled studies are lacking (Bush 2009).

The majority of patients have been treated with steroids alone or in combination with other medication. The positive effect of steroids in chILD is mainly presumed to be related to their immunosuppressive effect. In practice there are two common ways of steroid therapy. They can either be given as steroid pulse therapy or as long term oral administration over weeks and sometimes months, sometimes the two therapies are combined (Benedictis 2012). The main problem with the steroid therapy is that there are many dose dependent side effects, especially if given over a long period of time. To reduce the dose of steroids, they are often combined with one of the other anti-inflammatory medications mentioned above.

To evaluate the use of hydroxychloroquine till now, we made a literature research to summarize all previously described cases of chILD starting from year 1984 that were treated with hydroxychloroquine alone or in combination with other drugs. We found 83 cases of chILD that were treated with chloroquine (CQ) or HCQ. Outcome from this treatment was very variable from case to case. There are reports about cases that were resistant to the treatment with steroids and responded very well to hydroxychloroquine. But there are also several cases that apparently did not benefit from the treatment with hydroxychloroquine. So far it is not possible to predict, which patient will benefit from the treatment with hydroxychloroquine and which will not.

The dose given ranged from 3.5 – 10 mg/kg bw/d. In this context it is notable, that there exist two pharmaceutical forms of hydroxychloroquine, the hydroxychloroquine-base and the hydroxychloroquine-sulfate; the correction factor is 200 mg Sulfate = 155 mg Base. The majority of case reports and small series did not indicate which of the two pharmaceutical forms the dose is referring to. In Germany, the common pharmaceutical form is the hydroxychloroquine sulfate and the dose given in chILD is 10 mg/kg bw/d. After extensive discussion with the German competent authorities (BfArM) and the European group of experts, on the basis of available safety data available and possible efficacy, a dose of 6.5 mg/kg b.w./d, after an initial week of treatment with 10 mg/kg b.w./d, was selected for the START study. In the STOP block, the individual dosage, a patient was on until enrollment, should be continued.

Pharmakokinetic
The half-life of HCQ is 30 to 60 days, the protein binding is 63% and the oral bioavailability is 74%. Kinetic and pharmacological effect and metabolism of chloroquine and hydroxychloroquine are quite similar. After oral application HCQ is resorbed quickly and nearly completely. The maximum drug level is achieved about 4 hours after the application. Elimination exists of two parts. The rapid elimination has a half-life of three days. The second part is a slow elimination from the deeper body compartments with a half-life of 18 days. The half-life is dependent on the dose and is lengthened by very high drug levels. Excretion goes mainly via the stool and only to a smaller part via the kidney.
Studies concerning the carcinogenicity have not been found in literature. There have been studies that analyzed the risk of HCQ during pregnancy. The authors concluded that the treatment with HCQ during pregnancy is without elevated teratogen risk (Diav-Citrin O, 2013).

## 1.4 Summarized risk-benefit assessment

The need for a trial:
So far for children with chILD no randomized or controlled trials have been performed. As almost each individual symptomatic child is empirically treated with the entire spectrum of potential drugs, we urgently need to clarify which patients, and if any at all, might benefit from this treatment and which will not. This is necessary to improve the everyday care, and to direct treatment of the patients with the chILD. Such knowledge will also reduce treatment burden in children who are treated despite the fact that this might not be effective.

As the type of diseases investigated in this trial, as well as the course of the diseases and the effects of the drug are not sufficiently similar in adults and pediatric patients, pediatric effectiveness

cannot be extrapolated from studies in adults. Almost all disease in question are unique to infants and children. Thus studies in adults cannot (and do not) exist, as type and course of diseases is specific for children. Thus the studies must be done in the population primarily affected by the diseases (chILD). In other settings no relevant results can be expected.
The clinical research interventions and procedures planned represent an appropriate balance of risk and potential benefit. Specific protections were implemented to ensure adequate protection for minors, including parental permission and assent of able children, assurance of direct benefit for the child or for the group of patients with the particular condition, and minimization of risk. The risks to which the children are exposed are low, both compared to the potential therapeutic benefit and the risk of the disease. Due to the cross-over design of the START trial, the children are neither placed at a disadvantage by being enrolled, nor failing to get necessary health care.

The additional burden put on the children from participation in the study is minimal. Except for a sample for HCQ blood level measurements, no investigations or tests are performed which would not be performed outside the study setting, including ophthalmological investigation (Chapter 5.1), liver function tests, ECG testing (Chapter 5.2). Special thresholds cannot be given as they are heavily dependent on the initial condition and co-morbidities of the child. Any significant deviation from baseline (usually > 2 fold upper limit of normal) will be reported as adverse event. These data are monitiored systematically according to the protocol (Chapter 7) and the infants and children are very closely monitored by their physicians who decide withdrawal from the study depending on the condition of the subject.

Summarized medical risk-benefit assessment:

In clinical practice HCQ is very frequently used in almost any patient with chILD at one or more occasions. Clear positive clinical improvements, usually occurring within 4 weeks, have been reported in 15 of 16 cases, when HCQ was given alone, and in 37 of 53 cases, when given in combination with glucocorticosteroids. Thus almost any child with a symptomatic form of chILD is treated with HCQ based on an empirical base.

The application, also for prolonged, uncontrolled periods over years, were obviously save with very few, if any reported side effects during off-label usage. Of course a significant underreporting may be associated; however from other conditions and situations, in which the drug was used for a very prolonged time, including pregnancy and rheumatologic disease at significant higher frequency application was apparently safe and without major side effects even if given over a long period of time. Appropriate baseline testing (ophthalmologist, liver function values, blood count, electrolytes) is recommended before starting treatment to obtain baseline values. Subsequent examinations are at the discretion of the ophthalmologist, routine blood monitoring is not required.

Hydroxychloroquine may have potential for several side effects such as i.e. retinal changes and abdominal pain. The retinal changes are dose dependent and can be irreversible. In the 83 case reports of chILD that were treated with either chloroquine or hydroxychloroquine, there were only three cases in which retinal changes were reported. All three patients with retinal changes were treated with chloroquine over periods between 20 months and 9 years. In the case reports we retrieved, no retinal changes were reported in patients that received hydroxychloroquine. In one series of patients, who received hydroxychloroquine, abdominal pain in the first week of treatment with hydroxychloroquine was reported in a minority of cases. So the risk for major side effects seems to be much lower with the use of hydroxychloroquine instead of chloroquine. There are several case reports, where the patients received hydroxychloroquine safely over years.

As it is not clear, if HCQ works in these conditions at all, a placebo controlled design is justified. The selected duration of the placebo phase was the result of a delphi questionnaire among European pediatric pneumologists and balanced the anticipated time point, when a treatment effect could be noted in a majority of patients if present, and the time period tolerated to withhold the drug from a placebo treated subject.

So we think, that in a patient with relatively stable disease it is justifiable to start the treatment with the study drug in the placebo arm four weeks later than in the study drug arm without relevant disadvantage for the patient, as till now we don't even know, if he will benefit from the pharmacological treatment or not. Due to this fact, we believe, that all patients should receive HCQ at one point during the study to avoid that patients who might benefit from the treatment with HCQ are not treated.

Due to the heterogeneity of the diseases with a wide spectrum of clinical symptoms and severity it is not possible to determine one specific HCQ treatment duration that will fit the majority of subjects. Physicians anticipate treatment of some patients that will be treated with HCQ only for some weeks and patients that will need HCQ treatment for several years. Due to the variety of conditions and our intention to be as inclusive as possible in this exploratory trial, we decided not to determine the time period patients are treated between the start and stop treatment with HCQ. However, we took the chance to investigate stopping HCQ in a double blind, placebo controlled fashion. As with longer treatment and the intention to terminate treatment the exact time point to stop the treatment does not matter, we suggest a placebo-controlled withdrawal of active drug. In this stop block patients on active drug are randomized in a blinded manner to either continue for three more months with their active treatment or to receive placebo.

In summary the risk of major side effects in these already often used pharmacological treatments as well as the risk of giving placebo instead of the study drug seems acceptable regarding the gain of useful knowledge and the possibility to create adequate treatment strategies for chILD.

# 2 TRIAL OBJECTIVES

## 2.1 Primary objective

The primary objective of the trial is to investigate the following:

***START* HCQ block**

To evaluate the efficacy of HCQ after 28 days of treatment in chILD compared to placebo.

***STOP* HCQ block**

To evaluate the efficacy of HCQ after 84 days of treatment in chILD compared to placebo.

## 2.2 Secondary objectives

Secondary objectives of the study are:

***START* HCQ block**

- To evaluate the efficacy of HCQ after 56 days of treatment in chILD compared to 28 days.
- To evaluate the safety of HCQ after 28 and 56 days of treatment in chILD.
- To evaluate blood levels of HCQ after 28 and 56 days of treatment in chILD.

***STOP* HCQ block**

- To evaluate the efficacy of chronic (> 3 months) HCQ treatment in chILD compared to placebo.
- To evaluate the safety of HCQ after > 3 months of treatment in chILD.
- To evaluate blood levels of HCQ before and after treatment in chILD.

# 3 TRIAL DESIGN

This study is an explorative, prospective, randomized, double-blind, placebo controlled investigation of hydroxychloroquine (HCQ) in pediatric ILD. The treatments are organized in START and STOP blocks, which can be initiated in sequence, as needed by the subjects. Each patient can participate in each block only once. In the START block subjects are randomized to parallel-groups, then the placebo group is switched to active drug. In the STOP block, subjects on HCQ are randomized into parallel-groups treated with placebo or HCQ to investigate the withdrawal of HCQ for assessment of its efficacy.

## 3.1 Trial duration and schedule

The duration of this trial is expected to be at least 36 months. The subject recruitment started in Q4 2015 and should last as long as possible, at least till the end of the chILD-EU project or longer if possible. The actual overall trial duration or subject recruitment period may vary from this time period.

## 3.2 Number of subjects

It is planned to assess >100 subjects for eligibility and to allocate 80 subjects. Recruitment and treatment of subjects is expected to be performed in up to 100 trial centres. We expect an equal distribution between START and STOP blocks.

## 3.3 Primary outcome parameters

***START* HCQ block**
Relative change trial day 1 (i.e. Visit 2) through day 28 (i.e. Visit 3) and relative change day 28 to day 56, (i.e. Visit 4): change active compound compared to change placebo

***STOP HCQ block***
Relative change trial day 1 (i.e. Visit 2) through day 84 (i.e. Visit 5): change active compound compared to change placebo

Oxygenation
As respiratory condition is also dependent on the support given to the patient this needs to be taken into consideration when assessing oxygenation. Therefore parameters to be measured were defined depending on the patient´s condition (Table 3.3-1). How to analyse these variables statistically is detailed in section 8.

Tab 3.3-1: Oxygenation - specific measurements used to determine, depending on Patient´s condition

| Patient's condition | Measured parameters | Assessment |
|---|---|---|
| In room air | In room air<br>O2 Saturation (mean value)<br>Respiratory rate (mean value) | After 5 min at rest room air, then measure twice over 1 minute each, at least 1 min apart |
| On O2-supplement | In room air<br>O2 Saturation (mean value)<br>Respiratory rate (mean value) | Before O2-withdrawal take same parameters, after 5 min withdraw O2 and obtain steady state O2 Sat in air. Steady state minimum SpO2 should be at least 30 seconds without change. Then measure twice, over 1 minute each, at least 1 min apart. If SpO2 falls below 80%, place back on oxygen. |
| On high- | O2-flow, air-flow | After 5 min stable rest measure twice over 1 minute |

| | | |
|---|---|---|
| flow nasal cannula | | each, at least 1 min apart |
| Ventilated | Oxygenation index | OI = (FiO2* $M_{PAW}$)/PaO2; with FiO2 = Fraction of inspired oxygen;<br>$M_{PAW}$ = Mean airway pressure (= ((frequency * inspiration time)/60) * ((inspiratory pressure (PIP) – PEEP) + PEEP)))<br>PaO2 = Partial pressure of oxygen in arterial blood |

## 3.4 Secondary outcome parameters

For both, ***START* and *STOP* HCQ blocks** absolute and relative change under the active compound from trial day 1 (i.e. Visit 2), to START block: day 28 (i.e. Visit 3), STOP block: day 84 (i.e. Visit 5) each, will be compared to change under placebo. The following variables will be investigated:

Oxygen saturation ($O_2$-sat, in room air) (only absolute, as relative already primary outcome)
Respiratory rate (RR, in room air) (relative and absolute)

Retractions (yes/no)
Coughing (yes/no)
Oxygen demand

$pO_2$, $pCO_2$ (capillary, in room air)
Chest x-ray
Quality-of-life
Health economics
Overall survival
Weight for height
Cumulative amounts of steroid equivalents. Clinical course of lung disease (since last visit): Healthy/ Sick-better/ Sick-same/ Sick-worse/ Patient died
Pulmonary exacerbation (since last visit)
If > 5y old (If a child ≤ 5 years is already able to perform the listed investigations (spirometry or bodyplethysmography), these should also be performed and documented at the discretion of the investigator.)
The following lung function parameters will be assessed:
FEV1 % predicted (recorded in L), FEV 1 (L), FVC % predicted (recorded in L), FVC (L); MEF 75 (L/s); MEF 50 (L/s); MEF 25 (L/s); TLC (L); ITGV (L); RV (L); R eff (kPa*s/L); R eff predicted (%).
➔ reference values according to the GLI 2012 lung function regression equations

6 minute walking distance (meter)
$O_2$-saturation before and after 6MWT
Borg scale

If ventilated:
Duration (h) of mechanical ventilation
NO (%), ECMO yes/no, if yes VA/VV, double lumen vs. single lumen, Flow-rate.

**Safety monitoring**
Adverse events, clinical laboratory values (GOT, Creatinine, gGT, blood count, differential, LDH, potassium, steady state drug level), ECG, ophthalmologic review

## 3.5 Measures taken to minimize/avoid bias

### *3.5.1 Randomization*

Patients will be allocated to the two treatments, i.e., oral hydroxychloroquine and placebo, in a ratio of 1:1 by central randomization within each age group.

The age-matched stratification will be performed according to 2 age groups defined as infants > 3 Wks, < 2 y and the age category Children > 2 y, because of an anticipated skewed frequency distribution of cases, the older ones being less frequent.

The randomization procedure will not consider the sex of the patients, since no sex-specific responses to HCQ therapy have been reported yet and are not expected. The randomization list will be generated by an independent institute using a validated system, which involves a pseudo-random number generator to ensure that the resulting treatment sequence will be both reproducible and non-predictable.

Only patients who participate in the chILD EU register can be included in the HCQ study. Inclusion in the chILD EU register and in the HCQ study can be performed at the same day.

Patients will not receive a distinct HCQ patient number. The HCQ patient number corresponds to the respective patient number of the chILD EU register.

At screening, each patient to be included will receive the next consecutive random/ patient number from a block of randomization numbers per age group. Study medication will be packed and blinded according to the random list. Each patient medication box will be sent together with the sealed unblinding codes (i.e. envelopes) to the sites. The investigator has to take care that each patient will be provided with the study medication box bearing the correct randomization number.
The randomization list is to be kept confidential and is only accessible to authorized personnel until the code is broken. At the end of the trial, any emergency opening of the envelopes will be controlled after collecting the explanations for unblinding and checking the unused treatment units. The code will be broken regularly only at the end of the study after freezing the statistics database (by checking the data, recording any protocol violations etc.) allowing the collected data to be analyzed.

The randomization list will be kept in safe and confidential custody.

### *3.5.2* Blinding

Blinding will be achieved by providing the study-specific HCQ-powder/substance and placebo-powder/substance in appropriately covered capsules to keep the content not visible both for the two study drugs hydroxychloroquine and placebo.

In the case of a medical emergency requiring identification of the treatment taken by the patient, the investigator has the right to open the respective envelope, but every effort should be taken to avoid unblinding of patients except the information will be needed for the emergency treatment. Opened envelopes have to be signed, dated and the reason for unblinding has to be documented. The envelope has then to be filed in the ISF and the sponsor and/or the responsible monitor has to be informed. Unblinded patients have to be withdrawn from the study. No other reason than an emergency may justify unblinding. After unblinding the investigator must also note the date, time and reason in the case report form.

## 3.6 Selection and withdrawal of subjects

### *3.6.1 Inclusion criteria*

For block specific inclusion criteria please see synopsis.
Subjects meeting the block specific inclusion criteria and all of the following criteria will be considered for admission to the trial:

| | |
|---|---|
| 1. | Patients should be clinically stable during baseline (between Visit 1 and 2) for inclusion into the study<br>a) To determine this, attending physicians can use $SpO_2$ in room air for patients on room air or on $O_2$-supplement; the absolute difference on $SpO_2$ is expected not to be ≥ 5% between Visit 1 and 2. For patients on respiratory support, the summary key parameters should not change ≥ 20% between Visit 1 and 2<br>and |
| | b) No major changes in other medications between Visit 1 and 2 |
| 2. | Mature newborn ≥ 37 weeks of gestation, age ≥ 3 wks and < 2y<br>or<br>Infants and children (≥ 2 y and < 18 y)<br>or<br>Adults (≥18 and ≤30 y)<br>or<br>Previously preterm (≤ 37 weeks of gestation) babies or children and adults of all ages if chILD genetically diagnosed (see inclusion criterion 3.) |
| 3. | Diagnosis of chronic (≥ 3 wks of duration) diffuse parenchymal lung disease (DPLD = chILD), defined in at least one of the following ways: |
| | **a) chILD genetically diagnosed**<br>Surfactant dysfunction disorders including patients with mutations in SFTPC, SFTPB, ABCA3, TTF1 (Nkx2-1), further extremely rare entities with specific mutations, for example in TBX4, NPC2, NPC1, NPB, COPA, LRBA and other genes. In this case, also previously preterm (≤ 37 weeks of gestation) babies or children and adults of all ages can be included into the study. |
| | **b) chILD histologically diagnosed**<br>• Chronic pneumonitis of infancy (CPI)<br>• Desquamative interstitial pneumonia (DIP)<br>• Lipoid pneumonitis / Cholesterol pneumonia<br>• Nonspecific interstitial pneumonia (NSIP)<br>• PAP after the exclusion of mutations in GMCSF-Ra/b and GMCSF autoantibodies*<br>• Usual interstitial pneumonia (UIP)<br>• Follicular bronchitis/ bronchiolitis/ Lymphogenic interstitial pneumonia (LIP)<br>• Storage disease with primary pulmonary involvement (e.g. Nieman Pick)<br>• Hermansky Pudlak Syndrome<br>• Idiopathic pulmonary haemorrhage (haemosiderosis)*<br>• Other histology diagnosing chILD, in particular combination of the above pattern, but not exclusively |
| 4. | Start block: no HCQ treatment in the last 12 weeks |

| | |
|---|---|
| | Stop block: stable HCQ treatment for at least the last 12 weeks |
| 5. | Ability of subject or/and legal representatives to understand character and individual consequences of clinical trial. |
| 6. | Signed and dated informed consent of the subject (if the subject has the ability) and the representatives (of underaged children) must be available before start of any specific trial procedures. |

*may be diagnosed in the absence of a lung biopsy by characteristic lung lavage cytology (PAS stain, Fe stain), CT pattern or autoantibodies (gliadin, endomysium; cANCA) and clinical course.

### *3.6.2 Exclusion criteria*

Subjects presenting with any of the following criteria will not be included in the trial:

- chILD primarily related to developmental disorders
- chILD primarily related to growth abnormalities reflecting deficient alveolarisation
- chILD related to chronic aspiration
- chILD related to immunodeficiency
- chILD related to abnormalities in lung vessel structure
- chILD related to organ transplantation/organ rejection/GvHD
- chILD related to recurrent infections
- Acute severe infectious exacerbations
- Known hypersensitivity to HCQ, or other ingredients of the capsules (lactose-monohydrate, povidone, maize starch, magnesium stearate, hypromellose, macrogol or titanium dioxide (E 171), silicon dioxide or mannitol), to sucrose-octaacetate or sodium saccharine.
- Proven retinopathy or maculopathy
- Glucose-6-phosphate-dehydrogenase deficiency resulting in favism or hemolytic anemia
- Myasthenia gravis
- Hematopoetic disorders
- Pregnancy and lactation (Women with childbearing potential have to practice a medically accepted contraception during trial and till three months after the end of the treatment with HCQ, and a negative pregnancy test (serum or urine) should be existent on Visit 1, if girls of childbearing age and only if sexual relations are known or probable. It is at the discretion and responsibility of the attending physician to decide, whether a pregnancy test is necessary or not. Reliable contraception are systematic contraceptives (oral, implant, injection). Women that are sterile by surgery can participate in the trial. At the discretion of the investigator, sexual abstinence is also accepted as contraceptive method. Girls after menarche have to receive a counselling about birth control methods in presence of at least one parent, which has to be documented in the patient notes.
- Participation in other clinical trials during the present clinical trial or not beyond the time of 4 half-lives of the medication used, at least one week.
- Hereditary galactose intolerance, lactase deficiency or glucose-galactose-malabsorption
- Renal insufficiency at screening, defined as glomerular filtration rate (GFR)
    - < 40 mL/min/1.73 $m^2$ in patients age 3 to 8 weeks
    - < 60 mL/min/1.73 $m^2$ in patients ≥ 8 weeks of age

  (KDIGO guideline 2012, K/DOQI guideline 2002)
- Liver disease, gastrointestinal disorder, haematological disorder, epilepsy or other neurological disorder, psoriasis, porphyria at the discretion of the treating physician
- Simultaneous prescription of other potentially nephrotoxic or hepatotoxic medication at the discretion of the treating physician

### *3.6.3 Withdrawal criteria*

Subjects or/and representatives can withdraw their consent at their own request without given reasons at all time during the trial. This should be without disadvantages for the subject. However the investigator should try to perform a final visit to get concluding findings of investigation.

Subjects may be withdrawn from the trial for the following reasons

- At their own request or at request of the legal representative.
- At the instigation of the sponsor. If, in the investigator's opinion, continuation of the trial would be detrimental to the subject's well-being.
- For women, if it becomes known that the subject is pregnant.
- Aggravation of disease with life threatening events
- Severe side effects (for example retinopathy, cardiomyopathy, ECG-modifications, liver value elevation)
- The subject/ patient is non-compliant or uncooperative
- The subject/ patient is not able to participate due to an Adverse Event
- The subject/ patient has to take any concomitant drugs interfering with the study medication
- The subject/ patient is no longer able to participate for other medical reasons (*e.g.*, surgery, other diseases, or death)

The investigator decides about withdrawal of subjects from the clinical trial in case of occurrence of criteria mentioned above.

In all cases, the reason for withdrawal must be recorded in the CRF and in the subject's medical records. In case of withdrawal of a subject at his/her own request, as far as possible the reason should be asked for and documented. The subject must be followed up and as far as possible; all examinations scheduled for the final trial day should be performed and documented and all trial medication should be collected at site.
All on-going serious adverse events of withdrawn subjects have to be followed up see 7.3.

Withdrawn subjects will not be replaced.

### *3.6.4 Premature closure of the clinical trial*

The whole trial may be discontinued at the discretion of the sponsor, e.g. for following reasons:

- New risks for subjects become known.
- Inefficacy of the trial medication becomes evident.
- Occurrence of AEs unknown to date in respect of their nature, severity, and duration or the unexpected increase in the incidence of known AEs.
- Medical or ethical reasons affecting disadvantageous the continued performance of the trial.
- Difficulties in the recruitment of subjects.
- The time schedule cannot be met (e.g., more than doubling of recruitment time)
- The sponsor and the investigator decide to discontinue this study because of failure to meet expected goals

The ethic committees (EC) and the competent authorities must then be informed. Should the trial be closed prematurely, all trial material must be returned to or fetched by the monitor.

# 4 TRIAL TREATMENTS

## 4.1 Investigational treatments

### *4.1.1 HCQ*

#### 4.1.1.1 General information about investigational medicinal product (IMP)

International non-proprietary name (INN): hydroxychloroquine
Formulation: Mannitol, Lactose-Monohydrate, Povidon (MW: ca. 25 000), maize starch, Magnesium stearate (Ph. Eur.), Hypromellose, Macrogol (4000), Titanium dioxide (E 171), Silicon dioxide, Sodium saccharine. Capsule
Manufacturer: University Hospital Munich, Pharmacy, Marchioninistrasse 15, 81377 Munich, Germany.

#### 4.1.1.2 Therapeutic effects

Hydroxychloroquine is an anti-malarial quinolone, which is used in rheumatologic disease as well as in interstitial lung disease. Its mechanism of action in interstitial lung disease is not yet understood. It is believed to change intracellular pH of organelles and affects trafficking of proteins through the cells. Several case reports of children with chILD describe the benefit of hydroxychloroquine either in combination with steroids or alone. This benefit was an improvement of the respiratory condition. In some cases treatment with hydroxychloroquine was successful even after the failure of treatment with steroids.

#### 4.1.1.3 Known important side effects

Side effects:

Hydroxychloroquine is considered to be a very safe drug. Nevertheless there is a low risk for several known side effects. The most important side effect is the change of vision.

The incidence of hydroxychloroquine-induced retinopathy is very low with only 2 cases of a series of 400 patients developing irreversible retinopathy, both after having taken maximum dose (400mg) for 6 years. The maximum dose and duration of treatment both appear to have the most impact on the development of retinopathy. Quinolones may also precipitate in the cornea- however this is much less common with hydroxychloroquine than chloroquine.

Further known side effects are

- Gastrointestinal disturbance - nausea, diarrhea, anorexia abdominal cramps.
- Headache
- Skin reactions - rash, pruritus. Rarely pigmentary changes, bleaching of hair and hair loss.
- ECG changes (especially conduction disorders (bundle branch block / atrio-ventricular heart block) as well as biventricular hypertrophy)
- Heart failure, cardiomyopathy in individual cases leading to death
- Severe hypoglycaemia with loss of consiousness
- convulsions
- ototoxicity
- Blood disorders, psychological disturbance, sensomotoric disorders, extrapyramidal disorders, myopathy, Steven Johnson syndrome, acute generalized exanthematous pustulosis, exfoliative dermatitis, photosensitivity, hepatic damage

(according to BSPAR guidance for hydroxychloroquine, October 2010 and Fachinformation Quensyl® January 2017)

For more detailed information please read the current country specific Summary of Product Characteristics of Hydroxychloroquinsulfate (SmPC).

#### 4.1.1.4 Dosage schedule

Start HCQ block
During trial: Hydroxychloroquine Sulfate (HCQ) in a loading dose of 10 mg/kg bw/d, p.o., one daily dose in the evening for 7 days, then reduction to 6,5 mg/kg bw/d; the maximum daily dose is 400mg.

Stop HCQ block
Individual dose, usually Hydroxychloroquine Sulfate (HCQ) 6 - 10 mg/kg bw/d, p.o., one daily dose in the evening; the maximum daily dose is 400 mg. The dose, on which the patient is included into the trial, should be continued for the duration of the trial.

#### 4.1.1.5 Overdose instructions

Symptoms of an overdose with hydroxychloroquine are headache, visual changes, seizures, hypokalaemia, cardiac arrhythmias (inclusive elongation of the QT-interval, Torsade de pointes, ventricular tachycardia, ventricular fibrillation) and cardiovascular failure. This can occur suddenly and can lead to death. As these symptoms can occur shortly after the overdose, an immediate medical treatment is necessary.
There exist no specific antidotes against hydroxychloroquine. In case of an overdose the stomach should be emptied by induced vomiting or gastric lavage. If the time point of overdose is less than 30 minutes ago, active coal - administered via gastric tube after the gastric lavage - can reduce further resorption of hydroxychloroquine. If necessary a support of pulmonary and cardiovascular function must be provided, e.g. adrenalin. Seizures have to be treated by benzodiazepines (diazepam), phenobarbital or if necessary by peripheral muscle relaxants and invasive ventilation. The cardiotoxicity of hydroxychloroquine can be reduced by the administration of parenteral diazepam. Haemodialysis is not suitable. Possibly a hypokalaemia has to be treated.
If the acute phase is over and the patient remains without any symptoms a strict monitoring for at least 6 hours is necessary.
(According to Fachinformation Quensyl®, January 2017)

For overdose instructions please refer also to the current country specific Summary of Product Characteristics of Hydroxychloroquinsulfate (SmPC).

### *4.1.2* Placebo

Formulation: Mannitol, Maize starch, Silicon dioxide, Sucrose octaacetate, Sodium saccharine.
Capsule
Manufacturer: University Hospital Munich, Pharmacy, Marchioninistrasse 15, 81377 Munich, Germany.

Warnings and precautions for placebo capsules: Patients with hypersensitivity against one of the ingredients of placebo (see formulation) should not take the placebo capsules.

### *4.1.3* Treatment assignment

The trial medication will be administered only to subjects included in this trial. Subjects withdrawn from the trial retain their identification codes. New subjects will always receive a new identification code.

### *4.1.4* Treatment after the end of the trial

Treatment after the end of the trial is at the discretion of the investigator.

### *4.1.5* Packaging and labelling

The trial medication will be labelled according to EU-GMP Annex 13.

The trial medication will be packed by pharmacy university medical centre Munich.

### *4.1.6* Drug distribution to subjects

For all patients capsules with individual, body weight adjusted drug or placebo will be manufactured and shipped by the pharmacy within a week to the site for distribution to the patients or their caregivers. No adjustments of dose are necessary throughout the trial, as all patients will receive their body adjusted dose from the beginning.

### *4.1.7* Drug storage, supplies and accountability

The investigator will take inventory and acknowledge the receipt of all shipments of the trial medication. All trial medication must be kept in a locked area with access restricted to designated trial staff. The trial medication must be dryly stored in accordance with manufacturer's instructions. The investigator will also keep accurate records of the quantities of trial medication dispensed, used, and returned by each subject on the drug accountability form. The site monitor will periodically check the supplies of trial medication held by the investigator to verify the correct accountability of all trial medication used. At the end of the trial, all unused trial medication and all medication containers will be disposed by the trial center according to the local regulations. It will be assured that a final drug accountability report is prepared and maintained by the investigator.

### *4.1.8* Procedures for monitoring subject compliance

Trial medication will be dispensed to the subjects by the investigator. Subjects will be instructed to bring all trial medication to the trial site at every visit (including all empty packages and unused trial medication), compliance will be assessed. Details will be recorded in the CRF and on the drug accountability form in the investigator site file.

### *4.1.9* Medication intake

Medication intake should take place with the meals or shortly after the meals.

These application forms are possible:

- Patients that can take the capsules:

  Whole capsules will be taken with liquid (50-100ml water, tea or apple juice).

- Patient that can't take the capsules:

  Capsules will be opened by the parents and content suspended in 5-20ml sweetened liquid (tea or apple juice) or taken with yogurt, jam, puree, apple sauce or pudding followed by liquid (50-100ml).

- Patient with feeding tube

  Capsules will be opened and content suspended in 5-20ml water and immediately administered. After this tube will be flushed by additional 2.5-10ml water.

### *4.1.10* Not permitted medication

Each previous and concomitant medication has to be documented in detail.

**Systemetic steroids:** pulsed glucocorticoids in the 4 weeks before entry into the study (day 1) and throughout the trail (V4 in START block and V6 in STOP block) are not allowed. A continous daily or alternate day oral dose of glucocorticoids is allowed and has to be stable in the 4 weeks before entry into the study (day 1) and troughout the trail.

| **Not permitted medication** | **Comedications very carefully to be considered (further explanation in the text)** |
|---|---|
| Hepatotoxic medications, also caution with alcohol | Antiepileptics |
| Inhibitors of the monoaminooxidase | **Digoxin** |
| Arrhythmogenic medications | **Cyclosporine** |
| Amiodarone | Methotrexate |
| Moxifloxacin | Corticosteroids |
| Halofantrin | Aminoglycosides |
| Metronidazole | Agalsidase-beta |
| Phenylbutazon | laronidase |
| Probenecid | Neostigmine, Pyridostigmine |
| Indomethacin | Antacids |
| Penicillamin | Caolin |
| Pyrimethamine/Sulfadoxine | Cimetidine |
| Other medications that decrease the convulsive threshold | Praziquantel |
| Bupropion | Rabies vaccination with HDCV |
| Mefloquine | Insulin, antidiabetics |
| Other antimalarial | Ampicillin |
| | Azathioprin |
| | Other disease-modifying antirheumatic drugs |

Due to an increased risk of ventricular arrhythmias the use of arrhythmogenic medication, as for example amiodarone or moxifloxacin, is not permitted during the trial. Halofantrin can prolong the QT interval with increased risk of arrhythmias and is therefore not permitted during the trial.

It is prohibited to use other hepatotoxic medication or inhibitors of the monoaminooxidase during the trial. Adolescent patients should be explained that no larger quantity of alcohol should be consumed during the treatment with HCQ.

The use of medication, that lowers the convulsive threshold, as for example mefloquine and bupropion, is not allowed during the trial, as there is an increased risk for seizures. The effect of antiepileptics can be reduced by hydroxychloroquine.

The use of digoxin and cyclosporine is not prohibited during the trial, but investigators must be aware that hydroxychloroquine may increase the plasma concentrations of digoxin and cyclosporine. So in this case a strict control of plasma-drug-level is necessary to avoid intoxication with digoxin or cyclosporine.

The use of other antimalarial drugs is not allowed during the trial because of a higher risk of side effects. With the use of phenylbutazon there is an increased risk for exfoliative dermatitis. If probenecid and indomethacin are used simultaneously there is an increased risk for sensibilisation and retinopathy. All three drugs are therefore not permitted during the trial.
The use of other disease-modifying antirheumatic drugs in patients who are already on the drugs is not prohibited during the trial, but the investigator must be aware of possible interactions and increased immunosuppression.

If hydroxychloroquine is combined with corticosteroids myopathies and cardiomyopathies can deteriorate. A combination with aminoglycosides leads to an increased neuromuscular blockade.

The combination with penicillamin can increase the risk for severe hematological and/or renal side effects and skin reactions. A combination with pyrimethamine/sulfadoxine increases the risk for skin reactions. Therefore these drugs must be avoided.

Simultaneous medication, which is toxic to the retina (e.g. tamoxifen) is not recommended.

Further, investigators must be aware, that hydroxychloroquine inhibits the effects of agalsidase beta (used in Fabrys disease), laronidase (used in mucopolysaccaridosis), neostigmine and pyridostigmine. It can also decrease the resorption of ampicillin.
In contrast, the effect of methotrexate is increased by hydroxychloroquine. Hydroxychloroquine can lead to an increased effect of antidiabetics (insulin, oral antidiabetics), so reduction of amount given can be necessary.

The effect of hydroxychloroquine can be reduced by caolin and antacids. If the use of antacids is necessary, there should be a time lag of 4 hours between the intake of hydroxychloroquine and antacids. The plasma concentrations of hydroxychloroquine can be increased by cimetidine.

Under the medication of the structural similar chloroquine-sulfate combined with metronidazole one acute dystonic reaction was observed, therefore the use of metronidazole during this trial is not permitted. The effect of praziquantel is reduced by chloroquine; so far it is not known if this is also the case with HCQ. In case of rabies vaccination with HDCV the production of antibodies can be reduced by HCQ.

(According to BSPAR guidance for hydroxychloroquine, October 2010 and Fachinformation Quensyl®, January 2017)

For interactions with other medications and further warnings and precautions please refer also to the current country specific Summary of Product Characteristics of Hydroxychloroquinsulfate (SmPC) for detailed information.

## 4.2 Rescue medication or emergency treatment

There exists no special rescue medication in this trial. Children with interstitial lung disease often are very sick. So far we do not know which patient will benefit from the use of hydroxychloroquine and which will not. It is possible, that some patients will deteriorate during the trial. As no evidence based standards for treating interstitial lung disease in children exist, it is in the responsibility of the treating physician to decide, what the further treatment will be.

# 5 TRIAL SCHEDULE

Tables 1-1 and 1-2 on page 9 to 13 provide the detailed schedule of assessments during the trial, from the Screening Period through the last visit.

## 5.1 Ophthalmological review

Recommendation to consult ophthalmologist at baseline for baseline visual assessment and at the end of the initiation or withdrawal, including:

1. Enquiry about any disturbance of central vision
2. Check visual acuity and reading acuity
3. Slit lamp examination from age 3 years onward
4. Funduscopy

Facultative, not requested by the study physician and only at the discretion of the ophthalmologist

1. Ocular coherence tomography (OCT),
2. Fundus auto fluorescence (FAF) imaging
3. Stereoscopic slit lamp examination of the retina (e.g. with a 90D or 78 biconvex lens)
4. Central visual field, using an Amsler Chart (preferably red on black) or automated perimetry
5. Evaluation may need to be extended according to signs and symptoms to include retinal photography and visual electrophysiological tests.

**Subsequent examinations should be at the discretion of the ophthalmologist**, but indefinite follow up is not likely to be required for most patients. For patients who have received continuous treatment for more than 5 years, an individual arrangement should be agreed with the local ophthalmologist.

Visual side effects are dose related and the drug should be stopped if they develop.

## 5.2 Electrocardiogram (ECG) and echocardiography (Echo)

Any signs of conduction disorders (bundle branch block / atrio-ventricular heart block) as well as biventricular hypertrophy in the ECG can be a sign of cardiomyopathy, which has been described under the medication with HCQ. In this case further cardiologic workup is necessary. If there are any signs or symptoms of cardiomyopathy the medication with HCQ must be discontinued immediately. (Fachinformation Quensyl® 2017) The Echo is done to assess for pulmonary hypertension and to exclude cardiomyopathy at the beginning of the study.

## 5.3 Check for Hypoglycemia

Any signs of hypoglycaemia like low blood glucose levels or reports of potential hypoglycaemic episodes will lead to intensived observation of blood glucose levels and if persistant change of medication (e.g. reduction or stop).

# 6 TRIAL METHODS

## 6.1 Assessment of efficacy

The primary outcome of the trial is the oxygen saturation, measured in room air. As the numbers of subjects that will be included into the trial will be low and cannot precisely be predicted, a spectrum of secondary outcome parameters will be interpreted exploratory, including patient oriented measures and outcomes, like quality of life.

# 7 Safety

## 7.1 Definitions

**Adverse Event (AE)**

According to GCP, an adverse event (AE) is defined as any untoward medical occurrence in a subject treated with a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An AE may be:

- a new symptom or a new diagnosis
- a new medical condition or an accident
- a change in laboratory parameters
- an intercurrent illness or accident
- worsening of a medical condition/diseases existing before the start of the clinical trial
- recurrence of a disease
- an increase in frequency or intensity of episodic diseases.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not AEs, if the condition leading to the measure was present before inclusion in the trial. In the latter case the condition should be reported as medical history.

Change in laboratory parameters: The criteria for determining whether an abnormal test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/ or
- Test result requires additional diagnostic testing or medical/ surgical intervention, and/ or
- Test result leads to a change in trial dosing outside of protocol-stipulated dose adjustments, or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy, and/ or
- Test result is considered to be an adverse event by the investigator or sponsor.
- Progression of chILD under treatment should not be reported as an adverse event. However, if chILD leads to a fatal outcome during the trial or within the safety reporting period, then disease progression should be reported as an adverse event and as a serious adverse event with outcome “death”.

**Serious adverse event (SAE)**

A serious adverse event (SAE) is one that at any dose (including overdose):

- results in death
- is life-threatening[1]
- requires subject hospitalization or prolongation of existing hospitalization[2]
- results in persistent or significant disability/incapacity[3] or
- is a congenital anomaly/birth defect
- is an important medical event[4].

Comment:
Death is an outcome of an event. The event that resulted in death should be recorded and reported as an SAE.

[1]"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2]If the admission is pre-planned (i.e., elective or scheduled surgery arranged prior to start of the trial) or not associated with an adverse event (e.g., social hospitalisation for purpose) or results in a hospital stay less than 12 hours, the serious criterion "hospitalisation" is not fulfilled. However, it should be noted that invasive treatment during a hospitalisation may fulfil the criteria of "medically important" and may be reportable as a serious adverse event dependent on clinical judgement.

An inpatient rehabilitation program per se does not fulfil the seriousness criterion "hospitalization". In this case the investigator should evaluate carefully whether the reason for the inpatient rehabilitation program has to be documented as an AE/ SAE.

[3]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions. The irreversible injury of an organ function (e.g., paresis, diabetes, cardiac arrhythmia) fulfils this criterion.

[4]Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse. A diagnosis of cancer during the course of a treatment should be considered as medically important.

**Clarification of the onset and end date of AEs and SAEs**

The onset date of the AE is defined as the onset of signs and symptoms or a change from baseline. The onset date of the SAE is defined as the date the signs and symptoms/diagnosis became serious, i.e., met at least one of the ICH criteria for seriousness.

The end date of the AE is defined as the date when the symptoms resolve, or the event is considered stable. The end date of the SAE is defined as the time the seriousness criteria are no longer applicable. The end date of the SAE must not be later than the end date of the corresponding AE. AEs and SAEs that are on-going at the time of death are considered not resolved or resolving.

**Clarification of the difference in meaning between "serious" and "severe":**

The terms "serious" and "severe" are not synonymous but are often used interchangeably. The term 'severe' is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor significance (such as severe headache). This is not the same as "serious", which is based on subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

**Suspected Unexpected Serious Adverse Reaction (SUSAR)**

A SUSAR is every SAE with an at least possible relationship to the investigational medicinal product which is unexpected. An unexpected serious adverse reaction is any adverse reaction, the nature or severity of which is not consistent with the applicable product information of the current country specific Summary of Product Characteristics of Hydroxychloroquinsulfate (SmPC)).

## 7.2 Assessment of AEs by investigator

Subjects must be carefully monitored for adverse events by the investigator. The intensity of the adverse events and the causal relation to trial medication and/or procedures are to be assessed.

**Intensity/ Severity**

The intensity of an AE will be assessed by the investigator as follows:

Mild: Temporary event which is tolerated well by the subject and does not interfere with normal daily activities.

Moderate: Event which results in discomfort for the subject and impairs his/her normal activity.

Severe: Event which results in substantial impairment of normal activities of subject.

If the event is serious, the severity reported in the adverse event must be consistent with the severity included in the adverse event report.

**Causal relation to trial medication/procedures**

The assessment of the relationship of an adverse event to the administration of study drug is a clinical decision based on all available information at the time of the documentation. Factors to be considered in assessing the relationship of the adverse event to study drug include:

• The temporal sequence from drug administration: The investigator has to consider, if the event occurred before first intake of study medication or long time after last intake. Additionally the length of time from drug exposure to event should be evaluated in the clinical context of the event.

• Recovery on discontinuation (de-challenge), recurrence on reintroduction (re-challenge): Subject's response after drug discontinuation (de-challenge) or subjects response after drug re-introduction (re-challenge) should be considered in the view of the usual clinical course of the event in question.

• Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.

• Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.

Positive causal relationship:

An assessment of 'related' implies a reasonable possibility of a causal relationship between the event and the investigational medicinal product (IMP).

This means that there are facts (evidence) or arguments to suggest a causal relationship, such as:

- A close temporal relationship
- A common drug reaction to the IMP
- No plausible alternative cause

Negative causal relationship:

An assessment of ‘not related‘ means that there is no reasonable possibility of a causal relationship between the event and the investigational medicinal product.

This includes for example:

- Another cause of the adverse event is more plausible
- A temporal sequence cannot be established with the onset of the adverse event and administration of the study treatment
- A causal relationship is considered biologically implausible.

## 7.3 Period of observation

In this trial, the period of observation for collection of adverse events extends from signing the inform consent up to the end of trial. If the investigator detects a serious adverse event in a trial subject after the end of the period of observation, and considers the event possibly related to the prior trial, he should contact the sponsor to determine how the adverse event should be documented and reported.

## 7.4 Documentation of AEs and Follow up

All AEs (whether serious or not) reported by the subject or detected by the investigator will be documented on the appropriate pages of the case report form (CRF). AEs must also be documented in the subject’s medical records. If the adverse event is serious (see Section 7.1), the investigator must complete, in addition to the “Adverse Event Page”, a “Serious Adverse Event Form” at the time the serious adverse event is detected.

Every attempt should be made to describe the adverse event in terms of a diagnosis. If a clear diagnosis has been made, individual signs and symptoms will not be recorded unless they represent atypical or extreme manifestations of the diagnosis, in which case they should be reported as separate events. If a clear diagnosis cannot be established, each sign and symptom must be recorded individually.

All subjects who have adverse events, whether considered associated with the use of the investigational products or not, must be monitored to determine the outcome. The clinical course of the adverse event will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up, but no longer than 90 days after the end of the trial.

Should the adverse event result in death, a full pathologist’s report should be supplied, if possible.

## 7.5 Immediate reporting of SAEs by investigator

SAEs must immediately (within 24 hours of the investigator’s awareness) be reported to:

**IZKS Mainz**
**Langenbeckstr 2**
**55131 Mainz**
**FAX 0049 6131/17-9916**

The initial SAE Report should be as complete as possible including the essential details of subject's identification (screening number, random number), the serious adverse event (medical term, diagnosis), the trial medication and the assessment of the causal relationship between the event and the trial medication. The SAE report must be reviewed and signed by the investigator.
The investigator should provide related additional information on the clinical course and the outcome of each SAE as soon as possible (Follow up report). The "Serious Adverse Event Form" will be provided.

Worsening of a sign or symptom of the condition under treatment will normally be measured by efficacy parameters. However, if the outcome fulfils the definition of "serious adverse event", it must be reported as such.

## 7.6 Safety evaluation and Reporting by sponsor

The sponsor will ensure that all legal reporting requirements are met. According to GCP the sponsor is responsible for the continuous safety evaluation of the investigational product(s) and the clinical trial. The IZKS on behalf of the sponsor will conduct the management of SAEs and the expedited reporting in Germany as required by German Drug Law (AMG) and GCP regulation (GCP-V). Suspected unexpected serious adverse reactions (SUSARs) and safety issues as defined by GCP-V are determined for expedited reporting: The competent authorities and the ethics committees should be notified as soon as possible but not later than 15 calendar days, and 7 calendar days if it was fatal or life-threatening. All investigators will be informed within the same timeframe. The marketing authorization holder of the IMP should be informed too. Work flow and procedures concerning Safety management will be described in a separate document.

During the clinical trial the sponsor will submit the Development Safety Update Report (DSUR) including a list of all serious adverse reactions to the ethics committee(s) and the competent authorities once a year.

## 7.7 Immediate Reporting of pregnancy by investigator

Any **pregnancy** diagnosed in a female subject during treatment with the investigational product must be reported immediately using the "Pregnancy Reporting Form" to:

**IZKS Mainz**
**Langenbeckstr 2**
**55131 Mainz**
**FAX 0049 6131/17-9916**

Pregnancy occurring during the clinical trial, although not considered a SAE, must be reported within the same timelines as a serious adverse event. The outcome of a pregnancy should be followed up carefully and abnormal outcome of mother or child should be reported if any.
When the outcome of the pregnancy and the definite condition of the child could be established, the investigator completes the "Pregnancy Outcome Form", and faxes the completed Report Form II to IZKS.

## 7.8 Documentation of Abuse, Misuse, Overdose and Medication Error

All special events such as study medication abuse, misuse, overdose and medication errors including dilution errors and infusion rate errors have to be documented in the subject's CRF and source documents. If any abuse, misuse, overdose, or medication errors lead to an (serious) adverse event, then the event has to be documented and reported as AE/SAE.

### 7.9 **Emergency procedures**

During and following a subject's participation in the trial, the investigator should ensure that adequate medical care is provided to a subject for any AEs including clinically significant laboratory values.
Emergency treatment: see 4.2
Emergency unblinding: see 3.5.2

### 7.10 **Other safety data**

7.10.1 Previous and intercurrent illnesses
Illnesses already known at the time of informed consent are to be documented in the CRF as medical history. Illnesses detected during the clinical trial are to be documented as Adverse Events (see above).

7.10.2 Previous and intercurrent medical treatments
All medical treatments with the exception of the Investigational Medical Products received by the participant at the beginning and / or during the clinical trial are to be documented in the CRF as concomitant medication.
Routine physical examination and laboratory determination as specified above at study visits.

## 8 STATISTICS

Details of the statistical analysis of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP) that will be generated by IZKS Mainz and finalized before closing the data base and prior to breaking the blind. The SAP is based on the protocol including all amendments. The document may modify the plans outlined in this protocol; however any major modifications of the primary outcome definition and/or its analysis will also be reflected in a protocol amendment. Any deviation from the original statistical plan must be described and justified in the final report. The statistical analysis will be conducted by means of SAS®.

### 8.1 **Sample size**

Due to the exploratory nature of the study there is no formal sample size calculation. The study aims to include 80 patients.

### 8.2 **Analysis populations**

All subjects with signed informed consent are considered as enrolled subjects, even if they did not receive any trial treatment. All randomised subjects will be included in the Intention-to-treat (ITT) population. This population is the primary analysis population. Within ITT population analyses subjects will be assigned to the treatment to which they were randomised. For the combined analysis the ITT Population consists of all patients that are at least in the START or the STOP block. The corresponding PP Populations consist of the patients from the ITT population without major protocol violations. Major protocol violations will be defined in the SAP. The safety population comprises all subjects who received at least one dose of trial treatment. In analyses of the safety population subjects will be assigned to the treatment which they actually received. The analysis populations will be defined prior to unblinding of the study.
For analysis, subgroups of patients will be defined, based on age, categories of diagnosis and further appropriate factors.

## 8.3 **Efficacy analyses**

The primary population for the analyses of efficacy are the ITT Populations (randomised patients) for each block. For the combined analysis the ITT Population consists of all patients that are at least in the START or the STOP block. For all hypotheses two-sided exploratory p-values will be provided.
If appropriate, the analyses will be adjusted for the stratification factor of the randomization: age group. The final efficacy analysis will be described in the Statistical Analysis Plan (SAP).

### *8.3.1* Definition and analysis of primary outcome

The oxygenation of the patient is the primary outcome variable. The primary outcome will be assessed as the response rate of oxygenation to the intervention. As the patient´s respiratory condition can vary over a broad range, may necessitate variable external support, and as these changes may occur over relatively short time periods, it is necessary to take all this into consideration when assessing oxygenation. Therefore we defined the parameters to be measured depending on the patient´s condition to define a responder (Table 3.8-1). The majority of children included into the study are expected to be on supplemental oxygen or in room air. In these subjects oxygen saturation in room air will be assessed (for assessments please see 3.2). However to include the broad continuum of respiratory support possible in individual patients, an approach was chosen accommodating that need. Responses to treatment judged as significant were defined depending on Patient´s condition. How and when to assess the variables is further detailed in the study protocol.
Oxygenation, the primary outcome parameter, was chosen as a dichotomous variable (response yes or no). Its components, i.e. O2-saturtation and respiratory rate, are also used continuously in a descriptive manner as secondary outcome variables.

Tab 3.8-1: Definition of responders to treatment depending on Patient´s condition

| Patient's condition | Measured parameters | Specific metric | Definition of significant change or responder to the **initiation** of HCQ | Definition of significant change or responder to the **withdrawal** of HCQ | Method of aggregation |
|---|---|---|---|---|---|
| In room air | In room air<br>O2 Sat (mean value)<br>Respir rate (mean value) | Change from baseline | Increase ≥ 5% in O2 Sat,<br>or<br>Decrease in resp. rate ≥ 20% | Decrease ≥ 5% in O2 Sat,<br>or<br>Increase in resp. rate ≥ 20% | Proportion of responders |
| On O2-supple-ment | In room air<br>O2 Sat (mean value)<br>Respir rate (mean value) | Change from baseline | Increase ≥ 5% in O2 Sat<br>or<br>Decrease in resp. rate ≥ 20%<br>or<br>Support no more needed | Decrease ≥ 5% in O2 Sat,<br>or<br>Increase in resp. rate ≥ 20%<br>or<br>Support newly needed | Proportion of responders |
| On high-flow nasal cannula | O2-flow, air-flow | Change from baseline | Decrease ≥ 20%<br>or<br>Support no more needed | Increase ≥ 20%<br>or<br>Support newly needed | Proportion of responders |
| Ventilated | Oxygenation index | Change from baseline | Decrease ≥ 20%<br>or<br>Support no more needed | Increase ≥ 20%<br>or<br>Support newly needed | Proportion of responders |

The definition of the threshold for a significant change or responder regarding oxygenation will be further assessed as a secondary outcome.

<u>Controlled initiation of HCQ</u>
Relative change trial day 1 (i.e. Visit 2), through day 28 (i.e. Visit 3) and relative change day 28 (i.e. Visit 3) to day 56 (i.e. Visit 4) active compared to change placebo
<u>Controlled withdrawal of HCQ</u>

Relative change trial day 1 (i.e. Visit 2) through day 84 (i.e. Visit 5): change active compound compared to change placebo

### *8.3.2* Analysis of secondary outcome

All analysis of secondary outcome will be interpreted purely exploratory. Continuous and quasi-continuous variables will be displayed by the descriptive statistics: N (number of observations), mean, standard deviation, minimum, median, maximum and the number of missing observations. Categorical variables will be displayed by absolute and relative frequencies. Exploratory p-values will be calculated when appropriate. Time to event data will be displayed by Kaplan-Meier Plot when a reasonable number of events occur.

### *8.3.3* Analysis of Subgroups

If appropriate, subgroups will be defined in the SAP.

### *8.3.4* Interim analyses

No interim analyses are planned.

## 8.4 **Analysis of adverse events**

All summaries and listings of safety data will be performed for the safety population.

Frequencies of subjects experiencing at least one adverse event (AE) will be displayed by body system and preferred term according to MedDRA terminology. Detailed information collected for each AE will include: A description of the event, duration, whether the AE was serious, intensity, relationship to trial drug, action taken, clinical outcome. Summary tables will present the number of subjects observed with AEs and corresponding percentages. Additional subcategories will be based on event intensity and relationship to trial drug. A subject listing of all AEs will be prepared.

## 8.5 **Analysis of clinical laboratory findings**

Listings will be prepared for each laboratory measure and will be structured to permit review of the data per subject as they progress on treatment. Summary tables will be prepared to examine the changes of laboratory measures over time. Additionally, shift tables will be provided to examine the changes of laboratory data from normal baseline to values outside the corresponding reference range during/after treatment.

## 8.6 **Other**

Steady state drug levels and ECGs will be monitored. Ophthalmologic exams will be done.

# 9 QUALITY CONTROL AND QUALITY ASSURANCE

## 9.1 **Requirements for investigational sites and staff**

The investigator should be able to demonstrate (e.g. based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period. The

investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period. The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.The investigator should ensure that all persons assisting with the trial are adequately qualified, informed about the protocol, any amendments to the protocol, the trials treatments, and their trial-related duties and functions.

## 9.2 Direct entries

Data entries be entered in the CRF as Direct, are listed in the Monitor Manual in the section source data control.

## 9.3 Direct access to source data/documents

The investigator/institution must permit trial-related monitoring and auditing, as well as inspections by the appropriate competent authorities and Ethics committees, providing direct access to source data/documents (Confidentiality see 11.3). The subjects will be informed that representatives of the sponsor, independent ethics committee (IEC) or competent authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

## 9.4 Investigator site file and archiving

The investigator will be provided with an investigator site file (ISF) at the start of the trial. The investigator will archive all trial data and relevant correspondence in the ISF. The ISF, all source data and all documents will be kept filed according to the requirements of the ICH-GCP guidelines after termination of the trial. After the end of the trial related documents e.g. trial master file (TMF) and CRFs will be stored in the archive of the sponsor. It is the responsibility of the investigator to ensure that the subject-identification sheets are stored for at least 15 years beyond the end of the clinical trial. All original subject files must be stored for the longest possible time permitted by the regulations at the hospital, research institute, or practice in question. If archiving can no longer be maintained at the site, the investigator will notify the sponsor.

## 9.5 Monitoring

Monitoring will be done by personal visits from a clinical monitor according to SOPs of the IZKS Mainz in Germany. In the other planned countries (e.g. Italy, Spain, Portugal, Turkey, Poland and Austria), the monitoring will be done by the ECRIN partners according to SOPs provided by the Lead CTU (IZKS Mainz) and the ERCIN ERIC coordination in Paris/Cologne. Each site will be visited by the monitor at regular intervals to ensure compliance with the trial protocol, GCP and legal aspects. The monitor will review the entries into the CRFs for completeness and correctness and verify the entries on the basis of the source documents. The presence of correct informed consents will be checked for every subject. Details will be specified in the monitoring manual for this trial.The investigator must allow the monitor to look at all relevant documents and must provide support at all times to the monitor. By frequent communications (letters, telephone, fax), the monitor will ensure that the trial is conducted according to the protocol and regulatory requirements.

## 9.6 Inspection by authorities and audits

Competent authorities and by the sponsor authorised persons (auditor) may request access to all source documents, CRF, and other trial documentation in case of an inspection or audit. Direct access to these documents must be guaranteed by the investigator who must provide support at all

times for these activities. Source data documents can be copied during inspection or audit in case the identity of the subject have been made unrecognizable.

## 9.7 **Audits**

No audits are planned for this trial.

# 10 DATA MANAGEMENT

The Central Information Office Marburg is responsible for data management. All data management activities will be done according to the current Standard Operating Procedures (SOPs) of Central Information Office Marburg. For reports and analysis the EDC system provides data export functionality for data management. The data can be exported in SAS or SPSS format for reports and analysis.

## 10.1 **Medical Database / eCRF (MDAT)**

The Central Information Office Marburg is responsible for programming the eCRF (electronic Case Report Form) and hosting the medical database (MDAT). The eCRF will be designed in accordance to the clinical trial protocol. As EDC system the secuTrial® system of the Central Information Office Marburg will be used. secuTrial® is an internet based system with connection to a rational ORACLE® database. The software serves as remote data entry system for pseudonymized medical data. It includes functions for data entry in electronic forms, for data view, analysis and export.

The software development was strictly done in accordance to a standardized procedural model, meeting all ISPE GAMP4 requirements of software validation. SecuTrial® is permanently audited to meet all requirements according to GCP, AMG, EMEA and FDA (21 CFR Part 11). It includes three different audit trail systems for medical data, user management and eCRF changes. Audit trail includes all changes made through the eCRF system within the database with additional login information and timestamp. This assures that any documentation and/or changes to database, user roles and medical items are traceable anytime. Changes or corrections can only be made by persons who have access to the system with user specific, role based access rights. Last audit was in May 2013.

Data management based on GCP refers to the activities defined to achieve safe routines to efficiently enter patient information into a database, avoiding errors. The data management routines include procedures for handling of CRF, database setup and management, data entry and verification, data validation, quality control (QC) of database, and documentation of the performed activities including information of discrepancies in the process.

Subjects' data are documented with the EDC (Electronic Data Capture) system directly by the sites via web browser and are transferred via SSL encryption to the central medical database (MDAT). The EDC system is 21 CFR Part 11 compliant and has an implemented audit trail.

## 10.2 **Secure Hosting of the Medical database (MDAT)**

The server-hardware of the Central Information Office Marburg is recently renewed in November 2012 to a currently up-to-date high-level processing power and storage system state. The server system is housed in a cage-in-cage-room in the High Security Data Center Itenos of the T-Systems AG, Nürnberg (20000-1 and ITIL certified). For the secure system administration the I-Motion GmbH, Fürth, is responsible (ISO-9001 and KV-Safenet certified). Server support is provided exclusively by high qualified and experienced personal.

The secure hosting concept includes the conception and implementation of the safety and security standard operating procedures, the professional audit of all formal processes of data security and the continuous support by competent personal.

Network traffic between the internet and the firewall systems, between the firewall systems and the application servers and between the application and the database servers is controlled by network based intrusion detection systems. All warnings and errors are logged in a separated database, located in the separated IT-center of the I-Motion GmbH, Fürth, permanently controlled and watched by internal implemented analysis tools.

The high availability of the medical research data is guaranteed by redundant hard disk systems (RAID) and a generation based data backup strategy.
All medical data on the database servers and all log files of the firewall systems are backuped daily. Exchange of the backup-tapes of the individual generations is weekly with a three-week rotation. Tapes of the last generation are stored in a bank safe-deposit box.

All systems are secured from power failures by a redundant uninterruptable emergency power supply system (USV, NEA).

The ASP-hosting and server connections (ISP-Connectivity) of the server farm, located in the T-Systems Data Center Itenos, Nürnberg, and their system administration by the I-Motion GmbH, Fürth, is audited regularly by the *Central Information Office Marburg*.
Audit is based on

- German National Institute of Security in Information Technology (BSI): Safeguard catalogues
- ISO 27000 (Management systems for Information Security)
- ISO 27001 (Information security management systems requirements specifications)
- ISO 27005 (Information security risk management)
- FDA Guidance for industry: Computerized Systems used in Clinical Trials (CSUCT)
- Good Clinical Data Management practices, ver. 4

Last audit was in June 2012.

## 10.3 **Data entry**

The investigator is responsible for the performance of the trial in accordance to the clinical trial protocol. All data collected during the trial have to be documented in the eCRF by authorized persons according to the personal log with delegation of authorities. Detailed requirements for using the EDC system are specified in an EDC-Manual.
The eCRF should always reflect the latest observations on the patients participating in the study. Therefore, the eCRF are to be completed as soon as possible during or after the patient's visit. To avoid inter-observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all effect and safety evaluations. The investigator must verify that all data entries in the eCRF are accurate and correct. If some assessments are not done, or if certain information is not available, not applicable or unknown, the investigator should indicate this in the eCRF. The investigator will be required to electronically sign off adverse and serious adverse event reports in the medical study database.

In order to use the EDC system all participants entering and monitoring data are provided with training materials and required documentation before start of the trial by IZKS Mainz. Every person using the EDC system has to complete a registration form (User-ID request) to confirm that they have received the training material and have been trained for data entry. For training of data entry a test/training database will be provided.

For support with data entry the Data management team of the national chILD-EU centers can be contacted. Each trial site has one responsible person who supports the national chILD-EU center

in implementation of technical and organisational processes. A list of these persons is enclosed to DMP.

Users with monitoring function are not able to enter or change data. They have the possibility to view the data write protected (review function) and they can raise discrepancies and/or SDV marks in case of queries. Discrepancies which appear at data management are forwarded to the site directly.

## 10.4 Data concealment for electronic transfer

Every investigator, study nurse, monitor or other person involved in the trial receives her or his personal login data (username and password). Access rights to the database will depend on the group affiliation. Every person who gets access to the system has to fill in a registration form (User-ID request) and has to confirm that they have been adequately trained. Thus it is guaranteed that only authorized persons have access to the EDC system to document subjects in the trial.

## 10.5 Database quality control

Data have to be entered into the Medical database by the clinical investigator's staff, using single data entry with electronic verification. The Medical database contains several completeness and plausibility data checks. During data entry these integrity checks help to minimize entry failures. They are programmed according to the data validation plan, signed by the coordinating investigator.Case report forms can only be stored after answer completeness and plausibility errors with correct data entries.
The data entry system allows the trial monitors to control the entry process with the help of several eCRF-internal review functions. Comments and requests can be processed by the trial site just in time. Subsequently, the entered data are systematically checked by the monitors, using the internal query system of the Medical database, completeness reports and printable queries details lists.

The investigator or a designated sub investigator, following review of the data in the eCRF, will confirm the validity of each subject's data by electronic signature. The EDC system is capable to make exact copies of data in legible paper form for inspections and audits. Quality control audits of all key safety and efficacy data in the database are made prior to locking the database. Concomitant medications, medical history, current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

At the conclusion of the clinical trial, the occurrence of any protocol violations will be determined.
After these actions have been completed and the database has been declared to be complete and accurate, it will be locked for additional data entries and final checks for plausibility, consistency and completeness of the data will be performed. Based on these checks, final queries can be produced. Any missing data or inconsistencies will be reported back to the respective site and clarified by the responsible investigator. A database audit will be accomplished to ensure and document the high-quality trial database. If no further corrections are to be made in the database it will be declared closed and used for statistical analysis.

## 10.6 Storage and archiving of data

According to GCP, the investigator will archive all trial data (subject identification list, source data) and relevant correspondence in the Investigator Site File (ISF). The ISF, all source data and all

documents itemized in section 8 of the ICH Consolidated Guideline on GCP will be archived after finalization of the trial according to the legal regulations.

Responsible for storage and archiving of other trial data will be the Coordinating investigator. Storage and archiving of the electronic data during the trial will be assured by the Central Information Office Marburg. After completion of the trial all electronic data will be handed over to the sponsor.

# 11 ETHICAL AND LEGAL ASPECTS

## 11.1 Good clinical practice

The procedures set out in this trial protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial abide by good clinical practice (GCP) and the ethical principles described in the Declaration of Helsinki. The trial will be carried out in keeping with local legal and regulatory requirements.

## 11.2 Patient information and informed consent

Before being admitted to the clinical trial, the subject and/or the representatives must consent to participate after being fully informed about the nature, scope, and possible consequences of the clinical trial. The documents must be in a language understandable to the subject and representatives and must specify who informed the subject and the representatives. A copy of the signed informed consent document must be given to the subject or representative. The original signed consent document will be retained by the investigator.

The investigator will not undertake any measures specifically required only for the clinical trial until valid consent has been obtained. If the subject has a primary physician the investigator should inform the subject's primary physician about the subject's participation in the trial and if the subject or his representatives agrees to the primary physician being informed.

After reading the informed consent document, the subject must give consent in writing. The subject's consent must be confirmed by the personally dated signature of the subject and by the personally dated signature of the person conducting the informed consent discussions.

Since the subjects in this trial are mostly children, the consent of both legally authorized representatives must be sought. Children who are able to understand the nature, scope, and possible consequences of the clinical trial must also give their informed consent. The consent must be confirmed by the personally dated signature of the representatives (and child, if applicable) and the personally dated signature of the person conducting the informed consent discussions. A copy or one of two originals of the signed consent document must be given to the representatives. The original signed consent document will be retained by the investigator.

## 11.3 Confidentiality

The name of the subjects and other confidential information will not be supplied to the sponsor. During the clinical trial, subjects will be identified solely by means of an individual identification code (e.g. subject number, randomization number). Trial findings stored on a computer will be stored in accordance with local data protection laws and will be handled in strictest confidence. For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized persons. The appropriate regulations of data legislation will be fulfilled in its entirety.

The subject will declare in the written consent to release the investigator from the medical professional secrecy to allow identification of subject's name and/or inspection of original data for monitoring purposes by health authorities and authorized persons (monitors).

The investigator will maintain a personal subject identification list (subject numbers with the corresponding subject names) to enable records to be identified.

## 11.4 Responsibilities of investigator

The investigator will ensure that all persons assisting in the trial are adequately informed about the protocol, any amendments to the protocol, the trial treatments, and their trial-related duties and functions. The investigator will maintain a list of sub investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties.

## 11.5 Approval of trial protocol and substantial amendments

Before the start of the trial, the trial protocol, informed consent document, and any other appropriate documents will be submitted to the independent ethics committee (IEC) for approval. The documents will also be submitted to the competent authorities (in Germany approval by BfArM), in accordance with the respective local legal requirements.
Investigational products can only be supplied to the investigator after documentation on all ethical and legal requirements for starting the clinical trial has been received by the sponsor ("regulatory green light"). Before the first subject is enrolled in the trial, all ethical and legal requirements must be met. The IEC and, if applicable, the competent authorities must be informed of all subsequent protocol amendments, in accordance with the respective local legal requirements. The sponsor must keep a record of all communications with the IEC and the competent authorities. The EC must be informed of the end of the trial in accordance with legal requirements.

## 11.6 Submission to local regulatory/competent authorities

Before the start of trial, the sponsor is responsible for submission of all documents necessary to the competent authorities for approval, in accordance to the respective local legal requirements.

## 11.7 Data monitoring committee (DMC)

Details will be specified in the charter of the DMC.

## 11.8 Insurance

According to legal requirements, the sponsor has to subscribe an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

Any impairment of health which might occur in consequence of trial participation must be notified to the insurance company. The subject is responsible for notification. The insured person will be agreed to all appropriate measures serving for clarification of the cause and the extent of damage as well as the reduction of damage.

During the conduct of the trial, the subject must not undergo other clinical treatment except for cases of emergency. The subject is bound to inform the investigator immediately about any adverse events and additionally drugs taken. The terms and conditions of the insurance should be delivered to the subject.

Insurance provisions for this clinical trial are given in separate agreements.

## 11.9 **Agreements**

### *11.9.1 Financing of the trial*

The trial is part of the EU research projects chILD EU, E-Rare 2016 and the DZL 2.0.

The general conditions of financing for this trial are given in separate agreements.

### *11.9.2 Report*

After conclusion of the trial, a report shall be written by the sponsor, in cooperation with the coordinating investigator. The report will include a statistical analysis and an appraisal of the results from a medical viewpoint. It will be based on the items listed in this trial protocol.

### *11.9.3 Publication policy*

It is planned to publish the results of the trial as an original article in an appropriate medical journal as well as presentation at congresses. The Principal Investigator is first author of the article and will present the data at the major congresses. The choice of the journal for the publication will be made by the Principal Investigator in agreement with the co-authors. Besides the Principal Investigator, further authors of this article have to meet the following points:

- Substantial contribution to the recruitment of subjects, i.e. one of the five best recruiting centers within the trial.
- Substantial contribution to interpretation of the data.
- Substantial contribution to drafting the article or revising it critically for important intellectual content.
  All details regarding authorship are given in the Contract with Participants in the European child Registry (chILD-EU) Research Project, which was signed by each participant involved in the study

# 12 SIGNATURES

The present trial protocol was subject to critical review and has been approved in the present version by the persons undersigned. The information contained is consistent with:

- The current risk-benefit assessment of the investigational medicinal product.
- The moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki and the principles of GCP.

**Coordinating/Principal Investigator**

Prof. Dr. M. Griese

_____ _____

Date Signature

**Trial coordination**

Dr. Kai Kronfeld

_____ _____

Date Signature

**Biometrician**

Christian Ruckes, MSc

_____ _____

Date Signature

# 13 DECLARATION OF INVESTIGATOR

I have read the above trial protocol and I confirm that it contains all information to accordingly conduct the clinical trial. I pledge to conduct the clinical trial according to the protocol.

I will enrol the first subject only after all ethical and regulatory requirements are fulfilled. I pledge to obtain written consent for trial participation from all subjects.

I know the requirements for accurate notification of serious adverse events and I pledge to document and notify such events as described in the protocol.

I pledge to retain all trial-related documents and source data as described. I will provide a Curriculum Vitae (CV) before trial start. I agree that the CV may be submitted to the responsible competent authorities.

I will conduct the trial in compliance with the protocol, GCP and the applicable regulatory requirements.

**Investigator**

Name
Address
Phone
Fax
e-Mail

_____ _____
Date Signature

**Sub investigator**

Name
Address
Phone
Fax
e-Mail

_____ _____
Date Signature

# 14 REFERENCES

1. Bush A, Nicholson A.G.. Paediatric interstitial lung disease. Eur Respir Mon, 2009, 46, 1–36.
2. Clement A, Nathan N, Epaud R, Fauroux B, Corvol H. Interstitial lung diseases in children. Orphanet J Rare Dis. 2010 Aug 20;5:22.
3. de Benedictis FM, Bush A. Corticosteroids in respiratory diseases in children. Am J Respir Crit Care Med. 2012 Jan 1;185(1):12-23.
4. Diav-Citrin O, Blyakhman S, Shechtman S, Ornoy A. Pregnancy outcome following in utero exposure to hydroxychloroquine: A prospective comparative observational study. Reprod Toxicol. 2013;39C:58-62.
5. Fachinformation Quensyl®. Sanofi-Aventis Deutschland GmbH 2017.
6. Griese M, Haug M, Brasch F, Freihorst A, Lohse P, von Kries R, Zimmermann T, Hartl D. Incidence and classification of pediatric diffuse parenchymal lung diseases in Germany. Orphanet J Rare Dis. 2009 Dec 12;4:26.
7. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl 2013; 3:1.
8. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39(Suppl 1):S1-S266. Table 24 (page S56).